From

Occupational Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå and
The Obstructive Lung Disease in Northern Sweden Studies, Department of Medicine, Sunderby Central Hospital of Norrbotten, Luleå

**Occupational air pollutants and non-malignant respiratory disorders especially in miners.**

The Obstructive Lung Disease in Northern Sweden Studies -

**Thesis IX**

by

**Ulf Hedlund**

2008
Cover photo and figure 1 LKAB, with permission

Printed by Print & Media Umeå University 2008:2004259

Detta verk skyddas enligt lagen om upphovsrätt (URL 1960:729)
Flitigt läsa gör dig klok. Därför läs varenda bok. (Diligent reading makes you clever. Therefore read all books.)

Falstaff Fakir, pseudonym for Axel Wallengren, 1865-1896, AD (Autodidactiae Doctor), Swedish author and philosopher.

My son, there is something else to watch out for. There is no end of the writing of books, and too much study will wear you out.

**Ecclesiastes 12:12**

To Bente

Laila Ingrid and Ellen
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>4</td>
</tr>
<tr>
<td>SAMMANFATTNING</td>
<td>6</td>
</tr>
<tr>
<td>LIST OF ORIGINAL PUBLICATIONS</td>
<td>8</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>9</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>10</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>10</td>
</tr>
<tr>
<td>Occupational exposure and respiratory health</td>
<td>10</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>15</td>
</tr>
<tr>
<td>Genetic and familiarly factors</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory health in metal miners</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory symptoms and obstructive lung disorders</td>
<td>15</td>
</tr>
<tr>
<td>Inflammation of the airways</td>
<td>18</td>
</tr>
<tr>
<td>Dose-response studies of silicosis</td>
<td>21</td>
</tr>
<tr>
<td>Extraction methods used in the examined mines</td>
<td>21</td>
</tr>
<tr>
<td>Air pollutants in the examined mines</td>
<td>25</td>
</tr>
<tr>
<td>AIMS OF THE STUDIES</td>
<td>26</td>
</tr>
<tr>
<td>MATERIAL AND METHODS</td>
<td>26</td>
</tr>
<tr>
<td>Population-based material of the OLIN cohorts (Studies I to IV)</td>
<td>26</td>
</tr>
<tr>
<td>Aims, study design, and study populations</td>
<td>26</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>26</td>
</tr>
<tr>
<td>Industry-based material</td>
<td>31</td>
</tr>
<tr>
<td>Study V</td>
<td>31</td>
</tr>
<tr>
<td>Study VI</td>
<td>32</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Exposure</td>
<td>32</td>
</tr>
<tr>
<td>Population-based material of the OLIN cohorts</td>
<td>32</td>
</tr>
<tr>
<td>Study I –II</td>
<td>32</td>
</tr>
<tr>
<td>Study III</td>
<td>33</td>
</tr>
<tr>
<td>Study IV</td>
<td>33</td>
</tr>
<tr>
<td>Industry-based material</td>
<td>33</td>
</tr>
<tr>
<td>Study V</td>
<td>33</td>
</tr>
<tr>
<td>Study VI</td>
<td>33</td>
</tr>
<tr>
<td>Analysis and statistical methods</td>
<td>33</td>
</tr>
<tr>
<td>RESULTS</td>
<td>35</td>
</tr>
<tr>
<td>Population-based material of the OLIN cohorts</td>
<td>35</td>
</tr>
<tr>
<td>Study I</td>
<td>35</td>
</tr>
<tr>
<td>Study II</td>
<td>35</td>
</tr>
<tr>
<td>Study III</td>
<td>36</td>
</tr>
<tr>
<td>Study IV</td>
<td>38</td>
</tr>
<tr>
<td>Industry-based material</td>
<td>38</td>
</tr>
<tr>
<td>Study V</td>
<td>38</td>
</tr>
<tr>
<td>Study VI</td>
<td>39</td>
</tr>
<tr>
<td>DISCUSSION OF METHODOLOGY</td>
<td>41</td>
</tr>
<tr>
<td>Study design</td>
<td>41</td>
</tr>
<tr>
<td>Bias</td>
<td>41</td>
</tr>
<tr>
<td>Selection bias</td>
<td>41</td>
</tr>
<tr>
<td>Information bias</td>
<td>42</td>
</tr>
<tr>
<td>Comparison bias</td>
<td>44</td>
</tr>
<tr>
<td>Confounders</td>
<td>44</td>
</tr>
<tr>
<td>Interaction</td>
<td>45</td>
</tr>
<tr>
<td>Exposure</td>
<td>45</td>
</tr>
</tbody>
</table>
DISCUSSION OF MAIN RESULTS ........................................... 48

Occupational exposure, socioeconomic status, and respiratory health in the general population .................. 48

Respiratory health in miners ................................................ 50
  Respiratory symptoms and obstructive lung disorders ........ 50
  Bronchial inflammation ................................................. 52
  Silicosis ......................................................................... 54

CONCLUSIONS .................................................................. 57

ACKNOWLEDGEMENTS ...................................................... 58

REFERENCES ..................................................................... 61

ERRATA ............................................................................. 75

APPENDIX .......................................................................... 77

STUDIES I TO VI
ABSTRACT

Aim. To assess associations between occupational air pollution and respiratory health, especially in miners.

Background
Indications of associations between occupational exposure or social economic status and respiratory health have been found in several population-based studies. However, there have been few longitudinal studies of the putative correlations, the effects of environmental and genetic factors have seldom been simultaneously studied, and studies of miners have generated conflicting results.

Material and methods. Population-based Obstructive Lung Disease in Northern Sweden (OLIN) cohorts surveyed in 1986, 1992 and 1996, and two industry-based materials, were used in cross-sectional and longitudinal studies. Inflammatory markers were compared in sputa from miners after a vacation of at least four weeks, after repeated occupational exposures for at least three months, and controls. The mortality from silicosis was studied in 7729 miners with at least 1 year of exposure. Multivariate analyses were used to adjust for confounders.

Results. Up to about 30-40% (etiological fraction) of incident symptoms in persons both with and without a family history of asthma could be explained by exposure to occupational air pollution. Low socio-economic status was associated with impaired respiratory health. Population attributable risks for most examined disorders were about 10%. Current and ex-miners had increased prevalence of recurrent wheeze, longstanding cough, physician-diagnosed chronic bronchitis, and a trend for increased sputum production. For physician-diagnosed chronic bronchitis a multiplicative interaction was found between exposure and smoking habits. Ex-miners that had been exposed for on average 13 years and whose exposure had ceased 16 years before the study had an increased prevalence of physician-diagnosed chronic bronchitis and chronic productive cough and a trend to increased use of asthma medicines. Miners exposed underground for 18 years, on average, to diesel exhaust (with 0.28 mg/m$^3$ nitrogen dioxide and 27 μg/m$^3$ elemental carbon on average) and particles (3.2 mg/m$^3$ inhalable dust on average) had signs of higher inflammatory activity in their airways, i.e. significantly higher frequencies of macrophages, neutrophils, and total cells compared with referents. The activity in miners was similar after a vacation of at least four weeks and after repeated exposures for three months.
There were 58 deaths from silicosis (underlying and contributing cause of
death) and a clear dose-response relationship. The data indicated an
increased risk of severe silicosis after long-term exposure to 0.1 mg/m$^3$
respirable quartz, the current maximum allowable concentration (MAC) in
Sweden and many other countries.

Conclusion. Occupational exposure to dust, gases, and fumes impaired
respiratory health, accounting for up to 30-40% of some respiratory
symptoms in the general population. Low socio-economic status was
associated with impaired respiratory health. The complex profiles of dust
and diesel exhaust substances found in mines may cause inflammatory
reactions in their lungs and persistent respiratory symptoms in
occupationally exposed miners. Long-term exposure to quartz at the
present MAC level may cause severe silicosis.
SAMMANFATTNING

**Frågeställning.** Kan luftburen yrkesmässig exponering hos framför allt gruvarbetare ge försämrad luftvägshälsa?


Gruvarbetare exponerade underjord under i genomsnitt 18 år för dieselavgaser (NO₂ 0,28 mg/m³, elementärt kol 27 μg/m³) och partiklar (inhalerbart damm 3,2 mg/m³) hade ökad inflammatorisk aktivitet i bronker, dvs. signifikant mer makrofager, neutrofiler och totalceller. Aktiviteten var densamma efter minst fyra veckors semester som efter tre månaders yrkes-exponering. I materialet fanns 58 dödsfall i silikos (underliggande och bidragande dödsorsak). Analysen påvisade en ökad risk för allvarlig silikos efter långvarig exponering för respirabel kvarts vid nivåer på 0,1 mg/m³, det nu gällande gränsvärde i Sverige och många andra länder.

**Slutsats.** Yrkesmässig, luftburen exponering medförde försämrad luftvägshälsa. Den bidrog med upp mot 30-40% av vissa symtom i den
allmänna befolkningen. Den komplicerade exponeringen för damm och dieselavgaser i gruvarbete kan orsaka inflammation i lungor och kvarstående luftvägssymtom. Långvarig exponering för respirabel kvarts vid halter motsvarande det nu gällande gränsvärde kan orsaka allvarlig silikos.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following studies, which will be referred to by the corresponding Roman numerals.


The studies are reproduced with permission from the publishers.
ABBREVIATIONS

CI 95% confidence interval
COPD Chronic obstructive pulmonary disease
EF Etiologic fraction
FHA Family history of asthma
MAC Maximum allowable concentration
NO$_x$ Nitric oxides
NO Nitric oxide
NO$_2$ Nitrogen dioxide
OLIN Obstructive lung disease in northern Sweden studies
OR Odds ratio
PAR Population attributable risk
SES Socio-economic status
INTRODUCTION

Occupational exposure to air pollutants can impair respiratory health. The risk depends on the type of exposure, dose and susceptibility factors. Miners have been heavily exposed to such pollutants for thousands of years, and very high morbidity and mortality rates associated with respiratory disorders in miners have been described by many authors from classical antiquity onwards, e.g. Hippocrates (ca. 470-360 B.C), Pliny the elder (23-79 A.D.), Georgius Agricola (1494-1555), Paracelsus (1493-1541) and the father of occupational medicine, Bernardini Ramazzini (1633-1714). The latter reported that women who married miners were repeatedly widowed [Ramazzini; 1991]. He also doubted whether there was a pious duty to give medical aid to miners, since he thought it would only prolong their suffering. In addition, Carl von Linné (1707-1778), best remembered for his work on botany and taxonomic classification of organisms, noted that limestone workers in Orsa (Dalacarlia, central Sweden) were seldom older than 20 to 40 years.

BACKGROUND

*Occupational exposure and respiratory health*

A population-based study of occupational exposure in relation to respiratory symptoms and lung function was presented by Lebowitz in 1977 [Lebowitz; 1977]. It was based on the Tucson Epidemiological Study of Obstructive Lung Disease. In the introduction he points out that several previous studies had all been industry-based indicating higher risks after exposure to dust, but that “All these studies examined subjects actively employed in specific occupations and, therefore, were subject to self-selection factors.” Exposure to quartz, asbestos, smoke, and auto exhaust was also after adjustments to age and smoking associated with increased prevalence of chronic productive cough, breathlessness, wheeze, and impaired lung function. The Dutch Zutphen study started in the 1960s [Heederik et al.; 1989; Heederik et al.; 1990]. CNSLD (chronic nonspecific lung disease) was defined as episodes of cough and phlegm for longer than three months, or of wheezing and shortness of breath, or diagnosis of chronic bronchitis or emphysema. Significantly increased prevalence was reported in the entire population for cough and sputum, OR 3.1, and for CNSLD 2.4, when subjects exposed to dust, gases, and fumes
were compared with unexposed. In a 25-year follow-up the incidence of CNSLD was found to be significantly higher (OR 1.8) among blue collar workers than among white collar workers. Subgroups such as tailors and wood, paper, textile, construction and transport workers also had significantly increased incidences. The subjects of the Zutphen study mainly consisted of smokers; 91% of them had smoked at some time and 46% in the year preceding the study, so it is difficult to evaluate the effects in non-smokers.

Some other population-based studies of the effects of exposure to dust, gases, chemicals and fumes are summarized in table 1. Most of these studies were cross-sectional and only a few were longitudinal. The exposure data considered in them were generally qualitative, although semi-quantitative (none, low, high) data were sometimes used [Kogevinas et al.; 1999; Sunyer et al.; 2005]. Increased risk estimates for dyspnea, wheezing, phlegm and cough were consistently obtained. Several of the studies also indicate that exposure to gases and fumes poses lower risks than exposure to dust [Korn et al.; 1987; Xu and Christiani; 1993; Sunyer et al.; 2005]. However, the studies provide conflicting indications regarding lung function; some indicating that exposure results in impaired function [Krzyzanowski & Kauffmann; 1988]; Viegi et al.; 1991; Xu et al.; 1992] while others found no apparent differences in this respect between exposed subjects and controls [Krzyzanowski & Kauffmann, 1988; Bakke et al.; 1991; Sunyer et al.; 2005]. One study reported an amelioration (sic) of FEV₁, which was interpreted as a selection phenomenon [Viegi et al.; 1991]. A few population studies have indicated risk occupations for asthma [Fishwick et al.; 1997b; Kogevinas et al.; 1999].
Table 1. Population-based studies of the association of occupational exposure to dust, gases, and fumes and respiratory health.

<table>
<thead>
<tr>
<th>Author year</th>
<th>Country</th>
<th>Type of study</th>
<th>Occupational exposure</th>
<th>Dyspnea (OR)</th>
<th>Wheeze (OR)</th>
<th>Phlegm (OR)</th>
<th>Cough (OR)</th>
<th>Asthma (OR)</th>
<th>Chronic bronchitis (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Korn et al.; 1987]</td>
<td>US</td>
<td>I CS</td>
<td>I Dust</td>
<td>Ia 1.6 (1.4-1.9)</td>
<td>Ia 1.5 (1.3-1.8)</td>
<td>Ia 1.2 (1.2-1.8)</td>
<td>Ia 1.3 (1.1-1.5)</td>
<td>Ia 1.5 (1.2-2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ib Gases and fumes</td>
<td>Ib 1.4 (1.2-1.7)</td>
<td>Ib 1.3 (1.1-1.6)</td>
<td>Ib 1.3 (1.1-1.5)</td>
<td>Ib 1.4 (1.2-1.6)</td>
<td>Ib 1.2 (0.9-1.5)</td>
<td></td>
</tr>
<tr>
<td>[Krzyznowski and Kauffmann; 1988]</td>
<td>France</td>
<td>CS</td>
<td>Dust, gases, fumes</td>
<td>♀ 1.4 (1.2-1.7)</td>
<td>♀ 1.6 (1.5-1.8)</td>
<td>♀ 1.4 (1.2-1.6)</td>
<td>♀ 1.5 (1.3-1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dust, gases, fumes</td>
<td>♂ 1.6 (1.4-1.9)</td>
<td>♂ 1.7 (1.5-2.0)</td>
<td>♂ 1.4 (1.1-1.7)</td>
<td>♂ 2.1 (1.1-1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Krzyznowski and Jedrychowski; 1990]</td>
<td>Poland</td>
<td>Long 13 years</td>
<td>I Dust</td>
<td>I ♀ 2.4 (1.5-3.7)</td>
<td>I ♀ 1.0 (0.6-1.8)</td>
<td>I ♀ 2.1 (1.5-3.0)</td>
<td>I ♀ 1.9 (1.2-3.0)</td>
<td>I ♀ 2.6 a (1.5-4.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II Chemicals</td>
<td>II ♀ 2.4 (1.4-4.2)</td>
<td>II ♀ 1.0 (0.6-1.8S)</td>
<td>II ♀ 2.8 (1.5-5.0)</td>
<td>II ♀ 1.5 (0.6-3.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1 (cont.). Population-based studies of the association of occupational exposure to dust, gases, and fumes and respiratory health.

<table>
<thead>
<tr>
<th>Author year</th>
<th>Country</th>
<th>Type of study</th>
<th>Occupational exposure</th>
<th>Dyspnea (OR)</th>
<th>Wheeze (OR)</th>
<th>Phlegm (OR)</th>
<th>Cough (OR)</th>
<th>Asthma (OR)</th>
<th>Chronic bronchitis (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Bakke et al.; 1991b]</td>
<td>Norway</td>
<td>CS</td>
<td>Dust, gases, mists, fumes</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>3.6&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>3.6&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>[Bakke et al.; 1991a]</td>
<td>Norway</td>
<td>CS</td>
<td>Dust, gases</td>
<td>1.7 (1.4-2.2)</td>
<td>1.9 (1.6-2.3)</td>
<td>1.9 (1.6-2.2)</td>
<td>1.8 (1.4-2.2)</td>
<td>1.8 (1.3-2.6)</td>
<td>..</td>
</tr>
<tr>
<td>[Viegi et al.; 1991]</td>
<td>Italy</td>
<td>CS</td>
<td>Dust, chemicals, gases</td>
<td>♂ 2.8 (0.96-8.0)</td>
<td>♂ 1.4 (0.9-2.0)</td>
<td>♂ 1.6 (1.1-2.4)</td>
<td>♂ 1.7 (1.2-2.4)</td>
<td>♂ 2.0 (1.1-4.0)</td>
<td>♂ 2.3&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>[Xu et al.; 1992]</td>
<td>China</td>
<td>CS</td>
<td>I Dust</td>
<td>♂ 1.4 (1.2-1.7)</td>
<td>♂ 1.0 (0.8-1.4)</td>
<td>♂ 1.3 (1.1-1.5)</td>
<td>♂ 1.3 (1.1-1.6)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>[Kogevinas et al.; 1999]</td>
<td>Western Europe and other industrialized countries</td>
<td>CS</td>
<td>Biological and mineral dust, gases, fumes</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>1.2 (1.0-1.4)</td>
<td>..</td>
</tr>
<tr>
<td>Author year</td>
<td>Country</td>
<td>Type of study</td>
<td>Vocational exposure</td>
<td>Dyspnea (OR)</td>
<td>Wheeze (OR)</td>
<td>Phlegm (OR)</td>
<td>Cough (OR)</td>
<td>Asthma (OR)</td>
<td>Chronic bronchitis (OR)</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>[Forastiere; 1998]</td>
<td>US</td>
<td>CS</td>
<td>Dust, gas, vapors, fumes</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>♀ 1.8</td>
<td>(1.1-3.2) 0</td>
</tr>
<tr>
<td>[Eagan et al.; 2002]</td>
<td>Norway</td>
<td>Long 11 years</td>
<td>Dust or fumes</td>
<td>1.4          (1.1-2.2)</td>
<td>1.4         (1.1-1.7)</td>
<td>1.7         (1.3-2.3)</td>
<td>1.7         (1.3-2.4)</td>
<td>1.6         (1.0-2.5) . .</td>
<td></td>
</tr>
<tr>
<td>[Sunyer et al.; 2005]</td>
<td>Western Europe and other industrialized countries</td>
<td>Long 9 years</td>
<td>I Mineral dust</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>I ♀ 1.9 (1.3-2.9) ♀ 0.5 (0.1-3.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II Gases, fumes</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>II ♀ 1.5 (0.99-2.4) ♀ 1.2 (0.5-3.2)</td>
</tr>
</tbody>
</table>

CS Cross-sectional · Long Longitudinal · a. 41 to 50 years of age · b. With the lowest education · c. Obstructive lung disease, includes asthma and chronic obstructive lung disease · d. Present job. Highest exposure group compared with no exposure · e. Job longest held. Highest exposure group compared with no exposure · f. COPD.
Socio-economic status
Respiratory disorders have been less intensively studied in relation to socio-economic status (SES) than in relation to occupational exposure. Various criteria have been used for classifying SES, either singly or in combination, such as income, occupation/occupational status and educational level [Liberatos, Link and Kelsey; 1988; Eagan et al.; 2004]. Many diseases are associated with low SES, especially in the Nordic countries [Mackenbach et al.; 1997]. However, the opposite has been reported for asthma, although this has recently been questioned [Viegi, Annesi and Matteelli; 2003]. There are diverging results regarding asthma. Several studies of children and adolescents, mostly cross-sectional, have shown an association with high SES [Peat et al.; 1980; Kaplan and Mascie-Taylor; 1988], while others have found associations with low SES [Beckett et al.; 2001; Ng Man Kwong et al.; 2002], or no relation to SES at all [Mitchell et al.; 1989; Ernst et al.; 1995]. Indications of associations between low SES and asthma or obstructive lung disease and respiratory symptoms have been found in a number of studies of adults, several of them from the Nordic countries and Estonia, including both cross-sectional [Isoaho et al.; 1994b; Bakke, Hanoa and Gulsvik; 1995; Pallasaho et al.; 2004] and longitudinal [Eagan et al.; 2004] studies. A Swedish study found no such association with asthma, but did find indications of associations between low SES and chronic bronchitis or emphysema [Montnemery et al.; 1998].

Genetic and familiarly factors
It is well known that persons with a family history of asthma and/or atopy have increased risks for asthma and asthmatic symptoms. However, the interactions between occupational exposure and genetic factors have been seldom studied [London; 2007]. In many OLIN studies a family history of asthma has been found to be a strong determinant of respiratory symptoms and asthma, with odds ratios ranging from 2.0 to 5.5 [Pallasaho et al.; 1999; Lundback et al.; 2001; Lindstrom et al.; 2001].

Respiratory health in metal miners
Respiratory symptoms and obstructive lung disorders
There have been several studies of respiratory symptoms and lung function of workers in metal mines (Table 2). During the 1960s and 1970s interest was mostly focused on chronic bronchitis. Several authors have
subsequently studied respiratory symptoms such as dyspnea, wheezing, phlegm or cough as well as lung function, but there have only been a few studies of asthma in miners [Cowie and Mabena; 1996]. Reference groups have often been non-dust exposed workers, lightly-exposed workers, surface workers or non-miners. Some have been internal, dose-response analyses based on cumulative exposure estimates of dust or gas variables such as total dust, respirable dust, NO₂ (nitrogen dioxide), NOₓ (nitrogen oxide) or (as a substitute for exposure) years of mining. Comparing the results from these studies is difficult due to differences in their design, ability to handle possible confounders, material, exposures, statistical methods and definitions. Most of the studies have been industry-based cross-sectional studies, and few of the authors have discussed the potential problems associated with selection bias.

In the 1960s and 1970s some authors only found statistically significant increases in the prevalence of chronic bronchitis amongst smoking miners, with non-significant increases in non-smoking miners, and hence speculated that there may be interactions between mining exposure and smoking. One such investigation was a population-based study of gold miners [Sluis-Cremer, Walters and Sichel; 1967]. The others were Swedish industry-based studies of underground iron ore miners; one of workers in the mine in Malmberget examined in the work underlying this thesis [St Clair Renard; 1977] and the other of workers in a similar mine in Kiruna [Jorgensen and Svensson; 1970]. Another study found significantly more chronic bronchitis amongst both non-smoking and smoking miners than amongst the controls [Wiles and Faure; 1975].

Increased risks of respiratory symptoms such as dyspnea, wheeze, phlegm or cough have also been found in some studies of miners [Wiles and Faure; 1975; Manfreda et al.; 1982; Gamble, Jones and Hudak; 1983; Gamble and Jones; 1983], sometimes not [Attfield MD; 1978; Clark et al.; 1980; Attfield, Trabant and Wheeler; 1982].

Significant dose-response relationships between dust and respiratory symptoms, chronic bronchitis and lung function have been described by some authors [Rae, Walker and Attfield; 1970; Wiles and Faure; 1975; Gamble and Jones; 1983; Gamble et al.; 1983]. In addition, a dose-response relationship between exposure to diesel exhaust and phlegm has been found in an American salt mine [Gamble and Jones; 1983; Gamble et al.; 1983], although no association between diesel exhaust and respiratory
symptoms was found in a study of an American coal miners [Attfield MD; 1978; Ames, Hall and Reger; 1984].

Of the studies in Table 2 only one detected impaired lung function [Wiles & Faure, 1975], but not the others [Jorgensen & Svensson, 1970; Clark et al.; 1980; Manfreda et al.; 1982; Attfield, Trabant & Wheeler, 1982; Gamble, Jones & Hudak, 1983; Gamble & Jones, 1983; Jorgensen, Kolmodin-Hedman & Stjernberg, 1988].

Although selection bias may be an important issue in occupational health and industry-based studies only about a third of the reviewed studies discussed this problem [St Clair Renard; 1977; Manfreda et al.; 1982; Gamble et al.; 1983; Jorgensen, Kolmodin-Hedman and Stjernberg; 1988; Pham et al.; 1992; Cowie and Mabena; 1996].

COPD, chronic obstructive pulmonary disease, is characterized by impaired lung function and is associated with chronic bronchitis. In two reviews of COPD-related morbidity or mortality it was concluded that occupational exposure to dust was an important cause of COPD. One, by Becklake, was largely based on 11 longitudinal, industry-based studies (two of coal mines, one of an iron mine, and three of unspecified or hard rock mines) [Becklake; 1989]. The other, by Oxman et al., reviewed 13 reports focusing on three cohorts of coal miners and one of gold miners [Oxman et al.; 1993].

To summarize, there is some evidence of associations between mining exposure and both chronic bronchitis and respiratory symptoms such as dyspnea, wheeze, phlegm, and cough. Associations between exposure to dust and respiratory symptoms, chronic bronchitis and impaired lung function have also been found in dose-response studies, although there have been few such investigations. Possible associations between mining exposure and asthma, as well as between exposure to diesel exhaust in mining and all the respiratory disorders considered in this thesis have been insufficiently examined. This background review is mainly based on industry-based studies, which provide better exposure estimates than population-based studies, but poorer control of the healthy worker effect if workers are not followed-up after their employment ceases (selection out of the job bias). Generally the reviewed studies have collected no detailed exposure estimates, and did not follow-up the subjects after the end of their employments. A selection into the job bias may be an important
phenomenon and is difficult to control or evaluate in either industry-based or population-based studies.

**Inflammation of the airways**

There have been several short-term, experimental studies of healthy subjects or mild asthmatics exposed to NO₂ or diesel exhaust (see below, under *Air pollutants in the examined mines*), but only a few of airway inflammation after mining exposure. Coggon et al. [Coggon and Newman Taylor; 1998] reviewed three bronchoalveolar lavage (BAL) studies of long-time coal exposure, two in coal miners [Rom; 1990, 1991] and one in rats [Brown and Donaldson; 1989]. In exposed individuals the cited authors found increased frequencies of neutrophils in the airways, together with activation of neutrophils and alveolar macrophages, which secreted free radicals and proteolytic enzymes that are suspected to play important roles in the destruction of lung tissue.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Type of study</th>
<th>Kind of mining</th>
<th>Exposure levels reported</th>
<th>Diesel exhaust exposure</th>
<th>Ref. group</th>
<th>Studied exposure</th>
<th>Dyspnea</th>
<th>Wheeze</th>
<th>Phlegm</th>
<th>Cough</th>
<th>Asthma</th>
<th>Chronic bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Sluis-Cremer et al.; 1967]</td>
<td>South Africa</td>
<td>PB CS</td>
<td>Gold</td>
<td></td>
<td></td>
<td>Not dust exposed non-miners</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>[Jorgensen and Svensson; 1970]</td>
<td>Sweden</td>
<td>IB CS</td>
<td>Iron</td>
<td>Yes</td>
<td>Yes</td>
<td>Surface workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>[Wiles and Faure; 1975]</td>
<td>South Africa</td>
<td>IB CS</td>
<td>Gold</td>
<td>Yes</td>
<td></td>
<td>Internal analysis</td>
<td>Dust</td>
<td>+#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+#</td>
</tr>
<tr>
<td>[St Clair Renard; 1977]</td>
<td>Sweden</td>
<td>IB CS</td>
<td>Iron</td>
<td>No</td>
<td>No</td>
<td>Surface workers</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>[Clark et al.; 1980]</td>
<td>US</td>
<td>IB CS</td>
<td>Taconite (iron)</td>
<td>Yes</td>
<td>No</td>
<td>Non-dust exposed</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>[Attfield et al.; 1982]</td>
<td>US</td>
<td>IB CS</td>
<td>Potash</td>
<td>Yes</td>
<td>Yes</td>
<td>Mine pop.</td>
<td>Dust NO₂</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 (cont.). Metal mining exposure and respiratory health.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Type of study</th>
<th>Kind of mining</th>
<th>Exposure levels reported</th>
<th>Diesel exhaust exposure</th>
<th>Ref. group</th>
<th>Studied exposure</th>
<th>Dyspnea</th>
<th>Wheeze</th>
<th>Phlegm</th>
<th>Cough</th>
<th>Asthma</th>
<th>Chronic bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Gamble et al.; 1983]</td>
<td>US</td>
<td>IB CS</td>
<td>NaCl</td>
<td>Yes</td>
<td>Yes</td>
<td>Four working pop.</td>
<td>Dust NO₂</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Gamble and Jones; 1983]</td>
<td>US</td>
<td>IB CS</td>
<td>NaCl</td>
<td>Yes</td>
<td>I. Yes</td>
<td>I. Internal analysis</td>
<td>I NO₂</td>
<td>I.</td>
<td>I + #</td>
<td>I. 0</td>
<td>I. 0</td>
<td>I. 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>II NO₂</td>
<td>II.</td>
<td>II +</td>
<td>II +</td>
<td>II +</td>
<td>II +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Jorgensen et al.; 1988]</td>
<td>Sweden</td>
<td>IB CS</td>
<td>Iron</td>
<td>Yes</td>
<td>Yes</td>
<td>I, II Surface workers</td>
<td>Dust</td>
<td>I. 0</td>
<td>I. 0</td>
<td>I. 0</td>
<td>I. 0</td>
<td>I. 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Pham et al.; 1992]</td>
<td>France</td>
<td>IB CS</td>
<td>Iron</td>
<td>Yes</td>
<td>Yes</td>
<td>Internal analysis</td>
<td>Dust</td>
<td>I.</td>
<td>I.</td>
<td>I. 0</td>
<td>I. 0</td>
<td>I. 0</td>
<td></td>
</tr>
</tbody>
</table>

PB Population-based ∙ IB Industry-based ∙ CS Cross-sectional ∙ Long Longitudinal ∙ CC Case-control ∙ 0 No effect ∙ + Significantly increased prevalence or incidence ∙ ↓ Significantly decreased lung function ∙ # Dose-response relationship ∙ a. Dust, NO₂ or NOₓ ∙ 0 No data
Dose-response studies of silicosis

The link between quartz and silicosis was not established until 1866, by Zenker, who introduced the term pneumoconiosis [Greaves; 2000]. The term silicosis is attributed to Visconti in 1870 [Greaves; 2000]. There have only been a few published exposure-response studies of silicosis morbidity with follow-up after end of employment [Hnizdo and Sluis-Cremer; 1993; Steenland and Brown; 1995; Chen et al.; 2001; Churchyard et al.; 2004] and one of silicosis mortality ['t Mannetje et al.; 2002], but they have all indicated that long-term exposure to respirable quartz at a level of 0.1 mg/m³, the current maximum allowable concentration in many countries, poses significant risks for workers.

Extraction methods in the examined mines

The studies of miners that this thesis is based upon were carried out in the Swedish iron ore mines in Malmberget (Studies III to VI) and Kiruna (Study VI), which have been operating for more than a century [Andersson and Kågström; 1998]. An open pit is a mine where the ore can be reached from the surface. The ore body generally dips to some degree, with a hanging wall on one side and a foot wall on the other. As the mined depth increases more and more of the surrounding waste rock must be extracted. As the height of the hanging wall increases it will eventually crack and fall down, so sooner or later it will be economically advantageous to switch to underground mining. Mining at both of the examined mines started from open pits, and all mining since the 1920s in Malmberget and 1960s in Kiruna has been underground. The first underground mining method to be used was shrinkage stoping, in which miners drilled bores upwards into the roof inside a cavity in the ore body, blasted, and removed the ore from the bottom of the cavity. During the drilling they initially stood on the bottom of the cavity and later on the top of the blasted ore. It was a very dusty kind of mining, with self-draught ventilation supplemented solely by compressed air from the drilling equipment, no mechanical ventilation and dry drilling until well into the 1930s. Figure 1 presents an actual view of the mine in Malmberget and figure 2 presents a diagram of sublevel caving, the dominant mode of mining at both Malmberget and Kiruna since the 1960s. This starts with drilling a horizontal gallery, a tunnel, into the ore body (development drifting). From the gallery the miners drill upwards, to the left, straight upwards, and to the right (fan-drilling). Each layer (or “slice”, 2.5 to 3 meters thick), is blasted, the blasted ore mixed with varying amounts of waste rock (crude ore) falls down, is moved via a raise (vertical chute) along the foot wall to the main level and then
transported via hoisting shafts in skips (lift cages) to processing plants on the surface.

All loading was also done manually using shovels with handles on each side and pickaxes. With increasing mechanization dusting increased considerably. Pneumatic drilling was introduced from the 1920s and mechanical loading in the 1940s. Wet drilling, which was introduced in the 1930s, decreased dusting appreciably, but wetting of blasted rock (applied since the 1950s) was not as effective as wet drilling. Diesel-powered engines were introduced in the mid-1960s. At the same time exposure to radon daughters was discovered. This prompted considerable improvements in the working environment, which were completed in about 1974. The ventilation capacity was increased five-fold, from one to five metric tons of air per metric ton of crude ore, from 1969 to 1974.
Figure 1. View of the mine in Malmberget.
Figure 2. Schematic diagram of sublevel caving.
Air pollutants in the examined mines

The air pollution in the investigated mine has been, and still is, complex. The most important contributors include rock dust, radon, and diesel exhaust. The ore itself is magnetite (Fe₃O₄) and hematite (Fe₂O₃). The quartz content of the waste rock is about 7.5%. Blasting is routinely done at midnight. The mine is then ventilated until five o’clock in the morning, when the miners can enter the mining areas, if the levels of carbon monoxide and nitrogen dioxide are satisfactory. These blasting gases are also released to some extent during the handling of the blasted rock and ore.

Diesel engines produce less carbon monoxide, but more particles, nitric oxides, and aldehydes, than petrol engines. The particles are ultrafine; 80% of them are <0.1μm [Sydbom et al.; 2001]. They consist of a carbon core, upon which are adsorbed about 18 000 (sic) different high-molecular organic compounds. The gas fraction contains nitric oxides (NO, NO₂), carbon monoxide (CO), sulfur dioxide (SO₂), hydrocarbons, aldehydes and transition metals. Diesel-equipment is used in most modern mines around the world. From an environmental perspective electrically powered equipment would be a better alternative, but not always from an economic perspective since suitable electric equipment is less mobile and less readily commercially available than diesel equipment.

Health effects of diesel exhaust have been reviewed by Sydbom et al [Sydbom et al.; 2001]. Air pollution is more harmful to patients with asthma than to healthy subjects. Several studies have found that short-term experimental exposures of healthy subjects can cause inflammation in the small airways, with associated increases in frequencies of neutrophils, lymphocytes, and mast cells as well as markers of the activation of various cell types. Impaired phagocytosis in vitro of alveolar macrophages has also been detected. High exposure of asthmatics to diesel exhaust has been found to results in more pronounced inflammation than allergen provocation, and adverse effects have been detected in asthmatics even following inhaled corticosteroid therapy. However, even with pronounced inflammatory responses there may be no apparent lung function reactions. Diesel exhaust can increase IgE production in the nasal mucosa and act as an adjuvant to allergens. It has been speculated that diesel exhaust may be an important cause of the increased incidence of allergic airways diseases.
Systemic effects such as increased carcinogenicity, intensification of autoimmune diseases, altered blood coagulability, and increased risk of cardiovascular diseases have been described.

At the start of the work underlying this thesis it was not known if current air pollution in the Swedish mines was responsible for impairments to respiratory health and, if so, what the causes were.

AIMS OF THE STUDIES

The overall aim was to assess the association between occupational air pollution and respiratory health, especially in miners.

The specific aims were to assess:

the importance of occupational exposure to dust, gases, and fumes and impaired respiratory health in the general population and the possible modifying effects of a family history of asthma, (Study I),

if low socio-economic status increased the risk of impaired respiratory health (Study II),

if there was an increased risk of airway diseases, symptoms or airway inflammation in underground miners (Studies III and V),

if respiratory symptoms persisted in ex-miners many years after cessation of the exposure (Study IV),

the exposure-response relationship between respirable quartz and severe silicosis (Study VI).

MATERIAL AND METHODS

Population-based material of the OLIN cohorts (Studies I to IV)

Aims, study design, and study populations
The Obstructive Lung disease in Northern Sweden (OLIN) studies, are population-based epidemiology studies that started in 1985. Their overall
aim is to find determinants, especially for asthma and COPD (chronic obstructive pulmonary disease), but also for allergy and OSAS (obstructive sleep apnea syndrome). Prior to this thesis about 100 papers and seven doctoral theses [Lundbäck; 1993; Rönmark; 1999; Larsson; 2001; Lindström; 2002; Perzanowski; 2003; Lindberg; 2004; Jansson; 2006] based on data collected on OLIN cohorts have been published, and work towards another doctoral thesis is in progress.

The collection of the first OLIN dataset started in December 1985 and was completed in 1986 [Lundback et al.; 1991]. Eight geographical areas of the Swedish county of Norrbotten, including coastal, inland, urban and rural areas with varying economic activities were selected [Lundback et al.; 1991], and a postal questionnaire was sent to all subjects of both sexes born in the years 1919-1920, 1934-1935, and 1949-1950 living in these areas (n=6 610, Figure 3, 1986). There were 2 896 men, who constituted the population used in Study III. To those who did not respond a reminder was sent six to eight weeks later, together with copies of the questionnaire in both Swedish and Finnish. Three quarters (75%) lived in urban areas and 15% in rural areas, 53% in the coastal area, and 47% in the rest of the county. Details are presented by Lundbäck et al. [Lundback et al.; 1991].

In 1992 the 1986 cohort was followed-up and extended. All subjects of both sexes born in the years 1940 – 1941, 1949 – 1950, 1955 – 1956, and on the 15th of each month in the period 1923 – 1956 living in the mentioned areas were included (Figure 3, 1992). A postal questionnaire was sent to all of these subjects (n=20 489), corresponding to almost 10% of all inhabitants in the county. To those who did not respond a reminder was sent six to eight weeks later, together with copies of the questionnaire in both Swedish and Finnish. The number of responders was 17 793 (85% of those invited), of whom 8 838 were men, who constituted the population used in Study VI.

In 1996 the 1992 cohort was re-surveyed in the same manner, by sending them the same questionnaire used in 1992. Of the 6 610 subjects invited to participate in 1986, ca. 90% (5 933) remained to be invited in 1996. To those who did not respond a reminder was sent six to eight weeks later together with copies of the questionnaire in both Swedish and Finnish. In both 1986 and 1996 there were 4 754 responders (80% of those invited in 1996, 72% of those invited in 1986). These subjects of both sexes
constituted the population used in the longitudinal studies in Studies I and II (Figure 3, 1986 – 1996).

Questionnaire
The questionnaire [Lundbäck; 1993] was largely based on one used by the British Medical Research Council [Medical Research Council Committee; 1960] with some expansions. It included questions about respiratory symptoms and diseases, family history of respiratory diseases, smoking habits, and occupation classified according to the Nordic Classification System of Occupations [Labor Market Board; 1983]. The subjects were asked about the duration of their current jobs, previous jobs of more than five years duration, and if they were (or ever had been) employed by any of the major companies operating in the county, notably LKAB. The questionnaire has been used in a number of studies in Baltic and Nordic countries [Pallasaho et al.; 1999; Lindstrom et al.; 2001; Meren; 2001; Kotaniemi et al.; 2001; Larsson et al.; 2003]. All asthma diagnoses reported by the respondents have been clinically validated using a structured interview and methacholine tests [Lundback et al.; 1993], which elicited reactions in 90% of the incident cases of physician-diagnosed asthma [Lundback et al.; 2001]. The results indicate that a self-administered questionnaire is sufficiently reliable to estimate the prevalence of asthma in a population [Samet; 1987] [Lundbäck; 1993; Toren, Brisman and Jarvholm; 1993]. However, the prevalence of chronic bronchitis was underestimated from responses to the questionnaire [Lundbäck; 1993]. The postal questionnaire used in 1986 was slightly revised in 1992 [Lundbäck; 1993].

The socio-economic classification developed by Statistics Sweden has been used in the OLIN studies and many other Swedish studies [Statistics Sweden; 1982] (Appendix 1). It is based on occupation, but also takes educational level and years of education into consideration.

To avoid compromising statistical power by dividing the cohorts into too small sub-sets, simplified versions of the classes have been used in the OLIN studies, comprising seven categories in Study II: 1) Manual workers in industry; 2) Manual workers in services; 3) Assistant non-manual employees; 4) Professionals, including executives and civil servants at high and intermediate levels; 5) Housewives or their male equivalents; 6) Self-employed persons, including small- and large-scale entrepreneurs and farmers; 7) Unclear, subjects who provided unclear or too little information
to classify them according to the above groups. Subjects who were retired were classified according to their last occupational title.
Figure 3. The OLIN cohorts used in these studies and the study design.

1986

**Inclusion criteria**

Both sexes

All subjects born

1919 – 1920

1934 – 1935

1949 – 1950

Living in eight study areas.

Invited to postal questionnaire

n=6 610

Responders

n=5 698

n=2 896 ♂

n=2 801 ♀

1992

**Inclusion criteria**

Both sexes

All subjects as defined in 1986.

All subjects born

1940 – 1941

1949 – 1950

1955 – 1956

on the 15th of each month 1923 – 1956.

Living in the eight study areas defined in 1986.

Invited to postal questionnaire

n=21 029

Responders

n=17 793

n=8 838 ♂

n=8 955 ♀

1996

Re-invited to postal questionnaire

n=5 933

Responders in both 1986 and 1996

n=4 754

n=3 028 ♂

n=2 905 ♀
Industry-based material (Studies V and VI)

Study V
The study base comprised iron ore miners who had been exposed for more than three years to diesel exhaust at underground work sites in the mine. The primary goal was to select only life-long non-smokers, but to survey sufficient miners we had to include a few ex-smokers. To be included they had to be healthy and be undergoing no medical treatment. Eligible subjects were identified from the occupational health service and the staff register of the company. The inclusion criteria were fulfilled by 29 miners. Six were excluded due to inability to produce acceptable sputum and one could not take part in both examinations. Thus, we can present data from 22 miners with paired sputa.

As referents, healthy non-smoking workers (research workers not affiliated with the study, technical staff and office workers), who had no history of respiratory conditions, allergies, or other disorders and were not taking any relevant medications were invited to participate as control subjects. Of the 24 referents three were excluded because they did not produce acceptable sputa. Thus, data from 21 referents can be presented.

The study design is summarized in figure 4. The miners were first examined after a wash-out period of at least four weeks of a summer holiday in August before restarting their work. The second examination took place in November after at least three months of regular work in the mine. Referents were studied at a single point of time during the following winter.
Study VI
Miners (defined as workers who had been employed by the mining company in this capacity for at least a year some time between 1923 and 1996) were selected from the company’s personal records. The inclusion criteria were fulfilled by 7,729 miners. The personal records include each miner’s employment time, occupation, and place of work in the mine. Data on causes and dates of death were taken from the Swedish Causes of Death Register 1952-2001.

Exposure

Population-based material of the OLIN cohorts

Studies I-II
An experienced occupational hygienist and co-author (KE) recoded occupational codes prior to 1986, in 1986, and 1996 to occupations in which exposure to dust, gases, and fumes were high or low. All exposure up to 1986 and up to 1996 was taken into consideration in the analyses performed in Study I. Those who had never worked in an occupation with high exposure were categorized as lightly exposed. Those who had ever worked in an occupation with high exposure were categorized as highly exposed. In Study II subjects were classified into those with or without an occupation in 1986 and 1996 in which exposure to dust, gases and fumes was common.
Study III
Exposed subjects were those who had worked as a current or previous miner for at least five years according to their responses to the questionnaire. The referents had never worked as miners or been employed by the mining company.

Study IV
Exposure classifications were based on responses to the questionnaire and data from personal records of the mining company. Exposed subjects were ex-miners who had worked as miners for at least one year and had been ex-miners for at least one year. Referents were responders who had never had an occupation with high exposure to dust, gases and fumes.

Industry-based material

Study V
An experienced safety engineer from the mining company used measurements of nitrogen dioxide acquired over many years by the company’s routine health surveillance system to select eligible work sites with high exposure to diesel exhaust. Multiple air samples were taken from the subjects’ breathing zones and analyzed for elemental carbon (EC), nitrogen dioxide (NO₂), and inhalable dust.

Study VI
Since 1965 the company has measured exposure to respirable dust and quartz by gravimetric methods. There were no such measurements before 1965. The content of quartz (SiO₂) in the samples was estimated by X-ray diffraction.

Analysis and statistical methods
Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, release 11.0.0 (SPSS for Windows, 2001). P values <5% were considered statistically significant.

The cumulative incidences in Studies I and II were calculated as the ratios between those who developed the studied conditions between 1986 and 1996 and those who did not have the conditions in 1986.
The etiologic fraction (attributable risk) in Study I was calculated as \( \frac{\text{OR}_E - 1}{\text{OR}_E} \), where \( \text{OR}_E \) = the adjusted odds ratio in the exposed group [Rothman and Greenland; 1998].

The population attributable risk in Study II was calculated as \( p_c \times \frac{\text{OR}_E - 1}{\text{OR}_E} \), where \( p_c \) = the fraction of exposed subjects among cases in the total population and \( \text{OR}_E \) = the adjusted odds ratio in the exposed group [Rothman and Greenland; 1998].

In Studies I to IV the Chi-squared test was used for bivariate calculations. Multiple logistic regression analysis was used to estimate odds ratios for the studied variables with adjustments for possible confounders. The analyses were repeated in never-smokers in order to detect indications of confounding factors (if any) that had not been controlled in the studies (rest-confounding).

Study V. Empirical data indicate that occupational exposure to most substances is usually log-normally distributed. Therefore, the procedures recommended by Kromhout et al. were followed to estimate homogeneity and between-worker and within-worker variability [Kromhout, Symanski and Rappaport; 1993], and the Shapiro–Wilk test was used to test the hypothesis of log-normal distributions. Parameter-free tests were used to test the significance of differences in numbers of cells and inflammatory mediators amongst miners and between miners and referents.

In Study VI the sampling protocols provided information about job titles, which was combined with exposure data over time to create a job exposure matrix (JEM). In this procedure, similar exposure estimations were used for the period prior to 1965 to those used for the period 1965 - 1973. Thus, for the entire period before 1965 we used the time-average level for 1965-1973 in those jobs for the analysis. Cumulative exposure (mg*years/m^3) was estimated by multiplying the estimated concentration by the number of years at that exposure level. Numbers of person-years of observation and deaths from silicosis were derived for each category of cumulative exposure. The crude rates were adjusted to attained age and year of birth in a Poisson regression model. To assess the effects of the possible underestimation of previous exposure we also performed a complementary analysis, in which we assumed that the exposure levels were five times higher before 1940 than after 1940.
RESULTS

Population-based material of the OLIN cohorts

Study I
Before the 1986 survey, the subjects had worked on average for at least 16 years. Fifty-one of the 3333 persons stopped working in the time between the 1986 and 1996 surveys. The proportions of respondents classed as having had high exposure were 30% and 19% in 1986 and 1996, respectively. FHA was reported by 27% of the men and 34% of the women.

Cumulative incidence of the examined symptoms was highest in persons with both FHA and high occupational exposure to pollutants. The findings corresponded best with a multiplicative effect model between exposure and FHA, but for longstanding cough and chronic productive cough an additive effect model was more probable. An analysis restricted to only non-smokers showed similar results.

FHA explains more of the occurrence of these symptoms than occupational exposure in this population. High exposure accounts for up to 30-40% (etiologic fraction) of the symptoms in persons both with and without FHA. Still more, up to about 60%, can be explained by FHA. Together these factors explain up to about 70% of the symptoms.

Study II
Manual workers represented the largest socio-economic group among both males (50%) and females (39%), while professionals comprised 23% of males and 17% of females. In all the material the 10-year cumulative incidence of asthma was 6.2%, chronic productive cough 6.9%, use of asthma medicines 9.2%, and symptoms used in the analyses 10–12%.

Manual workers in industry had significantly increased incidence of asthma and increased risks of symptoms common in asthma: wheezing, attacks of shortness of breath, and the combination of the two, the asthmatic symptom complex. Furthermore, manual work in industry was also associated with a high incidence of chronic productive cough. Manual workers in services, like manual workers in industry, had significantly increased incidence of wheeze, attacks of shortness of breath, the asthmatic symptom complex, and chronic productive cough. Compared
with manual workers in industry they had significantly increased incidence of use of asthma medicines but not of asthma.

The population attributable risks of manual workers in industry for the incidence of asthma, attacks of shortness of breath, wheezing, asthmatic symptom complex and chronic productive cough ranged from 8.9 to 11%. With the exception of asthma, increased incidences, ranging from 7.6 to 12%, were also found for manual workers in services.

**Study III**

In miners after adjustment for age, smoking habits and a family history of asthma there were significantly higher odds ratios of respiratory symptoms, recurrent wheeze, longstanding cough and physician-diagnosed chronic bronchitis, range 1.5 to 2.4, while there was a trend to increased risk of sputum production. Attacks of shortness of breath and asthma manifestations were similar between miners and referents. In a multivariate analysis with a family history of asthma, age, exposure, and smoking habits as independent variables we found for physician-diagnosed chronic bronchitis odds ratios for miners compared with referents (OR\textsubscript{Miners}) of 2.2 (95% CI 1.4 - 3.3) and for smokers compared with non-smokers (OR\textsubscript{Smokers}) of 2.5 (2.0 - 3.2). A multiplicative interaction was detected by SPSS between exposure and smoking habits. A new combined variable comprising six categories (two categories of exposure x three categories of smoking habits) was created. In the new multivariate analysis with adjustment for a family history of asthma and age OR\textsubscript{Miners, Smokers} was found to be 9.7 (3.2 - 29). Based on the original multivariate analysis, OR\textsubscript{Miners, Smokers} values of 3.7 and 5.5 were found when additive and multiplicative interactions were assumed, respectively. Thus, our results are best described by a multiplicative risk model.

An analysis by smoking category indicated that the relative risks were highest among non-smokers, e.g. the relative risk for physician-diagnosed chronic bronchitis was 9.2 among non-smokers and 2.2 in smokers.

A corresponding analysis according to age indicated that the relative risks were highest among the youngest age group, table 3.
Table 3. Prevalence in miners and referents of obstructive lung diseases, use of asthma medicines, and respiratory symptoms for all subjects and by age. OR: adjusted odds ratios in miners compared with referents.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>All (95% CI)</th>
<th>35 – 36 years (95% CI)</th>
<th>50 – 51 years (95% CI)</th>
<th>65 – 66 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician-diagnosed asthma</td>
<td>1.4 (0.59 - 3.3)</td>
<td>1.3 (0.30-5.8)</td>
<td>2.1 (0.61-7.4)</td>
<td>0.81 (0.10-6.3)</td>
</tr>
<tr>
<td>Physician-diagnosed chronic bronchitis</td>
<td>2.2 (1.0 - 4.5)</td>
<td>5.0 (1.3-1.9)</td>
<td>2.9 (1.1-8.1)</td>
<td>0.50 (0.066-3.8)</td>
</tr>
<tr>
<td>Asthma medicines</td>
<td>0.96 (0.34 - 2.7)</td>
<td>0.99 (0.13-7.15)</td>
<td>1.3 (0.29-5.5)</td>
<td>0.63 (0.081-4.9)</td>
</tr>
<tr>
<td>Attacks of shortness of breath</td>
<td>1.3 (0.72 - 2.4)</td>
<td>1.5 (0.51-4.5)</td>
<td>1.4 (0.52-3.7)</td>
<td>1.1 (0.36-3.2)</td>
</tr>
<tr>
<td>Recurrent wheeze</td>
<td>2.4 (1.5 - 3.9)</td>
<td>3.6 (1.5-8.3)</td>
<td>2.9 (1.4-6.3)</td>
<td>1.1 (0.41-3.1)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>1.5 (0.96 - 2.4)</td>
<td>1.2 (0.51-3.1)</td>
<td>1.8 (0.89-3.7)</td>
<td>1.4 (0.63-3.3)</td>
</tr>
<tr>
<td>Long-standing cough</td>
<td>1.8 (1.0 - 3.2)</td>
<td>2.2 (0.88-5.6)</td>
<td>2.2 (0.96-5.0)</td>
<td>0.89 (0.20-3.8)</td>
</tr>
<tr>
<td>Any respiratory symptom</td>
<td>2.2 (1.4 - 3.1)</td>
<td>3.0 (1.4-6.2)</td>
<td>2.4 (1.2-4.7)</td>
<td>1.4 (0.60-3.0)</td>
</tr>
<tr>
<td>Asthma-associated symptoms</td>
<td>1.4 (0.69 - 2.9)</td>
<td>1.6 (0.47-5.7)</td>
<td>1.4 (0.40-4.8)</td>
<td>1.4 (0.40-4.9)</td>
</tr>
</tbody>
</table>

a. 0.05<\(p<0.10\)
**Study IV**

The ex-miners had been exposed for 13 years, on average, and their exposure had ceased, on average, 16 years before the study.

The prevalence of all studied symptoms or conditions except long-standing cough was higher in ex-miners than in referents, but according to the multivariate analysis only physician-diagnosed chronic bronchitis and chronic productive cough were significantly higher in ex-miners (OR = 2.5 and 1.7, respectively). Amongst ex-miners there was a trend to increased use of asthma medicines. In a similar multivariate analysis restricted to non-smokers a significantly increased risk of chronic productive cough in ex-miners was detected (OR=2.8).

A multivariate analysis restricted to the 206 ex-miners showed that years since the last exposure in mining was positively and significantly associated with the use of asthma medicines, i.e. the use of medicines increased with increases in years since cessation of exposure (OR for 10 years=2.0; p=0.01).

**Industry-based material**

**Study V**

The mean (range) number of years the miners included in the study spent working underground was 18 (3–39) years, and the means (and ranges) of the nitrogen dioxide, EC and inhalable dust measurements were 0.28 (0.05–0.68) mg/m$^3$ or 0.16 (0.03–0.38) ppm, 27 (5–61) μg/m$^3$, and 3.2 (0.1–35) mg/m$^3$, Appendices 2 to 4. For nitrogen dioxide and EC the variations within miners were higher than those between miners and the analysis indicated that they constituted a homogenous group. However, the variability between workers was higher for inhalable dust.

There were signs of higher inflammatory activity in the miners’ airways than those of the referents, including significantly more macrophages, neutrophils, and total cells in their induced sputa. However, there was no significant difference in inflammatory activity in the miners’ airways between the two occasions (August and November) when they were studied.
Study VI
Measurements between 1968 and 1973 showed there were relatively high levels of exposure to respirable quartz during this period (annual average exposure, 0.1 to 0.4 mg/m$^3$). The exposure levels were much lower after 1974 following the implementation of measures to reduce them. The median cumulative exposure among the 7,729 miners was 0.9 mg*years/m$^3$, and 58 miners (with a median cumulative exposure of 4.8 mg*years/m$^3$) reportedly died from silicosis. The crude mortality rate was 53 cases per 100,000 person-years, ranging from 11.0 cases per 100,000 person-years in the lowest exposure category (0–0.9 mg*years/m$^3$) to 214 cases per 100,000 person-years in the highest (>7 mg*years/m$^3$).

There was a clear dose-response relationship, and clearly increased risks of severe silicosis in the groups exposed to >3 mg/m$^3$ (figure 5).
Figure 5. Rate of mortality from silicosis (per 100 000 person-years) according to cumulative dose of respirable quartz (mg*year/m$^3$).

A. Crude mortality rates derived using the original cumulative exposure estimates with no adjustment for possible confounders.

B. Adjusted mortality rates according to a Poisson regression model using the original cumulative exposure estimates as a categorical variable with adjustment for attained age and years of birth.

C. Adjusted mortality rates obtained using a five times higher estimate of exposure before than after 1940, otherwise similar to model B.
DISCUSSION OF METHODOLOGY

Study design
Studies I and II were both longitudinal population-based studies. Incidence studies have a time perspective, they do not initially include prevalent cases and they are more informative than cross-sectional studies, since they provide indications of incidence rates, and thus the time subjects take to develop examined symptoms. However, although we recognized the advantages of such information, we only had access to cumulative incidence data, which can reveal that conversion from a healthy to a diseased state has occurred sometime during the study period, but not when.
Studies III and IV were cross-sectional, population-based studies. It is easier to follow-up those who have left mining in advance due to poor respiratory health in such studies than in industry-based studies, and thus reduce selection out of the job bias. In addition, we did not use surface workers as referents, as in many other mine studies. Population referents may be a better choice than workers from the same company, since the latter may have been exposed to similar levels of potentially harmful substances or previously worked as miners. However, the sets examined were small, and thus the statistical power of the analysis was modest.

Study V was an ad hoc cross-sectional study. The referents may have been healthier than the miners, since they had higher socio-economic status. On the other hand, the miners may have been healthier than the referents due to selection into the job bias. The possibility of differential bias is considered to be low.

Study VI was a follow-up and dose-response study. Such a design is superior to a design with only a dichotomous exposure variable, i.e. exposed/not exposed. There is no need for an external referent group.
Since silicosis is an exclusively occupational risk, there is no background risk in non-exposed subjects.

Bias

Selection bias
Health-based selection into and out of jobs are two kinds of bias that are often called healthy worker effects [Hernberg, S; 1991]. Selection into the job bias, which is difficult to control [Hernberg, S; 1991], may affect
exposure studies since subjects who have impaired respiratory health may avoid occupational exposure to dust, gases and fumes more than healthy subjects [Hernberg, S; 1991; Bakke et al.; 1992; Burge; 2000]. Therefore, before the exposure workers in such occupations are in better respiratory health than the rest of the population, which is often used as the reference group. In contrast, selection out of the job bias describes the higher tendency of workers with poor health than healthy workers to leave their jobs [Hernberg, S; 1991; Bakke et al.; 1992; Burge; 2000], which may lead to underestimation of the risks if they are not included in follow-up studies. A population-based study is better than an industry-based study for preventing loss of follow-up by finding such workers, who have left their employments. Studies I, II, III and IV were all population-based studies that included follow-up surveys after the end of the subjects’ employment, and thus reduced risks of selection bias. However, Studies III, IV and V were cross-sectional studies, in which the risks associated with the occupational exposure may have been underestimated, although such underestimation may have been less pronounced for markers of inflammatory activity than for readily apparent symptoms and disease states. The drop-out rate was low in all of the OLIN studies (Studies I to IV), and the industry-based studies (Studies V and VI). In Study V the observation time was short and in Study VI the fate of the subjects could be traced in the staff register and different national registers.

Being obliged to include ex-smokers in Study V as well as non-smokers was a drawback, which may have increased the variability in the measured parameters and reduced the potential for detecting possible differences between the groups. However, the ex-smokers had not smoked for several years, they only had a few pack-years, and were in good respiratory health.

Bias may also be introduced by non-responses. However, the response rate was high in all the studies; 85% in the OLIN studies, with consequent reductions in possible selection bias caused by non-responses.

**Information bias**

Information bias arises when there is asymmetry in the quality of data between exposed and reference groups [Hernberg, S; 1991], and could have been introduced if different diagnostic criteria had been used for exposed and not-exposed subjects. However, in the OLIN studies all subjects were observed in the same way and to the same extent using a postal questionnaire, which ought to have minimized diagnostic bias.
Nevertheless, there may have been such bias in the responses to questions about physician-diagnosed asthma and chronic bronchitis. This is because physicians may have a tendency to classify a respiratory disorder as asthma in non-smokers and as chronic bronchitis in smokers [Sandstrom and Lundback; 2004], and they may show similar bias between miners and non-miners. However, the correlations in the occurrence of corresponding asthmatic and bronchitic symptoms indicate that the degree of such bias (if present) was low.

Using occupational titles in Studies I and II from the OLIN questionnaires in recoding to occupations with high or low exposure to dust, gases and fumes provided crude exposure estimates. Since the recoding was blinded according to outcome there was a low risk of differential bias due to the classification of exposure. This kind of bias is mainly non-differential.

In Study III all miners and referents were classified from their occupational titles reported in the responses to the questionnaires, which also showed the subjects who had been employed by LKAB. Some of them may have been wrongly classified as miners, which would have decreased the risk estimates. In addition, some miners who did not work for LKAB may have been wrongly included as referents, but since they probably comprised a very small proportion of the referents, the consequent bias would probably have been minor. In Study IV miners were classified from the staff register of LKAB, but the referents from their occupational titles in the questionnaires. The intention was to select a reference group who had had little or no occupational exposure to dust, gases and fumes. If we failed to do so, and the reference group included a significant proportion of heavily exposed subjects, the risks would have been underestimated.

The dose-response curve obtained in Study VI may have been affected by bias in estimating the exposure or establishing the cause of death, figure 5. American studies have found both over- and under-diagnosis of silicosis [Cottrell et al.; 1992; Goodwin et al.; 2003; Rosenman, Reilly and Henneberger; 2003]. Silicosis may be misclassified as other lung diseases such as chronic obstructive pulmonary disease (COPD), tuberculosis, lung cancer, or cardiovascular diseases [Goodwin et al.; 2003]. Nowadays silicosis is a very rare disease, why it is probable that it is diagnosed only after a careful examination. Modest silicosis may have been neglected, especially if the case at the same time had other serious diseases. A misclassification according to exposure seems improbable, as the doctors
have hardly ever been aware of cumulative exposure. Thus, we think that it is more probable that our estimates are based on too few than too many cases of silicosis.

The estimates of exposure to respirable quartz before 1965, when we had no measurements, are probably more uncertain than the diagnosis of silicosis. We know that some miners have been exposed to quartz before their employment by LKAB, for instance in other mines or other industries, especially in the construction of hydro-electric plants, but we were unable to estimate the extent of such exposure. This may have affected the dose-response curve (Figure 5). Most cases were exposed before 1940, and if their exposure was severely underestimated the risks associated with low doses may have been overestimated. The observation that subjects born before 1909 had higher risks supports the assumption that exposure levels were higher in earlier years. In addition, despite the lack of exposure measurements there was strong evidence that the exposure had been higher before than after 1940, when all dry drilling had been substituted by wet drilling. Therefore, we reanalyzed the risks assuming exposure levels to be five times higher before than after 1940, but this resulted in only slight changes to the curve.

Thus, a possible underdiagnosis of silicosis as a cause of death may have led to underestimation of the risk, while a possible underestimation of exposure may have led to overestimation of the risk. We have no data to estimate the size or direction of the total bias.

**Comparison bias**

A third type of bias traditionally considered, comparison bias, can be regarded as originating to various degrees from selection and information bias, and will not be further discussed here.

**Confounders**

A confounder is an extraneous determinant of an outcome that is asymmetrically distributed between the exposed group and the referent group [Hernberg, S; 1991]. In studies of respiratory health smoking is usually an important confounder. If the numbers of pack-years are very different between the examined groups, there may be a risk of bias when smoking habits are categorized as never-smokers, ex-smokers or current smokers. Therefore, some analyses were also restricted to never-smokers, with the disadvantage of substantial losses in statistical power.
**Interaction**
The concept of interaction is controversial and dependent on measures of risk [Rothman and Greenland; 1998]. The definition used in statistical textbooks and programs corresponds to effect-measure modification or heterogeneity of effects. Usually it is described as “departure from additivity of effects on the chosen outcome scale”.

Suppose that two variables A and B both have an effect. The relative risk of the variables A and B are $\text{OR}_A$ and $\text{OR}_B$, respectively, and that of the combination AB is $\text{OR}_{AB}$. If it is an additive interaction, then $(\text{OR}_{AB} - 1) = (\text{OR}_A - 1) + (\text{OR}_B - 1)$, that is there is additivity of excess risk ratios on a linear scale. If it is a multiplicative interaction, then $\text{OR}_{AB} = \text{OR}_A \times \text{OR}_B$, which can also be written $\ln \text{OR}_{AB} = \ln \text{OR}_A + \ln \text{OR}_B$, that is there is additivity on a logarithmic scale. This means that if two variables both have an effect, there is always an interaction that may be best described by an additive or multiplicative model.

Most epidemiological statistical programs, including SPSS, are based on the multiplicative model. Negative results of tests in such models are usually presented as “no interaction”, but strictly they should be presented as “no multiplicative interaction”.

**Exposure**
All exposure estimates used in Studies I to IV were crude. Such estimates may increase the probabilities of misclassification, which may in turn reduce (or mask) apparent risks. Thus, findings of increased risks based on crude exposure estimates provide strong support for truly increased risks. In study II the exposure was broadly based on socio-economic status. Our study used a socio-economic classification system based on occupation as well as educational level and years of education [Statistics Sweden; 1982]. This classification reflects educational level, as well as income, quite well, whereas there are limits in defining socio-economic status by educational level alone. The classes obtained are also correlated to exposure to air pollutants since subjects with high levels of education tend to have occupations in which risks of exposure are relatively low.

Housewives are generally categorized by the occupations of their husbands according to Statistics Sweden, which has not been possible in the OLIN
studies, so they constituted a specific entity in the analyses, and a heterogeneous group from a socio-economic perspective.

Those who had worked as miners >5 years were defined as miners in Study III, but in Study IV the definition was >1 year. In the OLIN questionnaire there were two questions on occupations. Subjects were asked for their current occupation and how long they had worked in it, and for another previous occupation that had lasted more than five years. In Study I we had only these data to rely on. Consequently, subjects in Study I were defined as miners if they had worked as such for more than five years. However, using data in the staff register of LKAB, in Study II we were able to obtain reliable classifications of its miners, and whether they had worked for the company as miners for >1 year. Referents were those who had not worked as miners or been employed by the mining company in Study I, and those who had not had a job with high exposure to dust, gases and fumes in Study II. Thus, the contrast in exposure between exposed and reference individuals was higher in Study II than it would have been if a reference group defined as in Study I had been chosen. The risk of misclassification was higher in Study I than in Study II, which may have resulted in a reduction (or masking) of the apparent risks associated with mining.

If symptoms resulting from exposure occur within a short period, e.g. one to two years, applying a criterion of five years of mining may introduce selection/comparison bias since persons who develop symptoms may leave their jobs as miners before five years have elapsed. Such drop-outs may lead to underestimates of the risk.

The exposure measurements in Study V were intended to provide representative estimates of exposure to the rather complex mixture of dust from the mining process and substances released in diesel exhaust. Diesel exhaust is often regarded as the major source of nitrous dioxide in many environments, but in the mines it can also originate from blasting gases. Therefore, EC also was measured since there is no obvious source of EC in the mines other than diesel exhausts. The sampling procedure, with repeated sampling, allowed the variability between-workers and within-workers to be evaluated [Kromhout, Symanski and Rappaport; 1993]. Inorganic dust is nowadays classified according to the sizes of the particles presented as defined in Swedish Standard SS-EN 481 [Swedish Work Environmental Authority; 2000]. Inhalable dust comprises the particles inhaled through the nose and mouth, thoracic dust the particles penetrating
past the larynx, and respirable dust the particles reaching the lower bronchioles and alveoli. For measurements of inhalable, thoracic and respirable dust, samplers with 50% cut-offs for particles with aerodynamic diameters of 100 μm, 10 μm and 4 μm particles, respectively, are used. We chose to measure inhalable dust, since it is better defined than the old (but still used) variable “total dust”. A Swedish occupational exposure limit for inhalable dust of 10 mg/m$^3$ has recently been introduced. Thoracic dust would have been a better choice of exposure measure, but it is not used as often as inhalable dust, and no occupational exposure limit has been set for it. It should be noted that “total dust” does not include all particles in the air. The conventions for “total dust” and inhalable dust differ so much that they are not comparable. In the same environment the levels of inhalable dust may be two to three times higher than those of “total dust”.

All the measured exposures were lognormally distributed. Such a group is defined as a monomorphic group [Rappaport SM; 2000]. It is evident from Appendices 2 to 4 that there was a clear variation of all the measured exposures both between and within workers. It is also evident that the common practice of merely collecting single measurements for a few workers may provide insufficient and misleading indications of the exposure of a group. The variations between workers expressed as $B_{R_{0.95}}$ (the ratio between the 97.5$^{th}$ and 2.5$^{th}$ percentiles of the distribution of the means of the individual workers) were quite similar for nitrogen dioxide (1.2) and elemental carbon (1.6), but much higher (5.0) for inhalable dust. These results indicate that both nitrogen dioxide and elemental carbon may be of equal importance as indicators of diesel exposure. A uniformly exposed group is a group with $B_{R_{0.95}} < 2$. A low between-worker variability, that is a low $B_{R_{0.95}}$, may suggest the need for group-based intervention, whereas high between-workers variability, that is a high $B_{R_{0.95}}$, may suggest a need for individual-based intervention.

The average levels of all measured substances were far below the current maximum allowable concentrations (MAC): 0.28 mg/m$^3$ or 0.16 ppm for nitrogen dioxide (Swedish MAC 2 mg/m$^3$ or 1 ppm for nitrogen dioxide from motor exhaust), 27 μg/m$^3$ for EC (no Swedish MAC, German MAC underground 300 μg/m$^3$), and 3.2 mg/m$^3$ for inhalable dust (Swedish MAC 10 mg/m$^3$).

We had reliable gravimetric exposure data from 1965 onwards, but not before 1965, of respirable quartz, which was measured directly (except in a
few cases in which it was estimated indirectly from respirable dust measurements, and never from total dust). Thus, we obtained post-1965 data that should have been very reliable. Exposure levels prior to 1965 had to be estimated from later measurements, production rates and ventilation conditions before and after 1965. This method has been used in other studies [Mannetje et al.; 2002].

**DISCUSSION OF MAIN RESULTS**

**Occupational exposure, socio-economic status, and respiratory health in the general population**

We have like several other studies found an association between occupational exposure to air pollutants and respiratory health and similar risk estimates [Korn et al.; 1987; Krzyzanowski and Jedrychowski; 1990; Vestbo, Knudsen and Rasmussen; 1990; Bakke et al.; 1991a; Xu et al.; 1992; Garshick, Schenker and Dosman; 1996; Kogevinas et al.; 1999; Karjalainen et al.; 2001; Eagan et al.; 2002b; Mapp and Boschetto; 2003]. In all of these studies, including ours, it is possible that non-differential misclassification of the exposure may have reduced but not increased the estimated risks.

As expected, we found FHA to be a strong determinant of respiratory health, in accordance with other studies [Pallasaho et al.; 1999; Lundback et al.; 2001; Lindstrom et al.; 2001], and a stronger determinant than occupational exposure. Its interaction with occupational exposure was best described with a multiplicative relative risk model.

Previous, mostly cross-sectional, studies of the relationships between socio-economic status and asthma, and other airway disorders, have yielded divergent results, possibly due to differences in the study design, definitions of socio-economic status used, the age distributions of the studied samples, occupational and other kinds of exposures, and geographical aspects. Generally, Nordic studies have found high prevalence of respiratory symptoms or asthma [Bakke et al.; 1991b; Bakke, Hanoa and Gulsvik; 1995] and poor lung function [Prescott, Lange and Vestbo; 1999] to be associated with low SES. Our results are consistent with those of two previous cohort studies; one of Nordic adults [Eagan et al.; 2004] and the other of US adolescents [Beckett et al.; 2001].
Non-responses are often associated with low socio-economic status. This trend was detected in a previous OLIN study, in which the non-responders also had a somewhat higher prevalence of respiratory symptoms [Ronmark et al.; 1999]. Thus, the risk estimates may be somewhat underestimated due to the drop-outs.

Female gender was associated with increased incidence of asthma and use of asthma medicines. The incidence of asthma was also highest among females in a Norwegian cohort surveyed by [Eagan et al.; 2002a]. A family history of asthma or personal history as an ex-smoker, persistent smoker, or quitter were found to be indicators of increased incidence of all examined respiratory symptoms, asthma, and use of asthma medicines. For smokers a similar association has been found by other authors [Sandstrom and Lundback; 2004]. A review of ex-smokers has found that the prevalence of respiratory symptoms decreases after quitting, but remains higher for many years than in never-smokers, indicating that the symptoms are not completely reversible [Willemsen et al.; 2004]. No odds ratios for gender or smoking habits have been found in other Nordic population-based studies of socio-economic status.

Since passive smoking is associated with asthma and respiratory symptoms [Janson et al.; 2001; Larsson et al.; 2003] it is a drawback that data about passive smoking was not available. Smoking was more common among manual workers, and thus passive smoking was also probably more common among them, and could have contributed to their increased incidence of asthma and respiratory symptoms.

Obesity [Ronmark et al.; 2005], diets with a low intake of fresh fruit, vegetables and fish [Schwartz and Weiss; 1990; Peat, Salome and Woolcock; 1992], poor dwelling conditions with exposure to dampness, mould, mites, gas cooking and nitrogen dioxide [Chauhan et al.; 1998; Bornehag et al.; 2001] and poor access to healthcare may all be potential confounders that are associated, to carrying degrees, with low socio-economic status. However, there are no mites or gas cooking in Norrbotten [Perzanowski et al.; 1999].

In conclusion, our investigations are rare examples of longitudinal studies that have found correlations between low socio-economic status and asthma, respiratory symptoms, and chronic productive cough, with population attributable risks of about 10%.
Respiratory health in miners

Respiratory symptoms and obstructive lung disorders
In Study III miners were found to have higher risks of bronchitic disorders, sputum production, longstanding cough and physician-diagnosed chronic bronchitis than non-miners, especially when non-smokers were compared. However, diverging results have been presented in the literature. Some authors have found similar associations in metal miners [Wiles and Faure; 1975; Gamble et al.; 1983; Gamble and Jones; 1983] or coal miners [Rae et al.; 1970; Kibelstis et al.; 1973; Rogan et al.; 1973; Robertson et al.; 1984; Marine, Gurr and Jacobsen; 1988; Wouters, Jorna and Westenend; 1994; Carta et al.; 1996; Henneberger and Attfield; 1996], while others have found no such association amongst metal miners [Sluis-Cremer et al.; 1967; Jorgensen and Svensson; 1970; St Clair Renard; 1977; Attfield MD; 1978; Clark et al.; 1980; Attfield et al.; 1982; Jorgensen et al.; 1988; Pham et al.; 1992] or coal miners [Higgins; 1972; Reger et al.; 1982; Ames et al.; 1984; Love et al.; 1997]. However, the other cited studies were industry-based studies, except for one population-based study [Sluis-Cremer et al.; 1967], generally with no follow-up after the end of the subjects’ employments. Miners were compared with surface workers or diesel-exposed miners with workers who were not diesel-exposed. Population-based studies such as ours provide better control of selection out of the job bias. Thus, the differences in design suggest that Study III probably provided more valid results than the other cited studies.

A family history of asthma was an important risk factor for most respiratory symptoms and diseases. Adjustment to a family history of asthma is seldom used in epidemiological studies. This may be a weakness, since it may be a confounder and an even more important risk factor than age, gender and smoking habits. Similar indications have been obtained in other OLIN studies [Pallasaho et al.; 1999; Lundback et al.; 2001; Lindstrom et al.; 2001].

A multiplicative interaction was detected between exposure and smoking habits for physician-diagnosed chronic bronchitis. However, this finding should be interpreted cautiously due to wide confidence intervals. In the 1960s and 1970s some authors found significantly increased prevalence of chronic bronchitis only in smoking miners and a non-significant increase in non-smokers, leading to speculations that there may be an interaction between the mining exposure and smoking. One such study was a
population-based study of gold miners [Sluis-Cremer et al.; 1967]. The others were Swedish industry-based studies of iron ore underground miners, one of miners from the mine at Malmberget [St Clair Renard; 1977] and the other from the mine in Kiruna [Jorgensen and Svensson; 1970]. Our results provide some support for their hypothesis.

In Study IV when ex-miners were compared with referents the increased risk of physician-diagnosed chronic bronchitis was consistent with the increased risk of chronic productive cough. In the analysis comprising only ex-miners the use of asthma medicines but not physician-diagnosed chronic bronchitis was significantly increased with the number of years after the last exposure. There is some support in the literature for an association between impaired respiratory health and mining exposure or other occupational exposure to dust, gases and fumes. There have only been a few studies that examined subjects after their exposure ceased, but the results are similar to those of Study IV. In a South African cross-sectional study that compared ex-gold miners, who had not worked as miners for a year or more (how long was not reported), with still working miners a somewhat higher prevalence of chronic bronchitis was found amongst the ex-miners [Wiles and Faure; 1975]. The cited authors noted that this finding conflicted with reported trends following smoking cessation and concluded that the symptoms persisted after cessation of mining exposure. Higher risks of asthma-like symptoms have also been found among Swedish iron ore miners a year after unemployment than in controls from the general population [Friis, Carter and Edling; 1998]. In addition, after adjustments for confounders, workers who had been previously exposed, but not for the preceding three years, had significantly higher risks of cough, phlegm, wheeze and breathlessness than workers who had not had such exposure in a population-based longitudinal study of subjects exposed to dust, gases and fumes in various occupations [Korn et al.; 1987]. Furthermore, respiratory health was found to be poorer in ex-miners than in current miners (which was explained as a survivor or hire effect) in a South African study of coal miners [Naidoo et al.; 2006]. Thus, findings in other studies also provide evidence of persistence of symptoms, but our follow-up period (16 years on average) was much longer than those applied in the other studies.

A possible association between mining exposure and asthma has been remarkably little studied, although South African asthmatic and non-asthmatic gold miners have been compared in a case-control study without matching [Cowie and Mabena; 1996]. An increased risk following
exposure to paint and cement was found, but not for any genuine mining exposure. In Study III we concluded that an increased risk of asthma in miners could not be refuted. In study I high occupational airborne exposure was not found to be associated with asthma, but an association has been found in another longitudinal study from Norway [Eagan et al.; 2002b]. If there is any association at all between exposure in the examined mine and asthma, it can be considered to be low.

Ex-miners can be compared with ex-smokers. Stopping smoking will improve respiratory symptoms, mostly within a year, but dyspnoea is less likely to improve [Willemse et al.; 2004]. However, respiratory symptoms are more common in ex-smokers than in non-smokers, indicating that the symptoms are not totally reversible, and several histopathological studies suggest that airway inflammation persists, probably reflecting reparative rather than damaging processes [Willemse et al.; 2004]. Thus, in both ex-smokers and ex-miners symptoms persist after cessation of exposure. However, our findings are somewhat different from the findings after smoking cessation. In ex-smokers, symptoms improve after smoking ceases, but there was no indication of such improvement in ex-miners after they stopped mining. The increased use of asthma medicines we found is probably an effect of ageing [Medical Research Council Committee; 1960; Lundback et al.; 1994], which has also been demonstrated by other authors [Ames et al.; 1984; Bakke et al.; 1991b].

**Bronchial inflammation**
In study V the within-miner variations in NO₂ and EC exposure measurements were greater than the between-miner variations, indicating that they constituted a homogenous group and that EC can provide as good indications as NO₂ of exposure to diesel exhaust.

While planning Study V our hypothesis was that repeated exposure would induce bronchial inflammation, which would decrease or disappear after the summer vacation, but the findings did not support this hypothesis. The results can be explained as follows. The mining exposure initiated increases in mediators, resulting in an influx of inflammatory cells (such as phagocytizing cells, macrophages and neutrophils) and lymphocytes. Observed increases in fibronectin are indicative of the activation of macrophages. There was no support for the activation of neutrophils, since myeloperoxidase activities were not significantly increased. However, interleukin-10 inhibited the inflammation more effectively after repeated
exposure for three months than after the wash-out vacation of at least four weeks. The increase in matrix metallopeptidase 9 after the summer vacation indicates airway remodeling.

Inflammation in the small airways, with increases in frequencies of neutrophils, lymphocytes, mast cells and markers of activation of various cell types, have been found in healthy subjects following short-term exposure to diesel exhaust, and impaired phagocytosis in vitro of alveolar macrophages has been detected in such individuals [Sydbom et al.; 2001]. However, we know of no other similar study of metal miners, and only a few studies of airway inflammation after long-term coal mining exposures [Brown and Donaldson; 1989; Rom; 1990, 1991; Coggon and Newman Taylor; 1998]. The cited studies found increased numbers of neutrophils in the airways, activation of neutrophils and alveolar macrophages, which secreted free radicals and proteolytic enzymes that have suspected involvement in the destruction of the lung tissue. We have also found bronchial inflammation, but no activation of the neutrophils.

In a recently published Swedish study the authors presented levels of exposure to EC and NO\textsubscript{2} (mostly geometric means) that they had measured themselves in the city of Stockholm and measurements acquired in comparable studies [Lewne, Plato and Gustavsson; 2007]. The highest EC levels (87 μg/m\textsuperscript{3}) they found in air that tunnel construction workers were exposed to. Levels were much lower for outdoor workers, bus, lorry, and taxi drivers (4 – 7 μg/m\textsuperscript{3}). Corresponding levels found in other studies were 79 μg/m\textsuperscript{3} (arithmetic mean) and 2 – 9 μg/m\textsuperscript{3}, respectively. NO\textsubscript{2} exposure levels in their study amounted to 0.35 mg/m\textsuperscript{3} for tunnel construction workers and 0.032 - 0.053 mg/m\textsuperscript{3} for outdoor workers and drivers. Other studies reported levels ranging from 0.048 to 0.139 mg/m\textsuperscript{3} for drivers. Norwegian tunnel workers are also reportedly exposed to high levels of total dust and nitrogen dioxide (geometric means, 6-7 and 0.8-1.8 mg/m\textsuperscript{3}, respectively [Bakke et al.; 2001]. Common background levels of 0.03 – 0.1 mg/m\textsuperscript{3} NO\textsubscript{2} have been reported in some European cities [Le Tertre et al.; 2002], and in the general environment there is a limit of 0.09 mg/m\textsuperscript{3} [Swedish Environmental Protection agency; 2003]. We found the miners’ levels of exposure to EC (27μg/m\textsuperscript{3}), NO\textsubscript{2} (0.28 mg/m\textsuperscript{3}) and inhalable dust (3.2 mg/m\textsuperscript{3}) to be much higher than levels in the general environment, and the environments of most workers, even if somewhat lower (especially exposure to EC) than those of the tunnel construction
workers. In conclusion, miners are highly exposed to inorganic dust and diesel exhaust.

An environmental field study with some similarities to Study V has recently been published [McCreanor et al.; 2007], in which the effects of diesel exhaust exposure were assessed at several sites in London, UK, using induced sputa. In contrast to Study V the subjects were mild and moderate asthmatics and no induced sputum was examined before the exposure. They were exposed for two hours at a London street with heavy, entirely diesel-powered traffic (Oxford Street) and a central park (Hyde Park). They found more pronounced reactions after exposure on Oxford Street than in Hyde Park, and less pronounced reactions in mild than in moderate asthmatics. In the sputa MPO was strongly associated with the number of neutrophils, but in Study V there were no signs of neutrophil activation.

Our miners had been exposed to the mine environment for 18 years, on average. We do not know how their inflammation developed and changed during these years. Biological organisms have various systems that have evolved to counter exposure to harmful substances, neutralize their effects and maintain a state of equilibrium. However, when exposures exceed the capacity of the systems to maintain equilibrium the exposure will be harmful and tissues will start to be destroyed. We do not know if the detected bronchial inflammation provides adequate defense to counter the exposure or if it indicates an early stage in the development of a diseased state. Neither do we know if it is caused by exposure to inorganic dust, diesel exhaust or both. The contrasts in exposure are too small to attempt to separate the effects of these exposures as yet.

Silicosis
A few years ago [Steenland; 2005] reviewed dose-response studies of respirable quartz, an agent that is potentially capable of causing many serious diseases, including silicosis (an exclusively occupational and preventable disease), lung cancer, kidney disease, arthritis, and other autoimmune diseases. In the 1950s silicosis was thought to have been largely eradicated in developed countries, but this has subsequently been shown to be incorrect, and in developing countries it is a major hazard to miners. It has been estimated that there are several hundred thousand cases of silicosis and it causes 8 800 deaths per year globally. The life-time risk of silicosis (diagnostically defined by X-rays with International Labour
Categories ≥1/1) following occupational exposure to 0.1 mg/m³ respirable quartz for 45 years has been estimated to be 47 - 77% in studies including post-employment follow-up, but only 2 - 20% in studies with inadequate follow-up. The lifetime risk of death from silicosis before 75 years of age after a similar exposure, based on just one relevant study, has been estimated to be 1.9% ['t Mannetje et al.; 2002]. US authors often refer to the acceptable lifetime excess risk set by the US Occupational Safety and Health Administration (OSHA) of 1/1000 in both morbidity and mortality studies, which is remarkable since the risk of disease must be higher than the risk of death from that disease in a population.

The samples surveyed in the mortality study published by ‘t Mannetje et al. ['t Mannetje et al.; 2002] were larger but more heterogeneous than our samples, which may have led to more heterogeneity in their estimates of exposure and diagnoses of causes of death. They also had no, or few, measurements of historical exposure. They largely had to estimate exposure by converting particle measurements to mg/m³ of respirable quartz, while almost all our measurements were directly based on gravimetric measurements of respirable quartz. However, our exposure estimates (medians of exposure years, average levels, and cumulative exposures) were remarkably similar to theirs, as were our crude mortality rates based solely on underlying causes of death, which we and they estimated to be 20/100 000 and 29/100 000 person-years, respectively.

It should be borne in mind that we studied very severe silicosis, i.e. deaths from silicosis. There were probably several more cases of silicosis in the cohort, ranging from non-symptomatic to severe cases. An American study found the ratio of living to deceased confirmed silicosis cases to be 6.44 [Rosenman et al.; 2003]. If this ratio is also valid in Sweden, it corresponds to an unadjusted morbidity rate of 343 per 100 000 person years in our study. Furthermore, the morbidity rate would be still higher if other diseases caused by quartz were included.

We could not exclude the possibility that workers with cumulative exposures < 3 mg*years/m³ may be at risk. The samples were too small and the exposure estimates too uncertain to allow a detailed analysis of risks at such low exposure levels. US authors often refer to the acceptable lifetime excess risk established by the US-OSHA of 0.1%. Two US reviews have shown that at a lifetime exposure level of 0.1 mg/m³ (the current exposure limit in many countries), this risk level was considerably exceeded in both
morbidity and mortality studies [Greaves; 2000; Steenland; 2005]. It was exceeded even if the exposure was decreased to 0.01 mg/m\(^3\). Both authors recommended that the current exposure limit value should be decreased, but did not think that it would currently be feasible to decrease it sufficiently. Our study indicates that exposure to respirable quartz at a cumulative dose of about 3 mg*years/m\(^3\) is associated with an increased risk of fatal silicosis. This finding indicates that permissible exposure limits around of 0.05- 0.1 mg/m\(^3\) are too high to protect workers exposed to such levels for a full working life from severe silicosis.
CONCLUSIONS

- In an occupationally active Swedish population occupational exposure to dust, gases, and fumes explains up to 30 to 40%, a family history of asthma up to 60%, and these two variables up to 70% of impaired respiratory health.

- Low socio-economic status was a risk factor for asthmatic symptoms, asthma and chronic productive cough.

- The exposure profiles in iron mines are complex and include exposure to particulates and gases from several sources. The exposure causes increased risks of respiratory symptoms that do not seem to be totally reversible after cessation of the exposure.

- The exposure in the examined mine also caused bronchial inflammation, which was as pronounced after a vacation of at least four weeks as after a working period of three months. Biomarkers in sputum seem to be promising indicators for detecting the effects of exposure on airways in miners, but the predictive value of such markers for symptoms and diseases is currently unknown.

- Long-term average exposure to 0.1 mg respirable quartz /m$^3$, the current Swedish occupational exposure limit, is associated with an increased risk for severe silicosis.
ACKNOWLEDGEMENTS

Doctoral studies are rarely truly works of a single man or woman. Generally they are ongoing processes involving many persons. Therefore, I wish to express my sincere gratitude to all who were in some way or other involved in these studies; the subjects of the material used, and all friends and colleagues who have assisted, supported, comforted, and encouraged me.

My thoughts first turn to the late Nils Stjernberg, who supported me with great enthusiasm when I began to be interested in miners’ respiratory health.

I would also particularly like to express my thanks, mostly in chronological order, to:

Bo Lundbäck, my co-tutor, for taking over, continuing and developing the project Nils Stjernberg initiated, for the privilege of accepting me into the OLIN group, analysing some of the OLIN material, and guiding me through to production of this thesis.

Knut Sörensen, LKAB, Malmberget, the then chief engineer and vice president of Euromines, for engaging me as the medical expert of the Swedish Mining Industry and Euromines in discussions with SCOEL (the Scientific Committee on Occupational Exposure Levels) and other EU organizations concerned with the occupational environment in mines. You engaged me so much that I realized that I had better extend my interest as a PhD-student.

Tomas Sandström for your scientific support when I prepared my EU presentations and as a co-author.

Vagn Englyst, occupational physician of Boliden, for your support and interest during our years together in the Swedish mining industry and in the EU discussions.

Ulf Wettergren, then staff manager, and Leif Rönnbäck, then local manager, LKAB, Malmberget, for allowing me to participate in relevant courses, conferences and congresses, and by permitting me to include some research undertaken in my previous work as occupational physician.
All my previous colleagues at the Occupational Health Center of LKAB, Malmberget. I especially thank Leif Kågström, then safety engineer, for 20 years valuable cooperation in the mining industry, for continued cooperation in occupational health thereafter, and for technical advice and support in producing this thesis. I also thank Kurt Andersson, safety engineer, LKAB, Kiruna, for valuable cooperation for several years and for reviewing, together with Leif Kågström, the working environment in the examined mines from a technical perspective since mining began about 100 years ago.

Bengt Järvholm, my tutor. It has been a great privilege to have had you as my tutor. When Bo Lundbäck suggested you, before you had taken over as a professor at Umeå, I was delighted. Your reputation as a scientist, epidemiologist and tutor, and your interest in occupational respiratory disorders, had reached the north of Norrland before you. Your positive criticism has guided me in the arts of preparing a study, collecting material, analyzing it, and writing scientific papers.

All the friends involved in the OLIN studies for collecting the material and making it available to me, for your support, and for making the meetings and conferences we attended pleasant and stimulating. Thanks especially to Eva Rönmark for your devoted work during all the years of the OLIN studies, from their first beginnings, for all your cooperation and support, and for your inputs as a coauthor. Thanks also to other previous and current PhD-students, such as Lars-Gunnar Larsson, Anne Lindberg, Sven-Arne Jansson, Berne Eriksson, Anders Bjerg, and Linnea Hedman and also to Elsy Jönsson, Ann-Christin Jonsson, Sigrid Sundberg, Ola Bernhoff, and Staffan Andersson.

All the friends at the Dept. of Occupational and Environmental Medicine, especially Mari-Anne Engwall and my co-author Kåre Eriksson.

The staff of the Oncological Centre, especially Lena Damber, my co-author Håkan Jonsson and Göran Larsson, LKAB, Malmberget, for collecting the database of miners from Malmberget and Kiruna.

Hans Stenlund, Anders Emmelin, and Leif Nilsson for giving me basic knowledge of statistics and epidemiology.
My co-authors at the Dept. of Pulmonary Medicine and the National Institute for Working Life; Ellinor Ädelroth, Anders Blomberg, Ragnberth Helleday, Maj-Cari Ledin, Jan Olof Levin, and Jamshid Pouraza.

Iris Rönnqvist, of the Health Center of Malmberget, and the Local Health Authority of Norrbotten for allowing me to include some research undertaken when I worked there as a district medical officer.

John Blackwell of Sees-editing Ltd. for linguistic revision of this thesis.

Bobo Spetz and his staff at Print and Media for printing this thesis.

Last, but far from least, my family; Bente, Laila, Ingrid, and Ellen for their endurance, comfort, support, and love.
REFERENCES


Attfield MD. The effect of exposure to silica and diesel exhaust in underground metal and nonmetal miners. *Industrial Hygiene for Mining and Tunneling* 1978;;129-35.


Lindström M. Epidemiological studies of chronic obstructive pulmonary disease (COPD) and related conditions. The Obstructive Lung Disease in Northern Sweden Study IV. Umeå: Umeå University Medical Dissertations; 2002.


Lundbäck B. Asthma, chronic bronchitis and respiratory symptoms: Prevalence and and important determinants. The Obstructive Lung


Rappaport SM. Interpreting Levels of Exposures to Chemical Agents. In *Patty's Industrial Hygiene and Toxicology, Fifth Edition, Volume 1.*


Rönmark E. Asthma - Incidence, Remission and Risk Factors. The Obstructive Lung Disease in Northern Sweden Study II. Umeå: Umeå University Medical Dissertations; 1999.


Samet JM. Epidemiologic approaches for the identification of asthma. *Chest* 1987;**91**(6 SUPPL):74S-8S.


ERRATA

Study II, page 304, Socio-economic classification, subjects, line 5 and 6: “and normally requiring $\leq 2$ years of post-comprehensive school education” should be deleted.

Study II, page 304, Socio-economic classification, subjects, line 7 and 8: “and normally requiring $\leq 2$ years of post-comprehensive school education” should be deleted.

Study II, page 304, Socio-economic classification, Subjects, line 15 and 16: “non-professional” should be deleted.

Study II, page 304, Material and methods, Analyses, last paragraph, third from last line: “multiplicative interactions” should be substituted for “interactions”.

Study II, page 30, Results, Socio-economic group, fourth paragraph, first line: “multiplicative interaction” should be substituted for “interaction”.

Study III, page 953, Introduction, fourth paragraph, second sentence: “In Malmberget there has been no case of silicosis…” should been deleted.

Study III, page 954, Material and methods, Analyses, line 5: ”Multiplicative interactions” should be substituted for ”Interactions”.

Study III, page 956, Results, last paragraph, line 3: “multiplicative interactions” should be substituted for ”interactions”.

Study III page 956, Results, last paragraph, line 7: ”multiplicative interaction” should be substituted for “interaction”.

Study III, page 957, Discussion, fifth paragraph, line 1: “multiplicative interaction” should be substituted for “interaction”.

Study III, table 4: “chronic bronchitis” should be substituted for “asthma”.

Study IV, page 381, Methods, second from last paragraph, line 10: “multiplicative interactions” should be substituted for “interactions”.
Study IV, page 382, Results, last paragraph: “multiplicative interactions” should be substituted for “interactions”.

Study V, page 714, Abstract, second paragraph, line 1: “four weeks” should be substituted for “2 weeks”.

Study V, page 715, Methods, Subjects, line 6: “≥” should be substituted for “≤”.

Study V, page 716, Methods, Air sampling, line 13: “≤” should be substituted for “≥”.
APPENDIX 1

Brief description of socio-economic classes recognized by Statistics Sweden

1 (11-12) Unskilled and semi-skilled workers
2 (21-22) Skilled workers
2 (33-36) Assistant non-manual employees
3 (44-46) Intermediate non-manual employees
4 (54-60) Employed and self-employed professionals, higher civil servants and executives
5 (76-87) Self-employed (other than professionals)

11-22 MANUAL WORKERS

11 Unskilled employees in goods production: occupations involving the production of goods and normally requiring less than two years of post-comprehensive school education
12 Unskilled employees in service production: occupations involving service production and normally requiring less than two years of post-comprehensive school education
21 Skilled employees in goods production: occupations involving the production of goods and normally requiring two years or more of post-comprehensive school education
22 Skilled employees in service production: occupations involving service production and normally requiring two years or more of post-comprehensive school education

33-57 NON-MANUAL EMPLOYEES

33 Assistant non-manual employees, lower level: occupations normally requiring less than two years of post-comprehensive school education

34-35 Assistant non-manual employees, higher level: occupations normally requiring two, but not three, years of post-comprehensive school education

44-45 Intermediate non-manual employees: occupations normally requiring three, but not six, years of post-comprehensive school education
54-55 Professionals and other higher non-manual employees: occupations normally requiring at least six years of post-comprehensive school education
57 Upper-level executives: Upper-level executives in private enterprises or organizations with at least 100 employees or upper-level executives in public service

60-87 SELF-EMPLOYED (including farmers)

101-687 OTHERS: students, housewives, pensioners, unemployed, conscripts
APPENDIX 2
Measurements of miners’ exposure to nitrogen dioxide (mg/m$^3$).
APPENDIX 3
Measurements of miners’ exposure to elemental carbon ($\mu$g/m$^3$).

Subject, number

Elemental carbon (mg/m$^3$)

0 10 20 30 40 50 60 70
APPENDIX 4
Measurements of miners’ exposure to inhalable dust (mg/m$^3$).