Epidemiological Aspects of Asthma in Primary Care

Special Reference to Prevalence, Clinical Detection and Validation

MIKAEL HASSELGREN
Dissertation presented at Uppsala University to be publicly examined in Rudbeckssalen, Rudbeckslaboratoriet, Uppsala, Friday, December 9, 2005 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English.

**Abstract**


Objectives. To describe the prevalence of asthma in a mid-Swedish region and measure the detection rate of asthma in primary care. To compare clinical outcomes for adolescents with asthma in primary care or in paediatric care and to perform a clinical validation in children with airway, nose and skin symptoms.

Material and methods. A questionnaire survey of respiratory symptoms and disease in an adult population and an investigation of the occurrence of clinically detected asthma in primary care. A cross-sectional study comparing management, asthma control and quality of life in adolescents. The last study was a nested case-control study with a clinical validation of reported allergic symptoms in children.

Results. The prevalence of asthma in the adult population was 8%. The clinical prevalence of asthma in primary care was 2%. The detection rate was higher in primary health care centres with asthma clinics, as compared to primary care without such clinics. In adolescents with asthma there was no difference in clinical outcomes between primary care and paediatric care. The validation study showed a high correlation between assigned cases and disease.

Conclusions. Asthma is a common disease where the majority of cases are managed in primary care. Many cases are, however, not diagnosed and the detection rate becomes a quality care indicator. The study of adolescents confirms that proactive care can be further improved regardless of whether their management is in primary or paediatric care. The nested case-control design is suitable to suggest causational risk factors for asthma and for prediction of allergic disease development.

**Keywords:** Adult, Adolescent, Asthma, Case-Control Studies, Causality, Child, Cross-Sectional Studies, Diagnosis Computer-Assisted, Epidemiology, Prevalence, Primary Health Care, Validation Studies

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List of Papers

This thesis is based on the following papers, referred to in the text by their Roman numerals.


II  Mikael Hasselgren, Mats Arne, Gunnar Johansson. Primary care based asthma clinics improves detection of asthma and COPD in the population. Submitted.


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### Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACG</td>
<td>Adjusted Clinical Groups</td>
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<tr>
<td>ARIA</td>
<td>Allergic Rhinitis and its Impact on Asthma</td>
</tr>
<tr>
<td>BHR</td>
<td>Bronchial Hyperresponsiveness</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIA</td>
<td>Confidence Interval Analysis, Software program</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>EBM</td>
<td>Evidence Based Medicine</td>
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<tr>
<td>ECRHS</td>
<td>European Community Respiratory Health Survey</td>
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<tr>
<td>FEV(_1)</td>
<td>Forced Expiratory Volume in One Second</td>
</tr>
<tr>
<td>GINA</td>
<td>Global Initiative on Asthma</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Disease, tenth revision</td>
</tr>
<tr>
<td>ICPC</td>
<td>International Classification of Primary Care</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled Glucocorticosteroids</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin, class E</td>
</tr>
<tr>
<td>IPAG</td>
<td>International Primary Care Airways Group</td>
</tr>
<tr>
<td>ISAAC</td>
<td>The International Study of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>OLIN</td>
<td>Obstructive Lung disease in Northern Sweden Study</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak Expiratory Flow</td>
</tr>
<tr>
<td>PHCCs</td>
<td>Primary Health Care Centres</td>
</tr>
<tr>
<td>SABA</td>
<td>Short Acting Beta Two Agonist or Reliever Medications</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>VC</td>
<td>Vital Capacity</td>
</tr>
<tr>
<td>WONCA</td>
<td>World Organisation of Family Doctors</td>
</tr>
<tr>
<td>WQ</td>
<td>Written Questionnaires</td>
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</table>
Foreword

This work came into being thanks to a combination of fortunate opportunities in my professional life, a caring and supportive family, tutors, friends and colleagues. In a time perspective, this thesis can also be described as a roller coaster of ups and downs propelled by clinical labor and intellectual struggles.

There are three themes in this thesis: asthma, primary care and epidemiology, each with its own complexity. Asthma is a chronic disease of the airways with variable severity and prognosis at different ages and in the two sexes. Primary care has a general first line population-based, unselected approach and interfaces with almost every part of society. It is, however, different in different counties, in organizational respects. Epidemiology is both a general method for many types of studies and a highly specialized discipline of its own. There are two fundamental ideas in epidemiology, the methodological issues related to study design and the identification of causal pathways [1].

This work concerned two broad questions. First, if asthma is as common as claimed in prevalence studies why does not primary care manage more patients with asthma? To assess if asthma is a common disease in Värmland required doing prevalence measurement in the adult population with clinical validation. To evaluate asthma management, all primary health care centers in the Uppsala-Örebro region were surveyed. The second question is why asthma has become such a common public health disorder. This involved studying children with asthma and possible causal factors in the indoor environment.

This thesis applies two macro-perspectives on asthma care: the epidemiological and the clinical perspectives. These views are verbalized in two mottos. One from the University of Copenhagen “Coelestem Adspicit Lusem” – it looks at the heavenly light, where “it” refers to an eagle in the coat of arms. The other motto is from the University of Aarhus “Solidum Petid in Profundis” – seek a firm footing in the depths, symbolised by two dolphins. I hope this thesis both sheds some light on and gives a foothold regarding asthma in primary care.
Introduction

Asthma

Asthma is a common disease worldwide, with a heavy burden on society in terms of both direct and indirect health care costs [2, 3]. Asthma is prevalent in all age groups, in women and in men and in all types of societies, although there are major regional variations in occurrence. Asthma prevalence in Western Europe has doubled in the last ten years [4, 5] and there is a great deal of data in support of an increasing prevalence in many other parts of the world as well [6-8]. However, recent studies suggest a levelling out or even decrease in prevalence among children and young adults [9-12]. The fundamental causes of asthma and its changing prevalence are not known. In the last few decades there have been improvements in medical treatment and changes in management of the disease.

History of Asthma

The Greek word asthma (ασθμα) is derived from the verb aazein, meaning to breathe with an open mouth or to pant [13]. Asthma has often been used as a symptom, intermediate between orthopnoea and dyspnoea. The first known description of a patient with the typical symptoms dates back to a classic text from of ancient China, the Nei Ching, and the third mythical yellow Emperor Huang Ti (2698-2598 B.C.) [14].

The first epidemiological observation on causes to asthma was described by Aurelianus Caelius, a Roman physician who supposedly practiced about 200-300 A.D. [15]. He described that asthma was more common in the winter than in the summer and more at night than in the day. The first written account on the treatment of asthma was from the Jewish physician, Moses Maimonides (1135-1204) who worked as a court physician of Sultan Saladin. He gave advice on treatment through diet, self-conduct and a clean environment [15].

The connection between allergic asthma and occupational hazard was first described by the Italian physician Bernadino Ramazzini (1633-1714), in his work on occupational medicine De Morbis Artificum in 1713. It contained a description of what happened in bakers and millers when they inhale particles of flour.
Autopsies were forbidden for centuries and it was not until the beginning of the 19th century that a German physician, F.D. Reisseisen, demonstrated that there were circular muscles in the bronchi. He postulated that if the muscles contracted it would cause obstruction and asthma. In 1835, French scientist A. Lefevre found obstruction of mucus in the bronchii at autopsy [15]. The debate between mucus theorists and spasm theorists regarding what was the primary clinical manifestation of asthma continued into the 20th century.

Asthma pathophysiology
In hindsight it is clear that both theories were right. Asthma is both a neurological/muscular and an inflammatory/mucosal disease. According to a modern definition, asthma is an inflammatory disorder of the airways which causes recurring episodes of wheezing, breathlessness, and coughing [16].

Asthma is triggered either by allergic or non-allergic factors. In children allergic asthma dominates, and it is also common in adults. Allergic asthma is often linked to conditions like atopic eczema and allergic rhinitis [17, 18]. Allergic rhinitis and allergic asthma can be regarded as different manifestations of the same disease entity [19].

Asthma is a chronic condition, although intermissions and even complete remission are possible [20]. Both the incidence and remission rate is higher in children than in adults [21]. The definition of asthma is complex since it has variable symptoms, grades of severity, and different presentations in various age groups and cannot be assessed in relation to gold standard [22].

Asthma diagnosis and management
In modern medicine it is important to follow practice guidelines when trying to achieve treatment results. In evidence based medicine (EBM), the best possible research results are fit into well formulated guidelines. There are several sets of EBM guidelines with implication for asthma, for instance the Global Initiative for Asthma (GINA) [16] and Allergic Rhinitis and its Impact on Asthma (ARIA) [23].

One recent contribution is Chronic Airways Diseases - A Guide for Primary Care Physicians, from the International Primary Care Airways Group [24]. The latter has made great efforts to combine various guidelines into one with a primary care and an age perspective. The epidemiology of asthma is strongly correlated with age; and thus separating the general practice population into different subgroups based on age provides a practical approach to diagnosis.

In children under six years of age it is primarily a diagnosis of exclusion. The cardinal symptom is wheezing, but viral infections in children of this age may also cause wheezing. The younger the child, the likelihood that
wheezing is not caused by asthma increase [25]. Children who wheeze may either have a transient form or a persistent form [26]. The latter in combination with sensitisation to airborne allergens is highly predictive of future asthma [20, 27].

In children aged 6–14, asthma and allergic rhinitis are predominant airways diseases. Any patient with allergic rhinitis should also be evaluated for asthma, and vice versa. In adults aged 15–39, asthma and allergic rhinitis remain common airway diseases. In adults age 40 and over, Chronic Obstructive Pulmonary Disease (COPD) is the predominant chronic airways disease. Asthma is also prevalent in the elderly although presentation may be less pronounced and confounded by comorbidity [28].

In children under six, treatment is also a part of the diagnostic test, since improvement increases the likelihood of an asthma diagnosis. Not all children who wheeze when infected will develop asthma that persists throughout childhood, so discontinuation of medication may be warranted [29]. As the child gets older, additional diagnostic investigations may be performed to confirm or exclude the asthma diagnosis.

Lung function tests can be performed in children over five or six years of age [30]. Sometimes testing in younger children [31] has also been done. Tests such as peak expiratory flow (PEF) and spirometry can demonstrate variable and reversible airflow limitation. Measurement of allergen-specific immunoglobulins, class E (IgE) in serum or allergy skin testing confirms the presence of allergic disease which, in this age group, is a predominant trigger. In adults over 40 spirometry is particularly important in order to distinguish asthma from COPD [32].

It is important to assess asthma severity in all age groups since severity guide treatment. Asthma should be classified as intermittent, mild persistent, moderate persistent, or severe persistent based on the combined assessment of symptoms and lung function tests. Periodically, however, anyone’s asthma may be exacerbated. Such asthma attacks are episodes with progressive increases in shortness of breath, cough, wheezing, or chest tightness, or a combination of these symptoms.

According to the guidelines, asthma should be treated in a stepwise manner based on the severity of the disease. The number of drugs and the frequency of medications are increased with severity, and are decreased when the asthma is under control [16, 33]. Inhaled glucocorticosteroids (ICS) are the first line controller medication to affect the inflammation. Bronchodilators relieve the muscular contraction.

The treatment arsenal has become more effective. The contemporary medical treatment is characterised by local treatment with the lowest effective dose and the development of specific drugs addressing the various manifestations of asthma. This approach has been successful in controlling but not in curing asthma. Proper medical management has the potential to lessen the patient’s personal burden from asthma [34].
Primary care

Primary care supplies the basic medical treatments, proactive care and rehabilitation to the whole population. It has been defined in many different ways but some key characteristics are accessibility to the whole population, not limited to certain ages or conditions [35]. It should be able to provide good quality health service to satisfy the population’s basic medical needs and concerns [36]. Apart from providing accessible and comprehensive care, it should also be co-ordinated with other levels of health care.

Primary care has two distinguishing features; watchful waiting and referral [37]. Watchful waiting – not having to embark on an immediate line of action – is a consequence of the fact that many diseases come and go. Patients consult primary care in the course of a condition when the first symptoms but no other clinical manifestations are at hand, or for worries about diseases that will not be confirmed. Referral can follow recommendations or local traditions as well as the individual physician’s competence in diagnostics and treatment of various disorders. A referral may not be definite, sometimes a concept of shared care is used in chronic conditions such as asthma and diabetes [38] (Paper II).

In Sweden, since the 1960s paediatric specialists have been working in ambulatory settings, often located close to or inside a primary health care centre. These paediatricians do not deliver primary care since their services are not available to all patients and age restricted, but should according to Swedish guidelines provide care for children with asthma [39].

General Practitioners

The history of Swedish primary care started with the GPs and midwives in the 17th century. Physicians were appointed by the King, to report on the health status of the population and to provide medical services at low costs [40]. The county councils were established in 1860 mainly to administer the hospitals. After the Second World War primary care started to organise prophylactic child health and special care for the elderly. Midwives and district nurses were employed, and this laid the foundation for primary health care centres (PHCCs).

The increase in hospitals and the setting up of specialised hospital doctors made recruitment to posts as GPs more difficult [41]. The work in itself was strenuous as described by Dr. Märta Palmborg, who worked in Värmlands Nysäter [42]. To alleviate the solitary situation of physicians, group practices were introduced and more district nurses employed. In 1963 the county councils took over primary care. In the 1970s the PHCCs were large, and organised like small hospitals with wards and various specialist outpatient clinics, for instance paediatric care. In the 1980s, the new PHCCs were made
smaller, three to five GPs working in teams with nurses, physiotherapists and welfare officers [41].

The Swedish health care system has undergone major structural transformations since the late 1980s owing to the poor growth rate of the economy and demographic changes [43]. The proportion of the Gross National Product (GNP) spent on health care was 9.1% in 1984, and declined to 7.5% by 2000 [1]. There is a trend for primary care to be taking increasing responsibility for management of the majority of patients with chronic diseases, although the time for such managements is scarce [44], it decreases hospital admissions [45].

Research in Primary Care

By applying Thomas Kuhns idea of a paradigm – an overall way of regarding phenomena within which scientists normally work – medical research can be divided into three paradigms: The pre-clinical, the clinical and the public health paradigms. Primary care research encompasses both the clinical and the public health paradigms. In the 1980s Swedish general practice also became an academic discipline [41]. The first professors of general practice took up their chairs in 1982, and the first dissertation was defended in 1985 at Uppsala University [46].

Primary care based asthma clinics

Most patients with asthma can be managed in primary care, while specialist care is only necessary for certain patients [47]. In countries with strong primary care such as the UK and the Netherlands almost all persons with asthma are managed in primary care as compared to Sweden with about 60–75%, depending on how managed is defined [24, 48]. Some patients will attend several care givers at need in both primary and secondary care. Others have shared care, both in primary and secondary care and there are probably different interpretations of which level of care is the main provider.

Another reason for there being proportionally fewer asthma patients in Swedish primary care is that children in Sweden are treated by paediatricians [49]. There are Swedish recommendations for treatment by age group in paediatric and primary care: preschool children, 0–6 years should be in paediatric care, schoolchildren, 7–12 years in either, and adolescents 13–19 years mainly in primary care [39]. Some patients continue to attend paediatric care into adolescence, but after 19 years of age referral to primary care, or for some people secondary care, is warranted.

In the UK, primary care based asthma clinics were set up in the 1980s and 1990s [50]. Such asthma clinics have also gained some but not dominant prominence in Australian [51] and Swedish primary care [52, 53]. These clinics have been considered resource effective, and have improved outcome
in uncontrolled before-and-after studies [54, 55]. It has, however, been difficult to confirm reduced asthma morbidity in population based organisational interventions [56] or effectiveness of asthma clinics in randomised controlled trials [51, 57].

The first primary care based asthma clinic opened in Sweden in 1987. Ten years later the Swedish Respiratory Group in Primary Care, within the Swedish Association for General Practice (SFAM) found it appropriate to define what was meant by a primary care based asthma clinic and introduced the following criteria for a complete primary care-based asthma clinic [58]:

1. Availability of a nurse trained in asthma management and treatment.
2. GP responsible for the asthma clinic.
3. Access to a spirometer in the clinic.
4. Investigations according to guidelines.
5. Patient education according to guidelines.
6. Scheduled surgery for the asthma nurse.
7. A minimum of 0.5 hours per week per 1000 residents is allocated for the asthma nurse.

Clinical Detection

One of the characteristics of general practice is that it: “has a specific decision making process determined by the prevalence and incidence of illness in the community” [35]. Diagnostic coding for asthma and COPD might be regarded as a measurable endpoint or an outcome in the decision making process.

The ideal clinical diagnosis of asthma would be based on observations of unambiguous biological phenomena [59]. In reality, diagnosis is less precise, being defined to finding groups of patients who have some common features [60]. Since there is no such gold standard for diagnosing asthma the true asthma prevalence will never be found because of there being different interpretations of the diagnostic criteria. It is estimated that 25–50% of patients with obstructive lung disease, are known to their GPs [61, 62]. This under presentation might be explained by peoples adaptation to symptoms and their not seeking care, or to the GPs not being aware of their symptoms [61].

Almost all Swedish PHCCs use electronic medical records, and GPs are accustomed to using the ICD-10 codes. Swedish primary care should, but is not obligated to, classify the main reason of consultation with these codes. Other countries like the Netherlands and Norway have made the International classification of Primary care (ICPC) their official coding system. The ICPC is better adapted to primary care than ICD [63] and it is the coding system officially recommended by WONCA. It is also accepted by the WHO. These two coding systems are, however, interchangeable. In the UK a different types of codes, called Read codes are used. Many times compari-
sons of aggregated data as in the Adjusted Clinical Groups (ACG) is useful [36, 64]. This allows for comparisons between different systems and also acknowledged that co-morbidity, that patients often have more than one disease, is common in primary care.

Electronic informatics in primary care has turned into a discipline of its own, also in scientific research [65]. One of the most useful applications in this context is the possibility to use electronic records, and codes as outcomes in measuring clinical incidence and prevalence [64, 66, 67].

It is essential to understand that the diagnostic/consultations codes are not only registered at the time of first diagnosis but on every visit related to that disease. If codes from the first diagnosis of a condition are retracted they estimate incidence [68]. If diagnostic codes used upon consultation, i.e. consultation codes they can be used to estimate clinical prevalence. Clinical detection in this thesis refers to the rate of clinical prevalence to epidemiological prevalence.

**Epidemiology**

Epidemiology studies health and diseases on a population level. Epidemiology is a part of social sciences, referred to as public health epidemiology [69]. It is also a branch of medical science, sometimes referred to as clinical epidemiology. There are two fundamental ideas in epidemiology, the methodological issues related to study design and the identification of causal pathways [1]. These ideas will be discussed under the headings asthma prevalence and causal pathways under asthma aetiology. One common method for all epidemiology is the use of statistics.

Statistics is the science of collecting, summarizing, and analysing data that are subject to random variations [70]. To analyse data, to draw inferences, statistical test are used to pick out the patterns that are not likely to be coincidental and to prevent overinterpreting randomness as patterns [71]. But there is no single truth of inference, as exemplified by the asthma death epidemic in New Zealand. In figures and charts it was pointed out that people with asthma would die from their reliever medication [72]. However, another statistical regression analysis contradicted this view, revealing a stronger correlation to non-ICS use, which is biologically a more plausible cause of death [73].

**Asthma prevalence**

In cross-sectional prevalence studies, asthma has commonly been defined in two different ways: 1) Self-reported asthma, i.e. asthma symptoms sometimes combined with clinical validation [74] and 2) Bronchial Hyper-responsiveness (BHR), a measure of the concentration of stimuli such as
methacholine or dry air that provoke a reaction in the lungs [75]. Asthma can also be defined in a pragmatic way by combining symptoms and measuring actual consequences of asthma such as medication use [76].

None of these methods corresponds perfectly to a clinical definition of asthma. In epidemiology, questionnaires such as the International Study of Asthma and Allergies in childhood (ISAAC) written questionnaires (WQ) [77] and the parental ISAAC WQ [78] are used in school and preschool children respectively. For young adults the European Community Respiratory Health Survey (ECRHS) [79], or the Obstructive Lung disease in Northern Sweden Study (OLIN) questionnaire [80] for adults, are preferred. They better enables comparisons of differences in prevalence than BHR [81]. Table 1 illustrate studies with validated WQs in the Uppsala–Örebro region with an indication of a temporal increase.

Some of the main indicators of asthma are wheezing, whistling, chest tightness, cough, dyspnoea, self reported asthma and asthma treatment [74]. But even in validated WQs there are different wordings and language differences which hamper comparison of, for example wheezing, which is a cardinal symptom of asthma.

Many languages, like Swedish, do not have a colloquial term for wheezing. The word wheeze stems from Old Norse “Hvæsa”, meaning a hissing sound which is still the meaning in the Scandinavian languages, but the word is not used to describe the physical symptom [82]. Thus wheezing has to be translated into a description – a whistling sound from the chest, and some studies even use a video to demonstrate the symptom [83].

Population prevalence estimates measured with the same method still vary geographically, with a pattern that is fairly consistent [2] for both children [77] and young adults [4]. It is possible that this approach, to compare disease rates and exposure levels among populations could provide clues as to the causes of asthma. There are also temporal changes in prevalence estimates [12]. There was an increase in asthma prevalence over time in recent decades, but current data now suggest a levelling off [10, 11, 84, 85]. Thus prevalences estimation must be judged locally and be reasonably recent in time.
Table 1. Cross-sectional asthma studies in the Uppsala-Örebro region during 1989-2004 with validated questionnaires: ISAAC for children, ECRHS for young adults and the Swedish OLIN questionnaire for adults. The year marks when the study was performed and prevalence is given with a 95 percent confidence interval (95% CI)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>County/Method</th>
<th>Age intervals</th>
<th>Population sample</th>
<th>Response rate (%)</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larsson [86]</td>
<td>1989</td>
<td>Gävleborg/OLIN</td>
<td>16</td>
<td>1848</td>
<td>89</td>
<td>6.1&lt;sup&gt;a&lt;/sup&gt; (4.9-7.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30–39</td>
<td>2542</td>
<td>84</td>
<td>6.3&lt;sup&gt;a&lt;/sup&gt; (5.3-7.3)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>60–69</td>
<td>6466</td>
<td>88</td>
<td>5.5&lt;sup&gt;a&lt;/sup&gt; (4.3-6.7)</td>
</tr>
<tr>
<td>Björnsson [87]</td>
<td>1990</td>
<td>Uppsala/ECRHS</td>
<td>20–44</td>
<td>3600</td>
<td>87</td>
<td>5.9&lt;sup&gt;a&lt;/sup&gt; (5.1-6.8)</td>
</tr>
<tr>
<td>Hasselgren [48]</td>
<td>1995</td>
<td>Värmland/OLIN</td>
<td>18–70</td>
<td>5949</td>
<td>81</td>
<td>8.2&lt;sup&gt;a&lt;/sup&gt; (7.4-8.9)</td>
</tr>
<tr>
<td>Larsson [88]</td>
<td>1996</td>
<td>Örebro/OLIN</td>
<td>15–69</td>
<td>8008</td>
<td>84</td>
<td>6.7&lt;sup&gt;b&lt;/sup&gt; (6.1-7.3)</td>
</tr>
<tr>
<td>Uddenfeldt&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2003</td>
<td>Gävleborg/OLIN</td>
<td>29</td>
<td>2196</td>
<td>73</td>
<td>15.7 (14.3-17.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>43–52</td>
<td>3573</td>
<td>73</td>
<td>9.5 (8.8-10.7)</td>
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<td></td>
<td></td>
<td></td>
<td>73–82</td>
<td>2306</td>
<td>73</td>
<td>10.3 (9.1-11.6)</td>
</tr>
<tr>
<td>Lembke [89]</td>
<td>2003</td>
<td>Uppsala/ECRHS</td>
<td>19–65</td>
<td>2900</td>
<td>64</td>
<td>7.3&lt;sup&gt;b&lt;/sup&gt; (6.2-8.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> With clinical validation and a period prevalence of one year.
<sup>b</sup> Without clinical validation, period prevalence of one year.
<sup>c</sup> Personal communication Dr Monica Uddenfeldt, response to “if asthma ever”.

Figure 1 demonstrates previously unpublished data from the Dampness in Buildings and Health Study (DBH) with ISAAC question on asthma ever, and the public health survey, Life and Health, with a positive response to the question “Have you had any of the listed chronic conditions (asthma yes) in the last year” [90, 91]. Asthma was found to be more common in young boys than in young girls, but this relationship was reversed after adolescence, consistent with other studies [92]. In people over 40, the asthma prevalence is likely to be in part attributable to the prevalence of COPD. The figure also illustrates the minor geographical differences in five of the seven counties in the Uppsala–Örebro region.
Figure 1. Prevalence of asthma in the Uppsala-Örebro region: in women and in men. The width is the age span, the bars the 95% confidence interval. The table shows the total prevalence and the minor differences between counties in the region.

### Asthma burden

With these prevalence estimates and the knowledge of management in primary care, it is possible to calculate the burden of asthma in an average Swedish county, figure 2. The calculation assumes that a county has 250,000 inhabitants and that the average life span is 80 years. The symptom wheezing is age dependent, and this accounted for in the calculations. In the DBH study 19% of children aged 1–6 reported wheezing in the last year [93]. In school children in northern Sweden 11% reported wheezing [94]. In adolescents and adults about 9% reported wheezing in the last year [48, 95]. The current asthma prevalence was about 5% in preschool children [96], 6% in schoolchildren, and 8% adolescents and adults.
On the basis of these estimates of asthma occurrence, it is possible to calculate primary care contact for adults and children. Of the adults with asthma, 60% have their main contact with primary care (Paper I). Almost all pre-school children with asthma are in paediatric care, as well as half of all children between 7 and 14 and about 20% of young people between 15-18 years (Paper III).

Hospital admission rates for asthma have decreased especially for children in Sweden [97] and Norway [98]. This may be thanks to better medicines, but there have also been changes in organisation, with primary care taking increasingly more responsibility for management of several chronic diseases [45]. The hospitalisation figure of 150 is taken from the National Board of Health register of causes for hospitalisation. Asthma mortality in Sweden has declined to low levels in an international comparison, which also may be thanks to the widespread use of ICS [2]. The current Swedish asthma mortality rate is about 2 per 100,000 inhabitants and year.

Figure 2. The asthma burden during one year in an average Swedish county. The five at the top is the expected mortality rate from asthma.
Asthma aetiology

The first main idea of epidemiology concerns methods, the second idea is to suggest causal pathways. Causality is of special interest since asthma has become an increasingly common disease in the last 40 years. It must, however, be acknowledged that increased public awareness of asthma, thanks to information campaigns, may have affected prevalences. Parents are more willing to accept a label of asthma for their child. Physicians find it wise to give early and specific anti-asthma treatment, and to label patients even with mild disease as having asthma [99]. Therefore, some of the increase in prevalence can be explained in terms of information bias [100].

However there are also many studies that establish a real increase in asthma, on the basis of validated questionnaire and repeated measurements [5]. Examples include national studies in Australia [101], Norway [102], Finland [103], Italy [85], Scotland [104] and different areas and age groups in Sweden [105, 106]. But the most convincing evidence of a real increase is derived from large international studies using the same validated methods for children [107] and adults [4].

Another problem in asthma aetiology is that asthma is not one disease, but rather a symptom complex [25]. Different models of causation might be present for different kinds of asthma. The general thought is that there is a web of causation including aspects of the social environment and individual susceptibility.

A genetic link to asthma with, strong candidate genes, has been identified [108]. Although the role of the phenotype is strong, the majority of children that will develop asthma are born in families without any manifestation of asthma [109]. The relationship between the genotype and the phenotype of asthma is complex; there are a number of factors affecting the expression of the genotype in what is called epigenetics [110]. One such complexity is that even though a cause of asthma may be present, such as sensitization to specific IgE, there may be no penetrance. Some causes are associated with other diseases as well, such as allergic rhinitis. Asthma might also need several causes to develop, having “aetiologic heterogeneity” [36].

Although it is unlikely that a genetic change can explain the increase since such changes evolve slowly, suggestions of a dramatic genetic shift have been proposed. In this hypothesis, atopic constitution was advantageous in defending the body against severe viral infection, such as the Spanish influenza of early 20th century [111]. The increase in allergic disease and asthma would, therefore, be an effect of the survival of the fittest.

In spite of the fact that the genetics of asthma probably does not explain the increase in asthma prevalence, it could set an upper limit for the number of affected cases. Current data suggesting a levelling of the prevalence [10, 112], which could mean that the phenotype limit for the genotype of asthma
has been reached. However, this levelling off or decrease could just as easily attributable to improved treatment [84] or changes in the environment [113].

The hygiene hypothesis postulates that the increase in allergic disease and allergic asthma is attributable to a reversed contagion theory, which claims that infectious agents are essential to us, in order to teach our maturing immune systems to react normally. This hypothesis originated a decade ago from the epidemiological observation of an inverse correlation between family size and the prevalence of allergic rhinitis [114]. The hypothesis was strengthened by the T-helper paradigm of adaptive immune response although this model is regarded today as overly simplistic [115, 116]. At first, the focus on this theory was on the idea that respiratory infection could protect us. In recent years the focus has changed to the intestinal flora and a possible role of bacteria. Such probiotics could teach the body immune defence in the first few years of life, so that we react in a non-allergic way [117, 118]. This hypothesis is still evolving and might provide clues to what causes allergic disease as well as possible evolving into a unified theory including causes of autoimmune diseases [116, 119].

The question of whether early life exposure to farm environments is protective against development of asthma, by inducing tolerance is related to the hygiene hypothesis [120, 121]. The scientific literature is inconclusive regarding the possible protective effect of pets [122, 123]. This effect could also be explained by a “healthy pet keeping effect” [124], of families without allergic disease more easily have pets with a false association in cross-sectional studies. There are practical complications in this issue since families with manifest allergic disease sometimes misinterpret a possible primary prevention effect, and obtain pets, which cause undesired exacerbations of symptoms. In children with clinical allergy, it is more relevant to decrease the load of allergens in the environment [125].

Major lifestyle changes have been seen in Western societies since the end of World War II. There are many potential exposure candidates that could induce or augment asthma. Smoking is one such candidate, with a temporal trend similar to that of asthma prevalence. However, studies on smoking as a cause of asthma are inconsistent, partly owing to methodological problems like “the healthy smoker effect” as well as reluctance on the part of physicians to classify someone who smokes as having asthma. A recent longitudinal community survey with high response rate found a high smoking load is a probably risk factor for asthma. It certainly causes exacerbations of existing asthma, which adds to the already numerous arguments against smoking [126].

There are also iatrogenic possibilities, i.e. that the treatment in itself causes the asthma. Vaccinations has been proposed as an iatrogenic factor, but this ideas has basically been rejected [74]. Paracetamol given to pregnant women has also been put forward as a candidate [127, 128] as have antibiotics [129]. The problem of medication lies in temporality, what comes first,
and the possibility of reversed causation. For instance, are antibiotics given to someone because misinterpretation of asthma symptoms as pneumonia or is asthma caused by the antibiotics, which negatively affect the intestinal flora, in line with the hygiene hypothesis. These two possibilities are still under discussion [130], and the antibiotics question will be further assessed in the case-control part of the DBH study (Paper IV).

Another candidate is the outdoor environment, in particular particles from diesel engines [131]. But the impact of outdoor factors is not likely to be strong [132]. The indoor environment is emerging as a potentially stronger causal source of asthma and allergies. Several reviews have point out a relationship between dampness and symptoms [133]. Specific causative agents have, however been more difficult to find, although this was the main aim of the DBH study [93]. One such relatively new, possible causative agent is phthalates, softeners in plasticisers [90].

There is no claim that any of these potential agents are mutually exclusive. Like the debate between mucus theorists and spasm theorists in the past, there may be several causative factors.
Aims of the study

One general aim was to describe the age related aspects of asthma epidemiology in children, adolescents and adults. Another aim was to describe asthma prevalence estimates in a methodological context. Another contextual issue is the setting in which the prevalence is presented, the general population or primary care. A third general aim was to discuss causal inference and problems of validity between written questionnaires and clinical disease on the basis of a case-control study.

The more specific aims of this thesis were:

1. to investigate the prevalence of asthma in a representable sample of the adult population,
2. to investigate the ecology of care for asthma in primary health care,
3. to evaluate whether primary care based asthma clinics affect detection rates of asthma,
4. to evaluate paediatric care as compared with primary health care concerning process and outcome measures for adolescents with asthma,
5. to evaluate whether a written parental questionnaire can identify clinically relevant asthma and allergic diseases and distinguish between cases and healthy controls.
Material and Methods

This thesis contains four different epidemiological studies. In addition, data from four adjacent studies which make important contributions are illustrated in figure 3 and table 2.

The OLV Study

Paper I

The Obstructive Lung Disease in Värmland Study (OLIV) was a population based cross-sectional study among adults. This two-stage study involved a WQ in the spring of 1995 and clinical examinations within a year. Our study base was adults, 18–70 years of age, corresponding to 184,572 individuals persons from among whom a random sample of 5949 people was selected. The WQ used had previously been validated [105], but we added one question on health care visits in the previous two years. Non-respondents received two reminders. The final response rate was 80.9%, corresponding to 4814 individuals. Of non-respondents 50 persons were selected randomly and asked to participate in a telephone interview. Forty-nine of them responded positively, giving us the opportunity to estimate possible differences between respondents and non-respondents.

Of those who stated respiratory symptoms in the WQ, 300 were randomised and invited for a clinical examination. At these validating examinations, 206 participated in a structured interview, as well as standardised spirometry in accordance with the OLIN study methods [105]. Normal values for spirometry and criteria for reversibility were used, from the European Respiratory Society [134].

In the validation study a single diagnosis was used, asthma had priority over COPD if both definitions were upheld. Asthma was defined using five criteria: recurrent wheeze, recurrent shortness of breath, normal breathing between obstructive attacks, and two exacerbating factors (excluding infections and effort), and they had to be current, i.e. within a two-year period. The asthma diagnosis was also confirmed if a person had four of the five criteria plus significant reversibility or regular asthma medication.
Figure 3. The papers in this thesis with adjacent contributing studies. C-S cross-sectional, C-C case-control, WQ- written questionnaire.

A COPD diagnosis required a measurable airway obstruction, FEV₁ < 80% of predicted and FEV₁/VC ratio < 70%, without significant reversibility, according to the guidelines [135]. In addition, symptoms such as wheeze, constant shortness of breath and/or longstanding cough were required [86]. Chronic bronchitis required normal lung function, productive cough during two periods of three months in two consecutive years, and asthma/COPD were excluded.

The AIM Study

Paper II and III were a part of Asthma in mid-Sweden Study (AIM). This study has two steps, firstly a descriptive part on organisation of care in the Uppsala-Örebro region [52], and secondly a patient survey [49].

The first step was conducted in the year 2000 in a population of 1.9 million. Two hundred and thirty-eight primary health care centres (PHCCs) were categorised according to type of primary care based asthma clinic. They either had a complete asthma clinic (16%), an incomplete asthma clinic (37%) or no asthma clinic (47%). Swedish criteria for complete asthma clinic have been described previously. For this study, a complete asthma clinic was also to have been operational for more than one year.

Paper II

The aim of Paper II was to evaluate whether primary care based clinics facilitate detection of asthma in the population. Since only one of the PHCCs with a catchment area fewer than 3000 had an asthma clinic, this group did
Table 2. Baseline characteristics for the different studies in the thesis. Primary health care centres (PHCCs), Written Questionnaire (WQ)

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method</strong></td>
<td>Cross-Sectional WQ with clinical validation</td>
<td>Cross-Sectional WQ and electronic records</td>
<td>Cross-Sectional WQs</td>
<td>Case-Control with clinical validation</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Adults in Värmland</td>
<td>PHCCs in the Uppsala-Örebro region</td>
<td>PHCCs and paediatric ambulatory care</td>
<td>Children in Värmland</td>
</tr>
<tr>
<td><strong>Population sample</strong></td>
<td>5449 adults</td>
<td>214 PHCCs</td>
<td>238 PHCCs</td>
<td>Nested from 10,853 WQ answers</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>4814 responders</td>
<td>113 ICD codes</td>
<td>320 adolescents</td>
<td>400 children</td>
</tr>
<tr>
<td><strong>Response rate</strong></td>
<td>89.9%</td>
<td>81.9%</td>
<td>52.3%</td>
<td>77%</td>
</tr>
<tr>
<td><strong>Main outcomes</strong></td>
<td>Prevalence of asthma and COPD</td>
<td>ICD coded asthma and COPD</td>
<td>Management Asthma control Quality of life</td>
<td>Verified asthma, rhinoconjuntivitis and eczema.</td>
</tr>
<tr>
<td><strong>Ages</strong></td>
<td>18-70 years</td>
<td>0-99 years</td>
<td>15-18 years</td>
<td>3-8 years</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Women 49.9%</td>
<td>–</td>
<td>Women 58.4%</td>
<td>Girls 43.2%</td>
</tr>
<tr>
<td><strong>Statistics</strong></td>
<td>Student’s t-test Chi-square test</td>
<td>Kruskal-Wallis Chi-square test</td>
<td>Student’s t-test Z-test</td>
<td>Student’s t-test Chi-square test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Linear regression</td>
<td></td>
</tr>
</tbody>
</table>

not allow for comparisons. There were 216 PHCCs with catchment areas over 3000 inhabitants. They all received questionnaires concerning structure and process measurements according to the nomenclature for evaluating the quality of medical care [136].

The outcome measure was the number of consultation codes for asthma or COPD during the years 2000 and 2001 as a measure of clinical prevalence. Each patient could only report such a code once in the study period. The PHCCs were instructed how to extract the information from their own electronic records. In two counties, Dalarna and Örebro, data from central servers were used to accumulate the codes from all PHCCs. These ICD codes from the different types of clinics were compared using a regression model. The clinically detected prevalence of asthma and COPD was also compared to populations prevalence figures in the study area.

**Paper III**

This study used data from all the 238 PHCCs and from the three types of asthma care; 14 clinics matched to size were randomly selected. Altogether a stratified random sample of 42 PHCCs was created. The aim of Paper III
was to compare asthma management, asthma control and quality of life scores between primary care and paediatric ambulatory care. There were 27 paediatrics ambulatory clinics in the region; we randomly selected one clinic from each county.

The patient survey part of the AIM study was conducted between January and March 2001. All clinics made a list of patients with a current asthma diagnosis. Owing to the new millennium, and the necessary upgrading of computer systems, “current” was defined as within the previous 1.5 years. From each clinic a maximum of 40 patients aged 15 to 45 was randomly selected. For this report, all patients aged 15 to 18 years were selected.

Asthma control was assessed using measurable treatment goals from the GINA guidelines [16]. These goals were: achieved and maintained control of symptoms, prevention of asthma exacerbations, and maintaining normal activity levels including exercise. A disease orientated questionnaire, in Appendix Paper III, and the self-administrated asthma-specific quality of life questionnaire, MiniAQLQ [137] were sent to all patients, with two subsequent reminders if necessary. Patients are asked to recall their experiences during the last two weeks and respond to each question on a seven-point interval scale, where 1 = severe impairments and 7 = no impairments. The questions are grouped into four domains activity limitations (4 items), symptoms (5 items), emotional function (3 items) and environmental stimuli (3 items).

Means of each domain and a total mean were calculated. The minimal important difference, i.e. clinically significant difference is half a point (0.5) of the mean score [137]. All questions were answered anonymously.

The DBH Study

Paper IV

The Dampness in Buildings and Health Study (DBH) is a large study with several international institutions participating in the different parts. The overall aim of this study was to identify health relevant exposures in buildings [93]. The study was divided into five phases, as illustrated in figure 4.

Phase 1 was a cross-sectional ISAAC WQ [138] with added environmental information to all 14,077 preschool children in Värmland (March–April 2000). Phase 3 was a follow-up questionnaire to children in phase 1 (March 2005). Phase 4 is ongoing experimental investigations of findings from phases 1 and 2, in climate chamber studies (2004–2008). Phase 5 is a planned Swedish Environmental Longitudinal Mother-Child and Allergy (SELMA) cohort study to assess possible causative factors found in previous phases.
Phase 2 and Paper IV was a nested case-control study of 198 cases with symptoms and 202 healthy controls. Each case and control was medically examined and their housing examined for different exposures. The aim of Paper IV was to validate the parental WQ with clinical examinations, in order to judge whether adequate cases and controls can be selected using this design.

Nested cases had to report at least two symptoms: “wheezing during the last year” and/or “rhinitis during the last year without a cold” and/or “itching typical eczema during last year”. Inclusion criteria for controls were the absence of any such symptoms. This is illustrated in the Venn diagram, figure 5, where the overlapping parts are the selected cases, control were not within any circle.

In a follow-up questionnaire after 18 months, each case had to confirm at least two of the three symptoms, and controls still had to be asymptomatic. This process selected persistent cases and controls, and made the time lag between the last questionnaire and clinical validation about six months. Since this study focused on the indoor environment, an additional exclusion criteria was change of residence or major rebuilding due to dampness.

Of all those invited to participate, 198 cases and 202 controls were randomly selected, without matching. In this process a selection bias regarding smoking in the family, pet-keeping and higher social class became evident (personal communication Carl-Gustaf Bornehag, 2005).
Phase 2 was carried out during the period October 2001- April 2002 to ensure winter-like conditions of indoor living. The examinations were performed by four physicians and two experienced child health nurses. This team was mobile and offered examination at any of four different health care facilities in the county. At each location a child-friendly environment was established. Examinations were not performed if the children had a current infection; they received a new appointment to ensure evaluation at steady state. All children had their medical history reviewed, and underwent standardised physical examinations and tests including serum samples for specific IgE.
Ethical considerations

Biomedical research in humans must comply with the principles of the Helsinki Declarations from 1964. This declaration is under constant revision to satisfy the new ethical challenges, for instance in genetics [139]. But the foundation remains: scientific research must be truthful, honest, impartial and objective to uphold the four main ethical principles of: autonomy, justice non-maleficence, and beneficence.

Autonomy
Cross-sectional and case-case control studies dealing may come into conflict with autonomy. We used reminders to the WQ and non-response telephone interview even though this was an intrusion of the personal autonomy. Press-releases were used to increase public awareness to increase the response rate. The regional ethical committee approved the wording of the WQs, the accompanying letter and the procedure for reminders.

Justice
A new legislation concerning Bio-Banks was launched in Sweden in 2003. This legislation affected the case-control children described in Paper IV, for which biological material was collected. No tests were taken without informed consent being obtained from guardians. The DBH study has an approved bio-bank but we have made added limitations on storage time. We regarded the written consent as valid for ten years, after which all the material will be destroyed. Any case or control can demand that their material shall be destroyed at any time. One problem with the Swedish bio-bank law is that it is national. A great deal of scientific research, including the DBH study, is international and sending biological material abroad is strictly regulated.

Non-maleficence
The clinical examination of preschool children in the DBH study was questioned by the regional ethics committee in Örebro on the grounds of potential harm, non-maleficence. We had to motivate each test. In this procedure
one measure of nose-volume, acoustic rhinometry [140], was not acceptable to the small children and consequently excluded.

To avoid possible harm written informed consent, well informed parents and children, a professional child friendly environment and staff competence were all essential. We reported how the procedure worked to the ethics committee. This report was published, it showed that is was possible to perform tests without harming the children [141].

Beneficence

Studies must have a sound scientific design, and raise funding for the research. External funding, sponsorship, is greatly appreciated, but there are ethical complications. Paper I was partly subsidised by two pharmaceutical companies and a patient organisation. One company and the patient organisation later launched a campaign suggesting, on the basis on epidemiological findings, a substantial underdiagnosis and subsequent undertreatment. This campaign was withdrawn after criticism of the validity that all should be medically treated.

The DBH Study was partially financed by the European Council for Plasticisers and Intermediates. Their response to our results concerning the association to allergic disease and phthalates was not favourable [90]; they suggested we had misinterpreted the scientific data. Our study group had to defend the results [90, 142]. The DBH study must take responsibility for its findings in order to further explore possible causal relationship in future studies.

It is also important, when communicating risks that they are put in perspective. The scientific community does not gain from “whistle blowing” about risks. On such example was the acrylamide alarm and the risk of cancer report that later large epidemiological studies deemed unlikely [143].
Statistics

Data was analysed with SPSS statistical programme software. Summary statistics such as means were computed using standard parametric methods. Differences of means were calculated with the Student’s-test. In test of proportion in ordinal or nominal data the chi-square test was used for groups and the related Z-test for differences in one parameter. In non-normally distributed ordinal data, non-parametric tests and medians values were used. The test of distribution was Kruskal Wallis and for proportion the chi-square test as it is a non-parametric test. Only two-tailed tests were used, p-values less than 0.05 were regarded as statistically significant.

Non-parametric test in general have lower discriminative power than parametric test. In a multivariate model normal distribution is usually needed and transformation of data with logarithmic was used.

To calculate sensitivity and specificity and positive and negative predictive values, a special software programme was used, Confidence Interval Analysis (CIA) [144]. Sensitivity is the proportion of truly diseased persons that have a positive test. Specificity is the proportion of truly nondiseased persons who are so identified by a test. When compare differences in prevalence of asthma between populations the combined Youden’s Index (sensitivity + specificity - 1) has been proposed as the best single measure of validity [81]. The positive predictive value is the proportion of positive test that really has a disease. This is sometimes referred to as the yield of test. The negative predictive value is proportion of negative tests that are nondiseased.
Results

The results are from three different studies, each with a specific aim of its own. This thesis extracts results in terms of epidemiological aspects of asthma prevalence from these studies.

Paper I

The results from paper I, the WQ with 4,814 answers gave self-reported asthma diagnosed by a physician in 6.0%, and anti-asthmatic drugs were used by 7.3% of the population. Symptoms such as recurrent wheeze corresponded to 8.0% and shortness of breath to 11.4%. In total 40.4% reported at least one respiratory symptom. The telephone interview of non-respondents did not show any statistical differences in symptoms as compared to the responses in the WQ.

In the clinical validation we randomly selected and examined 206 individuals with symptoms. Previous validations of this WQ of non-symptomatic individuals were not able to identify persons with asthma, apart from the few that can be attributable to the incidence in the time lag between the WQ and the validation [145].

At the time we used a COPD definition with measurable obstruction and symptoms. In recent years there has been a great deal of focus on COPD in primary care [146], and the diagnosis should be based only on the measurable obstruction [24]. Staging of COPD requires post dilation measurement of FEV₁. We recalculated the prevalence of COPD in table 3 with FEV₁/VC according to European reference values [134] with stages according to GOLD [147]. The results increased the COPD prevalence marginally from the original figures in Paper I.

In the validation, equal numbers of men and women satisfied our definition of asthma, 40% had significant reversibility, 44% had nocturnal symptoms and 82% had recurrent wheeze during the last year. Only 67% were current users of asthma medication, and 81% of them used SABA and 53% used ICS.

In the WQ all subjects were asked to state the type of care, if any they had attended for own illness in the last two years. About 75% of patients with a
Table 3. Recalculation of prevalence of disease with new criteria of COPD with measurable obstruction according to GOLD

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>Severity</th>
<th>Prevalence (%)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>8.2</td>
<td>8.2</td>
<td>(7.4 to 8.9)</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>4.0</td>
<td>4.0</td>
<td>(3.4 to 4.5)</td>
</tr>
<tr>
<td>COPD total</td>
<td>2.6</td>
<td>2.6</td>
<td>(2.2 to 3.1)</td>
</tr>
<tr>
<td>Stage I Mild COPD</td>
<td>0.4</td>
<td>0.4</td>
<td>(0.2 to 0.5)</td>
</tr>
<tr>
<td>Stage II Moderate COPD</td>
<td>1.4</td>
<td>1.4</td>
<td>(1.1 to 1.7)</td>
</tr>
<tr>
<td>Stage III Severe COPD</td>
<td>0.7</td>
<td>0.7</td>
<td>(0.5 to 0.9)</td>
</tr>
<tr>
<td>Stage IV Very Severe COPD</td>
<td>0.2</td>
<td>0.2</td>
<td>(0.06 to 0.3)</td>
</tr>
</tbody>
</table>

stated doctor diagnosed asthma had attended primary health care for any reason within the period. In the validation study of 206 patients this issue of health care consumption was further explored. Of those with validated asthma, nearly 60% stated that their main contact was in primary care, 15% secondary care and another 13% private care including occupational health care services. The remaining 13% did not seek any health care at all.

Paper II

In paper I, we lacked information about how many had been diagnosed or had an asthma or COPD related visit in primary care. Finding this out was one of our aims in Paper II. Another was to evaluate whether primary care based asthma clinics facilitate detection of obstructive lung disease in the population.

Of the sample of 216 PHCCs, 137 were able to extract reliable ICD codes data. Some did not have appropriate computer software, a few used paper records and at a few PHCCs none of the GPs used ICD-10. Most non-respondents did not state a reason. There was an organisational difference between respondent and non-respondent clinics, in that there were more asthma clinics than in the original sample. Therefore all statistical tests were done with and without weighting to make the respondents representative of the full sample. This did not, however, change the results in any significant way.

Most GPs registered ICD codes on consultation concerning chronic diseases. The pattern of children and young people with asthma that was referred to paediatric care, have shared care or stay in general practice adhered to guidelines [49]. More of the complete asthma clinics treated children, but this trend was not statistically significant. The most distinct difference was in the number of lung function tests performed. Asthma clinics performed many more than ordinary care.
Table 4. The univariate and multivariate linear regression models with slope (B) and significance levels of which factors correlated to the logarithmic value of proportion diagnosed asthma.

<table>
<thead>
<tr>
<th></th>
<th>Univariate B</th>
<th>p-value</th>
<th>Multivariate B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of ICD codes</td>
<td>0.014</td>
<td>&lt;0.001</td>
<td>0.012</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of asthma clinic</td>
<td>0.173</td>
<td>0.004</td>
<td>0.154</td>
<td>0.019</td>
</tr>
<tr>
<td>PHCC size</td>
<td>0.111</td>
<td>0.051</td>
<td>0.180</td>
<td>0.081</td>
</tr>
<tr>
<td>Full time GP posts</td>
<td>0.028</td>
<td>0.231</td>
<td>0.039</td>
<td>0.321</td>
</tr>
<tr>
<td>Vacancies among GPs</td>
<td>0.001</td>
<td>0.528</td>
<td>0.000</td>
<td>0.944</td>
</tr>
<tr>
<td>Distance to specialist care</td>
<td>0.002</td>
<td>0.133</td>
<td>0.002</td>
<td>0.358</td>
</tr>
<tr>
<td>Type of electronic record</td>
<td>0.050</td>
<td>0.397</td>
<td>0.010</td>
<td>0.877</td>
</tr>
<tr>
<td>Nr. of lung function tests</td>
<td>0.005</td>
<td>0.153</td>
<td>0.004</td>
<td>0.309</td>
</tr>
<tr>
<td>Treatment of children &lt;7 y.</td>
<td>0.080</td>
<td>0.263</td>
<td>0.045</td>
<td>0.579</td>
</tr>
<tr>
<td>Treatment of children 7-14 y</td>
<td>0.043</td>
<td>0.436</td>
<td>0.012</td>
<td>0.864</td>
</tr>
<tr>
<td>Treatment of youths 15-18 y</td>
<td>0.046</td>
<td>0.547</td>
<td>0.030</td>
<td>0.814</td>
</tr>
</tbody>
</table>

The outcome was the proportion of individuals with any asthma or COPD related visit in the catchment population as a measure of clinical prevalence. There was a statistically significant difference between the three types of care for clinical asthma. In ordinary care the prevalence of clinical asthma was (1.69%), in incomplete asthma clinics (2.03%) and in complete asthma clinics (2.46%). The prevalence for clinical COPD was in ordinary care (0.46%), in incomplete asthma clinics (0.51%) and in complete asthma clinics (0.59%).

The structural and process factors in the PHCCs were compared using a multivariate linear regression model. The only two independent variables that increased the coding practise for asthma significantly were the use of ICD codes and completeness of the asthma clinics, table 4. The whole multivariate model with ICD coding use and organisation was significant (p=<0.001) with ANOVA and a coefficient of determination, $R^2$ of 0.294.

Paper III

The result in Paper III is a subgroup analysis of all who responded to the patient questionnaire and the quality of life questionnaire in the AIM study. Of the adolescents aged 15—18 years were 146 patients in paediatric care and 174 in primary care. They were compared in terms of management, asthma control and quality of life measurements as demonstrated in table 5.

Management differences as annual follow up was performed in three quarters of the paediatric care patients and the same percentage knew their care physician by name. These figures were significantly lower in primary care; about half stated that they had annual follow-ups and knew who their
Table 5. Asthma management, control and quality of life for 320 adolescents, aged 15-18 y, in paediatric ambulatory care or primary care

<table>
<thead>
<tr>
<th>Management</th>
<th>Paediatric ambulatory care n = 146 (%)</th>
<th>Primary care n = 174 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual follow-up care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76.6</td>
<td>46.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>20.0</td>
<td>44.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Do not know</td>
<td>3.4</td>
<td>9.3</td>
<td>0.030</td>
</tr>
<tr>
<td>Known responsible physician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>72.4</td>
<td>54.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Sufficient knowledge of asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, absolutely or yes, partially</td>
<td>86.2</td>
<td>76.7</td>
<td>0.028</td>
</tr>
<tr>
<td>Inhaler instructions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>95.8</td>
<td>92.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Change of medication at need</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, absolutely/partially</td>
<td>80.7</td>
<td>76.2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

| Control                          |                                        |                          |         |
| Use of rapid acting beta-2 agonist >twice in the last week | 39.2 | 31.8 | n.s. |
| Oral corticosteroids due to exacerbations >once in the last six months. | 5.5 | 8.0 | n.s. |
| Woken at night last week?        |                                        |                          |         |
| Yes, one night                   | 14.0                                   | 12.1                     | n.s.    |
| Yes, several nights              | 9.8                                    | 9.2                      | n.s.    |
| No                               | 76.2                                   | 78.6                     | n.s.    |
| Unscheduled, urgent care in the last six months                  |                                        |                          |         |
| Yes, once or twice               | 15.3                                   | 13.8                     | n.s.    |
| Yes, >two times                  | 0.7                                    | 1.2                      | -       |
| No                               | 84.0                                   | 85.0                     | n.s.    |
| Absence from school/work in the last six months                   |                                        |                          |         |
| Yes, once or twice               | 14.8                                   | 9.3                      | n.s.    |
| Yes, >two times                  | 13.3                                   | 9.4                      | n.s.    |
| No, never                        | 71.9                                   | 81.3                     | n.s.    |
| ICS use in the last six months? |                                        |                          |         |
| Yes, regularly                   | 33.1                                   | 29.4                     | n.s.    |
| Yes, periodically                | 43.0                                   | 32.9                     | n.s.    |
| No                               | 23.9                                   | 37.7                     | 0.008   |

| Quality of life, domain means   |                                        |                          |         |
| Symptoms                        | 5.52                                   | 5.61                     | n.s.    |
| Activities                      | 6.00                                   | 6.08                     | n.s.    |
| Emotions                        | 5.75                                   | 5.83                     | n.s.    |
| Environment                     | 5.71                                   | 5.88                     | n.s.    |
| Overall                         | 5.72                                   | 5.84                     | n.s.    |
Table 6. Referral and treatment habits for children and adolescents as stated by 177 primary health care centres. Only affirmative answers are shown, a negative answer implies a referral to paediatric care.

<table>
<thead>
<tr>
<th>Affirmative answers</th>
<th>0–6 years (%) (95% CI)</th>
<th>7–14 years (%) (95% CI)</th>
<th>15–18 years (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHCCs that evaluate and treat asthma in all aspects</td>
<td>10 (6–15)</td>
<td>50 (42–57)</td>
<td>87 (82–92)</td>
</tr>
<tr>
<td>PHCCs that initiate ICS treatment</td>
<td>32 (25–39)</td>
<td>68 (61–74)</td>
<td>91 (87–95)</td>
</tr>
<tr>
<td>PHCCs that follow up treatment after paediatric consultation</td>
<td>36 (29–43)</td>
<td>69 (62–76)</td>
<td>89 (84–93)</td>
</tr>
</tbody>
</table>

doctor was. Most patients in both settings stated they knew how to change their medication when they had infections, more asthma symptoms or lower peak flow rates. Almost all of them had received instructions on how to use their inhalers.

Symptoms indicating allergy, asthma and smoking habits did not differ significantly between the groups. Symptoms indicating asthma control did not differ apart from that adolescents without ICS were more common in primary care. There was no significant difference in the use of SABA; about one third had used them more than twice for their asthma symptoms during the last week. One fifth had woken up at night because of their asthma symptoms during the last week in both groups. Nearly 30% of the young people in paediatric care had stayed home because of asthma symptoms at least once in the past six months, as compared with about 20% in primary care.

The results of the MiniAQLQ were generally high, indicating good quality of life in relation to different aspects of living with asthma. Paper III also included answers from the questionnaire used in Paper II to reveal the referral patterns between primary care and paediatrician (table 6). Almost all preschool children are referred to paediatricians. It was also apparent that PHCCs are willing to initiate and followup treatment for a third of preschool children in connection with an evaluation by a paediatrician. This implies a form of shared care for this age group. In schoolchildren about half were referred and for adolescents few were referred.

Paper IV

The part of the case-control study relating to exposure measurements has already been published, with an association found between phthalates, softeners in PVC and allergic diseases suggesting a novel causative environmental factor [90].
The results from the validation showed no statistical difference in mean age between cases and controls, 5.5 and 5.6 years.

It was possible to analyse serum samples from 387 (96%) children. Almost half, 48% of the cases, had positive IgE screening tests. Among controls, 12% were positive. The most frequent specific IgE was birch and cat, followed by timothy grass, dog, and horse, followed by mugwort, house dust mites and moulds.

The symptom of wheezing during the last year represented 18.9% of the whole pre-school population (figure 5). In the clinical validation there were 71 boys and 50 girls with asthma who, on average, had their first symptoms at age one. In the previous year, 75% had had heavy breathing, 73% wheezing and 43% coughing at night. Almost all of them used asthma medication, 111 SABA, 48 used ICS periodically and 38 regularly.

On examination, ten children had ronchi and one had heavy breathing. As 113 children had a prior diagnosis of asthma, only 13 were newly detected in the study. Five had had neither symptoms nor medication in the last year and were regarded as being in remission.

The primary validation was case status versus presence of any diagnosed asthma, allergic rhinoconjunctivitis or eczema. This validation had high concordance, as had the control status of, not having any disease. A secondary
validation was performed between the individual questions on symptoms and asthma. Wheezing during the last year and previously diagnosed asthma had good Youden's Indices of about 70%, but the symptom “night cough for more than 2 weeks” had a low index of less than 40%.

The results of the study, with high concordance in the validation, are attributable to selection bias in forming cases and controls and severity bias by requiring repeated symptoms in two WQs.
Discussion

Prevalence of asthma
The estimation of asthma prevalence in Paper I is similar to findings from other studies done with the same method in Sweden [86, 88, 105] and in the same region as illustrated in table 2. The prevalence estimates also correspond to findings from neighbouring countries, from Norway in the Oslo area [102] and from Finland in the Helsinki area [103], both with similar climate zones around the latitude of 60° north, and with comparable socio-economical levels.

There are variations in prevalence measurements in Europe and even in Sweden [106]. Asthma is more common in the north than the south [148]. The reasons for this pattern are not known, but indoor conditions [149], colder outdoor climates [150], and different exposures to domestic pets [151] have all been proposed.

The difference in sex distribution seen in figure 1 is well in line with other findings [20, 92] and the question of what could explain these differences arise. A simplified relationship between prevalence and incidence is: Prevalence = Incidence x Duration of disease.

The higher prevalence found in boys could be attributable to the fact that the incidence is higher in boys in their preschool years [152] although sex difference is not evident in schoolchildren [94]. Remission rates, which affect duration of disease, seem to be higher in boys than in girls [152, 153]. Hormonal changes have been implicated as causing this difference in remission rates [154]. In adults, the incidence of asthma increases with age [155] and is higher in women [156] which could explain why asthma prevalence continues to be high. Occupational factors [4] and smoking [155] may also be more important causal factors later in life. This is a simple model of explanation of the differences seen. It is known from previous studies that the relationship between prevalence and incidence in asthma epidemiology is complex [157].

Clinical prevalence
Respiratory symptoms were reported by 40% of the population in paper I and of these 8% had asthma. It is important to detect asthma among all those with symptoms, since the prognosis of the disease benefits from treatment
Good health care contact provides the foundation for well informed patient who can regulate their medication in response to the changes in their disease severity [74, 158].

A clinical diagnosis of asthma in primary care can be regarded as highly specific in the sense that it excludes healthy individuals [159, 160]. But a diagnosis in primary care is not sensitive, it does not detect everyone with symptoms who could clinically be defined as having asthma, which explains the existing underdiagnosis situation [159].

We found that about 2% of the population had received an asthma diagnosis in primary care. By comparison with previous studies from Sweden [53], Denmark [161], Holland [162], France [163] and Australia [164], the prevalence of diagnosed asthma in primary care seems to fall within a range from 2-4%. These figures suggest substantial underdiagnosis [61, 159] and it is important to assess the factors that increase detection rate.

Clinical detection

Primary care, in its first line capacity, has a role to play in detecting chronic disease [35]. In paper II, two factors increased detection, primary care based asthma clinics and the use of ICD codes.

The process of diagnosing asthma should include a typical medical history, clinical signs and preferable objective measurements. Since asthma is disease with variable severity it is possible that patients with asthma have different needs of visiting health care. A diagnosed patient can be identified in a questionnaire by asking if they ever have been given a diagnosis. They can also be found in register searching for how many of all registered patients that ever have received diagnostic code.

In this study the registered ICD codes could be set at the point of diagnosing but equally well on a regular or unscheduled visit related to asthma. One patient with asthma could only be counted once, during a two year period. In this way the codes could be used as a period prevalence measure of clinical asthma. The codes represent all types of severity and visits in primary care. The number of asthma visits per catchment population constituted the detection rate, i.e. clinical asthma in the population.

In stating a higher detection rate in primary care based asthma clinic meant controlling for confounding factors that could give alternative explanations. The difference was not caused by size, staffing, location, type of electronic records or how children and adolescents were treated. All these confounders were possible factors affection the number of asthma related visits, the numerator of the detection rate calculation.

The denominator in this ratio was the catchment population and this is more difficult to control. There are different ways of interpretation how large a population each PHCC has. The centres that only used listed patients to define catchment areas probably have the most accurate estimations. Those
centres with an assigned catchment area have no real knowledge on how large a proportion of their population that actually have or will attend the PHCCs. With these known problems at hand and without any real possibility to control for the differences each PHCCs had to define themselves how many they had. This hopefully prevented introducing a systematic bias in the calculations.

The higher detection rate of asthma in primary care based asthma clinics is a simple measurement of effectiveness. High detection rates are good argument in relation to policymakers about why primary care should include asthma clinics. Asthma clinics deliver care to a larger part of the population.

Whether the clinical outcomes of such care are better will be discussed in future papers from the AIM Study. One argument against these clinics is that they take resources away from other parts of primary care. Primary care based asthma clinics could give rise to an unwanted effect in diminishing resources for other diseases, such as diabetes. This argument is difficult to contradict and its validity has not been examined scientifically, to my knowledge.

The use of consultation, ICD-codes is a prerequisite for other aspects of quality of care [36]. To be able to code a consultation or to set a diagnosis is a part of the art of and science of clinical work [165]. This practice could be developed and encouraged in primary care. One possible way of encouraging coding is to consider financial incentives for chronic disease coding which could be a way of directing funding.

Feedback to the primary care centres about their overall detection rates for different conditions could also be developed as a measure of quality. These suggestions require centralised registers of consultation codes in primary care. A database should contain many different aspects of structure and process measurements, not only for asthma. This database should ideally retrieve codes automatically and combine them with clinical outcomes to measure a wider perspective on quality in primary care. There are examples of such registers in the Netherlands [84]. However, many registers should be able to be constructed, in several countries, with the help of primary care informatics, regardless of which type of record keeping system is used [66]. A common register in the European Union might even be possible.

This approach probably requires written consent from patients which might reduce the general validity of the data register. Another risk is that financial incentives would introduce overdiagnosis. But if a register of diagnostic codes were combined with compulsory outcome measures, that risk should be reduced.

The potential of a consultation code registers in primary care in terms of quality assessment and for demonstrating the work done in general practice must be regarded as great. The type of diagnostic classification system used, for example the International Classification of Primary Care (ICPC), Read codes used in the UK, or ICD-10 is not decisive since the codes for most
conditions are interchangeable. The codes are probably used as aggregate data, such as the adjusted clinical groups [64], since co-morbidity is more the rule than the exception in primary care [36]. Instead of discussion under-diagnosis, primary care should promote the better detection rate.

Methodological issues

Cross-sectional studies are like fishing trawls and they can, as Herakleitos (around 400 B.C.) said of the dynamic world, never descend twice into the same water [166]. Still, several cross-sectional measurements give a probability of “true” prevalence according to a frequentist view. The probability of an event is its relative frequency of occurrence in a large number of trials repeated under virtually identical conditions [167].

Cross-sectional studies require large populations and fair response rates in order to make reasonable estimates, with small confidence intervals. Papers I and IV had large study base populations. Paper II, with 137 primary health care centres, is not a large sample in itself, but in relation to the Swedish total of about 1000 PHCCs, it is reasonably large. The differences seen with non-parametric test were, however, regarded as statistically probable, and not attributable to chance. In paper III the comparison between paediatric and primary care failed to show differences in outcomes for adolescents with asthma. This could indicate that the study lacked the power to show differences that were actually there, as an effect of the small sample sizes, 146 and 174 adolescents in paediatric and primary care, respectively.

Another problem in cross-sectional studies is that non-response increases over time, a trend that can be seen in the decreasing response rates to the asthma WQ in table 1. The reasons for this could be information overload, a lower sense of social obligation to respond, and that the benefit of a survey to the individual might not be clear. If this trend of falling response rates continues, the present models of large cross-sectional WQs will become less reliable. Alternative techniques may be used; such as capture-recapture [168, 169] or neural networks, computer aided technique for identifying patients with asthma in populations where resources for diagnostic examination or willingness to participate is limited [170].

The standard approach to the problem of non-response in cross-sectional studies is to do a non-response study. In paper I, 50 non-respondents were called and asked a few key questions. There was no statistically significant difference between respondents and non-respondents, and therefore respondents were regarded as representative. An obvious methodological problem in this comparison of 50 out of nearly 5000 is that the differences must be quite large in order to find a statistically significant difference. Non-response studies are, however, often used. When they cannot be performed, as in the
Papers II and III, this is a limitation. In such cases a worst case model, assuming that non-respondents never have asthma could be used.

One of the methodological problems associated with WQs is the choice of asthma definition. Usually, asthma as diagnosed by a physician and clinical asthma usually have high concordance, as in paper IV. But a WQ can also identify previously undiagnosed asthma, although this requires the use of symptoms. The ECRHS uses current symptoms, within the last year, to define asthma, the OLIN study defined current symptoms as in the past two year period. This difference might explain some of the usually higher prevalence figures seen in OLIN as compared with the ECRHS studies [2, 80]. From a clinical point of view it could be argued that the epidemiological definitions are too broad, and do not refer to current, relevant asthma. One obvious methodological difference is that a survey actively assesses all possible symptoms, an approach seldom used in clinical practise. On the other hand, asthma is a chronic disease with variable clinical manifestations that might go unnoticed in clinical practice. It is possible that primary care better detects the most obvious, more severe forms of asthma. There is support in the literature for such a trend in Dutch general practice [162]. It is not known whether this is true for Sweden. It will be interesting to assess the severity of the patients in the three different types of asthma care as will be done in future papers from the AIM-study.

Results discussion

Paper I estimated the validated prevalence of asthma to be 8% in the adult population. With data on the how adults with asthma attend health care combined with the prevalence of asthma in primary care in paper II it was possible to illustrate the relationship between epidemiological asthma and clinical asthma, as shown in figure 7. In that figure half of the adults with asthma stated that they had received an asthma diagnose, which is in line with other studies [61, 159, 171]. These self-estimations concur well with the clinical prevalence of 2% in primary care, as judged by the use of ICD codes on consultation.

Illustrated as eight individuals with asthma, see figure 7, one does not seek care at all even though she has symptoms. This person avoids triggers instead of seeking care to control of disease manifestations. The approach of adapting the lifestyle to fit the disease is, unfortunately, still common in individuals with asthma [61, 172]. The two people in the middle have health care contacts and have been diagnosed. One with severe asthma might be seen by a specialist in pulmonary diseases. The other might just have mild intermittent asthma and receive medication on request at a visit to the company health service at his or her workplace.
Figure 7. The ecology of medical care for adults with asthma. A population prevalence of 8%, form three groups left to right: one does not seek any care, two are seen by non-primary care physicians, and five attends primary care. The dark people state that their physicians have labelled them to have asthma, they have been diagnosed.

A group of five have attended primary care at some point in the last two years. Two received a consultation code and get regular follow ups. These two represent patients who were assessed in the AIM study, where records were used to locate individuals with asthma. It is this group of five who can be detected in primary care. Two have not received a consultation code, are undiagnosed, in spite of having received prescription for asthma medication. One might have intermittent asthma and have sought primary care for other reasons. This person will be captured in a cross-sectional study but not in clinical practise.

There are several reservations about generalising these results. One is that Värmland is only one county, which might not be representable either of the health care services or of the total prevalence of asthma. The asthma prevalence is however, as shown in figure 5, approximately 8% in the entire mid-Swedish region. But even in other regions, with different prevalence measures, the general idea that it is not possible to determine total population prevalence in primary care is still relevant. How large the proportion of primary care of the whole health care system is might also differ between coun-
tries. But it probably true in most countries with general practice that most patients with asthma have some form of contact with their primary care providers [24]. Another reservation is that the information in figure 7 is not applicable to children or adolescents. In figure 1, prevalence for pre-school children is shown. One problem about that estimate is that the question asked was about asthma ever. In a preschool population with high remission rates, asthma ever might not be a representative question about what is clinically current or relevant asthma. In an attempt to validate this pre-school population, the subjects were matched, using their personal identity numbers to examine medical records in paediatric care. The concordance between stated WQ asthma and clinical record asthma was not good but the total prevalence of around 5% seemed to be accurate (personal communication, Dr Carl-Axel Hederos 2005). The ecology of care for preschool children with asthma will have to be further described in other studies.

This thesis contains no data on schoolchildren apart from what the PHCCs stated about how they usually treat children with asthma. It seems that the guidelines for where children should be treated [39] corresponds well to what the PHCC say they do, table 6 and Paper III.

Adolescents with asthma are managed in both paediatric and primary care, but the number treated in either setting cannot be determined on the basis of the results in Paper III. It is, however, reasonable to assume that the majority are treated in primary care. In any case adolescents with asthma as a population have specific needs in terms of asthma management, and might require a different approach [173]. Swedish adolescents are managed and treated somewhat differently in paediatric and primary care but with equivalent and generally satisfactory results, in an international comparison [174]. The difference between the findings from the two settings probably reflects both differences in severity of asthma and different treatment traditions. The comparison is also between two levels of care, primary and specialised secondary care.

There is concern among paediatricians how referral and treatment of adolescents with asthma are best accomplished [173, 175]. In neither setting were the treatment goals of minimal symptoms and prevention of exacerbations fulfilled. Referral to primary care in itself should not be a hindrance for paediatricians but there is room for improvement in both settings. A more flexible care adopted to the special needs and concerns of adolescents with asthma should be further developed [176].

Validation was done in both Papers I and IV to assess whether questionnaire answers reflected real disease. In Paper I the validation was done on a stratified selection with symptoms, since previous studies with the same method found few with asthma among persons without symptoms [105]. Support for this approach is also found in Paper IV, since no control child had asthma. Paper IV also illustrates that validity is much a matter of selection of who is validated. The high concordance between questionnaire symp-
toms and clinical disease is both related to selection bias in establishing cases and controls, and in severity bias regarding persistent disease and lasting health.

Although a causal relationship was not a finding in Paper IV, it is one of the implications of the case-control part of the DBH study. A current concept in science is that it is not possible to prove causality [167]. Still, many attempts have been made to draw up rules, laws or criteria of causality. The main problem in asthma causation lies in temporality and the possibility of a reversed causation, i.e. what is the cause and what is the effect. This problem can be illustrated by the relationship between gastroesophageal reflux disease and asthma. The causational route has been thought to be that reflux caused irritation of not only the oesophageal but also the respiratory tract and thereby inducing asthma. It could, however, be the other way around, that asthma causes gastroesophageal reflux [177].

A less scientific/philosophical, a more pragmatic view of causality is to compare it to a courtroom. The prosecutor represents all scientists, who will naturally reject the hypothesis of causality. The defence builds its case around the criterion of causality. The court has to judge whether or not there is support for a causal relationship beyond reasonable doubt. The jury is still out regarding whether or not phthalates can cause asthma and allergies.

Further validation of the parental ISAAC questionnaire is still needed since there are only a few studies done with this WQ. The selection of cases and controls in combination with a professional organisation made the validation possible as demonstrated in Paper IV. The great contrast between the cases and controls in the disease status but not in any other meaning is advantageous when exposure differences were determined in the case-control study.

Both the prenatal and early childhood period is important in the development of asthma and allergic disease [178]. Further research is needed to assess possible causal pathways. There is support for causes related to the hygiene hypothesis [179] or to chemical exposure [180]. This search will have to be open to all types of explanatory factors with the goal of finding means of preventing asthma in the future.
Concluding remarks

This thesis summarise four papers from three different studies, showing that:

- The prevalence of asthma in the mid-Swedish population is about 8%, judged from written questionnaires with validation. The population prevalence of asthma that visits primary care is about 5%. The clinical prevalence of detected asthma is about 2% in primary care.
- The ecology of asthma care shows that the majority of adults are seen in primary care but less than half have been diagnosed. Children with asthma are mostly seen in paediatric ambulatory care but adolescents can be seen in either setting.
- The existence of primary care based asthma clinics increases detection of asthma in the general population. Use of consultation codes and measurements of detection rates of chronic diseases are important in order to judge the quality of primary care.
- In the evaluation between primary care and paediatric care there were differences in process measures for adolescents with asthma. There were no differences in outcome measures, and some but not all treatment goals were fulfilled. The discussion on how best to deliver care to adolescents with asthma must continue.
- A written parental questionnaire can be used to establish cases with clinically valid persistent disease and healthy controls. The case-control part of the DBH Study will continue to suggest and discuss potential risk factors for asthma and allergic diseases in children.
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Swedish summary

Bakgrund och syfte


Behandlingsriktlinjer beskriver hur astma skall behandlas utifrån dess svårighetsgrad och med hänsyn tagen till patientens ålder. Idag behandlas de flesta svenska vuxna med astma inom primärvården under det att barn har sin huvudkontakt hos barnläkare. Ungdomar kan behandlas av såväl striktsläkare som barnläkare.

Vissa vårdcentraler har infört så kallade astmamottagningar. En fullvärdig astmamottagning definieras av fastlagda kriterier: Den bör ledas av en specialutbildad sjuksköterska med egen mottagningstid, ha en verksamhetsansvarig läkare, vara utrustad med spirometer, kunna genomföra strukturerade utredningar, och erbjuda patientundervisning. Dessutom bör mottagningen ha tillräckligt med tid för sin verksamhet.

Det finns visst veteskapligt stöd för att astmamottagningar har en gynnsam effekt på akutbesök och sjukskrivningar. Samtidigt har det varit svårt att i evidensbaserade utvärderingar tydligt verifiera positiva effekter av ett strukturerat omhändertagande av astma i primärvård.

Huvudsyftet med avhandlingen var att beskriva astmaförekomsten i befolkningen i relation till antalet diagnostiserade fall. Ett annat syfte var att jämföra utfallet av vård för tonåringar med astma som gick hos distriktsläkare jämfört med hos barnläkare i öppenvård. Ytterligare ett syfte var att validera enkätsvar med avseende på astma och allergisk sjukdom hos barn.

Metod

Avhandlingen omfattar fyra epidemiologiska studier. Den första studien var en tvärnittsstudie av den vuxna värmländska befolkningen med frågor om astma. I den studien gjordes även en klinisk validering. Den andra studien var även den en tvärnittsstudie men av vårdcentraler i Uppsala-
Örebroregionen och med ett befolkningsunderlag som översteg 3000 personer. Studien jämförde struktur- och processmått för olika typer av astmamottagningar. De resultatmått som jämfördes var andelen patienter som fått en astmadiagnos registrerad under de senaste två åren.


Den fjärde studien var en fall-kontrollstudie av barn. Fallen valdes ut från en befolkningsekät genom att ha angett två eller tre symptom: pipande andning, hösnuva eller eksem. Kontrollbarn fick inte ha något av dessa symptom.

Resultat

I den vuxna värm landlordska befolkningen hade 8 % astma. Hälften av dessa uppgav att de fått en astmadiagnos. Två tredjedelar av alla med astma hade sin huvudkontakt med primärvården under en två års period.

Den andra studien undersökte förekomsten av astma i vårcentralernas diagnosregister. I genomsnitt hade 2 % av varje vården centralers befolkningsunderlag sökt för astmabesvär under en två års period. Det var en högreandel av befolkningen som sökt för astma på vårcentraler med astmamottagningar jämfört med de vårcentraler som inte hade någon astmamottagning. Denna skillnad kunde inte förklaras av andra faktorer som storlek, bemanning eller om vården centralen låg i stad eller på landsbygden. Den enda ytterligare förklarande faktorn var att de mottagningar som regelmässigt registrerade en diagnoskod också hade en högreandel med astmapatienter i befolkningen.

Den tredje studien visade att det fanns skillnader i hur man behandlade och följde ungdomar mellan barnmottagningar och vårcentraler. Men med avseende på behandlingsmål kunde studien inte påvisa skillnader mellan grupperna. Av alla de studerande ungdomarna hade en femtedel vaknat på natten på grund av sin astma under den senaste veckan, 15 % hade fått söka akut för sina besvär och en tredjedel använde snabbverkande luftrorsvidgare mer än två gånger per vecka.

I den sista studien av barn i ålder 3-8 år påvisades att det gick att genomföra en validering som inkluderade blodprover och andra undersökningar. Det fanns en stor överensstämmelse mellan de som valts ut som fall och att de verkligen hade astma eller annan allergisk sjukdom. Av kontrollbarnen var det endast ett fallet som hade hösnuva och eksem men ingen hade astma.
Konklusion


För ungdomar med astma förefaller organisationsformen vara av mindre betydelse för att se skillnader i behandlingsutfall. Om alla ungdomar fick adekvat förebyggande behandling och ett anpassat omhändertagande skulle astmasymtom och andelen akutbesök kunna minska.

Den goda överensstämmelsen i valideringen av fall och kontroller förklaras till viss del av att urvalet selekterade barn som var långvarigt sjuka eller långvarigt friska. Effekten av selektionen med den goda överensstämmelsen i validering ger förutsättningar för att kunna formulera nya hypoteser om orsakssamband mellan astma och inomhusmiljö.
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