Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 622

A Longitudinal Study of Asthma

Risk Factors and Prognosis

MONICA UDDENFELDT
Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Ing 50, Akademiska Sjukhuset, Uppsala, Thursday, December 16, 2010 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

The aim of this thesis was to identify risk factors for the onset of adult asthma. Other objectives were to study determinants of smoking habits and the association between sensitization and outcome of asthma.

In 1990, a questionnaire was distributed to 12,732 individuals from three age groups (16, 30-39 and 60-69 years) in two counties of Sweden. In a second phase, 2538 subjects who had reported respiratory symptoms and 600 controls were invited to clinical investigations, 81% participated. At the follow-up in 2003 subjects of the remaining cohort (11,282) were re-invited. Analyses are based on the 67% (n=7563) who responded to both questionnaires 1990 and 2003.

In 2003, 17.2% of the young adults, 11.4% of the middle-aged and 10.3% of the elderly reported having, or having had, asthma. A total of 791 subjects reported onset of asthma during the 13-year study period. Lifestyle factors such as smoking, obesity, hard physical training and a low consumption of fruit and fish were constant risk factors for onset of asthma after adjusting for socioeconomic group. A smoker’s risk of asthma onset was increased by 37%. The impact of risk factors differed between the age-groups. BMI had a significantly higher impact in the middle-aged and elderly.

In subjects participating in the clinical investigations in 1990, sensitization to pets, were determinants of both persistent asthma and onset of asthma in 2003. The risk for persistent asthma was threefold. The risk for onset of asthma was more than doubled.

Smoking at baseline in 1990 was the strongest determinant of being a smoker in 2003. Allergic sensitization and clinically verified asthma were not associated with smoking habits in 2003. No differences in changing smoking habits could be identified between smokers with or without asthma.

In conclusion, modifiable lifestyle factors are important risk factors for adult onset asthma. The co-occurrence and interplay between asthma and cigarette smoking is still puzzling.

Keywords: asthma epidemiology, longitudinal studies, obstructive airway symptoms, risk factors, BMI, diet, smoking, allergic sensitization, atopy

Monica Uddenfeldt, Department of Medical Sciences, Occupational and Environmental Medicine, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

© Monica Uddenfeldt 2010

ISSN 1651-6206
ISBN 978-91-554-7948-0
urn:nbn:se:uu:diva-133218 (http://urn.kb.se/resolve?urn=nbn:se:uu:diva-133218)
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV Uddenfeldt M, Janson C, Lampa E, Rask-Andersen A. Smoking habits are not influenced by respiratory health and allergic status. *In manuscript.*

Reprints were made with permission from the respective publishers.
Contents

Introduction .....................................................................................................9
  Asthma and allergic disease .........................................................................9
    Asthma is not a single disease entity .........................................................9
  Occurrence and time trends of asthma .......................................................10
  Risk factors for asthma and wheezing .......................................................10
  Allergic sensitization and asthma ............................................................11
    Asthma and respiratory symptoms in relation to smoking .......................11
  Smoking ...................................................................................................12
  Snuff .......................................................................................................12

Aims ...........................................................................................................14

Material and methods ....................................................................................15
  Study area .................................................................................................15
  Study population .......................................................................................16
    Paper I ...................................................................................................16
    Paper II ................................................................................................16
    Paper III and IV ....................................................................................16
  The questionnaire .....................................................................................18
  Data collection ..........................................................................................18
  Clinical investigations ................................................................................18
    Interview ..............................................................................................18
    Skin prick test ......................................................................................19
    Spirometry ............................................................................................19
    Bronchial hyperresponsiveness ...............................................................19
    Peak flow measurements .......................................................................19
  Definitions ...............................................................................................20
    Asthma ..................................................................................................20
    Asthma (broad definition) .......................................................................20
    Asthma diagnosis ..................................................................................20
  Ethics approval .........................................................................................20
  Statistical methods ....................................................................................21
    Paper I ..................................................................................................21
    Paper II ................................................................................................21
    Paper III ................................................................................................21
    Paper IV ................................................................................................21
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive pulmonary Disease</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced Expiratory Volume in one second</td>
</tr>
<tr>
<td>GER</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin, class E</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>PC 20</td>
<td>Provocative concentration of an agonist in the inhaled aerosol leading to a 20 % fall in FEV₁</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak Expiratory flow</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>SCB</td>
<td>Statistics Sweden</td>
</tr>
</tbody>
</table>
Introduction

Asthma is a serious global health problem, affecting an estimated 300 million individuals (GINA 2009). The fundamental causes of asthma and its changing prevalence are still not known: “There are still more questions than answers” quoting a Lancet editorial (Lancet 2008). The cardinal clinical diagnostic criteria of asthma, including episodes of chest tightness due to bronchoconstriction generally associated with expiratory wheezing alternating with periods of complete recovery, have been consistent throughout the last centuries. In daily clinical practice “All that whistles is not asthma” should, however, always be kept in mind. Ongoing treatment is often continued and seldom varied, without thinking too much of the exogenous agents provoking or causing symptoms, or the validity of the original diagnosis.

Asthma and allergic disease

The guidelines from the Global Initiative for Asthma (GINA) give the following operational description of asthma: “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing particularly at night or in the early morning. These episodes are usually associated with a widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment”. International guidelines do not provide strategies to confirm or exclude asthma.

Asthma is not a single disease entity

Asthma is a heterogeneous condition and causative factors, age at onset, natural history, severity, eliciting factors, remission probability and responsiveness to medications vary between individuals. Clinicians have recognized different presentations of asthma for a long time, that are defined according to general or clinical criteria: recent literature describes asthma as a syndrome rather than a single disease entity (Eder, Ege et al. 2006). Several phenotypes, each defined by its unique interaction between genetic
and environmental factors have been described (Wenzel 2006; Haldar, Pavord et al. 2008). Different strategies have been developed to classify asthma into different phenotypes on the basis of onset age and prognosis, severity, biomarker profile (e.g. eosinophilic/neutrophilic asthma), risk/trigger/prognostic factors (e.g. allergic sensitization) and clinical presentation (e.g. exercise-induced asthma). This thesis did not focus on asthma phenotypes, but this aspect has important implications for the general discussion.

**Occurrence and time trends of asthma**

Asthma prevalence has increased over the last fifty years. Epidemiological studies have suggested that the prevalence of asthma in adults is approximately 7-10% in different parts of the Western world. In Sweden asthma prevalence in adults has been intensely studied since the 1970s (Boman 1991). Prevalence has increased: 1.9% 1971, 2.8% 1981 (Aberg 1989), 3.5% 1985 (Stjernberg, Eklund et al. 1985), 5.0% 1991 (Lundback, Nystrom et al. 1991) and 8-10% in the mid 1990s. The increase was first noticed in the north of Sweden (Larsson, Boethius et al. 1993) and was, to some extent, explained by improved diagnostics (Lundback, Ronmark et al. 2001). A recent study (Ekerljung, Ronmark et al. 2008) has concluded that the incidence of asthma among adults has been stable in Sweden for the past two decades, which might indicate that a plateau has been reached. In Western Sweden the prevalence of asthma was 8.3%, when asthma was defined as diagnosed by a physician (Lotvall, Ekerljung et al. 2009). In comparison with studies performed 18 years ago, the prevalence of asthma had not increased. This is consistent with a tendency of decreasing childhood asthma in Sweden (Almqvist, Pershagen et al. 2005).

**Risk factors for asthma and wheezing**

The most important risk factors for asthma are family history of asthma (Sibbald, Horn et al. 1980; von Mutius 1996) and allergic sensitization (Anderson, Pottier et al. 1992; Barbee and Murphy 1998). In some studies the hereditary component seems to be stronger in subjects with allergic asthma, while other investigations have shown that a family history is equally common in subjects with allergic and non-allergic asthma. Among adults where the non-allergic asthma phenotype is common, risk factors are often environmental and include smoking (Toren and Hermansson 1999; Piipari, Jaakkola et al. 2004) and occupational exposure (Kogevinas 2007). The relationship between socioeconomic status and asthma has been less studied. In adolescents and adults some studies have shown an association with high socioeconomic status (Kaplan and Mascie-Taylor 1988), while others have found associations with low socioeconomic status (Basagana,
Sunyer et al. 2004; Eagan, Gulsvik et al. 2004; Braback, Hjern et al. 2005) or no relationship at all (Montnemery, Adelroth et al. 1998). Recently a higher incidence of non-atopic asthma was reported to be associated with low educational level in a large prospective European study (Ellison-Loschmann, Sunyer et al. 2007).

The relationship between obesity and asthma is also inconsistent in the literature (Beuther and Sutherland 2007). The association between onset of asthma and body mass index (BMI) has been most consistent in women (Camargo, Weiss et al. 1999; Chen, Dales et al. 2002). Other studies have linked underweight to a higher risk for developing asthma (Luder, Ehrlich et al. 2004). In a study from Sweden an increased BMI was significantly associated with onset of asthma independent of sex (Ronmark, Andersson et al. 2005). In a recent review (Eneli, Skybo et al. 2008) the authors found a rather consistent association between weight loss and improved asthma, which is an important epidemiological criterion of causality.

This thesis focuses mainly on two of the most important risk factors: allergic sensitization and smoking, which are presented in detail below.

**Allergic sensitization and asthma**

Allergic sensitization or atopy refers to the development of specific antibodies of the E subclass (IgE) against allergens. The term allergic sensitization is used throughout this thesis, except in paper I where “atopy” was used. Specific IgE against allergens can be recognized directly by serum analyses or indirectly by skin prick tests. The correlation between direct and indirect methods is high.

Rackemann was the first to report a distinction between what is now called allergic and non-allergic asthma (Rackemann 1947). He estimated that less than half of all asthmatics had allergic asthma. Many studies have found an association between sensitization to allergens and asthma in children (Martinez 2002; Bjerg-Backlund, Perzanowski et al. 2006). Previous studies of Swedish children have indicated that sensitization to household pets is important in pediatric asthma (Ghunaim, Wickman et al. 2006). In a longitudinal study of Swedish young adults onset of asthma was associated with sensitization to household pets (Plaschke, Janson et al. 2000). At the time of this study, it was not fully known to which degree sensitization was associated with onset and outcome of asthma in Swedish adults, nor was it known which allergens were most important.

**Asthma and respiratory symptoms in relation to smoking**

The single most important and preventable risk factor for all respiratory symptoms is smoking. The strong association between smoking and COPD is well established (Lindberg, Jonsson et al. 2005; Mannino and Buist 2007).
Considerably less information is available about the co-occurrence and interplay between asthma and cigarette smoking. The relationship between smoking and asthma is inconsistent in the literature (Ulrik and Lange 2001; Sandstrom and Lundback 2004; McLeish and Zvolensky 2010). Passive smoking has been linked to asthma both in children and in adults while the role of active smoking is less clear (Ekerljung, Ronmark et al. 2008). Prospective studies have more often reported significant associations between smoking and onset of adult asthma (Ronmark, Lundback et al. 1997; Eagan, Bakke et al. 2002; Piipari, Jaakkola et al. 2004).

**Smoking**

Smoking is a major risk factor for morbidity and mortality worldwide. Although Sweden is the first country to reach the goal of the World Health Organization with less than 20% active smokers in the population, there are still many challenges. Sweden is the only country in the world with a majority of female daily smokers (13%) compared to men (11%). We also face a situation, where changing smoking habits widens health inequalities between different socioeconomic groups. The proportion of daily smokers among single mothers in 2005 was doubled compared to adult women living with a partner with or without children (ULF, SCB). The prevalence of adolescent smokers in Sweden decreased during the last 25 years. There is still a significant recruitment of new smokers.

Since 1983 the Swedish Council for Information on Alcohol and Other drugs has performed annual surveys of tobacco use among school children. In 2009, 23% of boys and 30% of girls among 9th graders answered “yes” to the question “Do you smoke?” 7-12% of 9th graders smoked daily.

**Snuff**

Sweden is the only country in the European Union where the sale of moist snuff is allowed. The use of moist snuff leads to exposure to similar or higher doses of nicotine than tobacco smoking, but not to airway exposure to non-nicotinic components of tobacco smoke (Holm, Jarvis et al. 1992). Nicotine, the major component in tobacco smoke, is a strong modifier of the inflammatory response (Sopori 2002). There is only a limited knowledge of health effects of moist snuff.

The addictive habit of moist snuff placed under the upper lip has increased considerably in one generation. The users of today are younger and more often women. Paternal use has been shown to increase the risk for establishing the habit among boys (Rosendahl, Galanti et al. 2003). Smokeless tobacco in adolescence does not substitute cigarette smoking and
can be an indicator of a drug- and risk-seeking lifestyle (Galanti, Wickholm et al. 2001). Dual users among adolescents have emerged as a high risk group for tobacco dependence and tobacco-related harm (Rosendahl, Galanti et al. 2008).
Aims

- To investigate the prevalence of asthma in three age groups in 1990 and 2003.
- To study risk factors for onset of asthma in adulthood.
- To investigate the relationship between allergic sensitization and asthma in adults.
- To study the relationship between asthma and smoking behavior in adults.
Material and methods

Study area

The study area included participants from two counties in Sweden: Jämtland and the southern part of Gävleborg, i.e. the historical province Gästrikland. The study area is approximately the size of Denmark, located in the middle of Sweden, bordering Norway in the west and the Gulf of the Baltic Sea in the east. The population is 273,851 (2009-12-31 SCB) and the population density is 35 inhabitants per square kilometer in the south and only 3 in the western, mountainous area.

Figure 1. The study area.

The southern parts are industrialized while the central and the western areas are dominated by farming and forestry. Eighty-five percent of the population is lives in towns and cities, none of which have more than 100,000 inhabitants. Air pollution is generally low but there are considerable local variations.
The area has four distinct seasons: the winter, with snowfalls from November through April, spring, summer and autumn. The birch and grass pollen seasons (i.e. spring and summer) in the study area last approximately 4 months.

Study population

Paper I
The cohort consisted of three age-groups: all individuals born in 1974, and a random sample of middle-aged (1951–1960) and elderly (1921-1930). A total of 12,732 questionnaires were distributed at the starting point in 1990. A total of 139 individuals living abroad and 31 deceased were excluded. The response rate was 90%, n=11,294 (Figure 2).

Paper II
In 2003, 11,282 subjects of the remaining cohort were invited to the follow-up study. Response rate was 73 %, of which 53 % were females. Those participating included 2190 young adults, 3557 middle-aged and 2319 elderly individuals. Analyses in paper II are based on the 67% (n=7563) who participated in both surveys (1990+2003).

Papers III and IV
In paper III and IV subjects were selected from the responders to the questionnaire in 1990. All subjects reporting respiratory symptoms (n = 2538) and a random sample of 600 subjects without respiratory symptoms were invited to the clinical investigations. The participation rate was 81% in this phase of the study. After the clinical investigations all participants were classified into diagnostic groups by two physicians.

Analyses in paper III were based on the 460 subjects fulfilling the diagnostic criteria for asthma and 521 subjects without asthma who participated in the clinical investigations and both surveys (1990+2003). Subjects with respiratory diseases other than asthma or airway symptoms of uncertain significance were excluded.

Analyses in paper IV were based on the 1791 subjects who participated in the clinical investigations and both surveys (1990+2003).
Figure 2. Study population and design of the study.
The questionnaire

The 22 item questionnaire in 1990 included questions on respiratory symptoms, asthma, hay fever, heredity, and smoking habits. This questionnaire was a modification of a questionnaire used previously in the Obstructive Lung Disease in Northern Sweden studies, based on the British Medical Research Council questionnaire. In 2003 the questionnaire consisted of 114 questions. The first part was identical to the 22 item questionnaire in 1990. The second part of the questionnaire in 2003 included 92 new items covering weight, height, physical activity, dietary factors, gastroesophageal reflux, sleep disorders, snoring, occupational exposure and indoor environment: most of those items previously used in the European Community Respiratory Health Survey. Most of the additional question were in the same format and used a fixed set of responses. Working life through the lifespan was documented in an open question by the respondents. The respondents answers were used to create a socioeconomic index based on current occupation in 2003.

Data collection

The questionnaire and a cover letter were distributed by mail and returned to the study group in a pre-paid sealed envelope. Nonparticipants were sent two remainders by regular mail, including a short letter with study information, a questionnaire, and a pre-paid envelope.

Clinical investigations

Subjects invited to the clinical investigation in 1990 were selected from the responders to the postal questionnaire. The clinical investigations consisted of an interview, a skin prick test, pre- and post-bronchodilator spirometry, recording of PEF variability and a methacholine challenge. After the clinical investigations, all participants were classified in diagnostic groups by two physicians.

Interview

In Papers III and IV a structured interview was performed using a questionnaire regarding medical history, respiratory symptoms, medication, smoking habits, type of housing and pets. The interview took place before the skin prick test and was performed in a standardized manner by nurses with special training in questionnaires, allergy testing and other study-related issues.
Skin prick test

The skin prick tests were performed between April 1990 and September 1991 or 2-17 months after the postal survey. Allergen extracts included a Swedish standard panel with common airborne allergens (Phazet, Pharmacia Diagnostics AB). The test followed the guidelines from the European Academy of Allergy and Clinical Immunology (EAACI). A mean wheal diameter of 3mm or larger was regarded as positive. Skin test results with a mean diameter for the negative control of more than 2mm, or with negative histamine in the positive control, were excluded from the analyses.

Spirometry

Lung function was tested with a pneumotachograph (Vitalograph Alpha, London, UK). This study adhered to recommendations for spirometry testing to by the ATS recommendations for spirometry testing. Vital capacity (VC) and forced expiratory volume in 1 second (FEV1) were measured before, and 15 minutes after, 0.6mg salbutamol inhaled with a spacer.

Bronchial hyperresponsiveness

Bronchial hyper responsiveness is a cardinal feature of current asthma. If the methacholine challenge is positive the diagnosis of current asthma is verified. However if the test is negative and symptoms occurred a long time ago asthma is not excluded. Bronchial hyper responsiveness was estimated using a standardized bronchial methacholine challenge test (Lowhagen and Lindholm 1983). Two ml of methacholine chloride in doubled concentrations from 0.03mg/ml to 16 mg/ml were nebulized on demand with an Aiolos nebulizer with a mean output of 0.7 (0.05) ml/min at 200 kPa and inhaled by tidal breathing for two minutes at five minute intervals. FEV1 was recorded two and four minutes after each dose. The result was expressed as provocative concentration causing a 20% fall in FEV1 (PC20).

Peak flow measurements

When investigated all subjects were asked to record PEF for one week with a mini-Wright peak flow meter as described by Higgins 1989 (Higgins, Britton et al. 1989). All days with at least three recordings were identified and the amplitude in percent of the mean was calculated.
Definitions

Asthma

In papers I and II the presence of asthma was defined as “yes” to the question-“Do you have or have you had asthma?”

Asthma (broad definition)

In papers II, III and IV the presence of asthma defined as “yes” to one or more of the questions: “Do you have or have you had asthma?” “Have you ever been diagnosed with asthma by a doctor?”, “Do you use asthma medication?” and “Do you have or have you had symptoms of asthma?”

Asthma diagnosis

The same diagnostic criteria were used in papers III and IV. The protocol to confirm asthma involved two visits. The first visit consisted of interview, pre- and post-bronchodilator spirometry and instructions to record peak expiratory flow for one week after the examination with a mini-Wright peak flow meter. If all of the following symptoms and findings were present asthma was confirmed and no further testing was required:

- repeated attacks of wheezing or shortness of breath in the last year
- identified exogenous agents provoking wheeze or shortness of breath
- complete recovery between attacks
- best FEV₁ ≥ 80%

If symptoms and findings were inconclusive the diagnosis was confirmed at the first visit by the following:

- an increase of FEV₁ of ≥300mL and 15% after bronchodilator

Subjects who did not meet the above criteria returned for a bronchial challenge test on visit two. The asthma diagnosis was confirmed by a provocative concentration of methacholine causing a 20% fall in FEV₁:

- PC20 ≤ 4 mg/ml
- PC20 4-8 mg/ml, and variability in peak expiratory flow >20% in 3 of 7 days

Ethics approval

The study in paper I was approved by The Ethics Committee at Umeå University (§ 222, 1989-12-12). The study in papers II-IV was approved by the Ethics Committee, Faculty of Medicine at Uppsala University (01-313).
Statistical methods

Paper I

Comparison of prevalence between groups was performed using the Chi- squared test. P-values of <0.05 were regarded as statistically significant. In calculations of prevalence of symptoms and diseases, missing answers were treated as negative responses.

Paper II

Logistic regression was used to estimate associations with incident asthma and the determinants. Age was allowed to interact with all determinants to allow for effects to differ with increasing age. The relationship between BMI and incident asthma was allowed to be non-linear by the use of restricted cubic splines. Predicted probabilities were used to calculate the expected annual incidence per 1,000 person years.

Paper III

Two logistic regression models were built; one for predicting persistent asthma and one for predicting incident asthma in the subsample that were clinically examined in 1990. Missing data patterns were analyzed using cluster analysis and logistic regression. Missing values were subsequently imputed using multiple imputation creating 15 completed datasets.

Paper IV

Logistic regression was used to determine the effect of the determinants on smoking status in 2003 among the subsample that were interviewed in 1990. As in Paper III multiple imputation of the missing values was performed. Asthma diagnosis was allowed to modify the effect of the determinants.
Results

Paper I

At baseline in 1990 the asthma prevalence, defined as a positive answer to the question “Do you have or have you had asthma?” was 7.2 % in the county of Jämtland and 5.8 % in Gästrikland (p<0.01). Self-reported asthma-like symptoms, wheezing, doctor-diagnosed asthma and use of asthma medication were all more prevalent in the county of Jämtland. No difference between the three age-groups was found. The prevalence of doctor-diagnosed chronic bronchitis was the same in both counties: 2 % in the middle-aged, and 5 % in the elderly.

Table 1. Prevalence of asthma and wheeze in the three age groups 1990.

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>16</th>
<th>30-39</th>
<th>60-69</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma heredity</strong></td>
<td>Jämtland</td>
<td>Gävleborg</td>
<td>Jämtland</td>
<td>Gävleborg</td>
</tr>
<tr>
<td>18.3**</td>
<td>14.1</td>
<td>21.7***</td>
<td>16.9</td>
<td>19.1***</td>
</tr>
<tr>
<td><strong>Asthma ever</strong></td>
<td>6.8</td>
<td>6.4</td>
<td>8.3***</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Asthma symptoms</strong></td>
<td>11.5**</td>
<td>9.2</td>
<td>13.0***</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>Doctor diagnosed asthma</strong></td>
<td>5.9</td>
<td>5.4</td>
<td>6.6***</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Wheeze</strong></td>
<td>7.4</td>
<td>6.1</td>
<td>10.3**</td>
<td>8.0</td>
</tr>
</tbody>
</table>

In addition self-reported, doctor-diagnosed asthma in all subjects (method of diagnosis not specified) was identified in 5.4 % (unpublished results).

Paper II

At the follow up in 2003 self-reported doctor-diagnosed asthma was identified in 11.3 % of subjects. As shown in figure 3, the prevalence of
asthma, defined as a positive answer to at least one of the four questions in the broad definition, had increased significantly in all age groups (p<0.001). In young adults, the asthma prevalence was 25 %.

Figure 3. Prevalence of “Doctor diagnosed asthma” in 1990 and 2003.

During the study period 791 of the participants reported onset of asthma. Lifestyle factors such as smoking (RR 1.37), BMI (RR 1.49), hard physical training (1.6) and nocturnal gastroesophageal reflux (GER) (RR 2.16) were significant, independent risk factors for the cumulative incidence of asthma after adjusting for socioeconomic group (Table 2). The impact of risk factors differed between the age groups. BMI and had a significantly higher impact in the middle-aged and the elderly (p<0.05) and GER had a higher impact in the young adults and the middle aged, table 3. High consumption of fruit and fish was protective especially in the elderly age group (RR 0.52).

No significant difference was found in the impact of risk factors between men and women. But, the relationship between the cumulative incidence of asthma and BMI was U-shaped for the men in the present study, but not for the women (figure 4). An analysis restricted to the nonsmokers showed a more linear relationship between BMI and the cumulative incidence of asthma (figure 5), but a U-shaped relationship for the smokers and ex-smokers.
Table 2. Adjusted relative risks (RR) for onset of asthma.

<table>
<thead>
<tr>
<th></th>
<th><strong>Onset of asthma</strong></th>
<th><strong>p-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td>1.45(1.23-1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Young</td>
<td>1.70(1.41-2.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Middle aged</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>1.07(0.86-1.33)</td>
<td></td>
</tr>
<tr>
<td><strong>Asthma heredity</strong></td>
<td>1.47(1.24-1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hay fever</strong></td>
<td>2.34(1.93-2.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Non-smokers</strong></td>
<td>1</td>
<td>0.008</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>1.16(0.96-1.40)</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>1.37(1.12-1.68)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI per IQR</strong></td>
<td>1.49(1.25-1.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Basic physical activity</strong></td>
<td>1</td>
<td>0.005</td>
</tr>
<tr>
<td>Training 3 times a week</td>
<td>1.15(0.94-1.39)</td>
<td></td>
</tr>
<tr>
<td>Hard training several times a week</td>
<td>1.60(1.19-2.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Nocturnal GER &gt; 1 week</strong></td>
<td>2.16(1.72-2.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Snoring &gt; 3 week</strong></td>
<td>1.23(1.01-1.49)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Building dampness in home</strong></td>
<td>1.10(0.89-1.36)</td>
<td>0.376</td>
</tr>
<tr>
<td><strong>Managers and professionals</strong></td>
<td>1.17(0.89-1.54)</td>
<td>0.501</td>
</tr>
<tr>
<td>Other non-manual</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skilled manual</td>
<td>0.91(0.70-1.19)</td>
<td></td>
</tr>
<tr>
<td>Semi-skilled or unskilled manual</td>
<td>0.98(0.81-1.19)</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable or unknown</td>
<td>0.86(0.65-1.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Fish and fruit consumption</strong></td>
<td>0.78(0.66-0.92)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Figure 4. The cumulative incidence of asthma and BMI in men and women.

Figure 5. The cumulative incidence of asthma and BMI in different smoking categories.
**Paper III**

At follow-up in 2003, a total of 305 subjects with persistent asthma and 155 subjects with asthma remission were identified in those with asthma at baseline in 1990, while 76 subjects with asthma onset were identified in the group without asthma in 1990.

Sensitization to household pets and a higher self-reported responsiveness to airway irritants were significant determinants of both persistent asthma (OR 3.2 [1.9-5.6], and 1.6 [1.1-2.2]) and onset of asthma (OR 2.6 [1.1-6.0] and 1.2 [1.0-1.6]), table 3, figures 6-7. A higher symptom (OR 5.7 [2.5-13.3]) and medication score (OR 2.0 [1.3-2.9]) at baseline were additional risk factors for persistent asthma at the follow up. Smoking habits and decreased FEV$_1$ at baseline were not significant determinants for persistent asthma.

Asthmatics sensitized to pets had a more severe outcome than asthmatics not sensitized to pets. Sensitization to pets was also a strong predictor for onset of asthma.

**Table 3. Independent determinants of persistent asthma and onset of asthma.** The results are expressed as adjusted odds ratios with a 95% confidence interval (OR (95% CI)).

<table>
<thead>
<tr>
<th></th>
<th>Persistent asthma OR (95% CI)*</th>
<th>New asthma OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td>1.0 (0.6-1.5)</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 year-olds</td>
<td>1.0 (0.5-1.7)</td>
<td>1.6 (0.9-3.1)</td>
</tr>
<tr>
<td>30-39 year-olds</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60-69 year-olds</td>
<td>0.5 (0.3-0.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking habits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>1.0 (0.5-1.7)</td>
<td>1.0 (0.5-1.9)</td>
</tr>
<tr>
<td>Smokers</td>
<td>0.6 (0.3-1.1)</td>
<td>1.0 (0.5-2.1)</td>
</tr>
<tr>
<td><strong>Pos. skin prick tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pets</td>
<td>3.2 (1.9-5.6)</td>
<td>2.6 (1.1-6.0)</td>
</tr>
<tr>
<td>Mites</td>
<td>0.8 (0.4-1.5)</td>
<td>0.6 (0.3-1.3)</td>
</tr>
<tr>
<td>Moulds</td>
<td>0.9 (0.4-2.1)</td>
<td>2.1 (0.5-8.8)</td>
</tr>
<tr>
<td>Pollen</td>
<td>1.0 (0.6-1.7)</td>
<td>1.3 (0.7-2.4)</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>0.8 (0.6-1.0)</td>
<td>1.0 (0.7-1.4)</td>
</tr>
<tr>
<td>Response irritants</td>
<td>1.6 (1.1-2.2)</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td>Symptoms score</td>
<td>5.7 (2.5-13.3)</td>
<td>1.7 (1.2-2.3)</td>
</tr>
<tr>
<td>Asthma medication</td>
<td>2.0 (1.3-2.9)</td>
<td>0.7 (0.3-1.3)</td>
</tr>
</tbody>
</table>
Figure 6. Determinants of persistent asthma 2003 in subjects with clinically verified asthma 1990 analysed with multiple logistic regressions. Results shown as ORs (odds ratios) with different levels of confidence intervals with figures and shades of grey (light grey 95% CI, see the determinant “Symptom severity”). The values of the independent determinants that are compared are indicated in the figure (Interquartile distance for airway responsiveness, symptom severity and FEV$_1$).

Figure 7. Determinants of asthma onset 2003 in subjects without asthma in 1990 analysed with multiple logistic regressions. Results shown as OR (odds ratio) with different levels of confidence intervals with figures and shades of grey (light grey 95% CI, see the determinant “Mould”). The values of the independent determinants that are compared are indicated in the figure (Interquartile distance for airway responsiveness, symptom severity and FEV$_1$).
More women than men were smokers in 2003. Also, smoking was more prevalent among the middle-aged subjects compared to the young adults and elderly. Eighty-one percent of the smokers in 2003 were already smokers in 1990 - more than the 11 % who were non-smokers in 2003. More of the smokers in 2003 had smoking parents. The FEV1 and the three well-being quality-of-life scores (Social, Physical and Mental) were lower in the smokers in 2003. In contrast, the snuff habits in 1990, the socioeconomic groups, and the results of the skin prick tests did not differ between the smokers and non-smokers in 2003.

Comparing smoking habits 2003 in subjects with and without clinically-verified asthma in 1990, it was found that 72 % of the smoking asthmatics were women compared to 59 % in the asthmatic who did not smoke 2003 (Table 4). No differences in smoking habits were found between men and women in the subjects without clinically-verified asthma in 1990. There were more smokers in the middle-aged group, in both the asthmatics and non-asthmatics. Snuff habits did not differ between the groups although the prevalence of moist snuff use was 7 % in the smoking asthmatics compared to 13% in the other three groups. Parental smoking was reported at a higher frequency in the smokers, both in the asthmatics and non-asthmatics. The respiratory-symptom score also differed: the smoking asthmatics reported the highest prevalence of severe symptoms, with 20 % reporting breathlessness on most days of the week. More positive skin prick tests were found in the asthmatics and especially in the non-smoking asthmatics. FEV1 did not differ between the smoking and non-smoking asthmatics, but was lower in 2003 in those smokers who did not have clinically-verified asthma in 1990. The asthmatics also reported a lower quality of life, but the socioeconomic index did not differ.

The multiple logistic regressions showed that the strongest determinants of being a smoker in 2003 were being a smoker in 1990 (OR 32.7 [95% CI 22.9-46.5]), table 5. Young age was also a significant determinant for being a smoker, after adjustment for confounders (p=0.005). Other factors that seemed to be of importance were female sex, respiratory symptom score in 1990, as well as low scores for respiratory symptom and physical wellbeing. Having a clinically-verified diagnosis of asthma in 1990 did not have any effect on smoking habits 13 years later nor did parental smoking and snuff habits in 1990.
Table 4. Characteristics of study population separated by smoking habits 2003 and asthma 1990.

<table>
<thead>
<tr>
<th></th>
<th>Asthma 1990</th>
<th>P-value</th>
<th>No asthma 1990</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young adults</td>
<td>20% (22)</td>
<td>29% (124)</td>
<td>14% (29)</td>
<td>22% (226)</td>
</tr>
<tr>
<td>Middle aged</td>
<td>64% (69)</td>
<td>37% (157)</td>
<td>64% (133)</td>
<td>38% (394)</td>
</tr>
<tr>
<td>Elderly</td>
<td>16% (17)</td>
<td>33% (141)</td>
<td>22% (47)</td>
<td>40% (410)</td>
</tr>
<tr>
<td>Smokers 1990</td>
<td>86% (93)</td>
<td>11% (47)</td>
<td>79% (165)</td>
<td>11% (118)</td>
</tr>
<tr>
<td>Parental smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28% (30)</td>
<td>41% (169)</td>
<td>36% (74)</td>
<td>46% (463)</td>
</tr>
<tr>
<td>At least one</td>
<td>41% (44)</td>
<td>41% (168)</td>
<td>39% (80)</td>
<td>40% (403)</td>
</tr>
<tr>
<td>Both</td>
<td>31% (34)</td>
<td>19% (77)</td>
<td>26% (53)</td>
<td>15% (147)</td>
</tr>
<tr>
<td>Respiratory symptom score 1990</td>
<td>5% (5)</td>
<td>9% (37)</td>
<td>39% (81)</td>
<td>57% (585)</td>
</tr>
<tr>
<td>No symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze during last year</td>
<td>7% (8)</td>
<td>17% (72)</td>
<td>31% (64)</td>
<td>22% (228)</td>
</tr>
<tr>
<td>Nightly symptoms/Asthma attacks</td>
<td>68% (73)</td>
<td>66% (278)</td>
<td>25% (52)</td>
<td>18% (190)</td>
</tr>
<tr>
<td>Breathlessness on most days</td>
<td>20% (22)</td>
<td>8% (35)</td>
<td>6% (12)</td>
<td>3% (27)</td>
</tr>
<tr>
<td>Skin prick test 1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>45% (48)</td>
<td>57% (239)</td>
<td>31% (64)</td>
<td>30% (310)</td>
</tr>
<tr>
<td>Negative</td>
<td>55% (59)</td>
<td>43% (182)</td>
<td>69% (142)</td>
<td>70% (711)</td>
</tr>
<tr>
<td>FEV\textsubscript{1} 1990 percent of pred\textsuperscript{2}</td>
<td>90/96/105</td>
<td>90/98/108</td>
<td>84/96/109</td>
<td>89/102/111</td>
</tr>
<tr>
<td>Gothenburg QoL 1990\textsuperscript{2}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom scale</td>
<td>7/12/16</td>
<td>5/8/13</td>
<td>5/8/12</td>
<td>3/6/10</td>
</tr>
<tr>
<td>Social wellbeing</td>
<td>4.3/5.0/5.6</td>
<td>4.9/5.6/6.1</td>
<td>4.7/5.1/5.7</td>
<td>5.0/5.6/6.1</td>
</tr>
<tr>
<td>Physical wellbeing</td>
<td>3.5/3.8/4.6</td>
<td>3.8/4.3/4.8</td>
<td>3.7/4.2/4.7</td>
<td>4.0/4.5/5.0</td>
</tr>
<tr>
<td>Mental wellbeing</td>
<td>4.0/4.6/5.6</td>
<td>4.6/5.2/5.8</td>
<td>4.4/5.0/5.8</td>
<td>4.6/5.4/6.0</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Chi-square tests for all except for FEV\textsubscript{1} and the Gothenburg Quality of Life scores there \textsuperscript{2}Kruska Wallis was used, \textsuperscript{2}Median, 25th and 75th percentile are shown.
Table 5. Independent determinants of smoking 2003 based on imputed data. The results are expressed as adjusted odds ratios with a 95% confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>Smoker 2003 OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>1.4(0.9-2.0)</td>
<td>p=0.131</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td>p=0.005</td>
</tr>
<tr>
<td>16 year old</td>
<td>1.3(0.8-1.9)</td>
<td></td>
</tr>
<tr>
<td>30-39 yrs olds</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>60-69 yrs olds</td>
<td>0.6(0.4-0.8)</td>
<td></td>
</tr>
<tr>
<td>Smoker 1990</td>
<td>32.7(22.9-46.5)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Snuffer 1990</td>
<td>1.0(0.6-1.6)</td>
<td>p=0.934</td>
</tr>
<tr>
<td>Parental smoking</td>
<td></td>
<td>p=0.888</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>1.0(0.7-1.4)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1.0(0.7-1.6)</td>
<td></td>
</tr>
<tr>
<td>Pos. skin prick tests</td>
<td>0.9(0.8-1.1)</td>
<td>p=0.382</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.0(0.8-1.2)</td>
<td>p=0.893</td>
</tr>
<tr>
<td>Respiratory symptoms score</td>
<td>1.2(0.8-1.9)</td>
<td>p=0.295</td>
</tr>
<tr>
<td>Clinically verified asthma 1990</td>
<td>1.0(0.7-1.4)</td>
<td>p=0.809</td>
</tr>
<tr>
<td>Gothenburg QoL 1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom scale</td>
<td>1.1(0.8-1.6)</td>
<td>p=0.514</td>
</tr>
<tr>
<td>Social wellbeing</td>
<td>1.0(0.7-1.5)</td>
<td>p=0.899</td>
</tr>
<tr>
<td>Physical wellbeing</td>
<td>0.8(0.5-1.2)</td>
<td>p=0.199</td>
</tr>
<tr>
<td>Mental wellbeing</td>
<td>1.0(0.7-1.4)</td>
<td>p=0.854</td>
</tr>
<tr>
<td>Socioeconomic index 2003</td>
<td></td>
<td>p=0.586</td>
</tr>
<tr>
<td>Managers and professionals</td>
<td>0.9(0.5-1.7)</td>
<td></td>
</tr>
<tr>
<td>Other non-manual</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skilled manual</td>
<td>0.7(0.4-1.1)</td>
<td></td>
</tr>
<tr>
<td>Semi-/ unskilled manual</td>
<td>0.8(0.5-1.3)</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable or unknown</td>
<td>1.0(0.6-1.7)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion of main results

The results of this 13-year follow-up study of three age groups in Sweden suggests an independent relationship between several risk factors for adult asthma onset, and is an illustration of the multi-factorial genesis of asthma. The main findings are that lifestyle factors such as smoking, BMI, physical training, GER, and low consumption of fruit and fish are significant, independent risk factors for asthma onset after adjusting for socio-economic group. The impact of BMI and GER differed significantly between age groups. BMI had a greater impact in the middle-aged and the elderly, GER in the middle-aged and the young adults. No difference in the impact of risk factors between men and women was found. As previously reported, family history of asthma, hay fever, female sex and young age were strong risk factors in all age groups.

The three age groups studied could roughly be categorized at baseline 1990: teenagers, parents and grandparents. At follow up, they had turned into young 29-year adults, middle-aged 43-52 year-olds and elderly people, 73-82 years old. The asthma prevalence in 2003 was higher in all age groups compared to 1990, most strikingly in the young adults. Prevalence of doctor-diagnosed asthma in all subjects was 11.5 % in this study. In the youngest age group, prevalence was higher, at 15 %, which is about the same as in Swedish teenagers in this cohort ten years ago (Larsson 1995). A recent study (Ekerljung, Ronmark et al. 2008) has concluded that the incidence of asthma among adults has been stable in Sweden for the past two decades, which might indicate that a plateau has been reached.

Smoking

Smoking habits have changed considerably in one generation. It is worth noting that 74 % of the young adults in this study, parents or parents-to-be, are never-smokers, compared with only 41 % in the middle-aged who had left the child rearing period. Our results support the hypothesis that smoking is a risk factor for asthma onset in adult age. Studies regarding the effect on smoking on asthma is, however, still controversial: some researchers have shown that asthma increases with smoking (Larsson 1995; Plaschke, Janson et al. 2000; Piipari, Jaakkola et al. 2004), while others have failed to find an increased risk (Vesterinen, Kaprio et al. 1988; Troisi, Heinold et al. 1991; Huovinen, Kaprio et al. 2003). An increased remission rate of asthma was
observed among subjects who quit smoking during a 10-year observation period (Holm, Omenaas et al. 2007) and recent intervention studies with smoking cessation demonstrate improvement of asthma (Tonnesen, Pisinger et al. 2005; Chaudhuri, Livingston et al. 2006).

**BMI**

This study also adds evidence to an independent relationship between increased BMI and onset of adult asthma. Obesity and its related illness is a primary health concern today. During the 13-year study period obesity rates, defined as BMI $\geq 30$, in the included age groups increased from 35% in males to 55% and 27% to 40% in females in Sweden. Only one third of 30-, 40-, 50- and 60 year olds who were of normal or overweight in 1990 were able to maintain or lose body weight during a 10-year observation period (Nafziger, Lindvall et al. 2007). The 30-year olds were least likely to maintain or lose body weight.

Strong positive association between BMI and onset of adult asthma has previously been reported. In a recent review (Eneli, Skybo et al. 2008) authors found a fairly consistent association between weight loss and improved asthma- an important epidemiological criterion of causality. Asthma was the primary outcome in five studies, two using low calories diet (Hakala, Stenius-Aarniala et al. 2000; Stenius-Aarniala, Poussa et al. 2000) and three using surgical procedures (Macgregor and Greenberg 1993; Narbro, Agren et al. 2002; Simard, Turcotte et al. 2004). Our results also suggest that being underweight is a risk factor for asthma onset, although we had small numbers of subjects in this category. These findings are supported by previous studies linking underweight to a higher risk of developing asthma (Braback, Hjern et al. 2005). The high cumulative incidence of asthma in the subjects with lowest BMI in our study might be explained by that some subjects with low BMI had been misclassified with asthma rather than COPD and/or emphysema. This is supported by the fact that men in the two oldest age groups had been significantly heavier smokers than the women. The opposite was found in the young adults, but the young women had not smoked long enough to get COPD.

**Gastroesophageal reflux GER**

An independent relationship between obesity, nocturnal gastroesophageal reflux and habitual snoring and the onset of asthma was reported in a 5-10 year European follow-up study (Gunnbjornsdollair, Omenaas et al. 2004). In the previously-mentioned review (Eneli, Skybo et al. 2008) authors comment on GER, as a condition which may mediate or confound an association between weight loss and change in asthma symptoms. Previous studies on the relationship between obesity and GER have provided inconsistent
results. Some studies demonstrated increased level of GER with obesity (Corley and Kubo 2006). Others report no relationship (Lagergren, Bergstrom et al. 2000). One of the strongest pieces of evidence that BMI and GER are connected is the result of prospective studies of gastric banding that results in weight loss (mean excess weight loss 45%) and significant reduction in co-morbidity (Spivak, Hewitt et al. 2005). Of 48 patients with preoperative GER 35 subjects (73 %) recovered completely and 7 (15 %) improved.

**Diet**

Some aspects of diet have been recently recognized as potential risk factors for asthma, but the evidence is conflicting. Our study was not designed to address dietary factors in detail, but seven questions on dietary intake were included. After controlling for possible confounders, the risk for asthma onset was significantly increased for subjects with low consumption of both fruit and fish. Other dietary factors did not affect the risk for asthma. Woods has previously reported apples and pears to be protective factors for current asthma (Woods, Walters et al. 2003) Romieu investigated whether fruit and vegetable intakes predicted the prevalence of adult asthma among French women participating in the E3N study (Romieu, Varraso et al. 2006). She concluded that some fruit and vegetables may decrease the prevalence of adult asthma. In another European study, high margarine intake increased the risk of asthma onset while dietary intake of antioxidants had no protective effect (Nagel and Linseisen 2005). Studying dietary patterns instead of specific foods and nutrients is a new approach in the French E3N study. A generally Western diet was associated with an increased risk of frequent asthma attacks, while a “nut and wine” diet seemed to be protective (Varraso, Kauffmann et al. 2008).

Comparing the impact of risk factors between the three age groups in this study, the impact of BMI was higher in the middle-aged and elderly. For diet, a trend was seen with a more asthma protective effect with increased age, p=0.06. The impact of gastroesophageal reflux was higher in the young and the middle-aged. These findings support the finding that asthma phenotypes differ over age groups as outlined in a recent review that discussed phenotypes of early/childhood asthma and late/adult-onset asthma (Wenzel, 2006).

**Socioeconomic status**

Diverging results concerning the relationship between asthma onset and socioeconomic status have also been published (Bakke, Hanoa et al. 1995; Eagan, Gulsvik et al. 2004). In our study socioeconomic status was not
related to adult asthma onset. In another recent Swedish study manual workers in industry had an increased risk of developing asthma compared to skilled workers (Hedlund, Eriksson et al. 2006). BMI was, however, not included in that analysis, which might be a problem as it is a well-known fact that BMI is related to socioeconomic status. In studies of asthma, BMI and smoking, socioeconomic status may be a confounding factor as low socioeconomic status has been associated with both smoking habits and obesity.

Physical activity

The impact of hard physical training on the onset of adult asthma has been described. Exercise induced asthma and other airway symptoms are common in athletes (Helenius, Lumme et al. 2005). Asthma occurs most commonly in athletes engaging in endurance events such as cross-country skiing, swimming, or long-distance running. Airway cooling and airway drying during physical exercise has been investigated in cross-country skiers in the study area (Larsson, Ohlsen et al. 1993). Mechanisms are still unclear (Anderson and Kippelen 2008). Our results indicate that not only hard athletic training but also physical training three times a week increases the risk of asthma onset compared to an active lifestyle including bowling, gardening, walking or riding a bicycle at least 4 hours a week. Exercise-induced asthma illustrates a fundamental problem; asthma is a syndrome with common features that arises from very different pathways.

Methodological aspects and limitations

There are few longitudinal studies of risk factors and onset of adult asthma. At the follow up in ECRHS II, after 8 years, data was collected from 15 countries with different lifestyles and diagnostic traditions. In the present study, a limited geographical area with a more homogenous lifestyle has been investigated. The strength of this study is also that three different age groups were reinvestigated after 13 years. The detailed information of the respondents’ entire working life was a solid base for socioeconomic grouping. Smoking habits was reported both at baseline and follow up, but other lifestyle factors were only reported on follow up. This is a weakness as lifestyle may have changed during the observation period. Another methodological problem is that onset of asthma is based on self-reported data with no objective measurements. Self-reported asthma was also shown to be biased in relation to disease severity in a recent Swedish study (Toren, Palmqvist et al. 2006). Subjects with mild asthma were less prone to report disease. The questions used in this study have, however, been evaluated in other studies and have been found to have high specificity for asthma (Toren, Brisman et al. 1993). The prevalence of self-reported doctor-
diagnosed asthma in this study is also similar to other studies in Sweden (Lotvall, Ekerljung et al. 2009), which supports external validation of the results. There are few previous studies of asthma onset in the elderly. Self-reported asthma in this age group could represent COPD, but smoking was not a risk factor for asthma onset in this age group contradicting misclassification.

Cohort studies can be influenced by errors in the selection process and loss of participants during the follow-up. In this study the initial response rate was very high and the risk of selection bias small. The average response rate was 73% in the follow-up study, but only 67% of the original cohort responded to both questionnaires, which could induce bias. The non-responders were more often men, younger and smokers. The non-responders reported significantly less prolonged cough, respiratory symptoms after exposure to air pollutants or having ever been diagnosed with asthma by a doctor. No significant difference was found between the groups regarding asthma heredity, hay fever, asthma symptoms, or asthma medication. Several studies of non-responders in Sweden, Finland and Norway have found that smokers are less likely to respond to questionnaires (Ronmark, Lundqvist et al. 1999; Kotaniemi, Hassi et al. 2001; Brogger, Bakke et al. 2003; Hardie, Bakke et al. 2003). As we found a positive correlation between ever being a smoker and asthma onset in Paper II, we may have underestimated the smoking prevalence. But since the number lost to follow up was low and the response rate was high this type of selection bias probably had no effect on the results.

Another common problem in epidemiological studies is recall bias. The risk for recall bias was reduced by asking for symptoms and exposure for environmental factors in the last 12 months. Another form of information bias is to judge who is responding to the questionnaire. Gender and age at the initial study in 1990 was based on population records. In the follow-up study questions were asked concerning gender and age. About fifty subjects reported a different gender men had become women. The mortality-rate was high in this group. One explanation might be the subject was unhealthy and unable to answer, and therefore a partner or relative answered on his behalf. A total of 84 respondents who reported wrong gender or age were excluded from analysis.

Allergic sensitization and asthma

The main results of paper III indicate that asthmatics sensitized to pets have a more severe outcome than asthmatics not sensitized to pets. Sensitization to pets was also a strong predictor for onset of asthma. Asthmatics with sensitization to pets were more likely to have persistent asthma. Sensitization to pets and self-reported responsiveness to airway irritants were significant determinants of both persistent asthma and onset of asthma. More symptoms
and more medication at baseline were additional risk factors for persistent asthma at the follow-up. We did not find that asthmatics had more pets at home. Nineteen percent reported a cat in the home in 1990 and 22% had a dog, but no significant difference between asthmatics and non-asthmatics was found.

Sensitization to cat allergen is very common in Sweden (Bousquet, Chinn et al. 2007). Cats and dogs, but not mites, were the sensitizing allergens most closely associated with asthma in a study of Swedish adults (Plaschke, Janson et al. 1999). Cat and dog allergens can be found in virtually all homes, but are also found in other settings, such as schools and other public buildings (Patchett, Lewis et al. 1997) and are passively transferred from one environment to another (Almqvist, Wickman et al. 2001). The combination of widespread exposure to pet allergens and high prevalence of allergic sensitization to pet allergens suggests that a substantial proportion of patients with asthma are at risk for cat or dog allergen-induced asthma symptoms. In fact, several studies have directly linked animal allergen exposure to poorer asthma outcomes among animal-sensitized patients with asthma (Munir, Einarsson et al. 1993; Almqvist, Wickman et al. 2001).

The lack of association between asthma and sensitization to mite and pollen was also confirmed in the present study. Due to the cold winter climate in this region, exposure to mite is low and pollen is only a seasonal allergen. The postal questionnaire was carried out in February 1990 and February 2003 and the clinical investigations were performed before and after the pollen season in 1990 and 1991. Perhaps the results would have been different if the study had been performed during the pollen season.

Our results indicate that asthmatics with allergic sensitization are less likely to remit than asthmatics without allergic sensitization. Greater reversibility in FEV₁ has been reported in patients with atopic asthma than in patients with non-atopic asthma in a Danish study (Ulrik, Backer et al. 1992). In the same study, non-atopic asthmatics had a steeper decline in FEV₁ during a follow up of ten years. In a French study, non-allergic asthma was more severe than allergic asthma (Romanet-Manent, Charpin et al. 2002). The discrepancy between the present study and the Danish and French studies regarding the outcome of atopic and non-atopic asthma may reflect differences in the selection of the asthma population. This study was population based. The previous studies were based on asthmatics referred to secondary care at expert clinics. The patients with a history of symptoms indicating allergy might have been referred to an allergy clinic to confirm the allergy, while patients without a history indicating allergy might have been referred if their asthma was more severe or more difficult to treat. Thus, a population based study on the difference in outcome between asthmatics with or without allergic sensitization could provide better information on the natural history of asthma than studies with selected patients attending expert clinics.
A weakness in this study is that weight was not measured at baseline. In a recent cross-sectional study of over 80,000 Canadians, the association between increased BMI and asthma was stronger among non-allergic adults compared with allergic adults especially in women (Chen, Dales et al. 2006). Other studies have confirmed that non-allergic asthma is more common in women (Romanet-Manent, Charpin et al. 2002) and that there is a stronger relationship between obesity and asthma in women. However, we could not confirm any sex differences in the relationship between obesity and asthma in a recently published analysis of our study where we used BMI at follow up (Uddenfeldt, Janson et al. 2010).

In this study we could not show that smoking was a risk factor for persistent asthma. Other studies have demonstrated that tobacco smoking is associated with accelerated decline of lung function in subjects with asthma, that it increases asthma severity, and may render patients less responsive to treatment with inhaled (Chalmers, Macleod et al. 2002) and systemic glucocorticosteroids (Chaudhuri, Livingston et al. 2003). In addition, smoking reduces the likelihood of asthma being controlled (Bateman, Boushey et al. 2004). Although the majority of studies have found an increased asthma severity with smoking, a 9-year prospective study among participants in the European Community found no differences between outcome between smokers and non-smokers (de Marco, Marcon et al. 2006).

**Smoking behaviour and asthma**

The main result of paper IV is that neither allergic sensitization, respiratory symptom score or FEV₁ were associated with being a smoker in 2003. No differences in changing smoking habits could be identified between smokers with or without asthma. This is consistent with the results from a study from California concluding that adults with asthma do not appear to selectively avoid cigarette smoking (Eisner, Yelin et al. 2001). The co-occurrence and interplay between asthma and cigarette smoking is still puzzling. The scientific information has primarily focused on the biological aspects leaving a gap in knowledge of the complete bio-psychosocial perspective (McLeish and Zvolensky 2010).

In the summary of the previously-mentioned review by McLeish it is suggested that smokers with and without asthma may have different risk factors for smoking onset as well as different smoking motives and outcome expectancies. Furthermore it is not known to what extent patients are aware of the specific problems of smoking with asthma beyond the general advice they receive from healthcare providers to quit smoking. Appropriate cessation treatments for asthma patients are lacking. They may need more specialized interventions than the general public (Uddenfeldt 2002). In a recent Swedish study smoking was reported to be a possible risk factor for asthma severity in asthmatics (Stallberg, Lisspers et al. 2007). Current
smoking increased the patients’ risk, of being classified as having severe asthma by 66%. Although asthmatics are reported to suffer from impaired quality of life compared with non-asthmatics (Leander, Cronqvist et al. 2009), the determinants of quality of life remain incompletely understood (Ford, Mannino et al. 2004). Female sex, smoking, respiratory symptom score, atopic status and absenteeism from work and school were associated with low health-related quality of life in asthmatics in a cross-sectional study in this cohort (submitted). Anxiety, socioeconomic status, ethnicity and gender, are related to both smoking and asthma, and these factors may be partially responsible for the observation that smoking and asthma occur together.
Conclusions

- The prevalence of asthma has increased in all age-groups from 1990 to 2003.
- Smoking, BMI, hard physical training and low consumption of fruit and fish are modifiable independent risk factors for onset of asthma.
- Sensitization to pets is a strong predictor for both persistent asthma and onset of asthma.
- Asthma diagnosis and allergic sensitization are not associated with changes in smoking habits.
Perspectives

In five years time we should have sufficient knowledge about risk factors for several asthma phenotypes to begin large-scale preventive studies. The level of knowledge is at present too low to perform such studies.

Preventive measures including regulations will be needed to minimize exposure to environmental tobacco smoke in all ages and all socioeconomical groups. Specific efforts of smoking prevention and cessation should be undertaken to adolescents and adults with asthma.

Preventive measures should also include efforts to maintain body weight within the normal range in adult age. It should include adults who are usually considered to be at low risk for weight gain in order to maintain their body weight over a 10 year period. The importance of preventative efforts for such individuals has not been widely recognized.
Astma är en av våra största folksjukdomar. Orsakerna till den ökade förekomsten av astma är fortfarande inte fullständigt kända. Sjukdomen debuterar i drygt hälften av fallen efter 15 års ålder varför kartläggning av riskfaktorer för vuxendebuterad astma är viktig.

Syftet med denna avhandling var att undersöka förekomsten av astma i tre åldersgrupper 1990 och 2003, samt att studera olika riskfaktorer för utveckling av astma. Ett ytterligare syfte har varit att närmare studera två av de viktigaste riskfaktorerna för astma nämligen allergisk sensibilisering och tobaksrökning.

Avhandlingen presenterar resultat från en långtidsstudie om astma i landskapet Gästrikland och Jämtlands län som påbörjades 1990. Individer i tre åldersgrupper inbjöds till studien (n=12,732); samtliga ungdomar födda 1974, samt ett urval av medelålders (1951-60) och äldre (1931-40). 90 % deltog genom att besvara en postenkät. Utvidgade undersökningar med intervjuer, lungfunktionsundersökningar och allergitester gjordes därefter på de ca 20 % som angivit luftvägssymptom samt kontroller (n=2542). En uppföljning med en ny postenkät gjordes 2003. 67 % (n=7563) besvarade båda enkäterna.

1990 rapporterade 7.2 % i Jämtlands län och 5.8 % i Gästrikland att de hade, eller hade haft, astma. Vid uppföljningen 2003 var astmaprevalensen, med samma definition 17.2 % bland unga vuxna, 11.4 % % bland medelålders och 10.3 % bland de äldsta. Vid studiens start 1990 rapporterade drygt 5 % att de fått diagnosen astma av läkare och att de använde astmamedicin jämfört med 11 % 2003.


Således visar denna avhandling att påverkbara livsstilsfaktorer är av betydelse för vuxendebeuterad astma.
Acknowledgements

I would like to express my sincere gratitude to:

- Anna Rask-Andersen, my supervisor and friend, thank you for reopening the door to research. Your enthusiasm and support made it possible to start and finalize this thesis. You have an incredible capacity to be everywhere and still available when needed.
- Christer Janson, assistant supervisor, for your time and patience, good advice and ideas, constructive discussions, optimism, support and encouragement over many years.
- Dan Norbäck, assistant supervisor for good advice.
- Ellinor Ådelroth, my colleague and good friend, for unhesitating support, constructive criticism and wise down-to-earth comments.
- Erik Lampa, for excellent statistical guidance.
- Lars Larsson, for active participation in the first phases of the study.
- Mai Leander, fellow PhD for collaboration on Health-Related Qualty of Life.
- Marieann Högman, FoU Gävleborg/CFUG for support and for promoting scientific work
- Ulla Waxin, Division of Primary Care Gävleborg for the possibility to finalize this thesis.
- All the members of the team at Björksätra Departement of General Practice and Primary Care for cooperation and support in the daily work.
- Per, my husband and life companion, for love, never ending support and for helping me to see research in perspective.
- Family and friends, for all you mean to me.
- Finally all men and women whom have answered questionnaires and participated in clinical examinations. You have given your valuable time and effort.
References


Kotaniemi, J. T., J. Hassi, et al. (2001). "Does non-responder bias have a significant effect on the results in a postal questionnaire study?" Eur J Epidemiol 17(9): 809-17.


Munir, A. K., R. Einarsson, et al. (1993). "Allergens in school dust. I. The amount of the major cat (Fel d I) and dog (Can f I) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog." *J Allergy Clin Immunol* **91**(5): 1067-74.


Toren, K., M. Palmqvist, et al. (2006). "Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate." J Clin Epidemiol 59(1): 90-3.


Uddenfeldt, M., C. Janson, et al. (2010). "High BMI is related to higher incidence of asthma, while a fish and fruit diet is related to a lower-Results from a long-term follow-up study of three age groups in Sweden." Respir Med.


Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 622

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)