Incidence and remission of asthma and respiratory symptoms in adults

*The Hordaland County Cohort Study*

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ACKNOWLEDGEMENTS

Large studies of the general population, followed for many years, obviously require a great effort. When the planning of the Hordaland County Study started, I was still in primary school. The Hordaland County Study is the brainchild of my second supervisor, professor Amund Gulsvik. Through relentless effort, and with sincere interest, he is largely responsible for the creation of the epidemiologic research environment at the Department of Thoracic Medicine. Not many weeks had passed after I started at the department, before he pulled me aside and told me he trusted I would want to seek answers only available through real science. We all know Amund as a man who follows up on our work closely, with great focus, support and eagerness. For the last part of the time I have been working on this project, he has remained almost uncharacteristically in the background, although always available for help and comments. I take that as a compliment of trust.

Of course, most of my training has come from my first supervisor, professor Per Bakke. Per is widely known among research fellows, far beyond the Department of Thoracic Medicine, as one of the best supervisors around. I know this first-hand. A popular man, Per is always short of time, but never fails to give me the time I need, no matter how inconvenient. A mild man, he never presses me when he knows better; which I think is a strategy of allowing me to come to my senses by myself. And, Per is a very skilled man, in treating people so they feel valuable, and in treating epidemiology so it makes sense.

My third supervisor is associate professor Geir Egil Eide. A statistician with particular knowledge of attributable fractions, he has provided the gravity needed to focus our analyses, both before and during. Geir has always been willing to teach me the how’s of analyzing, although it sometimes took more than one effort. And Geir is perhaps my best critic when writing in English; once he has approved a manuscript, I feel certain few errors remain.

I feel fortunate, as my three supervisors have complemented each other, helped me grow, and stood up for me. Thank you.

With data collection starting almost 20 years ago, I fear not paying tribute to all those participating. In alphabetical order, Eli Henricksen, Borghild Hovland, Peer Lilleng, Bjørg Meidell, Steinar Nielsen, Ernst Omenaas, Olav Overå, Sølvi Sletten, Lene
Svendsen, and Ida Welle have all had important or vital roles in the data collection of the baseline survey or follow-up survey or both. The Department of Thoracic Medicine relies upon the combined effort of all those regularly involved, and then some. On behalf of the department I wish to express my thanks to all those who help create the positive research environment at the department, by readily helping out, even when not directly involved. I also want to thank the Department of Thoracic Medicine itself, for enabling my work by means of paying my salary, while I have been working 50% clinically, and 50% on this dissertation.

Friends and colleagues are invaluable in sharing knowledge, frustrations and sometimes beer. I think you know who you are, but Tor Arne Strand, Jan Christian Brøgger, and Jon Andrew Hardie deserve special mention.

At times I have been absent-minded and remote, when at home. The love, patience and support I have received from Mikal, Erik and Christine is what makes everything worthwhile.

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I have worked at the Department of Thoracic Medicine since 1998 in a 50% clinical and 50% research position, as part of the Department’s ongoing support of active research. I have received a research grant from GlaxoSmithKline enabling equipment of computation. To present the results of my research at the American Thoracic Society (ATS), and European Respiratory Society (ERS) annual meetings, I have received support from GlaxoSmithKline, AstraZeneca, and the Norwegian Thoracic Society.


**LIST OF PAPERS**

**Paper I**
Nonresponse in a community cohort study. Predictors and consequences for exposure-disease associations.

**Paper II**
Incidence of asthma and respiratory symptoms by sex, age and smoking in a community study.

**Paper III**
Occupational airborne exposure and the incidence of respiratory symptoms and asthma.

**Paper IV**
Remission of respiratory symptoms by smoking and occupational exposure in a cohort study.
European Respiratory Journal; 23(4): 589-94.

**Paper V**
The effect of educational level on the incidence of asthma and respiratory symptoms.
**TERMS AND ABBREVIATIONS**

Terms:

**Prevalence** - The proportion of a population that has disease (or an event like a symptom) at a specific point in time. The time can be immediate, a point prevalence, or over a longer time period, like for instance lifetime prevalence.

Incidence can be presented as Incidence rates, or Cumulative Incidence:

**Incidence Rate** - The occurrence of new disease per unit of person-time.

**Cumulative Incidence** - The proportion of people who develop new disease during a specified period of time (a.k.a. incidence proportion).

Inversely,

**Remission rate** - The occurrence of a return to a non-disease state per unit of person-time.

**Cumulative remission** - The proportion of people who return to a non-disease state during a specified period of time.

**Prospective study** - A study in which the information about exposure(s) was gathered before the studied outcome occurred.

**Retrospective study** - A study in which the information about exposure(s) was gathered after the studied outcome occurred.

**Cross-sectional study** - A study where all information is gathered at one point in time.

**Prevalence study** - A cross-sectional study conducted to estimate prevalence is often called a prevalence study.

**Longitudinal study** - A study where the information is gathered over a period of time.

**Cohort study** - A study where a defined group of exposed and unexposed subjects is followed for a set amount of (follow-up) time, and outcomes are recorded within and/or after the follow-up time.

**Incidence study** - A cohort study conducted to estimate incidence is often called an incidence study.

**Odds** - The ratio of the probability that some event will occur over the probability that the same event will not occur.
Odds ratio - The ratio of the odds in one group of subjects over the odds in another group of subjects.

Attributable fraction - The fraction of new cases that would have been prevented had the exposure in question not occurred.

Logistic regression - A mathematical modeling approach used to describe the effects of multiple explanatory variables on a dichotomous response variable, based on the logistic model.

Logistic model - a statistical model of an individual’s probability of developing an outcome as a function of the possible risk factors $X$:

$$P(D=1|X_1,X_2,...,X_k) = \frac{e^{\beta_0+\beta_1X_1+\beta_2X_2+...+\beta_kX_k}}{1+e^{\beta_0+\beta_1X_1+\beta_2X_2+...+\beta_kX_k}}$$

The linear term $\beta_0+\beta_1X_1+\beta_2X_2+...+\beta_kX_k$ is called the logit.

**Abbreviations:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AF</td>
<td>Attributable Fraction</td>
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<tr>
<td>BAL</td>
<td>Broncho-Alveolar Lavage</td>
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<td>BHR</td>
<td>Bronchial Hyper-Responsiveness</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CD4</td>
<td>Cellular Determinant protein 4 (T helper cell)</td>
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<td>CDC</td>
<td>Centers for Disease Control</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<td>EBC</td>
<td>Exhaled Breath Condensate</td>
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<td>ECRHS</td>
<td>European Community Respiratory Health Survey</td>
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<tr>
<td>FEV1</td>
<td>Forced Expiratory Volume in 1 second</td>
</tr>
<tr>
<td>HMW</td>
<td>High Molecular Weight</td>
</tr>
<tr>
<td>HUNT</td>
<td>Helse Undersøkelsen i Nord Trøndelag</td>
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<tr>
<td>IgE</td>
<td>Immunoglobulin, class E</td>
</tr>
<tr>
<td>IL-#</td>
<td>Interleukin #</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union Against Tuberculosis and Lung Disease</td>
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<tr>
<td>LMW</td>
<td>Low Molecular Weight</td>
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<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
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<tr>
<td>OLIN</td>
<td>Obstructive Lung disease In Northern Sweden study</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analyses Systems</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Product and Service Solutions</td>
</tr>
<tr>
<td>Th1/Th2</td>
<td>T helper cell class 1 and 2</td>
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</table>
**INTRODUCTION**

In approximately the fifth century AC, the Greco-Roman physician Aurelianus Caelius phrased one of the earliest working descriptions of asthma (1):

“Asthma occurs oftener in men than in women, in middle age than in children or old men, and in the delicate rather than in the strong. More in winter than in summer and more at night than by day. In some it begins after disease, whereas in others it begins without obvious cause... the patient has a feeling of suffocation, heaviness and burning heat of the chest, and a feeling of spasm in the bowels. It begins with violent suffering, wheezing in the chest, and the voice is weak, the neck and face stretched and red, the expression anxious...there are tears...and the pulse is weak. Asthma is distinct from other diseases where there is difficult breathing...”

Central to our understanding of a disease is its distribution, as the first part of Aurelianus Caelius’ description so clearly shows. Apparently, the sex- and age- distribution of a disease has been a diagnostic help for many centuries. However, Caelius’ description also hints at seasonal variations of asthma, and a risk factor as an explanatory variable, namely a prior disease. Presumably this could be an airways infection, an occurrence no less common in the times of the Roman Empire. Finally, this description underscores how the diagnosis of asthma is dependent on observation of its symptoms, symptoms not necessarily specific for asthma.

Epidemiology can be defined as: “the study of the distribution and determinants of health-related states or events in specified populations and the applications of this study to control of health problems” (2). Included in this definition is not only the description of the occurrence of disease, but also the preventive purpose of the investigation.

The prevalence and incidence of a disease are the most central measures of occurrence in epidemiology. The prevalence is a point-measure in time, and is more easily measured than incidence, which requires a time-period of observation. This is reflected in the medical literature, where there are many times more papers describing the prevalence of any given disease than its incidence.
The measurement of respiratory symptoms can be part of the measurement of asthma. But measuring each symptom individually is attractive for other reasons. The perception of dyspnea or cough may not vary over time the same way as a diagnostic label, like asthma. Thus, some of the inherent bias one expects with self-reported asthma, may be avoided when asking specifically about a single symptom. The downside is the lack of specificity in the symptoms; for instance is dyspnea common in a wide range of diseases. This can partly be overcome by examining combinations of symptoms, like attacks of dyspnea and wheezing.

When evaluating the course of a disease over time, knowing the normally occurring distribution and development of a symptom can be helpful. Also, the effect of a risk factor may not be the same on dyspnea as on cough, although both symptoms can be part of the same diagnosis.

The three most common symptoms in asthma are cough, dyspnea and wheezing. Further distinction is usually sought, like whether the cough is productive or degrees of dyspnea. The most commonly examined respiratory symptoms in community health surveys are phlegm when coughing, dyspnea in varying degrees of exertion, attacks of dyspnea, and plain wheezing.

**Prevalence**

In Norway, four major studies from 1972 to 1998/99 have estimated the prevalence of asthma and respiratory symptoms in the adult general population (3-6). In the first phase of the Hordaland County Study on respiratory health in 1985, the adult prevalence of asthma was 3.5% with no difference between genders (7). The prevalence of phlegm cough and wheezing was higher in men than in women, 25%-17% for phlegm cough and 23%-19% for wheezing respectively (7). The prevalence of dyspnea grade 2 was higher in women, 13% versus 10% in men.

In the Nord-Trøndelag Health Survey (HUNT), the adult prevalence of asthma was 8.6%, and not significantly different in between genders (8). The prevalence of phlegm cough was roughly 8%, and daytime coughing approximately 15% (8).
In the most recent study, Brøgger et al examined the prevalence of attacks of dyspnea, wheezing, and asthma in Western Norway and Oslo, and compared them to the prevalences found in the earliest study, by Gulsvik in Oslo in 1972 (9). The prevalence of both symptoms and asthma had increased since 1972. In 1998/99 the prevalence of asthma was 7.6% in men, and 10.7% in women. The prevalence of wheezing was roughly 25% for both genders, whereas the prevalence of attacks of breathlessness was higher in women, 19%, versus 14% in men (9).

The prevalence of asthma varies greatly between countries. This is unlikely to be due only to methodological and diagnostic differences (10). In the European Community Respiratory Health Survey (ECRHS) conducted between 1991/93, the asthma prevalence varied from 2% in Tartu, Estonia, to 12% in Melbourne, Australia, with a median prevalence of 4.5%. The prevalence was highest in Australia, New Zealand, and the UK (11). In the Norwegian part of the ECRHS, with a study sample from Bergen, the asthma prevalence was found to be 4.3% (11). Further, wheeze within the last 12 months varied between 4% in Bombay, India to 32% in Dublin, Ireland, with a median of 20.7% (11).

In the last two decades, a great deal of attention has been given to the perceived rise in asthma prevalence, at least in the Western countries. This has been studied more extensively in children. Although there is some evidence of changing diagnostic labeling (12), the vast number of studies point towards a real increase in asthma prevalence, also among adults (6).

In a stationary population, the relationship between the prevalence and the incidence of a disease can be described as (13):

\[
\text{Prevalence} = \text{Incidence} \times \text{Duration of disease}
\]

If we define asthma as a chronic, or life-long disease, it follows that an increase in asthma prevalence should be due to an increase in asthma incidence. It should be noted that this is a simplification, and that the exact relationship between prevalence and incidence of asthma is not yet clearly defined (14).
**Incidence**

Before we can even approach the question of a possible increase in the incidence of asthma, we need to know what the adult incidence of asthma is. Unfortunately, there are few longitudinal studies from general populations, on the incidence of respiratory symptoms and asthma in adults.

While measuring the incidence of asthma and/or respiratory symptoms, three main designs have been applied: First, the cohort studies, which follow a cohort of subjects for a set period of time, and count the new events. Second, the cross-sectional studies, where subjects have been asked when in time they first were diagnosed or experienced symptoms.¹ Finally, there are register-based studies, using medical registers to obtain diagnoses in the population to which the register pertains.

An overview of the main studies on adult incidence of asthma and respiratory symptoms is given in table 1. Studies were identified through MEDLINE, with searches consisting of various combinations of the following keywords: respiratory symptoms, cough, dyspnea, wheezing, asthma, incidence, cohort, longitudinal, community, general population, and the MeSH terms: ‘Cohort Studies’, ‘Asthma’, ‘Signs and Symptoms, Respiratory’. Only English language papers were evaluated. From the bibliographies of retrieved papers, additional relevant papers were identified. All cohort studies on general populations were included (15-29), if calculations of incidence rates of asthma and/or respiratory symptoms were possible. Further, important cohort studies from selected populations, like the British National Child Development Study (30), the Finnish Twin Cohort Study (31, 32), and the Nurses Health Study (33) were included, as well as four large cross-sectional surveys (34-37), and one register-based survey (38).

The number of published articles presenting incidence rates is greater than the number of studies. For instance, the cohort from Tucson, Arizona had 10 follow-ups up until 1988.

¹ These are sometimes referred to as retrospective cohort studies. I find that somewhat confusing, and the term cohort study is used in this dissertation to denote a prospective study design.
Three papers have published incidence rates from this study, one based on the first three follow-ups (15), one on baseline, the fifth and the eighth follow-up (16), and one on baseline and the eighth or ninth follow-up (17). If we consider only the methodology, and counts for instance the Tucson, Arizona cohort for one study, then there are 21 studies in table 1.

Twelve studies used a random selection of the source population (table 1), and for two studies an entire geographical area was defined as the source population (23, 38). However, two studies did not give a clear account of the selection (18, 24). In eleven of the studies, information was collected by interview (15-18, 21, 23-26, 29, 30, 35). In none of these eleven studies have the numbers of interviewers involved been reported. Six of the studies did not report the exact wording of the questions used to define asthma or respiratory symptoms (table 1) (17, 18, 21, 23-25).
Table 1. Studies estimating adult incidence of asthma and respiratory symptoms

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Name</th>
<th>Location</th>
<th>Author, year</th>
<th>Years Study was conducted</th>
<th>Years on which incidence rates were based</th>
<th>Years of follow-up</th>
<th>Random sampling of source population</th>
<th>Age-span of study population</th>
<th>Self-employed questionnaire / Interview</th>
<th>Number of interviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort studies from a general population with more than one follow-up</td>
<td>The Obstructive Lung Disease in Northern Sweden (OLIN) Study</td>
<td>Tucson, Arizona, USA</td>
<td>Dodge, 80</td>
<td>1972 - 1988</td>
<td>1972/73 - 1976</td>
<td>3.5</td>
<td>no*</td>
<td>all ages</td>
<td>nurse-led interview</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>The Obstructive Lung Disease in Northern Sweden (OLIN) Study</td>
<td>Tucson, Arizona, USA</td>
<td>Krzyzanowski, 90</td>
<td>1972 - 1988</td>
<td>1972/73 - 1983/84</td>
<td>11</td>
<td>no**</td>
<td>19-70</td>
<td>nurse-led interview</td>
<td>not reported</td>
</tr>
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<td>The Obstructive Lung Disease in Northern Sweden (OLIN) Study</td>
<td>Tucson, Arizona, USA</td>
<td>Krzyzanowski, 92</td>
<td>1972 - 1988</td>
<td>1972/73 - 1984/85</td>
<td>12</td>
<td>no*</td>
<td>19-70</td>
<td>nurse-led interview</td>
<td>not reported</td>
</tr>
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<td>The Finnish Twin Cohort Study</td>
<td>Helsinki</td>
<td>Vestinen, 88</td>
<td>1975 - 1990</td>
<td>1975 - 1990</td>
<td>31</td>
<td>yes</td>
<td>18-64</td>
<td>mailed questionnaire</td>
<td>-</td>
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<td>32</td>
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<td>18-45</td>
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<td>The Nurses Health Study</td>
<td>Rochester, USA</td>
<td>Yunginger, 92</td>
<td>1964 - 1983</td>
<td>1964 - 1983</td>
<td>38</td>
<td>no*</td>
<td>15-70</td>
<td>mailed questionnaire</td>
<td>not reported</td>
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<td></td>
<td>The Obstructive Lung Disease in Northern Sweden (OLIN) Study</td>
<td>The Netherlands</td>
<td>Xu, 97</td>
<td>1965 - 1990</td>
<td>1965 - 1990</td>
<td>18</td>
<td>yes</td>
<td>15-64</td>
<td>interview</td>
<td>not reported</td>
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<td>The Coronary Artery Risk Development in Young Adults (CARDIA) study</td>
<td>Estonia</td>
<td>Broder, 74</td>
<td>1999 - 2000</td>
<td>1999 - 2000</td>
<td>23</td>
<td>no*</td>
<td>20-44</td>
<td>mailed questionnaire</td>
<td>-</td>
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<td>The Copenhagen City Heart Study</td>
<td>Denmark</td>
<td>Godtfredson, 91</td>
<td>1976 - 1994</td>
<td>1976 - 1994</td>
<td>22</td>
<td>yes</td>
<td>20+</td>
<td>questionnaire</td>
<td>-</td>
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<td>The Tecumseh Health Study</td>
<td>Michigan</td>
<td>Broder, 74</td>
<td>1965 - 1978</td>
<td>1965 - 1978</td>
<td>23</td>
<td>yes</td>
<td>12-74</td>
<td>interview</td>
<td>not reported</td>
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<td>The European Community Respiratory Health Survey (ECRHS)</td>
<td>Sweden</td>
<td>Broder, 74</td>
<td>1998 - 1999</td>
<td>1998 - 1999</td>
<td>23</td>
<td>yes</td>
<td>20-44</td>
<td>mailed questionnaire</td>
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<td>Lundback, 91</td>
<td>1976 - 1992</td>
<td>1976 - 1992</td>
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<td>yes</td>
<td>20-44</td>
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<td>1965 - 1981</td>
<td>1965 - 1981</td>
<td>23</td>
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<td>12-74</td>
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<td>Toren, 99</td>
<td>1998 - 1999</td>
<td>1998 - 1999</td>
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<td>20-50</td>
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<td>The Finnish Twin Cohort Study</td>
<td>Finland</td>
<td>Sunyer, 99</td>
<td>1999 - 2000</td>
<td>1999 - 2000</td>
<td>35</td>
<td>yes</td>
<td>20-44</td>
<td>interview</td>
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<td>The Italian Study on Asthma in Young Adults</td>
<td>Italy</td>
<td>deMarco, 90</td>
<td>1998/2000</td>
<td>1998/2000</td>
<td>36</td>
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<td>20-44</td>
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<td>Broger, 90</td>
<td>1998 - 1999</td>
<td>1998 - 1999</td>
<td>37</td>
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<td>15-70</td>
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<td>Exact wording of questions reported</td>
<td>Similar wording of questions at baseline and follow-up</td>
<td>Size of baseline study population</td>
<td>Response rate, baseline</td>
<td>% of original study sample on which the incidence rates are based</td>
<td>Outcomes</td>
<td>Predictors examined</td>
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<tr>
<td>yes probably**</td>
<td>2989 households</td>
<td>approximately 55% ***</td>
<td>not reported, but less than 50%</td>
<td>Asthma, attacks of dyspnea with wheeze</td>
<td>'Asthma syndrome', chronic cough, chronic phlegm, chronic bronchitis, wheeze, attacks of dyspnea</td>
<td>sex, age, smoking, city</td>
<td></td>
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<td>no probably**</td>
<td>2989 households</td>
<td>approximately 55% ***</td>
<td>not reported, but less than 25% (n=640)</td>
<td>Asthma, chronic cough, chronic phlegm, wheeze, attacks of dyspnea</td>
<td>sex, age, smoking, city</td>
<td></td>
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<tr>
<td>no probably**</td>
<td>2989 households approximately 4633 (exact number not reported)</td>
<td>approximately 55% ***</td>
<td>approximately 36% (n=1452)</td>
<td>Asthma, chronic cough, chronic phlegm, wheeze, attacks of dyspnea</td>
<td>sex, age, smoking, city</td>
<td></td>
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<td>no probably**</td>
<td>2989 households approximately 4633 (exact number not reported)</td>
<td>approximately 66% (n=3047)</td>
<td>approximately 37.5% (n=1738)</td>
<td>Asthma, chronic cough, chronic phlegm, wheeze, attacks of dyspnea</td>
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<td>9823</td>
<td>88.0%</td>
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<td>sex, age, smoking, city</td>
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<tr>
<td>no probably**</td>
<td>1686</td>
<td>96.1%</td>
<td>69.0%</td>
<td>Asthma, chronic bronchitis, respiratory symptoms smoking</td>
<td>sex, age, smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no probably**</td>
<td>unknown&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not reported</td>
<td>not reported, but less than 50%</td>
<td>Respiratory symptoms smoking</td>
<td>sex, smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes</td>
<td>6610</td>
<td>86%</td>
<td>81.6%</td>
<td>Asthma, attacks of dyspnea</td>
<td>sex, age, smoking, COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes</td>
<td>6610</td>
<td>86%</td>
<td>78.5%</td>
<td>Asthma</td>
<td>sex, age, smoking, chronic cough, chronic phlegm, dyspnea gr.3, persistent wheeze, attacks of dyspnea with wheeze, bronchitis (and univariately SES)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no no</td>
<td>10143</td>
<td>51.0%</td>
<td>40.3%</td>
<td>Asthma</td>
<td>sex, educational level, smoking, BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes probably**</td>
<td>19698</td>
<td>72.2%</td>
<td>51.8%/34.6%</td>
<td>Asthma</td>
<td>smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no no</td>
<td>9823</td>
<td>88.0%</td>
<td>66.8%</td>
<td>Asthma, allergic rhinitis allergic rhinitis</td>
<td>sex, age, smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no probably**</td>
<td>1686</td>
<td>96.1%</td>
<td>69.0%</td>
<td>Chronic bronchitis, respiratory symptoms smoking</td>
<td>sex, age, smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no probably**</td>
<td>unknown&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not reported</td>
<td>not reported, but less than 50%</td>
<td>Respiratory symptoms smoking</td>
<td>sex, smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes</td>
<td>not reported</td>
<td>not reported</td>
<td>unknown</td>
<td>Asthma, COPD</td>
<td>sex, age, smoking, income, race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes</td>
<td>2422</td>
<td>76.8%</td>
<td>56.1%</td>
<td>Asthma</td>
<td>sex, age, hay fever, chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes</td>
<td>3370</td>
<td>approximately 58%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41.8%</td>
<td>Asthma</td>
<td>sex, age, smoking, chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3786</td>
<td>89.0%</td>
<td>74.5%</td>
<td>Asthma, 10 symptoms</td>
<td>sex, age, smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>57 890 subjects in 1980 approximately 15 000 subjects (exact number not reported)</td>
<td>78.5%</td>
<td>31.3%</td>
<td>Wheezing illness Many&lt;sup&gt;ef&lt;/sup&gt;</td>
<td>Many&lt;sup&gt;ef&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes</td>
<td>18 559</td>
<td>approximately 87%</td>
<td>approximately 72%</td>
<td>Asthma</td>
<td>sex, age, smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes yes</td>
<td>18 559</td>
<td>approximately 87%</td>
<td>approximately 58%</td>
<td>Asthma</td>
<td>sex, age, hay fever, chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no not reported</td>
<td>74 072</td>
<td>not reported</td>
<td>impossible to calculate</td>
<td>Asthma</td>
<td>smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes not applicable</td>
<td>20 000</td>
<td>79.1%</td>
<td>79.1%</td>
<td>Asthma</td>
<td>sex, age, smoking, family history, hay fever, atopic dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes not applicable</td>
<td>30 000</td>
<td>63%</td>
<td>58.8%</td>
<td>Asthma</td>
<td>sex, age, smoking, family history, hay fever, atopic dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes not applicable</td>
<td>25 969</td>
<td>72.7%</td>
<td>72.7%</td>
<td>Asthma</td>
<td>sex, age, smoking, family history, hay fever, atopic dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes not applicable</td>
<td>2864</td>
<td>88.3%</td>
<td>88.3%</td>
<td>Asthma</td>
<td>sex, age, smoking, family history, hay fever, atopic dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes not applicable</td>
<td>57 890 subjects in 1980 approximately 15 000 subjects (exact number not reported)</td>
<td>unknown % of available records</td>
<td>unknown % of available records examined</td>
<td>Asthma, single wheezing episodes</td>
<td>sex, age</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
The perhaps most important quality measures next to random sampling, are the response rates. An extensive literature search was necessary to obtain the response rates (39-53), as there seem to be little agreement on how to report the response rates. For some of the studies, the method-sections of several papers describing each study were inadequate for exact calculation of the response rates. The most often under-reported response rates were the actual number of responders at baseline or the actual number of study subjects invited (15-18, 25, 31-33, 38). For the cohort studies, the incidence rates are based on subjects responding to one or more follow-ups. The most important measure of response is the percent of the original study sample on which the incidence rates were based. The numbers in table 1 reveal that many studies have rather low response rates.

The four cross-sectional studies and the register-based study were retrospective, and as such open to recall bias.

Ideally, a study should be prospective, of randomly sampled study subjects, with at least two time points, similar methodology at baseline and follow-up, and a high response rate. Only two such studies have been conducted besides the Hordaland County Cohort Study; namely the study from Krakow, Poland (17), and the Obstructive Lung disease In
Northern Sweden (OLIN) Study (19, 20). Only the study from Krakow, Poland had been published at the time the Hordaland County Cohort Study follow-up was planned.

**Remission**

A few of the studies in table 1 have also examined the remission of asthma or respiratory symptoms (17, 18, 28, 36, 54, 55). In the current paradigm of asthma as a chronic disease, it is a matter of debate whether ‘true’ remission of the airways inflammation really occurs. Regardless, some subjects with a label of asthma at one time will state at a later time that they no longer have asthma. It is of interest to know the size of that fraction, and perhaps more so, which factors influence a migration out of the diagnosis of asthma. Estimating this fraction (which can be defined as the cumulative remission) is fraught with some serious questions regarding methodology, which are discussed later.

The Hordaland County Cohort Study did not allow for a reasonable estimation of the remission of asthma, due to the wording of the asthma question at follow-up. A reasonable estimation of the remission of respiratory symptoms was possible; previously only conducted in the Tucson and Krakow cohorts (17), and later in the Vlagtwedde/Vlaardingen cohort (18).

**Risk factors**

Defining asthma is difficult. The clinical picture varies from patient to patient, and over time, in each patient. There is no ‘gold-standard’ test. Not surprisingly then, are the causes of asthma still not fully understood. Whether asthma is one or several diseases can be debated. Before, asthma was often thought of as ‘allergic’, or ‘non-allergic’. The current consensus defines asthma as a chronic inflammatory disorder of the airways, associated with airway hyper-responsiveness, airflow limitation, and respiratory symptoms (56). Asthma is likely to be a multi-factorial disease, with several pre-disposing host factors and environmental factors.

A cohort study has the advantage of enabling an assessment of a risk factor before the incident event; a requirement if the risk factor is to be thought of as causal. If the effect of the risk factor is not strong, a larger sample is often needed to demonstrate the association. A selected cohort, of for instance specific occupational groups, can be of
great value in evaluation of potential risk factors. However, with a selected cohort there is
the question whether the findings are applicable to the population at large. If the
preventive potential of the risk factor is to be assessed in the whole population, a general
population study is the preferred design.

Thus, the Hordaland County Cohort Study enabled the assessment of some risk factors
for the incidence of respiratory symptoms and asthma, as well as their preventive
potential.

With recent advances in computational technology, sophisticated analyses of the impact
of several risk factors have become available. Whereas studies from the 1970’s rarely had
adjusted for more than one co-factor, recent studies often take several risk factors into
account, usually by some sort of regression analyses. In table 1, the potential risk factors
examined in each study are listed. The factors listed are either risk factors for which the
studies have determined the potential effect of, or as a confounder to be adjusted for.

Smoking is the most commonly assessed risk factor. Where several study centers are
involved, adjustment for study center is usually performed. Family history and/or atopy
are often taken into account, atopy being the strongest known risk factor for asthma.
Some assessment or adjustment for socio-economic status was performed in two of the
studies listed in table 1 (20, 21). Only one study examined the effect of occupational
exposure (26). One other paper from the cohort from Krakow, Poland, specifically
examined the effect of occupational exposure on the incidence of asthma and respiratory
symptoms (57).

Krzyzanowski et al examined the remission of respiratory symptoms by sex, age, and
smoking habits (17). Xu et al examined the remission of respiratory symptoms by
bronchial hyper-responsiveness (BHR) (18).
AIMS

The aims of the Hordaland County Cohort Study were:

1) To examine predictors for response at follow-up, and the consequences of increasing the response rates through several reminders.

2) To measure the occurrence of new cases of asthma and respiratory symptoms by sex and age in the adult general population in Norway.

3) To describe the effect of the risk factors smoking, occupational exposure, and educational level, on the incidence of respiratory symptoms and asthma.

4) To examine the remission of respiratory symptoms, and the effect of changes in smoking habits, previous occupational exposure, and educational level.
MATERIALS AND METHODS

Study design

The baseline survey was conducted in the fall of 1985, and has been well described previously (4, 58). All adults aged 15-70 years, in the county of Hordaland, were eligible for inclusion in the survey, comprising a total number of 267 403 individuals per 31st of December 1984. All Norwegian citizens are given a unique identification number at birth, and county registers have list of addresses for all citizens, based on these numbers. A random sample of 4992 subjects (or 1.87%) was drawn by the Norwegian Central Bureau of Statistics (4).

The follow-up survey was conducted between September of 1996 and May 1997. The survey was expanded, to allow for a voluntary examination at the Department of Thoracic Medicine, Haukeland University Hospital, as well as several questionnaires distributed only among those subjects who attended this examination. Due to the distances involved in traveling within Hordaland County, only subjects living in the city of Bergen and 11 surrounding municipalities were eligible for follow-up (table 2).

Table 2. Number of inhabitants in Bergen and 11 surrounding municipalities, aged 15-70, per 31st of December 1984.

<table>
<thead>
<tr>
<th>Municipality</th>
<th>Women</th>
<th>Men</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergen</td>
<td>73001</td>
<td>71480</td>
<td>144481</td>
</tr>
<tr>
<td>Voss</td>
<td>4653</td>
<td>4768</td>
<td>9421</td>
</tr>
<tr>
<td>Samnanger</td>
<td>728</td>
<td>777</td>
<td>1505</td>
</tr>
<tr>
<td>Os</td>
<td>3734</td>
<td>3845</td>
<td>7579</td>
</tr>
<tr>
<td>Sund</td>
<td>1381</td>
<td>1447</td>
<td>2828</td>
</tr>
<tr>
<td>Fjell</td>
<td>3829</td>
<td>4056</td>
<td>7885</td>
</tr>
<tr>
<td>Askøy</td>
<td>5809</td>
<td>6068</td>
<td>11877</td>
</tr>
<tr>
<td>Vaksdal</td>
<td>1484</td>
<td>1593</td>
<td>3077</td>
</tr>
<tr>
<td>Osterøy</td>
<td>2064</td>
<td>2286</td>
<td>4350</td>
</tr>
<tr>
<td>Øygarden</td>
<td>820</td>
<td>961</td>
<td>1781</td>
</tr>
<tr>
<td>Radøy</td>
<td>1582</td>
<td>1682</td>
<td>3264</td>
</tr>
<tr>
<td>Lindås</td>
<td>3329</td>
<td>3575</td>
<td>6904</td>
</tr>
<tr>
<td>Sum</td>
<td>102414</td>
<td>102538</td>
<td>204952</td>
</tr>
</tbody>
</table>

2 The current dissertation is based on information sampled by mailed questionnaires only.
Of the initial 4992 subjects, 3786 were living in Bergen or one of the 11 surrounding municipalities per 31st of December 1984. Of these 3786 subjects, 3370 had responded to the baseline survey. Between 1985 and September 1996, 189 subjects were deceased, leaving 3181 subjects eligible for the follow-up survey (Figure 1).

**Figure 1. Flowchart of the Hordaland County Cohort Study**

**Data collection**

In 1985, all 4992 subjects received by mail a one-sheet questionnaire (Appendix A), together with a letter explaining the survey, and a paid reply envelope. If no reply had been obtained within three weeks, a new mailing (with a new questionnaire, letter, and
paid reply envelope) was performed. This was repeated one final time, thus each subject received the original letter and up to two reminders.

The questionnaire was expanded from 40 to 58 questions at follow-up (Appendix B), making room for questions regarding health care utility, environmental tobacco smoke, indoor climate, and family history. Altogether, the 1996/97-questionnaire comprised four pages.

Starting in September 1996, the subjects received by mail a letter explaining the intention of the follow-up phase of the survey, the questionnaire, a paid reply-envelope, and an invitation to the examination, scheduled approximately two weeks thereafter. If an individual did not show up at the examination, they were rescheduled, and sent a new letter with the new time. If this individual also had not returned the questionnaire by mail, a new questionnaire (and paid reply-envelope) was included in the reminder letter. This was repeated for a second reminder if necessary. If the individual had not responded after two reminder letters, one of three physicians from the Department of Thoracic Medicine would try to reach the individual by phone. Thus, there were the following categories of responders: Those responding only by mail, those attending after receiving the initial questionnaire, those attending after receiving the first reminder, those attending after receiving the second reminder, those attending after a telephone reminder, and finally those not responding at all. Data collection was finalized in May 1997.

Of the 3181 study subjects, 2819 (88.6%) returned the questionnaire (figure 1) after all reminders.

**Processing the data file**

**Inconsistencies**

The processing of the baseline data is previously described (4). The follow-up data was initially typed into Epi Info, and contained some programming to prevent wrongful

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3 Epi Info is a free program developed by the Centers for Disease Control (CDC), and can be obtained at: http://www.cdc.gov/epiinfo
typing. After all the data had been typed and transferred to SPSS, we conducted analyses of inconsistencies. For instance, if a subject had answered ‘no’ to ever having been treated by a physician, or at a hospital for asthma (question 21), but had given a specific year for age of debut of the disease, it would be considered an inconsistency. (This happened to have occurred in one instance for this particular question).

Based on the questionnaire, we constructed all theoretical inconsistencies we could think of, a total number of 50. Most of these were actually inconsistent missing values, for example saying ‘yes’ to having been treated for asthma, but leaving the space for ‘age at debut’ open. We then identified all individual inconsistencies, and manually checked all affected questionnaires. By then, either a true inconsistency existed in the questionnaire, or a typing error was present.

Previous to the identification of the affected questionnaires, we constructed rules for interpretation in the case of an inconsistency. For example, in the case on question 21 where a subject had stated no to being treated for asthma, but had given an age for debut of the disease, we interpreted the age as more specific, and the subject’s answer to question 21 would be labeled ‘interpreted as yes’. Obviously, if the inconsistency was merely a missing value, no changes were made.

Not considering inconsistent missing values, there were a total of 30718 potential individual inconsistencies. Altogether, 79 individual inconsistencies were found, or 0.26%. All the inconsistency-analyses conducted, lists of affected questionnaires, and rules for interpretation have been recorded, and stored, both digitally and on paper.

Typing errors

Although Epi Info was programmed to not allow wrongful typing of for instance a number not predefined, it was still possible to type ‘2’ (for no) instead of ‘1’ (for yes). After completion of the analyses on possible inconsistencies, we conducted a small-scale evaluation of typing errors. All questionnaires from each subject were identifiable by a unique number. The data was entered according to their numbering, so that the questionnaire number 1 was the first to be typed, and number 3370 the last. Fifty questionnaires, from five different time-periods of typing (#181-190, 861-870, 1541-
were chosen for closer examination of possible typing errors. No systematic errors were found, in that no particular question seemed prone for errors. Out of 3280 possible errors overall, only 31 were found. For the first 19 questions (regarding respiratory symptoms), no errors were found at all.

**Missing values**

Overall, the number of missing values was low. For the outcome variables, the number of missing values varied between 0.3% (morning cough – follow-up survey) to 2.4% (dyspnea grade 1 – baseline survey). The three main exposures examined in this dissertation are smoking, occupational exposures and education. Whereas almost all subjects reported whether they were smoking daily (0.9% missing values at baseline and 0.2% at follow-up), more subjects did not report numbers of year smoked (4.9% at baseline and 2.8% at follow-up) or numbers of cigarettes per day (5.6% at baseline and 4.7% at follow-up). 1.0% of responders at baseline did not answer the question about previous dust or fumes exposure, and 2.2% of the responders at follow-up failed to answer the question about educational level.

In the baseline survey, missing values were significantly more prevalent among women than men for the outcome variables, whereas no differences were found at follow-up, or for the exposure variables at either baseline or follow-up. For most of the questions, missing values were more prevalent with increasing age.

**Variables**

The outcome variables were categorized as dichotomous variables. ‘Yes’ and ‘interpreted as yes’ (if existent) were grouped into yes, and ‘no’ and ‘interpreted as no’ into no. Missing values were interpreted as no. For the exposure variables, it was felt imprudent to interpret the missing values, and they were left as missing. Thus, for some analyses, subjects with missing values would be excluded.

Outcome variables were questions 4 through 14, and question 26, in the baseline survey (appendix A), and question 1 through 13, and question 21, at follow-up (appendix B).
In question number 15 and 16 in the baseline survey, and number 34 and 36 in the follow-up survey, the subjects stated whether they were daily smokers, or former smokers. Based on these questions, a three-category variable was created, with categories never-, ex-, current- smokers.

One pack-year was defined as the equivalent of smoking 20 cigarettes per day for one whole year. This was calculated by combining question 17 and 18 in the baseline survey. In 1985, smoking only pipe tobacco was still not completely uncommon (among men). In subjects smoking pipe tobacco, one pack year was defined as smoking 50 gram (one pack) of tobacco per week. This information was available by combining question 17 and 20. By the time of the follow-up survey, pipe tobacco was considered to be as rare as to be irrelevant to the analyses, and the questions on pipe tobacco left out of the questionnaire.

The analyses on occupational exposures are based on question number 34, 35, and 39 in the baseline survey.

The analyses on educational level are based on question number 56 in the follow-up survey.

**Statistical analyses**

The main outcome was incident cases of respiratory symptoms or asthma. The two surveys were eleven years apart. At which time the incident event occurred within this eleven year time period, cannot be known from these two questionnaires. Incidence was defined as the number of new cases occurring in the study population during the follow-up time period divided by the number of persons at risk, i.e. subjects who did not have the symptom in question at baseline. Thus, the main outcome was the cumulative incidence over 11 years.

The cumulative remission of any symptom was defined as the proportion of subjects having a symptom at baseline who no longer reported the symptom at follow-up.
The main measure of association was the odds ratio (59). For evaluation of adjustment, all odds ratios were calculated by logistic regression. In the first three papers, SPSS (7.5-10.0) was used for computation (60, 61).

An important measure of effect is the attributable fraction (62). It has been a problem to compute confidence intervals for adjusted attributable fractions. However, with a module in Stata 6.0 (63) we were able to compute the confidence intervals, which are presented in paper III (64). Subsequent computation was mainly conducted in Stata 7.0–8.0 (65).4

4 After this researcher had been exposed to Stata, it quickly became the statistical program of choice.
SYNOPSIS OF PAPERS

Paper I

The overall worry with non-response is that those subjects not participating have a different chance of disease than those participating. In several cross-sectional studies, analyses of non-responders have often showed that they tend to be slightly different than responders with regard to some important variables, like socioeconomic status, smoking, and disease.

Thus, we asked whether demographic characteristics, or respiratory symptoms or asthma at baseline, would influence the response rates at the follow-up phase. Further, we examined whether the observed exposure-disease relationships were altered if the analyses were conducted with only the early responders, only the late responders, or all responders.

Among the non-responders in 1996/97 (follow-up), 12.7% were unemployed in 1985 (baseline) compared to 7.2% of the responders. 9.8% of the non-responders were retired in 1985, but only 3.3% of the responders. Whereas 72.6% of the responders in 1996/97 had been early responders in 1985, only 52.5% of the non-responders in 1996/97 had been early responders in 1985.

These relationships held up in the multivariate analyses. The OR (95% CI) for response at follow-up was 0.38 (0.25, 0.56) among the subjects who needed two reminders in 1985, compared to the early responders in 1985. Furthermore, being unemployed, retired, or a student in 1985 was predictive of a lower chance for response in 1996/97. Sex, age, smoking status in 1985, and respiratory health in 1985 did not influence the risk for non-response at follow-up.

The effect of smoking on the incidence of respiratory symptoms was slightly different when the analyses were conducted on only the late responders, compared to only the early responders. However, the overall impact was small, as the ORs for the incidences were nearly identical when comparing only the early responders, to all responders (table
For gender and age, there was no discernable difference in the ORs obtained by inclusion of various groups of responders.

**Paper II**

A large amount of papers have been published in the later years, describing a rise in the prevalence of asthma. Less is known about the true incidence of asthma, as there are fewer longitudinal studies from general populations. Asthma is difficult to define accurately, both clinically and in epidemiological studies, and the diagnosis is in large part dependent on symptomatology.

The objective of the second paper was to assess incidence rates for a wide range of respiratory symptoms and asthma, both overall and within sex-, age-, and smoking groups.

In 1985, the prevalence of asthma was 3.4% in the study sample. This increased to 6.0% at follow-up, however with a cohort now 11 years older. The cumulative incidence of asthma within the 11-year follow-up was 3.7%. The cumulative incidence of the cough symptoms varied between 9.0% for chronic cough to 16.5% for phlegm cough. The cumulative incidence of dyspnea grade 2 was 11.9%, and for attacks of dyspnea 10.3%.

Women had a higher risk for developing morning cough, chronic cough, any degree of dyspnea, attacks of dyspnea, and wheezing, but not asthma. The risk for developing wheezing and attacks of dyspnea decreased with age, whereas the chance of all other symptoms increased with age. Those subjects who started to smoke within the follow-up period (non-current), or smoked throughout (current-current), had an increased risk for developing wheezing and all cough symptoms, but not asthma or degrees of dyspnea. However, the subjects with the greatest smoking load, measured in pack-years, had a significantly increased risk for the incidence of both asthma and dyspnea, as well as wheezing and cough.
Paper III

In several industries, it has been shown that occupational exposures are a risk factor for obstructive lung disease. The impact of occupational exposure on the disease burden in the population will vary according to the composition of different industries in the specific population, as well as working regulations, controlling individual safety measures and the like.

The aim of the third paper was to assess the burden of asthma and respiratory symptoms attributable to occupational exposure in the general population of Hordaland County.

In 1985, 43.5% of the men reported ever having had a workplace with exposure to dust or fumes, and 13.0% of the women. The corresponding figures for quartz and asbestos exposures were 7.3% and 10.1% for men, and only 0.4% and 0.4% for women.

Among the subjects who did not report any previous occupational exposures in 1985, 3.2% later developed asthma, compared to 5.3% among subjects who did report previous dust or fumes exposure. Among subjects with previous asbestos exposure, 7.5% later developed asthma.

The same trend was seen for all respiratory symptoms examined; chronic cough, phlegm cough, dyspnea grade 3, attacks of dyspnea, and wheezing. The cumulative incidence was increased in subjects reporting dust or fumes exposures prior to baseline.

After adjustment for sex, age, educational level, smoking habits (never, ex, current), and pack-years among those having smoked, the risk of developing respiratory symptoms varied between an OR (95% CI) of 1.4 (1.1, 1.7) for wheezing, to 2.1 (1.3, 3.2) for dyspnea grade 3 for those previously exposed to dust or fumes, compared to those not exposed. The OR (95% CI) for developing asthma among those exposed was 1.6 (1.01, 2.5).

The adjusted attributable fraction (95% CI) of occupational exposure on the incidence of asthma was 14.4% (-1.2, 27.6). For the respiratory symptoms, the adjusted attributable fractions varied between 5.7% (1.1, 10.0) for wheezing to 19.3% (6.5, 30.4) for dyspnea grade 3.
**Paper IV**

Studies on risk factors for the incidence of a disease or symptom, is also a study of preventive potential. Studies on risk factors for remission are studies on the potential remedy, once a disease or symptom has occurred. Although the beneficial effect of smoking cessation on lung function decline has been shown in several longitudinal studies, only one previous cohort study had specifically studied the effect of smoking cessation to the remission of respiratory symptoms. No previous cohort study had examined the effect of previous occupational exposure to the remission of respiratory symptoms.

Thus, the aim of the fourth paper was to assess the cumulative remission of selected respiratory symptoms, and the factors that influenced the chance for remission.

The measured cumulative remission varied from 42.3% for morning cough to 58.4% for chronic cough. Younger subjects had higher remission rates for all symptoms, except wheezing. The cumulative remission of morning cough was 72.2% among those subjects giving up smoking in the follow-up period, and only 33.9% in those not giving up smoking. Among those ever having smoked, the lowest remission was seen among those having smoked more than 20 pack-years. For all symptoms, subjects with previous occupational exposure had a lower cumulative remission than subjects without occupational exposure.

The OR (95% CI) for remission of dyspnea grade 2 was 2.0 (1.01, 3.8) in men compared to women, after adjustment for age, educational level, smoking, and dust or fumes exposure. With increasing age, there was a lower chance of remission of the cough symptoms and dyspnea grade 2, after adjustment.

The OR (95% CI) for remission of the cough symptoms varied from 2.6 (1.5, 4.5) for phlegm cough to 6.2 (3.5, 11.2) for morning cough, in subjects who gave up smoking, compared to persisting smokers. Smoking cessation was beneficial also for the remission of wheezing, with an OR (95% CI) of 2.2 (1.3, 3.7), whereas for the remission of dyspnea grade 2 and attacks of dyspnea, smoking cessation had no significant effect.
Not having previous dust or fumes exposure was associated with an increased chance of remission for all symptoms, however not statistically significant for chronic cough and attacks of dyspnea.

**Paper V**

It is well known that lower socioeconomic status is associated with poorer health. Socioeconomic status is a term not easily defined, but is usually taken to describe ones social standing, by terms of income, education, and job opportunities. Conflicting results have been found when examining the effect of socioeconomic status on asthma in children. For adults, very few studies exist examining the relationship between incident asthma and socioeconomic status.

Using educational level as a marker of socioeconomic status, and adjusting for occupational exposures, as well as for sex, age, atopy, and smoking, we wanted to examine the effect of educational level on the incidence of respiratory symptoms and asthma.

Educational level was categorized as primary, secondary, or university, based on type and length of schooling. In 1996/97, the cohort consisted of subjects aged 26-81 years. By then, 18.2% had a primary, 55.7% a secondary, and 26.1% a university educational level.

More men (28.6%) than women (23.8%) had a university level education, as well as more never-smokers (33.4%) had a university level education compared to current smokers (18.2%).

The cumulative incidences of all symptoms examined were higher among subjects with the lowest educational level. Whereas the cumulative incidences ranged from 5.7% (dyspnea grade 2) to 13.6% (wheezing) among subjects with a university level education, they were generally higher among subjects with a primary educational level, ranging from 11.5% (chronic cough) to 20.4% (morning cough). The cumulative incidence of asthma was 1.8%, 4.1%, and 5.3% among subjects with a university-, secondary-, and primary educational level, respectively.
Whether one had a primary or secondary educational level did not matter as much as the difference observed for those with a university level education. The OR for the incidence of all symptoms and asthma was higher in those with a primary educational level, compared to those with a university educational level, after adjustment for sex, age, atopy, smoking, and occupational exposure.
**DISCUSSION**

**Methodological considerations**

**Study design**

To describe a possible causal relationship between an exposure and an outcome, the exposure must precede the outcome in time. Thus, in order to measure new cases of an event, one has to start out with subjects who have not yet experienced the event. For the current study aims, a longitudinal design was chosen. The main problems with this design are its cost, in terms of manpower, time and finances.

The Department of Thoracic Medicine, Haukeland University Hospital, has had a stable research environment for the last 20 years. The current study started out as a cross-sectional study in 1985, with the aim of describing the associations of risk factors to respiratory symptoms and disease (4), as well as their prevalences. With manpower intact, and a well functioning organization with expertise in conducting large population surveys, the undertaking of a new large survey (the follow-up) in 1996/97 was possible. However, the conversion of a cross-sectional study to a follow-up study carries with it some particular problems. All subjects participating in 1985, could be tracked in 1996, due to the Norwegian central registry of addresses, based on each subject’s unique personal number (“personnummer”). However, information about events occurring within the follow-up time would be obtained at follow-up. Thus, incidence rates, which have person-time in the denominator, cannot be accurately estimated unless the exact time of incidence within the follow-up is known. Preferably, one would use a survival-type analysis on incidence within a follow-up. However, this is extremely costly and time-consuming, as the cohort would need monitoring throughout the eleven years of follow-up. Thus, for asthma and respiratory symptoms in this study, we concentrated on cumulative incidence, which can be defined as the fraction of initially asymptomatic subjects being symptomatic eleven years later. Cumulative remission was defined as the fraction of initially symptomatic subjects being asymptomatic eleven years later.
**Wording of the questions**

In the baseline survey, some exposures and outcomes were measured as immediate; “Do you usually cough in the morning?” and others as lifetime: “Have you ever been treated by a physician or hospitalized for asthma?” At follow-up, the intention was to use the same wording of the questions on the exposures and outcomes (as well as adding new questions), to prevent a possible bias from different wording of the questions. However, it was not recognized at the time of follow-up (1996) that this could hamper some possible fields of investigation. For example, both at baseline and follow-up, a question regarding ever exposure to occupational dust or gases was used. This allows for describing the number of subjects coming into a workplace with dust or gas exposure within the follow-up. However, it is logically impossible to assess the number of subjects withdrawing from a workplace with dust or gas exposures. This information would have been valuable, as one could then have seen whether subjects who changed to a healthier work environment experienced fewer symptoms at follow-up. A similar problem exists with the question on ever having been diagnosed with asthma, which precludes analyses of asthma remission.\(^5\)

Finally, although the intention was to use the exact same wording in 1985 and 1996/97, a subtle error occurred in the question regarding wheezing. In 1985, the question was: “Do you ever have wheezing (a wheezing sound) in your chest?” whereas in 1996/97 the Norwegian word ‘hatt’ (had, in English) was unintentionally added, thus altering the question to one implying “Have you ever had wheezing (a wheezing sound) in your chest?” This error was realized after the publishing of the first three papers (66). Another wheeze question in 1996/97 asked about whether the subjects had had wheeze within the last 12 months, and this question was used for the analyses of remission. Theoretically, the analyses of wheezing incidence could also have been hampered, as some ‘new’ cases

\(^5\) This was realized in 1996, and a question was added, asking for the age at which the asthma remitted, if applicable. Unfortunately, this question is unanswered in most subjects, possibly because they did not remember the age of remission at the time of follow-up.
could theoretically have remembered the wheeze they had prior to baseline. We redid the incidence analyses on wheezing, and it is likely that the crude incidence of wheeze was overestimated, whereas the effect of the risk factors examined was the same (Appendix C).

**Statistical methods**

The main statistical tool for analyzing the impact of several cofactors on a dichotomous outcome is logistic regression. Assuming a binominal distribution in the outcome, a logit transformation of the logit function yields a linear function, which can be fitted to the data sample (67). When the model has been fitted, the coefficients of the covariates can be interpreted as representing the risk contribution from each covariable. Thus, the model allows for adjustment, where one can examine the impact of one variable, taking into account the contribution from other covariables. With increasingly powerful personal computers, and readily available statistical packages, such analyses are almost deceptively simple to do. However, a crucial part of conducting logistic regression is the model selection process, which often receives little attention when describing the results. The selection of which independent variables are to be included in the model is most important, but one also must pay attention to the treatment of continuous and categorical variables.

In general, there are two different modeling goals, with different strategies (68):

1) To obtain a valid estimate of an exposure-disease relationship.

2) To obtain a good predictive model given a large number of possible risk factors.

The Hordaland County Cohort Study was designed primarily with the first goal in mind, where the most important risk factors were smoking and occupational exposure. With this strategy, the stages of model building are variable selection, interaction assessment, and assessment of confounding. This is an important topic, but beyond the scope of this dissertation. However, it is important to realize that several choices are made in the model building, which to some extent may affect the results obtained.
One such choice is how to treat continuous variables, like age or pack-years. When age is entered into a model as a continuous variable, we assume linearity in the logit for age. This means that an increase (or decrease) in risk from say 20 to 30 years is the same as the increase (or decrease) from 60 to 70 years of age. This is clearly not always the case. A traditional solution has been to categorize the continuous variable into X categories. However, the problem with categorizing a continuous variable like age, is that considerable information about the variable age is not utilized, which can lead to residual confounding (69). Although linearity of the logit of the continuous variable is the underlying assumption, it has been shown that for many distributions of a continuous variable without linearity, the variable can still be added to the multivariate model as a continuous variable, and enhance the interpretation of the other variables (67). The method of fractional polynomials have been developed to test for the best possible transformation of a continuous variable (70), and this has recently been made accessible in Stata through the ‘fracpoly’ command.

(Figure 2)
In the Hordaland County Study Cohort, there was a strong increase in incidence in some respiratory symptoms after the age of 50, especially dyspnea (figure 2). (Whereas the incidence of wheezing decreased with age.) In Paper II, we made the choice of categorizing age into a categorical variable with categories 15-29 years (in 1985), 30-49 years, and 50-70 years. With this coding we avoided the linearity assumption, and obtained odds ratios for the incidence in subjects above 50 years compared with the youngest subjects. In Paper II, it was of interest to obtain adjusted odds ratios for the incidence of sex and age as well as smoking. In Paper V, the main interest was to examine the effect of educational level on the incidences, and the main concern was an efficient adjustment for age. By the time we undertook the analyses for Paper V, we were acquainted with the ‘fracpoly’ command, and this was used to determine that age could be treated as a continuous variable. The same argument holds for Paper III, where the
effect of occupational exposure was the main focus, and where we wanted to adjust for age. At the time we analyzed for Paper III, we still conducted most analyses in SPSS, and did not have the method of fractional polynomials available\(^6\).

**Internal validity**

Internal validity can be defined as the validity of the inferences drawn pertaining to the population being studied (59). The question to be asked is whether the study is free of systematic errors or biases. Various types of biases have been named, and a distinction between them is sometimes hard to draw. Three general types of biases are defined in the textbook “Modern Epidemiology”; selection bias, confounding, and information bias (59).

**Selection bias**

Selection bias can occur from the sampling procedure, or from factors that influence study participation. In the Hordaland County Cohort Study, subjects were selected by random sampling. The response rate was high, both at baseline and follow-up. Although several studies have shown that more smokers tend to be non-responders, Paper I shows that increasing the response rate from 65% to 89% did not affect the exposure (smoking) – disease relationships, further indicating that non-response bias would play a minor role in this study.

There is a larger tendency for smokers who become symptomatic or acquire disease to quit smoking than smokers who remain asymptomatic or disease-free. This is often termed the ‘healthy-smoker’ effect (71). A similar effect exists for occupational exposure (‘healthy-worker’ effect). If this was present in the current study, it could have worked to underestimate the effect of both smoking and occupational exposures on the incidences.

\(^6\) I have since reanalyzed the data with age as a continuous variable. No changes in the odds ratios of occupational exposure (or educational level) to the incidences of respiratory symptoms and asthma were found.
**Confounding**

Confounding can be thought of as the confusion or mixing of extraneous effects with the effects of interest (59). Imagine a multivariate model with several independent variables, one of which is the exposure of interest. Then all other independent variables are potential confounders, which we may or may not have fully adjusted for. If a variable is a confounder and the adjustment is imperfect, we have residual confounding by that variable. To what extent an independent variable is a confounder is most often evaluated in the data set by examining the estimates of the exposure-disease relationship with or without the suspected confounder in the model. If, there is a ‘significant’ difference, it is deemed prudent to keep the possible confounding variable in the model.

However, there may always also be other explanatory factors, not part of our model, which can confound our findings. Whether or not such a confounder exists is either unknown, or can be suspected based on information from other studies.

Numerous studies have linked smoking to respiratory symptoms, including the Hordaland County Cohort Study. Subjects exposed to occupational exposures have a higher smoking prevalence (and a lower educational level) in this study sample. Thus smoking was a possible confounder for the relationship between occupational exposure (and educational level) and the incidence of respiratory symptoms, and possibly asthma. Although we could adjust for smoking when examining the relationship of occupational exposure (and educational level) to the symptoms and asthma, one concern was the possibility of residual confounding by smoking. We only included baseline data on occupational exposures and smoking in the multivariate model, but we had information on smoking habits throughout follow-up. We therefore conducted analyses also including smoking throughout follow-up, knowing we then overestimated the smoking load, to see if the relationship between occupational exposure and the incidence of respiratory symptoms and asthma held up. The odds ratios were basically unaltered, so it did.

Although this is somewhat reassuring to our belief that an effect of occupational exposure (and educational level) is independent of smoking, there is still the possibility of a ‘factor X’; an unknown confounder.
What could such a factor be? Other factors that have been linked to asthma and respiratory symptoms are heredity, passive smoking, and air pollution. The Hordaland County Cohort consists of subjects from the city of Bergen, and 11 surrounding municipalities. One could speculate that subjects living in Bergen are more exposed to air pollution that subjects from the surrounding municipalities. However, the link between air pollution and asthma is weak when viewing the literature. In our study sample, living in Bergen is neither associated with increased asthma or symptoms, nor with reporting occupational exposure, compared to living in the surrounding municipalities.

Heredity could be linked both to an increased incidence of asthma and respiratory symptoms, and occupational exposure. The latter would depend upon that children of subjects who are occupationally exposed were more likely to choose similar work. This hypothetical factor is likely to have been partially adjusted for by the inclusion of educational level in the model, as a marker of socioeconomic status.

As for passive smoking, we only have information about passive smoking from the follow-up survey. This opens the analyses to a potential recall bias. A full analysis of the effects of passive smoking is planned for future papers, however a preliminary analysis have shown that the odds ratios of occupational exposure to the incidences are independent of passive smoking.

**Information bias**

The essence of information bias can be summarized by the question: Are we measuring what we think we are measuring?

With any diagnostic test or procedure, there is a chance of error, measured by the test sensitivity and specificity. This is also true for a mailed questionnaire. One possible source of error is false entry of data into the database. The steps taken in the Hordaland County Cohort Study to check for this has been described in the methods section of this dissertation. A different type of information bias can arise when subjects who in fact are exposed, say ‘no’ when asked about the exposure, or vice versa. This is commonly called misclassification or reporting error. A distinction is made between differential and non-differential misclassification.
Differential misclassification arises if there is a systematic error linking an exposure and an outcome (59). For example, if smokers under-reported symptoms, whereas non-smokers did not, there would be a differential misclassification, with an underestimation of the effects of smoking as the result. A differential misclassification can lead to both an over- and under-estimation of the effect of the exposure on the outcome. An important type of differential misclassification is recall bias.

Non-differential misclassification occurs when the misclassification of exposure is independent on the proportion of outcomes (or vice versa). In most instances, a non-differential misclassification in the exposures will produce a bias towards the null (59).

In the former chapter, I tried to show how we treated the smoking variables in different fashions in order to avoid residual confounding by smoking. However, there is a possible error we cannot adjust for, which may produce residual confounding by smoking, namely misclassification. To some subjects, answering questions about smoking may feel sensitive, and the answers may not be wholly true. This means that some subjects may underreport their smoking habits (or over-report, although that seems less likely). Indeed, studies with biological markers of cigarette smoking indicate that some subjects under-report their smoking habits (72-74). If under-reporting of smoking was the case, what would that mean?

Imagine a case where some smokers are erroneously classified as non-smokers. Those subjects (smokers) who are misclassified would have a true higher risk, but be mingled with subjects (non-smokers) with a true lower risk. The non-smokers would have a measured higher risk than the true value (relative to the smokers), and the risk estimates would be biased towards the null. Thus, if in our sample smoking is under-reported, this could lead to an underestimation of the effect of smoking. The more detailed our information on smoking habits are, the less bias (59). In the Hordaland County Cohort Study, we utilized a maximum of smoking information by considering whether each subject was a never-, ex-, or current-smoker both at baseline and follow-up, as well as considering the total smoking load, measured by pack-years.
With the questions on occupational exposure there is a different problem. With all the different possible exposures in different workplaces, specifying the burden of exposures by questionnaire is intrinsically difficult. In fact, the question: “Have you ever had a workplace with much dust or fumes in the air?” is extremely crude, as it groups subjects with varying types of exposure as well as different degrees of exposure. This could lead to a mixing of subjects with relevant exposure and subjects with irrelevant exposure, and introduce a bias toward the null, i.e. an underestimation of the effect of dust or fumes exposure.

Yet another case to consider is the possible effect of misclassification of the outcomes, which was of particular concern in Paper IV. Whereas misclassification of the exposures would influence the measured effects of the exposure in question, misclassification of the outcome influences the measured occurrence of the outcome. This is particularly important in longitudinal studies, where a misclassification can occur both at baseline and follow-up. Imagine a cohort where the true incidence is 10%, and the true remission is 5%, and the baseline prevalence of the outcome is 10%. Suppose that there is a misclassification in that 5% say they are sick when they are not, and 10% say they are well when they are not. In such an example, the measured incidence would be 14.3%, and the measured remission 38.3% (appendix D). The effect from the misclassification is strongly dependent on the baseline prevalence. The lower the prevalence, the smaller distortion of the incidence, but greater distortion of the remission. Also, over-reporting (imperfect specificity) produces greater distortions than under-reporting (imperfect sensitivity).

With this in mind, we discussed this caveat in Paper IV, and provided an example in the appendix (75). If the extent of misclassification were known, it would be entirely possible to correct the estimates of the cumulative remission. However, that would require knowing ‘the truth’ for a sample of the subjects, an entity in itself doubtful.

A pragmatic approach to the hypothetical misclassification is the ‘face value’ of replies. ‘Face value’ implies that if a subject says she coughs, she does. In a clinical setting, patients often receive treatment based on their history, and it is not always possible to
check to which degree a patient really coughs. However, when searching for ultimate scientific truths, ‘face value’ is altogether unsatisfying.

Unfortunately, a misclassification in the outcome in a logistic regression may also bias the estimates of the odds ratios of the explanatory variables (76). In a cross-sectional study with non-differential misclassification, this bias tends to bring the risk estimates toward the null (77). However, in a cohort study, the direction of the bias is not always towards the null (78). If the magnitude of the misclassification is known (rarely the case), there are statistical commands in Stata (79) and SAS (77), which will take the bias into account when estimating the odds ratios and confidence intervals. However, such analytic tools are currently only available for logistic regression in a cross-sectional study.

With all this emphasis on misclassification, the reader may wonder: Can the results from the Hordaland County Cohort Study be trusted? At this point it is important to remember we are discussing a hypothetical, although not unlikely, misclassification. All too often, potential problems with the methodology are not discussed, especially when journals demand a methods section with less than 500 words. The strong emphasis of misclassification in this discussion goes to the question of what if. It would be preferable to know if there was any misclassification, or how much. However, that is nearly impossible in practice in a study like this, so the second best thing is to make an opinion on the possible effects a misclassification might have. In general, the incidence estimates could be slightly over-estimated, but probably not by much. On the other hand, the estimates of cumulative remission are likely to be over-estimated. Studies with which we compare have the same problems, but evaluation of whether the studies differ in chance of having misclassification is speculative. The effects of smoking and occupational exposure are ‘positive’, in that there is an increased risk for the incidence of symptoms or asthma with these exposures. A bias is likely towards the null. Thus, it is unlikely that the effects we have found are spurious.

Another thing to bear in mind is biological plausibility. For example, the estimates of the effects of smoking cessation in Paper IV confirms what is believed to be true, namely that smoking cessation increases the chance for remission of symptoms, and is supported by
other studies which shows that the rate of decline in pulmonary function is decreased after smoking cessation (80-83).

The final part of the discussion on information bias goes to whether the questionnaire actually measures what the researcher intends it to. Specifically, if a patient states that she has been treated by a physician for asthma, does that mean she has asthma?

This question cannot be answered fully, as there is no accepted, easy-to-measure, gold standard of asthma. Various questions on asthma have been validated against spirometry, BHR, and clinical assessment by physicians (84). Since neither test represents a single true characteristic of asthma, such validations will not give an accurate assessment of diagnostic precision. The best measure is probably a combination of clinical history, measurements of lung function, and inflammation. With increasing complexity comes increasing cost, hence the widespread use of questionnaires in large population surveys. Burney et al assessed the International Union Against Tuberculosis and Lung Disease (IUALTD) questionnaire, with regard to precision and repeatability. When comparing subjects own reporting of asthma with a doctors’ assessment, they found that subjects probably under-reported asthma (85). Torén et al compared several studies on questionnaire-based data, compared to spirometry, BHR, and clinical evaluation. The questions using the phrase physician-diagnosed asthma had a high specificity (99%), which is preferable when evaluating a disease of lower prevalence (84).

In addition to under-reporting, there could be a confusion of diagnostic labels, most notably between asthma and chronic obstructive pulmonary disease (COPD). The term asthma was used less discriminately before, taken to mean obstructive lung disease in a broad sense, and typically involving all kinds of ‘bronchitis’. Only lately have COPD as a term replaced emphysema and chronic bronchitis in the general public.

In 1985, the subjects in the Hordaland County Cohort Study were asked whether they had ever been treated for emphysema. Six subjects reported having both asthma and emphysema in 1985, and these six subjects were not included in the analyses of asthma incidence. However, few subjects reported emphysema overall. Of 114 subjects with asthma in 1985, 12 had a combination of phlegm cough, chronic cough, and dyspnea.
grade 3. Although this could be the sign of intractable, serious asthma, it is likely that some subjects in fact had COPD. Of 3256 subjects without asthma in 1985, 25 had the symptom combination. Thus, although there is a likely misclassification between COPD and asthma, especially among the oldest subjects, the impact of this misclassification is likely to have been minor.

Further, for the multivariate analyses, we conducted separate regression analyses on subjects older and younger than 40 years of age. It is likely that a potential misclassification between asthma and COPD would primarily exist in the oldest age group. In general, the associations found in the younger age groups were the same as those found in the older age groups.

**External validity**

External validity can be defined as the ability of the study to produce results that would be true not only for the study population, but also for the reference population (13). This definition implies that the study population must be a representative sub-sample of the reference population.

Roughly 10% of the Norwegian population lives in Hordaland County. The adult sex and age composition of Hordaland was very similar to the composition of the overall Norwegian population, both in 1986 and 1996 (Figure 3).
Likewise, the level of education did not differ between Hordaland County and the whole of Norway (Figure 4, data shown for 2000).
Figure 4. Educational level in three categories among adults in Hordaland and all of Norway in 2000

For the two main exposures, smoking and occupational exposure, Bakke made an assessment in his dissertation on the baseline study; showing that the number of smokers were similar between Hordaland County and all of Norway, as well as having a similar composition of farmers and fishermen, industrial workers, and workers in the service industry, in 1983 (4). Data from Statistics Norway show that in 1996, 32% of the adult population in all of Norway was current smokers, whereas 34% of the adult population in Hordaland was current smokers\(^7\). However, the data material was not large enough to allow for age-stratification.

Thus, for the demographic variables and the main exposures, it should be a fair assessment that the population of Hordaland County closely resembles that of the rest of the Norwegian population.

\(^7\) Personal communication from Aina Holmøy, Statistics Norway
Discussion of main results

Measures of incidence

To compare the incidence rates between studies, a stipulation of the incidence rate per 1000 person years has been made. In most papers, the cumulative incidence has been reported. If the incidence rate is constant for the study population throughout the follow-up, an increasing number of subjects will no longer be ‘at risk’, as they experience incident events. Thus, when calculating the annual incidence rates, one cannot merely divide the cumulative incidence on the number of years of follow-up, as that will underestimate the incidence rates. The error is greater with increasing length of follow-up and for higher incidences. Thus, a stipulation of the annual incidence rate was preferable to compare the incidences from studies with differing lengths of follow-up.

With a yearly incidence of \( r \), the cumulative incidence after \( n \) years is:
\[
a = 1-(1-r)^n,
\]
which solved for \( r \) gives the yearly incidence as:
\[
r = 1-(1-a)^{(1/n)}.
\]
The latter formula was used to compare incidences from studies with varying lengths of follow-up.
**Incidence rates - asthma**

Estimates of the adult incidence of asthma are given in table 3.

**Table 3. An overview of studies on adult asthma incidence. To compare between studies, estimates of incidence rates per 1000 person years are given.**

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<th>Men</th>
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<tr>
<td>Toren, 99</td>
<td>20-50</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Sunyer, 99</td>
<td>20-44</td>
<td>1-4</td>
<td>1-4</td>
</tr>
<tr>
<td>deMarco, 02</td>
<td>20-44</td>
<td>2.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Bregger, 04</td>
<td>15-70</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td><strong>Register-based studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yunginger, 92</td>
<td>15+</td>
<td>0.5-0.7</td>
<td>0.5-0.7</td>
</tr>
</tbody>
</table>

* at baseline

† the reporting of the results did not allow an exact calculation of incidence rates, only a range
¶ 'best studies': Randomly sampled, prospective, response rate>50%, community survey, similar definition of asthma at baseline and follow-up
For comparison, self-reported asthma have been used whenever possible. Most of the studies used variations of one of two asthma questions: “Have you ever had asthma?” or “Have you ever been diagnosed as having asthma by a doctor?” In the OLIN Study, both questions were used, which allowed for a comparison (19). The estimates of incidence based on the two different wordings of the asthma question were almost similar. However, in the same study, an estimate of asthma incidence was given based on self-reported asthma medication, in which case the estimated incidence was somewhat higher.

In the paper from the Spanish part of the ECRHS, incidence rates were estimated based on the question: “Have you ever had asthma?” When BHR was included in the definition, the incidence rates were reduced by nearly a half (26). The wording of the questions on asthma and/or respiratory symptoms from all cited studies is given in appendix E.

In some studies where there is more than one follow-up, several papers have been published from the same study, with sometimes conflicting estimates of the incidence rates (15-17, 19, 20, 22). If for example a five years follow-up yields estimate A (baseline to first follow-up), and a nine years follow-up yields estimate B (baseline to second follow-up), which estimate is correct?

The estimates from the prospective studies are somewhat higher than the estimates from the retrospective studies. In a recently published paper, Brøgger et al compared the prospective estimates from the Hordaland County Cohort Study with retrospective estimates from the cross-sectional survey from Hordaland in 1998 (37). Brøgger et al showed that the estimates of asthma incidence were lower with retrospective estimates, especially in the oldest age groups.

The median (25 quartile, 75 quartile) estimated asthma incidence, from all the studies in table 3, is 3.2 (2.4, 6.0) per 1000 person years in women, and 2.8 (2.3, 4.3) per 1000 person years in men. If only the prospective general population studies are included, the median estimates are 5.0 (2.7, 7.6) and 3.7 (2.5, 5.0) per 1000 person years in women and men respectively.

The ‘best studies’ could be defined as being randomly sampled, longitudinal, from a general population, with a response rate above 50%, and with a similar definition of
asthma at baseline and follow-up (table 3). If so, the median estimates from these ‘best studies’ were 4.3 (2.7, 4.6) and 3.2 (2.4, 4.3) per 1000 person years in women and men respectively.

All but three studies (17, 27, 36) found a higher adult incidence of asthma in women than men. Not all studies provided confidence intervals for the incidence estimates for women and men, or provided significance testing of the difference. The differences in rank sums were significantly different (Wilcoxon matched pairs test, p<0.01) between women and men for the studies in table 3 which allowed for calculation of sex-specific incidence rates.

Thus, based on the current studies there seems to be a slightly higher adult incidence of asthma in women compared to men.

**Incidence rates – respiratory symptoms**

Estimates of the incidence of respiratory symptoms per 1000 person years are given in table 4.

<table>
<thead>
<tr>
<th>Study area</th>
<th>Age span*</th>
<th>Attacks of dyspnea</th>
<th>Wheezing</th>
<th>Dyspnea grade 3†</th>
<th>Phlegm cough</th>
<th>Chronic cough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucson, USA</td>
<td>19-70</td>
<td>6.9</td>
<td>6.5</td>
<td>7.8</td>
<td>10.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Krakow, Poland</td>
<td>19-70</td>
<td>6.5</td>
<td>6.5</td>
<td>10.4</td>
<td>10.7</td>
<td>24.1</td>
</tr>
<tr>
<td>Vlagtwedde/Vlaardingen,</td>
<td>15-64</td>
<td></td>
<td>8.4†</td>
<td></td>
<td>11.5</td>
<td>15.2</td>
</tr>
<tr>
<td>Norrbotten, Sweden</td>
<td>35-36; 50-51; 65-66</td>
<td>15.8</td>
<td>15.8</td>
<td>10.1</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>Lebanon, USA</td>
<td>7-55+</td>
<td>4.1</td>
<td></td>
<td>10.8</td>
<td>8.9</td>
<td>13.6</td>
</tr>
<tr>
<td>Hordaland, Norway</td>
<td>15-70</td>
<td>11.0</td>
<td>8.6</td>
<td>15.1</td>
<td>13.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

* at baseline
† dyspnea while walking at level ground at an ordinary pace
‡ persistent wheeze, i.e. on most days

As the table shows, surprisingly few studies have estimated the incidence of respiratory symptoms in general populations. A mean or median incidence rate is rather pointless with such few estimates. At best we can think of a likely range for the true incidence.
Clearly, further studies are necessary to enable a discussion about trends over time, regarding the incidence of respiratory symptoms.

**Age trends**

In the Hordaland County Cohort, the incidence of most symptoms increased with age (for the age spectrum 15 to 70 years). Wheezing declined with age. Physician-diagnosed asthma increased with age (figure 2), perhaps contrary to what we believed beforehand. In Paper II, we adjusted for sex, smoking and pack-years. After additional adjustment for previous dust or fumes exposure and educational level, the age trend was modified (Figure 5). This was primarily due to the adjustment for dust or fumes exposure, which was a powerful predictor of incident symptoms and asthma. Occupational exposures accumulate throughout life, and thus correlates with age.

![Figure 5. The effect of 10 years increase in age on the incidence of asthma and respiratory symptoms in the Hordaland County Cohort Study](image)
However, the curve for asthma in figure 2 begs the question: Is the increased risk for asthma with age real?

As discussed in the section on information bias, there is a chance that some subjects who state they have asthma in fact have COPD. The size of this fraction is unknown, although analyses of symptom-complexes and asthma points to minor interference. However, the misclassification is probably largest in the oldest age groups.

Of the longitudinal studies in table 1, only the studies from Tucson, Krakow, Norrbotten, as well as the Finnish Twin Cohort Study, allows for analyses on asthma incidence in those aged above 50. In both Tucson and Krakow, the incidence of self-reported physician-diagnosed asthma increased with age (17). No confidence intervals were given in this study. In Norrbotten, the incidence of asthma increased slightly with age if analyzed after six years (19), and more pronounced when analyzed after ten years (20). Interestingly, after exclusion of subjects with likely chronic bronchitis at baseline, the age trend disappeared. This could be due to a larger misclassification in the oldest cohort. However, the risk for both wheezing and attacks of breathlessness in Norrbotten increased with age (20). In the Finnish Twin Cohort, no age trends were found (31).

Based on these studies, it cannot be concluded that the incidence of asthma decreases with age, as is perhaps the popular belief. On the contrary, the evidence points towards a constant or a small increase in incidence with age, with the caveat that the extent of misclassification with COPD is not fully known. The cumulative occupational exposure and smoking load with age explains at least part of the increased incidence with age.

**Risk factors for the incidence of respiratory symptoms and asthma**

**Smoking**

Smoking is a cause of many cancers, as well as arteriosclerosis and chronic obstructive pulmonary disease. It seems almost untimely then, to ask: “Does smoking cause asthma?” Surprisingly though, the evidence is not all that clear (Figure 6).
Among the studies in table 1 where smoking was examined as a possible risk factor for asthma, five studies found an increase in risk (19-22, 28, 34), five studies found no increase in risk (17, 26, 27, 29, 31), and one study a decrease in risk of developing asthma (33).

The studies varied by choice of multivariate analyses. Most studies examined smoking as a baseline only variable, and not all studies accounted for varying amounts of smoking, like cigarettes per day or pack years. No apparent pattern in analytic strategy explains the difference in results between studies. However, the differences in methodology could help explain the variance of results, and make inferences more difficult.

The results could be biased by at least two important mechanisms inherent to all studies cited. Firstly, there is a strong possibility of a selection bias (or ‘healthy smoker effect’), where subjects who experience symptoms will quit smoking. In the one study where
smoking was associated with a decreased risk for asthma, the Nurses Health Study, there was an increase in risk in the first two years after quitting (33). This could be the result of such a selection bias, perhaps especially considering the survey consisted of health-conscious study subjects. In the Copenhagen City Heart Study, both current-current, and current-ex smokers had an increased risk for developing asthma (22). The greatest risk was seen among current-ex smokers. One could hypothesize that this is due to an immune-modulating effect by smoking, however scant biological evidence exists to that effect. It could also be the result of a healthy smoker effect, considering that symptoms usually persist for a time-period before diagnosis.

Secondly, a patient could be more likely to be labeled with an asthma diagnosis if she or he is a non-smoker. The two symptoms most often used to characterize asthma in epidemiologic studies are wheezing and attacks of dyspnea (alone or combined). In the Hordaland County Cohort study, smoking was a consistent risk factor for wheezing, independent of other factors like sex, age, educational level or occupational exposure. The risk for attacks of dyspnea was increased with smoking, but not significantly (27). Five other prospective studies examined smoking as a predictor of wheezing, and all found an increased risk for development of wheeze in smokers (17, 19, 25, 30). All other studies that examined attacks of dyspnea and smoking found an increased risk for this symptom with smoking (17, 19). Thus, smoking is a consistent risk factor for the adult incidence of both wheezing and attacks of dyspnea, and not so consistently a risk factor for the adult incidence of asthma. This could be due to a diagnostic bias, where the subjects are less likely to be labeled asthmatics when they smoke, even in the presence of classical symptoms.

Another possibility is that we are dealing with different phenotypes of asthma, some of which are more susceptible to smoking than others. The study which found the largest risk for asthma among smokers was the Swedish part of the ECRHS (28), with an OR (95% CI) of 3.0 (1.5, 5.8). The risk was largest among non-atopics, with an OR of 5.7 (1.7, 19.2). Strachan et al. observed a similar finding in the British National Child Development Study, where the risk of adult onset wheezing by active smoking was significantly greater in the non-atopic group (30).
Biological mechanisms

At this point it serves to ask: “By which mechanisms could smoking cause asthma?”

Tobacco smoke contains several hundred chemical substances, which can interact with the cells of the respiratory system. A full account of the current knowledge of inflammatory processes in asthmatics is clearly outside the scope of this thesis. However, it is worthwhile to reflect on the possible triggers of the inflammation seen in asthma.

Inflammatory changes in subjects with asthma

Increased mucus secretion, constriction of smooth musculature, and a thickening of the conducting airways characterize chronic inflammation in asthmatics (86). Classic thinking about asthma emphasized the role of allergens triggering an acute immune response from mast cells, and later eosinophils. Several studies have shown an increase in eosinophils from bronchoalveolar lavage (BAL), induced sputum, or bronchial biopsies in asthmatic subjects (87, 88). Eosinophils mediate the defense against parasites like helminthes, mainly through discharge of lytic proteins after contact with a parasite opsonized by IgE. The mechanisms by which allergens trigger the immune response are not yet fully understood.

An immune response is regulated by large numbers of cytokines; molecular messengers between cells participating in the defense. CD4+ lymphocytes (T-helper cells) have an important regulatory role in directing the immune response. In the last decade, two main patterns of cytokine secretion from T-helper cells have been recognized, termed the Th1 response and the Th2 response. In short, the Th1 response directs the immune system towards cell-mediated responses appropriate for action against intracellular microorganisms like viruses and some bacteria. A Th2 response directs the immune system against extracellular microorganisms, like bacteria or helminthes. Of the typical cytokines seen in a Th2 response, IL-5 stimulates eosinophils, and IL-4 and IL-13 stimulate production of IgE. The eosinophilic inflammation seen in asthmatics is thought to be the hallmark of an increased Th2 response. Whether the immune response goes in the direction of a Th1 or Th2 response is in principle determined by which antigen the immune system encounters.
At the same time as there has been an increase in asthma in children in the western world, there has been an increase in atopic disease. Arguably, the currently prevailing theory behind the increase in prevalence of atopic disease is the ‘hygiene hypothesis’ (89, 90). In brief, the theory says that young children encounter fewer or a different set of microbes than what was common say 50 years ago, and that this leads to a bias towards a Th2 response to later challenges to non-microbial antigens.

However, a large number of typical asthmatics, including some patients with known atopy, have a ‘non-eosinophilic’ pattern of inflammation (91, 92), for which there is no established theory of pathogenesis. The immunologic mechanisms are yet poorly understood. An increase in neutrophils in broncho-alveolar lavage (BAL) is a common finding (92, 93).

**Inflammatory changes in smokers**

Several studies have shown that smoking induces inflammatory changes in the lungs (93-96). Consistently, smokers have higher numbers of macrophages and neutrophils in BAL (94, 95, 97), as well as an increase in IL-8 (95) and a change in CD4/CD8 lymphocyte ratio, with a higher number of CD8 lymphocytes (94). There seems to be a dose response relation in that the inflammatory changes increase with increasing smoking load, measured by pack years (95). Studies have shown that subjects with known chronic bronchitis or COPD have an even greater neutrophil inflammation than do healthy smokers (98, 99). An increase in neutrophil inflammation corresponds with a decrease in FEV1 (93, 99), and this is thought to be one of the pathological processes driving the development of COPD (100).

A study comparing induced sputum in asthmatic smokers and non-smokers found that asthmatic smokers had a higher total cell count, with an increase in neutrophils, but normal eosinophils in percent of total (93). Healthy smokers had the same increase in neutrophils by percentage, but a lower total cell count of neutrophils, than did asthmatic smokers (93).

Thus, it is possible that the current group of patients labeled with asthma have at least two different phenotypes, with differing underlying pathology. The neutrophil
inflammation in some asthmatics could be a sign of a different immunological disease mechanism than that responsible for the classic eosinophilic inflammation. Or, the neutrophilic inflammation is a byproduct of for instance smoking, and not necessarily related to the underlying process responsible for asthma. Yet another speculation could be that smokers experience respiratory symptoms at a lesser degree of eosinophilic inflammation (93). Finally, the effects of smoking could be related to the amount smoked.

*Smoking related to asthma severity*

Smoking seems to induce the same inflammatory changes in asthmatics as in non-asthmatics, and possibly an increased total inflammatory response. These inflammatory changes have been shown to correlate with increased airways obstruction measured by a decline in FEV1, both in asthmatics (93) and patients with COPD (99). If this is the case, asthmatic smokers could have an increased risk for a more severe asthma, and for developing COPD.

There is some evidence to support this. In an Australian longitudinal study, asthmatic smokers had a steeper decline in FEV1 than asthmatic non-smokers (101). However, the study included only 92 asthmatics, and the finding did not reach statistical significance. In the Copenhagen City Heart Study, including a total of 1095 subjects with asthma, asthmatics had a larger decline in FEV1 over time than non-asthmatics, and asthmatic smokers a larger decline in FEV1 than did asthmatic non-smokers (102). And, in a case-control study from France, it was shown that asthmatic smokers have increased asthma severity, measured by both symptoms and FEV1, compared to asthmatic ex- or never smokers (103).

Due to the invasive nature of studies with bronchial biopsies and BAL, most studies have relatively few study subjects, where selection of cases and controls can induce powerful biases. Whether other less invasive techniques, like exhaled breath condensate (EBC), can replace the more invasive procedures remains to be seen (104). Clearly, we need more longitudinal studies with biological markers other than those used so far, as well as
studies on the inflammatory processes in smokers and non-smokers, with or without asthma.

**Occupational exposure**

There is no doubt that occupational exposures can cause asthma. More than 250 different agents have been identified as causal agents in the pathogenesis of human asthma (105). Work-related asthma can be divided into occupational asthma, work-aggravated asthma (pre-existing asthma exacerbated by workplace exposures), and variant syndromes (106). One variant syndrome of particular interest in Norway is ‘potroom asthma’, for which there is no established mechanism yet (107).

Occupational asthma is further subdivided into immunological occupational asthma and non-immunological occupational asthma (often labeled ‘irritant-induced asthma’). With immunological occupational asthma there is usually a latency period, whereas ‘irritant-induced asthma’ occurs within hours of inhaling a workplace substance at high concentration. Although the definitions of occupational asthma have varied over the last centuries, the central theme is a causal relationship between an agent found in the workplace and new cases of asthma (106). The inflammatory changes in immunological occupational asthma are generally thought to be the same as with ‘regular’ asthma. As with regular asthma, there are cases of a clear IgE-mediated eosinophilic inflammation, as well as yet unknown immunologic mechanisms.

The occupational agents responsible for asthma are usually divided into two groups, by molecular weight. Molecules larger than 1 kiloDaltons (kD) are termed high-molecular weight (HMW) agents, and molecules less than 1 kD low molecular weight (LMW) agents (108). The larger HMW agents are typically animal or vegetable proteins, usually biologically active like enzymes, but also structural, like latex (rubber proteins) (109). These proteins typically induce an IgE-mediated inflammation.

The LMW agents are typically reactive chemicals, like metals (for example platinum salts), diisocyanates, dyes, antibiotics, and wood products to name but a few (110). Some LMW agents probably acts as haptens, and evoke an IgE-mediated immune response. Specific IgE has been found against albumin-bound LMW agents, like diisocyanates and
plicatic acid (108). However, not all subjects with diisocyanate-induced asthma have specific IgE, and BAL have shown a predominant neutrophilic inflammation (111). For most LMW agents, no specific IgEs have been found, and the mechanisms through which LMW agents induce asthma are still unresolved (108).

Whereas the inhalation of a cigarette guarantees instant exposure to several hundred active chemicals, exposures at the workplace are diverse. Thus, to study the association between a suspected agent and asthma, cohorts of defined working groups are best suited. In the Hordaland County Cohort Study, the main focus was to determine the burden of asthma attributable to occupational exposures in the general population.

At baseline, the subjects were asked about their lifetime prevalence of having had a job with exposure to dust or fumes. This question did not allow for analyses on degrees of exposure. There is reason to believe that there is a dose-response relationship between occupational exposures and obstructive lung disease. In a Norwegian longitudinal study, FEV1 decline increased with increasing number of known occupational agents to which subjects had been exposed (112). Further, it is likely that workplace exposure is under-reported in the older age groups, and we did only take occupational exposure up until baseline into account. With different degrees of exposure grouped into one category, together with the possibility of under-reporting, the measured effect is in danger of having been underestimated. Still, for asthma and almost all symptoms, previous occupational exposure was a risk factor with ORs varying from 1.24 to 1.77 (Figure 7). In the only previous longitudinal general population study we were aware of, dust or fumes were related to respiratory symptoms, but not significantly to asthma (57).
Figure 7. The effect of dust or fumes exposure on the incidence of asthma and respiratory symptoms in the Hordaland County Cohort Study

Occupational asthma seems more related to level of exposure than individual susceptibility (108). In the Hordaland County Cohort Study, the effect of previous dust or fumes exposure was independent of smoking, and educational level (Paper III)(64). Later analyses from the Hordaland County Cohort Study have shown that the effect of occupational exposure was independent of atopy, and without interaction with atopy.

The attributable fraction can be interpreted as the proportion of new asthma cases that could be prevented if there were no exposure. Having established previous occupational exposure as a risk factor both for respiratory symptoms and asthma, we estimated the adjusted attributable fraction of asthma in the adult population to be 14%. This was in accordance with earlier estimates from cross-sectional studies (113). The estimates are based on the logistic regression model used to obtain the odds ratios (63). Thus, if the effect were underestimated, so was the attributable fraction.
Subjects with occupational asthma are advised to avoid the causative exposure. Although this is likely to alleviate the symptoms, studies from selected work-groups have shown that substantial fractions of subjects are left with continued inflammation and airways obstruction (114). In the Hordaland County Cohort Study, remission of respiratory symptoms was less likely in subjects with previous occupational exposure (Paper IV) (75).

The results from the Hordaland County Cohort Study underscore the importance of prevention of irreversible obstructive lung disease originating at the workplace.

**Socioeconomic status**

The Scandinavian countries are characterized by small differences in income, access to health care, and access to education, relative to other western countries. It is somewhat surprising that differences in socioeconomic status have been found to correlate closer with the risk for several diseases in Scandinavia, than in other parts of Europe (115). At the same time, smoking differs more by socioeconomic status in Scandinavia than other European countries, with a higher smoking prevalence among those with a lower socioeconomic status (116). This has been put forward as one explanation for the inequality in health along social class in Scandinavia.

Socioeconomic status denotes one’s standing in society. Social stature is often associated with income, educational level, and line of occupation, and these three variables are the ones most often used to represent socioeconomic status in epidemiologic studies (117).

None of these measures are perfect. Income varies greatly with age, and many people will be reluctant to report their income. Income alone is therefore not suitable for measurement of socioeconomic status in a general population setting with a wide age span. Occupation has often been categorized into ‘blue-collar’ and ‘white-collar’, with white-collar representing a higher socioeconomic status. These are crude categories, becoming less relevant with the growth of the service sector, which can be hard to define into blue-collar or white-collar. Complex job-matrices have been developed to better grade occupation into a measure of socioeconomic status (117). These require regular revisions, as job-titles today and 50 years ago may not be directly comparable. Finally,
most subjects will have several jobs throughout their adult life. The information necessary to obtain for the construction of specific job-matrices would be large in a population with a wide age span, and was not attempted in the Hordaland County Cohort Study. Educational level will also vary with age cohort, at least when measured as years of schooling. In the Hordaland County Cohort Study, the questions were directed towards what type of school a subject concluded. Thereby, 10 years of schooling 40 years ago could be equivalent with 12 years of schooling today. However, for the oldest generation of women, social stature could to some extent be related to their husbands’ educational level more than their own.

Not many community cohort studies have examined socioeconomic status and incidence of asthma and respiratory symptoms. In the Hordaland County Cohort Study, educational level was related to sex, age, hayfever, smoking, and occupational dust or fumes exposure (Paper V)(118). Even after adjustment for all these factors, educational level predicted the incidence of asthma and most examined respiratory symptoms (Figure 8).

Figure 8. The effect of educational level on the incidence of asthma and respiratory symptoms in the Hordaland County Cohort Study

* presented as OR (95% CI), adjusted for sex, age, atopy, smoking, pack years, and dust/fumes exposure
Which factors associated with educational level could explain these findings? Although this will be the task of later studies, it is tempting to outline some potential explanatory factors:

First, there could be residual confounding. Adjustment for smoking took into account both changes in smoking habits and smoking load measured by pack years. Also, adjustment were made for smoking up until follow-up, thus probably over-adjusting for smoking, which still did not alter the effect of education. Thus, residual confounding of smoking is less likely. With occupational exposure, the measure was crude, and adjustment was not made for exposure within the follow-up period. Residual confounding by occupational exposures could explain part of the effect of educational level.

Second, body mass index (BMI) have been linked to asthma in several studies, at least for women (21, 119-122). This could be due to dietary factors, structural changes in the airways of obese subjects, or a difference in perception of for instance dyspnea in overweight subjects.

Third, passive smoking has been associated with asthma in children (123). In adults the picture is less clear. Early, yet unpublished, data from our sample points towards a role for passive smoking, though not explaining the effect of educational level.

Fourth, poorer housing conditions could be associated with an increased exposure to allergens like moulds or dust mites. However, hayfever was more common in subjects with a higher educational level (table 1, paper V). This is in accordance with some studies on children, where atopy is more common with higher socioeconomic status (124, 125). This has been one of the arguments for the hygiene hypothesis, where it has been argued that excess cleanliness is more common with higher socioeconomic status. However, studies of social class and asthma in children show an inconsistent pattern (126). We found no interaction between hayfever and educational level in the Hordaland County Cohort Study, and hayfever did not confound the relationship between educational level and asthma. Thus we think other factors than atopy must be sought to explain the effect of educational level. In some countries gas stove usage is clearly
associated with an excess risk for asthma and respiratory symptoms (127), but gas stoves are rarely in use in Norway.

Fifth, we like to think access to quality health care is evenly distributed in Norway. Yet, the strong association between socioeconomic status and several diseases could indicate this is not altogether true. Subjects with different educational level could utilize the health services differently, or be more or less perceptive to health advice.
Perspectives

The Hordaland County Cohort Study has provided a reasonable estimate of the adult asthma incidence in the Norwegian adult population. Likewise, estimates of the incidence of key respiratory symptoms have been established. These estimates have value for health planners, enabling the calculation of the burden of asthma in the adult population in the years to come. Further, the estimates are available for later comparison, for instance for evaluation of increases or decreases in the incidences.

However, some methodological issues remain unresolved. Misclassification can distort the estimates of incidence and remission, and in some instances the evaluation of the effect of the risk factors. Recently, estimation techniques have been developed to adjust for the possibility of misclassification of the exposure variables in longitudinal models. It is likely that further developments in the field of statistics will lead to techniques to adjust also for a possible misclassification of the outcome.

There seems to be a difference in the adult incidence of asthma and respiratory symptoms between genders. Women could be more susceptible to the factors causing asthma than men, or they could be exposed at a higher level than men. There could be some gender-specific risk factors responsible. Another possibility could be that the perception of symptoms was different between women and men, or the tendency to receive a diagnostic label. Yet another question is whether the distribution of severe asthma is similar between women and men. Studies searching for factors that are different between women and men could highlight these issues, and all studies should pay attention to the study power needed to discover significant differences in the effect of examined risk factors in women and men.

Smoking is a cause of respiratory symptoms. A high smoking load is a likely risk factor of asthma, and it is likely that smoking causes a worsening of asthma in asthmatic subjects who start to smoke. However, biological studies are needed to confirm the relationship between smoking and asthma, as it seems unlikely that epidemiologic studies will fully clarify this issue. The current study still underscores the ill effects of smoking on respiratory health, and the preventive potential from avoiding to smoke.
This could be put to test by conducting community intervention trials. Several antismoking campaigns have been conducted in the general population previously. By allocating an intervention to for instance half the teenage population, one could compare the incidence of asthma and respiratory symptoms in the intervention group compared to the control group, within for example a 10-year period after the intervention.

Although biological studies exist on the inflammation in asthma, there is no established method for studying the key events responsible for the inflammation. An all-encompassing theory of the events responsible for the disease asthma is yet not formulated. This is reflected by the continually changing definition of asthma. Ultimately, a multi-disciplinary approach is needed, combining epidemiological data with physiological and biochemical data. At present, more epidemiologic data is available than data on the inflammatory changes.

One approach to further characterize the inflammatory changes in asthma may be done with studies on subjects with and without occupational asthma, where specific work cohorts may allow for a stricter control of the exposures.

The Hordaland County Cohort Study has shown that the fraction of incident asthma attributable to working exposures was high in the general population. This partially reflects the high prevalence of self-reported occupational exposure in the population, especially among men. The estimation was based upon estimates of lifetime exposures, and the level of exposures in the population may be different today. There is an important preventive potential here. It is preferable to have an updated estimate of the prevalence of occupational exposure in the general population, and particularly which exposures are common in which industries.

Which factors that are responsible for the association of a lower risk for asthma and most symptoms with higher educational level should be a matter of future research. Herein lies the potential to find causal factors for the development of asthma. Longitudinal studies should preferably contain baseline data on heredity, early life factors, and lifestyle factors like dietary factors, body weight, passive smoking, as well as characterization of indoor
environment and occupational environment, in addition to the commonly assessed sex, age, and smoking.

It has long been recognized that genetic factors are likely to contribute to the development of asthma. Asthma is likely to be a disease where several genes can predispose to the disease, perhaps given later environmental exposures. The search for asthma genes have increased rapidly during the last decade, yet much is still unknown. In order to characterize the interplay between genetic factors and the environment, it will be important with larger population samples with characterization of both phenotype and genotype.
CONCLUSIONS

1) The Hordaland County Cohort Study is a randomly sampled longitudinal community survey with a high response rate, and a high internal and external validity.

The response rate was 89% both at baseline and follow-up. From the original sample of 3786 subjects, 2819 contributed data at both time-points (74%).

Significant predictors of a high response at follow-up were being in the age group 30-49 years, being employed, and having been an early responder at baseline. A total of up to three reminders were used at follow-up, increasing the response rate from 65% to 89%. Increasing the response rate from 65% to 89% did not alter the associations of sex, age, and smoking to the incidence of asthma and respiratory symptoms.

2) The adult incidence of asthma per 1000 person years (95% CI) in the Hordaland County Cohort Study was 3.2 (2.4, 4.3) in women, and 3.7 (2.8, 4.8) in men. Combined, the total adult asthma incidence per 1000 person years (95% CI) was 3.4 (2.9, 4.2).

Although the incidence of adult asthma did not differ significantly between genders in the Hordaland County Cohort Study, it was found that the asthma incidence was slightly higher in women than men when comparing all known international studies on adult incidence of asthma.

Women had a higher incidence of most respiratory symptoms.

The incidence of cough and dyspnea on exertion increased with higher age, whereas the incidence of wheezing decreased. The incidence of asthma increased with higher age.

3) Smoking was a risk factor for the incidence of all respiratory symptoms, either by changes in smoking habits, or amount smoked.

Subjects with a high tobacco consumption had an increased risk for asthma.
Occupational exposure was a risk factor for asthma and respiratory symptoms, even after extensive adjustment for smoking and educational level.

14% of the incidence of asthma was attributable to occupational airborne exposure.

Subjects with the highest educational level had the lowest incidence of asthma and respiratory symptoms. This could not be explained by differences in smoking habits or occupational exposures.

4) Subjects who gave up smoking had an increased chance of remission of the cough symptoms and wheezing, for morning cough by a factor of six.

The remission of respiratory symptoms was decreased in subjects with previous occupational exposures compared to subjects without previous occupational exposures.

Differences in educational level did not show a consistent effect on the remission of respiratory symptoms.
REFERENCES


65. StataCorp. 2003. Stata Statistical Software. 8.0 ed. Stata Corporation, College Station, TX.


APPENDICES

Appendix A - The baseline questionnaire and two reminder letters

LUNGEAVDELEN
HAUKELAND SYKEHUS, UNIVERSITETET I BERGEN
5016 HAUKELAND SYKEHUS

Undersøkelse over utbredelsen av allergi, astma og andre lungesykdommer i Hordaland.

KJÆRE INNBYGGER I HORDALAND!

Ved Lungeavdelingen, Haukeland Sykehus utfører vi nå en undersøkelse over forekomsten av astma og bronkit i Hordaland fylke. Blant fylkets innbyggere er det trukket ut 5000 personer som blir bedt om å svare på et spørreskjema. Og De er en av disse.

Det er frivillig å svare, men det er av største betydning for undersøkelsen at flest mulig fyller ut spørreskjemaet. Jeg vil derfor be Dem være vennlig å fylle ut dette og sende det tilbake i svarkonsulten innen 14 dager.
Hvis De ikke kan gi et helt nøyaktig svar, så fyll ut etter beste skønn. Hvis det er spørsmål De ikke kan svare på, så la det stå åpent. For hvert spørsmål settes et kryss i den som passer best!
Skulle De mot formodning ikke ønske å svare, er det helt tillatt. Vi vil sette pris på at De anfører dette på skjemaet og sender det tilbake. Alle opplysninger vil bli behandlet under full taushetsplikt.

På forhånd takk for hjelp!

Vennlig hilsen

[Signature]

AMUND GULSVIK
Oslofylke - helse

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<table>
<thead>
<tr>
<th>BOSTED</th>
<th>ARBEIDTRYGD</th>
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<tr>
<td>1. Er hus og businvener på samme adresse?</td>
<td>Arbeidstaker heldigstilling</td>
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<tr>
<td>Hus nummer:</td>
<td>Arbeidstager, minus</td>
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<td>Postnummer</td>
<td>Selvstendig fotavl bartverk, minus</td>
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<td>Husavdel, husmor</td>
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<td></td>
<td>Skolelev, student</td>
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<td>Sjukmaelt med sykdommer, over inntektsmengen</td>
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<td>Arbeidsdag med stønad</td>
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<td>Arbeidstaker uten stønad</td>
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<td>Utenpersonlig, fekehygiene</td>
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<td>Arbeidspersonal</td>
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<td>Almen situasjon</td>
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### Allergier

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<tr>
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<th>Nei</th>
<th>Ikke vises</th>
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<tr>
<td>Har De noen gang haft en av de sykdommer som er nevnt nedenfor?</td>
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### Andre Lungesykdommer

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<tr>
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<th>Nei</th>
<th>Ikke vises</th>
<th>Vises ikke</th>
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<tr>
<td>Er De noen gang blitt behandlet av lege eller har De vært innlagt i sykehus for en av de sykdommer som er nevnt nedenfor?</td>
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### Årbesvarelse forurensninger

Disse spørsmålene gjelder dem som har vært eller er i lænet arbeid eller selvstendig næringsdrivende.

- Har De noen gang haft en arbeidspluss med mye støv eller gasser i luften?  1 Ja  2 Nei
- Har De i Deres arbeid noen gang vært i kontakt med asbeststov?  1 Ja  2 Nei
- Når kom De første gang i kontakt med asbest? Angi årstall:  
- Hvor mange år har De i tillegg hatt arbeid hvor De har arbeidet med asbest? Angi antall år:  
- I hvilket grad vil De anstå at De har vært utsatt for asbeststov?  1 I liten grad  2 I middelgrad  3 I stor grad
- Har De i Deres arbeid noen gang vært utsatt for kvartsstov eller steinstov med kvarts?  1 Ja  2 Nei
- Hvis Ja, anslag i hvilke år har De vært utsatt for siitt stov i arbeidslivet?
Investigation regarding the occurrence of allergies, asthma, and other lung diseases in Hordaland.

DEAR RESIDENT OF HORDALAND!
At the Department of Thoracic Medicine, Haukeland Hospital, we are now performing an investigation regarding the occurrence of asthma and bronchitis in the county of Hordaland. Among the inhabitants of the county, 5000 subjects have been chosen and asked to answer a questionnaire, and you are one of these.
Answering is voluntary, however it is of great importance to the investigation that as many as possible complete the questionnaire. I will therefore ask you to be so kind as to complete it and return it in the reply envelope within 14 days.
If you cannot give an exact answer, complete it to the best of your judgment. If there are questions that you cannot answer, leave them open. For each question place a cross in the best suited.
If you should not wish to answer at all, I would appreciate if you state it on the form and return it.
All information will be treated with full confidentiality.
In advance, thank you for your help!
Yours sincerely,

Amund Gulsvik
Senior Physician, professor

Place of residence
1. Is the name and address on the form correct and complete? Yes No
   If ‘No’, please state your full name and address
   Name.............
   Address..........
   Postal code.....

Work, social security
3. Please mark the option which best describes your situation:
   Employee, full-time employment
   Employee, part-time employment
   Self-employed
   Housework, housewife
   Student
   Sick-leave, receiving sickness benefits or rehabilitation benefits
   Unemployed, receiving unemployment benefits
Unemployed, without unemployment benefits
Disability pensioner, state disability pension scheme
Retired pensioner
Other situation

**Irritations from the airways**

4. Do you usually cough or clear your throat in the morning? Yes No
5. Do you usually cough during the day? Yes No
6. Do you usually have phlegm when coughing? Yes No
7. Do you have cough for three months or more altogether during a year? Yes No
8. During the last two years, have you had cough and/or phlegm in connection with a cold for more than three weeks? Yes, once Yes, several times No
9. Are you more breathless than people of your own age when walking uphill? Yes No
10. Are you breathless when you climb two flights of stairs at an ordinary pace? Yes No
11. Are you breathless walking at a normal pace on level ground? Yes No
12. Are you breathless while at rest? Yes No
13. Do you sometimes experience attacks of breathlessness? Yes No
14. Do you ever have wheezing (a wheezing sound) in your chest? Yes No

**Smoking habits**

15. Do you smoke daily at present? Yes No
   If the answer was ‘yes’, then answer:
   Do you smoke cigarettes daily? (handrolled or factory made) Yes No
16. If you do not smoke cigarettes now, then answer:
   Have you smoked cigarettes daily before? Yes No
   If you answered ‘yes’, how long is it since you stopped?
   1. less than 3 months ago?
   2. 3 months – 1 year ago?
   3. 1 year – 5 years ago?
   4. more than 5 years ago?
17. For those who smoke or have smoked previously:
   For how many years have you smoked daily? # of years
18. How many cigarettes do you or did you smoke daily?
   Give number of cigarettes per day (handrolled or factory made) # of cigarettes
19. Do you smoke anything other than cigarettes daily? Yes No
   Cigars or cigarillos? Yes No
   Pipe? Yes No
20. If you smoke pipe, how many packs of tobacco (50 gram) do you smoke per week?
   Give average number per week. # of packs
21. If you smoke, has any physician advised you to stop smoking? Yes No
Allergies
Have you ever had one of the diseases mentioned below?
22. Eczema  Yes  No  Don’t know
23. Urticaria Yes  No  Don’t know
24. Hay fever Yes  No  Don’t know
25. Have you been allergy tested by a practitioner or in hospital? Yes  No  Don’t know

Other lung diseases
Have you ever been treated by a physician or have you been hospitalized for one of the below mentioned diseases?
26. Asthma Yes  No  Don’t know
27. Bronchitis Yes  No  Don’t know
28. Emphysema (inflated lungs) Yes  No  Don’t know
29. Pleuritis Yes  No  Don’t know
30. Lung tuberculosis Yes  No  Don’t know
31. Heart infarction Yes  No  Don’t know
32. Angina pectoris Yes  No  Don’t know
33. Other heart disease Yes  No  Don’t know

Occupational environment, pollutants
These questions refer to those who have been employed or self-employed.
34. Have you ever had a work place with much dust or fumes in the air? Yes  No
35. Have you ever been exposed to asbestos dust in your work? Yes  No
If no, please continue at question number 39.
36. When did you first come into contact with asbestos? State the year:
37. How many years altogether have you had a job in which you worked with asbestos? State number of years. # of years
38. To what extent would you say you have been exposed to asbestos?
To a small extent
To a moderate extent
To a large extent
39. Have you ever been exposed to quartz dust or stone-dust with quartz at work? Yes  No
40. If yes, please state how many years you have been exposed to such dusts at work. # of years
Some time ago I sent you a questionnaire, of which I now would like to remind you. It is of the greatest importance that the questionnaire is filled in by anyone who ever received one, no matter whether they feel completely well or ill.

I have enclosed a new questionnaire in case the previous one has been mislaid. I would be very grateful if you could please find the time to read it, fill it in, and return it in the enclosed envelope. The return postage has already been paid.

Thanks for your help!

With kind regards,

Amund Gulsvik (s.)
Kjære bergensere og hordalendinger.

Har De litt dårlig samvittighed, vet De at vår professor forgjøves har forsøkt å oppnå kontakt med Dem i forbindelse med undersøkelsen over astmatiske sykdommer i Hordaland.

Selv om De kanske ikke er like interessert i slik kontakt som ham vil jeg likevel spørre Dem igjen om De vil være brydd med å lese og besvare vedlagte spørrebeskjema. Husk at returportoen er betalt.

Med optimistisk hilse

O.Overå, consultant physician
Department of Thoracic Medicine
5016 HAUKELAND HOSPITAL

Bergen, fall of 1985

Dear residents of Bergen and Hordaland.

If your conscience has been bothering you, you will know that our professor in vain have tried to establish contact with you in connection with the survey on asthmatic diseases in Hordaland County.

Even if you may not be as interested in such contact as him I shall again ask you if you please could take the time to read and answer the enclosed questionnaire. Remember the return postage has already been paid.

With optimistic regards

Olav Overå (s.)
Appendix B - The follow-up questionnaire and the accompanying letters

Vennligst besvar spørreskjemaet. Hvis du ikke kan gi et helt nøyaktig svar, fyll ut etter beste evne. Hvis det er spørsmål du ikke kan svare på, la det stå åpent.
For hvert spørsmål setter du et kryss i den ☐ som passer best.

Returadresse:
Astma og inneklimaundersøkelsen
Lungeavdelingen
5021 Haukeland sykehus

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1. Luftveissymptomer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Hoster eller harker (kremter) du vanligvis om morgenen?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>2. Hoster du vanligvis ellers om dagen?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>3. Har du vanligvis oppspytt når du hoster eller harker?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>4. Hoster du tilsammen 3 måneder eller mer i løpet av ett år?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>5. Har du i løpet av de siste par årene i forbindelse med forkjølelse hatt hoste og/eller oppspytt som har vart mer enn 2 uker?</td>
<td>☐ Ja, flere ganger ☐ Ja, en gang ☐ Aldri</td>
</tr>
<tr>
<td>6. Blir du mer tungpusten (andpusten) enn jevnaudrende når du går i motbakker?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>7. Blir du tungpusten når du går opp 2 etasjer i vanlig fart?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>8. Blir du tungpusten når du går med vanlig fart på flat mark?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>9. Blir du tungpusten når du sitter i ro?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>10. Hender det at du får anfall av tungpust?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>11. Har du noen gang hatt piping (pipelyd) i brystet?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>12. Har du vært innlagt på sykehus før du har vært 2 år gammel på grunn av lungenesykdom (astma, bronkkitt, bronkiolitt, lungebetennelse)?</td>
<td>☐ Ja ☐ Nei ☐ Vet ikke</td>
</tr>
<tr>
<td>13. Har du noen gang i løpet av de siste 12 måneder hatt pipelyder (piping) i brystet? (med pipelyder menes høye eller dype lyder som også kan være svake)</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td></td>
<td>Hvis du svarte nei på spørsmål 13 gå direkte til spørsmål 15</td>
</tr>
<tr>
<td>14.1 Har du noen gang vært andpusten samtidig som du har merket piping i brystet?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>14.2 Har du hatt slike pipelyder i brystet selv om du ikke har vært forkjølet?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>15. Har du noen gang i løpet av de siste 12 måneder våknet opp med følelse av å være tungpusten?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>16. Har du noen gang i løpet av de siste 12 måneder våknet opp med anfall av hoste</td>
<td>☐ Ja ☐ Nei</td>
</tr>
<tr>
<td>17. Har du i løpet av de siste 12 måneder hatt astma anfall?</td>
<td>☐ Ja ☐ Nei</td>
</tr>
</tbody>
</table>
## 2. Allergi

19. Hvis ja, har du siste 12 måneder hatt høysnue? □ Ja □ Nei □ Vet ikke
19.1 Når hadde du plagene siste året? □ Vår □ Høst □ Sommer □ Vinter
(kreys av en eller flere)
20. Har du noen gang hatt barneeksem (atopisk dermatitt)? □ Ja □ Nei □ Vet ikke
20.1 Hvis ja, har du fortsatt slikt eksem (atopisk dermatitt)? □ Ja □ Nei □ Vet ikke

## 3. Lungesykdommer

Er du noen gang blitt behandlet av lege eller har du vært innlagt i sykehus for en av de sykdommene som er nevnt nedenfor?

21. Astma
   21.1 Hvis ja, hvor gammel var du da sykdommen begynte? □ Ja □ Nei □ Vet ikke
   Alder: □□□ år
   21.2 Hvis du ikke lenger har astma, hvor gammel var du da den ga seg? □□□ år

22. Bronkit
   22.1 Hvis ja, hvor gammel var du da sykdommen begynte? □ Ja □ Nei □ Vet ikke
   Alder: □□□ år
   22.2 Hvis du ikke lenger har bronkit, hvor gammel var du da den ga seg? □□□ år

23. Emfysen
   23.1 Hvis ja, hvor gammel var du da sykdommen begynte? □ Ja □ Nei □ Vet ikke
   Alder: □□□ år

24. Kronisk obstruktiv lungesykdom (KOLS)
   24.1 Hvis ja, hvor gammel var du da sykdommen begynte? □ Ja □ Nei □ Vet ikke
   Alder: □□□ år

## 4. Bruk av helsetjenester og trygd

25. Har du astma, bronkit, emfysen eller kronisk obstruktiv lungesykdom? □ Ja □ Nei
   *Hvis ja, besvar da spørsmål 26-33*

26. Bruker du astmamedisiner nå? □ Ja □ Nei
   *(inkludert spray, pulverinhalasjoner, tablett)*

27. Går du til kontroll hos lege for overnevnte sykdommer? □ Ja □ Nei

28. Hvis ja, går du til □ almenpraktiker, kommunlegele
   *(kreys av en eller flere)* □ bedriftslege □ lungelege □ annen lege

29. Hvis ja på spm. 27, når var du til kontroll sist? for □□□ måneder siden
30. Hvor mange ganger har du vært innlagt på sykehus for overnevnte sykdommer siste 12 måneder? □□□ antall
31. Er du i lønnet arbeid? □ Ja □ Nei
32. Hvis ja, hvor lenge har du vært sykemeldt tilsammen pga. overnevnte sykdommer siste 12 måneder?
   Ingen dager 0-7 dager 8-30 dager 31-90 dager over 90 dager □ □ □ □ □
33. Er du uføretrygdet pga. overnevnte sykdommer? □ Ja □ Nei
5. Røykevaner

34. Røyker du daglig for tiden? □ Ja □ Nei
35. Hvis svaret var “ja” på forrige spørsmål, røyker du sigaretter daglig? (håndrullete eller fabrikkframstilte) □ Ja □ Nei
36. Hvis du ikke røyker sigaretter nå:
   Har du røukt sigaretter daglig tidligere? □ Ja □ Nei
37. Hvis du svarte “ja”, hvor lenge er det siden du sluttet?
   □ Mindre enn 3 måneder?
   □ 3 måneder - 1 år?
   □ 1 - 5 år?
   □ Mer enn 5 år?
38. Følgende spørsmål besvares kun hvis du røyker nå eller har røukt tidligere
39. Hvor mange år har du røkt daglig? Antall år: □□□□□
40. Hvor mange sigaretter røyker eller røykte du daglig?
   Oppgi antall per dag (håndrullete og fabrikkframstilte) Antall sigaretter: □□□□□
41. Hvis du røyker, har noen lege anbefalt deg å slutte å røyke? □ Ja □ Nei
42. Har du prøvd nikotinplaster eller nikotintyggegummi? □ Ja □ Nei
43. Har du deltatt på røykeavvenningsmøter/kurs? □ Ja □ Nei

6. Passiv røyking

44. Er du utsatt for passiv røyking hjemme? □ Ja, daglig □ Ja, noen ganger □ Nei
45. Hvis svaret var “nei”, besvar da:
   Har du vært utsatt for passiv røyking hjemme tidligere? □ Ja, daglig □ Ja, noen ganger □ Nei
46. Er du utsatt for passiv røyking på arbeid? □ Ja, daglig □ Ja, noen ganger □ Nei
47. Hvis svaret var «nei», besvar da:
   Har du vært utsatt for passiv røyking på arbeid tidligere? □ Ja, daglig □ Ja, noen ganger □ Nei
48. Røykte din mor da hun var gravid med deg? □ Ja □ Nei □ Vet ikke
49. Røykte din mor da du var barn? □ Ja □ Nei □ Vet ikke
50. Hvis «ja», hvor gammel var du da?
   (kryss av på et eller begge alternativene) □ under 5 år □ fra 5-15 års alderen
51. Røykte andre i din husstand da du var barn? □ Ja □ Nei □ Vet ikke
   Hvis «ja», hvor gammel var du da?
   (kryss av på et eller begge alternativene) □ under 5 år □ 5-15 år
7. Inneklima

52. Har du obeserte fugtssader i huset ditt de siste 2 årene? □ Ja □ Nei
53. Har du obeserte mugg eller vekst av muggsopp i huset ditt de siste 2 årene? □ Aldri □ Av og til □ Ofte
54. Har du eller noen du har bodd sammen med noen gang hatt husdyr? (Hund, katt, fugl eller smågnagere) □ Ja □ Nei
55. Hvis ja, har du fortsatt slike husdyr? □ Ja □ Nei

8. Utdannelse og arbeid

56. Vennligst kryss av for det utdanningsalternativ som passer best for deg:
Tidligere folkeskole eller nåværende 9-årig skole □
Framhaldsskole, folkehøyskole, bibelskole og andre tilsvarende skoler □
Middelsskole, realskole, gymnas, videregående skole, yrkesskole, eller annen fagskole □
Høyskole, universitetet □
57. Har du noen gang hatt en arbeidsplass med mye støv eller gasser i luften? □ Ja □ Nei

9. Astma i familien

58. Har følgende av dine biologiske slektninger hatt astma?
   Mor □ Ja □ Nei □ Vet ikke
   Far □ Ja □ Nei □ Vet ikke
   Hvor mange søskne har/hadde du? Antall □□□□
   Hvor mange av dine søskne har astma? Antall □□□□ □ Vet ikke
   Hvor mange barn har/hadde du? Antall □□□□
   Hvor mange av dine barn har astma? Antall □□□□ □ Vet ikke

Takk for at du tok deg tid til å fylle ut spørreskjemaet.
Vennligst returner det i vedlagte svarkonvolutt til

Aスタマ og inneklimaundersøkelsen
Lungeavdelingen
5021 Haukeland sykehus
Please answer the questionnaire. If you cannot give an exact answer, fill in using your best judgment. If there is a question you cannot answer, leave it open. For each question, place a mark in the appropriate column.

Return address:
Asthma and indoor-climate survey  
Department of Thoracic Medicine  
5021 Haukeland Hospital

<table>
<thead>
<tr>
<th>1. Symptoms from the airways</th>
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<tbody>
<tr>
<td>1. Do you usually cough or clear your throat in the morning? Yes No</td>
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<tr>
<td>2. Do you usually cough during the day? Yes No</td>
</tr>
<tr>
<td>3. Do you usually have phlegm when coughing? Yes No</td>
</tr>
<tr>
<td>4. Do you have cough for three months or more altogether during a year? Yes No</td>
</tr>
<tr>
<td>5. During the last two years, have you had cough and/or phlegm in connection with a cold for more than three weeks? Yes, several times Yes, once Never</td>
</tr>
<tr>
<td>6. Are you more breathless than people of your own age when walking uphill? Yes No</td>
</tr>
<tr>
<td>7. Are you breathless when you climb two flights of stairs at an ordinary pace? Yes No</td>
</tr>
<tr>
<td>8. Are you breathless walking at a normal pace on level ground? Yes No</td>
</tr>
<tr>
<td>9. Are you breathless while at rest? Yes No</td>
</tr>
<tr>
<td>10. Do you sometimes experience attacks of breathlessness? Yes No</td>
</tr>
<tr>
<td>11. Have you ever had wheezing (a wheezing sound) in your chest? Yes No</td>
</tr>
<tr>
<td>12. Were you hospitalized before you were 2 years old because of lung disease (asthma, bronchitis, bronchiolitis, pneumonia)? Yes No</td>
</tr>
<tr>
<td>13. Have you ever had wheezing (a wheezing sound) in your chest in the last 12 months? (By wheezing is meant high or low pitch sounds which can also be weak) Yes No</td>
</tr>
<tr>
<td>If you answered no to question 13 proceed to question 15</td>
</tr>
<tr>
<td>14.1 Have you ever been breathless at the same time you have noticed a wheezing sound in your chest? Yes No</td>
</tr>
<tr>
<td>14.2 Have you had such wheezing sounds in your chest even if you did not have a cold? Yes No</td>
</tr>
<tr>
<td>15. Have you ever within the last 12 months awoken with a feeling of breathlessness? Yes No</td>
</tr>
<tr>
<td>16. Have you ever within the last 12 months awoken with attacks of cough? Yes No</td>
</tr>
<tr>
<td>17. Have you within the last 12 months had an asthmatic attack? Yes No</td>
</tr>
</tbody>
</table>
2. Allergy

18. Have you ever had hay fever? Yes No Don’t know
19. If yes, have you had hay fever within the last 12 months? Yes No Don’t know
19.1 When did you experience symptoms last year? (mark one or more) Spring Fall Summer Winter
20. Have you ever had children’s eczema (atopic eczema)? Yes No Don’t know
20.1 If yes, do you still have this eczema (atopic eczema)? Yes No Don’t know

3. Lung diseases

Have you ever been treated by a physician, or have you been hospitalized for one of the diseases mentioned below?

21. Asthma Yes No Don’t know
21.1 If yes, how old were you when the disease started? Age: ___________ years
21.2 If you no longer have asthma, how old were you when it stopped? Age: ___________ years

22. Bronchitis Yes No Don’t know
22.1 If yes, how old were you when the disease started? Age: ___________ years
22.2 If you no longer have bronchitis, how old were you when it stopped? Age: ___________ years

23. Emphysema Yes No Don’t know
23.1 If yes, how old were you when the disease started? Age: ___________ years

24. Chronic obstructive pulmonary disease (COPD) Yes No Don’t know
24.1 If yes, how old were you when the disease started? Age: ___________ years

4. Health services and social security

25. Do you have asthma, bronchitis, emphysema, or chronic obstructive pulmonary disease? Yes No

If yes, then answer questions 26-33

26. Are you using asthma medication now? (including spray, metered dose inhalers, tablets) Yes No

27. Do you see a physician for the above mentioned diseases? Yes No

28. If yes, do you see general practitioner physician employed by workplace pulmonary specialist other type of physician (mark one or more)
29. If yes to qt. 27, when did you last check in? |__|__| months ago
30. How many times have you been hospitalized for the above mentioned diseases the last 12 months? |__|__| times
31. Are you employed? Yes No
32. If yes, what is the total number of days you have been on sick-leave due to the above mentioned diseases within the last 12 months.
   No days 0-7 days 8-30 days 31-90 days more than 90 days
33. Are you receiving disability pension due to the above mentioned diseases? Yes No

5. Smoking habits
34. Do you presently smoke daily? Yes No
35. If the answer to the last question was ‘yes’, do you smoke cigarettes daily? (handrolled or factory made) Yes No
36. If you do not smoke cigarettes now:
   Have you smoked cigarettes daily before? Yes No
37. If the answer was ‘yes’, how long is it since you quit?
   Less than 3 months? 3 months – 1 year? 1-5 years? More than 5 years?
38. The following questions are to be answered only if you smoke currently or have smoked before
39. For how many years have you smoked daily? Number of years: |__|__|
40. How many cigarettes do you smoke or did you smoke daily?
   Give number per day (handrolled or factory made) Number of cigarettes: |__|__|
41. If you smoke, has any physician advised you to quit? Yes No
42. Have you tried nicotine transdermal patches or nicotine gum? Yes No
43. Have you participated in smoking cessation courses? Yes No

6. Passive smoking
44. Are you exposed to passive smoking at home? Yes, daily Yes, sometimes No
45. If the answer was ‘no’, then answer:
   Have you been exposed to passive smoking at home before? Yes, daily Yes, sometimes No
46. Are you exposed to passive smoking at work? Yes, daily Yes, sometimes No
47. If the answer was ‘no’, then answer:
   Have you been exposed to passive smoking at work before? Yes, daily Yes, sometimes No
48. Did your mother smoke when she was pregnant with you? Yes No Don’t know
Did your mother smoke when you were a child?  Yes  No  Don’t know

If ‘yes’, how old were you then?
(mark one or both alternatives)  less than 5 years old  5-15 years old

Did others in the household smoke when you were a child?  Yes  No  Don’t know
If ‘yes’, how old were you then?
(mark one or both alternatives)  less than 5 years old  5-15 years old

7. Indoor climate

Have you observed moisture damage in your house the last 2 years?  Yes  No

Have you observed moulds in your house the last 2 years?  Never  Sometimes  Often

Have you or someone you have lived with ever had had pets? (Dog, cat, bird or pet rodents)  Yes  No

If yes, do you still keep pets?  Yes  No

8. Education and work

Please mark the educational level which best describes your level:
Former primary school or present 9-year primary school
Continuation school, 1-year people’s college, bible school, or the like
Lower or upper secondary school, or technical school
College or university

Have you ever had a work-place with much dust or fumes in the air?  Yes  No

9. Asthma in the family

Have any of your following biological relatives had asthma?
Mother  Yes  No  Don’t know
Father  Yes  No  Don’t know
How many siblings do you/did you have?  Number |___|___|
How many of your siblings have asthma?  Number |___|___|  Don’t know
How many children have you or have you had?  Number |___|___|
How many of your children have asthma?  Number |___|___|  Don’t know

Thank you for taking the time to fill in the questionnaire. Please return it in the enclosed reply envelope to
The Asthma and indoor climate survey
Department of Thoracic Medicine
5021 Haukeland Hospital
Kjære Hordalending!


Lungeavdelingen, Haukeland sykehus, Universitetet i Bergen og Norges Forskningsråd ønsker nå å finne årsakene til at astmatiske sykdommer øker, for bare slik kan vi forebygge deres opptrede. Vi ber deg derfor straks om å fylle ut det vedlagte spørreskjemaet og sende det tilbake i svarkonvolutten senest innen 14 dager.

Hvis du ikke kan gi helt nøyaktige svar, så fyll skjemaet ut etter beste skjønn. For hvert spørsmål sett kryss i den rubrikken som passer best. Selv om du ikke har luftveisplager, ber vi deg fylle ut alle spørsmålene på skjemaet og returnere det i vedlagt frankert konvolutt.

Etter at du har returnert spørreskjemaet ønsker vi å invitere deg til en medisinsk undersøkelse med lungetesting ved poliklinikken, Lungenbygget, Haukeland sykehus. Lungeavdelingens poliklinik er vist på baksiden av dette arket. Undersøkelsen vil være uten kostnader for deg.

For undersøkelsen på Haukeland sykehus er det avgitt tid til deg.

<table>
<thead>
<tr>
<th>dag, den</th>
<th>/</th>
<th>199</th>
<th>klokken</th>
</tr>
</thead>
</table>

Dersom denne dagen eller tiden ikke skulle passe, vennligst gi beakjede mellom kl.08.00 -11.00, tlf. 55 97 40 66 eller 55 97 40 96 for avtale om ny time. Forevrig kan du møte mandag, tirsdag, onsdag, torsdag og fredag fra kl.08.00-10.00 og kl.12.00-13.00 fra og med den 16/09/96.

Deltagelsen er frivillig, men dersom det av en eller annen grunn ikke er mulig å besvare spørreskjemaet, så vil vi likevel be om at skjemaet returneres med angivelse av grunnen til dette.

Alle opplysningene vil bli behandlet med full taushetsplikt. Undersøkelsen er godkjent av Datatilsynet. Din deltagelse bidrar til å gjøre undersøkelsen bedre. På forhånd takk for hjelpen!

Anmund Gulsvik, professor, avdelingsoverlege.

Ida Welle, lege, stipendiat, Norges Forskningsråd.
Dear Resident of Hordaland!

In 1985 you participated in a survey regarding asthma and bronchitis. In 1987 or 1988 nearly half of you participated in a medical examination that included a test of heart-lung functions and a chest x-ray at the Haukeland Hospital.

The Dep. of Thoracic Medicine, Haukeland Hospital, University of Bergen, and the Norwegian Research Council wish to find the causes for the increase in asthmatic diseases, so that they can be prevented. We therefore ask you to immediately fill in the enclosed questionnaire and return it in the enclosed reply-envelope no later than 14 days from now.

If you cannot give exact answers, please still use your best judgment to fill in the questions. Mark the most fitting category for each question. Even if you do not experience any symptoms from the airways, please fill in the questionnaire and return it in the stamped return-envelope.

After you have returned the questionnaire we wish to invite you to a medical examination with lung-function testing at the outpatient clinic at the Dep. of Thoracic Medicine, Haukeland Hospital. A map of the hospital area with the outpatient clinic is shown at the back of this letter. The examination will be free of charge.

The time reserved for the examination at Haukeland Hospital for you is:

____day, the____/____/199__ at ___.___

If you are unable to come at the reserved time, please phone us between 08.00-11.00 at 55 97 40 66 or 55 97 40 96 to reschedule. You can attend Mondays, Tuesdays, Wednesdays, Thursdays, or Fridays from 08.00 (am) to 10.00 (am) and between 12.00 (am) to 13.00 (pm) from September 16th 1996.

Participation is voluntary, but if you for some reason cannot fill in the questionnaire, we ask you to still return it with a notification of the reason for this.

All information will be treated with full confidentiality. The survey has been approved by the Data Inspectorate. Your participation improves the quality of the survey. Thank you for your help!

Amund Gulsvik
Professor, Head of Dep.

Ida Welle, research fellow,
Norwegian Research Council
Kjære Hordalending!

For en tid siden sendte vi deg et spørreskjema om astma og inviterte deg til en legeundersøkelse ved Haukeland sykehus. Vi tillater oss å minne deg om dette.

Det er av største betydning for resultatet av undersøkelsen at alle besvarer spørreskjemaet og møter fram til undersøkelsen. Dette gjelder også de som føler seg helt friske, og ikke har astma.

I tilfelle det forrige spørreskjemaet er kommet bort, vedlegger vi et nytt som vi ber deg fylle ut og returnere i vedlagte svarkonvolutt. Vi har også gitt deg time til en lungeundersøkelse:

___dag, den ___/___/199__ klokken___

Frammøtested: Poliklinikken, Lungebygget, Haukeland Sykehus
(se kart på baksiden)

Dersom denne tiden ikke passer, vennligst gi beskjed mellom kl. 08.00 og 11.00, tlf 55 97 40 66 eller 55 97 40 96 for avtale om ny time. Forovrig kan du møte mandag, tirsdag, onsdag, torsdag eller fredag kl. 08.00-10.00 eller kl. 12.00-15.00.

Er du varig forhindret fra å møte, ber vi deg også ta kontakt med oss.

Vel møtt,

Amund Guls Vik
professor, avdelingsoverlege.

Ida Welle, lege, stipendiat,
Norges Forskningsråd.
Asthma and indoor-climate survey  
Dep. of Thoracic Medicine, University of Bergen  
Haukeland Hospital, 5021 Bergen  
Bergen 1996/97

Dear Resident of Hordaland!

A while ago we sent you a questionnaire regarding asthma and invited you to a medical examination at Haukeland Hospital. We allow ourselves to remind you of this.

It is of utmost importance for the results of the survey that everyone answers the questionnaire and participates at the examination. This is also true for those who feel healthy, and do not have asthma.

In case the last questionnaire has been lost, we enclose a new sample of the questionnaire, which we ask you to fill in and return in the enclosed return-envelope. We have also reserved the following time for a medical examination

<table>
<thead>
<tr>
<th>Day</th>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Place of examination: **Outpatient clinic, Dep. of Thoracic Medicine, Haukeland Hospital**.

(see map on back of letter)

If the scheduled time is inconvenient, please phone us between 08.00-11.00 at **55 97 40 66** or **55 97 40 96** to reschedule. You can attend Mondays, Tuesdays, Wednesdays, Thursdays, or Fridays from 08.00 (am) to 10.00 (am) and between 12.00 (am) to 15.00 (pm).

If you are permanently incapable of participating, we ask that you make contact with us.

We look forward to seeing you,

Amund Gulsvik
Professor, Head of Dep.

Ida Welle, research fellow,
Norwegian Research Council
Kjære Hordalending!

Vi har forgjeves prøvd å komme i kontakt med deg i forbindelse med en undersøkelse om astma i Hordaland. Det er av største betydning for resultatet av undersøkelsen at alle deltager. Dette gjelder også de som føler seg helt friske, og ikke har astma.

Selvom du kanskje finner dette besværlig, tillater vi oss derfor å be deg fylle ut vedlagte spørreskjema og returnere det i svarkonvoluten. Vi har også gitt deg tid til en lungeundersøkelse.

---

dag, den /___/199____ klokken ____________

---

Frammøtested: Poliklinikken, Lungebygget, Haukeland Sykehus.
(se kart på baksiden)

Dersom denne tiden ikke passer, vennligst gir beskjed mellom kl. 08.00 og 11.00, tlf 55 97 40 66 eller 55 97 40 96 for avtale om ny time. Forøvrig kan du møte mandag, tirsdag, onsdag, torsdag eller fredag kl. 08.00-10.00 eller kl. 12.00-15.00.

Er du varig forhindret fra å møte, ber vi deg også ta kontakt med oss.

---

Vel møtt,

Ernst Omenås
Overlege
Lungeavdelingen.
Asthma and indoor-climate survey  
Dep. of Thoracic Medicine, University of Bergen  
Haukeland Hospital, 5021 Bergen  

Dear Resident of Hordaland!

We have failed in making contact with you in connection with a survey on asthma in Hordaland. It is of utmost importance for the result of the survey that all those invited participates. This is also true for those who feel healthy, and do not have asthma.

Even if you may find it bothersome, we allow ourselves to ask you to fill in the enclosed questionnaire and return it in the return-envelope.

We have also reserved the following time for a medical examination

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>_<strong>/</strong><strong>/199</strong></td>
<td><em><strong>.</strong></em></td>
</tr>
</tbody>
</table>

Place of examination: **Outpatient clinic, Dep. of Thoracic Medicine, Haukeland Hospital.**

(see map on back of letter)

If the scheduled time is inconvenient, please phone us between 08.00-11.00 at **55 97 40 66** or **55 97 40 96** to reschedule. You can attend Mondays, Tuesdays, Wednesdays, Thursdays, or Fridays from 08.00 (am) to 10.00 (am) and between 12.00 (am) to 15.00 (pm).

If you are permanently incapable of participating, we ask that you make contact with us.

We look forward to seeing you,

Ernst Omenås
Senior physician
Dep. of Thoracic Medicine
HAUKELAND SYKEHUS
Appendix C - Analyses of incidence of wheeze using the question on wheeze within the last 12 months at follow-up, compared to wheeze ever

Table 5. A comparison of risk estimates obtained with analyses of wheeze ever at follow-up, or wheeze within last 12 months of follow-up

<table>
<thead>
<tr>
<th></th>
<th>wheeze ever</th>
<th></th>
<th>within last 12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>1.4</td>
<td>(1.1, 1.7)</td>
<td>1.3</td>
<td>(1.0, 1.7)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30-49</td>
<td>0.8</td>
<td>(0.6, 1.0)</td>
<td>0.9</td>
<td>(0.6, 1.1)</td>
</tr>
<tr>
<td>50+</td>
<td>0.7</td>
<td>(0.5, 0.9)</td>
<td>0.6</td>
<td>(0.4, 0.9)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never-never</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>non-current</td>
<td>2.3</td>
<td>(1.5, 3.6)</td>
<td>2.0</td>
<td>(1.2, 3.4)</td>
</tr>
<tr>
<td>current-current</td>
<td>2.0</td>
<td>(1.4, 2.8)</td>
<td>2.1</td>
<td>(1.4, 3.1)</td>
</tr>
<tr>
<td>current-ex</td>
<td>1.4</td>
<td>(1.0, 2.1)</td>
<td>1.2</td>
<td>(0.8, 2.0)</td>
</tr>
<tr>
<td>ex-ex</td>
<td>1.1</td>
<td>(0.8, 1.5)</td>
<td>0.9</td>
<td>(0.6, 1.4)</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per 10 pack-yrs increase</td>
<td>1.1</td>
<td>(1.0, 1.3)</td>
<td>1.1</td>
<td>(1.0, 1.3)</td>
</tr>
</tbody>
</table>
Appendix D - Example of the effect of a hypothetical reporting error on the estimates of incidence and remission

Consider the 2x2 table of a cohort study with a sample size of 1000 subjects, a baseline prevalence of 10%, a true cumulative incidence of 10%, and a true cumulative remission of 5%:

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>No</th>
<th>Yes</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>810</td>
<td>90</td>
<td>900</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>815</td>
<td>185</td>
<td>1000</td>
</tr>
</tbody>
</table>

Next, suppose there was a reporting error in which 5% of those who are not sick say they are sick (over-report), and 10% say they are well when they are not (under-report).

Further, assume that the reporting error is of the same magnitude at both baseline and follow-up.

In order to calculate the true incidence and remission we need to set up the 2x2 table we would have measured given the reporting error. This takes several steps:

First we will consider those subjects measured to be ‘No’ at baseline:

\[0.95 \times 900 + 0.1 \times 100 = 865.\]

From this it follows that among those (865) we measured to be ‘No’ at baseline, the true ‘No’ at baseline was: \(0.95 \times 900 = 855\).

And, the true ‘Yes’ at baseline was: 865-855=10.

Still among those (865) measured to be ‘No’ at baseline, the true ‘No’ at follow-up would be: \((855-0.1 \times 855)+0.05 \times 10=770\).

And, the true ‘Yes’ at follow-up would be: \(0.1 \times 855+(10-0.05 \times 10)=95\).
We are now ready to fill in two of the cells in our 2x2 table, namely those subjects who are ‘No’ at baseline, and ‘No’ or ‘Yes’ at follow-up:

First subjects who are ‘No’ at baseline, and ‘No’ at follow-up:

\[0.95 \times 770 + 0.1 \times 95 = 741.\]

And those subjects who are ‘No’ at baseline and ‘Yes’ at follow-up:

\[(95 - 0.1 \times 95) + 0.05 \times 770 = 124.\]

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>No</th>
<th>Yes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td>865</td>
</tr>
<tr>
<td>No</td>
<td>741</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td>1000</td>
</tr>
</tbody>
</table>

Next, we will consider those subjects measured to be ‘Yes’ at baseline:

\[0.9 \times 100 + 0.05 \times 900 = 135.\]

Following the same logic as above, among those (135) we measured to be ‘Yes’ at baseline, the true ‘Yes’ at baseline would be: \[0.9 \times 100 = 90.\]

And, the true ‘No’ at baseline was: \[135 - 90 = 45.\]

Still among those (135) we measured to be ‘Yes’ at baseline, the true ‘Yes at follow-up’ would be: \[(90 - 0.05 \times 90) + 0.1 \times 45 = 90.\]

And, the true ‘No’ at follow-up would be: \[0.05 \times 90 + (90 - 0.1 \times 45) = 45.\]

Then, subjects who are ‘Yes’ at baseline, and ‘Yes’ at follow-up:

\[(90 - 0.1 \times 90) + 0.05 \times 45 = 83.25.\]

And subjects who are ‘Yes’ at baseline, and ‘No’ at follow-up:

\[0.95 \times 45 + 0.1 \times 90 = 51.75.\]
Thus, the final measured 2x2 table given the reporting error would be:

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Follow-up</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>741</td>
<td>124</td>
<td>865</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51.75</td>
<td>83.25</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td></td>
<td>792.75</td>
<td>207.25</td>
<td>1000</td>
<td></td>
</tr>
</tbody>
</table>

From this table, we would obtain a measured cumulative incidence of: \(124/865=14.3\%\).
And a measured cumulative remission of: \(51.75/135=38.3\%\).
Appendix E - The wording of the questions, or case definitions, used to determine self-reported asthma and respiratory symptoms in previous studies on asthma and symptom incidence

Dodge, Am Rev Respir Dis, 80 – Tucson, Arizona cohort
Asthma was defined as answering yes to “Have you ever had asthma?” and “Have you seen a doctor about your asthma?”
For the symptoms the wording was:
“Have you ever had attacks of shortness of breath with wheezing?” “Does your chest ever sound wheezy or whistling?” and, if so, “Do you get this with colds?” “ Do you get this even when you do not have a cold?” “ Do you get this on most days?”
When the outcomes were analyzed, they were mutually exclusive, this means that asthmatic subjects who had attacks of shortness of breath were excluded from the attacks of shortness of breath category. The rules for deciding which category to assign subjects were not given in the paper.

Krzyzanowski, Chest, 90 – Tucson, Arizona and Krakow, Poland
The exact wording not given in paper, below is a copy of the text from the methods section:
Chronic Cough and Chronic Phlegm: usually, most days, for 3+ months, 2+ years (“when you don’t have a cold” in final Tucson survey)
Wheeze: apart form colds.
Attacks of breathlessness (“with wheezing” in Tucson).
Exertional Dyspnea : “when walking with other people of same age on level ground” (Tucson and Krakow) and/or “must rest after climbing one floor upstairs” (Krakow).
Chronic bronchitis: chronic cough and chronic phlegm.
Asthma syndrome: at least two of the following: wheeze, attacks of breathlessness, asthma diagnosis.
Krzyzanowski, ERJ 92:
The same definition was given for the symptoms as above, for asthma it was specified as: ‘subjects reporting to have bronchial asthma diagnosed by a doctor’.

Xu, Lancet, 97 – Vlaardingen/Vlagtwedde cohort
The exact wording of the questions is not given.
Chronic cough: cough on most days or nights for at least 2 months of the year
Chronic phlegm: sputum production on most days or nights for at least 3 months of the year
Dyspnea grade 3: being troubled by shortness of breath when walking with other people of the same age on level ground
Persistent wheeze: a wheezing or whistling sound in the chest on most days or nights
Asthmatic attacks: ever having attacks of shortness of breath with wheezing
Bronchitis: episodes of cough and phlegm lasting for at least 3 weeks in the past 3 years

Ronmark, Allergy 97 and Lundback, Respir Med, 01 – The Obstructive Lung Disease in Northern Sweden Study (OLIN)
Questions on asthma:
“Have you ever had asthma?”
“Have you been diagnosed as having asthma by a doctor?”
“Do you currently use asthma medicines (permanently or as needed)?”
Respiratory symptoms:
Wheezing: “Do you usually have wheezing, whistling (or a noisy sound) in your chest when breathing?”
Attacks of shortness of breath: “Do you now have or have you had asthma symptoms during the last 10 years (intermittent breathing or attacks of shortness of breath; the symptoms may exist simultaneously with or without cough or wheezing)?”

Beckett, AJRCCM, 01 – The CARDIA study
The exact wording of the questions was not given. However, asthma was classified as being present if:
1. A subject was taking asthma medication typically used to treat asthma,
or
2. A subject reported at one examination taking a medication not typically used to treat asthma, but reporting at a later examination taking a medication typically used to treat asthma,
or
3. Self-reported doctor or nurse diagnosis of asthma.

Godtfredson, ERJ, 01 – The Copenhagen City Heart Study
Asthma: “Do you have asthma?”
Chronic bronchitis: (exact wording not given) defined as bringing up phlegm during ≥ 3 months per year for ≥ 2 consecutive years.

Broder, J Allergy Immunol, 74 – The Tecumseh Health Study
The wording of the questions is not given.
At baseline the diagnosis of asthma was based on the diagnostic impression of the physician in question.
At follow-up, diagnostic criteria for asthma included:
1. Report of asthma or wheeze
2. Associated with attacks of shortness of breath or trouble breathing out
3. Attributed to exposure to allergen(s)
4. Diagnosed as asthma or asthmatic or wheezy bronchitis by the examining physician
Probable asthma was diagnosed when asthma or wheeze was reported along with at least two of the other features (2, 3, or 4). The diagnosis of suspect asthma was applied either when asthma was reported in association with feature 3 or 4 or both components of 2.
The estimates of incidence were based on probable asthma.

Huhti, Eur J Respir Dis, 80 – Harjavalta, Finland
The exact wording of the questions is not given.
Chronic bronchitis was defined as production of phlegm on most days for at least 3 months in the year, unless attributable to some local or specific lung disease. Phlegm production may have occurred during all day or only part of it (usually morning).
Breathlessness was graded in four degrees:
I no breathlessness
II,III not explained in text
IV breathless when walking at their own pace on the level
Other symptoms not defined (wheeze, phlegm)

Beck, Am Rev Respir Dis, 82 – Lebanon, Connecticut
The exact wording of the questions is not given.
The definitions of the symptoms were:
Usual cough: cough in morning or at any other time of day or night on most days for as much as 3 months of the year
Usual phlegm: phlegm production first thing in the morning or at any other time of the day or night for as much as 3 months of the year
Recent wheeze: wheezing, whistling, or chest tightness within the last 12 months
Dyspnea 1+: breathlessness when hurrying on level ground or walking up a slight hill, or worse.
Chronic bronchitis: cough and phlegm production for as much as 3 months a year for at least 2 years or more
Subjects physically disabled for other causes than respiratory disease were not asked the questions concerning dyspnea.

McWhorter, Am Rev Respir Dis, 89 – NHANES I, USA
Asthma: “Has a doctor ever told you that you have asthma?” and “Do you still have it?”

Plaschke, AJRCCM, 00 – The Swedish part of the ECRHS
Asthma: One of either: “Have you had any asthma attacks during the last 12 months?” or “Are you currently using any form of medication (aerosols, powder inhalers, or tablets) against asthma?”
Basagana, AJRCCM, 01 – The Spanish part of the ECRHS
Asthma: “Have you ever had asthma?”

Eagan, Eur Respir J, 02 – The Hordaland County Cohort Study
Asthma: “Have you ever been treated by a doctor or have you been hospitalized for asthma?”
Morning cough: “Do you usually cough or clear your throat in the morning?”
Daytime cough: “Do you usually cough during the rest of the day?”
Phlegm cough: “Do you usually have phlegm when coughing?”
Chronic cough: “Do you have a cough for three months or more altogether during a year?”
Dyspnea grade 1: “Are you more breathless than other people of your own age when walking uphill?”
Dyspnea grade 2: “Are you breathless when you climb two flights of stairs at an ordinary pace?”
Dyspnea grade 3: “Are you breathless walking at a normal pace on level ground?”
Dyspnea grade 4: “Are you breathless while at rest?
Attacks of dyspnea: “Do you sometimes experience attacks of breathlessness?”
Wheezing (at baseline): “Do you ever have wheezing (a wheezing sound) in your chest?
Wheezing (at follow-up): “Have you ever had wheezing (a wheezing sound) in your chest?”
Wheezing (at follow-up): “Have you ever had wheezing (a wheezing sound) in your chest in the last 12 months?”

Strachan, BMJ, 96
The British national child development study
At age 7:
“Has your child ever had attacks of asthma?”
“Has your child ever had attacks of bronchitis with wheezing?”
At age 11:
“Has your child ever had attacks of asthma or wheezy bronchitis?”
At age 16:
“Has your child ever had attacks of asthma or wheezy bronchitis?”
At age 23 “Have you had an attack of asthma or wheezy bronchitis since your 16th birthday?”
At age 33:
“Some people feel that their chest is sometimes wheezy or whistling. Have you ever had wheezing or whistling in your chest at any time in the past?”
The exact wording of the asthma question at age 33 is not given, but the appendix states that: “All subjects at the age of 33 were asked whether they had ever been told that they had asthma.”

Huovinen, Chest, 99 – The Finnish Twin Cohort Study
The wording of the asthma question was (same wording in 1975, 81, and 90):
“Have you ever been told by a doctor that you have or have had asthma?”

Troisi, Chest, 95 – The Nurses Health Study
The exact wording of the questions is not given.
Cases were ‘based on the nurses’ responses about whether they had had physician-diagnosed asthma or chronic bronchitis’. In addition, subjects who reported concomitantly chronic bronchitis were excluded, and only those actively taking asthma medications were included.

Toren, IJTLID, 99 – Western Sweden
Asthma: “Have you been diagnosed as having bronchial asthma by a physician?” and: “If yes: What year? or How old were you then?”

Sunyer, Eur Respir J, 99 – The Spanish part of the ECRHS
Asthma: “Have you ever had asthma?” + “How old were you when you had your first attack of asthma?”

De Marco, Journal of Allergy and Clinical Immunology, 2002 – The Italian Study on Asthma in Young Adults
Asthma: “Have you ever had asthma?” + “How old were you when you had your first attack of asthma?”

Brøgger, Eur Respir J, 04 – Hordaland, Norway
Asthma: “Have you ever been treated by a doctor or have you been hospitalized for asthma?”
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