CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD):
Prevalence, Incidence, Decline in Lung Function and Risk Factors

The Obstructive Lung Disease in Northern Sweden Studies
Thesis VI

by
Anne Lindberg

Umeå 2004
To
Elge
Felix and Linnea
Karin and Lasse
ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD); prevalence, incidence, decline in lung function, and risk factors. - The Obstructive Lung Disease in Northern Sweden Studies, Thesis VI - Anne Lindberg

The Obstructive Lung Disease in Northern Sweden (OLIN) Studies started in 1985 as an epidemiological project with the aim to detect preventable risk factors for obstructive lung diseases and allergy. In recent years there has been a focus also on obstructive sleep apnoea syndrome (OSAS) and chronic obstructive pulmonary disease (COPD) besides asthma and allergy. The aim of this thesis was to estimate the prevalence and incidence of COPD, risk factors for COPD, and decline in lung function in relation to COPD.

The OLIN cohort I (cI) was recruited in 1985/86 and consisted of all 6610 subjects born 1919-20, 1934-35 and 1949-50 in eight geographical areas of Norrbotten. A postal questionnaire survey was performed in 1985/86, 1992 and in 1996. All subjects reporting respiratory symptoms at the questionnaire in 1985/86 were invited to examination in 1986, 1996 and 2002-03. A random sample of 1500 subjects from the participants at the 1996 postal questionnaire survey was invited to examination in 1996 and 2003. The participation rate has been high, ≥85%. The OLIN cohort III (cIII) was recruited in 1992, a postal questionnaire was sent to a random sample of 5681 subjects aged 20-69 years. In 1994/95 a random sample of 970 subjects were invited to examination of whom 666 participated.

The prevalence of COPD in the general population sample (cIII) in ages <45 was 4.1%, 11.6%, 9.1%, and 5.1% according to the criteria of BTS, ERS, GOLD, and ATS, respectively. The corresponding figures in ages ≥45 were 9.7%, 15.4%, 17.1%, and 16.5%, respectively. In the age-stratified general population sample (≥45 y, cI), the prevalence was 8.1% and 14.3% according to the BTS and GOLD criteria. The prevalence was strongly associated with higher age and smoking but not gender. The prevalence among smokers 76-77 years old was 45% and 50% (BTS and GOLD criteria). A majority of subjects with COPD had respiratory symptoms (in prevalent BTS 94%), most commonly cough and sputum production. Nearly a half of the subjects with COPD had contacted health care due to respiratory complaints other than common colds, but only a minority reported a physician diagnosis relevant for COPD (16% of prevalent COPD according to BTS in cIII, 31% in cI). The 10-year cumulative incidence of COPD (1986-1996) was estimated at 8.2% (BTS) and 13.5% (GOLD) in the symptomatics of cI, associated with higher age and smoking but not gender. Persistent smoking, male gender and reported chronic productive cough were associated with a faster decline in FEV1. Among incident cases of COPD a large proportion (23% of incident BTS) had a rapid decline in FEV1, >90 ml/year, corresponding to a decrease of 28 percent units of normal value during ten years. The 7-year cumulative incidence of COPD in the random sample of cI (1996-2003) was estimated at 4.9% and 11.0% (NICE guidelines and GOLD) and associated with smoking but not gender. The incidence according to GOLD, but not NICE, was associated with increasing age. In multi-variate analyses most respiratory symptoms were markers of increased risk for developing COPD.

In conclusion, the prevalence and the incidence of COPD were associated with age and smoking and affected by the use of different spirometric criteria. Respiratory symptoms marked an increased risk for developing COPD. A high proportion of subjects developing COPD had a rapid decline in lung function. Further, there was a substantial underdiagnosis of COPD.

1British Thoracic Society: FEV1/VC<0.70 & FEV1<80%predicted (pred), 2European Respiratory Society: FEV1/VC<80%pred in men, <80%pred in women, 3Global initiative for Chronic Obstructive Lung Disease: FEV1/FVC<0.70, 4American Thoracic Society: FEV1/FVC<0.75 + symptoms or physician diagnosis, 5The British National Institute for Clinical Excellence: FEV1/FVC<0.70 & FEV1<80%pred.
ORIGINAL PAPERS

This thesis is based on the following papers:


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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARP</td>
<td>Attributable Risk Percent</td>
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<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<td>BMRC</td>
<td>British Medical Research Council</td>
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<td>BTS</td>
<td>British Thoracic Society</td>
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<td>CAL</td>
<td>Chronic Airflow Limitation</td>
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<td>CAO</td>
<td>Chronic Airway Obstruction</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COAD</td>
<td>Chronic Obstructive Airway Disease</td>
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<tr>
<td>Cold</td>
<td>Chronic Obstructive Lung Disease</td>
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<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CORD</td>
<td>Chronic Obstructive Respiratory Disease</td>
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<tr>
<td>ECRHC</td>
<td>European Community Respiratory Health Survey</td>
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<tr>
<td>ERS</td>
<td>European Thoracic Society</td>
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<td>ETS</td>
<td>Environmental Tobacco Smoke</td>
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<tr>
<td>FEV$_{1}$</td>
<td>Forced Expiratory Volume in one second</td>
</tr>
<tr>
<td>FinEeS</td>
<td>Finland, Estonia and Sweden</td>
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<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
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<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
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<td>IUATLD</td>
<td>International Union Against Tuberculosis and Lung Diseases</td>
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<tr>
<td>LR</td>
<td>Likelihood Ratio</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
</tr>
<tr>
<td>OLD</td>
<td>Obstructive Lung Disease</td>
</tr>
<tr>
<td>OLIN</td>
<td>Obstructive Lung Disease in Northern Sweden</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>OSAS</td>
<td>Obstructive Sleep Apnoea Syndrome</td>
</tr>
<tr>
<td>PAR</td>
<td>Population Attributable Risk</td>
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<tr>
<td>PAF</td>
<td>Population Attributable Fraction</td>
</tr>
<tr>
<td>SEI</td>
<td>SocioEkonomin Indelning (Socio-economic subdivision)</td>
</tr>
<tr>
<td>SOB</td>
<td>Shortness Of Breath</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Science</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VC</td>
<td>Vital Capacity</td>
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INTRODUCTION

Severe Chronic Obstructive Pulmonary Disease (COPD) is a common problem in patients hospitalised on respiratory medicine wards. The burden of disease is great both for those directly affected and for society. The majority of the patients dependent on home oxygen treatment are former smokers with COPD. Still, this is just the top of an iceberg, since predominantly only cases of advanced COPD get hospital care. Mild and moderate cases seldom find their way to the hospital, and it is known that many of them are not recognised at all by medical care providers.

Several national and international guidelines concerning diagnosis and care of COPD have been published during recent years. There has been a focus on COPD also from the World Health Organisation (WHO), according to which COPD is to be expected to be the third most common cause of death in year 2020. Both patients and physicians are aware of the disease COPD to a considerably higher degree today than 15 years ago. Misclassification of advanced COPD as asthma is more unusual today compared to earlier. There has been a diagnostic shift over time. There are many consultations concerning respiratory symptoms and lung function impairment, and the question at issue today is more often than previously “is this COPD?” Increased awareness of COPD in both society and health care facilitates correct identification of the disease, and provision of proper information and care to the patients. However, there are still many questions to ask when encountering these patients. Which individuals will develop COPD and why? How can we measure and predict future decline in lung function in these patients, both early and late in the course of the disease? These questions lead further to other considerations. Is earlier identification of COPD possible in our health care system? What signs should raise suspicion of the disease? These questions are important, as early diagnosis will create the necessary conditions for preventive actions against further disease progress, above all smoking cessation. There is still lack of knowledge in the field of COPD-epidemiology, especially concerning the development and course of the disease.

The Obstructive Lung Disease In Northern Sweden (OLIN) Studies started in 1985, collecting longitudinal epidemiological data with a focus on allergy and obstructive pulmonary diseases. The overall aim was to find possible preventable risk factors permitting intervention in the course of these diseases. Work is in progress. This thesis is focused on COPD epidemiology, and is based on the analyses of both cross-sectional and longitudinal data from the OLIN studies. COPD and mainly prevalence, incidence, underdiagnosis, decline in lung function, risk factors and gender differences will be discussed.
BACKGROUND

The history of the term COPD

In European medical history chronic bronchitis and emphysema are known from the early 19th century. The classical description of emphysema was made by Laennec in 1827 [Laennec], and the term bronchitis is known from the beginning of the 19th century and Great Britain [Badham, 1808]. However, not until the fog catastrophe in London in 1952 was there an increased awareness of the concept chronic bronchitis. It was estimated that among those suffering from chronic respiratory and cardiac diseases, over 4000 subjects more than expected died during one week in December. Research performed later in this area suggest that the figures might have been considerably higher than 4000. The London Fog catastrophe provided motivation for the British Medical Research Council (BMRC) to guide and support the research in the field of chronic bronchitis during the following years. There was a confusion concerning the diagnosis of obstructive pulmonary diseases regarding the conditions emphysema and chronic bronchitis, where the former was understood to cause severe airflow obstruction and the latter to represent a clinical diagnosis. Further, there was a geographical difference; the clinical term emphysema in North America was used for the condition labelled chronic bronchitis in Great Britain. These topics are discussed by Fletcher [Fletcher et al, 1976].

Beginning of standardisation

It was obvious among researchers that a standardised and uniform definition for chronic bronchitis was necessary for further surveys, and questionnaires were developed to screen for chronic bronchitis. Asthma, chronic bronchitis, and emphysema were defined at the CIBA guest symposium published in 1959 [the CIBA guest symposium, 1959]. WHO made a statement two years later with a quite similar definition of chronic bronchitis, which was summarised as follows: “... cough and sputum production on most days for at least three months in a year during at least two consecutive years...” [World Health Organisation, 1961]. The standardised questionnaires of BMRC published in 1960 were further revised and expanded in 1965, 1966, and later [Medical Research Council, 1960; 1986]. They were of great importance for the future epidemiological research. Other important questionnaires have followed, among those the American Thoracic Society's (ATS) questionnaire in 1975 [Ferris, 1978], the International Union Against Tuberculosis and Lung Diseases (IUATLD) questionnaires in 1985 and 1986 [Burney et al, 1989; 1989], and the self-administered Tucson questionnaire [Lebowitz et al, 1976]. The discussion of the definition of chronic bronchitis continued during the 1960's. The ATS definition of
chronic bronchitis implied excessive sputum production, and added the condition “provided that other respiratory diseases had been excluded” [American Thoracic Society Committee, 1962]. In 1965, BMRC published a definition of chronic bronchitis divided by a “simple” and an “obstructive” form, bringing together the definitions of the CIBA symposium [Medical Research Council, 1965] and the ATS definition.

The British hypothesis and the Dutch hypothesis

According to “The British hypothesis”, stated at the CIBA guest symposium published in 1959, chronic bronchitis was a specific disease in which impairment of lung function may develop dependent on host factors, but mainly dependent on exogenous factors and environmental influence such as smoking, air pollution and respiratory tract infections. Asthma was considered to be a completely separate disease. The BMRC questionnaires were developed parallel to the British hypothesis.

“The Dutch hypothesis” was presented during the 1960s [Orie et al, 1961; van der Lende, 1969] in contrast to “the British hypothesis”, proposing that certain host characteristics (as atopy and bronchial hyperreactivity) predicted the subjects response to environmental exposure including smoking. Genetic and environmental factors interaction and modulation by age determined whether a subject remained healthy, developed asthma, bronchitis or irreversible lung function impairment. Thus, asthma, chronic bronchitis and emphysema were regarded as sub-groups of a single disease process, with the possibility of an overlapping clinical picture.

The Fletcher hypothesis

Fletcher is probably the most well-known researcher in this field from that time. He was involved early in the development of methods which aimed to screen for chronic bronchitis [Fletcher et al, 1959; 1961]. During the 1970s he stated “the Fletcher hypothesis”. According to his hypothesis, there were two different diseases: one was simple chronic bronchitis without lung function impairment connected to emphysema, and the other was chronic bronchitis with progressive obstructive lung function impairment and parenchymal damage [Fletcher et al, 1976]. Both were related to smoking but they had different natural histories, though they could co-exist in the same individual. The report by Fletcher on the relationship between smoking and decline in lung function is classic reading. Fletcher found male smokers to have a mean decline in FEV1 of about 50 ml/year and some with a rapid decline of about 90 ml/year, while smoking cessation returned the decline to a non-smoking level.
The term COPD

In 1964 the term Chronic Obstructive Pulmonary Disease, COPD, was first mentioned by Mitchell in USA [Mitchell et al, 1964]. During the following years, there was further confusion in terminology; terms like chronic obstructive lung disease, COLD, chronic obstructive airway disease, COAD, chronic obstructive respiratory disease, CORD, chronic airway obstruction, CAO, and chronic airflow limitation, CAL, were all used synonymous with chronic bronchitis and emphysema. In the 1980’s, the term COPD was used among researchers and in the 1990’s, it became common among physicians in respiratory medicine. Today COPD is the well-established term for obstructive lung function impairment most often due to chronic bronchitis and/or emphysema.

Further standardisation

Parallel with the change in terminology towards COPD, the standardisation for diagnosis proceeded. In 1979 the ATS published a document on standardisation of spirometry [ATS statement, 1979], and in November 1986 the ATS board adopted the “Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma” published during the following year [American Thoracic Society, 1987]. COPD was defined as emphysema, peripheral airway disease and chronic bronchitis. Subjects with COPD had one or all of these conditions. Chronic bronchitis was defined as “the condition of subjects with chronic or recurrent excess mucus secretion into the bronchial tree”. Chronic was defined as “occurring on most days for at least three months of the year for at least two successive years”.

Definitions of COPD according to guidelines

In the 1980’s and 1990’s, there were ongoing parallel discussions both nationally and internationally on the diagnosis and treatment of COPD, leading to the development of different guidelines. During the 1990s several new national and internationally guidelines concerning diagnosis and management of COPD were published. The most well-known are the ATS [American Thoracic Society, 1995], the European Thoracic Society’s (ERS) [Siafakas et al, 1995] and the British Thoracic Society’s (BTS) [British Thoracic Society, 1997]. Some years later, the US Heart, Lung, and Blood Institute (the NHLBI) together with the WHO founded the Global Initiative for Chronic Obstructive Lung Disease (GOLD). This was an international guideline for COPD [Pauwels et al, 2001] with the main aim to increase the awareness of COPD, and to decrease morbidity and mortality from the disease. The first GOLD Workshop Result
was presented in 2001, and there has been an update in 2003 and 2004 [www.goldcopd.com]. However, due to the heterogeneity in between guidelines, there have been requirements for further development. So far, another two guidelines have been published, both in 2004. The British National Institute of Clinical Excellence (NICE) guidelines have been developed from the BTS guidelines [Chronic Obstructive Pulmonary Disease, 2004], while the former ATS and ERS guidelines have been united in the new ERS/ATS standards [Celli et al, 2004]. The spirometric definitions of COPD (the ATS spirometric definition refers to a publication in 1986 [American Thoracic Society, 1986]) and classification of disease severity according to the different guidelines are shown in Table 1. Below follows a brief summary of these guidelines.

The ATS guidelines [American Thoracic Society, 1995]
COPD is “…a disease characterised by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible”. Further, ”COPD may include a significant reversible component and some patients with asthma may go on to develop irreversible airflow obstruction indistinguishable from COPD”. Chronic bronchitis is defined in clinical terms and emphysema in terms of anatomic pathology.

The ERS guidelines [Siafakas et al, 1995]
COPD is “…a disorder characterised by reduced maximum expiratory flow, and slow forced emptying of the lungs; features which do not change markedly over several months. Most of the airflow limitation is slowly progressive and irreversible. The airflow limitation is due to varying combinations of airway disease and emphysema; the relative contribution of the two processes are difficult to define in vivo”…Emphysema is defined anatomically, chronic bronchitis is defined clinically. Further, the guidelines states that ”…the most difficult problem is distinguishing COPD from chronic airflow limitation of chronic asthma in older subjects.” Also, ”…the distinction may sometimes be impossible…”

The BTS guidelines [British Thoracic Society, 1997]
“COPD is a general term which covers many previously used clinical labels that are now recognised as being different aspects of the same problem. Diagnostic labels encompassed by COPD include: chronic bronchitis, emphysema, chronic obstructive airway disease, chronic airflow limitation and some cases of chronic asthma.”

The GOLD guidelines [Pauwels et al, 2001; www.goldcopd.com]
“COPD is a disease state characterised 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”. There is a comment that asthma may overlap with COPD.
<table>
<thead>
<tr>
<th>Guideline</th>
<th>ATS</th>
<th>ERS</th>
<th>BTS</th>
<th>GOLD(^1)</th>
<th>NICE</th>
<th>ATS/ERS(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>FEV(_1)/VC &lt; 0.75</td>
<td>FEV(_1)/VC ≤ 80pp (^2)</td>
<td>FEV(_1)/VC &lt; 70</td>
<td>FEV(_1)/FVC &lt; 0.70</td>
<td>FEV(_1)/FVC &lt; 0.70</td>
<td>FEV(_1)/FVC &lt; 0.70</td>
</tr>
<tr>
<td>Severity(^4) “At risk”</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>normal spirometry (^5)</td>
<td>-</td>
<td>FEV(_1)/FVC ≥ 0.70</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;50 pp</td>
<td>≥70 pp</td>
<td>60-80 pp</td>
<td>≥ 80 pp</td>
<td>50-80 pp</td>
<td>≥ 80 pp</td>
</tr>
<tr>
<td>Moderate</td>
<td>35-40 pp</td>
<td>50-69 pp</td>
<td>40-59 pp</td>
<td>50% and &lt;80 pp</td>
<td>30-40 pp</td>
<td>50-80 pp</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;35 pp</td>
<td>&lt;50 pp</td>
<td>&lt;40 pp</td>
<td>30% and &lt;30 pp</td>
<td>&lt;30 pp</td>
<td>30-50 pp</td>
</tr>
<tr>
<td>Very severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;30 pp</td>
<td>-</td>
<td>&lt;30 pp</td>
</tr>
</tbody>
</table>

\(^1\)refers to values after bronchodilatation
\(^2\)in men, \(^3\)in women
\(^4\)based on percent predicted (pp) of FEV\(_1\) according to all guidelines
\(^5\)and reported respiratory symptoms
\(^6\)patients who smoke or have exposure to pollutants, have cough, sputum or dyspnea
The ATS/ERS standards [Celli et al, 2004]
“COPD is a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.”

The NICE guidelines [Chronic Obstructive Pulmonary Disease, 2004]
“COPD is characterised by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking.”

Similarities and dissimilarities

All guidelines, besides the ATS, define spirometric criteria for COPD, but there was a spirometric criterion in an earlier publication by the ATS [American Thoracic Society, 1986]. However, the spirometric criteria differ between guidelines. Consequently there are no generally accepted definite spirometric criteria for COPD, even if GOLD is to be regarded as the internationally established. Nevertheless, the current generally accepted view is that spirometry is necessary for the diagnosis of COPD and the diagnosis is based on obstructive lung function impairment. The classification of disease severity is even more heterogeneous between guidelines. This can possibly reflect different medical practise or is merely to be considered a pragmatic way of describing subdivision without any true medical basis. However, the most recent published ATS/ERS standards are more close to the staging of disease by the GOLD criteria than the formerly ATS and ERS guidelines were, and the NICE guidelines are closer to GOLD than the BTS were. Staging by disease severity in different guidelines seems to be becoming more similar and less heterogeneous.

All guidelines include symptoms as cough, sputum and dyspnoea as part of the clinical picture of COPD. The GOLD guidelines and the new ATS/ERS standards also define a population “at risk” for COPD (Table 1). This term includes subjects with respiratory symptoms but normal lung function, and the ATS/ERS also requires that the subject has a smoking history or exposure to pollutants. Whether these subjects are at risk for developing COPD is still not fully clarified. There is a report from the Copenhagen City Heart Study stating that GOLD stage 0 does not predict development of COPD [Vestbo et al, 2002]. The ATS/ERS standards definition also adds that COPD is a disease with systemic consequences.

There was a fixed quotient defining the airway obstruction in all guidelines except the ERS guidelines from 1995. The fixed criteria will overestimate the prevalence of COPD in elderly, and underestimate it in younger people. Thus, the 1995 ERS guidelines must be regarded as the most physiological, considering the predicted
values for evaluating airway obstruction. Still, it has not been widely used in clinical practice in Sweden, probably due to the ease-to-use fixed ratio. However, in the recently published ERS/ATS standards, the ERS have abandoned their gender-specific age- and height-adjusted definition of airway obstruction. Consequently there is today, as desired, a homogenous definition of airway obstruction (FEV1/FVC or VC <0.70) but at the cost of a non-physiological approach with regard to one of the main-predictors of disease, namely age.

The BTS and NICE guidelines have the most narrow spirometric criteria, as there is an upper limit of FEV1 (at 80 percent of predicted) which is not present in the other guidelines. They are quite similar to GOLD stage II (moderate COPD), moderate COPD according to ATS/ERS standards and also to the national guidelines in Sweden [www.slmf.se/kol/]. According to some authors [Celli et al, 2003] moderate GOLD is a practical threshold to define subjects with symptomatic disease.

The different guidelines' position on reversibility and COPD is not homogeneous. The BTS state that positive reversibility to beta-agonists (FEV1 increase 15% or 200 ml) should raise the suspicion of asthma, significant reversibility according to GOLD is 12% and 200 ml. The ATS declare that up to 30% of patients with COPD increase their FEV1 15% or more after beta-agonists. The ERS says that most individuals with COPD increase their FEV1 after sympathomimetics or anticholinergics, but does not specify any response level. According to GOLD and the 2004 ATS/ERS standards (and also the national Swedish guidelines) the diagnosis of COPD should be based on post-bronchodilator spirometry values. To the contrary, the recent NICE guidelines states that “…in most cases the diagnosis of COPD is suggested by the combination of the clinical history, signs and baseline spirometry. Reversibility testing does not add any additional information…”

Decline in lung function

Maximum lung function is normally reached at approximately 20 years of age, in men somewhat later than in women. There is a plateau phase with stable lung function until about 35 years of age. The lung function starts to decline from somewhere around 40 years of age, women usually earlier than men [Rijken et al, 1998]. This is a rough description of normal development and may vary in different populations. The decline in healthy non-smokers is reported to be 15-30 ml/year from approximately 35 years of age [Fletcher et al, 1976; American Thoracic Society, 1995]. Low FEV1 itself was related to rate of decline over time according to Fletcher, a phenomenon called the “horse-racing effect”. However, in a later publication by Burrows [Burrows et al, 1987] this was only found true among male smokers when age and smoking habits were taken into account. For healthy adults reaching normal lung function,
accelerated decline in FEV₁ create the necessary conditions for development of COPD. On the other hand, the inability to reach maximal adult lung function can result in COPD, by definition, despite a normal decline in FEV₁ [Rijcken et al, 1998; Bakke, 2003].

Increased decline

Increased decline is often used synonymously with accelerated decline in FEV₁. The early report by Fletcher reported a decline about 50 ml/year in male smokers, with some demonstrating a rapid decline of about 90 ml/year [Fletcher et al, 1976]. According to the ERS guidelines [Siafakas et al, 1995] a decrease in FEV₁ of >50 ml/year was considered to be an accelerated decline. Other reported limits for accelerated decline in FEV₁ are >50 ml/year according to discussions in the Euros cope study, >100 ml/year, >150 ml/year, and even >200 ml/year [Anto et al, 2001; Fletcher et al, 1976; Dompeling et al, 1993; Löfdahl et al, 1998; Postma et al, 1998]. The term rapid decline has no standardised definition. The terms accelerated decline and rapid decline are used in the literature in a mixed manner without stringency.

Risk factors for increased decline

Smoking is the most well-known risk factor for accelerated decline. Rijcken and Britton summarised the results from several longitudinal studies regarding the effects of smoking on decline in FEV₁ in the range of 7 to 33 ml/year [Rijcken et al, 1998]. There is a dose-dependent smoking effect on lung function, reported from the Dutch Vlagtwedde Vlaardingen studies [Xu et al, 1994], and others [Anto et al, 2001]. Environmental tobacco smoke (ETS), or passive smoking, is also reported to affect rate of decline in lung function [Jaakola, 2002].

After smoking cessation, decline seems to return to a non-smoking level. This was reported already by Fletcher [Fletcher et al, 1976] and has been repeated later by other studies [Camilli et al, 1987; Lange et al, 1989; Xu et al, 1994; Willemse et al, 2004]. Some data also support that women may benefit more than men from smoking cessation [Anthonisen et al, 2002]. Earlier chronic productive cough was considered to be a quite harmless condition, not considered to affect lung function. One of the first reports to question the innocence of chronic productive cough was made by Annesi [Annesi et al, 1986], according to whom chronic mucus production was significantly related to an increased over all mortality. Later studies have been published suggesting an association with an increased decline in lung function among subjects with respiratory symptoms as chronic mucus hyper secretion [Sherman et al, 1992; Vestbo et al, 1996; Vestbo et al, 2002].
Prevalence

Prevalence is the proportion of a population that has a specified disease at a specified point in time (point prevalence) or time period (period prevalence). Period prevalence most often refers to the time period one year.

Prevalence of COPD

There are quite a few reports on the prevalence of COPD based on recent guidelines. In a recent summary by Halbert [Halbert et al, 2003] COPD prevalence was 0.23-18.3%, but most commonly between 4-10%. Also, prevalence data from the Nordic countries [Gulsvik, 1979; Lange et al, 1989; Bakke et al, 1991; Lundbäck et al, 1991] were accounted for. Different demographics of the studied populations, such as age distribution, smoking habits, gender and socio-economic factors, probably explain a great part of the differences. Another important factor in prevalence reporting is the definition of COPD. Prevalence figures are based on a wide variety of definitions including self-reported or physician-reported diagnosis of COPD and also specified, but heterogeneous, spirometric criteria. One of the first reports on the prevalence of COPD using spirometric criteria eventually becoming generally accepted was published by Bakke [Bakke et al, 1991]. In that report, spirometric criteria similar to the criteria later published by the BTS were used.

Different spirometric criteria for COPD have been reported to change the prevalence more than fourfold in the same population [Viegi et al, 2000; Celli et al, 2003]. Comparison between studies is complicated due to the differences in definition of COPD and demographics of the studied populations [Jaakkola, 2000]. The reported increase in prevalence of COPD has to be interpreted in accordance with these factors as well as the increased awareness of COPD in relation to the underdiagnosis [Tirimanna et al, 1996].

Even if there are many reports on the prevalence of COPD in the general population, there are considerably fewer reports on the prevalence of COPD by disease severity. There is a Norwegian report where the prevalence of FEV\(_1\)/FVC<0.70 and FEV\(_1\)<40% predicted was 0.2% in both sexes [Bakke et al, 1991]. According to the NHANES I follow-up [Mannino et al, 2003], the prevalence of severe COPD defined as FEV\(_1\)/FVC<0.70 and FEV\(_1\)<50% predicted was 1.7% at entry in 1971-75, and it was strongly associated with age. There is also a publication on the prevalence of COPD according to GOLD among younger adults, <44 years, where 2.5% were classified as COPD stage I and 1.1% as COPD stage II-III [de Marco et al, 2004]. The ATS/ERS standards [Celli et al, 2004] refer to data from the NHANES reporting a prevalence of mild COPD (FEV\(_1\)/FVC<0.70 and FEV\(_1\)≥80% predicted) at 6.9% and
moderate and more severe COPD (FEV$_1$/FVC<0.70 and FEV$_1$≤80% predicted) at 6.6% among adults 25-75 years.

The complexity of the relationship between disease severity and quality of life, healthcare utilisation, cost of illness and death has become evident during the last years [Hansen et al, 1999; Engström et al, 2001; Gulsvik, 2001; Jansson SA et al, 2002; Kohler et al, 2002; Antonelli-Incalzi et al, 2003]. Thus increased knowledge of the prevalence by disease severity is important as it will reflect not only the presence of disease but also relate to the burden of the disease in the society.

**Incidence**

The cumulative incidence of a disease is the proportion of a population that during a specified time period develops the disease under study. The cumulative incidence can, by definition, never exceed 1, or 100%. The incidence rate of a disease is defined as the number of new cases of the disease under study divided by the sum of time periods of observation for all individuals in the population, the person-time. The incidence rate is expressed as the number of cases/person-time, and, by definition, the incidence rate of a non-chronic disease can be infinite.

For a disease with a quite high incidence and remission, such as the common cold, the incidence rate will illustrate the number of colds over time in a defined population. Each subject can have several episodes of common cold, and each episode will be accounted for as an incident case. For a chronic disease with no or very low remission, such as diabetes, the cumulative incidence is a good way to illustrate the number of new cases during a specified time, as each subject will only be affected once. In a prospective cohort study, the population at the start of the observation period, or the "population at risk" which is free of the disease under study, has to be defined. Thus, all prevalent or known cases of the disease under study are excluded at the start of the study period.

**Incidence of COPD**

There are only a few reports on incidence of COPD, in which two older studies from the 1980's used spirometric definitions other than in the modern guidelines. There was a Finnish study, a 10-year follow-up of adults aged 40-64 year at entry, in which COPD was defined as FEV$_1$/VC <0.6 [Huhti et al, 1980]. The incidence was estimated at 0.2%/year (in smokers 1.0%/year). In a report from the Krakow study of a 13-year follow-up of adults aged 19-70 years at entry, COPD was defined as
FEV₁<0.65% predicted and the incidence was 0.5%/year [Krzyzanowski et al, 1986]. In 1990, there was a Dutch publication in which the diagnosis of COPD was based on respiratory symptoms and not spirometry [Heederik et al, 1990]. The 20-year follow-up of subjects aged 40-59 years at entry showed an incidence of 1.5%/year. There is also a Swedish report on the incidence of self-reported physician's diagnosis of COPD [Nihlen et al, 2004], in which the eight-year cumulative incidence was estimated at 2.9%. The only published report on incidence of COPD using modern guidelines is from the Copenhagen City Heart study [Vestbo et al, 2002]. The 5-year cumulative incidence of COPD according to GOLD was found to be 9.7%, and the 15-year cumulative incidence 13.2% in a population aged 20 years and older at study start (in smokers 11.7% and 18.5%). There was also a Norwegian report on the 9-year cumulative incidence of COPD according to the GOLD criteria at the ERS congress in 2002 [Johannessen et al, 2002]. The overall cumulative incidence was 9.8% in the population aged 18-74 years at entry, strongly associated with age and smoking (23% in age group >60 years at entry, 16% in smokers).

**Risk factors**

Smoking and age are the most well-known risk factors for COPD [Siafakas et al, 1995; British Thoracic Society, 1997; Pena et al, 2000; Gulsvik, 2001; Johannessen et al, 2002; Mannino et al, 2003; Lundbäck et al, 2003]. Most published data originate from cross-sectional studies and clinical studies, while there are considerably less data from longitudinal studies.

Smoking affects not only the smokers. Environmental tobacco smoke, ETS, or passive smoking, is associated to an increased risk of respiratory symptoms [Robbins et al, 1993; Jansson C et al, 2002; Larsson ML et al, 2003], chronic bronchitis [Radon et al, 2002] and obstructive respiratory disease [Dayal et al, 1994; Berglund et al, 1999]. There is an excellent summary by Jaakkola published in 2002 on the health effects of ETS among elderly [Jaakkola, 2002]. However, data between studies are difficult to compare since methods of estimating ETS are heterogeneous. It is even more complicated to evaluate lifetime tobacco exposure because subjects exposed to ETS may also start to smoke themselves or vice versa. There is still lack of data about the impact of ETS as a risk factor for COPD. One plausible connection is reported from the European Community Respiratory Health Survey (ECRHC), where both intrauterine and environmental exposure to parental smoking were found to be related to lower lung function in adults [Svanes et al, 2004]. Inability to reach expected maximal lung function may predispose to development of COPD even though the age-related decline in lung function is normal. Consequently, there can be an association between parental smoking and development of COPD.
When evaluating age as a risk factor for COPD, an important issue is also the spirometric criteria of COPD. A fixed ratio for the definition of airway obstruction (FEV₁/FVC or VC<0.70) will overestimate COPD in elderly [Hardie et al, 2002] and underestimate COPD among young adults.

Occupational airborne exposure has in recent years gained increased interest as a risk factor for COPD [Bakke et al, 1991; Humerfelt et al, 1993; Viegi et al, 2002; Trupin et al, 2003]. The impact of occupational airborne exposure on decline in lung function and development of COPD is important both for affected subjects and society, as it is the effect of smoking. In a Swedish report published March 2004, the fraction of COPD attributable to airborne exposure among construction workers was close to 11% overall and >50% among non-smokers [Bergdahl et al, 2004].

Socio-economic factors are closely related to obstructive lung disease and COPD [Willemsen et al, 2004; Krzyzanowski et al, 1986; Bakke et al, 1995]. Socio-economic group has in different studies been variously indexed, for example by income, level of education, social class, and occupation. Independent of particular index, the results point in the same direction: low socio-economic group is associated with COPD. In a review in Thorax 1999, the socio-economic impact on COPD was the next most important, after that of smoking [Prescott et al, 1999]. There are also reports that low lung function itself is related to socio-economic status [Rijcken et al, 1998; Welle et al, 2004].

A genetic basis for COPD is established only in α₁-antitrypsin deficiency, but the deficiency is uncommon and can only explain a minority of cases of COPD [Rijcken et al, 1998]. There are studies reporting a familial aggregation of COPD [McCloskey et al, 2001] suggesting that other genetic factors are involved which contribute to development of COPD by an increased susceptibility to tobacco smoke and other pollutants [Sandford et al, 1997].

Other risk factors discussed for COPD are outdoor airborne pollution, airway hyperresponsiveness, nutrition, respiratory tract infections, chronic mucus production and other respiratory symptoms. There are some comprehensive reviews on the risk factors for COPD [Rijcken et al, 1998; Gulsvik, 2001; Viegi et al, 2001].

Gender aspects

The reported prevalence of COPD has been higher among men than women [Sobradillo et al. 1999; Mannino et al, 2000; Viegi et al, 2000]. This can be explained above all by differences in smoking habits, while men historically have been smokers to a considerably higher extent than women. However, smoking is increasing in
women worldwide. The proportion of smokers in adults has gradually decreased in Sweden and was in 2003 recorded at 17% [Statistics Sweden]. However, since 1992 women have been smokers to the same extent or more than men (year 2003 18% and 17%, respectively). More recent studies have reported increased prevalence of COPD among women [Soriano et al, 2000], and the gender related differences in prevalence of COPD seems to decrease. However, there are also data that support a hypothesis that women are more vulnerable to the noxious effects of tobacco smoke [Xu et al, 1994; Prescott et al, 1997; Langhammer et al, 2003]. If this hypothesis is true, there will be an increase in COPD among women exceeding the effect of changes in smoking habits.

Underdiagnosis of COPD

COPD is usually not diagnosed until the disease has progressed to moderate or severe stages. There are a number of reports on the underdiagnosis of COPD, among others from the Spanish IBERPOC [Sobradillo et al, 1999; Pena et al, 2000], the US NHANES III [Mannino et al, 2000], the Dutch DIMCA study [van den Boom et al, 1998] and a Swedish study [Nihlen et al, 1999]. A previous report from the OLIN studies indicated an underdiagnosis on a similar level with no major improvement in identifying COPD from 1986 to 1993 [Lindström et al, 2001]. Only one third or less of subjects with COPD seem to have a relevant diagnosis [Siafakas et al, 1995]. The magnitude of underdiagnosis was only slightly reduced in the early 1990’s compared to the 1970’s according to one report [Tirimanna et al, 1996]. Early detection of COPD is recognised by many authors as one of the most important issues in order to promote further disease progress [van den Boom et al, 1998; Calverley, 2000; Scanlon et al, 2000; Lundbäck et al, 2003] by for example supporting smoking cessation. Thus it is important to improve correct and timely COPD diagnosis.

Mortality in COPD

Underdiagnosis of COPD is well documented [van den Boom et al, 1998; Sobradillo et al, 1999; Mannino et al, 2000; Pena et al, 2000] and as a consequence also mortality in COPD is greatly underestimated. This view is supported by the existing register-data on death certificates [Camilli et al, 1991; Mannino et al, 2003]. There is also a recent report stating that underlying cause of death reported on death certificates underestimates the contribution of chronic obstructive disease to mortality [Hansell et al, 2003]. Further, there is a substantial difference between different countries
mortality data on COPD. According to a review by Gulsvik, it varies more than 5-fold among the European countries [Gulsvik, 1999].

Already in 1993 there was a report predicting that the mortality in COPD would increase three-fold from 1985 to 2015 [Bumgarner et al, 1993]. According to recent data, COPD was the 6th most common cause of death in 1990, but is expected to be the 3rd most common cause of death world-wide by year 2020 [Murray et al, 1996]. Further, the death rate in COPD among women is reported to have increased even more than among men during the last two decades of the twentieth century, and the COPD death rate among women exceeded that of men in USA in year 2000 [Mannino et al, 2002].

The 22-year follow-up of male workers in the Paris area published in 1986 revealed lung function and chronic phlegm to be related to mortality [Annesi et al, 1986]. In an 11-year follow up of Swedish men mortality was significantly related to age, smoking, dyspnoea and lung function [Olofson et al, 1987]. There are a number of studies reporting an association with decreasing FEV₁ and mortality, but many of them do not discriminate for COPD while including subjects with restrictive pulmonary disease [Neas et al, 1998; Schuneman et al, 2000]. In COPD, the reduction in FEV₁, age and smoking was reported to predict mortality [Hansen et al, 1999]. The long term follow-up of the US NHANES I survey, which started in the 1970’s, revealed that mortality was significantly associated with smoking and disease severity when COPD was classified according to GOLD [Mannino et al, 2003]. However, there are also studies stating that dyspnoea may be a better predictor of survival in COPD than disease severity based on level of FEV₁ [Nishimura et al, 2002].

The five most common causes of death according to the Swedish National Board of Health and Welfare statistics for year 2001 are shown in Table 2. Of the 6 080 deaths due to respiratory diseases, 2 361 were attributable to diagnoses consistent with COPD (out of 93 809) [www.sos.se/epc/dors/dodreg.htm#publicering].

Table 2. Mortality data in Sweden year 2001 based on the ICD 10 classification, the five most common registered causes of death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Domain</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>I00-199</td>
<td>Circulatory organ</td>
<td>42 695</td>
</tr>
<tr>
<td>C00-D48</td>
<td>Tumours</td>
<td>22 509</td>
</tr>
<tr>
<td>C34.0-C34.9</td>
<td>Lung cancer</td>
<td>3 144</td>
</tr>
<tr>
<td>J00-J99</td>
<td>Respiratory disease</td>
<td>6 080</td>
</tr>
<tr>
<td>J40-J44.9</td>
<td>COPD</td>
<td>2 361</td>
</tr>
<tr>
<td>V01-Y98</td>
<td>External cause</td>
<td>4 659</td>
</tr>
<tr>
<td>F00-F99</td>
<td>Psychiatric</td>
<td>4 278</td>
</tr>
<tr>
<td></td>
<td>Totally</td>
<td>93 809</td>
</tr>
</tbody>
</table>
Co-morbidity and COPD

Co-morbidity is reported to predict mortality in COPD [Antonelli-Incalzi et al, 1997] and cardiovascular disease is probably the most important co-morbid factor affecting the mortality among subjects with COPD [Pistelli et al, 2003]. Further, there is a recent review and meta-analysis published in Thorax concluding that reduced lung function is associated with increased levels of systemic inflammatory markers, which may be involved in the pathogenesis of co-morbid conditions such as cardiovascular disease, osteoporosis and muscle wasting. [Gan et al, 2004]. Systemic effects and under weight are pronounced in severe COPD [Slinde et al, 2003]. Other studies report association between anxiety and depression and COPD [van Manen et al, 2002], and association with lung cancer and COPD is under discussion. Obstructive lung function impairment in obstructive sleep apnoea syndrome (OSAS) contributes to deterioration in daytime blood gases [Krieger et al, 1989]. However, most data on co-morbidity and COPD originate from studies of subjects identified in health care and there are few population-based surveys.

Cross-sectional and cohort studies

Cross-sectional studies

Cross-sectional studies are designed to answer questions on prevalence. The relationship of disease with age, gender, smoking habits, and other demographic data can be evaluated in a cross-sectional study. The study design does not provide answers for whether associated factors are causes, consequences or parallel phenomenons to the studied disease. The analysis of risk and causal connection are limited to risk factors stable over time for a certain disease.

Cohort studies

Prospective and retrospective follow-up studies are often referred to as cohort studies [Persson LA, 2002]. The prospective studies are mainly long term follow-ups of defined populations (cohorts) examined repeatedly in a cross-sectional manner over a period of time. The disadvantages of these studies are mainly that they are time-consuming and expensive. The advantage is that there are data on exposure of risk factors at entry and also baseline characteristics that can be followed longitudinally together with health care outcomes. This design allows analyses of causal connection
even if the possibilities of consequences or parallel phenomena have to be taken into account.

Longitudinal studies in COPD

Most data on COPD are collected from cross-sectional studies. The longitudinal study-design of prospective cohort studies adds information which is not available from the cross-sectional studies. There are today only a few active longitudinal population-based studies, lasting for 20 years or more, which include data-collecting regarding respiratory diseases. In Europe these studies include amongst all the Danish Copenhagen City Heart Study [Lange et al, 1989; Prescott et al, 1997; Vestbo et al, 1996; 2002], the Italian River Po Delta study [Carozzi et al, 1990; Viegi et al, 2000; 2001; 2002], the Norwegian Bergen-Hordaland studies [Bakke et al, 1991; 1995; Omenaas et al, 1995; Hardie et al, 2002, Johannessen et al, 2002; Welle et al, 2004; Eagan et al, 2002; 2004], and the Swedish OLIN-studies. Additionally there are some large populations-based longitudinal studies that not have reported data in the last years, thus there is uncertainty of their present activity. These include the Dutch Vlaktwede Vlaardingen study [Xu et al, 1994; 1995], the Polish Krakow-study [Krzyzanowski et al, 1986] and the Finnish study by Huhtı [Huhtı et al, 1980].

The longitudinal studies allow estimation of the incidence of COPD, in which the population at risk has normal lung function (not fulfilling the criteria of COPD). The influence of reduced childhood growth of the lungs or premature decline that can be concealed in prevalence studies can thus be eliminated. Further, the early clinical signs and risk factors for development of COPD can be evaluated. Another important issue is the relationship between the decline in lung function and development of COPD, where easy-to-use methods and their predictive values have to be evaluated for use in the daily clinical work. In addition, the course of the disease progress in COPD can be surveyed in longitudinal studies. There are to date few reports on the course from asymptomatic subject to development of COPD. There is sparse knowledge on whether the decline in lung function is continuous and progressive or intermittent, or what factors influence the rate of decline, and consequently why some individuals develop severe COPD and respiratory insufficiency.

In summary, cross-sectional studies have provided important data on COPD. However, longitudinal studies are necessary to bring forward further knowledge on the incidence of COPD, early clinical signs of COPD, risk factors for incident COPD, and not the least to survey the progressive course of the disease or "natural history of COPD".
AIMS

-To estimate the prevalence of COPD in the general population of Norrbotten based on the spirometric criteria for COPD according to the BTS, ERS, GOLD and ATS guidelines.

-To estimate the prevalence of COPD in the middle-aged and elderly, in whom the disease is known to be particularly common.

-To estimate the distribution by disease severity in prevalent COPD according to the BTS and GOLD criteria.

-To evaluate to what extent subjects identified as COPD by different criteria express respiratory symptoms, and have properly been diagnosed by health care providers.

-To examine the impact of smoking on COPD.

-To examine other determinants of COPD, including gender.

-To estimate the 10-year cumulative incidence of COPD among subjects with respiratory symptoms, i.e. the population expected to need health care in future due to respiratory complaints.

-To evaluate the association between incident COPD and respiratory symptoms, different risk factors, and gender in a cohort with respiratory symptoms.

-To estimate decline in FEV₁ in an age-stratified cohort with respiratory symptoms and incident COPD illustrated by two methods of measurement: ml/year and change in percent-units of predicted normal value during ten years.

-To estimate the 7-year cumulative incidence of COPD and its determinants in an age-stratified general population sample.
MATERIAL & METHODS

This thesis is based on original research data from the Obstructive Lung Disease in Northern Sweden (OLIN) studies (please see Appendix).

Study area

Norrbotten is the northernmost county of Sweden. It has a sparsely populated inland that consists of a mountainous district, highlands and lower coastal areas rich in forests. The total area of Norrbotten is close to one fourth of the Swedish area, 105,886 km², with a population of 252,856 which is 3% of the 9 million Swedish inhabitants (August 2004). The main part of the population, approximately 190,000, lives in the coastal region where the city of Luleå and the towns of Boden and Piteå are situated, surrounded by nearby villages and rural areas. The population in the inland is concentrated mostly in the towns of Gällivare and Kiruna, with other sparsely inhabited municipalities covering large areas. The Arctic Circle runs through the county and it passes approximately 120 kilometres north of Luleå.

The climate is sub-arctic with more than six months of winter and snow. The mean annual temperature in 2003 was 3.1°C in Luleå (highest 32.1, lowest –33.8) and –0.6°C in Kiruna, compared to 7.7°C in Stockholm. During the summer-months the famous midnight sun brings twenty-four hours of daylight.

Historically, the main branches of industry have been mining, iron- and steel production, forestry, paper and paper-pulp production. Today, service occupations in the public sector, including health care, education, trade and tourism, are becoming more common as job opportunities.

The study sample of the OLIN Studies cohort I (Papers II, III, IV, V, and VI) was from eight representative areas of the province (Figure 1), while the sample from cohort III (Paper I) was a randomly selected sample from the whole county.
Figure 1. Map over Sweden and the county of Norrbotten. The eight geographical areas from which the OLIN cohort I was recruited. Cohort III was recruited from the whole county.

Study design and study population

In 1985-86 a postal questionnaire was sent to all 6610 inhabitants born 1919-20, 1934-35 and 1949-50 in eight representative geographical areas of Norrbotten (Figure 1), the OLIN cohort I. This age-stratified general population sample has been followed longitudinally, and repeated cross-sectional surveys have been performed. Data have been collected from the cohort by postal questionnaire in 1986, 1992 and 1996. All subjects with respiratory symptoms in 1986 were identified, and this symptomatic cohort has been examined by structured interview and spirometry in 1986, 1996 and 2003. A random population sampling was performed after the postal questionnaire in 1996, and this general population sample has been examined by interview and spirometry in 1996 and 2003.
In 1992, a postal questionnaire was sent to a random sample of the inhabitants in the whole county, including a total of 5681 subjects aged 20-69 years, which is the OLIN cohort III. A random sample of the responders was invited for examinations, including interview and spirometry in 1996.

Postal questionnaire surveys and examinations including interviews, spirometry and other tests were organised from the offices of the OLIN studies in Luleå (from 2003 Stadsvikens Health Care Centre) and in Boden (from 2000 Björknäs Health Care Centre). Local inhabitants of Luleå and Boden belonging to the adult cohorts were examined at the local offices, while all other examinations were carried out as fieldwork with the OLIN staff setting up casual stations mainly at the local health care centres throughout the county.

Study population

The OLIN cohort I was the age-stratified general population sample recruited in 1985 [Lundbäck et al, 1991]. From this cohort, all 1655 subjects reporting respiratory symptoms were identified and invited to a structured interview and spirometry, where 1506 (91%) participated [Lundbäck et al, 1993; Lundbäck et al, 1994]. In 1996, 1354 (90%) of the participants of 1986 were traced and invited to a second examination, where 1165 (86% of invited) participated. A total of 1109 subjects performed spirometry both in 1986 and 1996. Papers IV and V are based on these surveys.

In 1996 the OLIN cohort I comprised of 5933 subjects from whom 5892 could be traced and 5189 subjects (88%) completed the third postal questionnaire survey [Rönmark et al, 1999]. A random sample of the responders including 1500 subjects was invited to a structured interview and spirometry. Of these, 1282 subjects (85%) participated (Paper II, III). In 2003, there was a follow-up study in which 1009 subjects (79% of the participants from 1996) participated in the examination. Spirometry was performed by 963 of these subjects both in 1996 and 2003 (Paper VI).

In 1992 a postal questionnaire was sent to a random sample of 5681 adults aged 20-69 years in Norrbotten, and 4851 (85%) responded [Larsson LG et al, 2001; 2003]. In 1994-95 a random sample of the responders, 970 subjects, were invited to a structured interview and spirometry where 666 (69%) subjects participated. This cohort was labelled OLIN cohort III, and Paper I was based on these surveys.
Methods

Questionnaires

The postal and interview questionnaires have been developed from the BMRC questionnaire [Medical Research Council, 1960; 1986] with influence from the ATS questionnaire [Ferris, 1978], the IUATLD questionnaire [Burney et al, 1989], and the questionnaire used in the US Tucson studies [Lebowitz et al, 1975]. The questionnaires have been thoroughly described previously [Lundbäck et al, 1991; Pallasaho et al, 1999; Lindström et al, 2001]. Specially trained nurses and research assistants performed the interviews.

The following questions have been used in papers I-VI. The complete questionnaires are published in earlier OLIN-thesis [Medical Dissertations: Lundbäck 1993, Rönmark 1999, Lindström 2002].

Cough: "Do you usually cough in the morning?" or "Do you usually cough during other times of the day?"
Sputum production: "Do you usually have phlegm when coughing?"
Chronic productive cough: "Do you usually have phlegm when coughing, or have phlegm which is difficult to bring up, most days in periods of at least three months, during at least two successive years?"

Dyspnoea (MRC 0 (Eltyara et al 1996)): "Do you get short of breath at exertion?"
Dyspnoea (MRC 1 (Eltyara et al 1996)): "Do you get short of breath when hurrying on level ground or up a slight hill?"

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

Recurrent wheeze: "Do you usually have wheezing, whistling or a ‘noisy sound’ in your chest when breathing?"
Attacks of shortness of breath (SOB): "Have you had attacks of shortness of breath during the last 12 months?"
Contacts with health care: "Have you ever consulted medical care/attendance due to respiratory complaints, other than common cold?"

Physician-diagnosed chronic bronchitis/emphysema: "Have you been diagnosed by a physician as having chronic bronchitis or emphysema?"

Family history of obstructive lung disease (OLD): Yes to at least one of the questions of family history of asthma, chronic bronchitis or emphysema.

Lung function tests

All spirometries since 1986 have been performed on four parallel sets of the dry volume spirometer, Minjhard Vicatess 5, The Netherlands. They have been calibrated
in a standardised manner at the start of every working day. The test procedure followed the ATS recommendations [ATS statement, 1979] except that that nose clip was not used and the subjects were asked to stand up. Vital capacity (VC) has been defined as the best values of forced vital capacity (FVC) and slow vital capacity. Swedish normal values for FEV₁ have been used [Berglund et al, 1963], well conforming with and thus applicable for the adult population in Norrbotten [Lundbäck et al, 1994].

Definitions of COPD

The spirometric criteria of the following guidelines were used. Additionally, the ATS guidelines definition; “the obstructive form of chronic bronchitis and emphysema” gave rise to the forming of “clinical ATS”. In “spirometric ATS” only the spirometric criteria was used.

**BTS**

FEV₁/VC <0.70 and FEV₁ <80 % predicted [British Thoracic Society, 1997]

**GOLD**

FEV₁/FVC <0.70 [Pauwels et al, 2001; www.goldcopd.com]

**ERS**

FEV₁/VC < 88 % predicted in men and
FEV₁/VC < 89 % predicted in women [Siafakas et al, 1995]

**“Clinical ATS”**

FEV₁/FVC <0.75 and chronic productive cough (chronic bronchitis) or reported physician-diagnosis of chronic bronchitis or emphysema [ATS, 1986; 1995]

**“Spirometric ATS”**

FEV₁/FVC <0.75 [ATS, 1986]

**NICE**

FEV₁/FVC <0.70 and FEV₁<80% predicted [Chronic Obstructive Pulmonary Disease, 2004]

**ATS/ERS**

FEV₁/FVC ≤ 0.70 [Celli et al, 2004]

The classification of severity of COPD according to ATS/ERS [Celli et al, 2004] was used in Paper V.

- **Mild**
  - FEV₁/FVC ≤ 0.70 and FEV₁ ≥ 80% predicted
- **Moderate**
  - FEV₁/FVC ≤ 0.70 and FEV₁ 50 - 80% predicted
- **Severe**
  - FEV₁/FVC ≤ 0.70 and FEV₁ 30 - 50% predicted
- **Very severe**
  - FEV₁/FVC ≤ 0.70 and FEV₁ < 30% predicted
Determinants of disease

Age, smoking habits, gender, family history of obstructive lung disease, and socio-economic group by occupation have been used as determinants of disease. The following definitions have been used:

*Smoking habits* have been classified in all papers into the following categories: “non-smokers”, “ex-smokers” (stopped smoking more than 12 months prior to the study) and “smokers” (currently smoked every week or had stopped smoking within 12 months prior to the study). The two last categories (ex-smokers and smokers) were united to the category “ever smoker” in paper I and III.


*Family history of obstructive lung disease* (OLD) was considered present if at least one of the questions of family history of asthma, chronic bronchitis or emphysema was answered in the affirmative.

*Socio-economic classification*; the Swedish classification-system based on occupation, SEI [Statistics Sweden, 1982], was used in paper II, V and VI. The following main groups were used: 1- professional & executive, 2- assistant non manual employee, 3- manual worker in industry, 4- manual worker in service, 5- self-employed non-professional, 6- house-wife, and 7- occupation unknown. In paper V, the main groups were subdivided to reflect level of education where group 1 - 2 represented higher education and group 3 - 7 represented lower education.

**Statistics**

Statistical analyses were made using the software Statistical Package for the Social Science (SPSS) version 10.0 and 11.5. In 1980s, statistician Lennarth Nyström, PhD, and later on, from 1992, statistician Elys Jönsson, MSc, were engaged in the construction of the database and analyses. After Elys Jönssons retirement in year 2001, Eva Rönnmark, PhD, has been her successor in managing the database, assisted by Ola Bernhoff, BA. Statistician Anders Oden, associate professor, has as a consultant statistician given advise and support regarding the analyses (in this thesis mainly paper III and V).
The following statistical methods were used. The chi-squared analyses were used for bi-variate analyses and tests for trend. The t-test was used for comparison of means. Multiple logistic regression models were created for analyses of risk factors adjusted for possible confounders. The most commonly used possible confounders were gender, age, smoking habits (or smoking categories), family history of OLD, and socio-economic group. In Papers IV and VI, respiratory symptoms were singly added to the multiple logistic regression models in order to evaluate symptoms as markers for increased risk of developing COPD. In Paper III the combination of age group and smoking habits were used as an independent variable in risk assessment for COPD in a multivariate model. Further, in Paper III the attributable risk percent (ARP), the population attributable fraction (PAF) and population attributable risk (PAR) for ever smoking in COPD were calculated, and also the likelihood ratio (LR) for ever smoking in COPD. In paper I, also an interaction analysis (age and smoking) was performed by using the additive model. Furthermore, a linear logistic regression model was created to analyse risk factors for decline in FEV₁ (Paper V). Generally, the 95% significance level, p<0.05, was used.
RESULTS

Data from a cross-sectional survey of a random general population sample aged 23-72 years examined in 1994-95 are reported in Paper I. In Papers II and III cross-sectional data from an age-stratified random general population sample examined in 1996 are reported. The longitudinal data in papers IV and V are based on two cross-sectional surveys of an age stratified cohort of airway symptomatics from 1986 and 1996. In Paper VI the longitudinal data are based on two cross-sectional surveys of an age stratified random sample of the general population performed seven years apart, in 1996 and 2003.

Cross-sectional surveys (Papers I-III)

Prevalence of COPD

The prevalence was estimated in two samples investigated in 1994-95 and 1996. In the first, which was a random general population sample, the prevalence of COPD was analysed according to different guidelines in order to evaluate the effect of different spirometric criteria on the prevalence. The prevalence of COPD in the age group <45 years was 4.1%, 11.6%, 9.1%, 5.1%, and 21.5% according to the BTS, ERS, GOLD, “clinical ATS”, and “spirometric ATS” criteria, respectively. In the age group ≥45 years the corresponding figures were 9.7%, 15.4%, 17.1%, 16.5%, and 41.7%, respectively (in the total sample 7.4%, 14.0%, 14.1%, 12.2% and 34.1%). All, except the ERS criteria, were significantly associated with higher age and the prevalence were two to three times higher in subjects aged ≥ 45 years compared to in those <45 years (Paper I).

The second sample consisted of subjects aged 46-47, 61-62 and 76-77 years. In the analyses, 1237 spirometries were included. The prevalence was associated with higher age and smoking but not gender, similar to the first sample. The prevalence was 8.1% and 14.3% according to the BTS and GOLD criteria, respectively. The prevalence according to the GOLD criteria based on pre-bronchodilator spirometry values was higher, 17.2%, similar to the 17.1% in ages ≥45 years in the random sample. The prevalence of COPD according to the BTS criteria by age strata was 2.8% (46-47 years), 9.0% (61-62 years) and 19.7% (76-77 years), corresponding figures in non-smokers were 1%, 2%, and 16%, while in smokers 5%, 24% and 45%, respectively. The prevalence of COPD according to the GOLD criteria were 3%, 5% and 21% in non-smokers, while in smokers it was 11%, 42% and 50% (Papers II and III). The prevalence of COPD by age group and gender are summarised in Figure 2.
Figure 2. Prevalence of COPD according to the BTS and GOLD spirometric criteria, by age group and gender.

Distribution by degree of disease severity

In the age stratified general population sample, the prevalent cases of COPD according to the BTS were grouped by degree of disease severity. The following proportions were found: 65% mild, 27% moderate and 8% severe COPD. The corresponding figures for COPD according to the GOLD criteria were 57% mild, 37% moderate, 5% severe, and in 1% very severe COPD, Figure 3 (Paper III).

Figure 3. Distribution by disease severity, prevalent cases of COPD according to the BTS and GOLD criteria.
Symptoms in COPD

In the majority of cases of COPD, regardless of criteria, respiratory symptoms were reported. In the random general population sample respiratory symptoms were reported by 93.9%, 85.2%, 87.6%, 100% and 77.0% of the subjects classified as having COPD according to the BTS, ERS, GOLD, clinical ATS and spirometric ATS criteria, respectively. The most common symptoms were cough and sputum production (Paper I). In the age stratified sample respiratory symptoms were reported in 94% of the cases of COPD according to the BTS (GOLD 88%) and chronic productive cough was reported by 69% (GOLD 51%) (Paper II). Among the subjects with severe COPD (the BTS criteria) 100% had either cough, sputum production, recurrent wheeze or dyspnoea at least MRC II, and 88% reported chronic productive cough. For comparison, in mild COPD according to GOLD 70% was symptomatic and 21% reported chronic productive cough (Paper III).

Underdiagnosis of COPD

Among the subjects that fulfilled the criteria of COPD the proportion that reported physician diagnosis consistent with COPD was compared to the proportion that were indexed for contacts with the health care. The aim of this comparison was to illustrate the ability in the health care to properly label COPD. The indices for contacts with health care were "contact with health care due to respiratory complaints other than common cold" (Paper I) and "reported use of medicines for the airways including asthma medicines" (Papers II and III). In the random general population sample 49.0%, 37.1%, 38.2%, 46.1%, and 24.8% of the subjects with COPD according to the BTS, ERS, GOLD, clinical ATS and spirometric ATS criteria, respectively, were indexed for contact with health care. The corresponding figures for reported physician diagnosis were 16.3%, 12.2%, 11.0%, 23.4%, and 8.2% (Paper I). In the age stratified sample 42% and 26% (COPD according to the BTS and GOLD criteria) reported use of medicines, while physician-diagnosis was reported by 31% and 18%, respectively (Paper II). The findings of Papers I and II inclusive of data on reported respiratory symptoms are summarised in Figure 1. Among those with severe COPD according to BTS, all used medicines and 50% reported a physician diagnosis. For comparison, among those with mild COPD according to GOLD only 10% were using medicines and only 5% had a physician diagnosis (Paper III). The underdiagnosis is illustrated in Figure 4.
Figure 4. The underdiagnosis of COPD illustrated by the proportion of the prevalent cases of COPD according to the BTS and GOLD criteria, respectively, reporting respiratory symptoms, indexed for contacts with health care and reporting a physician diagnosis consistent with COPD (Papers I and II).

Risk factors and the population attributable fraction of smoking

The risk factor patterns in the two samples were similar (Papers I and II). In multiple logistic regression models the major risk factors for COPD were higher age and smoking. Family history of OLD was also a significant or close to significant risk factor for COPD, while gender was not. In the age stratified sample, the adjusted OR's for COPD, according to the GOLD and BTS criteria in subjects age 61-62 years, were 3.78 and 4.96, and in those aged 76-77 11.4 and 18.3 compared to the youngest subjects aged 46-47 years. Smoking >15 cigarettes/day yielded an adjusted OR of 8.04 and 8.77, respectively, when compared to non-smokers. The socio-economic class manual worker in industry was a significant risk factor for COPD according to GOLD. The OR's were most often higher when the BTS criteria for COPD were used in the analyses compared to the GOLD criteria.

The population attributable fraction (PAF) for ever smoking in COPD according to GOLD was 58% (BTS 47%) in subjects aged 46-47 years, 65% (BTS 76%) in subjects aged 61-62 years, and 22% (BTS 21%) in subjects aged 76-77 years. The PAF for ever
smoking in COPD (BTS) was 41%, while in men 64%, and in women 29% (GOLD 43%, 46% and 37%). Of all subjects fulfilling the GOLD criteria for COPD 23% reported that they never had been smokers (BTS 24%) and the relative proportion of non-smoking cases with COPD increased with increasing age and were more common among women (Paper III).

Longitudinal studies (Papers IV-VI)

Cumulative incidence of COPD in symptomatics

The 1109 subjects that performed spirometries in both 1986 and 1996 were included in the analyses. The age-strata were 36-37, 51-52 and 66-67 years old at entry. The 10-year cumulative incidence of COPD was estimated at 8.2% according to the BTS criteria and 13.5% according to the GOLD criteria (Paper IV). The incidence was significantly associated with higher age and smoking but not gender.

Decline in lung function

In the study sample described above, the decline in FEV₁ was calculated and expressed as mean ml/year and as change in percent-units of predicted normal value during ten years. The mean decline in FEV₁ in the whole study sample was 33 ml/year (-0.85 percent-units). Male gender, smoking, restart of smoking and chronic productive cough were associated with increased decline. The mean decline was 39 ml/year in men compared to 28 ml/year in women, p<0.001 (-1.53 vs. -0.12 percent-units, p=0.023), 39 ml/year in smokers vs. 28 ml/year in non smokers, p<0.001 (-3.3 vs. 0.69 percent-units, p<0.001) and 36 ml/year among subjects with chronic productive cough vs. 32 ml/year in those without the symptom, p=0.044 (-2.00 vs. -0.02, p=0.002). The gender differences found in different smoking categories and age groups, when decline in FEV₁ was assessed as mean ml/year, markedly decreased or disappeared when the decline was assessed as change in percent-units of predicted normal value, i.e. adjusted for age, height and gender. In incident cases of COPD (disease defined as moderate COPD according to the ERS/ATS standards) the decline in FEV₁ was 62 ml/year corresponding to a decrease of 12.6 percent-units of normal value during ten years, Table 3. In approximately one of every four of the incident cases of COPD the decline in FEV₁ was >90ml/year (-27.8 percent-units) (Paper V).
Table 3. Decline in FEV<sub>1</sub> among incident cases of COPD, mean ml/year and units change in percent predicted of normal value (units pp)

<table>
<thead>
<tr>
<th>Definition of disease</th>
<th>N&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Decline in FEV&lt;sub&gt;1&lt;/sub&gt; mean ml/year</th>
<th>percent-units</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATS/ERS</td>
<td>127</td>
<td>51</td>
<td>-7.4</td>
</tr>
<tr>
<td>mild</td>
<td>61</td>
<td>43</td>
<td>-2.9</td>
</tr>
<tr>
<td>moderate</td>
<td>60</td>
<td>54</td>
<td>-10.2</td>
</tr>
<tr>
<td>severe</td>
<td>6</td>
<td>102</td>
<td>-26.3</td>
</tr>
<tr>
<td>very severe</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moderate ATS/ERS</td>
<td>83</td>
<td>62</td>
<td>-12.6</td>
</tr>
</tbody>
</table>

<sup>1</sup>N=number of incident cases during the observation time 10 years

Cumulative incidence of COPD in a general population sample

The 963 subjects that performed spirometries in both 1996 and 2003 were included. The age-strata were 46-47, 61-62 and 76-77 years old at entry. The 7-year cumulative incidence of COPD was estimated at 4.9% and 11.0% according to the NICE guidelines and GOLD criteria, respectively. The incidence was significantly associated with smoking, and when measuring incidence by the GOLD criteria also to higher age, while there were no significant gender differences (Paper VI).

Risk factors for decline in lung function and incident COPD

Risk factor analysis for decline in FEV<sub>1</sub> was performed in a multiple logistic regression model and in a multiple linear regression model. Smoking and higher age were risk factors for increased decline, when adjusted for possible confounders. Gender-specific analysis performed in both models revealed smoking and restart of smoking to be significant risk factors in women and close to significant in men. Higher age was a significant risk factor in men only.

The risk factor pattern was similar in the symptomatic cohort and in the age stratified random general population sample. In multiple logistic regression models, smoking and higher age were associated with an increased risk for incident COPD. The only exception was incident COPD according to the NICE guidelines in the general population sample. The risk for COPD was increased in those aged 61-62 at entry compared to the youngest aged 46-47, but the oldest (aged 76-77 years) did not have an increased risk compared to the youngest. A significant higher proportion of the subjects that developed COPD reported respiratory symptoms at entry compared to the subjects that not developed COPD. For instance, in the random general
populations sample respiratory symptoms at entry were reported by 88.9% among subjects who later developed COPD according to the NICE criteria, compared to 59.2% among the subjects that not developed COPD, p<0.001 (incident GOLD 75.6% vs. not 57.5%, p=0.001). Multivariate analyses revealed that most respiratory symptoms were markers of increased risk for incident COPD when adjusted for confounders in both the symptomatic cohort and in the age stratified random general population sample.

The cumulative incidence of COPD in the symptomatic cohort and the age stratified random general population sample are summarised in Table 4.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Variables</th>
<th>Spirometric criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper IV</td>
<td>Age at entry</td>
<td>BTS</td>
</tr>
<tr>
<td></td>
<td>36-37 years</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>51-52 years</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>66-67 years</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>Smoking categories¹</td>
<td>persistent non-smoker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>persistent ex-smoker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>persistent smoker</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>8.2</td>
</tr>
<tr>
<td>Paper VI</td>
<td>Age at entry</td>
<td>NICE</td>
</tr>
<tr>
<td></td>
<td>46-47 years</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>61-62 years</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>76-77 years</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Smoking habits²</td>
<td>non-smoker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ex-smoker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>smoker</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>4.9</td>
</tr>
</tbody>
</table>

¹Refers to smoking categories paper III, persistent non-smokers, persistent ex-smokers and persistent smokers ²Refers to smoking habits at entry
DISCUSSION OF METHODOLOGY

There is an in-depth discussion on methodology in the first OLIN-thesis addressing the question of selection procedure and sample size, study design, bias concerned with questionnaires and interview. [Lundbäck, 1993] The background for establishing the OLIN cohort 1 and later on further surveys within the OLIN studies was described in the Material and Methods section. The longitudinal approach with repeated cross-sectional surveys raises new questions on methodology, of which some are discussed in this section.

Important definitions

Bias

Bias is a systemic error in a study that leads to distortion of the results. Bias is most commonly classified and divided into several types: a) selection bias, b) information bias, and c) confounding. The most common selection bias in cohort studies is that subjects are lost to follow-up. Thus the analysis of non-participation is important in order to evaluate if there is a possible selection bias that may affect the results. Information (or misclassification) bias can occur where there is inaccuracy in measurement. It can be applicable for example in the interview setting, in an incorrectly calibrated spirometer or in measurements of the subjects’ height. Recall-bias (different ability to recall previous activities and exposures) and interviewer-bias (how the interviewers collect and classify information) are two common types of information bias. Confounding is the term to describe that a factor disturbs the interpretation of the association between exposure and disease if it is both related to the disease and to the exposure. For example, age and smoking are often to be regarded as confounders.

Validity and Reliability

The concept of validity concerns the degree to which a measurement or study reaches a correct conclusion or the ability of the assessment tools to measure what they were intended to measure. Internal validity is the extent to which the results accurately reflect the true situation of the study population. External validity is the extent to which the results of a study are applicable to other populations. Different aspects of
validity within the OLIN studies are discussed in the second OLIN-thesis [Rönmark, 1999] and also in the fourth OLIN-thesis [Lindström, 2002].

Reliability is extent to which identical findings can be obtained in repeated measurements of a constant phenomenon.

**Spirometry**

The spirometers and the methods of performing lung function test have not been changed over time within the OLIN studies. The diagnosis of COPD is based on spirometry, and the standardised spirometry throughout the studies supports the validity of the results. The repeatability of spirometry in adults is good. In a US study of 18 000 adult patients, 90% reproduced FEV1 within 120 ml and FVC within 150 ml [Enright et al, 2004]. Another large study reports that the within-subject variability is small in men, but dependent on height and BMI as well as the technical performance [Humefelt et al, 1998]. A limited number of well-trained nurses and research assistants have performed the spirometries, and this act beneficial and minimises the possible inter-individual differences in performance of spirometric measurements.

When estimating the quotient of FEV1/FVC or FEV1/VC, normal values are unimportant, since the quotient is calculated from the crude values performed at spirometry. Thus, normal values are not needed for the definition of airway obstruction in COPD used in the current guidelines. However, the BTS and NICE definitions have an upper limit of FEV1 at 80 percent predicted, thus normal values of FEV1 are required. Also, the classification of disease severity according to all present guidelines require normal values of FEV1 as they are based on percent predicted of FEV1 (Table 1). A prediction equation for normal value of lung function in the studied population is preferable in epidemiological research, but there are at present no published data on spirometric normal values for the OLIN study population. The Swedish reference values of FEV1 according to Berglund have been used [Berglund et al, 1963]. It should be observed that the reference population of Berglund included also smokers. However, there are unpublished OLIN-data on the normal values of FEV1 which are very close to the normal values according to Berglund. Further, the values conform very well with the symptom-free adult population of Norrbotten [Landbäck et al, 1994], with the reservation that elderly (>66 y) not were included in the comparison.

It is a difficult task to develop new normal values. They are to be made in a population of respiratory healthy non-smokers without exposure to occupational airborne pollution known to affect lung function. Only 20-30% of the adult population fulfil these criteria. There are Norwegian normal values within the Nord-
Trondelag Study [Langhammer et al, 2001]. There is also a report of normal values from
northern Finland from a somewhat smaller study sample [Kotaniemi et al, 2004].
According to a report from the US, normal values in elderly have been reported to
differ as much as 20% when compared to commonly used reference equations
[Enright et al, 1993]. A recent Spanish report discusses the importance of using
prediction equations from the studied population also in elderly, which illustrates how
the normal values of the quotient FEV₁/FVC will be affected by age [Garcia-Rio et al,
2004]. It is a future aim of the OLIN studies to present an equation for normal lung
function the adult population of Norrbotten also including subjects over 80 years of
age.

Questionnaire and interview

The original set of questions at interview 1986 [Lundbäck, 1993] has been maintained
with only minor changes. A few new questions have been added. The questionnaires
are well validated [Lundbäck, 1993; Larsson L, 1995; Lundbäck et al, 2001]. They have
been used in several surveys within the OLIN studies, other studies in Sweden
[Larsson L et al, 1993; Montnemery et al, 1998; Hasselgren et al, 2001] and in a
modified form in the collaborating project between Sweden, Finland and Estonia, the
FinEsS studies [Pallasaho et al, 1999; Kotaniemi et al, 2001; Lindström et al, 2001;
Meren et al, 2001; Larsson ML et al, 2003].

An important question when surveying COPD is dyspnoea. In the questionnaire the
standardised wording of the MRC dyspnoea scale is used and referred to when the
data have been presented. However, there is need for caution when looking at data
based on the MRC dyspnoea scale. In the literature, the numerations of the different
grading of degree of breathlessness are not uniform. In the latest update of the MRC
dyspnoea scale [Eltyara et al, 1996] the first degree of breathlessness “not troubled by
breathlessness except on strenuous exercise” is labelled MRC grade 0, while the recent
NICE guidelines (Chronic Obstructive Pulmonary Disease, 2004)) use the adapted
model from Fletcher where the same wording is labelled MRC grade I. In this thesis
the latest version of the MRC dyspnoea scale is referenced [Eltyara et al, 1996].

Calculation of pack years is often used as a method of quantifying the burden of
smoking on individual level. However, our retrospective assessments of pack-years
were accompanied with some uncertainty.

When performing repeated surveys including interview, information bias must be
considered. To reduce the effect of interviewer-bias, specially trained nurses and
research assistants have performed all the interviews. Piloting and inter-interviewer
checks have been performed repeatedly. Further, the fortunate good continuity in the
OLIN-staff is beneficial in the longitudinal approach, as a limited number of interviewers also over time will reduce the inter-interviewer bias. Thus the inter- and intra-interview bias was minimised. Another issue is whether or not repeated interviews performed in the same population will cause bias by increasing the awareness of respiratory symptoms and diseases. Also, increased information in media in recent years regarding COPD may influence collected interview data. There are no obvious findings supporting this assumption in the results, but data from the examinations in 2002/2004 are so far only sparsely analysed.

Study population

This thesis is mainly based on data from the age-stratified general population sample of cohort I recruited in 1985. Sub-samples of cohort I have been examined several times. Age stratification was more common in the early eighties [Olofson et al, 1987] at the time of the design of the first OLIN surveys. Currently it is more common to perform surveys in general population samples similar to cohort III. However, the long time of follow-up of cohort I make the data valuable and interesting.

The general population sample is well established in the field of epidemiology. Among other things, it serves to reflect events of concern to public health. The questions on prevalence of a disease, the consequences of age structure in the population, prevalence and consequences of risk factors as smoking, socio-economic status and other determinants are important.

The cohort of subjects with respiratory symptoms represents a completely different category. All subjects reporting any respiratory symptom at the first postal questionnaire of cohort I were identified. The cohort is thus considered representative for the subjects in the general population with respiratory symptoms in current age groups in which COPD is common. This is the reason why this cohort is important from a clinical point of view. Health care professionals will confront subjects recruited from this cohort at all levels, from the health care advice service by telephone to the district medical centre and the hospital. They reflect the population from which patients seeking medical advice primarily due to respiratory complaints are recruited.

Participation vs. non-responding

High participation rate in epidemiological studies is worth striving for in order to minimise the risk of selection-bias. There are varying response rates reported between
different epidemiological studies and also between countries in multi-national projects. The variation in response rate for a postal questionnaire between countries in the European Community Respiratory Health Survey, ECRHS, were in absolute figures 36% - 99% (Dublin, Ireland - Algeria), median 75%, and when adjusted for subjects with the wrong age, those who were known to had moved, and those who had died 54% - 100% (Coimbra, Portugal - Algeria), median 78% [European Community Respiratory Health Survey, 1996]. The participation rate in the OLIN studies have been high, ≥85% in the postal surveys. In all surveys, besides in cohort III, the participation rate at the examinations including interview and spirometry has been almost optimal considering the number of subjects possible to attend. The most common reason for non-participation in follow-ups has been death. There are also a few subjects, particularly in higher ages, which have been institutionalised due to need for constant help. When analysing the non-responders among possible participants (alive, not institutionalised) there was either no difference or a tendency to report more respiratory symptoms compared to the participants. Young male smokers of low socio-economic group tended to be over-represented among non-responders [Rönmark et al, 1999]. Thus, the prevalence may be slightly underestimated. However, in cohort III, the participation rate at the interview and spirometry was somewhat lower than in other surveys, 69%. The non-participants may have affected the results of this particular study more than in the previous and also later surveys.

According to Norwegian results, the differences between participants and non-participants were not in the magnitude that the prevalence of disease was affected when the initial response rate rose from 42.7% to 79.9% by reminders and telephone-interview [Brogger et al, 2003]. The prevalence of respiratory symptoms and disease was neither affected by non-attendance in an elderly population with a response-rate of 57.4% [Hardie et al, 2003]. In a Finnish report, the non-participants were most often young smoking men that tended to report less respiratory symptoms at exercise and asthma than the participants, but a response rate at 83.6% was high enough to provide reliable results [Kotaniemi et al, 2001]. When analysing the non-responders in the OLIN-part of the comparative studies between Finland, Estonia and Sweden (the FinEsS-study), there were no major differences between participants and non-participants [Lindström et al, 2001]. In summary, from the over-all high participation rates in both postal questionnaire surveys and examinations, together with analyses of non-responders, we conclude that non-attendance is unlikely to have caused significant bias.

In the longitudinal study design, loss of follow-up due to death must be evaluated and a "healthy survivor effect" must be considered. The analysis of mortality data indicates that there is a "healthy survivor effect" in the follow-up of the symptomatic cohort, which results in a probable underestimation of the cumulative incidence of COPD. The analysis of loss of follow-ups of the age-stratified general population sample indicates similar results, but mortality data have yet not been completely analysed.
Different criteria of COPD

There are today several accepted spirometric criteria of COPD [American Thoracic Society, 1995; Siafakas et al, 1995; British Thoracic Society, 1997; Pauwels et al, 2001; www.goldcopd.com; Celli et al, 2004; Chronic Obstructive Pulmonary Disease, 2004]. Besides demography (mainly age distribution and smoking habits) of the studied populations, the spirometric criteria will strongly affect the prevalence of COPD [Viegi et al 2000, Celli et al 2003]. The corresponding relationship is expected also for the incidence of COPD. When presenting the data different spirometric criteria have been used, while one of the aims was to visualize the effect of different spirometric criteria on the prevalence and the incidence. In epidemiological surveys, the use of different definitions of COPD leads to difficulties in comparing data between studies [Jaakkola 2000; Mannino et al, 2002]]. The use of different criteria increases the possibility to compare the data with results from others and to evaluate the external validity of the results. Further, the results can contribute to the discussion of advantages and disadvantages of the different criteria. However, the latest guidelines, the NICE guidelines and ATS/ERS standards, were not published at the time for the writing of Papers I, II and IV.

Reversibility-testing

An important issue is the difference in approach between guidelines on reversibility-testing (Table 1). The GOLD guidelines and the recently published ATS/ERS standards refer to spirometry values after bronchodilatation while the other guidelines do not. In contrary, the NICE guidelines states “…in most cases the diagnosis of COPD is suggested by the combination of the clinical history, signs and baseline spirometry. Reversibility testing does not add any additional information.”

When the OLIN studies started in 1985 the modern guidelines of COPD were not published. Due to the standardised performance of spirometry throughout the OLIN studies, data can be used for estimates of prevalence and incidence of COPD by the different spirometric criteria. Yet, it should be observed that reversibility tests have not been performed in all subjects. Consequently, a modified GOLD criterion was used (and later the recent ATS/ERS standards) when analysing data from some of the early studies. In cohort III, metacholine tests were performed in a majority of the subjects on the same occasion as the interview and spirometry. Thus, it was not possible to perform reversibility testing, and the prevalence data are based on spirometry without bronchodilatation. In later surveys within the OLIN studies reversibility tests have been performed. The data referring to COPD according to the GOLD criteria in Papers II and III are based on spirometry after bronchodilatation. The estimation of a cumulative incidence calls for a special concern. It is important that the spirometries of the different occasions are performed in a standardised
manner, also with respect to bronchodilatation. In the 1986 examinations, not all subjects performed a reversibility-test and thus the pre-bronchodilator spirometries were used in the analyses of the cumulative incidence.

There are published Norwegian data in which the prevalence of COPD according to GOLD was reported to decrease from 18.2% (pre-bronchodilator) to 14.7% after bronchodilatation in ages 71-73 years [Hardie et al, 2002]. When analysing OLIN-data, the prevalence of COPD according to GOLD was reduced from 17% (pre-bronchodilator spirometry) to 14% (post-bronchodilator spirometry) [unpublished data, the OLIN studies], which is similar to the Norwegian results. The use or non use of post-bronchodilator spirometry will influence both the prevalence and the incidence of COPD even if not requested by any guidelines but GOLD and the ATS/ERS standards.

The issue of bronchodilatation and the use of the GOLD criteria has been discussed in editorials in the Thorax and in the European Respiratory Journal during this year [Sterk 2004; Vestbo 2004]. In the European Community Respiratory Health Survey, ECRHS, reversibility-tests were not performed [Burney et al, 1994]. In a publication based on data from the ECHRS, the GOLD criteria in staging COPD were used though only pre-bronchodilator FEV₁ were available [de Marco et al, 2004]. The methodology was in part questioned by Vestbo in the Thorax editorial, however, he stated “… in contrast to GOLD recommendations, prebronchodilator FEV₁ was used for staging but this seems acceptable in the epidemiological setting where administration of bronchodilators is often not feasible...“. The publication by Vestbo’s group on GOLD stage 0 and incidence of COPD according to GOLD refers also to spirometry without bronchodilatation [Vestbo et al, 2002]. We conclude and agree with the editorials that precautions need to be taken if the criteria not are used in concordance with the guidelines, and the results are to be interpreted in this context.

COPD vs. asthma

Most guidelines agree on that asthma developing chronic obstructive lung function impairment is almost impossible to distinguish from COPD. Some of the guidelines include chronic asthma as a cause of COPD. In the analyses asthma has not been excluded as a cause of obstructive lung function impairment. Further, asthma and COPD may co-exist in the same subject. According to earlier OLIN-studies the prevalence of co-existent asthma and chronic bronchitis/chronic obstructive lung function impairment was <1%, and approximately 1-2% in higher ages [Lundbäck, 1993]. We have not focused on this issue in this thesis, but there is no indication that there is major difference between data. Further, the risk of misclassification of disease is also to be considered.
Longitudinal data and cumulative incidence

By definition, the course of a progressive and fatal disease will not be visualised in a cross-sectional study. Further, the number of subjects affected by severe and very severe rapidly progressive disease will be underestimated in a cross-sectional study. This has been carefully discussed within cancer epidemiology, and it is generally accepted that incidence rate is a better measure of burden of cancer in the society. The corresponding relationship is to be argued in the case of COPD-epidemiology. There are cases of COPD with a very rapid decline in lung function. The magnitude of subjects with severe and rapidly progressive disease that will be missed both in cross-sectional and longitudinal studies is not known if the intervals between follow-ups are too long.

Cumulative incidence of COPD

The estimates of cumulative incidence in this thesis are based on longitudinal data collected by repeated cross-sectional surveys. In Paper IV the observation time is ten years, and in Paper VI it is seven years. A weakness in the study design is that the estimates are based on only two examinations, ten and seven years apart, respectively. COPD is known to be a progressive disease. There is a drop-out due to mortality during the observation time correlating to low lung function, indicating that the cumulative incidence of COPD may be somewhat underestimated. On the other hand, the size of the study population, the high participation rate, the standardisation of spirometry and interview are the strength of the studies. These validity aspects are reinforced in the longitudinal approach.

An important factor in incidence studies is the definition of the population at risk. By definition, all prevalent cases of the disease under study are to be excluded at entry. The population at risk will thus differ dependent on which spirometric criteria of COPD are used. When the cumulative incidence according to the GOLD criteria was estimated, all subjects with FEV$_1$/FVC <0.70 were excluded at entry. Correspondingly, all subjects with FEV$_1$/FVC <0.70 & FEV$_1$<80% were excluded at entry when the cumulative incidence according to the NICE guidelines was calculated. Consequently, the distribution of lung function in the populations at risk also differed. The results of the longitudinal studies illustrates that this factor has to be accounted for when comparing not only the cumulative incidence of COPD and but also the incident cases of COPD. The effect of defining the disease as mild COPD compared to moderate COPD according to the ATS/ERS standards are illustrated in Table 3. There are to date no comparable results published.
DISCUSSION OF MAIN RESULTS

Prevalence of COPD

The first study was important in order to visualize the effect of different spirometric criteria on the prevalence of COPD. The prevalence was strongly age dependent when using the criteria with a fixed ratio for the definition of airway obstruction, but less so when the gender-specific age-adjusted definition of the former ERS criteria was used. Further the prevalence of COPD in Norrbotten was found to be comparable to those reported from other parts of the world, both in the Nordic countries [Lange et al, 1989; Bakke et al, 1991], in Europe [Viegi et al, 2000], and in other parts of western society [Halbert et al, 2003] when differences in smoking habits and other demographic variables were taken into account. The results were also in accordance with reports that the different spirometric criteria will change the prevalence of COPD up to fourfold in the same population [Viegi et al, 2000; Celli et al, 2004].

The prevalence was similar in comparable ages between studies, i.e the random general population sample and the age-stratified general population sample. Thus the lower participation rate in the general population sample (69%) compared to earlier and also later surveys (≥85%) did not seem to have any major influence on the results. As the prevalence was largely dependent on age, smoking and the definitions of COPD, the prevalence estimates will be discussed together with risk factors, page 48 ff.

Incidence of COPD

There are only a few published studies in the literature on the incidence of COPD [Huhti et al, 1980; Kryzanowski et al, 1986; Heederik et al, 1990; Vestbo et al, 2002; Nihlen et al, 2004]. Only one of them used spirometric criteria of the modern guidelines of COPD [Vestbo et al, 2002]. There is also a Norwegian report on the incidence of COPD at the ERS congress in 2002 using the GOLD criteria [Johannessen et al, 2002]. Longitudinal data within the OLIN-studies have been used to estimate the cumulative incidence of COPD. The estimates were based on a 10-year follow-up of an age-stratified symptomatic cohort and a 7-year follow-up of an age-stratified randomly selected general population sample.

In the symptomatic cohort the 10-year cumulative incidence was estimated at 8.2% according to the BTS criteria and 13.5% according to the GOLD criteria. In the general population sample the 7-year cumulative incidence was estimated at 4.9%
according to the NICE criteria (similar to the BTS) and 11.0% according to the GOLD criteria (similar to the ATS/ERS standards) (Table 4). An estimation based on the cumulative incidence of COPD according to the NICE criteria yielded an overall annual incidence of 7/1000/year in the age-stratified general population sample. Corresponding figures among the non smokers were 2/1000/year and among the smokers 15/1000/year.

The only comparable published results are from the Copenhagen City Heart Study [Vestbo et al, 2002]. At 5- and 15-years follow-up of a general population sample without COPD at entry 9.7% (smokers 11.6%), and 13.2% (smokers 18.5%), respectively, developed COPD according to the GOLD criteria. The 5-year cumulative incidence was also recorded by disease severity; stage I: 4.3%, stage II: 5.3% and stage III: 0.1%, while the 15-year cumulative incidence was 7.2%, 5.8% and 0.2%, respectively. In a GOLD stage 0 population the 5- and 15-year cumulative incidence of COPD were 12.4% and 18.5% (smokers 13.2% and 20.5%), respectively. The Danish study population was a general population sample aged 20 years or older at entry. Smoking habits at entry were used in the analyses. The analyses in the Danish study were based on pre-bronchodilator spirometry values, thus a modified GOLD criteria was used.

At the ERS congress 2002, the Norwegian Bergen-studies reported a 9-year cumulative incidence of COPD at 9.8% in a general population sample aged 18-74 years at entry [Johannisen et al, 2002]. In contrary to the Danish study and the OLIN study, the Norwegian results were based on post-bronchodilator spirometry in accordance with the GOLD criteria. In the section "Discussion of Methodology", page 43, the reducing effect of bronchodilatation on the prevalence of COPD is discussed. A similar effect can be expected when estimating the incidence of COPD, provided that also the baseline values were based on post-bronchodilator spirometry. The different ages, selection of study populations, smoking habits, and also the use of GOLD criteria modified with respect to bronchodilatation partly complicate the comparison of results between studies.

In the Danish study, the 5-year cumulative incidence, 9.7%, appeared to be high in relation to the 15-year cumulative incidence, 13.2%. An approximate estimate of the annual incidence revealed a considerable difference. The estimate was 9/1000/year based on the 15-year cumulative incidence, which was substantially lower than the 19/1000/year based on the 5-year cumulative incidence. The lower estimate of annual incidence based on the 15-year cumulative incidence may be related to a healthy survivor effect, but the lost to follow-up of subjects with a rapid decline in lung function and severe COPD associated to high mortality may also affect the result of a 15-year follow-up. The possible effect of too large time intervals for follow-ups on cumulative incidence has been further discussed in section "Discussion of Methodology" on page 44. Only more frequent follow-ups in a longitudinal study design will be able remedy these problems. There are today no such data available in
the literature and there is an evident need to increase the knowledge on the course of COPD on a population-basis.

The annual incidence of COPD according to GOLD in our study of the age-stratified general population sample was estimated at 16/1000/year. In comparison with the Danish study population they were considerably older, but still the annual incidence was lower than the 19/1000/year based on the Danish 5-year cumulative incidence.

The two reports in this thesis on cumulative incidence of COPD were performed in different population samples, one symptomatic cohort and one general population sample. Besides this, there was a considerable difference regarding age. The age-strata in the general population sample were all ten years older at entry compared to the age-strata at entry in the symptomatic cohort. Consequently the data are difficult to compare. It is impossible to evaluate how much the selection of a symptomatic cohort and the age difference of ten years between studies affected the results. There are hardly any comparable data published to date, and only through future studies can the external validity of the results be evaluated.

Cumulative incidence of COPD in elderly

Interpretation of the effect of age on the incidence of COPD deserves particular caution. The constitution of the incident cases of COPD in the oldest age group in the general population sample, 76-77 years old at entry, was analysed. The incident cases of COPD identified by the NICE guidelines were all smokers or ex-smokers with respiratory symptoms, while the incident cases according to the GOLD criteria also included non-smokers without respiratory symptoms. Thus the NICE criteria seem to identify incident COPD of clinical relevance also among elderly, while the GOLD criteria were less specific. The prevalence of COPD according to the GOLD criteria has previously been reported to include non smokers without respiratory symptoms in elderly [Hardie et al; 2002], and consequently this seems to be applicable also in incident cases of COPD according to GOLD. As discussed, the use of current spirometric criteria of COPD among the elderly is sparsely evaluated, besides the paper by Hardie et al, and there is a need for further research in this area. Age-dependent spirometric criteria should be sought, and this issue is further discussed under the sub-headline risk factors.
Decline in FEV\textsubscript{1}

As expected, in the symptomatic cohort, the decline in FEV\textsubscript{1} was significantly related to smoking habits. The benefit of smoking cessation was obvious with the decline in FEV\textsubscript{1} returning to a non-smoking level. The effects were similar as previously reported by others [Fletcher et al, 1976; Camilli et al, 1987; Lange et al, 1989; Xu et al, 1994; Rijcken et al, 1998]. The decline in FEV\textsubscript{1} seemed to be even faster in the re-starting smokers compared to persistent smokers. This was more apparent in women. The results have to be interpreted with caution due to the low number of re-starters. However, there are earlier published data which are similar [Sherrill et al, 1996]. Whether or not restart of smoking is more vulnerable to the lungs, or if the re-starters represent a subgroup with different characteristics than the others of the population is unclear.

No comparable data on the decline in FEV\textsubscript{1} among incident cases of COPD on a population basis have been published earlier. The data indicate that a high proportion of the incident cases have a rapid decline in FEV\textsubscript{1}. Almost every fourth incident case of COPD (disease defined as moderate COPD according to the ERS/ATS standards) had a decline FEV\textsubscript{1} >90ml/year corresponding to a decrease of 28 percent-units of predicted normal value during ten years. For comparison, moderate COPD according to the ATS/ERS standards are similar to the BTS criteria and also to moderate COPD according to GOLD. Further surveys are needed to evaluate the course of decline in FEV\textsubscript{1} in COPD, if it is intermittent or continuous, and if there are factors, as possibly exacerbations, that affect the course of decline.

Risk factors

In chronic diseases risk factors which are stable over time (such as family history) and certain risk factors, of which the impact increases by ongoing exposure or over time (as smoking and increasing age), can be used for valid risk estimates also in cross-sectional studies. This explains why the most prominent risk factors in the studies of incidence were similar to those in the studies of prevalence, namely smoking and age. The prevalence study in the age stratified sample had a high participation rate and the sample was the largest, thus resulting in a greater power when performing risk factor analyses. This contributes to the fact that the risk factors were more apparent in the prevalence studies than in the incidence studies. Very large population samples are necessary if risk factors as specified occupation and different occupational airborne exposure are to be evaluated with accuracy on a population basis. The data collection in the present studies was thus limited to mainly demographic data.
The prevalence of COPD was significantly associated with higher age and smoking, confirming data from others [Siafakas et al, 1995; British Thoracic Society, 1997; Pena et al, 2000; Gulsvik, 2001; Mannino et al, 2003]. However, the finding of a very high prevalence of COPD among elderly smokers (BTS 45%, GOLD 50%) has not been reported earlier, with the exception of the US NHANES III [Mannino et al, 2000; Stang et al, 2000]. According to previous reports [Fletcher et al, 1976; Rijcken et al, 1998] only 15% of smokers develop COPD. There are also data from a Spanish study [Sobradillo et al, 1999] and a Finnish study [Isoaho et al, 1994] supporting the findings of a considerably higher prevalence of COPD among elderly smokers than previously reported. Smoking was the strongest risk factor also for incident COPD. This was further emphasised in the symptomatic cohort by the use of smoking categories reflecting changes in smoking habits. Persistent smoking yielded the highest odds ratios also when adjusted for confounders.

The population attributable fraction (or proportion), PAF, is a measure of the public health impact of a certain exposure, while it is a function of the potential harm of the exposure (through the relative risk) and how common the exposure is (through its prevalence, in our analysis proportion of ever smokers). The results indicate that factors other than smoking are of increasing importance for COPD among elderly.

The prevalence of COPD according to the BTS criteria, similar to the national guidelines in Sweden, yielded a prevalence of 4.1% in ages <45 years and 9.7% in ages ≥45 years in the general population sample, and 8.1% in the age-stratified general population sample in which all were ≥45 years. In the age-stratified sample the prevalence was low in ages 46-47 years; 1.8% in men and 3.7% in women (totally 2.8%). The prevalence increased markedly by age, especially in men. The prevalence in age 61-62 years was increased by four times, and in age 77-78 years it was increased by twelve times in men. In women, the prevalence was increased by almost three and almost five times in respectively age group.

Age as a risk factor has to be evaluated in relation to the spirometric criteria. A fixed quotient defining airway obstruction will overestimate prevalence in elderly [Lundbäck et al, 2003; Hardie et al, 2002]. It is reported that a large proportion of elderly non-smokers >80 years without respiratory symptoms will be classified as having COPD [Hardie et al, 2002]. The only spirometric criteria adjusting for age were the former ERS criteria [Siafakas et al, 1995], which has been replaced by a fixed quotient defining airway obstruction in the most recent update of 2004, the ATS/ERS standards. The prevalence of COPD on population level was similar when using the earlier age-adjusted ERS criteria [Siafakas et al, 1995] and the fixed quotient by the GOLD criteria in the general population sample aged 23-72 years (14.0% and 14.1%, respectively). However, when the prevalence was estimated by the age groups <45 years and ≥45 years, differences appeared. The prevalence of COPD according to the ERS was 11.6% in ages <45 years and 15.4% in ages ≥45 years (no significant difference), while the corresponding figures for COPD according to the GOLD were
9.1% and 17.1% (p=0.005). The age-distribution differed in the 11% of the prevalent cases not similarly identified by both criteria. The ERS-but-not-GOLD-cases were all <53 years of age, and the GOLD-but-not-ERS-cases were all >63 years of age.

Increasing age was a risk factor for incident COPD in the symptomatic cohort. In the random general population sample, increasing age was certainly a risk factor for incident COPD, however in elderly only according to GOLD but not the NICE criteria, as discussed under sub headline "Cumulative incidence of COPD in elderly" on page 47. Thus, age is a risk factor for incident COPD, but the spirometric criteria may add complexity when interpreting the results.

Even though the most physiologically correct criteria ought to include an age- and gender-adjusted definition for a quotient for airway obstruction, as with the former ERS criteria, all current spirometric criteria of COPD refer to a fixed quotient. This will in future add a great impact on the epidemiological estimates of the prevalence and incidence of COPD in an aging population, and cannot be considered equivalent to a clinically relevant disease. The use of different quotients depending on age when defining airway obstruction has been suggested: FEV1/FVC <0.70 in ages <70 years, <0.65 in ages 70-80 years and <0.60% in ages >80 years [Eagan et al, 2002]. However, the risk for under-diagnosis of COPD by the use of a fixed ratio in younger age groups should also be recognised.

Socio-economic class assessed by occupation was evaluated as a risk factor for COPD. Only manual work in industry was a significant risk factor for prevalent COPD according to GOLD when adjusted for confounders. Low education level was close to significant as a risk factor for incident COPD among the symptomatics when adjusted for confounders (OR 1.7, CI 0.98-3.04). There are several studies that have shown different indices of socio-economic class to be related to COPD [Bakke et al, 1991; Prescott et al, 1999]. The weak relationship between COPD and socio-economic class in our studies is probably due to several reasons. Indexing socio-economic class by occupation is a crude method of measurement. The retirement age in Sweden is 65 years, and early retirement has become common. In the studied populations of high ages, in which a majority already have retired, other indices of socio-economic classification than by former occupational title should be evaluated.

Family history of OLD was of less importance for COPD than what has been shown for asthma. In the process of publishing, the opinion that COPD solely is an environmental disease was also expressed. However, family history of OLD implied a small but significant increased risk for prevalent COPD, while there was no significant association to incident COPD, maybe due to a lack of power. It is reported that genetics may be involved and contribute to the development of COPD by an increased susceptibility to environmental factors [Silverman et al, 2000]. Thus studies on interaction between family history of OLD and environmental factors are important in future research.
Gender aspects

Earlier studies reported higher prevalence of COPD in men compared to women [Sobradillo et al, 1999; Mannino et al, 2000; Viegi et al, 2000]. Later studies have reported an increase in COPD among women and the prevalence in women is approaching the prevalence in men [Soriano et al, 2000]. Most of the reported changes in prevalence are probably due to women's change in smoking behaviour, where they are catching up to men.

We did not find any significant gender difference in the prevalence or in the cumulative incidence of COPD. Multivariate models for analysing risk did not reveal gender to be a risk factor for incident COPD when adjusted for possible confounders. However, the gender-specific risk factor analyses revealed a different risk factor pattern for incident COPD in men compared to women. Smoking and re-start of smoking were significant risk factors in women, while only close to in men. Age was a significant risk factor only in men. Lack of power and the age distribution of the studied sample, in which all were >45 years at start of the observation period, may explain this result. A healthy survivor effect may also contribute. There are no comparable studies published to date. However, our findings support the hypothesis that women are more susceptible to tobacco smoke than men [Prescott et al, 1997; Langhammer et al, 2003]. Women may also be more inclined to develop severe COPD [Silverman et al, 2000].

GOLD and ATS/ERS standards - "at risk for COPD"

Both the GOLD criteria and the ATS/ERS standards classify subjects “at risk for COPD” (Table 1), subjects with “normal lung function” and respiratory symptoms. What are the rationales for defining subjects “at risk for COPD”, and are they really at risk? The only publication in this topic is the previously referred Danish study [Vestbo et al, 2002], which stated that GOLD stage 0 does not predict development of COPD. In earlier studies, an association between respiratory symptoms and increased decline in lung function has been reported [Annesi et al, 1986; Sherman et al, 1992; Vestbo et al, 1996]. Thus a relationship between respiratory symptoms and increased decline in lung function leading to COPD could be expected. However, one possible explanation given was that GOLD stage 0 was not a stable condition. Also later studies have shown a remission of respiratory symptoms promoted by smoking cessation [Eagan et al, 2004].

The relationship between respiratory symptoms and development of COPD was analysed in the longitudinal studies. A significantly greater proportion of the subjects developing COPD during the observation period reported respiratory symptoms at entry compared to subjects that not developed COPD. Further, in multivariate logistic
regression models, most respiratory symptoms, singly added, were markers for increased risk of incident COPD when adjusted for possible confounders including smoking. The findings were similar in the symptomatic cohort and in the general population sample, and it was similar for all criteria of incident COPD. Our conclusion is that the classification of “at risk for COPD” by the GOLD criteria and the ATS/ERS standards really identifies subjects at increased risk for developing COPD, which is contrary to the Danish results. The results are highly applicable in the clinical setting. Repeated spirometries can be recommended in subjects with respiratory symptoms for the screening of COPD.

**Underdiagnosis**

The results indicate a large underdiagnosis of COPD. Most commonly, underdiagnosis is referred to as the lack of the health care system to recognise or label a certain disease. Reported physician diagnosis consistent with COPD was used as an index to reflect chronic obstructive lung disease identified by health care. In subjects fulfilling spirometric criteria of COPD, the index of health care identification was low. "Seeking medical advice due to respiratory complaints other than common cold" and "use of asthma medicines" were used to indicate contacts with health care due to respiratory disorder. Also among subjects contacting health care the index for identified chronic obstructive lung disease was low. Underdiagnosis of the same magnitude has also been reported by other large epidemiological studies, including the Spanish IBERPOC [Sobradillo et al, 1999; Pena et al, 2000], the US NHANES III [Mannino et al, 2000], and the Dutch DIMCA study [van den Boom et al, 1998]. It is possible that underdiagnosis is of greater magnitude among women than among men [Chapman et al, 2001], though this was not analysed in this thesis.

It is reported that subjects with COPD underestimate their symptoms [Rennard et al, 2002; van Weel, 2002]. However, in the interview setting, a great majority of the subjects fulfilling any of the spirometric criteria of COPD answered in the affirmative to presence of respiratory symptoms. Respiratory symptoms were actually reported by 94% of the subjects fulfilling the spirometric criteria of COPD according to the BTS. Cough and sputum production were the most commonly reported symptoms. Less than 50% of the subjects fulfilling spirometric criteria of COPD seem to have contacted health care for other reasons than common cold, despite of being symptomatic. Thus there is a lack of recognition of respiratory symptoms as signs of a disease among the subjects fulfilling the criteria for COPD.

In summary, a substantial underdiagnosis of COPD was found in the cross-sectional studies, where both the affected subjects and the health care system failed to recognise COPD. Even if 94% of the prevalent cases of COPD by BTS criteria reported respiratory symptoms less than 50% contacted health care and only 16% were aware of a physician-diagnosis consistent with COPD in the random general population
sample. In the age-stratified population sample, a higher proportion of the subjects with COPD (the BTS criteria), 31%, reported a physician diagnosis. The relationships between reported symptoms, health care contacts, and physician diagnosis are illustrated in Figure 3. In subjects >45 years of age, every other case of severe COPD (BTS classification) reported a physician diagnosis consistent with COPD. In mild COPD according to GOLD, only every twentieth reported a physician diagnosis. Thus, there was a relationship between disease severity and physician diagnosis, but still only half of the subjects with severe disease had a proper labelling.

There are studies of health economics reporting a close relationship between disease severity and health care utilisation [Jansson SA et al, 2002]. Surveys and analyses on the association between expression of respiratory symptoms and disease severity in relation to health care contacts on a population basis are lacking. This is an important area of future epidemiological research in order to remedy the underdiagnosis of COPD.

The Swedish report on the eight-year cumulative incidence of self-reported physician-diagnosed COPD at 2.9% [Nihlen et al, 2004] also indicates a large underdiagnosis compared to the estimated 7- and 10-year cumulative incidence. Provided that COPD is equally common in southern and northern Sweden, the underdiagnosis in Sweden is in accordance with other reports of underdiagnosis in Europe that only 20-30% of the COPD-cases are identified [Siafakas et al, 1995; Soriano et al, 2000].

Further consequences of the underdiagnosis are visualised when comparing the economic impact of obstructive airway diseases in Sweden estimated in a register-based study [Jacobsson et al, 2000] and a population-based survey [Jansson SA et al, 2002]. The register-based study showed a considerably lower cost, approximately a third, compared to the population-based study. The differences between the register-based and the population-based costs are to a large extent most probably due to the underdiagnosis of COPD. In the population-based study subjects were included who were not identified with a relevant diagnosis in the health care system. The impact of underdiagnosis on the expected health care utilisation thus seems to be great.

Clinical aspects

The symptomatic cohort

From a clinical point of view this cohort is very interesting. The cohort is considered to be representative for subjects with respiratory symptoms in the general population in current age groups. Consequently the symptomatic cohort reflects the population from which the patients seeking medical advice due to respiratory complaint are recruited. Thus the data on incidence and decline in lung function in this cohort are
relevant in the field of planning for health care. The results emphasize that spirometries in subjects with respiratory symptoms is an efficient tool in identifying new cases of COPD. Consequently, more frequently performed spirometries will counteract the considerable underdiagnosis of COPD indicated in the cross-sectional studies.

Decline in lung function

Lung function is an important factor related to mortality in the general population [Annese et al, 1986; Neas et al, 1998; Schuneman et al, 2000]. It is also one of the most important with regard to prognosis of COPD [Hansen et al, 1999; Mannino et al, 2003]. It is not unusual that crude ml is used for assessing decline in FEV1 in health care, however, our data indicate that an adjusted method of assessing decline is preferable. The decline in FEV1 assessed as change in percent-units of predicted normal value was found to be a very easy method, well suited for use in the daily work. Future studies may establish the predictive value in evaluating the risk for development of COPD and also the prognosis in already established COPD.

Clinically relevant disease

The terminology "clinical relevant disease" has elicited some discussion. In a report by Celli it is stated that GOLD stage II (FEV1/FVC<0.70 & FEV1 ≤80 % predicted) is considered to identify subjects with symptomatic COPD [Celli et al, 2003]. Is this synonymous with clinically relevant disease? As mention above, there are published data on health economics in which a close relationship between disease severity, health care utilisation, and costs were found [Jansson SÅ et al, 2002]. According to these data, mild COPD (GOLD stage I, subjects not identified by the BTS and NICE guidelines) also had a registered, though limited, health care utilisation for drugs and out-patient care.

Consequently, at least COPD according to GOLD stage II and similar definitions, including the Swedish national guidelines, seem adequate for identification of a clinically relevant disease on a population basis. However, subjects with mild COPD according to GOLD also have health care costs; 10% reported use of medicines for their airways and a majority of them, 70%, were symptomatic. The disease process in COPD starts long before the lung function impairment is manifest, and we have to keep in mind that the spirometric criteria for COPD in the different guidelines are arbitrary. Finally, I would like to highlight the variable disease progress in the concept of clinically relevant disease. Increased knowledge in this area can be achieved by future studies of “the natural history of COPD” previously outlined in this section.
CONCLUSIONS

In a random general population sample the prevalence of COPD in ages <45 years was 4.1%, 11.6%, 9.1%, and 5.1% according to the BTS, ERS, GOLD, and ATS criteria, respectively. In ages ≥ 45 years the corresponding prevalence was 9.7%, 15.4%, 17.1%, and 16.5%, respectively. The prevalence of all criteria, except of the ERS, was associated with increasing age.

The prevalence of COPD in an age-stratified sample of middle-aged and elderly >45 years was 8.1% according to the BTS criteria and 14.3% according to GOLD and increased markedly with increasing age from 2.8% in ages 46-47 years to 19.7 % in ages 76-77 years with no significant gender difference (BTS criteria).

Among the subjects in ages >45 years fulfilling the BTS criteria for COPD (similar to the Swedish criteria) 65% had a mild disease, 27% a moderate disease and 8% a severe disease. Corresponding figures among prevalent cases of COPD according to GOLD were 57% mild disease, 37% moderate disease, 5% severe disease, and 1% very severe disease.

A majority of all identified cases of COPD in the random general population sample reported respiratory symptoms; 94% of the subjects fulfilling the BTS criteria and 88% of those fulfilling the GOLD criteria, while physician diagnosis of chronic bronchitis or emphysema was reported by 16.3% and 11.0%, respectively. In the age-stratified sample >45 years physician-diagnosis consistent with COPD was reported by 31% and 18% (BTS and GOLD criteria), while 42% and 26%, respectively, reported use of airway-medicines.

The underdiagnosis of COPD was strongly associated with disease severity. Among subjects with severe COPD according to the BTS criteria, 100% were symptomatic, 88% had chronic productive cough and 50% reported a relevant physician-diagnosis. In mild COPD according to GOLD, the corresponding figures were 70%, 21% and 5%.

Among smokers the prevalence of COPD according to the BTS criteria was 5% in the ages 46-47 years, 24% in the ages 61-62 years and 45% in the ages 76-77 years while in non-smokers it was 1%, 2% and 16%, respectively. Corresponding figures on prevalence of COPD according to the GOLD criteria were 11%, 42% and 50% in smokers, while 2%, 5% and 21% in non-smokers. The risk (OR) for COPD according to the BTS criteria was nine times higher in smokers than in non-smokers when adjusted for confounders including age.
In the age-stratified sample >45 years, the fraction of COPD (BTS criteria) in the population attributable to ever smoking was 41% (GOLD 43%). Further, of subjects with COPD (BTS criteria) 24% had never been smokers (GOLD 23%), and this proportion was higher in elderly and women.

Besides smoking and age no risk factors yielded ORs above 2. An increased risk for COPD was found for family history of OLD and manual work in industry.

Among subjects reporting respiratory symptoms, the 10-year cumulative incidence of COPD was estimated at 8.2% according to the BTS criteria and at 13.5% according to the GOLD criteria. The incidence was significantly associated with increasing age and smoking but not gender. However, gender-specific multivariate analyses adjusting for confounders revealed smoking to be a significant risk factor in women and close to in men, while age was a significant risk factor in men only.

The decline in FEV₁ in the symptomatic cohort was estimated at 33 ml/year and was significantly associated with male gender, smoking and reported chronic productive cough. This corresponded to -0.85 percent-units change of predicted normal value during the ten years, and the gender-related differences were decreased or disappeared by this method of assessing decline. Among the incident cases of COPD (disease defined as moderate COPD according to the ATS/ERS standards) the decline in FEV₁ was 62 ml/year, corresponding to a decrease of 12.6 percent-units of predicted value during ten years. Almost every fourth incident case of COPD had a decline in FEV₁ of >90 ml/year (-27.8 percent-units).

The seven-year cumulative incidence of COPD was estimated at 4.9% according to the NICE guidelines and 11.0% according to the GOLD criteria in the age stratified general population sample. The risk factor pattern was similar as in the symptomatic cohort. In elderly, the NICE criteria seemed to be more reliable in identifying relevant disease compared to the GOLD guidelines.

Most respiratory symptoms were markers of increased risk for incident COPD both in the random general population sample and in the cohort with respiratory symptoms when singly added to multivariate models adjusting for confounders.
FUTURE ASPECTS

The following includes aspects on future research areas in the COPD-epidemiology.

There are limited data on the course of COPD, or “the natural history of COPD”. This is especially true among elderly. There are basically very limited data on the development of lung function among elderly in the general population. Also the use of current spirometric criteria of COPD in elderly has to be further evaluated. In an ageing population it is very important to increase the knowledge and evaluate the impact of a disease known to be associated with age, as COPD. Neither overestimation of disease due to inadequate spirometric criteria nor underdiagnosis is desirable for the patients and is also important when planning for future health care resources. Future studies on COPD in elderly are necessary to address these issues.

There are several reports on prevalence of COPD from cross-sectional data, but the relationship between decline in lung function and development of COPD on a population-basis is incompletely described. Further, there are to date hardly any data on whether the decline in lung function in COPD is continuously progressive or intermittent, and what factors affect the rate of decline in lung function and disease progress in established COPD. More frequent follow-ups including spirometry in large enough cohorts could answer these questions. These studies will be both time-consuming and expensive, but probably the most reliable to illustrate and increase the knowledge on the development of and course in COPD on a population basis.

There are several other important aspects of COPD and risk factors for COPD that not have been discussed in this thesis. It is impossible to cover all aspects of the complexity in the epidemiology of COPD, but some of them will be mentioned. Among other things passive smoking, occupational airborne exposure, the effect of socio-economic group and the interaction between family history of OLD and environmental factors are important risk factors that deserve more attention. The relative importance of the population attributable risk of occupational airborne exposure is expected to increase for COPD as an effect of decreasing smoking in the society. The impacts on quality of life for the affected subjects and the health economical burden of COPD in society have to be further recognised. Co-morbidity in COPD is incompletely surveyed. Further knowledge is very important in the care of COPD-patients and also for identification of COPD outside respiratory medicine and general practitioner. The consequences of underdiagnosis ought to be further evaluated amongst all in relation to health economic impact, co-morbidity and mortality.
ACKNOWLEDGEMENTS

I want to address and thank the participants in the surveys all over the county of Norrbotten. Your attendance is the very basic of the OLIN-studies. I want to express my sincere gratitude to all of you who have contributed to and supported the writing of this thesis. Among all, I wish to express my sincere gratitude especially to the following:

First of all my tutor and supervisor Bo Lundbäck, thank you for opening the door to research and the world of epidemiology. Your knowledge, enthusiasm, and support made it possible to start and also to finalise this thesis. I am also grateful for your incredible capacity to be every where and still available when needed.

My assistant supervisor Rune Lundgren, for your wise comments and support when writing my first papers and finalising this thesis.

Eva Rönmark for co-authorship, for good advice, managing of the data base, encouragement and support during the finalising of this thesis.

Ann-Christin Jonsson, for data collection, care for the patients, sharing with me your knowledge from the early years of the OLIN-studies, and for co-authorship.

Thomas Sandström, the head of the Umeå University Division of Respiratory Medicine and Allergy, for support, encouragement, and co-authorship.

Hugo Hagstad, the head of the Division of Respiratory Medicine at Sunderby Hospital, for your support since my very first days in Boden in 1988, and also when writing this thesis.

Amund Gulsvik, the mentor of respiratory epidemiology in the Nordic countries, for constructive comments and discussions with the Bergen group including Per Bakke.

Bengt-Eric Skoogh and Gunnar Boman for support and constructively and critically reviewing of the OLIN-studies since the early days.

Kjell Larsson for co-authorship and constructive support.

Maj Lindström for co-authorship and work in the OLIN-studies from the early days.

Berne Eriksson for co-authorship and stimulating discussions as a fellow PhD-student within the OLIN-studies. Staffan Andersson for co-authorship and participation in the OLIN study group. Anders Bjerg-Bäcklund for co-authorship.
Elsy Jönsson for statistical support from the beginning of the OLIN studies and co-authorship. Lennart Nyström for statistical support. Ola Bernhof for excellent computerising of data.

Karin Lundbäck, Ann Lundqvist, Ulla Jarlbring, Anne Kemi, Karin Östling and Ann-Christin Skogsberg for collecting data. Linnea Hedman and Sigrid Sundström for their present work within the OLIN-studies and also for collecting data.

Ulf Hedlund and Sven-Arne Jansson for support and sharing of mutual interest as fellow PhD-students within the OLIN studies.

All members of the OLIN studies scientific advisory board for active participation in constructive discussions contributing to further progress of the OLIN-studies.

My current and also former colleagues at the Division of Respiratory Medicine and Allergy at Sunderby Central Hospital of Norrbotten.

The staff at the Division of Respiratory Medicine, I cannot name you all. I especially wish to thank Hillevi Sandström, my next-door workmate and friend, for all those days of clinical work we have shared.

Michael Haney for linguistic revision of papers and this thesis, and a special thank for those works done with short notice.

All my friends, thank you for your support and for your patience with me during the time of writing. I hope you are still there.

Anders my brother, for all those phone-calls and sharing of thoughts. My mother and father, Anna and Arne, for your support.

I thank my family, I am most grateful for your patience when finalising this thesis. Lars-Gunnar, you are everything, my spouse and friend, but also my colleague, co-author and assistant supervisor when writing this thesis. Felix and Linnea, my children with love. Karin and Lasse for support and sharing.

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The Swedish Heart-Lung Foundation is acknowledged for continuous economical support to the OLIN studies, and also for the follow-up of results.
The studies in this thesis have also been supported by grants from the Local Health Care Authority of Norrbotten, the Swedish Foundation Against Asthma and Allergy, the European Commission BioMed I (concerted action on the epidemiology of COPD), the Swedish Council for Working Life (RALF) and the National Institute for Working Life.

Additional support was gratefully received from the companies GlaxoSmithKline and AstraZeneca.
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APPENDIX

The OLIN Studies

Brief description, aims and methods

The Obstructive Lung Disease in Northern Sweden (OLIN) studies started in 1985 with a cross-sectional study in an age-stratified sample of the general population in the county Norrbotten, which covers one-fourth of the area of Sweden. The diseases under study include asthma, allergy, COPD, chronic bronchitis, and obstructive sleep apnoea syndrome (OSAS). Descriptive, analytic and interventional research is included. The studies are currently mainly focused on prospective longitudinal studies of incidence, remission and risk factors for disease. The methods include cross-sectional studies measuring trends of disease in society, and they include also incident case-referent studies of risk factors for disease. The overall aim is to identify modifiable risk factors for obstructive airway diseases in order to promote prevention. Several cohorts are under study with approximately 40,000 subjects including children, young adults, middle aged and elderly living in Norrbotten involved in the cohorts of the OLIN studies. The cohorts are described below. The subjects of the original OLIN-thesis so far have been the prevalence of asthma, chronic bronchitis and respiratory symptoms [Lundbäck, 1993] asthma incidence, remission and risk factors among adults and children [Rönmark, 1999], prevalence of snoring and OSAS also in relation to respiratory disorders [Larsson LG, 2001], COPD-epidemiology [Lindström, 2002], and molecular epidemiological aspects of asthma in children [Perzanowski, 2003].

International co-operation

International co-operation includes co-work with research centres mainly in USA, the Nordic countries, Estonia, Italy, and United Kingdom. A previous EU-funded project on the epidemiology of COPD based on pooled data from Italy, Norway and Sweden has successfully been completed and reported in a supplement of European Respiratory Review in 2001 [Viegi et al, 2001, Lundbäck et al, 2001]. The collaboration within the comparative studies between Finland, Estonia and Sweden (The FinEsS studies) including totally 64,000 randomly selected subjects is mainly based on methods developed within the OLIN studies [Kotaniemi et al, 2001; Larsson ML et al, 2003; Lindström et al, 2001; Meren et al, 2001; Pallasaho et al, 1999; Raukas-Kivioja et al, 2003; Jannus-Pruljan et al, 2004]. The FinEsS studies are still in the process of being analysed and published. The OLIN studies of the year 2004 are entering their 20th year.
The OLIN cohorts

**Cohort I** is the sample of the first cross-sectional postal questionnaire survey collected during the fall of 1985. Data from this cohort are used in this thesis, and the cohort was further described under section Material and Methods. Methacholine tests and skin prick tests have been performed in sub-groups. The participation rate has been high, 83-91%, over the years. The latest survey of this cohort was performed in year 2003.

**Cohort II** was established in 1992. A postal questionnaire was administered to 9132 subjects living in the same areas as the Cohort I participants and born 1925-26, 1940-41, 1955-56, and 1970-71 (Figure 1). A random sample of 2860 subjects was invited to an interview and spirometry testing in 1994/95. Cohort II has been re-examined in 2003/2004.

**Cohort III** is comprised of a general population sample, age 20-69 years. Data from this cohort are used in this thesis and the cohort is further described in the section Material and Methods. During the examinations, skin prick tests and methacholine tests were performed besides spirometry and interviews. All participants from 1994/95 are at presently (2004) being invited to re-examinations.

**Cohort IV** is comprised of a random sample of 8333 subjects, in the ages of 20-69 years. They were invited to a postal questionnaire survey in the winter of 1996. A random sample of the responders has been participating in clinical follow-up studies including structured interviews, spirometry, methacholine tests, and skin prick tests. These studies are parts of a collaboration project, the FinEsS-studies, with centres in Finland (Lapland and Helsinki), Estonia (Tallinn, Narva and Saaremaa) and Sweden (Norrbotten, Stockholm and Örebro).

**Cohort V** was a case-control study of incident asthma performed in 1996-1999. Cases of incident asthma (n=315) were identified and a similar number of controls were examined with the overall aim to identify risk factors for incident disease. Investigations were also performed to evaluate the influence of out-door, home, and work environments.

**Cohort VI** is comprised of all 3525 children attending first and second grades in 1996 in three areas of Norrbotten (Luleå, Kiruna and Piteå). Postal questionnaire surveys have been performed annually, so far. The children in Kiruna and Luleå have been invited to skin prick tests in 1996 and 2000, and blood samples have been collected.