Asthma in Primary Care

Severity, Treatment and Level of Control

BJÖRN STÄLLBERG
Dissertation presented at Uppsala University to be publicly examined in Rudbeckssalen, Rudbecklaboratoriet, Dag Hammarskjölds väg 20, Uppsala, Friday, November 21, 2008 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Aims. The overall aim was to examine the severity, treatment and level of control in patients with asthma in primary care in Sweden. The specific aims were to assess what matters to asthma patients, evaluate symptoms, medication and identify factors related to asthma severity, compare the extent of asthma control in 2001 and 2005, and investigate the development of asthma and degree of asthma control in adolescents and young adults who had reported asthma six years earlier.

Methods. The first study was a telephone interview of a representative sample of Swedish asthmatics. In the second study a random sample of 1,136 patients answered two questionnaires. A classification of the asthma severity similar to that in the GINA guidelines was made. In the third study two surveys were performed, in 2001 and in 2005, with a random sample of 1,012 and 224 asthma patients, respectively, and a classification of asthma control similar to the recent GINA guidelines was made. In the fourth study 71 individuals who reported physician-diagnosed asthma in a population-based survey in 1997 and were defined as current asthmatics, were reinvestigated in 2003 with a skin prick test, methacholine challenge test, eucapnic voluntary hyperventilation test and measurement of exhaled nitric oxide.

Results. Common situations causing symptoms of asthma were physical exertion and contact with pets. Nocturnal symptoms were frequent. In primary care 35% of the women and 24% of the men were classified as having severe asthma. Female sex, increasing age, not filling the asthma prescription owing to cost, daily smoking, and pollen allergy increased the odds of having severe asthma. In 2001, 37% had achieved asthma control, as compared with 40% in 2005. Uncontrolled asthma was more common in women and smokers. In the 2003 study of adolescents and young adults with asthma six years earlier, the definition of current asthma was fulfilled by 50 of the 71 subjects and one third had achieved asthma control.

Conclusions. The majority of the asthmatics reported a large number of symptoms and limitations in their daily living. Many asthma patients in primary care have insufficient asthma control. One reason for lack of control might be undertreatment with inhaled corticosteroids.

Keywords: Adherence, adolescent, adult, asthma, asthma classification, asthma control, asthma severity, compliance, drug therapy, hyperresponsiveness, primary health care, smoking, asthma treatment.

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This thesis is based upon the following publications:


**PAPER IV**  Ställberg B, Hedenström H, Johansson G, Svärdsudd K. A follow up of adolescents and young adults with asthma - Airway hyperresponsiveness and asthma control. Submitted.

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<tr>
<td>AIM</td>
<td>Asthma in Middle Sweden</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>AHR</td>
<td>Airway hyperresponsiveness</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>ECRHS</td>
<td>European Community Respiratory Health Survey</td>
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<td>EVH</td>
<td>Eucapnic voluntary hyperventilation</td>
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<tr>
<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<td>GINA</td>
<td>Global Initiative for Asthma</td>
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<td>GP</td>
<td>General practitioner</td>
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<tr>
<td>ICS</td>
<td>Inhaled corticosteroid</td>
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<td>IPCRG</td>
<td>International Primary Care Respiratory Group</td>
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<tr>
<td>LABA</td>
<td>Long-acting beta2-agonist</td>
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<td>LTRA</td>
<td>Leukotriene receptor antagonist</td>
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<td>MiniAQLQ</td>
<td>Mini Asthma Quality of Life Questionnaire</td>
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<td>eNO</td>
<td>Exhaled nitric oxide</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>OLIN</td>
<td>Obstructive Lung Disease in Northern Sweden</td>
</tr>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>MVV</td>
<td>Maximal voluntary ventilation</td>
</tr>
<tr>
<td>PD20</td>
<td>Cumulative dose of methacholine causing a 20% decline in FEV1</td>
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<tr>
<td>PHCC</td>
<td>Primary Health Care Centre</td>
</tr>
<tr>
<td>Ppb</td>
<td>Parts per billion</td>
</tr>
<tr>
<td>SABA</td>
<td>Short-acting beta2-agonist</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
</tr>
<tr>
<td>SIFO</td>
<td>SIFO Research International</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>SPT</td>
<td>Skin prick test</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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Introduction

Asthma is a common chronic disease in people of all ages, affecting daily activities in many patients. It is a major public health problem with a great influence on the health-economic costs for medical services, dependent on disease severity [1-3]. Despite improved pharmaceutical treatment regimens, clinical and epidemiological studies have demonstrated that many patients with asthma still have a wide range of symptoms and have not achieved asthma control [4-7]. A considerable proportion of the patients of all ages also regard their disease as mild, even when their asthma is insufficiently controlled [8]. This suggests that many asthma patients have adapted their lives to accept their asthma symptoms [4, 9]. Monitoring the disease with regular follow up is a cornerstone in management of asthma in both international and Swedish asthma guidelines [10, 11]. Regular reviews of asthma patients including guided self-management plans have also been associated with improved outcomes in several studies [12, 13].

The majority of adolescent and adult patients with asthma in Sweden and in many other countries are treated in primary care [10, 14, 15]. A large proportion of school children and teenagers with mild and moderate disease are also treated in primary care.

Definition of asthma

Asthma has been defined in guidelines as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role [16, 17]. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment. When asthma is controlled, there should be no more than occasional recurrences of symptoms, and exacerbations should be rare [18].
Epidemiology - prevalence, incidence and remission

The prevalence of asthma has increased worldwide in recent decades, and the situation in Sweden is no exception [19-21]. Studies from Gothenburg and Uppsala in the mid-1960s reported an asthma prevalence of 2-3% [22]. More recent studies from Örebro, Stockholm and Norrbotten have estimated the asthma prevalence in the total population, defined as physician-diagnosed asthma, to 7-10% [23, 24]. In epidemiological studies in Sweden women had a higher prevalence of asthma than men [25]. The prevalence of intermittent och mild asthma in patients known in primary care has also been considerably lower in other studies than in epidemiological studies [26].

The asthma prevalence in teenagers is slightly higher than in adults, ranging from eight to eleven percent [27, 28]. The annual incidence among schoolchildren and teenagers has been estimated to 1/100/year in Swedish studies [29]. The incidence rate in adults has been estimated to 2.9/1000/year in women and 1.5/1000/year in men [30]. Remission of asthma among children and teenagers is common. In one study in children between seven and 13 years old, about 10% became symptom free and could discontinue their medication every year [31]. About half of them had relapsed within a few years. It has also been demonstrated in a long term follow-up study in asthmatics that asthma severity improves from childhood to adulthood [32]. The annual remission rate in adult asthmatics has been estimated to 2% in one study [33].

The reason for the increased prevalence during the 1980s to 1990s is still unknown. However, many studies have suggested that various environmental factors during early life may have a major impact [34-37]. There has also been discussion about the relationship between socio-economic status, asthma and atopy [38, 39]. In the study from the European Community Respiratory Health Survey (ECRHS), low educational level was associated with a higher incidence of non-atopic asthma [39]. Recent studies have demonstrated that the increase in asthma prevalence has levelled off, with unchanged incidence during the past decade [40, 41].

Allergy to pets and pollen is common in patients with asthma, and allergy sensitisation is associated with increased frequency of emergency consultations [42]. About one third of the adult population in the ECRHS study had allergy sensitization to at least one common allergen [21]. In school children aged seven to eight years, about one fifth were positive to at least one allergen in a skin prick test [27].

Although smoking in Sweden has declined in recent decades, smoking is a problem for asthmatics. Fifteen per cent (2006) of the population are still daily smokers, with a predominance for women (17%) as compared to men (13%) [43, 44].
Asthma guidelines

The Global Initiative for Asthma (GINA) is a set of internationally accepted guidelines with proposed goals for treatment and management of asthma [16]. Other well known international guidelines are the asthma guidelines from the National Heart, Lung, and Blood Institute (NHLBI) [17], the British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines (BTS/SIGN) [45], and the International Primary Respiratory Group Asthma Guidelines (IPCRG guidelines) [10].

The aim for the asthma treatment is to achieve control of the disease. The treatment goals has been described in the international guidelines as follows: minimal asthma symptoms, no activity limitations, minimal need for rescue medication (< two days a week), no emergency visits, minimal exacerbations, maintained normal lung function and minimal adverse effects from medications. These treatment goals have also been accepted and incorporated into the Swedish guidelines of the National Board of Health and Welfare as well as those of the Medical Products Agency 2007 [11, 46]. Optimal management, with a large proportion of asthmatic patients achieving these treatment goals, is important to decrease the influence and burden of the asthma for both the individual and the society [5, 47].

Implementation of these extensive guidelines in primary care has been a challenge. One reason might be that general practitioners in their daily routines are faced with patients presenting with hundreds of different types of medical, social and general problems, as opposed to specialist physicians in secondary care who deal with a relatively limited number of medical conditions [48]. To improve the adherence to the guidelines other authors have pointed out the need for effective and easily used tools to identify poor control [49-53].

Asthma treatment

The Swedish recommendations are similar to the GINA guidelines, implying early treatment with inhaled corticosteroid (ICS) and adding long-acting beta2-agonist (LABA) to low or medium doses of ICS when the asthma is insufficiently controlled [11, 16]. One common way of expressing this is to divide the treatment into steps. In patients with only intermittent asthma symptoms the recommendation is to use short-acting beta2-agonist (SABA) as needed (step 1). If the patient has symptoms more than twice a week, the recommendation is to add ICS (step 2). In patients insufficiently controlled with ICS, an addition of LABA is recommended instead of increasing the dose of ICS (step 3). A change in prescription habits in Sweden towards use of more fixed combination devices with ICS and LABA has also been noted recent years [54]. The development and use of inhaled corticosteroids during
the latest decades have decreased the demand for emergency and hospital care in both school children and adults [55, 56].

There has also been discussion about the heterogeneity of the underlying disease and the various phenotypes, which may require different treatment approach [57, 58]. Another important factor influencing the effects of medication is smoking, which has been demonstrated to have a negative impact on the effects of inhaled corticosteroids in asthmatics, as well as on the severity of the disease [59-61].

**Adherence**

The outcome of medical treatment is related to the patients’ adherence to prescribed medication. Adherence has been defined by World Health Organisation (WHO) as the extent to which a persons’ behaviour, such as taking medicines and changing lifestyle, corresponds to agreed recommendations from a health care provider [62]. According to several international studies, adherence to prescribed asthma treatment is low, and less adherent asthma patients are likely to have more frequent exacerbations [63]. Non-adherence to prescribed asthma medication has also been considered a major problem among adolescents with asthma [64]. Studies have demonstrated that it is quite common for both adult and adolescent patients to use their asthma medication only periodically [65]. This may result in undertreatment, which is likely to have a negative impact on disease outcome [66]. Some of the reasons given for non-adherence found in the study by Buston et al. were: belief that the medication is ineffective, denial that one is asthmatic, difficulty using inhalers, inconvenience, fear of side effects, embarrassment, and laziness. Another reason in Swedish patients could be the high cost of the asthma medication, in spite of the reimbursement system [67, 68].

**Asthma severity**

Assessment of the severity level of the asthma disease has been suggested in various guidelines and has also been used as prognostic factor [17, 69-72]. In recent guidelines these levels are based on the intensity of treatment required to achieve asthma control and are assessed during treatment [16, 17]. The GINA guidelines have proposed four severity levels in patients on asthma medication: intermittent, mild persistent, moderate persistent and severe persistent asthma. The definition of these four levels was in the earlier GINA guidelines based on medication, symptoms, exacerbations and lung function [69]. This classification has been used in various studies, but it has also been considered too complex for everyday use in primary care [73, 74].
Asthma severity may be influenced by many factors, such as the underlying disease and the patient’s phenotype. In patients with severe asthma there are reports of a sex-related difference, with female predominance [73, 75]. The reason for this difference between women and men is not fully understood, although factors like other allergic co-morbidities and hormonal factors have been suggested [76-78]. Other suggested factors influencing severity are age of onset and resistance to corticosteroid therapy [79]. Allergy sensitisation has also been found to be associated with asthma severity and increased frequency of emergency visits [42, 80]. However, factors that might influence the severity level in the population of asthma patients treated in primary care have not been specifically studied.

Asthma control

In the GINA guidelines until 2005, the severity of the disease was divided into four levels, but in more recent asthma guidelines an assessment of asthma control is also recommended [16, 81]. “Asthma control” refers to the extent to which the manifestations of asthma have been reduced or removed by treatment. The degree of asthma control is divided into three levels: “controlled”, “partly controlled” and “uncontrolled”. The aim of the treatment should be to achieve complete asthma control, characterised by no daytime symptoms or need for reliever (twice or less per week), no limitations of activities, no nocturnal symptoms, no exacerbations, and normal lung function. This classification is consensus-based, and has not yet been carefully validated. In the guidelines there is a link between the classification of asthma control and decisions about asthma treatment, with a recommendation that treatment should be stepped up if asthma is uncontrolled, and a stepping up also should be considered if the asthma is partly controlled [82, 83].

Insufficient asthma control may be attributable to underlying severe disease, but it is far more frequently due to poor adherence to prescribed medication, under-prescribing or environmental factors such as allergen exposure or smoking. Incorrect diagnosis may be another reason for poor asthma control. As a consequence of the new approach in recent guidelines, many recent authors have pointed out the importance of careful monitoring of the extent to which patients achieve asthma control [48, 49, 82].

Several studies have also demonstrated that a substantial number of asthma patients do not achieve the goals of asthma treatment as specified in international guidelines [4-7, 84]. Most of these studies of asthma control are population-based and included patients treated both in primary and secondary care [4-6, 85]. Some studies, performed entirely in primary care, have demonstrated a similar lack of asthma control as in the population-based studies [84, 86]. However, it is also important to evaluate possible changes
in asthma control between different periods in patients entirely treated in primary care.

**Quality of life**

Several studies, both population-based and in primary care, have demonstrated an impact of asthma attacks, nocturnal symptoms and exacerbations on patients’ quality of life [87, 88]. Lung function data has often been used to evaluate disease severity and treatment effects, but the lung function is poorly correlated to quality of life (QoL) and asthma symptoms [89-92].

Several disease-specific quality of life questionnaires have been developed. One that is very often used in clinical trials is the Mini Asthma Quality of Life Questionnaire (MiniAQLQ), which has fifteen questions [93]. It was developed to measure the functional impairments most troublesome to adults with asthma. It has been validated in patients 17 years or older, but has also been used in studies with younger patients (personal communication Juniper EF). It has been validated as useful on group level in different studies, but it has not yet been validated in the management of individual patients in primary care [94].

**Airway hyperresponsiveness**

Asthma is characterised by airway inflammation with activation of eosinophilic cells [16]. The eosinophilic inflammation is associated with increased airway hyperresponsiveness (AHR). This AHR is a characteristic abnormality of asthma, which results in airway narrowing as a response to various stimuli. AHR is linked to the inflammation and is partly reversible with therapy. AHR can be measured with a direct challenge test such as methacholine and histamine, or with indirect tests like eucapnic voluntary hyperventilation [95, 96].

**Test methods**

The methacholine challenge test has been used in many studies as a diagnostic tool for measuring AHR [97-100]. Methacholine, when inhaled, acts directly on the smooth muscle receptors causing bronchoconstriction. It is common to express the results as the cumulative dose for a 20% decrease in FEV1 as compared with the baseline value (PD20). In studies using the methacholine challenge test, various cut-offs for defining bronchial hyperreactivity have been used, depending on the method. A cumulative dose (PD20) between 1.6 mg and 2.0 mg has been used as cut-off by some authors [101-
The methacholine challenge test has high sensitivity but low specificity [106].

Increased levels of exhaled nitric oxide (eNO) are associated with eosinophilic inflammation [107, 108]. Measurement of eNO has been used more frequently during in recent years in follow up of asthma patients [109, 110]. A higher proportion of patients with normal eNO has been found among non-atopic asthmatics than atopics [111-114]. Measurement of exhaled nitric oxide is considered as a useful method in primary care, but its applicability in non-atopic asthmatics and in the management of mild asthmatics is debatable [109, 115-117]. Various eNO cut-off levels have also been used by different authors to describe a clinically relevant increase in eNO for identification of asthmatics having an eosinophilic inflammation and for follow up of asthma treatment with inhaled corticosteroids [118].

Eucapnic voluntary hyperventilation (EVH) is an indirect provocation test giving bronchoconstriction similar to that caused by inhaling dry cold air [119]. An indirect challenge test as EVH is thought to release mediators that provoke airway smooth muscle constriction [120]. The EVH test has been used in particular to identify exercised-induced bronchoconstriction [121]. A decrease in FEV₁ of 10% or more at any time compared with baseline has been defined as a positive test [97, 119]. The EVH test has high specificity but low sensitivity [119].

The health care system in Sweden

In the Swedish health care system the county councils are responsible for health care, which means that local organisation and financing may differ between counties. Primary care is organised into primary health care centres (PHCCs), where each centre is responsible for a defined population group, either a patient list or a defined catchment area. If there is a need for further consultation, patients are referred to secondary care, mostly hospital-based specialists. Many PHCCs have a nurse-based asthma clinic as an integrated part of the centre, but the presence of asthma clinics and the time allocated for nurse varies between centres [122-124]. Every patient who consults a physician in primary care in Sweden should receive a diagnosis in conjunction with the consultation, and the diagnosis should be listed in a special computer register at the clinic. Patients, especially with mild disease, may however, be given prescriptions from their general practitioner (GP) without a personal consultation, and are therefore sometimes not found in the diagnosis register. Information from these registers about the diagnosis of asthma was used in papers II and III.
Aims of the study

The overall aim of the thesis was to examine the severity, treatment and level of control among patients with asthma in primary care in Sweden.

The specific aims of this thesis were:

- to assess what matters to Swedish asthma patients with respect to the disease, the use of medicines and compliance with given prescriptions (Paper I),
- to evaluate symptoms and asthma medication and to identify factors related to asthma severity in asthma patients aged 15-45 years in primary care (Paper II),
- to compare the extent of asthma control in two cross-sectional surveys performed in 2001 and 2005 in asthma patients aged 18-45 years in primary care (Paper III),
- to investigate the longitudinal development of asthma and the degree of asthma control, using an asthma questionnaire and various objective measurements in a group of adolescents and young adults aged 13-22 years, who had reported asthma or airway symptoms six years earlier (Paper IV).
Study populations and methods

Paper I

Sampling

Paper I, the ALMA study, was carried out in the form of telephone interviews. The interviews were performed by the Swedish Institute of Public Opinion Research (SIFO Research International), and were conducted from November 2000 to February 2001. The patients’ perceptions about their asthma were compared with those of Swedish general practitioners by using a mailed questionnaire containing similar questions.

A random sample of 10,350 subjects from the whole Sweden aged 18-45 years were asked over the telephone by a SIFO representative whether they were willing to answer four screening questions about asthma. The questions aimed to identify a sample with current asthma.

The questions were as follows:

a) “Have you ever had asthma?” and
b) “Have you been diagnosed as having asthma by a physician?”

If yes to any of the two questions, two further questions were asked:

c) “Have you had problems or symptoms of your asthma during the last 12 months?” and
d) “Have you used asthma medicines during the last 12 months, regularly or as needed?”

Current asthma was defined by yes to either question (a) or (b), and to question (c) or (d).

The screening questions for asthma came from the Obstructive Lung Disease in Northern Sweden (OLIN) questionnaire [125], which is frequently used in Sweden and neighbouring countries [126-128]. Thus 348 subjects were identified as having current asthma, which corresponds to 3.3% of those who agreed to answer the screening questions. The subjects identified as having current asthma and who agreed to participate in a comprehensive structured interview by a SIFO representative about their asthma were interviewed over the telephone on a later occasion. Of the 348 individuals with current asthma, 240 (61% women) agreed to participate in the longer structured interview, while 108 (31%) abstained from participating.
Data collection

The interview questions and alternative responses were designed by the research group (i.e. the authors). During the interview the questions and alternative responses were read by the interviewer, one by one, without further explanations except for repetition of the questions when necessary.

The interview consisted of 51 questions, including questions about the frequency of symptoms common in asthma, such as coughing, wheezing, dyspnoea, and attacks of shortness of breath. There were also a large number of questions about activities that could provoke asthmatic symptoms, and whether the asthmatics avoided these activities.

Examples of such questions were:
- “Are you troubled by your asthma when running or hurrying for a bus or train?” and - “Do you ever avoid running or hurrying for a bus or train in order not to be troubled with asthma?”

Each question was followed by five alternatives: “often/frequently”, “now and then/occasionally”, “rarely”, “never”, or “the question is not relevant”.

The asthmatics were also asked to mention three activities or situations which they were forced to avoid on days with symptoms, because of their asthma. They were also asked to classify the degree of severity of their asthma.

Another part of the questionnaire included questions about their present asthma therapy, and how often they took medicines. Furthermore, the patients were asked about compliance with their doctor’s prescription of asthma medicines, how often and where they had their controls or check-ups for asthma, and the frequency of emergency consultations.

The GP questionnaire

A written questionnaire was mailed to 600 randomly selected Swedish GPs from the Swedish register of physicians. They were asked about their perception of how asthmatics aged 18-45 years feel, report symptoms, follow prescriptions, and use medicines. The questions and answer alternatives were identical, or as similar as possible, to questions put to the asthmatics regarding symptoms and asthma in special circumstances and at different exposures, as well as alternative responses. The GPs were asked to estimate how large proportion of the asthmatics they thought had chosen the different answer alternatives. Completed answers were received from 139 (65% men) GPs.
Paper II

Sampling

Paper II was part of the Asthma In Mid-Sweden study (AIM study). In the first phase of this project, the organisation of asthma care at primary health care centres (PHCCs) in the Uppsala-Örebro region, central Sweden, was investigated [122]. Of all the 238 PHCCs, 16% had a complete asthma clinic, 37% had an incomplete asthma clinic and 47% had no asthma clinic as defined by the Swedish Respiratory Group in Primary Care.

In the second phase, 28 PHCCs with catchment areas with fewer than 3,000 inhabitants (and generally no asthma clinic) were excluded from the study, as were four PHCCs that did not keep computerised medical records using the International Classification of Diseases (ICD-10) for diagnosis registration, and 13 PHCCs that declined to participate. The remaining 193 PHCCs were stratified into groups according to the completeness of their asthma clinics and their catchment area size. From these strata, a proportional random sample of 42 PHCCs was drawn.

Each of the 42 PHCCs generated a list of all patients with asthma diagnoses attending the PHCC during the past 18 months. From these lists, samples of patients in the age range 15-45 years were drawn. From lists containing 40 or fewer patients, all patients were sampled, and from the longer lists random samples of 40 patients were drawn, generating a total of 1,477 patients.

Data collection

Two questionnaires were mailed to the patients with two reminders when necessary. In the first questionnaire, returned by 1,136 (77%) patients, information was sought on demographics, asthma medication, symptoms, allergy, emergency consultations, smoking habits, occupation, sick leave and patients' knowledge about asthma treatment. Four questions concerned the use of beta2-agonists as rescue medication, nocturnal awakenings, emergency consultations and use of oral steroids, i.e. the attainment of treatment goals. An abbreviated English version of the first questionnaire has previously been published [129]. See also the appendix.

A simplified version of the asthma severity classification proposed in the GINA guidelines published in 2005 was constructed, based on questionnaire information on current treatment, the use of rescue medication, night symptoms, emergency consultations and use of oral steroids [69]. The main difference from the GINA guidelines was the absence of lung function data.

The second questionnaire was the asthma-specific quality of life questionnaire, MiniAQLQ, developed to measure the functional impairments most troublesome to adults with asthma [93]. This questionnaire was re-
turned by 1,098 (74%) patients. It has been validated in patients 17 years and older, but has also been used in studies with younger patients. Patients were asked to recall their experience during the last two weeks and respond to each question on a seven-point scale, ranging from severe impairment (=1) to no impairment (=7). The questions were grouped into the four domains: “activity limitations” (4 items), “symptoms” (5 items), “emotional function” (3 items) and “environmental stimuli” (3 items). The mean score for each of the four domains and the overall score was calculated and weighted with regard to the sampling proportion.

Of the non-responders, 104 (27% of the non-responders) were selected from a sample of the participating PHCCs for a telephone interview. Seventy (67%) of these agreed to be interviewed. In these interviews an abbreviated form of the disease-oriented questionnaire was used. In addition, some variables such as age and sex were known for 90% of the 104 non-responders.

Paper III
Sampling
The study in Paper III consists of subjects from two cross-sectional surveys: Patients in the age range 18-45 years in the Asthma In Mid-Sweden in 2001 (AIM study) and a subgroup of patients from the PRAXIS study in mid-Sweden in 2005. The sampling of the AIM study is described in paper II.

In the second survey, the PRAXIS study in the year 2005, fifty-six PHCCs were randomly sampled from the same geographic region as in the survey in 2001. PHCCs with catchment areas with fewer than 3,000 inhabitants were excluded, as well as three PHCCs that declined to participate. Each PHCC generated a list of all patients with an asthma diagnosis attending the PHCC during the past four years. From these lists, random samples of 22 patients in the age range 18-75 years were drawn. At the few PHCCs with fewer than 22 patients, all patients were sampled, generating a total of 1,221 patients.

In order to have comparable groups in the two surveys, only patients aged 18-45 and those who in addition had attended their PHCC owing to asthma at least once during the last 18 months were included in the 2005 survey. A total of 69% of the responders in this age group were included.

Data collection
The data collection in the questionnaire used in the 2001 survey is described in paper II. In the second survey in 2005, the questionnaire was returned by a total of 60% of the patients in the age group 18-45 years, and the same questions about demographics, asthma medication, symptoms, emergency
Table 1. Criteria for asthma control. The criteria are based on the definition of asthma control in GINA 2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled</th>
<th>Partly controlled</th>
<th>Uncontrolled¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nighttime awakening due to asthma symptoms</td>
<td>None</td>
<td>One or more nights last week</td>
<td>One or more nights last week, both present last week</td>
</tr>
<tr>
<td>Need for reliever</td>
<td>Twice or less last week</td>
<td>Three times or more last week</td>
<td>Three times or more last week</td>
</tr>
<tr>
<td>Exacerbations²</td>
<td>None</td>
<td>None</td>
<td>One or more exacerbations last six months</td>
</tr>
</tbody>
</table>

¹ Uncontrolled is defined as either nighttime awakening and need for reliever or exacerbation
² Emergency consultations or oral course of steroids

**Figure 1** Criteria for asthma control. The criteria are based on the definition of asthma control in GINA 2006

consultations, the use of oral steroids, smoking, and sick leave were asked. There were also questions about height, weight and the severity level of asthma as assessed by the patient.

A simplified version of the definition of asthma control with three levels: controlled, partly controlled, and uncontrolled was constructed. This was similar to the definition proposed in the GINA guidelines in both 2006 and 2007 [16]. The definitions of the levels of asthma control used in this study are shown in figure 1. The main difference from the GINA guidelines was the absence of lung function data.

Both the 2001 and 2005 surveys were performed during the winter season, and both questionnaires contained the same questions about asthma control. There was no telephone interview with the non-responders in the 2005 survey, but the age and sex of all non-responders was known.

**Paper IV**

**Sampling and data collection**

All 1,244 schoolchildren born between 1981 and 1989 and living in the municipality of Trosa in central Sweden, received a short screening questionnaire in 1997 about asthma and other allergic symptoms. The questionnaire was answered by their parents and/or the subjects themselves and returned by 1,224 (98.4%). In this initial screening survey, 205 of the 1,224 (16.7%) answered yes to the question: "Has your child had asthmatic symptoms in the past twelve months or taken medicine for asthma at least once during this period? We want you to answer yes, even if the symptoms were mild and of short duration, such as slight wheezing and breathlessness in connection with
a cold or occasional breathlessness in connection with exercise”. The question has also been used in another large study [40].

In the same year a new, more extensive questionnaire was mailed to these 205 subjects with two reminders when necessary. This second questionnaire was returned by 191 (93%) subjects. Information was sought about demographics, asthma and allergy symptoms, physician-diagnosed asthma, asthma medication, and emergency consultations. Of these 191 subjects, 107 had physician-diagnosed asthma.

In a second survey, from 2003, all 191 subjects who returned the questionnaire in 1997 were sent a new questionnaire including the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) mailed together with an invitation to participate in examinations with various asthma tests. The tests were performed at the primary health care centre in Trosa as two visits. The subjects returned the questionnaire at the first visit. Of the initial 191 subjects, 116 agreed to participate and came to the first visit. Of these 116 individuals, 71 had been judged as having current asthma in the 1997 survey. In the 2003 questionnaire, returned by all 71 subjects, the same questions were asked as six years earlier about demographics, asthma medication, symptoms and emergency consultations. There were additional questions about the severity level of the asthma as assessed by the subject and questions aimed at evaluating the level of asthma control. This paper presents the results from these 71 subjects.

The first survey was performed during the winter season, and the second during the winter and spring seasons.

Definition of current asthma

The following questions aimed at identifying subjects with current asthma in the 1997 and 2003 surveys:

1. Physician-diagnosed asthma – “Have your symptoms been diagnosed as asthma by a physician?”
2a. Use of asthma medicines – “Have you used asthma medication during the last six months, regularly or as needed?
2b. Symptoms – ”Have you had wheezing or shortness of breath at any time during the last 12 months”?

Current asthma was defined by “yes” to question (1), and to either question (2a) or (2b).

Mini Asthma Quality of Life Questionnaire

The MiniAQLQ used in 2003 was developed to measure the functional impairments most troublesome to adults with asthma [93]. It has been validated in patients from 17 years and older, but has also been used in studies with
younger patients [88]. Patients were asked to recall their experience during the last two weeks and respond to each question on a seven-point scale, ranging from severe impairment (=1) to no impairment (=7). The mean of the total score was calculated.

Skin prick test
Skin prick tests (SPT) were carried out using the following allergens: birch, timothy, mugwort, cat, dog, horse, D. pteronyssinus, D. farinae, Cladosporium, and Alternaria at concentrations of 10 HEP (histamine equivalent prick), Soluprick®, ALK-Abelló A/S, Denmark. Histamine and sodium chloride were used as positive and negative controls respectively. Atopy was defined as a weal reaction of at least three millimetres in diameter to at least one of the allergens.

Lung function measurements
Spirometry was performed according to the American Thoracic Society/European Respiratory Society recommendations [130]. The forced expiratory volume in one second (FEV$_1$), and forced vital capacity (FVC) were measured using a pneumotach spirometer (Flow screen, Jaeger). Predicted values of FEV$_1$ were based on reference values according to the European Community for Coal and Steel (ECCS) from 18 years and older and according to the Zapletal reference values in the age group up to 17 years [130, 131].

Exhaled nitric oxide
Exhaled nitric oxide (eNO) was measured at both visits according to the American Thoracic Society/European Respiratory Society recommendations with an NO analyzer (NIOX®; Aerocrine, Stockholm, Sweden) at a flow of 50 mL/s [132]. Two cut-off values were used in the calculations. Values > 30 parts per billion (ppb) in the age group up to 17 years, and > 35 ppb from 18 years and older were defined as positive “high cut-off” values and > 20 ppb in the age group up to 17 years and > 25 ppb from 18 years and older as positive “low cut-off” values in this study. The eNO results from visit one are used in this study.

Methacholine test
The methacholine challenge test was performed after the withdrawal of short-acting beta2-agonists (SABA) for at least eight hours and long-acting beta2-agonists (LABA) for at least 48 hours. After the baseline spirometric measurements, bronchial obstruction was provoked using a methacholine
inhalation challenge test with an automatic, inhalation-synchronized dosimeter jet nebulizer (Spira Elektro 2, Respiratory Care Centre, Hameenlinna, Finland), with stepwise increase of cumulative doses from 0.02 up to 8.8 milligram (mg). FEV₁ was measured at each step. The challenge was terminated when a ≥ 20% decrease in FEV₁ from the post-saline value was achieved or when a cumulative dose of 8.8 mg methacholine had been given.

A dose-response slope was calculated from the regression equation for the percentage decline in FEV₁ on the cumulative dose of methacholine. For those patients with a cumulative dose of more than 8.8 mg methacholine, the last three measurements were used in the regression equation calculation. A threshold for methacholine challenge (PD₂₀) with a cumulative dose of 1.8 mg or less was regarded as a positive reaction and higher figures as negative reactions [102].

Eucapnic voluntary hyperventilation

Eucapnic voluntary hyperventilation (EVH) was performed with dry air containing 5% CO₂, 21% O₂, and balanced N₂ at room temperature for four minutes with a target minute ventilation of 26 x FEV₁, equivalent to 75% of maximal voluntary ventilation (MVV) (Ailos Asthma test®, Karlstad, Sweden). FEV₁ was measured before (baseline) and 2, 5, 10, and 20 minutes after hyperventilation. The lowest FEV₁ value after the test was used to determine the maximum decrease in FEV₁. A decrease in FEV₁ of 10% or more at any time point compared to baseline was defined as being positive [119].

Flow chart for the different tests

At visit one, after the subjects had returned the questionnaire, exhaled nitric oxide was measured followed by a SPT. After the skin prick test a spirometry test was performed, and followed by the methacholine challenge test. At visit two, exhaled nitric oxide was measured first followed by a eucapnic voluntary hyperventilation test.

Asthma control

A simplified version of the definition of asthma control with only two levels, controlled and not controlled, was constructed. According to the GINA guidelines from 2007, all the following characteristics should be fulfilled for having asthma control: No need for reliever (three or less last two weeks), no limitations of normal activities, normal lung function (FEV₁ ≥ 80% of predicted), no daytime symptoms, no nocturnal symptoms, and no exacerbations during the last 12 months [16]. If one or more of these were not fulfilled the disease was classified as not controlled.
Summary of the baseline characteristics

Table 1. *Summary of the baseline characteristics for the various populations in the thesis*

<table>
<thead>
<tr>
<th>Setting</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2001 survey</td>
<td>2005 survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening population</td>
<td>10,350</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>1,224</td>
</tr>
<tr>
<td>Population sample</td>
<td>348 a)</td>
<td>1,477</td>
<td>1,477</td>
<td>542</td>
</tr>
<tr>
<td>Participants</td>
<td>240</td>
<td>1,136</td>
<td>1,012 c)</td>
<td>224 d)</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>69</td>
<td>77</td>
<td>77</td>
<td>60</td>
</tr>
<tr>
<td>Age group</td>
<td>18-45</td>
<td>15-45</td>
<td>18-45</td>
<td>18-45</td>
</tr>
<tr>
<td>Sex (women %)</td>
<td>61</td>
<td>60</td>
<td>61</td>
<td>63</td>
</tr>
</tbody>
</table>

*Defined as current asthma in the telephone interviews
b Defined as current asthma in 1997 survey
c 1,012 patients in the age group 18-45 years out of 1,136 in the total sample 15-45 years were included
d 224 out of 325 patients had attended the PHCC the last 18 months and were included

Ethical approval

The Research Ethics Board at Uppsala University, Sweden approved the studies in paper II and paper III and the Research Ethics Board at Örebro University, Sweden approved the studies in papers I and IV.

Statistics

In papers II - IV, data were analysed with the SPSS (version 13.0 and 15.0) and SAS (versions 6.12 and 9.1) statistical programme packages. Summary statistics such as means, proportions and measures of dispersion were computed using standard parametric methods. Simple differences between groups in continuous data were tested with Student's t-test or analysis of variance, and differences in proportions with the chi-square test. Multiple logistic regression was used for analyses of variables influencing asthma severity and asthma control, which also provided odds ratios and their 95% confidence intervals (CI). Linear regression was used to compute adjusted mean scores. The analysis models, shown in figures 5 and 6, was visualised by means of logistic regression technique. Skewed data in paper IV are also presented as median and range. Differences in skewed data were assessed by non-parametric methods. The means of the total score and the four domains were calculated in the MiniAQLQ. A difference between groups in the qual-
ity of life scores of 0.5 units or more is claimed to be clinically significant [133].

In paper I, the sample size was based on the assumption that at least 200 asthmatics and at least 100 GPs would participate, and that a difference between answers given by the two groups of 10% in the prevalence of a certain symptom or condition affecting half the studied sample represented statistical significance. The distribution of the percentage for each answer for the GPs is given as mean, 95%CI for the mean, and median values. For comparison of the asthmatics’ and GPs’ opinions regarding ordered and dichotomous variables, the percentages given by a GP were multiplied to the values (0, 1, 2, and 3) of the answers to give a score. These scores from the GPs were tested against the answers from the asthmatics using the Mann-Whitney U-test.

When listing activities or situations the asthmatics needed to avoid on days with symptoms, several activities could be reported by the asthmatics as well as when assumed by the general practitioners. For this reason no statistical comparisons of the outcome patterns were made.

All tests were two-tailed and conducted at the 5% significance level.
Results

Paper I

Frequency of symptoms and avoidance of activities

The proportion of asthmatics reporting symptoms daily during the previous month was 16%, and at least once every week, 49%. These proportions were greater than the GPs had estimated, which were 5% and 36%, respectively (Figure 2). The proportion of asthmatics with symptoms less than once per month was 34%. Nocturnal symptoms at least twice per week were reported by 19%, which was also higher than the GPs had expected, 11% (Figure 3). The response patterns about both daily and nocturnal symptoms as given by the asthmatics versus the GPs diverged significantly (p<0.001).

![Bar chart showing frequency of symptoms]

*Figure 2. Frequency of symptoms, day and night, reported by the asthmatics, and estimated by the general practitioners, respectively*
Every night, at least once
At least once/night during 2-6 nights/week
Around once/week
1-2 nights/month
Less often

Figure 3. Frequency of nocturnal symptoms, reported by the asthmatics, and assumed by the general practitioners, respectively

The frequency of symptoms in defined circumstances or attributable to exposure to various activities was generally similarly reported by the asthmatics and estimated by the GPs (Table 2). How frequently the asthmatics avoided these activities was also examined.

When the asthmatics were asked to mention three activities or situations they had to avoid on days with symptoms, 36% reported sports, 22% exposure to smoke or strong scents, 19% contact with animals/pets, and 18% going outdoors. When asked what the worst thing about having asthma was, 51% answered limitations of normal activities, 38% shortness of breath or tiredness, and 7% chronic disease or dependency on medicines.

Overall assessment and degree of severity

The GPs estimated that more than half of the asthmatics were almost or completely free from symptoms, while only one per cent of the asthmatics did state that they were completely free from symptoms and 26% felt they were almost symptom-free (Table 3). The vast majority, 59%, felt that they had symptoms “sometimes”. At the same time, 68% of the asthmatics classified their asthma as mild or very mild, while the GPs’ corresponding estimate was 52%.
Table 2. Frequency of symptoms in defined circumstances or attributable to different exposures, and avoidance of these situations, reported by the asthmatics and estimated by the general practitioners. Difference in p-value by groups

<table>
<thead>
<tr>
<th>Situation</th>
<th>Frequency</th>
<th>Symptoms in situation</th>
<th>Avoidance of situation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients n=240</td>
<td>GPs n=139</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% 95%CI</td>
<td>Mean 95%CI</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td></td>
<td>28 23-35</td>
<td>27 24-31</td>
</tr>
<tr>
<td>Now and then</td>
<td></td>
<td>38 31-44</td>
<td>27 25-29</td>
</tr>
<tr>
<td>Rarely</td>
<td></td>
<td>20 15-25</td>
<td>24 21-26</td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td>14 9-18</td>
<td>22 19-25</td>
</tr>
<tr>
<td>Physical activity in cold weather</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td></td>
<td>33 27-39</td>
<td>31 27-34</td>
</tr>
<tr>
<td>Now and then</td>
<td></td>
<td>28 23-34</td>
<td>27 25-29</td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td>24 19-30</td>
<td>20 17-23</td>
</tr>
<tr>
<td>Running or hurrying</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td></td>
<td>21 16-26</td>
<td>21 18-25</td>
</tr>
<tr>
<td>Now and then</td>
<td></td>
<td>34 28-40</td>
<td>31 28-34</td>
</tr>
<tr>
<td>Rarely</td>
<td></td>
<td>27 21-33</td>
<td>27 24-30</td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td>18 13-23</td>
<td>20 16-24</td>
</tr>
<tr>
<td>Visiting cafés or restaurants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td></td>
<td>13 9-18</td>
<td>27 24-31</td>
</tr>
<tr>
<td>Now and then</td>
<td></td>
<td>23 18-28</td>
<td>27 24-29</td>
</tr>
<tr>
<td>Rarely</td>
<td></td>
<td>16 12-21</td>
<td>22 19-25</td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td>48 41-54</td>
<td>24 20-28</td>
</tr>
<tr>
<td>Exposure to animals / pets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td></td>
<td>36 30-42</td>
<td>28 25-31</td>
</tr>
<tr>
<td>Now and then</td>
<td></td>
<td>22 16-27</td>
<td>25 23-27</td>
</tr>
<tr>
<td>Rarely</td>
<td></td>
<td>14 10-19</td>
<td>21 19-23</td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td>28 22-34</td>
<td>26 22-29</td>
</tr>
</tbody>
</table>
Table 3. Overall assessment of frequency of symptoms and degree of severity in the asthmatics’ own judgment and according to what general practitioners believed the asthmatics would assess. Difference, p-value, between the groups

<table>
<thead>
<tr>
<th></th>
<th>Patients n=240</th>
<th>GPs n=139</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% 95%CI</td>
<td>Mean 95%CI Median</td>
</tr>
<tr>
<td>Overall assessment of frequency of symptoms</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>4 2-7</td>
<td>7 6-8</td>
</tr>
<tr>
<td>Often</td>
<td>14 9-18</td>
<td>15 13-16</td>
</tr>
<tr>
<td>Sometimes</td>
<td>59 53-65</td>
<td>25 22-27</td>
</tr>
<tr>
<td>Almost free from symptoms</td>
<td>26 20-31</td>
<td>30 27-32</td>
</tr>
<tr>
<td>Completely free from symptoms</td>
<td>1 0-3</td>
<td>24 20-27</td>
</tr>
<tr>
<td>Degree of severity of asthma</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Very severe</td>
<td>1 0-2</td>
<td>7 6-8</td>
</tr>
<tr>
<td>Severe</td>
<td>5 2-8</td>
<td>12 11-13</td>
</tr>
<tr>
<td>Moderate</td>
<td>26 20-31</td>
<td>29 27-32</td>
</tr>
<tr>
<td>Mild</td>
<td>48 42-55</td>
<td>31 29-34</td>
</tr>
<tr>
<td>Very mild</td>
<td>20 15-25</td>
<td>21 19-23</td>
</tr>
</tbody>
</table>

Contacts with health care

The three most common professionals who performed the asthma check-ups were GPs 58%, specialists (pulmonary, allergy, or internal medicine) 13%, and occupational physicians, 7%, while 14% of the asthmatics reported that they did not have any check-ups. Twelve per cent reported that they had consulted a physician or an asthma nurse for their condition during the last month, 38% during the last six months, 55% during the last year, and 78% during the last two years. Unscheduled emergency consultations for asthma were made by 14% of the asthmatics during the last six months.

Use of medication

Seventy-six per cent of the asthmatics claimed that they often followed the prescriptions of the doctors, while 40% of the GPs estimated that they did so. However, in response to another question, only 34% stated they followed their prescriptions most days every week all year round.

During the previous seven days, 50% of the asthmatics had used inhaled short-acting beta2-agonist, 38% inhaled corticosteroid, 8% inhaled long-acting beta2-agonist, and 2% inhaled combined long-acting beta2-agonist and corticosteroid. Forty-three per cent used their inhaled short-acting beta2-agonist once or more every day. Although 179 (75%) had been prescribed inhaled corticosteroids, in this group only 27% used these medications as prescribed, 26% followed the prescription of inhaled corticosteroids “now
and then”, 12% only rarely, and 35% never. The GPs believed the compliance with inhaled corticosteroid treatment was greater than stated by the asthmatics.

Action at increase of asthma
During periods of increased asthma activity, 88% reported increased use of inhaled short-acting beta2-agonist, 48% increased their use of, or started to use, inhaled corticosteroid.

Paper II
Characteristics of the study population
Patient characteristics are presented in (Table 4). Sixty per cent were women. The total mean age was 30.3 (SD 9.2). There were no sex differences in terms of age, asthma history, reported allergies and annual follow up. Smoking was more frequent in women, 20% versus 10% for men. One third of the patients did not fill the asthma prescriptions owing to costs. This was most apparent among the younger patients (data not shown).

Women had experienced more frequent nocturnal awakenings owing to asthma symptoms during the previous week than men. During the previous six months, 28% of the women and 19% of the men had had emergency consultations at the hospital or in primary care. Oral courses of steroids due to exacerbations, one or more, had been taken more frequently by women (odds ratio 1.84, 95%CI 1.23-2.74) adjusted for smoking, medication level and occupation.

Severity classification
As shown in table 5, 30% of all patients were classified as having severe asthma according to the classification in figure 4. Women more often had severe asthma than men (p<0.05). Patients with severe asthma had more sick leave than patients with milder disease (p<0.001), but there was no sex difference. The distribution of the severity of asthma among the patients was not dependent on whether or not the PHCC had an asthma clinic.

Quality of life
There was a clinically relevant difference in the overall MiniAQLQ score between patients with severe asthma and those with less severe asthma. There was also a statistically significant difference in the overall MiniAQLQ score between all severity groups (p<0.01), but with no sex difference.
Table 4. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>682</td>
<td>60.1</td>
<td>453</td>
<td>39.9</td>
<td>&lt;0.001 a)</td>
</tr>
<tr>
<td>Time with asthma</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>43</td>
<td>6.4</td>
<td>35</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>199</td>
<td>29.7</td>
<td>117</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>429</td>
<td>63.9</td>
<td>294</td>
<td>65.9</td>
<td></td>
</tr>
<tr>
<td>Daily smokers</td>
<td>133</td>
<td>19.7</td>
<td>43</td>
<td>9.6</td>
<td>&lt;0.001 b)</td>
</tr>
<tr>
<td>Reported allergy to</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pets</td>
<td>438</td>
<td>65.0</td>
<td>300</td>
<td>66.7</td>
<td></td>
</tr>
<tr>
<td>pollen</td>
<td>439</td>
<td>64.8</td>
<td>278</td>
<td>61.9</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>&lt;0.001 b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>student</td>
<td>212</td>
<td>31.8</td>
<td>102</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>working full time</td>
<td>197</td>
<td>29.6</td>
<td>290</td>
<td>65.3</td>
<td></td>
</tr>
<tr>
<td>working part time</td>
<td>142</td>
<td>21.3</td>
<td>17</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>unemployed</td>
<td>37</td>
<td>5.6</td>
<td>22</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>78</td>
<td>11.7</td>
<td>13</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Sick leave for asthma last six months</td>
<td>142</td>
<td>23.5</td>
<td>84</td>
<td>19.4</td>
<td>ns</td>
</tr>
<tr>
<td>Rescue medication more than</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>twice the last week c)</td>
<td>325</td>
<td>48.5</td>
<td>212</td>
<td>48.0</td>
<td></td>
</tr>
<tr>
<td>Nocturnal awakenings due to asthma the last week</td>
<td>&lt;0.01 b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>462</td>
<td>68.6</td>
<td>336</td>
<td>78.5</td>
<td></td>
</tr>
<tr>
<td>one night</td>
<td>94</td>
<td>14.0</td>
<td>46</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>more than one night</td>
<td>117</td>
<td>17.4</td>
<td>46</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Emergency consultations the last six months</td>
<td>&lt;0.001 b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>483</td>
<td>71.7</td>
<td>364</td>
<td>81.3</td>
<td></td>
</tr>
<tr>
<td>once</td>
<td>105</td>
<td>15.6</td>
<td>60</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>twice or more</td>
<td>86</td>
<td>12.8</td>
<td>24</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Oral steroids the last six months</td>
<td>&lt;0.001 b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>553</td>
<td>82.3</td>
<td>402</td>
<td>91.0</td>
<td></td>
</tr>
<tr>
<td>once</td>
<td>69</td>
<td>10.3</td>
<td>21</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>twice or more</td>
<td>50</td>
<td>7.4</td>
<td>19</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Annual follow up</td>
<td>260</td>
<td>40.5</td>
<td>194</td>
<td>46.2</td>
<td>ns</td>
</tr>
<tr>
<td>Not filling the asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prescription owing to cost</td>
<td>197</td>
<td>29.2</td>
<td>140</td>
<td>31.3</td>
<td>ns</td>
</tr>
</tbody>
</table>

a) p-values were calculated with Z-test or b) p-values were calculated with chi-square test

c) Either short-acting beta2-agonist or long-acting beta2-agonist as rescue medication
Table 5. *Asthma severity*, asthma medication and percentage on sick leave once or more for asthma during the last six months

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Women</th>
<th>Men</th>
<th>p^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Asthma severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intermittent asthma</td>
<td>176</td>
<td>15.9</td>
<td>95</td>
<td>14.2</td>
</tr>
<tr>
<td>mild asthma</td>
<td>177</td>
<td>16.0</td>
<td>95</td>
<td>14.2</td>
</tr>
<tr>
<td>moderate asthma</td>
<td>419</td>
<td>37.9</td>
<td>246</td>
<td>36.9</td>
</tr>
<tr>
<td>severe asthma</td>
<td>334</td>
<td>30.2</td>
<td>231</td>
<td>34.6</td>
</tr>
<tr>
<td>Asthma medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>only SABA as needed</td>
<td>285</td>
<td>25.6</td>
<td>151</td>
<td>22.6</td>
</tr>
<tr>
<td>ICS regularly or in periods</td>
<td>456</td>
<td>41.0</td>
<td>287</td>
<td>42.9</td>
</tr>
<tr>
<td>ICS regularly or in periods and LABA or leukotrien antagonist, regularly or in periods</td>
<td>372</td>
<td>33.4</td>
<td>231</td>
<td>34.5</td>
</tr>
<tr>
<td>Reported sick leave for asthma last six months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intermittent asthma</td>
<td>6</td>
<td>3.9</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>mild asthma</td>
<td>15</td>
<td>9.4</td>
<td>8</td>
<td>9.5</td>
</tr>
<tr>
<td>moderate asthma</td>
<td>55</td>
<td>16.1</td>
<td>28</td>
<td>15.1</td>
</tr>
<tr>
<td>severe asthma</td>
<td>120</td>
<td>45.8</td>
<td>82</td>
<td>48.0</td>
</tr>
</tbody>
</table>

^1) Asthma severity is based on the classification in the GINA guidelines and slightly modified according to the classification in figure 4

^2) p-values for differences between women and men were calculated with chi-square

^3) SABA = short-acting beta2-agonist

^4) ICS = inhaled corticosteroid

^5) LABA = long-acting beta2-agonist

^6) Sick leave for asthma includes patients absent from work or studies. Only eligible patients, working full-time or part time or students, were included

Factors associated with asthma severity

Factors associated with asthma severity are presented in table 6. Age, female sex, reported pollen allergy, not filling the asthma prescription owing to the cost, and daily smoking were all independently associated with increased probability of reporting severe asthma.

The effects on the proportion of patients with severe asthma of various combinations of the factors sex, age, pollen allergy, and not filling the asthma prescription owing to cost are presented in figure 5. The proportion with severe asthma ranged from 10% among the youngest men with no pollen allergy and who filled their asthma prescriptions to 56% among the oldest women with pollen allergy who did not fill their asthma prescription.
| Patients’ symptoms on current treatment | Current treatment | Level of severity (n%/)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA&lt;sup&gt;1&lt;/sup&gt; as needed</td>
<td>ICS&lt;sup&gt;2&lt;/sup&gt; regularly or in periods</td>
<td>ICS regularly or in periods and LABA&lt;sup&gt;3&lt;/sup&gt;/LTRA&lt;sup&gt;4&lt;/sup&gt;, regularly or in periods</td>
</tr>
<tr>
<td><strong>- Rescue medication ≤ twice a week</strong>&lt;br&gt;- No nocturnal symptoms last week&lt;br&gt;- No unscheduled visits in last six months and no oral steroids in last six months</td>
<td>Intermittent asthma (176/15.9)</td>
<td>Mild asthma (147/13.3)</td>
</tr>
<tr>
<td><strong>- Rescue medication &gt; twice a week</strong>&lt;br&gt;- No nocturnal symptoms last week&lt;br&gt;- No unscheduled visits in last six months and no oral steroids in last six months</td>
<td>Mild asthma (30/2.7)</td>
<td>Moderate asthma (117/10.6)</td>
</tr>
<tr>
<td><strong>- Nocturnal symptoms one night last week</strong>&lt;br&gt;- One unscheduled visit in last six months and/or one oral course of steroids in last six months</td>
<td>Moderate asthma (45/4.1)</td>
<td>Moderate asthma (92/8.3)</td>
</tr>
<tr>
<td><strong>- Nocturnal symptoms &gt; one night last week</strong>&lt;br&gt;- More than one unscheduled visit in last six months and/or &gt; one oral course of steroids last six months</td>
<td>Severe asthma (31/2.8)</td>
<td>Severe asthma (98/8.9)</td>
</tr>
</tbody>
</table>

<sup>1</sup>SABA = short-acting beta2-agonist  <sup>2</sup>ICS = inhaled corticosteroid  
<sup>3</sup>LABA = long-acting beta2-agonist  
<sup>4</sup>LTRA = leukotriene receptor antagonist

**Figure 4.** Classification of asthma severity. The classification is based on the severity classification in the GINA guidelines 2005, slightly modified. A total of 1,106 patients were classified, 30 patients missing owing to lack of information.
Figure 5. Proportion of women (a) and men (b) with severe asthma in groups according to age, whether or not they failed to fill their asthma prescriptions owing to cost, and reported allergy, adjusted for the influence of smoking
Table 6. *Factors influencing asthma severity*

<table>
<thead>
<tr>
<th></th>
<th>Severe asthma</th>
<th></th>
<th>All four severity levels*4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n1) OR2) 95% CI3)</td>
<td>OR2) 95% CI3)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>- 1.03 1.02-1.05</td>
<td>1.04 1.02-1.05</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>231/682 1.60 1.20-2.12</td>
<td>1.49 1.19-1.86</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>103/453 1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Pollen allergy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>246/717 1.85 1.36-2.51</td>
<td>1.52 1.20-1.94</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>87/409 1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Pet allergy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>232/738 1.07 0.79-1.44</td>
<td>1.35 1.06-1.72</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>100/386 1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Not filling the asthma prescription owing to cost last year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>123/337 1.59 1.20-2.12</td>
<td>1.74 1.36-2.22</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>210/785 1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Daily smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>73/176 1.66 1.17-2.36</td>
<td>1.45 1.06-1.98</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>279/944 1.00</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

1) Number of patients with the characteristic and severe asthma as compared with the total number of patients with the characteristic
2) OR (odds ratio) adjusted for all other variables in the table
3) 95% confidence interval
4) Ordinal logistic regression

Paper III

Characteristics of the study population

Patient characteristics for the two surveys are presented in table 7. Women were in the majority in both surveys. The total mean age in each respective survey was 32.3 (SD 8.3) and 32.4 (SD 8.2), with no differences of distribution according to sex between the surveys.

Medication

Short-acting beta2-agonist (SABA) as needed as monotherapy was used by about one fourth of the patients in both surveys (Table 7).
Table 7. Patient characteristics and asthma medication during the last six months in the first survey, 2001, and in the second survey, 2005. P-values refer to differences between all patients in the first and in the second survey.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>n</td>
<td>mean or %</td>
<td>n</td>
<td>mean or %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>613</td>
<td>60.6</td>
<td>399</td>
<td>39.4</td>
<td>ns</td>
</tr>
<tr>
<td>Age, mean</td>
<td>32.1</td>
<td>31.8</td>
<td>32.4</td>
<td>32.9</td>
<td>ns</td>
</tr>
<tr>
<td>Daily smokers</td>
<td>122</td>
<td>20.2</td>
<td>40</td>
<td>10.2</td>
<td>ns</td>
</tr>
<tr>
<td>Sick leave due to asthma last six months</td>
<td>130</td>
<td>24.3</td>
<td>74</td>
<td>19.5</td>
<td>ns</td>
</tr>
<tr>
<td>Rescue medication for asthma symptoms more than twice last week</td>
<td>300</td>
<td>49.7</td>
<td>196</td>
<td>50.3</td>
<td>ns</td>
</tr>
<tr>
<td>Nocturnal awakening due to asthma last week</td>
<td>none</td>
<td>413</td>
<td>67.9</td>
<td>312</td>
<td>79.0</td>
</tr>
<tr>
<td></td>
<td>one night</td>
<td>85</td>
<td>14.0</td>
<td>41</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>more than one night</td>
<td>110</td>
<td>18.1</td>
<td>42</td>
<td>10.6</td>
</tr>
<tr>
<td>Emergency consultations last six months</td>
<td>180</td>
<td>29.6</td>
<td>78</td>
<td>19.7</td>
<td>ns</td>
</tr>
<tr>
<td>Oral steroids last six months</td>
<td>114</td>
<td>18.9</td>
<td>34</td>
<td>8.8</td>
<td>ns</td>
</tr>
<tr>
<td>Only SABA¹¹ as needed</td>
<td>128</td>
<td>21.0</td>
<td>106</td>
<td>26.8</td>
<td>ns</td>
</tr>
<tr>
<td>ICS² regularly or periodically</td>
<td>265</td>
<td>43.5</td>
<td>162</td>
<td>40.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICS and LABA³ regularly or periodically or ICS and LTRA⁴, regularly or periodically or combination of all three</td>
<td>216</td>
<td>35.5</td>
<td>128</td>
<td>32.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

¹¹SABA = short-acting beta2-agonist
²²ICS = inhaled corticosteroid
³³LABA = long-acting beta2-agonist
⁴⁴LTRA = leukotriene receptor antagonist
The proportion of patients who used inhaled corticosteroid (ICS) without addition of long-acting beta2-agonist (LABA) or leukotriene antagonist (LTRA) had decreased between the first and the second surveys, while the proportion of patients using ICS and LABA or ICS and LTRA or a combination of all three had increased. Inhalers with fixed combination of ICS and LABA were more frequent in 2005 than in 2001, used by 30% and 11%, respectively (p<0.001).

Of the patients taking ICS as a single treatment, 54% in the 2001 survey and 46% in the 2005 survey used their medication only periodically. In the subgroup of patients using ICS only periodically, 69% and 58%, respectively, did not achieve asthma control.

Asthma control

Approximately 40% of the patients had achieved asthma control in both surveys, with no difference between the two surveys (Table 8). There was no difference in the distribution of the levels of asthma control between the two surveys.

In both surveys there was a significant difference in asthma control between women and men, with more frequent uncontrolled asthma among women (p<0.001 in the first and p<0.05 in the second survey). Half of the patients with combination therapy (separate inhalers or fixed combination) had uncontrolled asthma in both surveys.

Uncontrolled asthma was also more common among daily smokers, 50%, as compared with 38% for non-smokers (p<0.01) in the first survey and 58%, as compared with 30% (p<0.01), in the second survey.

Uncontrolled asthma was more common among patients with reported allergy to both pollen and pets as compared with allergy to either or no reported allergy at all, 47%, 33%, 26% and 38%, respectively (p<0.001), data only available in the first survey.

Patients with controlled, partly controlled and uncontrolled asthma in the first survey had been on sick leave during the last six months in 8%, 15%, and 41%, respectively (p<0.001), while in the second survey the corresponding figures were 7%, 7%, and 39% (p<0.001).
<table>
<thead>
<tr>
<th></th>
<th>2001 survey</th>
<th></th>
<th>2005 survey</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled</td>
<td>Partly controlled</td>
<td>Uncontrolled</td>
<td>Controlled</td>
</tr>
<tr>
<td>n=10051)</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>SABA² as needed</td>
<td>148</td>
<td>63.2</td>
<td>38</td>
<td>16.2</td>
</tr>
<tr>
<td>ICS³ regularly or in periods</td>
<td>132</td>
<td>30.9</td>
<td>123</td>
<td>28.8</td>
</tr>
<tr>
<td>ICS and LABA⁴ regularly or in periods or ICS and LTRA⁵, regularly or in periods or combination of all three</td>
<td>88</td>
<td>25.6</td>
<td>78</td>
<td>22.7</td>
</tr>
<tr>
<td>Total⁶</td>
<td>368</td>
<td>36.6</td>
<td>239</td>
<td>23.8</td>
</tr>
<tr>
<td>women</td>
<td>205</td>
<td>33.7</td>
<td>130</td>
<td>21.3</td>
</tr>
<tr>
<td>men</td>
<td>163</td>
<td>41.2</td>
<td>109</td>
<td>27.5</td>
</tr>
</tbody>
</table>

1) The number of patients in the survey with information available about medication
2) SABA = short-acting beta2-agonist
3) ICS = inhaled corticosteroid (irrespective of dose)
4) LABA = long-acting beta2-agonist
5) LTRA = leukotriene receptor antagonist
6) Represents the distribution of asthma control for all patients, women and men
Table 9. The odds ratio (OR) for having controlled asthma compared with partly controlled/uncontrolled asthma adjusted for age, sex, smoking and survey with 95% confidence interval

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (increasing age)</td>
<td>0.98</td>
<td>0.96-0.99</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>1.28</td>
<td>1.01-1.63</td>
</tr>
<tr>
<td>female</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Daily smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>1.62</td>
<td>1.14-2.31</td>
</tr>
<tr>
<td>yes</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>1.16</td>
<td>0.87-1.58</td>
</tr>
<tr>
<td>2001</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Factors influencing asthma control

Age, sex and smoking had a significant influence on the degree of asthma control (Table 9). The combined effects of age, sex, smoking, and survey are presented in figure 6. The proportion of asthma control ranged from 20% to 53%, depending on these factors. In both surveys, young non-smoking men were most likely to have controlled asthma. The likelihood of having uncontrolled asthma was greatest for older, smoking women.

![Figure 6. Proportion of patients with asthma control in relation to survey, age, sex and smoking](image-url)
Disease severity according to the patients

The patients in the second survey also assessed their own disease severity. In figure 7 this self-assessment was compared with objective asthma control. Among patients with controlled asthma most patients assessed their asthma as very mild or mild, while 12% considered their asthma to be moderate or severe/very severe. Most patients with uncontrolled asthma assessed their disease as moderate or severe/very severe, while 33% assessed their asthma as mild, and 6% as very mild.

Twelve per cent of the patients using only SABA as needed, 24% of the patients using ICS, and 50% using a combination of ICS and LABA/LTRA assessed their asthma as moderate, severe or very severe. There was no difference between men and women.

Paper IV

Characteristics of the study population

Symptoms and medications from the survey in 1997 are presented in table 10. Boys were in the majority, 46 (65%) versus 25 (35%) girls. The mean
Table 10. Symptoms and medications in 1997 of the 71 subjects identified as current asthmatics in the survey in 1997. The results are presented in total and percentage with respect to the assessed asthma status six years later in 2003

<table>
<thead>
<tr>
<th>Questionnaire 1997</th>
<th>Asthma status 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No asthma</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Number</td>
<td>21</td>
</tr>
<tr>
<td>Symptoms of allergic rhinitis last 12 months(^1)</td>
<td>12</td>
</tr>
<tr>
<td>Symptoms of eczema last 12 months(^1)</td>
<td>8</td>
</tr>
<tr>
<td>Symptoms of food allergy(^1)</td>
<td>6</td>
</tr>
<tr>
<td>Reported asthma symptoms to pets(^1)</td>
<td>7</td>
</tr>
<tr>
<td>Reported asthma symptoms to pollen(^1)</td>
<td>9</td>
</tr>
<tr>
<td>Reported asthma symptoms to exercise(^1)</td>
<td>16</td>
</tr>
<tr>
<td>Nocturnal awakenings due to asthma last six months once or more(^1)</td>
<td>5</td>
</tr>
<tr>
<td>Emergency consultations the last year once or more(^1)</td>
<td>6</td>
</tr>
<tr>
<td>Parents smokers (yes)(^2)</td>
<td>14</td>
</tr>
<tr>
<td>Asthma medication in the 1997 survey</td>
<td></td>
</tr>
<tr>
<td>only SABA(^3) as needed</td>
<td>4</td>
</tr>
<tr>
<td>controller regularly or periodically(^4)</td>
<td>15</td>
</tr>
<tr>
<td>no prescribed asthma treatment</td>
<td>2</td>
</tr>
</tbody>
</table>

p-values for differences between all three groups
\(^1\) ns \(^2\) p<0.05 \(^3\) SABA = short-acting beta2-agonist
\(^4\) Controller is either inhaled corticosteroid (n = 41) or inhaled corticosteroid and long-acting beta2-agonist (n = 4)
The estimated prevalence of current asthma in 1997 in the total population of 1,224 schoolchildren was 8.6% (105 individuals). Of the 71 individuals judged as having current asthma in 1997 and participating in the follow-up survey, the definition of current asthma was not fulfilled in 21 individuals (30%) in the follow up. The changes between the two surveys are presented in figure 8. The mean annual remission rate between the two surveys was 5%. Individuals with current asthma in 1997, later classified as not having current asthma in 2003, less frequently had positive methacholine challenge test (PD_{20}<1.8 mg) as compared with individuals with current asthma, 43% and 86%, respectively (p<0.001).

The mean FEV\textsubscript{1} in per cent of predicted was in the two groups with current and not current asthma, 101.3 and 106.6, respectively (ns). Rescue medication more than three days the last two weeks was reported by 15% in 1997 and by 14% in 2003 of those with current asthma. Symptoms of asthma when visiting friends with pets were reported by 40% in the group with current asthma in 2003 and symptoms of asthma visiting disco by 12%.

\begin{figure}
\centering
\begin{tikzpicture}
\node[rectangle,draw] {Current asthma in 1997 \n=71};
\node[rectangle,draw,below] at (0,-1) {Current asthma in 2003 \n=50 \n70\%};
\node[rectangle,draw,right] at (2,-1) {No current asthma in 2003 \n=21 \n30\%};
\node[rectangle,draw,below] at (0,-2) {Asthma controlled \n=15 \n30\%};
\node[rectangle,draw,right] at (2,-2) {Asthma not controlled \n=35 \n70\%};
\end{tikzpicture}
\caption{The 71 subjects assessed as having current asthma in the first survey in 1997 and their asthma status in the follow-up survey six years later}
\end{figure}
<table>
<thead>
<tr>
<th>Questionnaire 2003</th>
<th>Asthma status 2003</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No asthma</td>
<td>Asthma controlled</td>
<td>Asthma not controlled</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n mean or %</td>
<td>n mean or %</td>
<td>n mean or %</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>21 18.8</td>
<td>15 15.3</td>
<td>35 16.7</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td></td>
<td>18.8</td>
<td>15.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Female</td>
<td>6 28.6</td>
<td>6 40.0</td>
<td>13 37.1</td>
<td></td>
</tr>
<tr>
<td>Symptoms of allergic rhinitis last 12 months</td>
<td>4 19.0</td>
<td>5 33.3</td>
<td>25 71.4</td>
<td></td>
</tr>
<tr>
<td>Symptoms of eczema last 12 months</td>
<td>6 28.6</td>
<td>2 13.3</td>
<td>14 41.2</td>
<td></td>
</tr>
<tr>
<td>Symptoms of food allergy</td>
<td>3 14.3</td>
<td>5 33.3</td>
<td>13 37.1</td>
<td></td>
</tr>
<tr>
<td>Asthma medication in the 2003 survey</td>
<td>only SABA</td>
<td>0 0</td>
<td>5 33.3</td>
<td>16 44.7</td>
</tr>
<tr>
<td>ICS regularly or periodically</td>
<td>0 0</td>
<td>2 13.3</td>
<td>7 20.0</td>
<td></td>
</tr>
<tr>
<td>ICS and LABA regularly or periodically</td>
<td>0 0</td>
<td>4 26.7</td>
<td>5 14.3</td>
<td></td>
</tr>
<tr>
<td>no prescribed asthma treatment</td>
<td>21 100.0</td>
<td>4 26.7</td>
<td>7 20.0</td>
<td></td>
</tr>
<tr>
<td>Mini AQLQ (mean)</td>
<td>6.94</td>
<td>6.39</td>
<td>6.19</td>
<td></td>
</tr>
</tbody>
</table>

p-values for differences between all three groups
1) p<0.001  2) ns  3) SABA = short-acting beta2-agonist  4) ICS = inhaled corticosteroid  5) LABA = long-acting beta2-agonist

The results from the questionnaire in 2003 with respect to the three groups: no asthma, asthma controlled and asthma not controlled are presented in table 11, and the results from the measurements in table 12. Figure 9 shows the percentage of individuals with a positive result of methacholine challenge test, EVH test and eNO separated into the same three groups: no asthma, asthma controlled and asthma not controlled.

Medication in patients with current asthma

The percentage of subjects with current asthma who used only short-acting beta2-agonists as needed as monotherapy was 30% in 1997 and 42% in 2003. The use of a controller, inhaled corticosteroid (ICS) with or without addition of LABA, had decreased between the first and the second surveys from 63% to 36%.

MiniAQLQ

All 71 subjects answered the quality of life questionnaire in the second survey. There was both a significant and a clinically relevant mean difference of the total score between subjects with no asthma and with current asthma, 6.94 and 6.25, respectively (p<0.001).
Table 12. Results from the 2003 examinations with respect to asthma status in 2003

<table>
<thead>
<tr>
<th>Asthma status 2003</th>
<th>No asthma</th>
<th>Asthma controlled</th>
<th>Asthma not controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=21</td>
<td>n=15</td>
<td>n=35</td>
</tr>
<tr>
<td>BMI(^1) (mean)</td>
<td>23.8</td>
<td>22.6</td>
<td>23.0</td>
</tr>
<tr>
<td>Positive skin prick test (%)</td>
<td>52.4</td>
<td>60.0</td>
<td>74.3</td>
</tr>
<tr>
<td>FEV(_1) (% of predicted)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>106.6</td>
<td>106.6</td>
<td>98.9</td>
</tr>
<tr>
<td>median</td>
<td>102.0</td>
<td>103.0</td>
<td>99.3</td>
</tr>
<tr>
<td>range</td>
<td>88.7-126.0</td>
<td>90.0-138.0</td>
<td>71.2-127.0</td>
</tr>
<tr>
<td>Methacholine test PD(_{20}) (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>2.7</td>
<td>3.6</td>
<td>0.9</td>
</tr>
<tr>
<td>median</td>
<td>2.1</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>range</td>
<td>0.07-16.8</td>
<td>0.09-28.3</td>
<td>0.01-8.1</td>
</tr>
<tr>
<td>eNO(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>22.6</td>
<td>20.2</td>
<td>26.3</td>
</tr>
<tr>
<td>median</td>
<td>14.5</td>
<td>11.7</td>
<td>17.4</td>
</tr>
<tr>
<td>range</td>
<td>5.8-71.4</td>
<td>5.7-92.3</td>
<td>4.4-192.8</td>
</tr>
<tr>
<td>EVH(^3) (maximum decrease in %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>-5.8</td>
<td>-8.1</td>
<td>-10.9</td>
</tr>
<tr>
<td>median</td>
<td>-4.0</td>
<td>-7.4</td>
<td>-7.6</td>
</tr>
<tr>
<td>range</td>
<td>-1.0 to -23.4</td>
<td>+1.4 to -21.9</td>
<td>+0.9 to -53.5</td>
</tr>
</tbody>
</table>

\(^1\) BMI = Body mass index (kg/m\(^2\)) \(^2\) eNO = Exhaled nitric oxide \(^3\) EVH = Eucapnic voluntary hyperventilation \(^a\) Difference in logPD\(_{20}\)
Figure 9. Percentage with a positive test to methacholine (p<0.01), to eucapnic voluntary hyperventilation (EVH) (ns), and increased exhaled nitric oxide (eNO) defined with a high cut-off (ns) and a low cut-off (ns) in groups according to asthma status in 2003. The p-values refer to differences between the three groups.

**Skin prick test**

Of subjects with no current asthma in 2003, 52% had a positive test with one or more of the tested allergens, as compared with 70% of those with current asthma (ns). Of all atopics, 24% had increased eNO with the high cut-off level, as compared with 8% of the non-atopics (ns). With a low cut-off level, the corresponding numbers were 41% and 8%, respectively (p<0.01).

**Exhaled nitric oxide**

There was no significant difference in the number with increased eNO using the high cut-off level in subjects with and without current asthma, 16% and 24%, respectively, or using the low cut-off level, 30% and 29%, respectively.

**Methacholine challenge test**

All 71 subjects performed the methacholine challenge test. There was a difference in hyperresponsiveness to methacholine among the groups: not current asthma, current asthma with and without asthma control (p<0.01).
Eucapnic voluntary hyperventilation

The EVH challenge test was performed by 65 subjects. There was a decrease by 10% or more in FEV$_1$ in 28%. There was no significant difference in the number of subjects with a positive test in the groups with and without current asthma (34% and 11%, respectively).

Asthma control

Thirty per cent of the subjects with current asthma in 2003 had achieved full control according to our definition. There was no difference in the distribution of the levels of asthma control with respect to sex, the number of atotics, increased eNO (either low or high cut-off level), a positive EVH test, methacholine challenge test or FEV$_1$.

Of the subjects with asthma without control only one third used ICS. Subjects with symptoms of allergic rhinitis during the last year more frequently had uncontrolled asthma (p<0.001). The distribution of positive results of methacholine challenge test, EVH test and eNO for subjects with current asthma in relation to asthma control and atopy is shown in figure 10.

![Figure 10. Proportion of subjects with a positive methacholine test, positive eucapnic voluntary hyperventilation test (EVH) and increased exhaled nitric oxide (eNO) defined with a high cut-off and a low cut-off in groups according to presence of asthma control and atopy (positive skin prick test)
Figure 11. Self-assessed disease severity in relation to asthma control in subjects with current asthma in 2003

Disease severity according to the patients

The subjects in the second survey assessed their own disease severity. In figure 11 this self-assessment was compared with objective asthma control.

Summary table of main results

Table 13. Summary table of main results in the thesis

<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></td>
<td>2001 survey</td>
<td>2005 survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment with ICS (%)</td>
<td>30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treatment with ICS + LABA or LTRA (%)</td>
<td>12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>34&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nocturnal symptoms (%)</td>
<td>23&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Emergency consultations (%)</td>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Self-assessed disease severity&lt;sup&gt;f&lt;/sup&gt; (%)</td>
<td>32&lt;sup&gt;g&lt;/sup&gt;</td>
<td>5.52</td>
<td>5.49</td>
<td>5.62</td>
</tr>
<tr>
<td>MiniAQLQ (mean of total score)</td>
<td>g&lt;sup&gt;g&lt;/sup&gt;</td>
<td>37</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Asthma control, yes (%)</td>
<td>g&lt;sup&gt;g&lt;/sup&gt;</td>
<td>37</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup> last week  <sup>b</sup> last 6 months  <sup>c</sup> > once a week  <sup>d</sup> > once a month  <sup>e</sup> last 12 months  
<sup>f</sup> moderate-very severe  <sup>g</sup> not measured
Discussion

Methodological issues

Sampling and response rate

Paper 1

This study aimed to recruit a sufficiently large sample of subjects representative of asthmatics in Sweden. Both asthmatics and GPs were recruited from the whole country. The asthmatics were recruited by telephone interviews performed by a market research agency, SIFO Research International, an investigation group entirely external to the researcher group. This agency (SIFO) performs all kinds of interviews on a wide range of topics. Our study design made it impossible to perform a non-response study, which is a limitation of this study.

The total prevalence of asthma according to the interview was lower than found in other prevalence studies using postal questionnaires [125, 126, 134, 135]. One possible explanation may be that asthmatics were reluctant to admit they had asthma for reasons of personal integrity. Furthermore, the number of subjects who fulfilled the definition of asthma but were not willing to participate was 31%. This may have influenced how representative the sample was of asthmatics. This non-participation rate was high compared with results from Swedish epidemiological studies of asthma based on the general population [125, 126, 134-136]. One explanation for the high non-participation rate may be reluctance to participate in time-consuming interviews performed by persons not involved in health care. Possible bias may, in that case have resulted in random errors with little or no effect on the results.

On the other hand, asthmatics with more severe symptoms may have been more likely to participate than asthmatics with mild or intermittent asthma. If so, a bias of that kind would have caused a systematic error in the sense that asthmatics with milder symptoms would have been somewhat underrepresented in the study.

The participation rate of the GPs was quite low which raises the question of whether their answers are reflective of all Swedish GPs. The age and sex distribution of the GPs suggests that they were a representative group, although the participation rate was low. One possible explanation for the rela-
tively close correlation between the GPs’ opinions and the answers given by the asthmatics may be that the GPs who participated had a special interest in asthma care and treatment. If GPs who were not very interested in asthma did not participate, it may be possible that the participating GPs’ opinions about the asthmatics’ problems and well being could differ from those of GPs in general.

Papers II and III
The surveys in paper II and III were performed in a random sample of patients in primary care with an asthma diagnosis. In the survey in 2001 the patients were randomly sampled from a random sample of 42 PHCCs in the Uppsala-Örebro region. These PHCCs were stratified with respect to size and the existence of an asthma clinic. The Uppsala-Örebro region has two million residents, representing more than one fifth of the Swedish population.

In the 2005 survey, patients were randomly sampled from a random sample of 56 PHCCs in the Uppsala-Örebro region. In 2005, the PHCCs were stratified, with eight PHCCs from each of the seven counties in the region. The patients in both surveys in paper III were in the same age group, 18-45, and had had appointments at the primary care centres owing to asthma during the last eighteen months.

The response rate of 77% in the survey in 2001 was high, considering the fact that many of the responders were young. In paper II, 27% of the non-responders were selected from a sample of the participating PHCCs for a telephone interview. Seventy (67%) of these agreed to be interviewed. The non-response analysis revealed no signs of selection bias. In the second survey in 2005, in paper III the response rate was lower, 60%.

No follow up of the non-responders was performed in the survey from 2005. This survey was carried out with the same design and in the same region as the survey from 2001 and there were no differences according to sex or age between responders and non-responders in the second survey. We therefore assumed that the non-responders did not differ from the responders in any crucial respect. In our opinion, the results in papers II and III are representative of a population of asthma patients managed in primary care in Sweden.

One limitation concerning the sampling of patients in papers II and III is that the random sample of patients was based on those who had a diagnosis of asthma and had been to their GP during the last year and a half owing to asthma. Patients with very mild disease might not have had the need to attend their primary health care centre often, and would therefore be excluded from the study, which might be an explanation for the low proportion of patients with asthma control in this report. Patients, especially those with mild disease, might also receive prescriptions without an appointment with a physician, and would therefore not be found in the diagnosis register for the
selected period. The prevalence of intermittent and mild asthma known in primary care in other studies is also considerably lower than in epidemiological studies [26].

**Paper IV**

The screening question about asthma and airway symptoms used in paper IV has been used in another large Swedish study [40]. The definition of current asthma has also been used in several other studies [29, 137].

Of subjects fulfilling the criteria for current asthma in the survey in 1997, 68% participated in the follow up in 2003. With respect to the age of the group, this is a satisfactory number. Nor were there any differences regarding sex or age between participants and non-participants in 2003. Of the 71 subjects in the survey in 2003, six did not perform an EVH test at visit two, but all 71 performed all the other tests at visit one.

The questionnaires and the classification of asthma severity and asthma control

**Papers 1-IV**

Potential recall bias may be involved in the symptom and exacerbation reporting and reporting of medication use. However, similar questions with a recall period up to the last six months have been used in several other large asthma studies reporting asthma severity and asthma control both in Sweden and in international studies [4, 21, 138]. One limitation of the studies in papers I-III is that the results were entirely based on patient questionnaires.

The classification of severity levels in paper II was based on the GINA guidelines in 2005, modified according to the information obtained from the postal survey. The GINA guidelines include lung function in the severity grading, but as no clinical examination was performed in this study this information was not available. The results from the study would probably not have changed even if this information had been available.

The questionnaires used in papers II and III were constructed some years before the definitions of asthma control were published in the latest GINA guidelines [16]. As a consequence, the classification of asthma control in paper III was slightly different from the classification used in the new GINA guidelines. In contrast to the guidelines our classification did not include lung function test. The majority of general practitioners do not normally perform spirometry regularly in asthma patients to evaluate asthma control, and therefore the level of control in real life is based only on clinical data in most cases. However, the definitions are similar and comparable to the definitions of control in these guidelines.

Both surveys in paper III were performed during the winter season, and the questionnaires contained the same questions about asthma control. One
limitation of the study in paper III might be that the time interval of four years used between our two surveys to compare asthma control could be too short to measure any changes in the degree of control as a result of a possible improvement in the management of asthma in primary care.

Discussion of main results

The aims of this thesis were to focus on asthma patients, both adults and adolescents, treated in primary care. The main findings of the present thesis were that the asthmatics had considerably more symptoms of asthma than expected, particularly symptoms in situations common in daily life. Many patients with asthma treated in primary care did not have asthma control, and there was also a discrepancy between the patients’ own assessments of their disease severity and asthma control according to the guidelines.

Asthma symptoms

Minimal asthma symptoms, no activity limitations, minimal need for reliever and no exacerbations are all important treatment goals in the management of asthma patients [16, 17]. But still, as has been demonstrated in this thesis, a large portion of asthma patients in primary care have many symptoms and also exacerbations.

In paper I, where two thirds of the patients had their contacts with the health care system in primary care, the patients reported many asthma symptoms. These were also more than the physicians had expected. Surprisingly many, almost one out of five, had nocturnal symptoms at least twice a week, which was also more frequently than the physicians had expected.

The findings of nocturnal symptoms almost as high as in paper I were also demonstrated in the 2001 survey in paper II. The figures were lower in the 2005 survey in paper III, but still about one fourth of the asthma patients in primary care had nocturnal awakenings due to asthma at least once a week. These results confirm the findings from other international studies [4, 139, 140]. The majority of asthmatics in paper I had symptoms when performing different physical activities. When exposed to pets, the majority also experienced asthma symptoms frequently. The assumptions of the physicians in paper I conformed surprisingly well with reference to the answers given by the asthmatics. These results are in contrast to findings from other studies [49, 139].

A Dutch study has demonstrated that Dutch paediatricians and general practitioners underestimate the severity of their patients' disease state and overestimate their patients' knowledge of disease management [141]. The same results were found in a British study [139].
Asthma severity

The concepts of asthma severity and control are considered important in the assessment of asthma patients [79]. Different guidelines and authors have used the term “severity” in different ways during the last decade, which is sometimes confusing. It has been used in evaluation of patients both before and after treatment.

A recent review, carried out by an American Thoracic Society/European Respiratory Society Task Force, recommends the term “asthma severity” for referring to the intensity of treatment required to control the patient’s asthma [82]. The recommendation also presumes that the severity of asthma is closely related to its responsiveness to treatment. This implies that patients with severe asthma may be well controlled on high doses of treatment. The asthma severity may also change over the months or years, and may be influenced by both the disease activity and by the patient’s phenotype. Before a label of severe asthma can be applied to a patient, other diagnoses or readily treatable disease should be excluded, to avoid classifying patients with poor asthma control as having severe asthma [142].

The classification of asthma severity in paper II was slightly different from the classification for patients on asthma treatment used in GINA guidelines in 2005. As in GINA, we divided asthma into four severity levels: intermittent, mild, moderate and severe. This classification was based on information on current treatment, the use of rescue medication, nocturnal symptoms, emergency consultations, and use of oral steroids, but in contrast to the GINA guidelines it did not include lung function data.

Using this classification, two-thirds of the patients treated in primary care in paper II had moderate or severe asthma. In recent years, many patients have received additional treatment to ICS with LABA or LTRAs, and consequently more patients, with both our classification system and the GINA guidelines from 2005, are classified at higher severity levels.

Furthermore, it is unknown whether patients, despite very mild disease, use combinations with ICS and LABA in spite of the fact that monotherapy with ICS is recommended in mild asthma in the Swedish guidelines [11]. These patients will be classified as having more severe asthma both in our study and in the original classification in the GINA guidelines. Another possible explanation for the results is that most patients with asthma in Sweden, including those with moderate and severe disease, are managed in primary care nowadays.

The patients in paper II were recruited from patient records with an asthma diagnosis during the previous eighteen months. As many patients with intermittent and mild asthma seldom seek health care, this could also be an explanation for the low proportion of those groups of patients.

There was a strong association between asthma severity and MiniAQLQ both concerning the overall score and the domains. This was especially ap-
parent when comparing patients with severe asthma and patients with less severe disease. This implies that severity classification has also an impact on the patients’ quality of life. A total score of 6.0 or more has been proposed as a level describing good asthma control [143, 144]. In paper II, 12% of the patients with severe asthma had an overall score of more than 6.0, implying that in some cases severe asthma does not have a dramatic impact on quality of life.

Like in some other studies, there was a significant sex-related difference in asthma severity, with 35% of the women having severe persistent asthma, as compared with 24% of the men [73, 75]. When adjusted for other risk factors, there was a 60% greater risk of women having severe asthma. Women reported more symptoms, more frequent exacerbations and also more courses of oral steroids. This indicates that the sex difference in severity was dependent not only on the level of medication but also on the extent of symptoms.

The reason for this sex difference is not explained, although factors like other allergic co-morbidities and hormonal factors have been suggested [70, 76-78, 80, 145, 146]. Allergy to pets and pollen is common in patients with asthma, and allergy sensitisation is associated with increased frequency of emergency visits [21, 42]. However, it was not possible to demonstrate any difference in self-reported allergy to pollen or pets between women and men.

Smoking also influences the disease and the effects of the asthma medication [59, 60, 147]. In Sweden, smoking has declined in recent decades, but about 15% of the population are still daily smokers, with a predominance of women [43, 44]. The proportion of smokers in the 2001 survey in paper II was lower than in the corresponding segment of the general Swedish population at the time, while the sex difference in smoking habits was higher [43]. Smoking was also a factor associated with an increased probability of severe asthma, which highlights the importance of smoking cessation.

Asthma control

Asthma control is of importance both with regard to current status and to future risk of adverse outcomes [82]. In recent years, many guidelines have emphasised the importance of the patient achieving asthma control [10, 16, 17, 148, 149].

Paper III, a comparison between two surveys performed in 2001 and 2005, demonstrates that many patients aged 18-45 years with asthma treated in primary care do not achieve asthma control, with no differences between the two surveys. The study in paper IV in individuals aged 13-22 years, also demonstrates a high prevalence of patients without asthma control. The same result and difficulties in achieving asthma control have been pointed out in a large number of international studies [4-7, 84-86]. One reason for this absence of asthma control might be that the patients are undertreated with in-
haled corticosteroids according to current guidelines [150]. Another reason for insufficient control might be lack of adherence to prescribed medication [65, 84, 151-153]. The studies in papers III and IV, and other studies, indicate that many patients with insufficient control only use SABA as needed, or only inhaled corticosteroid [7]. A large number of these patients should probably be at a higher treatment level, according to current guidelines [154, 155].

In the surveys in paper III, we found that many patients used their inhaled corticosteroid only periodically, in contrast to treatment guidelines and probably to the prescription from their doctor. This conceivable undertreatment might also be a contributory cause of insufficient control, and demonstrates the importance of improving adherence to medication among asthmatic patients [49, 156-158]. Women had also achieved asthma control less often, which is in accordance with other studies [73, 75, 159]. Patients with uncontrolled asthma in our study had been on sick leave more often, which is of importance in terms of the economics of public health [160].

Although poor asthma control may be attributable to underlying severe disease or resistance to therapy, it is far more frequently due to poor adherence, poor inhaler techniques, under-prescribing, or environmental factors such as allergen exposure or smoking. Patients may also appear to have poor clinical asthma control owing to incorrect diagnosis.

Difficulties with implementation of novel treatment guidelines in primary care might be another cause of this apparent undertreatment [48]. Other authors have also pointed out the need for effective tools for identifying patients with poor control in clinical practice [49-52].

In paper III in the 2001 survey 37% and in the 2005 survey 40% had achieved asthma control. This can be compared with the level of control achieved with treatment of other chronic diseases in primary care. In a study from 2001 among patients with diabetes mellitus in primary care in Sweden, 57% reached the goal regarding HbA1c [161].

In another study, 55% of the patients treated with statins reached their goal for total cholesterol [162]. In comparison with those findings, it seems more difficult to achieve the treatment goals in asthma treatment. One reason might be that the goals in asthma treatment are more complex to define and need structured patient consultation, as compared with diseases where treatment goals are defined in terms of laboratory parameters.

The number of smokers decreased between the two surveys in paper III, but more women than men still smoked. This decrease is in line with the national trend in Sweden [44]. Smoking has been demonstrated to have a negative influence on the effects of inhaled corticosteroids in asthmatics, and on the severity of disease [59, 60]. This might be one reason why fewer smokers than non-smokers in our study had achieved asthma control.
Patient assessed severity

In papers I, III and IV, the patients assessed their disease severity. The majority of these patients assessed their asthma as mild or very mild, in spite of the frequency of symptoms and lack of asthma control defined according to the guidelines. This finding is in concordance with other international studies, demonstrating a lot of symptoms while patients consider themselves to have mild asthma [8, 150, 163, 164].

This repeated discrepancy suggests that asthmatics have adapted to living their lives without becoming symptom free [4, 9]. Another reason for this discrepancy might be that the patients have different treatment goals from the goals defined in guidelines [156, 165]. On the other hand, in the 2005 survey in paper III some patients had controlled asthma but still judged their own asthma to be moderate or severe. One reason for this may be that our definitions of control do not take into account all the limitations in daily life, which are important to the individual patient when judging his/her own asthma [166, 167].

Asthma treatment

An important finding in paper I was that the asthmatics felt they adhered well to the prescriptions issued by their physicians, but in fact a large discrepancy was found between the prescriptions and the patients’ actual use of medications. In line with others’ findings, the adherence to regular treatment with ICS was low in the study in paper I. Patients handled their increased asthma activity in a similar way to that described in other studies, i.e. they mainly increased their use of inhaled short-acting beta2-agonist [4, 150, 168].

In the study in paper I, a majority of the asthmatics with inhaled corticosteroids increased their use of, or started to use ICS, during periods of worsened asthma symptoms. One explanation could be that many patients with asthma underestimate their symptoms and therefore discontinue their medication in periods [169-172]. This also indicates that asthmatics very often make their own decisions about when to use or not to use their medications. Another reason for low adherence could be that many patients neglect to fill their asthma prescriptions owing to cost. In paper II, not filling the asthma prescription owing to cost also increased the odds for having severe asthma. Low adherence to prescribed treatment is also common in adolescents and young adults, which might be a reason for the high number of asthmatics with insufficient control in the study in paper IV [65, 66, 173]. In the study in paper I, the adherence to prescriptions was lower to an extent that was not anticipated by the GPs in their estimates. In paper III a large proportion of patients with exacerbations frequently used rescue medication and had noc-
turnal awakenings also when they were not having exacerbations, indicating undertreatment.

More patients were treated with inhaled corticosteroid combined with long-acting beta2-agonist in the 2005 survey than in the 2001 survey. This may be attributable to the changes in the recent guidelines, which recommend adding LABA to ICS instead of increasing the dose of ICS. A change in prescription habits in Sweden towards use of more fixed combination devices has also been noted [54]. However, in spite of these changes in prescriptions, a substantial number of patients still had uncontrolled asthma in both surveys.

Additional findings in paper IV

In the study in paper IV, in the initial screening questionnaire to 1,244 school children, slightly more individuals answered the question about asthma and airway symptoms affirmatively than in another Swedish study using the same screening question. Our figure was 16.7% as compared with 14.5% [40, 174]. The prevalence of current asthma in these populations of children aged 7-15 years was estimated to be 8.6% which is comparable to figures in other Swedish studies [31, 175].

In the second survey, six years after the first, the same questions for evaluation of current asthma as in the first survey gave fewer individuals with current asthma, corresponding to a mean annual remission rate of five per cent. A high remission rate in this age group has been demonstrated by many other authors [31, 176, 177]. It has also been demonstrated in a long term follow-up study in asthmatics, that asthma severity improves from childhood to adulthood [32].

In this follow up of individuals with mainly mild asthma it was not possible to predict the asthma outcome based on the results of the questionnaire answered six years earlier. Some of the adolescents and young adults who had asthma six years earlier in the first survey and who were defined as not having current asthma in the follow up had abnormal test results, which may indicate a risk that their asthma will resurface in the future.

Not surprisingly, we found that individuals with current asthma more often had a positive methacholine challenge test than individuals without current asthma. Although the methacholine challenge test is of diagnostic value and is a marker for airway hyperresponsiveness, it cannot be used routinely in primary care, owing to the complexity of the method.

Exhaled nitric oxide measurement is a usable method in primary care, but its applicability in non-atopics asthmatics and in the management of mild asthmatics has been debated [116, 117, 178-180]. In the study in paper IV, as in other studies, a higher proportion of individuals with normal eNO was found among non-atopic asthmatics, independent of cut-off level [111, 112, 181]. This points out the importance, when using eNO, of taking into con-
sideration possible coexisting atopy. Another reason for the high proportion of low eNO values in subjects with no asthma control could be that many subjects with current asthma had mild disease, and some of them also used ICS.
Conclusions

- The majority of asthmatics report a large number of symptoms and limitations in their daily lives. Adherence to treatment with inhaled corticosteroids is low. A large proportion of asthmatics report nocturnal symptoms. Swedish general practitioners often have good knowledge about the well-being of asthmatics.

- Age, female sex, reported pollen allergy, not filling the asthma prescription owing to cost and smoking are factors associated with an increased probability of severe asthma in patients in primary care. These factors may be important to consider when managing asthma patients in clinical practice.

- In spite of treatment recommendations and effective asthma medications, many patients in primary care still have insufficient asthma control. It is important to evaluate the degree of asthma control when monitoring patients with asthma. There was also a discrepancy between the patients’ own assessments of their disease severity and asthma control according to the guidelines.

- A follow up of adolescents and young adults with asthma demonstrated that many with current asthma do not achieve asthma control. One reason might be undertreatment with inhaled corticosteroids. Some of the adolescents and young adults with asthma six years earlier and defined in the follow up as not having current asthma had abnormal test results, which may indicate a risk that their asthma will resurface later.
Swedish summary

Syfte

Avhandlingens syfte var att undersöka svårighetsgrad, behandling och graden av astmakontroll hos patienter med astma i primärvården.

Frågeställningar i respektive delarbete:

- Delarbete I: Hur mår och hur medicinerar astmatiker i Sverige och vilka begränsningar innebär deras astma (ALMA-studien)?
- Delarbete II: Hur mår och hur behandlas patienter med astma som kontrolleras i primärvården i åldern 15-45 år och vilka faktorer är relaterade till svårighetsgraden av deras astma (AIM-studien)?
- Delarbete III: Har graden av astmakontroll förändrats mellan åren 2001 (AIM-studien) och 2005 (del av PRAXIS-studien) och vilka faktorer kan relateras till otillräcklig astmakontroll i åldersgruppen 18-45 år?
- Delarbete IV: Vad karakteriseras astmasjukdomen hos de ungdomar och unga vuxna som i en enkät sex år tidigare angivit att de hade läkardiagnostiserad astma?

Metod

I det första delarbetet genomfördes en telefonintervju med ett slumpvis urval av 240 astmatiker i åldern 18-45 år.

I det andra delarbetet besvarade ett slumpvis urval av 1136 patienter med astma i åldern 15-45 år i primärvården i Mellansverige, ett frågeformulär som innehöll frågor om medicinering, symtom och akuta försämringar samt ett livskvalitetsformulär. Baserat på internationella riktlinjer kunde svårighetsgraden av deras astma bedömas.

I det tredje delarbetet jämfördes graden av astmakontroll hos ett slumpvis urval av 1012 patienter år 2001 och 224 patienter 2005, samtliga från primärvården och i åldern 18-45 år.

I det fjärde delarbetet besvarade 71 ungdomar och unga vuxna med astmadiagnos sex år tidigare ett frågeformulär för att bedöma graden av astmakontroll. De undersöktas även med allergitest, metakolin- och torrluftsprovokation för att bedöma graden av luftvägskänslighet samt utandad kväveoxid.
Resultat


Konklusion

En majoritet av individer med astma rapporterade en hög andel symtom och begränsningar i sitt dagliga liv på grund av astma. En majoritet av astmapatienter i primärvården hade inte fullgörd astmakontroll. En orsak till detta kan vara underbehandling med inhalationskortison och låg följsamhet till ordnerad behandling.
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Appendix

English condensed version of “Questions about your asthma”. Answers were mostly multiple choice but sometimes open answers were required. Typical choices were “Yes”, “No” and “Don’t know” if not otherwise specified. Abbreviations used: Inhaled corticosteroids (ICS), short- and long-acting beta2-agonist (SABA) and (LABA).

**Background data**
1. What is your age and gender? ____ years  Female/Male
2. How many years have you had asthma? < 1 year, 1-5 years, > 5 years
3. What is your main occupation? – full-, part-time or domestic worker, unemployed, student or other specified alternative?
4. Do you smoke daily?

**Symptoms**
5. Do you get asthma or rhinitis symptoms from pollen (birch, grass or mugwort) or to furred animals (cat, dog or horse)?
6. Have you woken up due to cough, wheeze or shortness of breath in the last week?
7. Have you made emergency/unscheduled urgent care visits to hospital, primary care or paediatric care due to asthma in the last six months? If yes: once, twice, > two times.
8. Have you been hospitalised due to asthma in the last six months?
9. Have you been home from work or studies due to asthma in the last six months? If yes: once, twice, > two times. If yes, the number of days?

**Medication** – answers if not otherwise specified - regularly, periodically or not at all.
10. Have you used SABA due to asthma symptoms more than twice in the last week?
11. Have you used ICS the last six months?
12. Have you used LABA the last six months?
13. Have you used leukotriene antagonist the last six months?
14. Have you used systemic corticosteroids due to asthma exacerbation the last six months? If yes, specify how many times.
15. Have you used homeopathic drugs, zone therapy or acupuncture the last six months?
16. Have you renounced to pick up your prescribed asthma medication due to costs in the last year?

**Medical care**
17. Do you go to annual follow-ups for your asthma?
18. Do you know which doctor is responsible for your asthma treatment?
19. Do you use a peak flow meter? Often, sometimes, seldom or never
20. Have you ever received instructions on how to inhale your medication?

**Knowledge** – answers “Yes absolutely”, “Yes partially” and “No”.
21. Do you know how to change your medicating at: infections, more asthma symptoms, deteriorated peak flow value?
22. Do you consider yourself to have sufficient knowledge of your asthma disease?
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