ASTHMA, CHRONIC BRONCHITIS
AND RESPIRATORY SYMPTOMS:
PREVALENCE AND
IMPORTANT DETERMINANTS

The Obstructive Lung Disease in
Northern Sweden Study I

AKADEMISK AVHANDLING
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Umeå universitet för avläggande av medicine doktorsexamen
kommer att offentligt försvaras i hörsal B, Samhällsvetarhuset,
fredagen den 29 oktober, kl 09.00.
Fakultetsopponent professor Jacob Boe, Oslo.

Bo Lundbäck

University of Umeå
Umeå 1993
From National Institute of Occupational Health, Medical Division, S-907 13 Umeå, Sweden, Department of Medicine, Division of Lung Medicine, University of Umeå, and Department of Lung Medicine, Central Hospital, Boden.

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* To assess the prevalences of asthma, chronic bronchitis and respiratory symptoms in adults.
* To compare the influence of various diagnostic criteria on prevalence.
* To identify subjects with obstructive lung diseases, in particular asthma, for case-referent and prospective longitudinal studies.
* To examine whether the trend towards an increase in the prevalence of asthma persists.

Study factors that may influence the development of obstructive lung diseases; age, gender, smoking habit, occupation, socio-economic group, population density and area of domicile.

The first part of the OLIN study consisted of three phases. A postal questionnaire regarding respiratory symptoms and diseases, smoking habit and profession was sent to all subjects aged 35-36 y, 50-51 y and 65-66 y (n=6,610) living in eight representative areas of Sweden’s northernmost province; 86% completed the questionnaire. Those reporting symptoms suspicious of asthma or chronic bronchitis (n=1,340), together with a stratified sample (n=315) of those not suspected of having the diseases according to the postal questionnaire, were invited to structured interviews and lung function tests. The prevalence of asthma, 5-6% according to both the postal questionnaire and to the structured interview, prompted a validity study, which included bronchial provocation tests. While the prevalence remained unchanged, the validity study better identified the subjects with asthma and chronic bronchitis, thus improving the representativeness of the subjects with the diseases. In 1992, the study base was expanded by a postal questionnaire study which included 20,489 subjects 20-69 y in order to assess whether the prevalence had changed, to create possibilities to estimate the incidence, and to be better able to detect determinants of diseases.

The results show that the prevalence of asthma in adults in 1992 was 7-8% according to postal questionnaire and was considerably higher, approximately 10%, in young adults. Further, the prevalence of asthma in 1986-1987 in subjects aged 35-36 y, 50-51 y and 65-66 y was 5% by using a combination of epidemiological and clinical methods. Various operational criteria yielded a prevalence of 4-7%. Between 1986 and 1992 the prevalence of asthma in these age groups increased with 1% according to the postal questionnaire. Chronic bronchitis in subjects aged 35-36 y was 3% in 1986-1987. The prevalence of chronic bronchitis increased with age, particularly in men. The mean prevalence in the three age groups 35-36 y, 50-51 y and 65-66 y was 12% in men and 8% in women. Chronic bronchitis was strongly associated with smoking, age and a family history of obstructive airways disease. Regarding socio-economic group chronic bronchitis was related to manual workers in industry and to self-employed other than professionals, and it was particularly common in miners and in those employed in agriculture. The strongest risk factor for asthma was a family history of asthma, and asthma was more common in manual workers in service, in non-manual assistant employees as well as in farmers. The results also indicate the presence of an urban factor in asthma in northern Sweden, in spite of the fact that respiratory symptoms in general tended to be more common in the colder interior of the province compared with the coastal area.

Key Words: asthma, chronic bronchitis, epidemiology, prevalence, determinants.
ERRATA

Editorial errors
Where an author has several papers in the reference list published during a single year, and
where no letter is given after the publication year in the reference citation in the text, then
reference a is indicated. For example [Gulsvik, 1979] should be read [Gulsvik, 1979a].

Page 52: Paragraph 3, line 4: "15%" should be substituted for "17%".
Page 55: Paragraph 2, line 7: "Ex-smoker" should be substituted for "smoker".

Paper I. The Abstract and Table 3 are corrected and given immediately after the Paper.

Paper II. Methods, line 1: "1,655" should be substituted for "1,654". Table 1: first line, column 1:
"884" should be substituted for "844", column 4: "1,019" should be substituted for "1,015".

Paper III. Table 3, column 2: the following substitutions should be made: line 16: "56" instead of
"58"; line 17: "7.3" instead of "7.6"; line 21: "29" instead of "39"; line 22: "3.8%" instead of "5.1%".

Paper IV. The final two sentences in Results prior to Discussion have been abridged and are
consequently inaccurate and should be omitted.

Paper VI. Table 3, column 6, line 15: "3.0%" should be substituted for "6.3%".

Calculation errors
Paper IV. Table 3 should be as follows:
(The correction results in the following modifications to the text: page 49, final paragraph, line 5
and line 6: "92%" should be substituted for "93%" and "55%" should be substituted for "56%". In
lines 6 and 8 of the penultimate paragraph of the Results section of Paper IV: "92%" should
be substituted for "93%", and "55%" should be substituted for "56%").

Table 3. Validity of wheezing (a), attacks of breathlessness (b), and interview diagnosis of asthma (c) as tests for bronchial reactivity, defined as $PC_{20} < 8mg/ml$ methacholine in examined subsample.

<table>
<thead>
<tr>
<th></th>
<th>Reactive</th>
<th>Unreactive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Wheeze</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>129</td>
<td>110</td>
<td>239</td>
</tr>
<tr>
<td>no</td>
<td>11</td>
<td>34</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>144</td>
<td>284</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92%</td>
<td>(129/140)</td>
<td></td>
</tr>
<tr>
<td>Pos. predictive value</td>
<td>54%</td>
<td>(129/239)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>24%</td>
<td>(34/144)</td>
<td></td>
</tr>
<tr>
<td>b) Attacks of breathlessness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>88</td>
<td>56</td>
<td>144</td>
</tr>
<tr>
<td>no</td>
<td>52</td>
<td>88</td>
<td>140</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>144</td>
<td>284</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>63%</td>
<td>(88/140)</td>
<td></td>
</tr>
<tr>
<td>Pos. predictive value</td>
<td>61%</td>
<td>(88/144)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>61%</td>
<td>(88/144)</td>
<td></td>
</tr>
<tr>
<td>c) Asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>77</td>
<td>21</td>
<td>98</td>
</tr>
<tr>
<td>no</td>
<td>63</td>
<td>123</td>
<td>186</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>144</td>
<td>284</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>55%</td>
<td>(77/140)</td>
<td></td>
</tr>
<tr>
<td>Pos. predictive value</td>
<td>79%</td>
<td>(77/98)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>85%</td>
<td>(123/144)</td>
<td></td>
</tr>
</tbody>
</table>
ADDITIONAL ERRATA

Paper II, page 130, paragraph 2, line 2: "281" should be substituted for "282".

Paper IV, page 118, calibration of....., line 10: "over" should be substituted for "lower".

Paper VI, page 9, paragraph 2, line 5: "service" should be substituted for "industry", and page 7, paragraph 2 should be substituted with the following:

"The highest prevalence of both chronic productive cough (16.8%) and chronic bronchitis (15.0%), as well as wheezing (20.4%), was found among miners. High prevalences of wheezing were also found in people working in agriculture and forestry (19.1%), transport and communication (15.9%), and in industrial production and in construction workers (13.4%). Attacks of breathlessness were most common in subjects working in agriculture and forestry (16.5%), and these also had a high prevalence of chronic productive cough (14.9%) and chronic bronchitis (14.4%). In general the prevalences of these bronchitic conditions increased with age."
ASTHMA, CHRONIC BRONCHITIS
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The Obstructive Lung Disease in Northern Sweden Study I

By
Bo Lundbäck
To Karin
and my daughters
Anna and Elin
From National Institute of Occupational Health, Medical Division, S-907 13 Umeå, Sweden, Department of Medicine, Division of Lung Medicine, University of Umeå, and Department of Lung Medicine, Central Hospital, Boden.

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Bo Lundbäck

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**Key Words:** asthma, chronic bronchitis, epidemiology, prevalence, determinants.
THIS THESIS IS BASED ON THE FOLLOWING PAPERS

I. Lundbäck B, Nyström L, Rosenhall L, Stjernberg N.
   Obstructive lung disease in northern Sweden; respiratory symptoms assessed in a
   postal survey.

II. Lundbäck B, Stjernberg N, Nyström L, Lundbäck K, Lindström M, Rosenhall L.
    An interview study to estimate prevalence of asthma and chronic bronchitis - The
    Obstructive Lung Disease in Northern Sweden Study.

III. Lundbäck B, Stjernberg N, Nyström L, Forsberg B, Lindström M, Lundbäck K,
     Jönsson E, Rosenhall L.
     Epidemiology of respiratory symptoms, lung function and their important
     determinants. Tubercle & Lung Disease (in press).

IV. Lundbäck B, Stjernberg N, Rosenhall L, Lindström M, Jönsson E, Andersson S.
    Methacholine reactivity and asthma. Report from the Northern Sweden
    Obstructive Lung Disease Study.

V. Lundbäck B, Stjernberg N, Nyström L, Rosenhall L.
   Estimating asthma prevalence: Implications of methods of measurement. Report
   from the Obstructive Lung Disease in Northern Sweden Study. Submitted.

VI. Stjernberg N, Lundbäck B, Jönsson E, Lindström M, Lundbäck K, Forsberg B,
    Sandström T.
    Chronic bronchitis, asthma and respiratory symptoms in relation to occupation
    and socio-economic group. Report from the Obstructive Lung Disease in
    Northern Sweden Study.
    Scandinavian Journal of Work Environment & Health (accepted for publication).

VII. Lundbäck B, Stjernberg N, Jonsson A-C, Lindström M, Jönsson E, Forsberg B,
     Nyström L, Rosenhall L.
     The prevalence of asthma and respiratory symptoms is still increasing. Report
     from the Obstructive Lung Disease in Northern Sweden Study. Submitted.

The above papers are referred to in the text by their roman numerals.
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INTRODUCTION
Morbidity and mortality from respiratory diseases have increased in recent decades in industrialised societies [Gregg, 1983; Sly, 1984; Burr, 1987; Woolcock, 1991; Boman, 1991], while those from cardiovascular diseases have decreased in recent years [Thom, 1989; Sverre, 1993] and the incidence of cancer has remained unchanged. Similar trends have also occurred in Sweden where relative sales of cardiovascular drugs have decreased while those of drugs for respiratory diseases have increased [Drug Sales Statistics in Sweden, 1982, ... 1991].

Several risk factors for the development of respiratory diseases are known, however, incompletely. An increase in the prevalence of type-1-allergy has been seen in children and adolescents that parallels the general increase in respiratory diseases [Åberg, 1988]. A number of theories [Björksten & Kjellman, 1990], including hereditary factors, tobacco smoke, diet and dietary salt intake have been proposed to explain the increase in respiratory diseases. Experts agree that the most important risk factors, apart from heredity, should be sought in the air we breathe.

The obstructive lung diseases make up the largest group of respiratory diseases and include asthma, chronic bronchitis and emphysema. Patients with these diseases can develop obstructive airflow limitation. The obstructive forms of chronic bronchitis and emphysema have been termed chronic obstructive pulmonary disease (COPD).

There are sound reasons for performing large-scale epidemiological studies on obstructive lung disease in northernmost Sweden, principally their high prevalence and assumed high incidence [Åberg, 1989; Åberg et al., 1989]. A high incidence provides conditions for studying potential risk factors for these diseases. The aim is prevention; not only secondary prevention, which is what traditional health care works with. One prerequisite for prevention is that modifiable risk factors for the development of the disease can be identified.

The first step toward prevention is to perform a survey of the prevalence of the disease and to identify cases in the population through cross-sectional studies, which also permit studies of basic, primarily demographic, determinants of the diseases. Cross-sectional studies also form the base for
longitudinal studies of cohort type as well as case-referent studies, which provide better prospects for the identification of risk factors for the development of disease.

This dissertation gives an account of the basic studies on the prevalence of asthma and chronic bronchitis and of some of the main determinants of these diseases. The project started at the Department of Lung Medicine at the Central Hospital in Boden, in co-operation with the Department of Lung Medicine at the University Hospital in Umeå, Sweden. It has developed into a joint venture between the Medical Division of the National Institute of Occupational Health in Umeå, as well as institutions at the University of Umeå and several departments within the Local Health Authority in Norrbotten. The project has been named the Obstructive Lung Disease in Northern Sweden Study (OLIN) and it is the author's hope that the project will continue to yield research data in the field of epidemiology of respiratory diseases.
BACKGROUND
BACKGROUND

History

Asthma has a long history. It was well-known in early civilisations; the Chinese have used Ma-Huang (containing ephedrine) as a treatment for asthma and cough for more than four thousand years. The ancient Egyptians described a condition very similar to asthma more than 3,000 years ago. However, Hippocrates is credited as being the first European to describe asthma [Fåhraeus, 1944; Underwood, 1953; Sakula, 1988].

Claudius Galenos (Galen, 130-200 AD) thought the causes of all disease were to be found in imbalances in the four "humours" yellow bile, black bile, blood and mucus, and the humoral basis of disease predominated in medical thought until the renaissance. However, less than one hundred years after Galen, Aretaeus the Cappodocian described asthma as "If from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called Asthma (Ασθμα); and the disease Orthopneoa (Ορθοπνευ) is also called Asthma, for in the paroxysms the patients also pant for breath [Adams, 1856].

The causes of asthma were unknown and in ancient times considered to be due to idiosyncrasies in the body fluids. Johann Baptista van Helmont (1578-1644) suggested in his sometimes revolutionary Ortus medicinae, published after his death, that asthma was the result of cramp in the air passages [Fåhraeus, 1949].

Willis (1621-1675) in his Pharmaceutice Rationalis called asthma "a most terrible disease" [Willis, 1679]. He divided asthma into an obstructive and a convulsive type. The obstructive type he suggested was due to "straightness of the Bronchia" (sic) which were said to be obstructed by thick "humours". The convulsive type arose "without any great obstruction or compression of the Bronchia" by affliction of all the parts involved in breathing, including the lungs, diaphragm and muscles of the chest and the cause, he suggested, lay in the muscles themselves or in the nervous system. In 1776, Scotson described asthma as an exogenous disease. In 1873, Charles Blackley, showed the association between respiratory symptoms and pollen by using a skin test. In 1906, Clemens von Pirquet (1874-1929) coined the term "allergy" to describe an altered physical reaction when an organism is further exposed to a previously encountered substance [Alanko, 1970].
Asthma came to be considered to be an allergic disease and it was paediatricians and allergologists who primarily became interested in the field of asthma epidemiology. Early reports on the prevalence of asthma and its consequences came from the USA [Frankel & Dublin, 1917]. Estimates of prevalence in both children and adults up until 1950 were all very low, less than 1%, compared with recent estimates. The descriptive epidemiology of asthma and the estimates of the prevalence were initially based on hospital admissions [Rackemann, 1931], or from physicians [Claussen, 1948; von Knorre, 1959; Irnell, 1964], or on the occurrence of typical asthma attacks [Stocks, 1949]. The first larger-scale studies that reported an asthma prevalence over 1% were published during the 1950s. The prevalence of asthma in school children in Stockholm was reported to be 1.4% [Kraepelin, 1954]. Simultaneously, it began to be realised that differences in reported prevalence could be due to methodological differences between the studies and observational bias was described [Cochrane et al., 1951; Schilling et al., 1955; Fairbairn et al., 1959].

The methodological discussions on the classification of obstructive lung diseases, diagnostic criteria and methods of estimating prevalence that began in the 1950s reflected the way in which results began to be reported. An example is the reported prevalence of a history of asthma of 3.3% in students at the University of Wales, of whom 1.9% had active asthma [Grant, 1957]. An exceptionally high asthma prevalence for the time (4.1%), was reported from Michigan, USA [Broder et al., 1962]. However, in this study, asthma was defined as non-specific lung disease associated with wheezing.

This presentation of the background to the epidemiology of obstructive lung diseases will mainly focus on the discussion of definitions, diagnostic criteria and methodology for the estimation of the prevalence of asthma and chronic bronchitis. To-day’s epidemiological methodology for estimating the prevalences of obstructive lung diseases started with chronic bronchitis that was believed to be epidemic in the 1950s, particularly in Great Britain [Fletcher et al., 1959; Fletcher et al., 1976].
The emergence of chronic bronchitis

Chronic bronchitis is a "new" disease compared to asthma. Badham, from Great Britain, is said to be the first to have used the term "bronchitis" [Badham, 1808]. Little interest was shown in "bronchitis" or "chronic bronchitis" during the 19th and early part of the 20th century despite many reports on these diseases, mainly from Great Britain. The first larger symposium on chronic bronchitis was held in 1951 by the Association of Physicians of Great Britain and Ireland. There was thus awareness of the problem when the fog catastrophe in London during a single week in December 1952 caused an additional 4,000 deaths in people known to be suffering from chronic respiratory or cardiac diseases. The following year, the British Medical Research Council (BMRC) made chronic bronchitis a priority and set up a committee to guide research into the disease. Screening for chronic bronchitis lead to the design of questionnaires [Fairbaim et al., 1959; Higgins et al., 1959; Fletcher et al., 1959]. Several British investigators, including Fletcher, realised the importance of a uniform classification and methods to enable the comparison of the results of different prevalence studies and in order to be able to study the natural history of the diseases. The definitions and the diagnostic criteria for obstructive lung diseases and the structured questionnaires for epidemiological studies that were later put forward can thus, at least in part, be said to be due to the catastrophic fog in December 1952 in London.

The newly-awakened interest in chronic bronchitis probably initially caused a considerable degree of confusion in the diagnosis of obstructive lung diseases [Fletcher et al., 1976]. In 1951, the British Postgraduate Medical School stated that any subject with severe persistent airflow obstruction should be assumed to suffer from emphysema, but the same subjects in clinical practice were referred to as having "advanced chronic bronchitis". In the USA, according to Fletcher, these patients were classified as having emphysema without reference to chronic bronchitis. Epidemiological studies, as well as clinical observations, often showed a long disease history with chronic productive cough preceding impairment of lung function in subjects with chronic bronchitis [Oswald et al., 1953; Reid & Fairbairn, 1958]. This together with pathological changes in the airways and the lungs lead to the "British hypothesis" that chronic bronchitis is a single disease entity in which impairment of lung function may develop at different speeds depending on host defense factors as well as on the degree of exposure to tobacco smoke, occupational and general air pollution, and
bronchial infections [Fletcher et al., 1976]. Asthma was considered to be a completely different disease.

The 'British' and 'Dutch' hypotheses and the CIBA Guest Symposium

The "British hypothesis" was an important starting point for the classification of obstructive lung diseases that the British investigators agreed upon at the 1959 CIBA Guest Symposium [CIBA Guest Symposium, 1959]. The symposium's consensus had considerable influence on both clinical pneumonology and research for many years. In the classification different criteria were used for different respiratory diseases as suggested by Scadding [Scadding, 1959].

Clinical criteria were suggested for chronic bronchitis; the presence of chronic expectoration and the term "chronic" was accorded temporal limits. Chronic bronchitis was defined as:

Cough and sputum production on most days for at least three months in the year during at least two consecutive years, if expectoration was not attributed to some local or specific lung disease.

Asthma was defined functionally or physiologically as intermittent or reversible airways obstruction. Emphysema was defined on an anatomical-physiological basis; air space enlargement peripherally in the lungs beyond the terminal bronchioles. The term chronic non-specific lung disease (CNSLD) was suggested for the whole group of obstructive lung- and airway diseases. The term had only limited use during the 1960s and 1970s because of the fact that it was not recommended for clinical use. The even more rarely used term "generalized obstructive lung disease" was recommended for irreversible airway obstruction.

The results of the CIBA Guest Symposium were accepted internationally in 1961 by a World Health Organisation (WHO) Expert Committee, which made some clarifications on chronic bronchitis and emphysema [WHO, 1961]. WHO agreed to the earlier definition on diagnostic criteria for chronic bronchitis:

Chronic bronchitis is a chronic or recurrent increase above the normal in the volume of bronchial mucous secretion, sufficient to cause expectoration when this is not due to localized broncho-pulmonary disease. The words chronic or recurrent may be further defined as present on most days during at least three months in each of two successive years.
Partly in contrast to the "British hypothesis" on the pathogenesis of obstructive airway diseases the "Dutch hypothesis" was proposed by Orie et al. [1961] and Van der Lende [1969]. They suggested that special host characteristics, such as atopy and bronchial reactivity, determine the subject's response to different exposures. Cigarette smoke, environmental exposures, etc., could provoke wheezing and dyspnoea in one group of subjects, while another may develop cough and sputum production, and others might remain free from symptoms. Some may develop reversible and variable airways obstruction, while others develop a progressive and irreversible obstruction. Combinations of the pathological conditions are common. The hypothesis thus proposes that asthma is closely related to chronic bronchitis and emphysema, and that all three diseases are, in fact, sub-groups of a single disease or syndrome.

Based mainly on the "British hypothesis", the first widely-accepted questionnaire for epidemiological studies of chronic bronchitis and obstructive lung diseases, the BMRC questionnaire, was developed in 1960 [Medical Research Council's Committee, 1960]. The questions focused on different degrees of dyspnoea, on cough, sputum production and wheezing. There were no questions on asthma. The questionnaire was of considerable importance for later epidemiological research into obstructive lung diseases.

**The American Thoracic Society definition and its influence**

Attempts to devise precise definitions for the airway diseases continued. The American Thoracic Society (ATS) agreed in 1962 to a definition of asthma that has been widely used [American Thoracic Society Committee, 1962]:

> Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.

and further:

> The term "asthma" is not appropriate for the bronchial narrowing which results solely from widespread bronchial infection; from destructive disease of the lung such as pulmonary emphysema, or from cardiovascular disorders. Asthma may occur in subjects with other broncho-pulmonary or cardiovascular diseases, but in these instances the airway obstruction is not causally related to these diseases.
The ATS suggested clarification of the definition of chronic bronchitis. In practice uncertainties remained both in clinical and epidemiological examinations, particularly with regard to excluding other diseases that may cause chronic productive cough. Furthermore, the term "excessive" leaves room for subjective valuations. The ATS definition of chronic bronchitis:

Chronic bronchitis is a clinical disorder characterized by excessive mucous secretion in the bronchial tree. It is manifested by chronic or recurrent productive cough. Arbitrarily, these manifestations should be present on most days for a minimum of three months in the year and for not less than two successive years.

and further:

The diagnosis can be made only by excluding other broncho-pulmonary or cardiac disorders as the sole cause for the symptoms.

The discussions on definitions and diagnostic criteria for chronic bronchitis also continued in Europe. Fletcher, in particular, suggested new ideas that he tried and sometimes discarded. Changes were discussed at congresses. At the conference Bronchitis II in Groningen in 1964, Fletcher suggested the following sub-division that had been supported by British opinion and that still forms the basis for the classification of chronic bronchitis in the International Classification of Diseases [Fletcher et al, 1976]:

1. Simple chronic bronchitis:
   Chronic or recurrent increase in the volume of mucoid bronchial secretion, sufficient to cause expectoration.

2a. Chronic mucopurulent bronchitis:
   Chronic bronchitis in which the sputum is intermittently purulent.

2b. Chronic purulent bronchitis:
   Chronic bronchitis in which the sputum is persistently purulent.

3. Chronic obstructive bronchitis:
   Chronic bronchitis in which generalized airways obstruction is persistent.

During 1965, the BMRC formulated a definition of chronic bronchitis that brought the definition from the CIBA Guest Symposium nearer the ATS definition, and, further, divided between a "simple" and an "obstructive" form of chronic bronchitis [Medical Research Council, 1965]. By 1964, the term chronic obstructive pulmonary disease (COPD) had been proposed in the USA [Mitchell & Filley, 1964]. In the period that followed, measurement of the amount of
expectorated sputum was common. Both dynamic spirometry and chest x-ray examinations were used to differentiate the obstructive form of chronic bronchitis, or emphysema, as it was called in some studies. The early, very large studies performed by Huhti in Finland are one example [Huhti, 1965]. These studies contributed new knowledge, not least by documenting the prevalence of chronic bronchitis.

The Fletcher hypothesis

In the 1970s, Fletcher, on the basis of his own extensive epidemiological studies, began to question this view of chronic bronchitis and chronic obstructive pulmonary disease. This debate was supported by physiological and anatomical-pathological data. On clinical grounds, Fletcher suggested there to be two completely different diseases which could both cause bronchitic symptoms. One progressed without affecting lung function and without causing emphysema, while the other form was a progressive disease that caused a varying degree of obstructivity and peripheral tissue damage [Fletcher et al., 1976].

Fletcher and co-workers found that about 25% of smokers with definite impairment of lung function were relatively free from bronchitic symptoms and denied chronic productive cough, while 20% of smokers with chronic bronchitis had a completely normal forced expiratory volume (FEV₁). The majority of those with impairment of lung function, however, had a history that suggested past or present chronic bronchitis. In a longitudinal study, symptomatic smokers were reported to have a more pronounced decline in FEV₁ than asymptomatic smokers and non-smokers [Fletcher & Peto, 1977]. However, when controlling for smoking and the initial level of FEV₁, sputum production was not found to be a significant predictor of a more rapid decline in FEV₁. Other investigators also reported epidemiological data during the 1980s which argued against the previously widely accepted "British hypothesis". Results from a 12 year study of male workers in Paris [Kaufmann et al., 1979] and from a 20 year follow-up study [Peto et al., 1983] supported the results from Fletcher's studies. An association between occupational exposure, with the exception of smoking, and impairment of lung function, has been reported, without an association between chronic sputum production and impairment of lung function [Becklake, 1985]. These large-scale studies indicating a dissociation between bronchitic symptoms and progressive airways obstruction were mainly occupational epidemiological
studies, and the selection of the study populations may have influenced the outcomes.

The definition of the bronchitic syndrome is still being debated and no consensus on newer definitions has been reached despite agreement on Fletcher’s suggestions. The various viewpoints are reflected in the plethora of terms that are in current use. The terms chronic obstructive lung, pulmonary, airway, respiratory disease (COLD, COPD, COAD, CORD) are used more or less synonymously with chronic bronchitis with emphysema; with COPD being used most commonly at present. In addition, the conditions chronic airway obstruction (CAO) and chronic airflow limitation (CAL) are sometimes used synonymously with COPD, particularly in current Swedish discussions on terminology in pulmonary medicine. Internationally, the term airway obstructive disease (AOD) has been introduced although it is used imprecisely instead of obstructive airway disease (OAD) as a cover term for the whole group of diseases formerly classified by the CIBA Guest Symposium as CNSLD, as well as having more precise definitions as in the Tucson Epidemiological Studies and as defined by Ferris and Speizer [Lebowitz, 1989]. The Dutch hypothesis has been revisited in 1991 in review articles in the European Respiratory Journal. The Dutch still argue for their theory [Sluiter et al., 1991], while Vermeire and Pride [1991] discuss the CNSLD as an umbrella term.

This lack of agreement on terminology often linked with differences in the application of the same definitions may cause even wider variations in prevalence data on chronic bronchitis than on asthma. When compared to Huhti’s data, the lower prevalence figures for chronic bronchitis reported by Kiviloog et al. [1974] and Stjernberg et al. [1985], even when smoking habits are taken into account may be explained by the use of the ATS criteria, that add the term "excessive amounts". Furthermore, obstruction is still a diffuse term, and there is still no general agreement on the physiological criteria upon which it should be defined. Different limitations are used in different studies.

Approximately one third of all patients with chronic bronchitis are said to develop the obstructive form [Huhti, 1967; Kiviloog et al., 1974; Stjernberg, 1985]. This estimation may be exaggerated, however, as the figures are often based on cross-sectional studies.
Defining asthma in epidemiology

The definition and classification of asthma has also been frequently discussed in Scandinavia. Birath, among others, suggested that as soon as wheezing or attacks of dyspnoea appear, the subject is usually considered to have asthma [Birath, 1964]. The view that asthma only could be defined by its symptoms had supporters in Scandinavia [Arnoldsson, 1969]. One method of assessing the prevalence of asthma was to only ask questions on those symptoms that were considered to be principal or typical of the disease [Julin & Wilhelmsen, 1967]. Additional questions were added to the BMRC questionnaire by several investigators in order to improve its usefulness in epidemiological studies of asthma [Alanko, 1970]. Simultaneously, in 1962, French, German, Italian and Dutch translations of the BMRC questionnaire were made, the European Community for Coal and Steel (ECSC) questionnaire, which included additional questions regarding asthma [ECSC, 1967]. The BMRC questionnaire was revised and expanded in 1966 and questions about attacks of shortness of breath with wheezing were added, including the question "Have you ever had bronchial asthma?". The ECSC questionnaire was also revised a year after the revision of the BMRC questionnaire [Minette, 1989].

Even if symptoms are typical for asthma, they are, however, not specific for the disease. In accordance with the CIBA Guest Symposium consensus, which stated that the diagnosis of asthma should be physiologically defined, epidemiological studies of asthma soon began to use physiological methods. The CIBA Guest Symposium consensus on diagnostic classification of asthma was followed in practice, particularly in Scandinavia [Alanko, 1970; Kiviloog et al., 1974].

In 1968, the ATS published the BMRC questionnaire in the USA, with instructions for its use [American Thoracic Society, 1969]. The questionnaire was modified by the National Heart and Lung Institute, the NHLI questionnaire, and questions regarding asthma was included [Dept of Health Education & Welfare, 1971]. The NHLI questionnaire was used initially in the epidemiological studies of obstructive lung diseases which started in Tucson, Arizona, in 1970. Later, the investigators involved in the Tucson studies developed a new self-administered questionnaire, which was validated against the BMRC and the NHLI questionnaires [Lebowitz & Burrows, 1976]. The ATS and the National Health Institute's Division of Lung Diseases simultaneously worked on the standardisation of epidemiological methods and developed a new questionnaire that has become generally known as the ATS questionnaire [Ferris, 1978]. The
major difference compared with previous questionnaires was that this contained more numerous and more detailed questions concerning asthma and asthma-associated conditions.

Yet another questionnaire, the International Union Against Tuberculosis and Lung Diseases (IUATLD) Bronchial Symptoms Questionnaire, appeared in a longer (1984) and a shorter (1986) version [Burney et al., 1989a,b]. This questionnaire was designed from both the BRMC and the ATS questionnaires, as well as from a questionnaire that had been used in British children, and other local questionnaires. The aim was to produce a questionnaire with which asthma could be identified; if possible, solely on the basis of symptoms. The symptoms were validated against bronchial hyperresponsiveness demonstrated by provocation tests. A simplified version of the IUATLD questionnaire is currently being used in the European Commission Respiratory Health Study.

The discussion on definitions of asthma continued and resulted in minor changes. The ATS emphasized the importance of increased responsiveness [ACCP & ATS, 1975], while WHO declined to mention hyperresponsiveness, but stressed the importance of recurrent bronchospasm as the main characteristic of asthma [WHO, 1975]. The BMRC and the ECSC questionnaires were revised in 1986 and 1987, respectively. The BRMC questionnaire was not radically altered [MRC, 1986] but the ECSC questionnaire was expanded, particularly in the asthma section [Minette, 1989].

The era of bronchial challenge testing in the detection of asthma

While there were considerable discussions on questions of classification and methodology concerning chronic bronchitis during the 1960s and the 1970s, a reasonably unified theoretical agreement was reached in Europe during the 1970s on methodology for epidemiological studies of asthma, despite the continued debate on diagnostic criteria. The methods reflected an increasing agreement that a considerable degree of current airway variability had to be demonstrated even in epidemiological study situations. Provocation tests became important [Samet, 1987]. In practical terms a diagnosis of asthma was considered nearly equivalent to bronchial hyperresponsiveness [Cockcroft et al., 1977; Hargreave et al., 1981; Hopp et al., 1984; Hargreave et al., 1986; Ädelroth et al., 1986]. Asthmatic patients were also widely believed to have little intra-individual variability in bronchial hyperresponsiveness, and some support for this had been reported
[Juniper et al., 1981; Löwhagen & Lindholm, 1983; Chinn et al., 1987]. The discrepancy between self-reported or physician-diagnosed asthma or symptoms associated with asthma on one hand and bronchial hyperresponsiveness on the other [Britton & Tattersfield, 1986; Enarson et al., 1987; Burney et al., 1987a; Rijcken et al., 1987; Dales et al, 1987] was interpreted as mainly reflecting that physician-diagnosed and self-reported diseases and symptoms could not be used alone in the estimation of asthma prevalence [Mortagy et al., 1986; Samet, 1987; Pride, 1989].

This view was mainly practised by Woolcock [Woolcock, 1982; Woolcock, 1983]. She developed a practical and reproducible provocation test for the demonstration of bronchial hyperresponsiveness. She required only symptoms of current or past breathlessness together with a positive provocation test or a positive reversibility test for the epidemiological diagnosis of asthma [Woolcock, 1983]. However, positive provocation tests were not always found to be present in asthma [Stanescu & Frans, 1982; Hargreave et al., 1984], or specific for asthma [Ramsdale et al., 1984] and the severity of bronchial hyperresponsiveness was seen to change over time [Woolcock, 1987; Josephs et al., 1989].

Hyperreactivity has been used as a means of validation, to assess the relevance of reported symptoms, symptom complexes and asthma [Burney et al., 1989a,b; Abramson et al., 1991]. However, hyperreactivity is no longer equated with asthma [Samet, 1987; Enarson et al., 1987; Pride, 1989], and is known to occur in chronic bronchitis [Simonsson, 1965; Ramsdale et al., 1984; Pride, 1988] and to be dependent on broncho-obstruction [Ramsdale et al., 1984; Pride, 1988; Bakke et al., 1991a]. A new suggestion has been made, particularly by Burney, that conditions rather than diseases should be used when comparing results of epidemiological surveys [Burney & Chinn, 1987]. The European Commissions Respiratory Health Study is one example of this.

American studies have been wary of making axiomatic assumptions as starting points for study design. Several epidemiological and other studies have assessed both the association between bronchial hyperresponsiveness and asthma, and between hyperreactivity and respiratory symptoms [Weiss et al., 1984; Enarson et al., 1987; Dales et al., 1987]. Studies in the USA have laid more credence on self-reported diseases and symptoms [Broder et al., 1974; Bronniman & Burrows, 1986; Dodge et al., 1986]. This view, complemented by interviews, has been
applied in the Norwegian studies of Gulsvik [1979] and Bakke [1992], and by
the group including Paoletti and Viegi in Italy [Paoletti et al., 1989a].

In the USA, the adage "for epidemiological studies [of asthma], questionnaires
remain the most readily applied method for identifying persons with asthma"
[Samet, 1987] remains widely believed. This is partly in contradiction to the
suggestion of Woolcock, while Pride in an editorial in the European Respiratory
Journal summarized a redrafted point of view: "It has become obvious that
asthma is not synonymous with bronchial hyperresponsiveness or any other
simple test" [Pride, 1989]. While Woolcock [1987] still maintained that it was
impossible to estimate the prevalence of asthma in a population without tests of
bronchial hyperresponsiveness, by 1992 she had modified her position [personal
communication].

Chronic bronchitis dominated the debate on definitions and diagnostic criteria
during the 1950s, 1960s and 1970s, but has been overshadowed by asthma
during the 1980s. There is considerable agreement on the clinical features of
asthma, but the diagnosis remains arbitrary. Symptoms are non-specific and the
results are often based on different physiological tools, which explain the lack
of an agreed epidemiological definition of asthma. The apparently inconsistency
between Samet and Woolcock is therefore not surprising.

**Criteria application in Scandinavia**

Scandinavian epidemiological studies including those of Huhti [1965],
based on the CIBA Guest Symposium view. Understanding for the
"Dutch hypothesis" can be discerned in the studies of Kiviloog, despite the fact
that he keeps to the then currently accepted definitions [Stjernberg et al., 1985].
He used the ATS definitions and Stjernberg et al. later adopted those used by
Kiviloog et al. in order to make comparisons of the results. There are, however,
even more obvious leanings towards the ATS stand-points in Stjernberg's
studies, and this may be reflected in the results. Other important Scandinavian
prevalence studies include Haahtela [1980] and Terho et al. [1987], in Finland,

Early on, Gulsvik in Norway, used a modern approach using exact definitions
and methodological descriptions that are quoted with extreme clarity [Gulsvik,
1979a,b,c]. The Norwegian school uses the basic Gulsvik model, focusing
respiratory ill-health to clearly pathological conditions that are defined more narrowly than in other studies. The Norwegian studies define current asthma as active asthma within the six months preceding the study [Gulsvik, 1979a; Bakke, 1992] instead of the 12 month time limit usually applied. Similarly, the term obstructive airway disease is preferred to chronic bronchitis. Focusing on these clearly pathological conditions is combined with early reporting of individual respiratory symptoms. Thus speculation can be avoided and results can be based on clearly defined terms. The condition of bronchial hyperresponsiveness, for example, is clearly differentiated from the disease, or condition, of asthma.

When the Obstructive Lung Disease in Northern Sweden (OLIN) study started the operational epidemiological situation was as follows. There had been a trend towards giving increasing importance to pulmonary function tests in the diagnosis and assessment of the prognosis of obstructive airway diseases during the years preceding the study. There was also a tendency to reduce both the prognostic and diagnostic importance of respiratory symptoms. Asthma was separated from chronic bronchitis and from chronic obstructive pulmonary disease both in regard to epidemiological methods of measurement and as a cause of persistent airflow obstruction. All these contributed to the design and methods of our study. There were numerous diverging opinions on how to estimate the prevalence of asthma in epidemiological studies. Clinicians in Sweden regarded the importance of the demonstration of bronchial hyperresponsiveness, or, alternatively, the demonstration of considerable reversibility after a broncho-dilatation test, as almost obligate in diagnosing asthma even in an operational epidemiological examination situation. There was agreement about the clinical features of asthma, but differing opinions on how it should be diagnosed in epidemiological studies. Classifications and definitions of bronchitis and chronic obstructive conditions were still under debate.

**Determinants of obstructive airways disease**

Various factors in the indoor environment as well as urban-living, in addition to a family history of asthma and an atopic constitution in children in Sweden, have been found to be associated with type-1-allergy, and, according to recent studies, even asthma [Åberg, 1991]. When it comes to asthma in Swedish adults, no clearly proven determinants apart from particular working environments have been found. Various environmental effects that may contribute to the excess susceptibility to asthma, including a possible urban effect, an island effect, or climatic effects have been discussed.
Other important causes for the development of asthma in temperate and sub-tropical areas are type-1-allergy against moulds and mites [Sears, 1991]. In Sweden, the indoor air climate as a cause of the increase in asthma and type-1-allergy is a main hypothesis [Svenska Statens Offentliga Utredningar, 1989]. A recent study in northern Sweden, suggests that low concentrations of air pollutants affect sensitized airways [Forsberg et al., 1993].

The association of smoking with chronic bronchitis is well known [Burrows et al., 1977; Bossé et al., 1980]. Various occupational exposures make up the other important risk factor in the northerly and sparsely-populated area in which the OLIN studies were performed. Urban living has not been found to be associated with excessive ill health from chronic bronchitis in Sweden, which has been reported from cities in other countries [Holland & Reid, 1965; Wichmann et al., 1989; Detels et al., 1991; Viegi et al., 1991b; Tzonou et al., 1992]. Environmental risk factors for chronic bronchitis will not be extensively discussed here. Recent Scandinavian dissertations and research papers have presented original research data and excellent reviews on this topic: including obstructive airways diseases and their relation to sulfur dioxide [Stjernberg, 1985], mining [Jörgensen et al., 1970], farming [Terho et al., 1987; Iversen et al., 1988], various occupational airborne exposures [Bakke, 1992], paper dust [Torén, 1992], aluminium potroom work [Kongerud et al., 1990].

Environmental factors and the development of asthma

Occupational asthma has been defined as "a newly developed form of hyperreactivity secondary to some occupational exposure" [Chan Yeung & Lam, 1986] and as "a reversible airways obstruction caused by the inhalation of some substance present in the working environment" [Blanc, 1987]. According to these definitions, up to 15% of all asthma in the USA has been estimated to be occupational asthma [Chan Yeung & Lam, 1986; Blanc, 1987]. Over one hundred substances found in the working environment are considered to be able to cause asthma in previously healthy individuals [Sheppard, 1982]. In Sweden, occupational asthma has been described in particular working environments [Stjernberg, 1985; Torén, 1992]. Obstructive lung diseases and their relations to occupation have often been studied in cross-sectional studies. Cross-sectional studies, however, are not suitable for the study of the development of asthma because of the "healthy worker effect". It is also difficult, in case-referent studies with prevalent cases, to determine the exact
point in time at which a disease develops and this also complicates the assessment of exposure and confounders.

There is little available data on building-related asthma despite the attention paid to "sick houses" [Welch, 1991]. Formaldehyde in the working environment has been shown to cause asthma symptoms but there appear to be no studies that confirm that formaldehyde or other substances give rise to asthma [Marbury & Krieger, 1991]. The risk for mites and moulds increases in buildings with damp problems and the evaporation of chemicals from buildings and decorating materials may also increase. Mite allergy is common in people with an atopic constitution [Whyte & Flenley, 1986; Croner & Kjellman, 1992; Wickman, 1993] and has been described in northern Sweden in 20% of adults with asthma [Lundbäck et al., 1991].

Problems of dampness in buildings are associated with an increased occurrence of self-reported diagnosis of asthma and respiratory symptoms in adults [Dales et al., 1991], and similar associations have been seen in children. In Sweden, allergic asthma is more often caused by pets such as cats, dogs and rodents than by mites and moulds. Horses and cage birds are also common causes of allergic asthma. Tobacco smoke has been shown to increase the risk for the development of allergy in children [Young et al., 1991; Hood et al., 1992], but passive smoking has been considered more of a problem for asthmatics more as a risk factor for the development of asthma in adults [Samet et al., 1991]. Substances in car exhaust fumes have been shown to facilitate sensitization in animal experiments and the prevalence of allergy has been reported to be greater in some densely-populated areas than in less exposed areas [Bylin, 1990]. Swedish studies that consider the outer environment as a risk factor may be based on vague data on quantification of levels of exposure and are marred by a substantial risk that confounders are not adequately controlled [Lundbäck et al., 1992]. However, greater prevalence of type-1-allergy and asthma symptoms has been shown in children in Swedish urban or polluted compared with rural areas [Andrae et al., 1988; Bråbäck & Kälvesten, 1991].

Pollution from gas stoves, open fires and wood ovens have been related to an increased occurrence of respiratory symptoms in children [Honicky & Osborne, 1991] as well as in adults in some studies [Viegi et al., 1991a]. Asthma caused by this type of exposure does not appear to have been reported.
Knowledge about the causes of sensitization and the development of asthma is still fragmentary when it comes to exposures in working places, in homes and in the outer environment. It is improbable that there is any major environmental cause that contributes to the development of asthma in the vast majority of cases. However, there may well be a number of factors that together contribute to the development of asthma. From a point of view of prevention, these contributing factors and risk environments must be identified as there is a large number of people at risk and the problem is growing.
AIMS
AIMS

Overall aims

The Obstructive Lung Disease in Northern Sweden study's overall aim is:

☐ Prevention of obstructive airways disease.

In order to design a programme of measures with the ultimate aim of primary prevention and improved secondary prevention of obstructive lung diseases it is necessary to study:

☐ The incidence and prevalence of asthma and chronic bronchitis including chronic obstructive pulmonary disease (COPD).

☐ The effects of occupational and environmental as well as climatic factors on these diseases, in particular on their onset.

☐ The progress and remission of the diseases and on the effects of intervention through prospective longitudinal studies.

The first part of the project was a cross-sectional study which aimed to estimate the prevalence of obstructive lung diseases and to collect demographic data (OLIN 1).

Second, prospective longitudinal studies of the progress and remission of obstructive lung diseases started in 1988. This part (OLIN 2) also includes studies on type-1-allergy, lung function, the relationship between COPD and the obstructive sleep apnoea syndrome, compliance aspects as well as qualified nursing. In 1989 to 1991 a case-referent study on indoor climate, occupational and other environmental factors' influence on the onset of asthma was performed (OLIN 3). In 1992, the study base was expanded to 20,489 adults in Norrbotten to increase the power of the study in calculating risk ratios (OLIN 4). OLIN 4 also aims to examine possible changes in the prevalences of obstructive lung diseases as well as to assess their incidences.
This dissertation is based on the main reports from OLIN 1 and on the postal questionnaire data from the 1992 survey (OLIN 4), which are included in order to permit discussion of the external validity of the first part of the project and to assess possible changes in the prevalences of obstructive lung disease between 1986 and 1992.

Specific aims

The specific aims for this dissertation were:

☐ To assess the prevalences of asthma, chronic bronchitis and respiratory symptoms in adults in the province of Norrbotten, in northern Sweden.

☐ To compare the influence of various diagnostic criteria on the estimates of prevalence.

☐ To identify subjects with obstructive lung diseases, in particular asthma, for case-referent studies and prospective longitudinal studies.

☐ To examine whether the trend towards increases in prevalence of asthma and respiratory symptoms persists.

☐ Study factors that may influence the development of obstructive lung diseases:
  ☐ Age
  ☐ Gender
  ☐ Smoking habit
  ☐ Occupation and socio-economic group
  ☐ Population density and area of domicile, which may be indirect measures of air pollution and environmental exposure.

☐ To contribute to the discussion on the probable existence of a north-south gradient and a possible effect of climate on the prevalence of asthma.
MATERIAL & METHODS
MATERIAL & METHODS

Study area

Norrbotten is the northernmost province of Sweden. It is sub-arctically situated at latitude 65.40-69.40°N and is bisected by the Arctic Circle. The province makes up 24% (105,886 km²) of Sweden’s area. In December 1985 it had 262,301 inhabitants, less than 3% of Sweden’s population. The majority live in the coastal region, where most of the towns and industries are located. The average yearly temperature is close to 0°C, with cold, dry winters that last for 6 months. January and February are the coldest months with an average daily temperature of -12°C.

In the first part of the OLIN project, reported in Papers I-VI, eight geographical areas of the province were selected, including three coastal and five inland areas. The sample included both urban and rural districts, with varying population densities and degrees of industrialization. The localisations and the characteristics of these areas are described in Paper I, Figure 1 and Table 1.

In the second part of the project the study base was chosen from the whole province, from which a random sample was selected in addition to the stratified samples from the same study areas as in the first part of the project.

Study population

The inhabitants of Norrbotten are mainly from three ethnic groups. The majority are Swedish. About 40,000 people living mostly in the east of the province near Finland have Finnish as their mother language, and about 10,000 Laplanders live mostly in the interior of the province with the majority in the towns of Kiruna, Gällivare/Malmberget and Jokkmokk.

The industrial setting in the area comprises mainly heavy industry for the exploitation of the province’s natural assets, and include mining, iron and steel production, forestry, and paper- and paper-pulp industries. Building and maintenance of hydro-electric power stations played a major role during the 1950s to 1980s. Farming has decreased in importance. More recently, trade, commerce, education, administration and tourism have increased in importance.
In December 1985, the population of the eight study areas of the first part of the OLIN project was 87,316, or approximately one-third of Norrbotten's population. Three age cohorts were selected for the study; all the 6,610 individuals born in 1919-1920, 1934-1935 and 1949-1950 living in the eight study areas. The distribution of the study population by year of birth, gender and geographic area is shown in Paper I, Table 2. Of the sample, 75% were living in urban areas including small towns, 10% in densely-populated areas, and 15% in rural areas and villages with less than 500 inhabitants. Fifty-three percent were living in the coastal area and the remainder in the interior of the province.

In the second part of the project the study population was selected from the whole province. The selection procedure is described in detail in Paper VII.

Study design

The first part of the OLIN study consisted of three phases; a postal questionnaire study, a structured interview study with lung function tests, and validation examinations. The study design is summarised in Figure 1.

The first phase was a postal questionnaire study [Paper I]. The 6,610 people received a postal questionnaire in the winter of 1986 enquiring into respiratory symptoms and diseases, smoking habits and occupation. It was satisfactorily completed by 5,698 subjects (86%). A further 4% returned the questionnaire incomplete or with a notice that they did not want to participate. Those who did not respond within 6-8 weeks were sent a reminder and a second questionnaire in both Finnish and Swedish. Similar proportions of men and women returned the questionnaires and there was little difference in response rates between the three age groups and the eight geographical areas.

Of the questionnaire responders, 1,340 (23%) reported symptoms suggestive of asthma or chronic bronchitis. These were invited to the second phase, which consisted of a structured interview and lung function tests [Papers II and III] and 1243 (93%) took part. The interview followed an expanded Swedish questionnaire concerning respiratory symptoms and diseases, of co-existing heart disease, medication, and data on determinants. We did not select a random sample as one of the aims was to collect large representative cohorts with asthma, chronic bronchitis and COPD for prospective longitudinal studies. In order to ensure that the selection procedure did not generate any bias, a
reference group was randomly selected from strata among the questionnaire responders who had not reported symptoms suggestive of asthma or chronic bronchitis.

Figure 1. The study design of OLIN 1.
Out of the 315 invited subjects 263 (84%) participated. The selection procedure is reported in detail in Paper II; Table 1 and in the text, and in Paper III; Figure 1 and in the text.

The examinations were performed by two specially trained nurses, Mai Lindström and Karin Lundbäck, and took place at the participating subjects' local Health Care Centres or at the Departments of Lung Medicine at the hospitals in Boden and Gällivare.

The third phase consisted of a validity study [Papers IV and V], which was not planned at the beginning of the study, but was decided upon because of the high prevalence of asthma according to the estimates received from both the postal questionnaire study and from the structured interview study. The diagnosis of asthma made in the second phase of the study was considered definite when there was a history suggestive of asthma and the subjects had a positive broncho-dilatation test at the study examination, or the diagnosis could be confirmed from case notes. A diagnosis of chronic bronchitis was considered definitive in subjects in whom no other cause for chronic productive cough could be found. Of the 565 subjects invited to the clinical validation examinations, 521 (92%) attended. The 151 subjects in whom a diagnosis had not been made in the second phase of the study were also invited to the examinations. A further 5 subjects from the control group were examined at the same time.

As a part of the validation examinations, 320 subjects were invited to methacholine testing, of whom 284 (89%) took part [Paper IV], and of these three subjects were from the non-responders to the postal questionnaire study.

A study of the 912 subjects who failed to participate in the postal questionnaire study was also made. Attempts were made by telephone to reach all the subjects who had not returned a completed questionnaire and ask the questions contained in it. Data were thus collected from 496 subjects (54% out of the 912). Of the 97 subjects who had stated respiratory symptoms in the postal questionnaire but who failed to attend the second phase of the study, data were received from 95, although they were incomplete in 34 subjects. The examinations of the non-participants are described in Paper V.
Postal questionnaire data from the second part of the OLIN project are reported in Paper VII in order to give an impression of the trend of the prevalences of respiratory symptoms and diseases and to examine the representativeness of the results of the first part of the OLIN study. These comparisons are as the same methods and questions as in the postal questionnaire phase of the first part of the OLIN study have now also been used in a random sample of subjects aged 20 - 69 years from the whole province.

Methods
Postal questionnaire

The questionnaire used was developed from a revised version [Stjernberg, 1985] of a BMRC questionnaire [MRC, 1960] that had previously been used in northern Sweden. The questionnaire developed for the study was influenced by the ATS questionnaire [Ferris, 1978] and the questionnaires used in the Tucson studies [Lebowitz & Burrows, 1976]. Questions about the symptoms: attacks of breathlessness, wheezing, long-standing cough, sputum production, diagnoses and use of anti-asthmatic drugs required either "yes " or "no/don't know" answers. The question on wheezing expressed recurrent wheezing and was formulated "do you have..." or "do you usually have" (in Swedish; "brukar du ha ...."), and not with the formulation "have you ever during the last 12 months had....". The questions regarding bronchitic symptoms also included repetitive moments and temporal limitations.

In addition, the questionnaire included questions on the occurrence of wheezing, breathlessness, or severe cough occurring in special circumstances or after specific exposures, which included dust or tobacco smoke, car-exhaust fumes or air pollution, and strong scents and perfumes. Subjects were also asked whether they had been diagnosed as having asthma, chronic bronchitis or emphysema, by a physician and whether they considered themselves to have any of these diseases.

Smoking habits were assessed; subjects who had never smoked were classed as non-smokers, those who currently smoked or had stopped smoking within the 12 months prior to the survey were classified as smokers. Subjects who had stopped smoking more than 12 months previously were classified as ex-smokers. When appropriate, the subjects were asked how much they smoked and how old they were when they started to smoke.
In the questionnaire, questions were also asked about current occupation and previous occupations, in case the subjects had worked in the latter for more than 5 years. The occupations were classified using the Nordic Classification System on Occupations, NYK [National Board of Occupational Safety & Health, 1983], and the Socio-economic classification system, SEI, used by Statistics Sweden [Statistics Sweden, 1982]. Questions were also asked whether or not, and for how many years, the subjects had been working at the main industries in the province, which included mining, steel industry, paper- or paper-pulp industries, hydro-electric power plant construction or maintenance, or in forestry and farming. The characteristics of the study population by age and gender according occupation, socio-economic group and employment at the main industries are shown in Paper VI, Table 1.

Structured interview questionnaire

The questionnaire used was developed from an expanded Swedish questionnaire [Stjernberg, 1985] mainly based on the BMRC questionnaire [MRC, 1960]. It contained 50 questions which could generally be answered by "yes" or "no/don’t know". The subjects were interviewed about:

☐ Cough, sputum production and chronic productive cough including temporal aspects as formulated by the CIBA Guest Symposium [1959].

☐ Attacks of breathlessness, wheezing alone and accompanied by breathlessness, and wheezing on most days of the week.

☐ Factors that provoked attacks of breathlessness, wheezing or severe cough; including allergens, a number of indoor and outdoor irritants, cold air, exercise, infections and psychological stress.

☐ Known diagnosis of asthma or chronic bronchitis, and the use of anti-asthmatic drugs.

☐ The presence of heart or lung diseases other than the obstructive lung diseases, and details of any medications for these.

☐ Smoking habit and details of parental smoking.

☐ Previous and current occupations.
The interviewers were allowed to repeat questions as well as to briefly explain the questions when required. The procedure was piloted prior to the study in order to improve the inter-observer agreement.

**Lung function tests**

At the screening examination, phase two in the first part of the OLIN-project, lung function tests were performed according to ATS recommendations [ATS, 1979] using a dry spirometer (Mijnhardt Vicatest 5). Spirometry was performed with the subjects standing and without a nose clip as forced expiratory volume measurements only were used in the analyses. FEV₁ was calculated after fully performed FVC manoeuvres. Measurements were corrected for body temperature and pressure saturated (BTPS) values. The predicted FEV₁ values were taken from the Berglund normal values [Berglund et al., 1963] estimated from a Swedish population sample. At the screening examination subjects currently taking anti-asthmatic or other medication were not asked to stop these prior to lung function testing. At the validation examinations, phase 3, the subjects taking anti-asthmatic drugs were asked to refrain from these medicines prior to the examination according to given instructions before methacholine tests [Paper IV], and in case methacholine tests were not planned, from the evening before the day of the examination.

Bronchodilatation tests were not planned in the early stages of the design of the study as it was decided for both safety and ethical reasons that subjects taking anti-asthmatic drugs would not be asked to stop these prior to testing lung function. At the start of the study, it was decided to include bronchodilatation tests in subjects whose FEV₁ was <85% of their predicted values, and also in subjects with decreased FEV₁ when the FEV₁/FVC ratio was lower than 85% of predicted values. However, the tests were actually performed because of wider indications, particularly where asthma was suspected.

Six doses (0.1 mg/dose) of salbutamol (Ventoline*) aerosol were given via a Volumatic® spacer (Glaxo) at the bronchodilatation tests. The test was considered positive if FEV₁ increased by at least 15%, provided the increase was at least 0.3 l, or if the FVC increased by at least 20% in subjects whose FEV₁ increased by 10-15%. At the validation procedure, the two first conditions were required if subjects fulfilled the OLIN history criteria for the diagnosis of asthma.
Methacholine tests

The methacholine tests [Paper IV] were performed by using a rapid method well-suited for use in epidemiological studies. An Aiolos on-demand nebulizer with an electrically-driven compressor were used. The tests were done by a trained nurse (Mai Lindström). The method was developed from a method used at the Department of Lung Medicine (Ass Prof Zetterström) at Karolinska Hospital in Stockholm. Subjects were not permitted to take oral beta agonists, theophyllines, disodium chromoglycate or anti-histamines in the 24 h, and inhalatory bronchodilators or corticosteroids in the 12 h before testing. They were also asked to refrain from smoking in the 3 h before the tests. The methacholine concentrations used were 0.1, 0.25, 0.5, 1.0, 2, 4, 8, and 16 mg/ml methacholine chloride. The method was calibrated [Paper IV] against a well-established, but time-consuming, method originally described by Hargreave and co-workers [Juniper et al., 1978], a method that conforms to the SEPCR guidelines [SEPCR, 1983]. The relationship between PC$_{20}$ values with our (Aiolos) method and the method described by Hargreave and Juniper was close to 1:2, which means that the PC$_{20}$ value in most cases was reached one dose-step earlier with our method.

Definitions and diagnostic criteria
Definitions of respiratory symptoms

In the postal questionnaire, the questions on the four main respiratory symptoms; wheezing, attacks of breathlessness, long-standing cough, and sputum production were similar to the formulations in the Swedish questionnaire used by Stjamberg [1985].

At the structured interview, the symptoms were defined as follows:

- Wheezing was defined as any wheeze irrespective of whether the subject had a cold.
- Persistent wheeze was defined as wheezing on most days a week.
- Attacks of breathlessness refers to the symptom at rest and assumes variability of symptoms. The term is close to attacks of shortness of breath which is rarely used in Swedish. Neither breathlessness in general nor on exertion are included.
- Cough was said to be present when a positive response was obtained to the question: "Do you usually cough in the mornings?" or "... at other times during the day?"
Productive cough was said to be present when sputum production occurred with cough on most days of the week.

Chronic productive cough was said to be present if productive cough was present on most days for periods of at least three months per year during at least two successive years.

Respiratory symptoms at different exposures or in special circumstances were asked for more extensively at the structured interview compared with the postal questionnaire. The questions were formulated: "are you breathless, or do you wheeze or have severe cough when....?" The number of exposures and special circumstances were expanded compared to the postal questionnaire.

**Definitions and criteria of asthma**

Asthma was defined according to the ATS [ATS, 1962]. Asthma was diagnosed by using defined, but, different criteria in all three phases of the study's first part; questionnaire-based criteria, structured interview-based criteria and a various criteria based on the two phases. The prevalence of asthma according to all these criteria is expressed, as were the results, in terms of specificity and sensitivity as tests for the validated asthma diagnoses according to phase 3.

According to the postal questionnaire [Paper I], cumulative prevalence [Gregg, 1983; Charpin et al., 1988a] of asthma are based on the question "Do you have, or do you have had asthma?" which express if the subjects have or have had asthma due to their own opinion of whether or not they have or have had the disease, and to the question "Have you been diagnosed as having asthma by a physician?" When assessing current asthma according to the postal questionnaire, the principles used at the Tucson, USA, studies were performed [Bronnimann & Burrows, 1986].

Current asthma was said to exist when the subjects answered they have or have had asthma, and also answered that they were using anti-asthmatic drugs, or had wheezing, or attacks of breathlessness, or the symptoms in at least two of the specific circumstances. Asthma must have been active at least twice, or during two periods in the previous twelve months ("period" prevalence). Other models for estimating asthma prevalence were also used [Paper V].
According to the structured interview, we formulated an interview based diagnosis of current asthma by using a symptom complex including five criteria, the OLIN-interview criteria. All of the following were required;

- wheezing,
- attacks of breathlessness,
- periods of normal breathing between attacks or periods with asthmatic symptoms,
- attack provoking factors including allergens or irritants, other than colds and physical exertion,
- at least two periods of asthmatic symptoms or attacks of asthma during the 12 months prior to the study,

Symptoms apart from those of the common cold and more than one symptom-provoking factor, with the exception of physical exertion, were required for the interview diagnosis of asthma. The diagnosis was not made if any of the above conditions were not fully met.

Asthma was also diagnosed in the absence of one of the above criteria if asthmatic symptoms had occurred on more than one occasion during the previous year and four of the five criteria stated above were fulfilled, if a bronchodilatation test was positive. Bronchodilatation tests was judged positive when FEV$_1$ increased by $\geq 15\%$, provided the increase was $\geq 300$ ml after inhalation of 0.6 mg salbutamol (Ventoline$^R$). Confirmation of the diagnosis of asthma was made at the validation procedure, phase 3, by examining subjects' study protocols or previous case notes. A description of variable broncho-obstruction herein was required. When this was not satisfied, the subjects with asthma, as well as those with suspected asthma, were examined clinically. Methacholine tests or further bronchodilatation tests were performed. The methacholine test was considered positive if hyperreactivity ($PC_{20} \leq 4$ mg/ml methacholine) was shown. Further, the diagnosis of asthma was considered definite when $PC_{20} \leq 8$ mg/ml in subjects fulfilling the OLIN-interview criteria for asthma.

**Definitions and criteria of chronic bronchitis**

For the definition of chronic bronchitis the CIBA Guest Symposium criteria [CIBA Guest Symposium, 1959] was used, which was later adopted by the WHO [WHO, 1961].
According to the postal questionnaire [Paper I], the prevalence of chronic bronchitis are based on the question "Do you have, or have you had chronic bronchitis?" which expresses whether in their own opinion the subjects have or have had chronic bronchitis, and to the question "Have you been diagnosed as having chronic bronchitis by a physician?" Postal questionnaire-based symptom combinations were not used when diagnosing chronic bronchitis, except in a few cases in the non-participants' study.

According the structured interview, chronic bronchitis was diagnosed when the subjects fulfilled the criteria for chronic productive cough, and when no other disease or condition, such as asthma, could explain the symptoms. In the validation study the diagnoses were said to be confirmed when no other cause of the symptom complex of chronic productive cough was suspected.

**Definitions and criteria of combined asthma and chronic bronchitis**

Subjects who had an FEV₁ <80% of their predicted values and symptoms strongly suggestive of both asthma and chronic bronchitis were classified as having the combined diagnosis of asthma and chronic bronchitis. These subjects are not included in the groups with asthma and chronic bronchitis alone, but are reported separately as has been the case in previous Swedish prevalence studies [Kiviloog et al., 1974; Stjernberg, 1985]. In the structured interview phase of the OLIN 1 study some subjects who also had minor impairment of lung function were also classified as having the combined diagnoses of asthma and chronic bronchitis. This was corrected at the validation examinations, as the aim of the OLIN study was to opt for the diagnosis which the symptoms suggested was the most probable.

**Definitions of other conditions**

When known lung diseases other than asthma or chronic bronchitis could explain respiratory symptoms suggestive of asthma or chronic bronchitis, the subject was classified as having the known disease. Similarly, when diseases other than lung diseases, such as heart disease, were associated with respiratory symptoms, neither asthma nor chronic bronchitis were diagnosed if the symptoms could be explained solely by the other disease.

Subjects with respiratory symptoms that failed to satisfy the criteria for asthma or chronic bronchitis have been classified as "respiratory symptoms, neither
asthma nor chronic bronchitis" if the subjects did not suffer from any known condition which could explain their respiratory symptoms.

The classification of suspected asthma was used at the validation examinations for subjects with a history suggestive of asthma, but in whom no variable broncho-obstruction could be demonstrated at the examination or from the subject's case notes. This classification was also used in subjects with a history of asthma who had been free from symptoms associated with asthma for at least 12 months prior to the examination.

Further basis of classification: At the structured interviews, the interviewing nurses also made diagnostic considerations based on their over-all impressions of the examined individuals. This method corresponds to qualified methods which are commonly used in research in advanced nursing. Some results have been presented, and these corresponded well to the other results, even if the number of unclassified subjects was greater. These data may be included in a future dissertation from the OLIN project.

Determinants of symptoms and diseases

Data on the determinants of symptoms and diseases were collected in the postal questionnaires and included the following:

- age,
- gender,
- smoking habit.
- heredity
  - family history of asthma
  - family history of chronic bronchitis
- area of domicile
  - population density
  - residence in inland or coastal areas
- occupation
  - current occupation according to NYK [National Board of Occupational Safety & Health, 1983]
  - previous occupations according to NYK where these had been practiced for more than 5 years
  - current socio-economic classification according to SEI [Statistics Sweden, 1982]
  - previous socio-economic classification according to SEI in subjects who had been in that class at least 5 years
  - employment in the main industries in the province, including forestry and farming
  - length of employment in the main industries.
The postal questionnaire data concerning smoking habit and occupation were validated at the structured interview and errors corrected prior to performing the analyses. Further data on hereditary factors, subjects' residence near industries producing air pollution, together with quantification of smoking and parental smoking were collected. These data are not reported in the Papers in this dissertation.

**Statistical methods**

Statistical analyses have been performed using the Statistical Package for the Social Sciences (SPSS+) [Nie et al., 1975] at the National Institute of Occupational Health, Umeå, at the Department of Epidemiology and Public Health and at the Computer Centre (UMDAC), University of Umeå. In addition the Swedish program QUEST, designed for epidemiological studies has been used [Gustafsson, 1990]. Lennarth Nyström, statistician and epidemiologist, was the project's principal statistician, assisted by Elsie Jönsson MSc of the National Institute of Occupational Health, and was responsible for the OLIN project's data bank.

Bivariate comparisons were performed using Student's t-test and by $\chi^2$ analysis. One-way analysis of variance (ANOVA) was used to test for trends according to various factors including age group and smoking habit. Multiple logistic regression analysis was used to estimate the simultaneous effects of a set of possible risk factors of a certain outcome variable such as a symptom, disease or impaired lung function. When examining occupation and socio-economic group as risk factors for symptoms and diseases, Mantel-Haenszel (MH) analysis was used when considering the influence of age and smoking as confounders to occupation and socio-economic group. Linear regression analysis and a linear logistic model were used when comparing methacholine test methods and when assessing the probability of impaired lung function in a variety of symptom combinations.

In the analyses in Paper I, non-responders to specific questions in the postal questionnaire were excluded when the answers to these questions were analysed. In the analysis in Paper V, VI and VII, those subjects who failed to answer specific questions in the postal questionnaire were considered to have answered "no/don't know". In Paper VII, the results of the questions on asthma have also been analysed when the subjects who failed to answer specific questions had been excluded.
RESULTS
RESULTS

Part 1, Phase 1: The Postal Questionnaire Study

Results are reported in Paper I. Respiratory symptoms were reported by 41% of men and 40% of women. The most prevalent symptoms were sputum production (22%) and wheezing (14%), followed by attacks of breathlessness (11%) and long-standing cough (10%). Both the simultaneous occurrence of attacks of breathlessness and wheezing were reported by 7% of respondents. A similar proportion (7%) reported the simultaneous occurrence of long-standing cough and sputum production. Attacks of breathlessness, or wheezing, or severe cough were reported after exposure to dust or smoke by 22%, after exercise in cold air by 21%, to strong-smelling scents by 17%, and to car-exhaust fumes or air pollution by 16% of subjects.

Smokers were more common in the towns than in rural areas (33% vs 27%), in men than in women (34% vs 30%), and decreased with age, particularly in women. There was a strong association between smoking and sputum production, wheezing and long-standing cough, while the association between smoking and attacks of breathlessness was weaker. Sputum production was reported by 30% of smokers and 16% of non-smokers. The corresponding figures for wheezing were 20% and 9%, respectively. However, the association between smoking and these symptoms was weak in women in the oldest age group.

There were 323 subjects who stated that they have or have had asthma, corresponding to 5.7% of the participants in the postal questionnaire study, and to 5.9% of the 5,483 subjects who answered this question. Attacks of breathlessness were reported by 80% of the 323 subjects, wheezing by 63%, and asthmatic symptoms after exercise by 74% of the 323 subjects. One in 20 of the respondents (5.1%) was taking anti-asthmatic drugs as were 200 (62%) of the 323 subjects who reported past or current asthma.

Two hundred and thirty subjects (4.4%) of the 5,468 subjects who answered this question reported that they had or have had chronic bronchitis. Of those who stated that they had or have had chronic bronchitis, 68% were smokers or ex-smokers, 72% reported that their chronic bronchitis had been diagnosed by a physician. Only 22% of those who reported that they had long-standing cough and sputum production stated that they have or have had chronic bronchitis.
The probability of symptoms and diseases was estimated by a logistic model as a function of smoking habit, population density, inland versus coastal residence and gender. With the exceptions of smoking and age, no certain associations could be found. A tendency toward inland dominance was seen in bivariate analysis between the presence of symptoms in inland or coastal areas.

**Part 1, Phase 2: Structured interview & lung function test**

The results on the prevalence of asthma and chronic bronchitis are reported in Paper II. All subjects reporting symptoms suggestive of asthma or chronic bronchitis (the symptomatic group) were invited to a structured interview and lung function tests performed by specially-trained nurses. In addition, randomly selected samples of subjects from each age group who did not report respiratory symptoms suggestive of asthma or chronic bronchitis were invited to attend the structured interview and lung function tests (the reference group).

The diagnostic criteria for asthma was fulfilled by 292 subjects, corresponding to 5.1% of the total study population (4.5% of men and 5.7% of women). The differences between the different age groups were small. Of the 292, 11 failed to satisfy all five history criteria but had a positive broncho-dilatation test. The prevalence of asthma was similar in all three age groups, with a small female preponderance. Thirty-six percent of the 292 subjects had an FEV₁ below 80% of predicted values, of whom 40% had a positive bronchodilatation test (subjects were not asked to refrain from using anti-asthmatic drugs prior to the examination). No subject in the control group with both attacks of breathlessness and wheezing, or with asthma was found.

Chronic bronchitis was diagnosed in 334 subjects in the symptomatic group, corresponding to 5.9% of the total study population, and, of these, 31% had an FEV₁ below 80% of predicted values. However, 14 subjects in the control group (ten from the oldest age group and four from the middle age group) were diagnosed as having chronic bronchitis. Of these 14 subjects, 12 were smokers and one was an ex-smoker. None of them had reported long-standing cough or sputum production in the postal questionnaire. Thus, when the influence of the results from the reference group is taken into account, the prevalence of chronic bronchitis is approximately 9% (10% in men, 7% in women). The prevalence was about 3% in subjects in the youngest age group in both men and women and increased with age, particularly in men.
A further 53 subjects, 32 men and 21 women, were classified as having both asthma and chronic bronchitis, of whom 36 were from the oldest age group and none were from the youngest. An FEV₁ below 80% of predicted values was found in 87% of these, 57% of whom had a positive bronchodilatation test.

All but 151 of the 1243 subjects in the symptomatic group could be assigned a diagnosis or be classified as healthy on the basis of the nurses' interviews. Of these 151, 70 (corresponding to 1.2% of the total study population) were strongly suspected of having asthma or chronic bronchitis.

Further, in the symptomatic group, 59 subjects were suffering from other diseases than asthma or chronic bronchitis. Mild respiratory symptoms, not fulfilling the diagnostic criteria for asthma, chronic bronchitis or other respiratory or lung diseases were found in a further 238 subjects. No diagnosis or pathological conditions were found in 116 subjects.

The results regarding symptoms and symptom complexes, lung function and their important determinants are reported in Paper III. Both attacks of breathlessness and wheezing were reported by 400 subjects in the symptomatic group, with no age or gender differences, corresponding to 7% of the total study population. Chronic productive cough was reported by 524 subjects and was more common in men and increased with age. The simultaneous occurrence of chronic productive cough, attacks of breathlessness and wheezing was reported by 155 subjects.

The probability of impaired lung function, defined as an FEV₁ <80% of predicted values in relation to persistent wheeze, attacks of breathlessness and wheezing and chronic productive cough was greatest in subjects with persistent wheeze, followed by those with attacks of breathlessness and wheezing. Chronic productive cough had the lowest effect. The probability of impaired lung function in those with all three conditions was 0.78 in the 65-66 year-old group, 0.63 in the 50-51 year olds and 0.46 in the 35-36 year olds (if all subjects in a group had FEV₁ <80% of predicted values, the probability of impaired lung function would be 1.0).
Table 1: Estimated prevalences in the study population (n=5,698) impairment of lung function in percent, defined as FEV1 <80% of their predicted values (FEV1 <80), and FEV1 <50% of their predicted values (FEV1 <50), respectively, by age and gender. (The estimation was performed as described in Table 3, Paper II).

<table>
<thead>
<tr>
<th>FEV1 level</th>
<th>35-36 y</th>
<th>50-51 y</th>
<th>65-66 y</th>
<th>All</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>W</td>
<td>M</td>
<td>W</td>
<td>M</td>
</tr>
<tr>
<td>FEV1 &lt; 80</td>
<td>7.4</td>
<td>5.5</td>
<td>9.8</td>
<td>15.3</td>
<td>11.9</td>
</tr>
<tr>
<td>FEV1 &lt; 50</td>
<td>0</td>
<td>2.1</td>
<td>0.4</td>
<td>3.2</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Odds ratios (OR) calculated by multiple logistic regression analysis when age, gender, family history of asthma and socio-economic group were taken into account, were significantly greater in respect of symptom combinations than for individual symptoms. With regard to chronic productive cough reported at the structured interview, the independent variables age, family history of asthma, smoking habit and socio-economic group all significantly increased OR. This was most pronounced for age (with an OR 6 for subjects in the 65-66 year old group compared to the 35-36 year olds) and smoking habit (OR 6 for smokers versus non-smokers). Subjects in the socio-economic groups "manual workers in industry" and "manual workers in service" and "self-employed people other than professionals", all had ORs that were increased in comparison with the group which included professionals and executives. In subjects with attacks of breathlessness and wheezing, a family history of asthma was the only major risk factor and had a trebled risk. Impaired lung function showed a similar correlation with the independent variables as did chronic productive cough.

Part 1, Phase 3. Methacholine tests and validation examination, examination of non-participants.

The results of the methacholine tests are reported in Paper IV. Ninety-eight subjects classified as having asthma at the structured interview, and 186 who were classified as having respiratory symptoms that might be due to asthma but which failed to satisfy all the diagnostic criteria underwent a methacholine test. Subjects who already had a well-defined diagnosis of asthma or who had an FEV1 <70% of predicted values were not invited to the methacholine testing. Of those 98 subjects classified as having
asthma, 60 (61%) reacted to doses $\leq 4$ mg/ml methacholine chloride and 77 (79%) to doses $\leq 8$ mg/ml, while the corresponding figures in the symptomatic, non-asthma group were 20% and 34%, respectively.

In the asthma group, 16 of the 21 subjects with a $\text{PC}_{20} > 8$ mg/ml were reclassified. Five of the 21 remained classified as having asthma as they had an obvious asthma history.

The non-asthma group consisted of 100 subjects with no diagnostic classification after the structured interviews. Thirty-eight subjects fulfilled the diagnostic criteria for chronic bronchitis, while 34 had mild respiratory symptoms. Of the 100 with no definite diagnosis, 27 reacted to methacholine doses $< 4$ mg/ml, six of the 27 did not have a convincing history of current asthma. Of those classified as having chronic bronchitis, five of six subjects with a $\text{PC}_{20} < 4$ mg/ml were reclassified as having asthma as they also had a history commensurate with asthma. In the group with mild respiratory symptoms, 4 subjects (12%) reacted to methacholine doses $\leq 4$ mg/ml. None of them had a history strongly suggesting current asthma.

The repeatability of the interviews in 98 subjects classified as having asthma was good and the results of the two examinations strongly disagreed in only two subjects, while the results differed in a further 17 subjects, suggesting the consistency between the two interviewers to be 81%, despite the fact that 2-16 months had elapsed between the interviews.

In this sub-sample of 284 subjects, the validity of wheezing, attacks of breathlessness, and the interview diagnosis of asthma as a test for bronchial hyperreactivity was expressed in terms of sensitivity, specificity and positive predictive value. Of the subjects who showed reactivity to methacholine as defined by a $\text{PC}_{20} < 8$ mg/ml, 93% has reported wheezing, 63% attacks of breathlessness, and 56% reported a current asthma history. Thus wheezing had a high sensitivity. The converse was found for specificity and positive predictive value, indicating that wheezing is common without bronchial hyperreactivity. In contrast, the likelihood of having current asthma according to our criteria appeared to be low in the absence of methacholine reactivity. In addition, no significant association between chronic productive cough and methacholine reactivity could be shown.
Prevalence results after the validation procedure, examination of non-attenders, different estimates of asthma prevalence, are reported in Paper V. After inclusion of the results from the validation procedure, the prevalence of asthma was 5.3%; 4.8% in men and 5.8% in women, with small age and gender differences. Fifty-three percent of the subjects with the validated diagnoses of asthma had either a positive methacholine test or a positive broncho-dilatation test in the epidemiological study situation. The diagnosis was confirmed in 40% from case notes, while the remaining 7% had a history-based physicians’ diagnosis at the time of the study. Sixty subjects, corresponding to 1.1% of the study population, were classified as suspected asthma, as they did not fulfil the criteria for asthma used at the validation procedure.

Of the 151 subjects out of the 1,243 symptomatic subjects, in whom diagnostic classification could not be made with reasonable certainty, 26 could be classified as having asthma, 31 as having chronic bronchitis and 3 as having a combined diagnosis of asthma and chronic bronchitis. The validation procedure modified the interview-based asthma diagnosis in only 35 of the 292 subjects with asthma diagnosed at the interview. Of these, 26 were classified as having suspected asthma, as data confirming a variable airways obstruction could not be obtained, and a further 3 had chronic airways obstruction and chronic productive cough in addition to asthma, which caused them to be reclassified as having the combined diagnosis. In only 6 subjects was the diagnosis of asthma in serious doubt.

The estimated prevalence of chronic bronchitis, after inclusion of the results from the reference group was 10.2% in men and 8.3% in women. The prevalence increased with age and was greater among smokers. The combined diagnosis of asthma and chronic bronchitis remained in 38 subjects, corresponding to 0.7% (Table 2).

The prevalence of chronic bronchitis in smokers was estimated to be 22%. It was 7% in ex-smokers and 3% in non-smokers. There was only one subject classified as having chronic bronchitis among the 35-36 year-old non-smoking men, while 1% of the non-smoking women in this age group had chronic bronchitis. The corresponding figures for 35-36 year old smokers were 8% and 6%, respectively.
The estimates of the prevalence of asthma derived from using various diagnostic criteria varied from 3.6% to 6.7% according to the postal questionnaire-based criteria, and from 5.3% to 7.0% according to the structured interview-based criteria.

Table 2: Prevalence of asthma, chronic bronchitis, the combined diagnosis of asthma and chronic bronchitis and suspected asthma by age and gender after the validation examination. The prevalence of chronic bronchitis is an estimate. (Results from the study of non-responders have not been included).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>35–36 y</th>
<th>50–51 y</th>
<th>65–66 y</th>
<th>All</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>W</td>
<td>M</td>
<td>W</td>
<td>M</td>
</tr>
<tr>
<td>asthma</td>
<td>%</td>
<td>4.9</td>
<td>5.4</td>
<td>4.5</td>
<td>6.5</td>
</tr>
<tr>
<td>chronic bronchitis</td>
<td>%</td>
<td>3.2</td>
<td>2.8</td>
<td>14.3</td>
<td>9.3</td>
</tr>
<tr>
<td>combined asthma &amp; chronic bronchitis</td>
<td>%</td>
<td>0.2</td>
<td>0</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>suspected asthma</td>
<td>%</td>
<td>1.1</td>
<td>1.7</td>
<td>0.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

The use of identical criteria at the interview as in the postal questionnaire gave good agreement in estimates of disease prevalence. Of the postal questionnaire-based criteria, the question "have you ever had asthma?" [in Swedish: "har Du, eller har Du haft astma?"] had the highest sensitivity; 64.9%, when the validated asthma diagnosis was used as a gold standard. The best specificity, 98.4%, was obtained from answers to the question "have you been diagnosed as having asthma by a doctor?" combined with the presence of asthma-related symptoms or current use of anti-asthmatic drugs. In general, the test characteristics, improved compared with the postal questionnaire when the structured interview-based diagnostic criteria were used.

Of the subjects with asthma in the 35-36 y age group, 67% had a type-1-allergy. The corresponding figure in the 50-51 y age group was 43%. The proportion of type-1-allergy in asthma was similar in the sexes.

Data, however, incomplete, were collected from 496 subjects out of the 912 subjects who did not participate in the postal questionnaire study. Four were judged to have asthma and 21 to have chronic bronchitis, while 15 reported symptoms suggestive of both asthma and chronic bronchitis. Among the 97
symptomatic subjects who failed to take part in the structured interview study, data were collected from 95 subjects, of whom 14 were judged to have asthma and 33 chronic bronchitis. Thus the proportion of subjects with asthma among non-participants appeared lower than in participants. However, the prevalence estimates of asthma and chronic bronchitis were not significantly affected.

Part 1, phases 1-3. Respiratory symptoms and diseases in relation to occupation and socio-economic groups are reported in Paper VI

The prevalences of wheezing, attacks of breathlessness, chronic productive cough, and of asthma and chronic bronchitis by occupation classified according to NYK, and by socio-economic groups classified according to SEI, were assessed. References to the NYK and SEI are given in the methods section. Odds ratios (OR), corrected for smoking habit and age as confounders, were calculated using the occupational group and the socio-economic group, respectively, with the lowest prevalence as the reference level.

Prevalence rates and occupation: The greatest prevalence of wheezing (20%), chronic productive cough (17%), and chronic bronchitis (15%) was found in miners. Corresponding figures for people working in the agriculture and forestry sectors were 19%, 17% and 14%. The prevalence of asthma was greatest (7%) in people working in the trade and commerce sector, and it was generally high in people with indoor occupations, including those working in the healthcare sector (6%) and in the administrative and office work sector (6%). People in the occupational group including technical, scientific and social sciences, teaching and creative occupations had the lowest prevalences of chronic bronchitis and the three symptoms. OR, when smoking habit and age were considered, reflected the prevalences of the symptoms and the diseases.

Socio-economic groups: Professional people, executives and higher civil servants had the lowest prevalences of asthma, chronic bronchitis and the three symptoms. Chronic bronchitis as well as chronic productive cough appeared strongly related to specific socio-economic group with high OR (2.7 and 2.2, respectively) found in self-employed non-professionals, including farmers), in manual workers in industry (OR 2.5 and 2.1, respectively), and in manual workers in service (OR 1.7 and 1.6, respectively). A similar pattern was seen for wheezing in the three socio-economic groups, with odds ratios of 1.8, 1.5 and 1.5, respectively. A significant increase in the odds ratios for asthma was seen in manual workers in service (1.5) and in assistant non-manual employees (1.5).
Chronic bronchitis, chronic productive cough as well as wheezing were all strongly associated with smoking. The age-adjusted prevalences of chronic bronchitis by smoking habit in different socio-economic groups also showed considerable differences. In non-smoking manual workers in industry, the age-adjusted prevalence of chronic bronchitis was 5% compared to 1-3% in all other socio-economic groups. The corresponding prevalence in smokers was 21% in manual workers in industry, 17% in manual workers in service, and 9% in all non-manual employees, professionals and executives.

**Main industries:** Of the main industries, farming was associated with the greatest prevalences of all three symptoms and the two diseases in men (8% with asthma, 23% with chronic bronchitis). Compared to all men who were not employed in the major industries as the reference group, the OR for the diseases and symptoms were greatest in subjects working in agriculture, except for attacks of breathlessness, for which forestry and the steel industry had the greatest OR.

**Part 2, phase 1: Enlargement of the study base. 1992 postal questionnaire study**

These results are reported in Paper VII: The definitions of self-reported asthma, physician-diagnosed asthma and current asthma estimation are described in the Methods section. Comparisons between the subjects in the same age groups (35-36 versus 50-51 versus 65-66 y in 1992), living in the same eight geographical areas as the subjects in the 1986 study, were made with the results of the 1986 study. The prevalence of self-reported asthma was found to be 1% greater in 1992, and had increased from 5.5% to 6.5% in men and from 5.8% to 6.8% in women. The prevalences of physician-diagnosed asthma, current use of anti-asthmatic drugs and the estimate of current asthma increased from 4.9% to 5.7%, from 5.0% to 6.8% and from 5.4% to 6.2%, respectively. The increase was supported by an increase of 2-3% in the symptoms attacks of breathlessness, long-standing cough, productive cough for more than 3 months, and of chronic productive cough, while the prevalence of wheezing was not significantly different. The proportion of smokers was 31% in both sexes and had decreased between 1986 and 1992 by 4% in men, while it had increased by 1% in women.

In subjects aged 20-21 y the prevalences of self-reported asthma, physician-diagnosed asthma, and the current use of anti-asthmatic drugs were all very
high (12.2%, 10.1% and 10.6%, respectively). Attacks of breathlessness were more prevalent than in the other age groups. There was a similar prevalence of long-standing cough, while chronic productive cough was less common. All of the symptoms were significantly increased in smokers in this group of young subjects, of whom 19% of men and 31% of women were smokers.

In the random sample of 20-69 y old subjects, the prevalences of self-reported asthma and physician-diagnosed asthma were 8% and 7%, respectively. In subjects aged 20-29 y, the corresponding prevalences were 11% and 9%, respectively. The prevalences of both conditions decreased successively to just over 5% in the subjects aged 50-59 y and then increased to 9% and 8%, respectively, in subjects aged 60-69 y.

Eight percent of subjects aged 20-69 y in the random sample were currently using anti-asthmatic drugs and 12% reported attacks of breathlessness in the 12
months prior to the study, recurrent wheeze, and long-standing cough. Sixteen percent reported sputum production, 10% reported productive cough for more than 3 months and 7% reported chronic productive cough. There were no gender differences in the reporting of symptoms and conditions with the exception of attacks of breathlessness in the 12 months prior to the study, which was slightly more common in women. Productive cough for more than 3 months and chronic productive cough were more commonly reported with increasing age, while age had only a limited influence on the reported prevalence of the other symptoms according to the postal questionnaire data.

The simultaneous influences of the possible determinants age, gender, smoking habit, population density, coastal versus inland residence and family history of asthma or chronic bronchitis on symptoms and diseases were assessed. Family history of asthma was associated with an increased risk of self-reported asthma (OR 4.38). Subjects living in urban areas with a population greater than 10,000 had significantly greater odds ratios (OR 1.22) compared to those living in sparsely-populated areas. Smokers had greater odds ratios than non-smokers (1.20). The analysis also showed a decrease in asthma prevalence with increasing age. There were significantly increased odds ratios for chronic productive cough with increasing age (OR increased by a factor of 1.025 per year), family history of asthma or chronic bronchitis (OR 4.06), and for smoking habit (OR 2.00 for smokers and 1.26 in ex-smokers). Subjects living in the interior of the province had greater odds ratios than subjects living in the coastal areas for many of the symptoms, though not significantly so.
DISCUSSION OF METHODOLOGY
he validity of the results of a study is influenced by a variety of types of bias, or skewness, that are due to inherent problems in the study’s design or performance, in the methods used, or to errors made during data analysis. The errors that occur may be divided into either randomly occurring or systematic errors; the former mainly associated with reliability, the latter correlated with validity.

Validity refers to the ability of the tools used in the study to measure that which they were designed to measure and may be assessed by comparing the results of a study with criteria which are independent of the study. Validity can thus be measured and expressed in terms of specificity and sensitivity (Table 3). Reliability may be measured by repeating the examination procedure. For instance, the questions in a questionnaire may be repeated after a certain period using the same methods as in the first study, thus measuring the repeatability. One measure of repeatability is consistency (Table 4). Thus, validity and reliability cannot be determined in a single examination procedure. Bias is an unwanted, or unexpected, influence on the results due to systematic or randomly occurring errors and may reduce both reliability and validity.

Important aspects of methodology will be discussed in this section including possible biases mainly due to systematic errors, that may influence the results of the OLIN studies reported here.

Table 3. Measurement of validity.

<table>
<thead>
<tr>
<th>Test (e.g. questionnaire response)</th>
<th>Condition or disease</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{a}{a+c} \)

Specificity = \( \frac{d}{b+d} \)

Positive predictive value = \( \frac{a}{a+b} \)
Table 4. Measurement of reliability.

<table>
<thead>
<tr>
<th>First test</th>
<th>Second test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>a</td>
</tr>
<tr>
<td>Negative</td>
<td>c</td>
</tr>
</tbody>
</table>

Consistency (%) = \( \frac{(a+d)}{(a+b+c+d)} \times 100 \)

Selection procedure and sample size

The size of the sample is important when interpreting results. When a condition has a prevalence of, say, 6% a sample of approximately 2,200 subjects will be required to achieve an accuracy of less than ±1% within the limits of the 95% confidence interval. In order to compare prevalences in different studies of the order of around 6%, sample sizes of approximately 4,000 subjects will be necessary to detect a statistically significant difference in prevalence of 1% (defined as p<0.05).

If the aim of a study is to estimate the prevalence of a symptom or disease in a defined population, screening of a randomly selected sample of the population will provide a reasonable result. However, if, in addition to estimating the prevalence in the population, differences in prevalence within various age groups or geographical areas are to be estimated, then sufficiently large groups will have to be included to yield a "true" estimate. A stratified selection may be made to achieve this. This will ensure a good internal validity for the results, but this selection procedure will limit the external validity.

One factor that has limited the selection in the OLIN studies is Norrbotten's large geographical area; approximately 25% of Sweden's area. The study was therefore concentrated to areas considered to be representative of the province. In addition to this limitation, specific age groups were examined in order to better assess how age affected prevalence, and to define cohorts for future prospective studies.
Study design

The first stage of the study consisted of a postal questionnaire and the samples for the follow-up examinations were selected from among the respondents to the questionnaire. Various selection procedures could have been used, depending on the aims of the follow-up studies. If an assessment of the prevalence of respiratory symptoms in the population had been the only aim, then a random selection from the questionnaire sample would have been the best selection method. However, the inclusion of all subjects in the original study sample who had asthma and chronic bronchitis was an important aim. Therefore, as had been done in earlier Swedish studies [Stjernberg et al., 1985], subjects who responded to the postal questionnaire and reported symptoms suggestive of asthma and chronic bronchitis were invited to the follow-up study, together with a random sample of subjects from the various age groups without such symptoms.

This division into a symptomatic and a reference group is not uncontroversial and has been criticized by several referees, who suggested that only subjects reporting symptoms in a questionnaire study should be examined. In retrospect, with the results of the study in hand, it is clear that the prevalence of asthma would not have been affected. However, the prevalence of chronic bronchitis would have been seriously underestimated, particularly in older smokers, had a reference group not been examined.

Basing the estimate of the prevalence of chronic bronchitis solely upon examination of subjects reporting symptoms in the questionnaire would thus carry a poor sensitivity. Specificity, however, would be little affected, resulting in less effect on risk ratios and odds ratios in the assessment of potential determinants of chronic bronchitis.

Effects of non-responders

The effects of non-responders on the results may depend on several factors, primarily their numbers. Previous Scandinavian studies have reported only small numbers of non-responders [Huhti, 1965; Gulsvik, 1979a,b; Stjernberg, 1985; Bakke, 1992] and these have not significantly affected the results. Large numbers of non-responders may cause both random and systematic errors and thus affect the study’s internal validity. Furthermore, there is evidence that subjects with some diseases are less likely to participate in questionnaire studies, while those with others may be more likely to participate
[Locker et al., 1991], and the prevalence of asthma, for instance, may therefore be overestimated. The literature does not allow any conclusions, however, to be drawn in regard to chronic bronchitis. Some smokers have been reported to be hesitant to participate in studies in which smoking habits are examined [Burney & Chinn, 1987]. There were few non-responders in the OLIN studies and no general conclusions can be drawn on whether non-responders affected the prevalence estimates. However, asthma appeared to occur less frequently among non-responders than in those who took part in the study. The number of non-responders in the OLIN studies was small and probably caused no important effects on the results.

**Bias concerned with questionnaires**

The first questionnaire studies into respiratory diseases aimed to identify chronic bronchitis and were performed at the same time as discussions on the classification and definitions of obstructive lung diseases were underway. The need for standardized interview questionnaires had been recognized and the aim was primarily to control observer bias [Cochrane et al., 1951]. In the preliminary studies to the BMRC questionnaire assessments of reliability were made that showed a high degree of repeatability. Two interviews, with a new interviewer at the second, gave a response consistency of 85% [Fairbairn et al., 1959]. These results thus indicate a low observation bias when using standardised questionnaires. In the early Tucson epidemiological studies no inter-observer variation was detected [Lebowitz & Burrows, 1975]. These interviewers were specially trained nurses. No observer or interviewer bias of importance was observed in other British and American studies [Fletcher & Tinker, 1961; Holland et al., 1966].

However, interviewers may ask questions with differing emphasis or in different ways and may also interpret responses differently. Self-administered questionnaires were developed with the dual aim of reducing costs and to further reduce bias. These were often abridged versions of the original questionnaires. There is no general agreement as to whether the responses to interview-based questions can be considered equivalent to those from self-administered questionnaires. In the Tucson studies the two interview questionnaires, the BMRC and the NHLI questionnaires, were compared with the self-administered Tucson questionnaire, the same or similarly worded questions about the four main respiratory symptoms, cough, phlegm, wheeze and dyspnoea, gave the same prevalences and there was good agreement
between the responses to the questions [Lebowitz & Burrows, 1976]. Opinions differ, however, as to whether results from interview-based studies can be compared with those from self-administered questionnaires. Considerable agreement, with a consistency of 80-90%, was found between a BMRC interview questionnaire and a similarly, but not identically, worded self-administered American questionnaire including questions about cough, phlegm, wheeze and dyspnoea [Samet et al, 1978]. Other studies gave similar results [Higgins et al., 1959; Helsing et al., 1979], indicating that the method of administration of standardized questionnaires caused only limited bias. The importance of self-administered questionnaires increased during the 1970s.

Modification of questions within the questionnaires affected the results in both British [Holland et al., 1966] and American studies [Lebowitz & Burrows, 1976], which thus create a bias when comparing results. Training effects by repeated questionnaires, mass media attention and the subjects' attitude towards the questionnaire may all create recall bias. Seasonal bias may be generated, for example by the fact that bronchitic symptoms occur more frequently in winter.

Language may produce another source of bias. Translation may cause considerable bias which has been shown by using English and French versions of the same questionnaire [Osterman et al., 1991], and was discussed when the IUATLD questionnaire was developed [Burney et al., 1989b]. In the OLIN study the symptoms "wheezing" and "shortness of breath" could have given rise to considerable difficulties. Further, the OLIN study area is a three-language area, which may have created an uncontrolled bias, which will be discussed later.

The questionnaires reflected the view that certain symptoms and combinations of symptoms reflect disease. Thus cough and sputum production in combination with temporal aspects were expressions of chronic bronchitis. How wheezing should be interpreted was a subject for debate.

The validity of the questionnaire-based methods, that is whether these instruments succeeded in achieving their aim of estimating the prevalence of chronic bronchitis or asthma came into question in the 1980s [Pride, 1989]. Samet [Samet, 1987] suggests that the BRMC questionnaire has only been thoroughly validated with respect to sputum production. However, even this as well as the whole questionnaire's validity in predicting a progressive disease
was criticized, indirectly by Fletcher et al. [1976]. These aspects are discussed in the sections on the diagnosis of asthma and chronic bronchitis.

It was decided that the OLIN studies would not rigidly adhere to the classifications and formulations used in previous questionnaires. Some modifications were made to a questionnaire that had been used by Stjernberg & Rosenhall [Stjernberg, 1985], mainly by the addition of questions on respiratory symptoms in defined circumstances. The OLIN questionnaire included fewer questions on bronchitic symptoms than had the original BMRC questionnaire. Attempts were also made to avoid composite questions which included a number of conditions in order for the questions to be answered "yes" or "no/don't know".

**Interview**

There were two important changes in the view of respiratory symptoms in the 1980s: there was a "reduction in the prognostic importance of chronic cough and expectoration" and an "increasing importance of pulmonary function tests in the diagnosis and prognosis" of obstructive airways diseases [Pride, 1989]. The increased importance attached to lung function tests has carried with it the opportunity for clinical contact with the subjects under study. A number of studies, including the European Commission Respiratory Health Study, include an interview as a mandatory constituent. A further reason was the ability of the interview to provide a more detailed penetration of individual symptoms and diseases/conditions than would be possible through a self-administered questionnaire [Sears, 1986]. Further, when considering questions on bronchitis, the original purpose of the BRMC questionnaire, the sensitivity of self-administered questionnaire has been questioned, particularly in smokers [Burney et al., 1987]. In spite of the early reports of excellent reliability, more recent studies have reported a reliability of 75% which has been considered to be fair [Olsson et al., 1984]. Poor agreement between questionnaire and interview data concerning bronchitic questions were found in the OLIN studies, in elderly smokers, in whom the interview as a method showed a considerably greater sensitivity.

It has become standard practice when performing standardized interviews in epidemiological surveys to follow the question closely, and in cases of uncertainty or ambiguity, to merely repeat the question. However, adherence to this rule may vary. The interview may also be conducted by providing the same
clearly defined questions with definite responses but in which the interviewer may clarify and explain the questions. A third method, that has been used in validation [Olsson et al., 1984; Kongerud et al., 1989], follows clinical history-taking. Kongerud et al. [1989] reported that a self-reported questionnaire gave better agreement with their own clinical interview than an interview performed by a nurse or technician. However, in their study, the selection procedure to the interviews may have created a bias, which at least in part could explain the results. A further method, free interview, is used in psychiatry and advanced nursing. It cannot be used in the measurement of prevalence.

Major differences in wording and the structure of specific questions will affect prevalence estimates [Fletcher et al., 1959; Fairbairn et al., 1959; Holland et al., 1966]. However, this will not limit the validity of a particular investigation, but may introduce bias when comparisons are made with other studies [Samet, 1978]. In the OLIN studies the questions at the structured interview were more numerous and more detailed than in the postal questionnaire, explaining why exact measurements of consistency cannot be made. At the structured interview questions were asked which had fixed answer alternatives. Explanation of a question was permitted if a subject was unsure of its meaning. I believe that this procedure gives a better assessment of the occurrence of a disease in a single study, despite the fact that the external validity of the results may be affected. In the OLIN study this procedure was necessary, in particular because of the diversity of languages in the study area (three lappish languages, the Finnish dialect spoken in the Torneå River Valley, as well as Finnish and Swedish). A questionnaire that kept strictly to each language could have created considerable bias. The OLIN method required that the interviewers were well-trained and that they had been piloted on the same subjects to improve interobserver agreement.

The diagnosis of asthma

As the diagnosis of asthma is arbitrary it is not surprising that different studies have approached the diagnosis in different ways. The aims of the studies have, or rather should have, defined which methods and diagnostic criteria were used. A high specificity is required when assessing risk ratios and odds ratios due to exposure to various provoking factors. A high sensitivity as well as a high positive predictive value are needed in studies which aim to assess the prevalence of a disease in the community.
During the 1970s and 1980s the association between bronchial hyperresponsiveness and asthma was emphasized. Hargreave, amongst others, graded the severity of asthma according to the results of bronchial provocation tests [Hargreave et al., 1981] and other investigators have regarded proven bronchial hyperresponsiveness as a requirement for the diagnosis of asthma [Löwhagen & Lindholm, 1983; Ådelroth et al., 1986]. Earlier Scandinavian studies have, in keeping with the CIBA Guest Symposium’s definition of asthma, also required demonstrable variability in broncho-obstruction in the examination situation for the diagnosis of asthma [Alanko, 1970; Kiviloog et al., 1974]. The view and the methods developed by Woolcock during the 1980s are the clearest and most consistent applications that the hyperresponsiveness and asthma are closely related [Woolcock, 1983]. Woolcock and co-workers’ current position for the definition of asthma in epidemiological studies is wheezing in combination with bronchial hyperreactivity [Toelle et al., 1992]. However, this describes a condition that may occur more frequently than the clinical presentation of asthma.

In addition to the attempts to objectively validate various symptoms against bronchial hyperresponsiveness [Burney & Chinn, 1987, Burney et al., 1989a,b; Abramson et al., 1991], a clear discrepancy has been reported between bronchial hyperresponsiveness and the clinical diagnosis of asthma and asthma-associated respiratory symptoms [Britton & Tattersfield, 1986; Enarson et al., 1987; Pattemore et al., 1990]. Different stimuli have been shown to cause different degrees of bronchial reactivity [Allegra & Bianco, 1980; Pauwels, 1983]. Reports on asthma without proven bronchial hyperreactivity had been published [Stanescu & Frans, 1982; Hargreave et al., 1984], as well as the reverse, that many individuals with positive provocation tests did not have respiratory symptoms [Bakke, 1992; Rijcken et al., 1987]. The partly altered view of hyperreactivity has been reviewed by Hargreave et al. [1986]. Twenty-two subjects with asthma were given provocation tests at 2-3 week intervals during one year [Josephs et al., 1989]. The results showed that there was considerable intra-individual variation in broncho-reactivity and that in several subjects with definite asthma, that bronchial hyperresponsiveness could not be demonstrated in these subjects at more than 50% of examinations. This study suggests that some previous estimates of asthma prevalence that were only based on variable broncho-obstruction probably underestimated its prevalence or measured a possible point prevalence.
The importance of questions on the variability of symptoms together with whether questions about both self-reported and physician-based diagnosis of asthma are emphasized by several authors [Lebowitz et al., 1975; Bronnimann & Burrows 1986; Enarson et al., 1987; Paoletti et al., 1989]. The importance of the interview is also stressed [Cerveri et al., 1988], and its superior ability to detect asthma in individual cases has been pointed out [Sears, 1986]. This has been used by Norwegian investigators [Gulsvik, 1979; Bakke et al., 1991b], among others. The importance of including questions about respiratory symptoms in defined circumstances in the questionnaires has now been emphasised [Venables et al., 1993].

As stated in the OLIN study reports, the study has not restricted the definition of asthma to one single exact definition but has also estimated the prevalence of asthma according to various criteria. Both symptoms reported at the postal questionnaire and at the interview have been used as the basis for the diagnosis. The reversibility test and the methacholine provocation test have been used as complements.

In addition, OLIN formulated its own interview-based criteria for asthma, the OLIN criteria, that were used in phase 2 of the study. This may have given a slight underestimate of asthma prevalence, as asthmatics who are relatively symptom-free will not be classified as having asthma. A small number of well-treated asthmatics fell into this group. No attention was paid to previous diagnoses or to the subjects’ own opinions on their diagnoses at the structured interview and at the validation procedure in the OLIN study. The aim was to assess whether or not the subjects satisfied predetermined conditions for the diagnosis of asthma.

**Validation against what?**

Two models have been used in the validation of epidemiological diagnoses of asthma; a provocation test or a clinical interview, which in practice has meant a physician’s interview [Samet, 1987; Torén et al., 1993]. Neither of these methods is in itself satisfactory. They constitute only extremes of two forms of operative methods, and may cause systematic errors. A different starting point has been used in the OLIN studies, which have used the ATS definition, and striven to combine a history of asthma with objective signs of variable broncho-obstruction. The demonstration of bronchial variability has been the aim in cases with current asthma according to the interview. Towards
this end, those data have been accepted that could be found indicating the presence of variable broncho-obstruction by broncho-dilatation tests, methacholine test, case notes citing broncho-obstruction, or other convincing evidence such as rhonchi in acute situations, or improvement after emergency treatment. Data from both the epidemiological study situation's different phases and from existing case notes were accepted at the validation procedure. Questionnaire responses and interview information provide indirect evidence suggesting variable broncho-obstruction, therefore the term suspected asthma has been used to describe the condition in subjects in whom evidence of variable broncho-obstruction did not exist. Finally, it is important to emphasize that no gold standard has been agreed for the diagnosis of asthma in epidemiological studies.

The diagnosis of chronic bronchitis

The first large-scale questionnaires were developed to identify subjects with chronic bronchitis. Individuals were considered to have chronic bronchitis when they reported cough with sputum production to be present on most days during periods of at least three months during at least two successive years, provided that they had no other diseases or conditions that could explain the symptoms. The considerable difference in prevalence between the Finnish studies with very high prevalence estimates [Huhti, 1965] and the Swedish studies reported by Kiviloog et al. [1974] and Stjernberg et al. [1985] can only be partly explained by the higher proportion of smokers in the Finnish than in the Swedish population samples. The Swedish studies had used ATS criteria, which included the term excessive amounts with regard to sputum production, as their starting point [ATS, 1962]. The ATS criteria were initially chosen for the OLIN studies, but because of uncertainty over what constituted excessive amounts, the earlier CIBA Guest Symposia criteria, as formulated by WHO [WHO, 1961] were chosen instead.

The other important question of classification concerned whether the obstructive form of chronic bronchitis should be differentiated as a particular disease or condition, chronic obstructive pulmonary disease (COPD), together with other non-symptomatic obstructive conditions. A number of widely differing definitions of COPD have been advanced [Mitchell et al., 1964; Fletcher et al., 1976; Snider, 1989] and some authors even include incompletely reversible forms of asthma in the term [Gulsvik, 1979]. Furthermore, the division into two forms described by Fletcher et al. has not produced distinct new definitions. This,
together with the fact that positive questionnaire responses in the postal questionnaire made up a selection criterion to the structured interviews, resulted in our refraining from differentiating an obstructive form as a separate disease based on physiological data in the OLIN studies.

Since the OLIN studies began, new data from longitudinal studies have partly refuted conclusions drawn from data that Fletcher et al. [1976] and others [Kauffmann et al., 1979; Peto et al., 1983; Becklake, 1985] presented in predominantly occupational studies. Compared to these, the study from six cities in the eastern USA, from which data from 3,948 subjects followed for 12 years are now available, that chronic cough and chronic sputum production, in contrast to persistent wheeze and dyspnoea [Sherman et al., 1992], predict an accelerated decline in lung function even after correction for known determinants such as smoking, age, height, etc.. Results from the Tucson, USA, studies, support these data and demonstrate a natural history of airways obstructive diseases with an overall incidence of chronic obstructive pulmonary disease of more than 7/1000/year and of asthma of more than 4/1000/year [Lebowitz, 1989]. In the term chronic obstructive pulmonary disease the author includes chronic bronchitis and emphysema, and the impairment in lung function in chronic bronchitis is described physiologically without using further classifications, except the collective term airways obstructive disease (AOD), which also includes asthma. However, different investigators define the term COPD very differently both with regard to content about what constitutes the diseases and conditions that may be included in the term and the physiological limits against health and non-obstructivity. Chronic airway obstruction (CAO) and chronic airflow limitation (CAL) are often confused with the term chronic obstructive pulmonary disease (COPD) in discussions in Sweden.

Deciding which criteria should be included should be simpler for COPD than for asthma. Which groups of diseases should be excluded? Which lung function tests and which measures of lung physiology should be used? The difficulty with using the ratio of FEV₁/VC is that both vital capacity (VC) in free or slow speed and forced vital capacity (FVC) are approximations of the correct denominator, total lung capacity (TLC), as the residual volume (RV) is important in the presence of chronic obstructivity. In the OLIN studies, computed tomography in maximal expiration has shown the best correlation between low degree of attenuation and RV in comparison with several physiological variables, including FVC and VC.
Combined diagnosis of asthma and chronic bronchitis

One of the background factors to the Dutch hypothesis was similarity in the clinical presentation of the disease in subjects with obstructive disorders. The British investigators also admitted considerable overlapping between asthma and chronic bronchitis [MRC, 1965]. In the Tucson, USA, epidemiological studies wheezing and reported asthma were associated with concomitant diagnoses of chronic bronchitis and/or emphysema, and the authors suggested that in subjects older than 40 years persons with asthma could not definitely be distinguished from those with chronic bronchitis [Dodge & Burrows 1980]. The same investigators have also demonstrated a tendency among physicians toward calling obstructive lung disease in older men "emphysema" and in older women "asthma" or "chronic bronchitis" irrespective of similarity in symptoms, lung function and smoking habits [Dodge et al., 1986].

In the Swedish studies performed by Kiviloog et al. [1974] and Stjernberg et al. [1985] a combined diagnosis of asthma and chronic bronchitis was used for the condition with typical clinical pictures for both of the conditions. In the OLIN study we have tried to opt for either asthma or chronic bronchitis. However, we have also used the combined diagnosis of asthma and chronic bronchitis in subjects with FEV₁ <80% of predicted values in whom we were not able to distinguish between the two conditions. In subjects with FEV₁ >80% of predicted values we followed strictly the definitions of chronic bronchitis [CIBA Guest Symposia, 1959; WHO, 1961; ATS, 1962] which state that the diagnosis of chronic bronchitis can only be made when other existing diseases do not explain the symptoms. Thus, when subjects with a clinical presentation in accordance with asthma also reported chronic productive cough, they were classified as having asthma.

Validity aspects in the estimation of determinants of symptoms and diseases

It is important from the outset to state two important aspects in the calculation of determinants of symptoms and diseases. First, the cross-sectional study design in itself limits the ability to define risk factors for the development of disease. The cross-sectional study situation will only provide a cross-sectional picture without information on the examined population's history. Questions about certain background factors, such as previous occupations, smoking, etc., may be included, but it will be practically impossible to include all factors of importance for the development of disease. Great care
must be exercised in the handling of these data in discussions on the causality of the disease in question, as these data are incomplete and do not permit control over possible confounders. It is doubtful whether these results should be expressed in terms of risk or odds ratios as the terms are often associated with causality. The cross-sectional study rather permits a discussion of relationships with basic demographic data, such as the relationships of symptoms or diseases with factors such as age, gender, smoking habit, etc. [Rothman, 1986]. However, the studies are also important in that they are hypothesis-generating.

Second, it must be realized that the precision with which the results are expressed is dependent on the conditions and limitations that the data included in the model allow. The precision of the results, in epidemiological surveys of prevalence of symptoms and diseases as well as risk and odds ratios, usually quoted to one or more decimal places, should thus be regarded as approximations and be accepted with a large pinch of salt. However, they do reflect reality.

The calculation models are not the less important for the validity of the results. It is important to maintain a careful sceptis to questionnaire data in the field of the epidemiology of respiratory diseases. Calculations of risk ratios based solely on self-reported questionnaire data may be marred by considerable uncertainty. Misclassification of both exposure and of symptoms and diseases may easily result. Furthermore, it is always difficult to quantify exposure in this type of study, even when it comes to such relatively simple data as smoking habit. Designing a model that will both yield a high sensitivity and a high specificity is difficult. In the study of the prevalence of a disease in a society, methods that give a reasonable sensitivity are necessary or the results will yield an underestimate of the disease’s prevalence. However, if only risk factors for the development of asthma, or diseases with a moderate prevalence, are to be studied, sensitivity is immaterial, but a high specificity is required to guarantee the validity of the results.
DISCUSSION OF MAIN RESULTS
DISCUSSION OF MAIN RESULTS

In this section the prevalence estimates of respiratory symptoms, asthma and chronic bronchitis, and the results in comparison with other investigations will be discussed. The validity of the results is discussed, as are the results of the use of different methods and different criteria. This facilitates the fixing of the relevant level of ambition for prevalence studies. The underdiagnosis of the diseases is discussed in the light of the prevalence estimates. As the results of the 1992 study indicate an increase in symptoms and asthma, the consequences of these findings will be discussed. As our lung function data primarily constitute the starting point for prospective studies, only FEV₁ and its relation to symptoms will be discussed. Discussion of the main determinants of symptoms and diseases including occupation and socio-economic class will be included.

Prevalence of symptoms

Over forty percent of the study population reported respiratory symptoms in the postal questionnaire in the 1986 study, results comparable to, or greater, than those reported in other Scandinavian studies [Huhti, 1965; Gulsvik, 1979a; Bakke, 1992]. Twenty percent of respondents reported sputum production, the single most common symptom. Recurrent wheezing was reported by 13% of respondents, attacks of breathlessness by 12% and longstanding cough by 11%. As expected, the prevalence of symptoms increased with age, especially chronic productive cough, confirming the results of other studies [Kiviloog et al., 1974; Stjernberg, 1985]. Other symptoms, such as attacks of breathlessness, showed only small age-related differences. In contrast to other studies, particularly those from Finland [Huhti, 1965; Alanko, 1970], there was no gender difference in the prevalence of symptoms, despite significant gender differences in the proportions of smokers. Smoking was most common in young women.

More subjects in the symptomatic group reported wheezing and cough at the structured interview than at the postal questionnaire. However, the converse was true of attacks of breathlessness. This may have been due to different wording of the questions at the structured interview, as discussed above. However, 13 subjects in the control group, who had not reported either longstanding cough or sputum production at the postal questionnaire, stated at
the interview that they had chronic productive cough, suggesting that the self-administered questionnaire had a low sensitivity for bronchitic symptoms in elderly smokers.

**Asthma**

Compared with Scandinavian studies performed prior to the middle of the 1980s [Julin & Wilhelmsen, 1967; Alanko, 1970; Kiviloog et al., 1974; Gulsvik, 1979b; Stjernberg, 1985; Pedersen & Weeke, 1987; Vesterinen et al., 1988], a surprisingly large proportion, nearly 6%, reported that they had or had had asthma, the cumulative asthma prevalence [Charpin et al, 1988a,b]. The methods and the criteria used were comparable to those in many of the studies reported in the 1980s. Recent studies in southern Europe have shown similar cumulative prevalences of asthma. That reported in Marseilles was 4% [Charpin et al., 1988a,b] and that in North Italy 5% [Paoletti et al., 1989]. Comparison with the results from large studies, some of which are reported below, is difficult because they used different methods and diagnostic criteria.

Lower prevalences have been reported in Europe with a prevalence of asthma of 3% reported in south-central Finland [Haahtela, 1980; Vesterinen et al., 1988], and 2% in Prague [Vondra et al., 1989], however, these rates were not cumulative prevalence rates. In North America [Miller et al., 1988; Manfreda et al., 1993], despite the use of different methods and operational criteria, similar or somewhat lower estimations of asthma prevalence have been found to those in the OLIN study. The prevalences of current asthma are reported to be even higher in Australia [Woolcock et al., 1987; Abramson et al., 1991; Toelle et al., 1992] and New Zealand [Sears, 1987], which may, at least partly, have been due to the methods and criteria used.

The follow-up examinations and the validation procedure verified the size of the prevalence estimates of asthma assessed by the postal questionnaire. As the cumulative prevalence is difficult to validate, the follow-up studies aimed to measure the prevalence of current asthma in accordance with the ATS criteria [ATS, 1962], for which operational criteria were formulated. This contrasted with the postal questionnaire analysis, as no weight was attached to previous physicians' diagnoses or the subjects' own opinion as to whether or not they had the disease. This procedure follows the recommendations that were used before provocation tests but in practice became to be considered as the gold
standard for the diagnosis of asthma in epidemiological studies [Julin & Wilhelmsen, 1967; Samet, 1978; Gregg, 1983]. No simple gold standard was formulated in the OLIN studies, as there is none [Pride, 1989]. Several of those with case note diagnoses of asthma were invited to the validation examinations as case notes did not accurately verify the diagnosis.

The prevalence of asthma remained at 5% with a somewhat higher prevalence in women. The validation procedure contributed to the validity of the study, but entailed considerable expenditure of time. Performing these examinations was considered important as surprisingly high prevalence estimates of asthma were being questioned by the late 1980s. Further, they were also necessary for the identification of subjects for cohort and case-referent studies.

The validation procedure modified the interview-based asthma diagnosis in only 35 of the 292 subjects with asthma diagnosed at the interview. Of these, 26 were classified as having suspected asthma, as data confirming a variable airways obstruction could not be obtained, and a further three had chronic airways obstruction and chronic productive cough in addition to asthma, which caused them to be reclassified as having the combined diagnosis. In only six subjects was the diagnosis of asthma in serious doubt. At the validation procedure the repeatability in a sub-sample with mild asthma of 81%, results similar to those of British and American studies [Fairbairn et al., 1959; Holland et al., 1966; Lebowitz & Burrows, 1976].

The sub-sample of subjects with asthma invited to the methacholine tests had, according to their histories, a relatively mild or moderate asthma, and their diagnoses had not been previously physiologically verified. The tests demonstrated a significant correlation with the interview diagnosis of asthma, but the two were not identical. Sixty percent reacted to dose levels previously considered diagnostic of asthma [Hargreave et al., 1981], and, if a further dose step was included, 79% reacted. The association between the interview-based diagnosis of asthma and bronchial hyperreactivity was similar or somewhat higher than previously reported [Britton & Tattersfield, 1986; Enarson et al., 1987; Trigg et al., 1990; Abramson et al., 1991]. Bakke, in Norway, used somewhat narrower diagnostic criteria for asthma than were used in the OLIN studies. A poor specificity for the bronchial provocation test as a screening test for asthma was found [Bakke, 1992]. This supports the results of Josephs et al. [1989]. If the OLIN criteria for diagnosing asthma had only required a positive
methacholine test and a history of past or present breathlessness [Woolcock, 1983], no exact estimate of prevalence can be calculated although it appears that it would be at least as great as that found, if not greater. The same applies if wheeze together with a positive methacholine test had been used as the diagnostic criterion [Toelle et al., 1992].

Despite the fact that interview-based criteria for asthma were used in the OLIN studies, the diagnostic criteria used in epidemiological surveys should not be limited to these criteria alone. The OLIN studies have therefore applied various criteria for the diagnosis of asthma in order to assess the effects of the use of different criteria on prevalence estimates and on the validity of the diagnoses in relation to the validated OLIN diagnosis. A range of estimates of the prevalence of asthma was obtained from a large number of both postal questionnaire- and interview-based criteria of between 4% and 7%. Thus it is impossible to draw definite conclusions on possible differences in the prevalence of asthma at these prevalence levels, unless fully comparable methods and diagnostic criteria are used. It is, however, surprising how similar the test characteristics are using the different operational diagnostic criteria. Specificity is generally high, due to reasons of definition and to the fact that the results are based on a population study rather than upon a selected sample. The choice of validation methods used in the OLIN project contributed to an improved sensitivity and positive predicted value for several of the interview-based methods. It is interesting that the criteria taken from the Tucson epidemiological studies [Bronniman & Burrows, 1986] agrees so well with the validated results.

The best tool for making a questionnaire-based diagnosis of asthma according to the results of the OLIN studies is self-reported asthma and was based simply upon asking the question "have you ever had asthma?". If the prevalence of current asthma is to be estimated, both this question or the question on physician-diagnosed asthma must be included together with the simultaneous reporting of current use of anti-asthmatic drugs or asthma-related symptoms. In addition to the Tucson studies, other American and Canadian investigators have emphasised the use of self-reported or physician-diagnosed asthma in self-administered questionnaires [Enarson et al., 1987]. In Europe, the importance of self-reported asthma has been emphasised by Paoletti et al. [1989].
Chronic bronchitis

The questionnaire-based results suggest the prevalence of chronic bronchitis to be much lower than in Finland [Huhti, 1965] and of the same order of magnitude as reported by other Scandinavian, including Swedish, studies [Wilhelmsen & Tibblin, 1966; Kiviloog et al., 1974; Stjernberg et al., 1985]. It is difficult to make international comparisons because of the considerable divergence of interpretations of the content of the term chronic bronchitis, reviewed by Pride et al. [1989].

Self-reported and physician-diagnosed chronic bronchitis were both reported by 4%, while 7% reported they had both sputum production and longstanding cough. In contrast to asthma, chronic bronchitis and bronchitic related symptoms were strongly related to smoking. According to the interview results, taking into account the results from the reference group, and the results after the validation procedure, the prevalence of chronic bronchitis was estimated to be around 10%, results comparable to those of Huhti [1965]. The prevalence estimates must be considered to be approximations, particularly in the elderly. The interview results demonstrated that the postal questionnaire failed to yield an accurate prevalence of chronic bronchitis because of the number of subjects in the reference group found to have chronic bronchitis. If a reference group selected from among respondents to the postal questionnaire who were relatively symptom-free had not been included, the internal validity of the study concerning chronic bronchitis would have been poor.

The subjects who were classified as having suspected asthma or the combined diagnosis of asthma and chronic bronchitis had no major influence on the prevalences of obstructive airways diseases in the OLIN study. The condition of suspected asthma, prevalence 1%, was found mainly in the youngest age group, while the combined diagnosis of asthma and chronic bronchitis was mainly found in the elderly subjects. The prevalence of the combined diagnosis of asthma and chronic bronchitis was 0.7%, similar to the results reported by Kiviloog et al. [1974] and Stjernberg [1985].

Underdiagnosis of obstructive airways diseases

In the first phase of the OLIN study, two-thirds of the subjects who had a validated diagnosis of asthma reported that their asthma had been diagnosed by a physician. This suggests that about one-third of subjects with asthma are undiagnosed. A positive response to the question "do you have
asthma diagnosed by a physician?" predicted a validated diagnosis of asthma in 65%. If subjects classified as having suspected asthma, chronic bronchitis, or the combined diagnosis of asthma and chronic bronchitis were added to those with a validated asthma diagnosis, a positive response to the question "do you have asthma diagnosed by a physician?" predicted a diagnosis of obstructive or potentially obstructive disorders in approximately 90% of sufferers. Thus the question did not only indicate asthma, it also suggested the presence of obstructive airway disease. The somewhat poor sensitivity is balanced by a good specificity.

The diagnosis of chronic bronchitis made by clinicians, differs considerably from that made from the questionnaire, and even more from the interview diagnoses, which are also similar to the results of the Tucson studies [Burrows & Lebowitz, 1975]. The diagnosis made by clinicians, mainly in the primary health care centres, seriously underestimated the prevalence of chronic bronchitis as only 20-30% were diagnosed. This may be due to the fact that subjects do not seek treatment for bronchitic symptoms that they do not consider to indicate disease. Thus the underdiagnosis does not necessarily imply a deficiency in the diagnostic ability of primary health care physicians. However, the underdiagnosis was also considerable in subjects with impaired lung function. There is a deficiency in that lung function testing is underused, as many subjects with bronchitic symptoms have chronic airflow limitation, which results in a delayed diagnosis of airways disease and an unnecessarily tardy instigation of secondary preventive measures, such as combating smoking.

The ratio between chronic productive cough reported in the questionnaire and the diagnosis of chronic bronchitis, both physician-diagnosed and according to the subjects' own opinion of whether they had it, were similar, had also increased between 1986 and 1992, indicating that chronic bronchitis is still considerably underdiagnosed.

Have the prevalences of asthma and respiratory symptoms increased?

The results of the postal questionnaire study performed in 1992 indicate that the prevalence of asthma had increased since 1986. Some form of bias may conceivably have been responsible for the difference in results and it is important to discuss this. An important form of bias that could have affected the results is recall bias. Subjects from the same eight geographical areas have been examined in the OLIN study for several years and
as more cases of asthma have been identified there is likely to be a greater awareness of asthma and allergic diseases in health care workers and in the media. The increases in both self-reported and physician-diagnosed asthma are supported by increases in the prevalences of several respiratory symptoms and by a 36%-39% increase in the proportion of subjects using anti-asthmatic drugs. Furthermore, the proportion of various respiratory symptoms associated with asthma in the subjects with self-reported asthma, or in those with physician-diagnosed asthma, were similar in 1992 and 1986. These data, supplemented by the high response rates in the OLIN studies, suggest a genuine increase in the prevalence of asthma between 1986 and 1992.

The results from the sample from the whole province of Norrbotten show an even greater prevalence of asthma reported in a postal questionnaire than was found in the stratified samples from the subjects in the selected age groups and study areas. The measurement variables of self-reported asthma, physician-diagnosed asthma and current use of anti-asthmatic drugs all had a prevalence of 7-8% in the 1992 postal questionnaire survey of the random sample.

The results of the 1992 survey allow a discussion of the external validity of the results of the 1986 survey. The 1992 survey confirmed that the geographical areas from which the subjects in the 1986 study were selected, were, indeed, representative of the whole province. The choice of the three age groups 35-36 y, 50-51 y, 65-66 y allowed the demonstration of an age-related increase in the prevalence of chronic bronchitis. The results in the different age groups suggest a slight underdiagnosis of asthma compared to that in the whole province.

Trends in asthma prevalence and a possible north-south gradient

The same questionnaire as that used in the OLIN study had been used in Stockholm and in Skåne (the southernmost part of Sweden) at the same time as the 1992 OLIN survey was made. The prevalences of asthma and respiratory symptoms were lower than in Norrbotten [Axelsson G, personal communication; Heuman K, personal communication]. In recent Swedish studies using a similar questionnaire and similar methods and criteria, the prevalence of asthma has been reported to be 5-7% [Larsson et al., 1993; Hermansson, 1991] and these results are similar to the questionnaire-based estimate of the prevalence of asthma reported in the Swedish part of the European Commission Respiratory Health Study [Boman G, personal communication].
The prevalence of asthma in young adults was considerably greater, around 10%, in the OLIN study than in studies from the late 1970s [Haahtela, 1980] or early 1980s [Åberg, 1989], and greater than the 7% found in teenagers in Umeå [Norrman et al., 1993], or the 9% found in Jämtland, Sweden [Larsson et al., 1993]. Data from 1992 comparing the prevalences of type-1-allergy in military conscripts and in children in Gothenburg and Norrbotten, in particular the town of Kiruna, have shown increases in the prevalences in both areas with a higher prevalence in Norrbotten [Åberg, personal communication]. Furthermore, results from 70 geographical areas throughout Sweden show a greater prevalence of asthma in the north [Forsberg et al, 1993b], supporting the existence of a north-south gradient in the prevalence of asthma, with a greater prevalence in the north, first suggested by Åberg in 1984 [Åberg, 1988].

Despite the fact that the different studies used differing methodology and diagnostic criteria, all the data collected during the last 30 years show a clear increase in the prevalence of asthma (Figure 3). Epidemiological research needs to concentrate resources on identifying modifiable risk factors that are responsible for the increase in asthma and in type-1-allergy. There are many theories about how to achieve this, which have been discussed in terms of cohort effects, age effects and period effects. The appearance of a disease may be explained by an imbalance in the host individual's defence and the exposure to which the host individual is subjected. In the cases of asthma and type-1-allergy, this imbalance is most pronounced in children and young adults, although it may be seen in all age groups, with the possible exception of the very old.

The dramatic increase in the prevalence of asthma in conscripts between 1971 and 1981 [Åberg, 1989] suggests a better evaluation of environmental or other changes that could affect the onset of asthma that has occurred during this period. One such factor may be the change in building techniques brought about by the oil crisis in the mid 1970s, with the introduction of new building materials. Several other theories, including maternal smoking and the increase in the number of household pets, have also been discussed. These factors, together with the outdoor climate, the long, cold winters and air pollution caused by industries, heating homes as well as car exhaust fumes in the villages and towns in northern Sweden, may affect the prevalence of asthma.
Figure 3. Trends in asthma prevalence in Nordic countries. The studies made by the Norwegian investigators, by Åberg, Mikaelsson & Stjernberg and by Lundbäck et al., have been performed using similar methods at the two investigations. In the Finnish and the other Swedish studies, different methods were used, except in those performed by Larsson et al. and Hermansson, in which the methods by Lundbäck et al. were used. *Teenagers, **conscripts, the other samples were adults.

Prevalence

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<th>Year</th>
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<td>1990</td>
<td>Norrman et al. [1993] in northern Sweden in 1990, in Jämtland in Gästrikland 7.2%</td>
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Lung function

Consideration should be paid to the limitations imposed by a cross-sectional study design when analysing lung function data. In addition, the selection procedure from the postal questionnaire imposes a further limitation in the ability to present numerical values on lung function for the whole study population. The data permit a discussion of respiratory symptoms' association with lung function impairment and data on FEV<sub>1</sub> have therefore been included. The existing data are also important starting points for the assessment of lung function data as prognostic markers in the prospective studies which are in progress.

The data allow analysis of respiratory symptoms' ability to predict impaired FEV<sub>1</sub> in the cross-sectional study population. Persistent wheeze was the single symptom associated with the greatest decrease in FEV<sub>1</sub>. Further, we found the combination of attacks of breathlessness and wheezing to be more associated with lung function impairment than chronic productive cough. However, the differences between the two conditions in decrease in FEV<sub>1</sub> were small. Kauffmann and co-workers [Kauffmann et al., 1979] found cough, sputum production and dyspnoea to be associated with low FEV<sub>1</sub>, the symptoms were, however, not related to a more rapid decline in lung function after controlling for the level of initial lung function, smoking, occupation and social class. In the cohort study, 575 male workers aged 30-54 y were followed for 12 years.

In the eight year follow-up study reported by Fletcher [1976], symptomatic smokers had a more pronounced decline in FEV<sub>1</sub> than asymptomatic smokers and non-smokers. OLIN data confirmed the significant decrease in FEV<sub>1</sub> in subjects aged 65-66 y who stated in the postal questionnaire that they were asymptomatic smokers, but not in younger asymptomatic smokers. Further, the decrease was not as pronounced as in those reporting symptoms. In the Fletcher study [1976], when controlling for smoking and initial level of FEV<sub>1</sub> as confounders, sputum production alone was not a significant cause of a more rapid decline in FEV<sub>1</sub>. In a 13-year follow-up study 2,378 subjects from Tucson, USA, and Cracow, Poland, with recently developed respiratory symptoms, a syndrome was identified that caused the greatest reduction in ventilatory capacity in the studied sample [Krzyanowski et al., 1990]. The syndrome consisted of at least two of the following three symptoms; wheezing, attacks of breathlessness, or asthma. No direct comparisons can be made with our cross-sectional data, however, there exist the same focusing on symptoms more
associated with asthma than with chronic bronchitis or COPD. The healthy worker effect should always be considered in occupational studies and sample selection may, in part, explain the results of the studies by Fletcher and Kauffmann et al. in which subjects with asthma may have been underrepresented in these study samples.

The estimate of the prevalence of more than 10% of the study population with an FEV$_1$ $<$80% of predicted values is high. The proportion of subjects with chronic bronchitis with this decrease of FEV$_1$ was similar, 30%-40%. to that found in other Swedish studies [Kiviloog et al., 1974; Stjernberg, 1985].

**Determinants of symptoms and diseases**

Analysis of possible determinants of respiratory symptoms and diseases is difficult. The cross-sectional study design makes great care necessary in the discussion of the importance of results showing significant relationships. Only exceptionally do cross-sectional data constitute a basis for the determination of causality.

The importance of smoking has already been discussed. The trend in smoking habits shows a small but significant decrease of the proportion of men who smoke, while there seems to be an increase in women. The multivariate analyses confirm the results from the bivariate analyses on the importance of smoking as a major causal factor for bronchitic symptoms including sputum production and longstanding cough, as well as for wheezing. A more complex pattern was seen for the symptom of attacks of breathlessness. A relationship with smoking was found, but there was no significant difference related to smoking habits when combined with wheezing. As for asthma, the greatest prevalence of the symptom combination attacks of breathlessness and wheezing was reported at the interview by ex-smokers. Results confirming those of Lebowitz [1977]. In the age group 20-21 y in the 1992 study all four main respiratory symptoms were significantly related to smoking, despite relatively few observations; 19% of men but 31% of women were smokers in that age group. These data, together with the increasing number of reports on the relationship between parental smoking and childhood asthma [Young et al., 1991; al-Frayh Bener et al., 1991], type-1 allergy [Witting et al., 1978; Wickman, 1992], impaired lung function in children [Lebowitz & Holberg, 1988; Sherill et al, 1992], and also of frequent infections during childhood and impairment of lung function [Paoletti et al., 1989b] suggest that the final word has not yet been said on smoking and its
A low sensitivity has only a limited influence on risk and odds ratios, as long as the specificity is high. Even if the interviews of the subjects in the symptomatic group yielded a considerable underestimation of the prevalence of chronic productive cough, it was still possible to base the analysis of determinants on it. This also explains the high odds ratios for smokers versus non-smokers in those reporting chronic productive cough.

Smoking and increasing age were the main risk factors for the development of chronic productive cough, followed by a family history of either asthma or chronic bronchitis. The large number of elderly non-smoking women with bronchitic symptoms was notable, even if the prevalences in smokers were higher. Age may be regarded as an independent risk factor, which can be partly explained by the reduction in the muco-ciliar clearance with increasing age [Wanner, 1977]. At the same time it should be remembered that everyone as they get older has a larger exposure for substances that affect the airways. These factors act as confounders in studies of the OLIN type. The sum of these, together with age become the "independent" variable "age". The influence of smoking and age is demonstrated by the fact that only 1 out of 50 men with chronic productive cough in the age group 35-36 y in the 1986 study was a non-smoker. The prevalence of the condition increased considerably with age, with estimates similar to previously reported results [Huhti, 1965], and also the proportion of non-smokers with the disease increased.

Significantly elevated odds ratios for the development of chronic productive cough were also found for the socio-economic groups of manual workers in industry, manual workers in service, and self-employed other than professionals, indicating occupational exposure to be of major importance. Of the various occupational groups, miners had the highest prevalence of chronic productive cough, with levels of prevalence similar to those reported by Jörgensen & Svensson [1970], followed by farmers. Higgins et al. [1977] described the relationship between smoking, socio-economic group and chronic bronchitis as early as 1977.

In the OLIN study, only a family history of asthma could be shown to be an important risk factor for the development of asthma. The slightly increased odds ratios for assistant non-manual employers and manual workers in service may
support the indoor climate hypothesis as a risk factor for asthma [Croner & Kjellman, 1992; Wickman, 1993]. However, the results of the OLIN study may also be explained by the fact that having asthma influences an individual’s choice of profession. Neither smoking nor age seemed to be of significant importance when the calculations were based on the study base of the 1986 study including 5,698 participants. When the study base was trebled in the 1992 study, low but significant questionnaire-based odds ratios could be demonstrated. The multivariate analysis showed ex-smoking as an independent risk factor, as shown by Lebowitz [1977]. These analyses also indicated urban living (towns vs sparsely-populated areas) as an independent risk factor. The indication of an urban factor in asthma has not previously been demonstrated in adults in Sweden, but has been shown in children [Andræ et al., 1988; Bråbäck & Kälvesten, 1991].

Apart from an indicated urban factor in asthma no clear effects of population density or area of domicile were found for either asthma or the bronchitis-associated conditions, which contrasts with the results of studies performed in more densely-populated areas [Viegi et al., 1991b; Tzonou et al., 1992]. However, there was a trend for several conditions towards a higher prevalence in the colder interior of the province indicating a climate factor, confirming the results of studies in Swedish conscripts [Åberg, 1989] and in part results based on a population study performed in two areas in northern Sweden [Larsson et al., 1993].

The cross-sectional study design means that results regarding determinants, with the exception of the influence of age, smoking and occupational exposure on chronic bronchitis as well as the importance of a family history of asthma, must be judged very carefully. The results are mainly considered as a basis for making hypotheses and must be validated by case-referent and cohort studies, which are in progress.
CONCLUSIONS
CONCLUSIONS

Asthma and chronic bronchitis are common diseases.

There is evidence of a continuous increase in the prevalence of asthma and many respiratory symptoms in northern Sweden.

Main determinants of the diseases must be identified in more detail in order to achieve prevention.

A self-administered questionnaire suffices to estimate the prevalence of asthma in a population. If valid cases with the disease have to be identified, more detailed methods are necessary. A self-administered questionnaire yields an underestimate of the prevalence of chronic bronchitis.

1. The prevalence of asthma in adults 20-69 y in Norrbotten in 1992 was 7-8% according to the postal questionnaire and was considerably higher, approximately 10%, in young adults.

2. In subjects aged 35-36 y, 50-51 y and 65-66 y, the prevalence of asthma in 1986-1987 was 5% using a combination of epidemiological and clinical methods. There were small age- and gender-related differences.

3. Various operational criteria yielded a prevalence of asthma in 1986-1987 of 4-7%. The combination of wheezing and bronchial hyperresponsiveness may be even more common.

4. Between 1986 and 1992 the prevalence of asthma increased by about 1% in subjects aged 35-36 y, 50-51 y and 65-66 y according to the postal questionnaire. This increase is supported by a greater increase in the use of anti-asthmatic drugs and of some respiratory symptoms, including chronic productive cough.
5. Chronic bronchitis in subjects aged 35-36 y, was 3% in 1986-1987. The prevalence increased with increasing age, particularly in men. The mean prevalence in the three age groups was approximately 12% in men and 8% in women. Differences in smoking habits mainly explain this difference in prevalence.

6. Determinants of diseases
a. Chronic bronchitis was strongly associated with smoking, age and a family history of obstructive airway disease. Regarding socio-economic group chronic bronchitis was related to manual workers in industry and to self-employment other than of professionals, particularly in miners and in those employed in agriculture.

b. Asthma was mainly associated with a family history of asthma and was more common in manual workers in service and in non-manual assistant employees, typical indoor occupations. In addition, asthma was common in farmers. Results of the OLIN study indicate the presence of an urban factor in asthma in northern Sweden, despite respiratory symptoms in general tended to be more common in the colder interior of the province.
PERSPECTIVES
A continuing theme in this dissertation has been the methodology of estimating prevalence. Therefore a discussion of which level to place these studies is of value. If the aim of an epidemiological study is to assess the crude prevalence of a disease, then a postal questionnaire will suffice. An underestimate of the prevalence of chronic bronchitis will result partly as a direct answer to the question and partly because bronchitic symptoms are underreported, particularly by older smokers. If the aim is also to identify cases of asthma and to achieve a high degree of specificity and an acceptable sensitivity and a relevant estimate of the prevalence of chronic bronchitis, then a structured interview is necessary that may be performed by trained nurses. If an assessment of the occurrence of CAL or CAO is required, lung function tests should be performed, for example together with the interview. If the aim is to identify cases with nearly 100% specificity, when sensitivity is not critical, important in case-referent studies with limited numbers of participants, then further examination moments are necessary. In these circumstances the OLIN interview criteria for asthma combined with a physiological verification of the diagnosis should be made by bronchodilatation or methacholine tests. A negative physiological test result in subjects with history-based symptoms of asthma the examinations may be supplemented by PEF-curves [Larsson, personal communication] over 2-3 weeks, preferably with more than two measurements every day; these may contribute to increasing sensitivity.

Michael Burr has asked "is asthma increasing?" [1987], and two years later he replied that it is [Burr et al., 1989]. Data from prevalence studies suggest that the prevalences of asthma and type-1-allergy are increasing in society. Whether or nor this is the case for chronic bronchitis and COPD is unknown. Clinical and experimental research has to greater extent than epidemiological research provided answers to important questions about asthma and aided in reducing the suffering caused by asthma and type-1-allergy [Gregg, 1983]. Those results produced by epidemiological research into asthma and type-1-allergy is still mainly descriptive in nature. However, epidemiological research is necessary for the identification of modifiable determinants of these diseases, in order to achieve primary prevention. This research may only be carried out as interdisciplinary studies by epidemiologists, clinicians, and natural and social scientists. Further, co-operation between epidemiological, clinical and experimental research must improve.
Experience from large-scale studies, primarily in the USA, that have been referred to in this dissertation, show the important steps that now must be taken as regards to both human, and environmental factors. In the case of environmental factors it is imperative that better techniques for characterising, classifying, and quantifying exposure in ways that may be used in epidemiological surveys. Modern computer technology, through multivariate analysis methods, allows the calculation of risks and permits control of confounders; thus it is important that the data collected are valid.

In order to study aetiology and early pathogenesis of airway diseases, large cohorts need to be followed for considerable periods of time. The disease processes may take considerable time to develop, particularly in the case of bronchitis and COPD. Large cohorts are required to ensure that associations may be explained by risk, rather than by chance. The co-operation of clinicians is important to ensure the validity of classification of diseases and to improve compliance in longitudinal studies.

It is as a clinician that the author would like clinicians not to hesitate to become involved in studies that extend classical medicine. It is important to break conventions, question traditional ways of working, test new methods and to develop new outlooks for research. Science must grasp opportunities for progress and not be impeded by difficulties, otherwise there will be stagnation in the attainment of new knowledge.
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