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# Asthma treatment in Primary Care – studies of variability and health economic aspects

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” I Started Out With Nothin’ and I Still Got Most of it Left”

Seasick Steve

To my dear family

## ABSTRACT

*Background:* Most asthma patients in Sweden are treated in primary care, but little is known about economic aspects of asthma treatment in that setting and about the regional variation in the use of antiasthmatic drugs and the adherence to national guidelines for the treatment of asthma.

*General aims:* To analyze treatment of asthma patients in terms of classification of severity, quality of life, variation in utilization, clinical practice and costs from a societal perspective.

*Methods:* A prospective cross-sectional design was used to study the pharmaceutical costs of asthma and their relationship to quality of life, asthma severity, clinical practice and lungfunction and to compare different approaches to classifying asthma severity, all in primary care. A prospective cluster-randomized controlled trial was carried out in primary care to study the effect of information and monitoring on asthma control. To study regional variations in antiasthmatics, a registry study based on the Swedish National Prescribed Drug Register was performed. In all studies, the population consists of adult patients. However, in the registry study, there was an upper limit of 44 years of age to exclude patients with COPD.

*Results and conclusions:* There are large variations in costs of pharmaceuticals for asthma treatment between primary care centers in Stockholm as well as between different regions in Swedish. Asthma severity explains only a small part of the variations in pharmaceutical costs and does not account for the differences between centers. When different approaches used to classify asthma severity were tested, no strategy tested was superior. Adherence to guidelines is low among caregivers. There is room for improvement of both asthma control and quality of life of asthma patients treated in primary care. Adding structured information and monitoring by diary can improve the patient's outcome.



*Keywords:* Drugs, prescribing, costs, regional variations, primary care, asthma, quality of life,

# SAMMANFATTNING


**Bakgrund.**
De flesta astmatikerna i Sverige behandlas i primärvården, men lite är känt om de ekonomiska aspekterna av astmabehandling inom primärvården. Det saknas också viss kunskap om kostnader och hur förskrivning av läkemedel för astma skiljer sig mellan olika vårdcentraler i ett landsting respektive mellan landstingen. Nationella riktlinjer för astmabehandling finns, men lite är känt om hur de efterlevs och om det finns regionala variationer därvidlag.

**Syfte**
Det övergripande syftet med avhandlingen var att studera astmabehandling i den svenska primärvården från ett hälsoekonomiskt perspektiv. Mer specifikt studerades (I) relationen mellan variabler som kan påverka läkemedelskostnaderna och skapa en prediktiv modell för dessa kostnader, (II) olika ansatser att klassificera svårighetsgrad samt hur dessa påverkade fördelningen av läkemedelskostnader, samt gemensamma faktorer mellan begreppen astmasvårighetsgrad och astmakontroll, (III) om fördjupad strukturerad information och monitorering med hjälp av astmadagbok, så som sker i kliniska prövningar, påverkar behandlingsresultat och läkemedelskostnader, (IV) samt regionala variationer i uttag av läkemedel för astma och följsamhet till nationella riktlinjer för läkemedelsbehandling vid astma.

**Metod**
En prospektiv tvärsnittsstudie användes för att studera läkemedelskostnader i relation till livskvalitet, svårighetsgrad, klinisk praxis och lungfunktion i studie I och studie II för att jämföra olika ansatser till klassificering av svårighetsgrad i astma. Studie III är en prospektiv cluster- randomiserad interventionsstudie. Studie IV är en registerstudie, baserad på Socialstyrelsens nya läkemedelsregister. Populationen i de fyra studierna innefattade vuxna patienter

från 18 års ålder och däröver. I registerstudien sattes dock övre gränsen till 44 år för att exkludera KOL-patienter, då indikationen för läkemedelsbehandlingen inte framgår i registret.

**Resultat och konklusion:**

- Läkemedelskostnader för en genomsnittlig astmapatient varierar mycket mellan landstingen och även mellan olika vårdcentraler inom Stockholms läns landsting.
- Läkemedelskostnaderna vid astmabehandling bestäms endast till en liten del av astmans svårighetsgrad.
- Relativt små extrainsatser från personalen kan förbättra patientens astmakontroll.
- Följsamheten till de nationella riktlinjerna för läkemedelsbehandling vid astma är låg.

## LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to in the text by their roman numerals (I-IV)

**I.** **Arnlind Heibert M,** Nokela M, Rehnberg C, Wikström Jonsson E. **The relationship between pharmaceutical costs, disease severity and health related quality of life in asthmatics in Swedish primary care.** J Asthma 2006, 43:585-591.

**II.** **Arnlind Heibert M*,** Nokela M*, Wikström Jonsson E. **Asthma Severity in Primary Care Asthmatics: A comparative study of different approaches to classification of severity.** Accepted 27 November 2008 in Primary Care Respiratory Journal.

**III.** Nokela M, **Arnlind Heibert M**, Ehrs P-O, Krakau I, Forslund L, Wikström Jonsson E. **The influence of information and monitoring on treatment outcome in primary care treated asthma: a cluster randomized study.** Submitted.

**IV.** **Arnlind Heibert M,** Wettermark B**,** Hjemdahl P, Nokela M, Rehnberg C, Wikström Jonsson E. **Regional variation and adherence to guidelines for drug treatment of asthma.** Manuscript.

*equal contribution

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACT | Asthma Control Test |
| ACQ | Asthma Control Questionnaire |
| AQLQ(S) | Asthma Quality of Life Questionnaire with standardized activities |
| COI | Cost of Illness |
| COPD | Chronic Obstructive Pulmonary Disease |
| DDD | Defined Daily Dose |
| DTC | Drug and Therapeutic Committee |
| EUR | Euro |
| $FEV_1$ | Forced Expiratory Volume in one second |
| GINA | Global Initiative of Asthma |
| GP | General Practitioner |
| HE | Health Economic |
| HRQoL | Health Related Quality of Life |
| ICS | Inhaled Corticosteroids |
| LABA | Long-acting $\beta_2$- agonist |
| NICE | National Institute for Health and Clinical Excellence, UK |
| QALY | Quality-Adjusted Life Year |
| SEK | Swedish kronor |
| PEF | Peak Expiratory Flow |
| PHCC | Primary Health Care Center |
| RCT | Randomised Control Trial |
| SFD | Symptom free day |
| SF-36 | Short-form-36 Health Survey |
| SBU | The Swedish Council on Technology Assessment in Health Care |

## CONTENTS

# INTRODUCTION

Approximately 40 percent of all Swedish teenagers and young adults suffer from allergy and hypersensitivity (2) and it is estimated that more than three million people in Sweden have or have had some type of allergy or hypersensitivity. During the last twenty years, the cases of asthma, eczema and hay fever have doubled in Sweden. These allergic diseases cause suffering, impair social participation and contribute to increased expenditures and burden for the families concerned. Due to the increased prevalence, increased costs for diagnosis, treatment, illnesses and production loss place a continuously growing burden on society as the number of persons with allergy and other hypersensitivity in the population increases (3).

## 1.1 ASTHMA – A GLOBAL PUBLIC HEALTH PROBLEM

Allergy constitutes an important risk factor for asthma. Asthma is one of the most common chronic diseases worldwide, with an estimated 300 million affected individuals. The prevalence, especially in children, is increasing in many countries (4). Wales, New Zealand and Ireland have the highest prevalence, about 15%, and Albania, Greece and the Russian Federation have the lowest, about 2%. The prevalence in Sweden was estimated to 6.5% (4). One out of four Swedish children has had asthma symptoms during their first four years of life. Probably, the prevalence of asthma increases with age (5). A recent report states that, in Sweden, 7% of four- years- old children and 5% of twelve-year-old children and approximately 10% of the adult population have asthma (6). The Swedish Environmental Health Report 2009 found no increase in prevalence between 1999 and 2007, but others state that the prevalence of asthma has increased during the last decades in Sweden as well as worldwide (7, 8). The “true” prevalence is not easy to establish, since definitions of asthma differ and there is no single objective diagnostic test. Definitions found in the literature include doctor’s diagnosis, “wheeze”, (which may have different

meanings), and use of anti-asthmatic drugs. The time-period covered by questions about asthma also influences the results: currently, the last 12 months, ever. Furthermore, differential diagnoses in childhood (e.g. bronchiolitis) and old age (e.g. COPD) can influence prevalence data. Thus, different methods of classification and different interpretations of symptoms in different countries can contribute to the differences reported (4). For example; Asher et al. showed that reported asthma increased but current wheeze decreased in children (9).

In Sweden the number of hospitalizations and emergency visits for asthma problems has decreased, although the prevalence of asthma has not. Most asthmatic patients are nowadays managed in primary care (10). According to a recent report**,** asthma is number 13 in the top-20 list of diagnoses in primary care in Sweden (11). Therefore, asthma was studied with special focus on asthma patients treated in primary care in the present project.

## 1.2 DIAGNOSIS AND CLASSIFICATION OF ASTHMA

"Asthma is like love – everyone knows what it is but nobody knows how to define it" (12)

The Global Initiative for Asthma (GINA) states that: "The main physiological feature of asthma is episodic airway obstruction characterized by expiratory airflow limitation. The dominant pathological feature is airway inflammation, sometimes associated with airway structural changes. Asthma has significant genetic and environmental components, but since its pathogenesis is not clear, much of its definition is descriptive." (13). Common symptoms are recurrent breathing problems, wheezing and cough. Most asthma patients have intermittent asthma, but about 50 percent have breathing problems weekly or daily.

The chronic inflammation in asthma is associated with airway hyperresponsiveness, which can lead to recurrent episodes of wheezing, breathlessness, chest tightness, coughing and a variable and often reversible airflow limitation (14). To set a diagnosis of asthma, the physician can use the history and patterns of symptoms, measurements of lung function; i.e. spirometry and/or peak expiratory flow and/or measurements of airway responsiveness. Measurements of allergic status can be used to identify risk factors (15).

The concept of asthma has developed during recent years. Asthma is nowadays regarded as a complex of multiple, separate, but partly overlapping syndromes (16), described as different phenotypes[1]. Traditionally, asthma was divided into "exogenous" or "endogenous" asthma depending on how attacks were triggered. In a similar fashion, it can be divided into allergic and nonallergic asthma. Allergic asthma is due to specific immunological reactions, usually mediated by IgE antibodies (IgE-mediated allergic asthma) (18). Besides classification into phenotypes related to environmental triggers, Wenzel et al (16) propose that asthma could be classified according to broad categories of phenotypes into two other groups: phenotypes defined by their pathobiology, for instance which type of inflammatory cell predominates, and phenotypes defined by clinical or physiological criteria, such as severity. By GINA, asthma has been classified in four different severities, intermittent, mild persistent, moderate persistent and severe persistent asthma. In the previous classification, both symptoms and asthma treatment were taken into account (19). However, regardless of approach, classification according to phenotype is not routinely performed in Swedish primary care. In papers I and II, severity-classification is further investigated.

[1] A phenotype is defined as "the visible characteristics of an organism resulting from the interaction between its genetic makeup and the environment" (17)

## 1.3 OUTCOME MEASURES

Different outcome measures are used in the evaluation of asthma drugs. When assessing the effects of pharmacotherapy for asthma in clinical trials, measurements of lung function are often used. The most common measures are $FEV_1$ (Forced Expiratory Volume in 1 second) and PEF (Peak Expiratory Flow). The clinical relevance of these two measures has been questioned (20).

The Swedish Council on Technology Assessment in Health Care (SBU) stated that four primary outcome measures were important in asthma research(20):

- Asthma-related mortality
- need for increased medication, treatment in the emergency department or admission to hospital
- health related quality of life (HRQoL)
- symptoms

It would be impracticable impossible to use mortality as a primary outcome measure in most clinical trials on asthma patients. Too many patients and/or too long a study period would be required, due to the low mortality rate.

Another outcome measure is frequency of exacerbations. There are several ways to define an exacerbation when it comes to design of clinical trials. Briefly, an exacerbation can be described as a severe episode of respiratory symptoms, sometimes requiring treatment with oral corticosteroids (21). Exacerbations occur only rarely when patients are well controlled, and this outcome measure thus makes it difficult to dimension studies using asthma exacerbations as a primary outcome measure if the study population consists of patients with mild and/or well controlled asthma patients.

Yet even patients whose asthma is mild or well controlled will have reduced quality of life over long periods of time, often several decades (22). HRQoL can be measured both with generic and disease-specific methods. Examples of generic questionnaires are SF-36 and EQ5D, which can be used for comparisons of HRQoL between different diseases. The Asthma Quality of Life Questionnaire (AQLQ) is an example of a disease-specific questionnaire, which may be more sensitive to changes caused by asthma than the generic questionnaires. Studies indicate that there is only a weak relationship, if any, between lung function and quality of life (23, 24). Therefore, measurement of HRQoL is a valuable complement to clinical assessments of disease severity to assess the health care needs, the effectiveness of interventions and in cost-utility studies (25). In recent years HRQoL has thus emerged as an important outcome measure in clinical trials. Using HRQoL questionnaires in clinical practice ensures focus on the patient rather than the disease (26). Indeed, the patients' own view of their asthma severity seems to correlate better with HRQoL measurements than with objective measures, such as $FEV_1$ (27). However, the use of HRQoL questionnaires has not yet been established in clinical practice.

Validated methods for measuring asthma control are among others the Asthma Control Test (ACT) (28) and Asthma Control Questionnaires (ACQ) (29).

## 1.4 THE PHARMACEUTICALS

The main objective of asthma treatment is to achieve and keep clinical control over the asthma symptoms. Pharmacological treatment is fundamental to reach this objective. Both nationally and internationally, there are clear guidelines regarding pharmaceutical treatment of asthma. For symptomatic treatment, rapidly acting bronchodilators, also known as "relievers" or "rescue medication" are used. They rapidly relax airway smooth muscle, thus minimizing obstruction. They are usually inhaled and consist of inhaled short-acting inhaled

$\beta_2$-agonists (salbutamol/albuterol or terbutaline), but the long-acting $\beta_2$-agonist (LABA) formoterol which has rapid onset is also sometimes used for this purpose. The inhaled short-acting anticholinergic ipratropium bromide is also used as a reliever. Under special circumstances, short-acting theophyllamine, and/or short-acting oral $\beta_2$-agonists can be used for bronchodilatation (30). When relievers are needed more than twice a week, regular maintenance treatment is advocated. Medications for maintenance treatment are sometimes referred to as "controllers". With our current understanding, treating the underlying inflammation is a key to success. According to Swedish guidelines (figure 1), daily use of inhaled corticosteroids is recommended for patients who remain insufficiently controlled. If relievers are still needed more than twice a week, an inhaled LABA such as formoterol or salmeterol, or the cysteinyl-leukotriene receptor antagonist montelukast is added. The combination of LABA and inhaled corticosteroids can be administered either from separate inhalers or as a fixed combination in one single inhaler. When asthma control still is unsatisfactory, sustained-release theophylline, systemic corticosteroids, immunosuppressants and sometimes anti-IgE can be tried (figure 1). Anti-IgE, omalizumab, inhibits the immune system's response to allergen exposure and can be used for severe allergic asthma associated with perennial allergens.

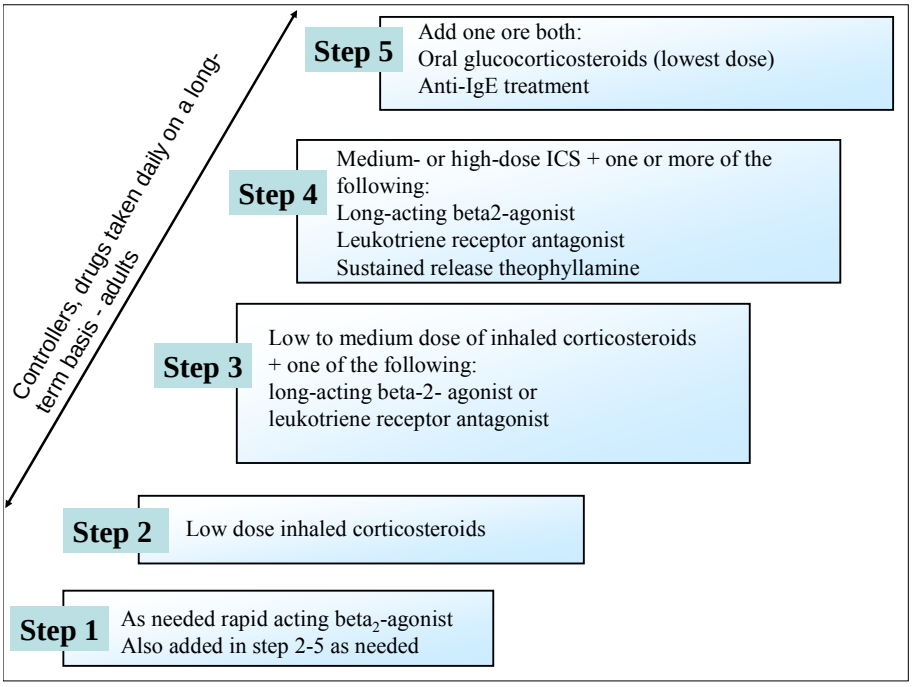


**Figure 1.** Swedish guidelines for pharmaceutical treatment of adult with asthma. Reference: Swedish Medical Products Agency 2007

## 1.5 HEALTH ECONOMIC EVALUATIONS

Asthma has negative consequences (both monetary and intangible costs as well as effects on health status) not only for the individual, but for the family, the municipality, the county council and for society as a whole. These consequences can be identified and measured by using the tools of health economics.

SBU concluded in their report from 2000 that the evidence for cost effectiveness of treatment regimens in asthma is inadequate (20) and that there is a need for more economic evaluations with good basic data material. The evaluation of costs and benefits of treatments is essential for priority-setting and development of health care programs and guidelines. From both a health policy and a management perspective, it is important to obtain knowledge about how

healthcare resources are used and distributed, and the impact of these factors on the benefit for patients and the society as a whole.

Health economics is based on economic theory and the methodology is applied in the area of health. Within health economics various effects that cannot be measured in monetary terms are taken into consideration, for example changes in quality of life (31). Health economic is a broad field which can be divided into the macro-perspective, economic evaluations and the broad societal perspective (32).

There are four main types of economic evaluations (33)

- Cost analysis
- Cost-effectiveness analysis
- Cost-utility analysis
- Cost-benefit analysis

A cost analysis is often a cost-minimizing analysis where the outcomes are assumed to be identical and only costs are compared. A cost-effectiveness analysis includes both costs and consequences: specific outcomes such as decreased blood pressures, disease-free time, disease-free life or years of life saved. The cost-utility analysis goes further by combining survival and quality of life and using saved quality-adjusted life years as an outcome. A cost-benefit analysis measures cost and benefit exclusively in monetary terms (34). Cost-benefit analyses have hitherto been rare in health care.

In an ideal economic analysis, direct, indirect and intangible costs are measured. Direct costs are due to for example hospital care, visits, drugs and medical procedures but also social services, informal costs and transportation. Indirect costs consist of loss of production due to mortality or morbidity and intangible

costs stem from reduced quality of life due to pain, disability, anxiety, social isolation etc (33).

A Cost-of -Illness (COI) study is not an economic evaluation. The COI-study describes the burden the disease places upon society and does not examine the outcomes (34). Three health economic reviews by Weiss et al. (35), Sullivan et al. (36) and Lee et al. (37) concerning allergies conclude that the majority of COI-studies and economic evaluations included only direct costs. On the other hand, an effort is to incorporate also indirect costs. In comparison with the relatively few published COI- studies, the literature contains many economic evaluations, mainly focused on pharmaceuticals.

This thesis examines only a small fraction of the health economic perspective. It focuses on costs of pharmacological treatment, regional variations and determinants of such costs.

## 1.6 HEALTH ECONOMIC ASPECTS ON ASTHMA CARE

The total annual cost for asthma in Sweden was estimated to be just over SEK 2.5 billion in the beginning of the 1990's (38). In 2005 it was calculated at about 7 billion, of which 30-40 percent was direct costs and 60-70 percent was indirect costs (39). The cost of inpatient care has decreased and the costs for outpatient care and drugs have increased (40). In recent decades, both in Sweden and internationally, the treatment of asthma has moved from inpatient to outpatient care, from hospitals to primary care centers. Hemp et al. (41, 42) showed that an often overlooked component in the indirect costs is the cost of impaired work capacity (presenteeism). The number of days with impaired work capacity for full time working was more than twice the registered absence due to sickness. One American survey (43) showed that about half of all children with asthma and a quarter of the adults with asthma had been away from school/work

during the last twelve months. Moreover, 41 percent of the children and 54 percent of the adults received treatment in an emergency department or as inpatients in hospital during the same time. Cisternas et al. show in their study that asthma-related costs are extensive and determined largely by use of pharmaceuticals and work loss (44). Barnes et al. showed that the costs for asthma to a large extent arise because the disease is not optimally treated, i.e. that the therapies are underused or incorrectly used (45). This can lead to unnecessarily high costs for society. The cost of pharmaceuticals for patients with mild to moderate asthma has previously been stated to make up approximately 37% of the total direct costs of asthma (45). In Sweden, the cost of asthma drugs has increased by nearly 300% between 1980 and 2000 (20). Since drugs are subsidized, ineffective use of drugs will place an unnecessary economic burden on patients and the health care system alike. Thus, increased understanding of factors that influence the total cost of pharmaceuticals is important.

## 1.7 THE SWEDISH HEALTH CARE SYSTEM

The health care system in Sweden is decentralized into 21 regions/county councils. Patient fees (i.e. out-of-pocket) are set by the county councils and account for only 2,7% of the county councils budget. The majority of the health care is publicly financed by regional taxes. County councils and municipalities are the main care providers. An increasing part of care is financed by the municipalities and the individual citizen. Although only 10% is delivered by private providers (46), they now stand for an increasing proportion of primary health care and thus become more difficult to obtain information about how resources are distributed. Within primary care, approximately 25% of the PHCCs are privately run (47).

In Sweden, there is a uniform national limit to the total amount that a patient must pay for health care during a 12-month period (out-of-pocket ceiling): this sum also includes subsidized medications. Each region/county councils has its own Drug and Therapeutic Committee (DTC) that gives recommendations to health care professionals about evidence-based and cost-effective drug treatment and guidelines. Marketing by drug companies has come under a tighter control in recent years, partly through the work of DTCs and new legislation. According to a Swedish law passed in 1996, the DTCs should promote the rational use of drugs through recommendations to health professionals and education of prescribers (47).

Most of the county councils have a budget system for allocating prescribing budgets for ambulatory care drugs (48, 49). Some county councils apply a central drug budget and others have decentralized the drug budget (50). In regions with decentralized drug budget, it is common for the clinics/PHCCs to be responsible for a certain percentage of the costs for drugs they prescribe. The multifaceted national and regional drug reforms in Swedish ambulatory care are described elsewhere (47).

## 1.8 REGIONAL VARIATIONS

Regional variation in the provision of health care has been the subject of a number of studies (51),(52). As early as in 1975, one of the first studies on regional variation in drug consumption patterns showed that the utilization of antidiabetic drugs varied both between countries and within countries (53).

We know that regional variations may indicate ineffective care that in addition may increase costs (54, 55,56, 57) and threaten patient safety (58) and equality (59, 60). Studies suggest that 30-40% of all patients do not receive care

according to current evidence-based knowledge and 20% of the care provided is not needed or potentially harmful (61).

However, relatively few studies have been published about regional variations in the treatment of patient with asthma. A search in PubMed resulted in 47 articles (search term: regional variation and asthma). A refined search on terms such as regional variation, drug and asthma resulted in 6 articles. These studied mortality (62), hospital admission rates and prevalence (63, 64) and standardization of treatment in a regional hospital (65). Roberts et al showed differences between general practices concerning diagnostic rates and therapeutic intervention patterns (66). Gerdtham et al studied the impact of inhaled corticosteroids on hospitalization for acute asthma in Sweden 1978-91 in 14 regions. The results indicated that when more money was spent on ICS the cost was compensated by fewer hospital days for asthma and conversely, that higher sales of inhaled bronchodilators (used as a proxy for asthma prevalence) were positively correlated with a higher number of bed-days (67).

National guidelines are one way to handle the problem of variations in clinical practice (68, 69). The Medical Products Agency, the National Board of Health and Welfare (SoS), SBU, the Dental and Pharmaceutical Benefits Agency (TLV) and local authorities in county councils in Sweden continually produce and update guidelines for evidence-based asthma drug treatment. Some of these guidelines are very concrete and should be straightforward to follow. It has however been shown e.g. in studies on treatment of low back pain and implementation of various disease prevention program in primary care, that adherence to evidence-based guidelines is far from complete (70, 71).

The Swedish Medical Products Agency has prepared guidelines for pharmaceutical treatment of asthma, which are implemented regionally for

example by the work of DTCs. The regional variations in pharmaceutical asthma treatment in relation to such recommendations had not previously been studied.

# 2 AIMS AND OBJECTIVES

The main objective of this thesis was to study determinants of costs of pharmacological treatment of asthma in Sweden.

Specific aims:

- To explore the relationships between variables that may influence the pharmaceutical costs for asthmatic patients treated in primary care, and to generate a predictive model for these costs. (Paper I)
- To explore factors predicting asthma severity and asthma control and to compare how the results of different approaches to asthma severity classification affect the distribution of costs of asthma medication. (Paper II)
- To investigate if addition of structured information and monitoring by diary, as in clinical trials, influences the treatment outcome when given to asthma patients in primary care. (Paper III)
- To describe the utilization of antiasthmatic drugs in Sweden and to explore regional variation in drug utilization and adherence to guidelines for rational drug prescribing in treatment of asthma. (Paper IV)

# 3 METHODOLOGY

Methods are described in papers I-IV, and are briefly summarized below.

### Paper I

This observational study was a part of a prospective multi-center study of quality of life among 105 asthma patients between 18 and 86 years old in 24 Primary Health Care Centre, PHCC, located in the city and suburbs of Stockholm (72).

Patients aged 18 and above who were considered by the general practitioner as having asthma were consecutively asked to participate in the study when they visited the enrolled PHCCs (regardless of the reason for that particular visit). Exclusion criteria were malignant disease, severe psychiatric disease, and dementia. Patients unable to understand written Swedish were also excluded, since included patients were obliged to fill in self-completed versions of HRQoL questionnaires SF-36 and AQLQ(S) and the asthma control questionnaire ACQ.

AQLQ(S) is a 32 item questionnaire with a seven-point scale (1=severe impairment to 7=no impairment) where patients score their experiences during the last two weeks. It contains 12 items on symptoms, 11 on activity limitations, 5 on emotional functions and 4 concerning environmental stimuli. ACQ is a symptom-focus questionnaire which measures asthma control during the last week using six questions for the patient concerning limitation of activities, shortness of breath, wheezing and puffs of short-acting bronchodilator. It also includes a lung function test, $FEV_1$. The questions are scored on a 7-point scale (0=good control) (29)

The patients visited the PHCC on two occasions. The data used in paper I were collected during the first visit. A test of pulmonary function was performed and questionnaires on HRQoL and asthma control were filled in. Dosages and types of drugs used for asthma during the week preceding the visit were recorded. The cost of the daily dose of each drug was calculated per patient and summarized to a total daily pharmaceutical cost. Asthma severity was classified into four groups according to GINA guidelines. Correlations for descriptive purposes were calculated using Spearman correlation coefficients. Spearman was chosen partly because the untransformed variable cost had a skewed distribution and asthma severity is only a categorical variable. The cost data were transformed by taking the square root of the costs in order to achieve normality in distribution before the data were used in the main analysis. A multiple linear regression model was used to explore the relationship between the dependent variable - transformed total cost of drugs per day per patient - and the independent variables asthma severity, AQLQ(S) total score and the use of spirometry. Multiple linear regression was chosen since we wanted to learn how each of these variables was as a predictor of costs. We chose a model where we assumed linear relationships between the variables, after inspection of bivariate scatterplots of the variables where no curvature was evident. Univariate correlation analyses were first performed for a number of variables. Variables shown to be significantly associated in the correlation analysis ($P < 0.05$) were included in a multivariate regression model. We built our regression model stepwise, using backward elimination. In other words this means that when we began building our model all variables were included in it and they were eliminated from the model one at the time. The model chosen is the one that consists of the subset of variables that has the highest adjusted R-square value.

## Paper II

The database constructed for this study consists of 246 patients, 18-87 years of age. It was based on data from the first visit of two studies on asthma patients in primary care in the Stockholm area, see papers I and III. All patients were required to have asthma diagnosed by a GP. Asthma control was measured with the Asthma Control Questionnaire (ACQ) (29) and disease-specific Quality of Life was measured with the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (73). The daily costs for drugs were retrieved from the original databases.

Asthma severity was classified according to four different approaches. The GINA guideline approach was used as a basis for three of the classifications (15). The first approach combines medical regimen and clinical features (GINA). The second approach ignored the medical regimen (GINA-NAÏVE). The third classification was carried out with the intention of elaborating the GINA classification system a bit. This was done by expanding it with two classes (GINA EXPANDED). The fourth classification was carried out on the basis of two parameters: treatment steps, as defined in the GINA guidelines, and lung function (TREATMENT INTENSITY). Cohen's kappa was calculated in order to estimate the degree of agreement between the different classifications. Kappa is considered to be a better estimate than using percent agreement. It is generally considered to be a conservative measure of agreement. The factor analytic (FA) technique Principal components analysis was performed with the intention of exploring whether asthma health status descriptor variables would reduce to one or more common factors. The two most common methods of conducting a FA are Principal Components Analysis (PCA) and Principal Factors Analysis (PFA). These two methods typically yield similar results. The characteristic that distinguishes the two models from each other is that in PCA it is assumed that all variability of a variable should be used in the analysis, while

in PFA only the variability of a variable that is common with the other variables is used. The most commonly used factor analytic model in asthma studies is the PCA (74). As already mentioned we chose to conduct a PCA.

We started out by determining the factorability of our dataset by the use of two tests, the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) and Bartlett's test of sphericity (75). The KMO tells us whether the variables measure a common factor. A KMO value ≈ 0 (0.0 – 0.49) indicates that the variables do not measure a common factor. In our case the KMO was 0.86. The Bartlett's test, tests the null hypothesis that the correlation matrix comes from a population in which the variables are noncollinear and that the non-zero correlations in the matrix are due to sampling error. The results from Bartlett's test in our study was $\chi^2 = 789.66$, Df 36, $p < 0.05$. Thus, the non-zero correlations in the correlation matrix were not due to sampling errors. The decision based on this was to proceed (75). Using the Principal Components Method we reached an initial solution. In the initial solution, each variable is standardized to have a mean of 0.0 and a standard deviation of ±1.0. Thus, the variance of each variable = 1.0. A useful factor must account for more than 1.0 unit of variance, or have an eigenvalue $\lambda > 1.0$ Otherwise the factor extracted explains no more variance than a single variable. We chose to go forward with two factors to be extracted in the final solution (table 1), based on the criteria eigenvalue ≥1.0 (75).

**Table 1**. Unrotated component matrix

| | Component (Factor) | |
|---|---|---|
| | 1 | 2 |
| Asthma day sym. | -.610 | -.184 |
| Asthma night sym. | -.624 | .035 |
| FEV1 percent pred. | .192 | .678 |
| MiniAQLQ sym. domain | .881 | .043 |
| MiniAQLQ Activities domain | .849 | -.003 |
| MiniAQLQ Emotional domain | .801 | -.061 |
| MiniAQLQ Environmental domain | .700 | -.114 |
| ACQ score | -.895 | -.024 |
| Treatment step | -.210 | .725 |

In order to improve interpretation of the nature of the factors we chose to rotate the final solution. This was done with the varimax method and Kaiser normalization. The rotation converged with 2 iterations but did not improve the final solution notably. Finally we checked for outliers and nonlinear associations between the components by looking at plots of component scores (fig 1).

(76)

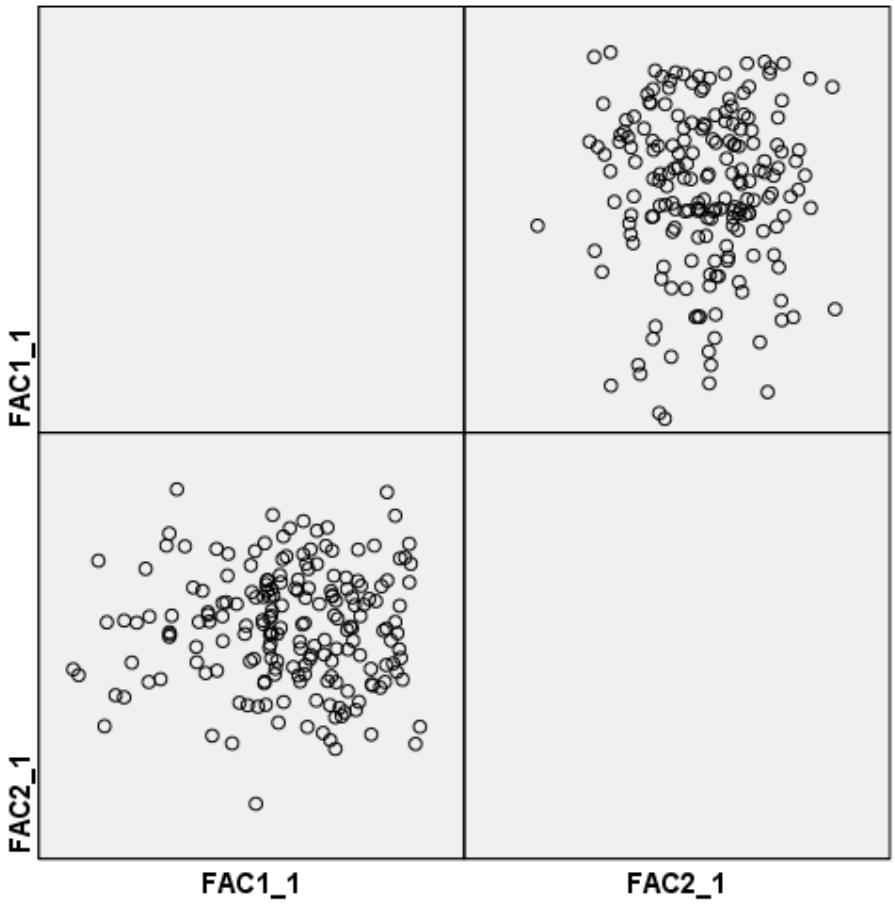


**Figure 2.** Scatterplot matrix of the component scores.

SPSS release 12.01. SPSS Inc. Chicago, Ill., USA was used for data handling and statistical analyses.

## Paper III

The study population consisted of 141 participants with an asthma diagnosis aged 18-87, from 24 primary care centers in Stockholm county councils during late fall 2003 and most of 2004. The study was designed as a prospective, cluster-randomized trial and intended to measure the effect of structured information and monitoring by diary on the outcome of treatment of asthma.

Study centers were randomized either to follow their local routine (controls) or to add extra, structured, written and verbal in depth information and monitoring of the patients by diary (intervention). Primary outcome variable was change in the score of the Swedish 5 question version of the ACQ (77) between the two visits. Secondary outcome were changes in score on the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (73), lung function, number of emergency visits, number of additional/unanswered questions, changes of drug treatment, patient perceived benefit and costs of asthma treatment. The cost of the daily dose of each asthma drug was calculated per patient and summarized to total daily pharmaceutical costs per patient. The effect of the intervention was described by the change in ACQ scores and differences between study groups were tested for with weighted T-test. Since we had only two groups the choice of a T-test was suitable. The Pearson Chi-square test was used to analyze differences between groups on the categorical variables and adjusted Chi-square values were calculated to account for the clustering effect. Accounting for cluster effects was necessary since this kind of design may have effects on the outcome. To put it simply, all patients coming from one and the same primary care center belonged to the same cluster. It was then the primary care centers rather than the patients that were randomized to control or intervention circumstances. The easiest way to account for cluster is by weighting means by cluster size when comparing groups with data on the interval/scale level and adjusting the Chi-squares when comparing groups with categorical level variables.

The adjusted Chi-square requires that the design effect is calculated though (78). To be able to do this one needs to first calculate the intracluster correlation (ICC) for each outcome variable. We obtained the ICC's by using mean squares values from a one-way analysis of variance (79). The ICC's are presented in table 2.

**Table 2.** Intracluster correlation coefficients and degrees of freedom for all variables in paper III.

| Variable | Intracluster correlation coefficients | Df within groups | Df Between groups |
|---|---|---|---|
| ACQ Change in score | 0.03 | 122 | 18 |
| Lungfunction Change in FEV1% predicted | 0.03 | 107 | 16 |
| COSTS Mean change | 0.10 | 122 | 18 |
| MiniAQLQ Change in scores | 0.004 | 122 | 18 |
| No of acute emergency department visits | 0.06 | 122 | 17 |
| Patient perception of drug benefit | 0.002 | 122 | 17 |
| Prescribed change in drug treatment | 0.29 | 121 | 17 |
| Having additional questions | 0.04 | 122 | 17 |

* Degrees of freedom from the ANOVAs table that was the basis for calculating the ICC's.

### Paper IV

The study is an observational registry study including all Swedish citizens 18-44 years old who purchased prescribed antiasthmatic drugs (ATC group R03) between July 2005 and December 2008. Data were extracted from the Swedish National Prescribed Drug register, which covers 99.7% of the Swedish population. Over-the-counter (OTC) medications and hospital drugs are not included in the register. The incidence and period prevalence was assessed from the register. The data were also described and compared on a regional level. Adherence to national guidelines for pharmaceutical treatment of asthma was assessed using three measures:

- the proportion of patients purchasing long-acting beta-agonists (R03AC12, R03AC13) who had not purchased any inhaled corticosteroids (R03BA and/or R03AK)
- the proportion of "new" patients who purchased fixed combinations of LABA and steroids (R03AK) without having purchased any antiasthmatics (R03) in the preceding 18 months
- the proportion of patients purchasing antiasthmatics who also purchased selective and non-selective beta-blocking agents (ATC C07)

In order to further investigate possible explanations for the observed regional differences, we explored the independent variables recommendations from DTCs, county-council model for pharmaceutical budgets and incentives, number of general practitioners (GPs) per inhabitant and number of pulmonary physicians per inhabitant and used a stepwise forward linear regression. Drug utilization and expenditure were based on complete data for the whole population in Sweden during the period. The Pearson correlation coefficient was used to choose variables for the stepwise forward multiple linear regression. We checked the tolerance to ensure that there was no multicolinearity.

## Costs

Health care units' costs for pharmaceuticals were obtained from the Swedish pharmaceutical desk reference: FASS ® 2003 for study I and II and FASS ® 2004 for study III. In study IV, we collected data on the total costs from the Swedish National Prescribed Drug register i.e. the pricelist of the National Corporation of Swedish Pharmacies (Apoteket AB) 2007.

**Table 3. Methodology used in studies I to IV**

| | **Study I** | **Study II** | **Study III** | **Study IV** |
|---|---|---|---|---|
| | Prospective Cross-sectional | Cross-sectional from study I and III (first visit) | Cluster - RCT | Register study |
| Study year | 2003 | 2003 | 2003-2004 | 2007 |
| Age group | 18-86 | ≥18 | 18-87 | 18-44 |
| Costs collected | FASS ® 2003 | FASS ® 2003 | FASS ® 2004 | Pricelist Apoteket AB 2007 |
| Material | 24 Primary Care Centres, 105 patients | 24 Primary Care Centres, 246 patients | 24 Primary Care Centres, 141 patients | Swedish National Prescribed Drug register |
| Methods | MiniAQLQ<br>SF-36<br>Lung function<br>ACQ<br>Regression | Comparison of four different approaches to classify severity of asthma<br>Correlation<br>Factor analysis<br>Kappa | Intervention: written and oral information<br>Diary<br>T-test<br>Chi-square | Descriptive<br>Regional variations<br>Regression |
| Ethical approval * | Dnr 02-508 | Dnr 2007/489-32 | Dnr 03-284 | Dnr 2007/1138-31. |

*Ethical consideration and approval by the Regional Ethical Review Board in Stockholm

# 4 RESULTS

## Study I

Paper I shows the relationship between variables that may influence pharmaceutical costs in asthma and the relationships between costs of drugs and quality of life, lung function and asthma severity. The study population consisted of 105 patients and the majority were females (63%). Most of the patients (70.5%) were classified as having severe asthma according to GINA. The daily cost of drugs varied between SEK 0 – 75. Among patients with severe asthma (GINA 4), the cost of asthma medication per day ranged from SEK 0.15 to SEK 75.34, with a median of SEK 12.59.

The correlations found between total costs of asthma medication per day and asthma severity (0.39), AQLQ(S) (0.35) and SF-36 Physical index (0.23) are statistically significant. However, SF-36 Mental index (0.02), age (0.23), sex (0.075), PEF (0.18) and, $FEV_1$ (-0.03) did not show significant correlation with total costs of asthma medication.

The final regression model showed that 23% of the observed variation in antiasthmatics drug costs could be explained by asthma severity, disease-specific quality of life and clinical practice. Costs were higher for patients with more severe disease and lower asthma-specific quality of life.

To study the impact of clinical practice on costs, we examined the cost of drugs per PHCC. Three of the PHCCs had larger median costs than the others**.** One hypothesis was that they had lower adherence to the DTC recommendation list, the "Wise List". To test whether the costs would change if the physicians implemented the recommendations in "the Wise List", we performed new

calculations after transforming the medications to the corresponding recommended alternatives. The result did not change significantly.

In order to investigate whether the case mix caused the difference between the PHCCs, we examined the differences in costs for medication separately in patients who had severe asthma (GINA class 4, n=74) in all centers. However, the distribution of costs between different PHCCs was almost unchanged.

## Study II

The patients in study I can be regarded as representative for the asthma patients that seek primary care most often. Since 70.5% of them were classified as having severe asthma, the classification method used was found to be insensitive and methodologically not optimal under these circumstances. The aim of study II was therefore to compare different approaches to asthma severity classification. We also felt that there could be overlap between the concepts asthma severity and asthma control and therefore wanted to explore factors that predict these characteristics.

### *Factor analysis of asthma descriptors*

We used a total of nine variables from ACQ and MiniAQLQ. From ACQ, the variables $FEV_1$% of predicted, diurnal asthma symptom frequency, nocturnal asthma symptom frequency, impact of asthma on activities and treatment intensity were used. From MiniAQLQ the domain scores for symptoms, activities, emotions and environment were used. This resulted in two factors which explained 54.2 percent of the variation in the material. The first factor consisted of variables that are related to asthma control and quality of life, whereas the other factor contained $FEV_1$% of predicted and treatment intensity. Then, we performed a qualitative estimation of all variables to see if they could

fit in the context. The results showed that asthma control and asthma severity forms overlap and are closely related.

***Different approaches to classification of severity***

The different approaches yielded quite different proportions of persons identified as having mild (2-16%), mild persistent (9-20%), moderate (23-58%), and severe asthma (12-66%), table 4. Both the GINA-NAIVE and the TREATMENT INTENSITY classifications included more patients in the mild levels than the other two. The GINA method identified 89% of the subjects as having moderate or severe asthma. The GINA- EXPANDED was the only method that yielded a symmetric distribution of subjects.

**Table 4.** Results of different classification approaches, percent of all patients

| | GINA | GINA NAIVE | GINA EXPANDED | TREATMENT INTENSITY |
|---|---|---|---|---|
| 1 (Mild ) | 2 | 15.8 | 2 | 12.2 |
| 2 (Mild Persistent) | 8.7 | 20.4 | 8.7 | 17.9 |
| 3 (Moderate) | 23.5 | 45.9 | 23.5 | 57.7 |
| 4 (Severe) | 65.8 | 17.9 | 36.2 | 12.2 |
| 5 | na | na | 27.6 | na |
| 6 | na | na | 2 | na |

na = not applicable, since the classification only has 4 categories.

When asthma control was taken into account, the GINA NAIVE and the TREATMENT INTENSITY classifications were still the methods that included the largest number of subjects in the mild levels. The GINA method still identified a large proportion of subjects as having severe asthma. The

distribution of subjects in each category identified by the GINA EXPANDED lost some of its symmetry. To further evaluate the extent of agreement between the three severity methods with the same number of categories, Kappa was calculated. GINA EXPANDED was left out, since it had been expanded with two classes in addition to the four classes in the other classifications. The agreement between the three compared methods was generally low, indicating that the methods rated the same patients differently.

### *Exploring the impact of the classification on pharmaceutical treatment cost data*

The pharmaceutical costs varied between SEK 0 and 75.34 per day, SEK 0 meaning that the patient had not taken any medicine during the last week before the visit. The median cost was lower in the non-smoking group but the cost range was widest (between SEK 0 and 75.34) in the non-smoking group. The study presented the correlation between costs of medication and the different classification approaches. Treatment intensity had a major impact on costs (0.626, $p < 0.05$) even when patients were stratified for good and poor asthma control.

## Study III

The aim of study III was to examine whether in-depth information similar to that given to patients who participate in clinical trials can improve the outcome of pharmaceutical treatment in ordinary care.

In total 64 participants in the intervention group (75% female), and 77 participants in the control group (65% female) completed the study. Comparison of change in asthma control measured as ACQ scores, between the control group (M= -0.29, SD=0.31) and the intervention group (M=-0.45, SD=0.23), $t(137) = 3.51$, $p=0.01$ showed that the groups differed significantly. Though changes

occurred within both groups, the mean change was less than the Minimal Important Difference (MID) of ≈ ±0.5 in the control group, whereas the change in the ACQ in the intervention group was close to the MID.

Both groups improved their disease-specific quality of life during the study (i.e. change scores in the positive direction). The magnitude of the change differed significantly between groups. For the intervention group the magnitude of change exceeded the threshold for the MID (0.5).

The change in lung function also differed significantly between the control group (M= 1.39, SD=3.53) and the intervention group (M=3.03, SD=4.34), $t(137) = -2.45$, $p=0.016$. Although statistically significant, these changes in lung function are small from a clinical point of view.

The proportion of participants who altered their pharmaceutical treatment was significantly larger in the intervention group than in the control group, cluster adjusted $\chi^2 = 3.96$, $p= 0.0466$.

Weighted total mean cost for the intervention group was SEK 8.14 and 12.59 for the controls at baseline. At follow up, there had been a movement towards increased total costs in the intervention group whilst the total costs remained almost the same for the control group. The weighted between-groups difference in change of costs was statistically significant. The movement towards increased costs could not be attributed to any single class of medications.

The mean total cost per center per day varied from SEK 2.79 to 17.40 for the intervention centers and from SEK 6.37 to 16.90 for the control centers at baseline. At follow up, the mean total cost per center varied from SEK 4.62 to

17.40 for the intervention centers and from SEK 8.02 to 23.05 for the control centers.

## Study IV

The aim of study IV was to describe the utilization of antiasthmatic drugs in Sweden 2007, and to explore regional variations in drug utilization, impact of budget control on prescribed drugs and adherence to guidelines for rational drug prescribing in the treatment of asthma.

### *Prevalence and incidence of antiasthmatic treatment*

In 2007, a total of 161 000 patients 18-44 years old purchased approximately 500 000 prescriptions for antiasthmatic drugs. The proportion of these patients who were purchasing prescriptions for antiasthmatic treatment for the first time was 2% for men and 3% for women, respectively. The period prevalence for antiasthmatics overall was 4% in men and 6% in women. Women purchased more beta-agonists, inhaled steroids and fixed combinations of inhaled corticosteroids and long-acting beta-agonists than men. Approximately 3.7% of the study population purchased beta-2-agonists. A majority of them, 90%, only purchased short-acting beta-2-agonists. The use of beta-2-agonists was skewed in the population, as only 10% of the patients accounted for 52% of the purchased volume in Defined Daily Doses (DDD). For the fixed combinations of inhaled corticosteroids and long-acting beta-agonists, the period prevalence was about 1.3% and 10% of the patients accounted for 29% of the volume. For inhaled corticosteroids, the period prevalence was about 2% and 10% of the patients accounted for 42% of the volume.

### *Expenditures*

The total expenditures for antiasthmatics drugs in 2007 for patients aged 18-44 were SEK 258 million; beta-2-agonists accounting for 22%, the fixed

combinations for 46% and inhaled corticosteroids for 23%. The cost of all antiasthmatic pharmaceuticals was SEK 1598 per patient. Individuals 18-44 years of age accounted for 16% of the total costs for dispensed antiasthmatics, while people over 45 accounted for 75% and children <18 about 9% of the total expenditures. On average, each patient purchased three prescriptions per year.

***Regional variations and adherence to guidelines***

The prevalence of antiasthmatic drug use varied between the county councils, ranging from 41.3 patients/1000 inhabitants on the island of Gotland to 67.9/1000 inhabitants in Norrbotten, the northern most sparsely populated region in Sweden.

During 2007, between 0.6 and 1.7% of all patients who purchased at least two prescriptions for antiasthmatic drugs also purchased non-selective beta-adrenoceptor antagonists. There were obvious differences between different regions.

Between 33 and 58 percent of the patients who purchased fixed combinations of antiasthmatics for the first time had not purchased any other antiasthmatics during the preceding 18 months. There were large variations between county councils concerning this parameter. Between 18 and 37% of all patients purchasing prescriptions for long-acting beta-2-receptor agonists in 2007 had not purchased any prescription with inhaled corticosteroids during the same period.

A significant positive correlation was found between the number of GPs per inhabitant in the region and purchases of prescriptions for fixed combinations. The independent variables county-council model for pharmaceutical budgets and

incentives, DTCs guidelines and the number of pulmonary physicians per inhabitant were not found to be significant in the correlations.

# 5 DISCUSSION AND CONCLUSION

From a societal perspective, it is important to create conditions that promote rational use of drugs. Resources are limited and must be used in the best possible way. Thus, there is a drive towards more cost-effective use of drugs. Furthermore, patient safety is also a growing concern. In this perspective, one must strive to optimize the effects, while minimizing side effects. The effect of medications are often significantly better in clinical trials than in everyday healthcare. An adjustment of conditions aiming at enhancing the effect of available pharmaceuticals is one way to improve the appropriate use of a treatment. An example of such an improvement may be increased information and monitoring as studied in paper III. Ensuring appropriate use may also include finding the right target population for a certain medication. Recommendations on how to achieve all these goals are often developed and disseminated through the work of regional DTCs. The adherence to a few such recommendations was studied in paper IV.

### *Strengths and limitations*

A naturalistic design with selection of asthmatic patients seeking care, thus constituting the bulk of asthma patients seen in primary care, is a strength when it comes to the applicability of our results. Another strength is that we formulated our research questions from a healthcare or societal perspective, as is the fact that all studies were designed and carried out independently of pharmaceutical companies.

The Swedish National Prescribed Drug Register used in paper IV is a crucial resource of a type that few countries have available to study their population. The register has hitherto not been used for studies on patients with asthma.

The stated intention of this was to use a societal perspective in costs analysis. However, paper I only considers the drug costs and no indirect costs were included. Furthermore, factors which we did not measure or investigate may have an impact on drug costs. It is important to point out that data on consumption of anti-asthmatic drugs and dosages during the week preceding the visits to the PHCCs were based on reports from the patients themselves. Of course this allows for some recall bias to slip into the data. Another bias could be "over-reporting" for example of drug consumption, since patients may want to appear good consumers. It is also possible that those who do not feel well remember better than others. Nevertheless, we tried to minimize this effect by letting a nurse collect these reports, rather than the prescribing doctor. We did not measure the difference between actual and reported pharmaceutical use. Nor did we investigate the difference between prescribed treatment and taken treatment, which could be a marker for adherence and influence the results. Built-in defects in the severity classification were also problematic.

In paper II, the sample was small and made up of patients who sought the primary care for their asthma. This will probably yield a study population representative for asthma patients seeking care at PHCCs, but they will probably have more severe disease than a sample of asthma patients from the general population. For the underlying study it was central to gain knowledge of about these patients, but it is important not to generalize the results to a sample of asthma patients from the general population.

In paper III, the cluster-randomization procedure would have benefited from inclusion of more patients and a longer observation time. It may look as if the study was underpowered, which could be a problem for the validity of the findings. Nevertheless, the observed differences in outcome were statistically significant. The lack of blinding of the PHCCs may also be a problem. We handled this by giving them minimal information about the study and keeping

the PHCCs in the intervention group separated from the PHCCs in the control group during training sessions and meetings for the participating GPs and nurses.

In paper IV, patients over the age of 44 had to be excluded since diagnosis is not included in the Presribed Drug register. Thus, the age-limits were set to exclude other groups of patients that use the same type of pharmaceuticals, e.g. patients with COPD. Furthermore, since the register contains purchased prescribed drugs rather than actual prescriptions, we were unable to study the many possible reasons patients' non-adherence to doctors' recommendations, and doctors' non-adherence to recommendations from the local DTC.

Performing studies in primary care is not uncomplicated. Primary care these days is under strong pressure to raise productivity and cut costs, leaving dwindling possibilities for research. In Sweden the proportion of the PHCCs that are private is increasing currently, about 25% (47). Since trials are time-consuming, the provider wants compensation which academic sponsors may be unable to provide. Furthermore, there is often a lack of research experience among the health professionals in the PHCCs. Frequent reorganizations and political changes also influence the research climate.

### *Interpretation of findings*

The prevalence of antiasthmatic treatment varied considerably between regions/county councils in Sweden. These regional variations can largely be attributed to regional differences in the prevalence of asthma. However, the regional variations in type of antiasthmatic treatment on a national level (paper IV) and between different PHCCs in the Stockholm area (paper I, III) cannot be explained by variations in the prevalence of the disease itself.

In paper I, only 23 percent of the observed variation between different PHCCs could be explained by asthma severity, disease-specific quality of life and clinical practice. Even when severity was accounted for, pharmaceutical costs varied considerably between primary health care centers. This indicates inefficiency in the use of resources which may be due to differences in clinical practice. We do not know what causes the large variations in costs for treatment of patients with equally severe disease. It is possible that some PHCCs overtreat patients and others undertreat them or that some oversubscribe expensive medications and others are overly reliant on cheap medications. The differences may result from a combination of all these factors. This was not further examined. Two patients have not used any drugs the last week before the visit. We checked the ACQ for these patients and found that they have very good scores for asthma control.

In some cases the variation could also be due to selection of expensive compounds which may or may not have been indicated. This possibility was addressed by a simulation where drugs were substituted with an alternative recommended by the DTC in one county, the recommendations known as the "Wise List". Nevertheless, this did not significantly influence the variations. One reason may be that some patients were treated with an expensive drug from a class of pharmaceuticals that was not recommended and therefore could not be substituted in the simulation. An example of such a compound is the leukotriene receptor antagonist montelukast. In real life, the patient might have fared equally well if treated with one of the recommended alternatives, but that would have to be tested in a prospective, interventional study.

In paper IV the costs for antiasthmatics were higher for the older patients. It has previously been shown that drug use increases with age, but the high-consumption counties had higher drug use in all age groups (80). Thus, it is

unlikely that differences in age distribution accounts for very much of the regional variations found. Nevertheless, it would be interesting to study this age effect in asthma in further research.

Since about 70% of the patients in paper I were classified as having severe asthma (GINA 4), we concluded that the GINA classification of asthma severity was not optimal for our purposes in the studied population, namely asthma patients seeking care at PHCCs. Also the range of drug costs both within and between severity classes indicated that the patients were not similar. The costs of drugs for patients with severe asthma ranged from SEK 0.15 to 30.85 per day, indicating differences between the patients. These differences indicate that the used severity classification lacks precision. A precise classification and definition of patients is important when performing economic evaluations and creating reimbursement systems.

However, none of the four classification approaches applied in study II provides an adequate solution to the classification problem and further research is needed. After we initiated our study, the problem has also been recognized by GINA. The revised GINA classification is now recommended only for patients who have not previously been treated pharmacologically (13). For regular assessments of asthma, the use of asthma control measures is recommended (13).

Poor patient adherence is an example of inappropriate use of medications. This may diminish the effect of a certain drug and thereby its cost-effectiveness (81). Reasons for poor patients adherence have been discussed and factors such as age, gender, duration of disease, the attitude of the staff and the information/education given to patients have been studied (82, 83) 84-86). Paper III describes the results of adding structured information about asthma and its

treatment and monitoring by diary to the care of asthma patients treated in PHCCs. The intervention improved asthma control, asthma-specific quality of life and lung function. For reasons we could not explain, the prescribed treatment of the patients in the intervention group was changed more often than the treatment of the controls. Thus, their improved outcomes may also be a result of changes in their medication. However, we find it conceivable that the change in prescribed treatment may in itself be an effect of the intervention. We can only speculate that the patients' increased knowledge and the few extra minutes spent on the information enhanced the dialogue between caregiver and patient, thus promoting adjustment of treatment in order to improve the patients' well-being. In some counties, the DTCs recommend that the patient be given a pamphlet about the pharmaceuticals given to the patient (87) (54), a recommendation based on notion that influencing and educating the patient will affect the prescriber. We found it surprising and encouraging that such a relatively small extra effort can influence the patients' outcome.

The pharmaceutical costs in the intervention group increased due to changes in medication. This may be due to both elimination of under-prescription of drugs and improved adherence of the patient and/or the physician. However, the study was too small and too short to enable analysis of possible long-term effects such as need for emergency treatment, additional visits to hospital or PHCCs, etc. Therefore, we do not know if the intervention would have long-term effects of on medical outcomes or costs.

Certain medications/administration forms have been suggested to improve patient adherence for instance, fixed combinations have been suggested to improve adherence (88) (89). On the other hand treatment with fixed combinations might decrease the flexibility of asthma treatment and lead to over-use of LABAs, since it is easier for the patient to decrease the dose of

LABA during periods with few asthma symptoms if the drugs are provided in separate inhalers. It would be possible to use the Prescribed Drug register to shed light on issues of continued patient adherence or refill adherence by determining the number of days between purchase of two or more prescriptions in relation to the ordination (80, 81).

The considerable differences between regions in adherence to guidelines shown in paper IV raise concerns not only inefficient use of resources but also patient safety and equality in treatment. Wettermark et al estimated that every percentage point of increased adherence to the "Wise List" guidelines in the Stockholm area saves more than SEK 30 000 annually per GP (54, 90).

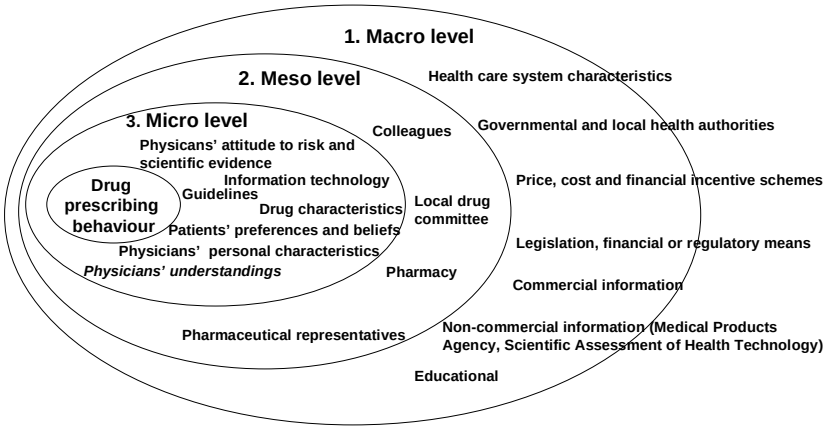


**Figure 3**. Factors at different levels in society influencing physicians' drug prescribing behaviour in clinical practice (91)

This thesis has focused on pharmaceutical costs and factors that influence them. There are many factors in society that influence drug prescription behaviors (figure 3). In this context, it must be borne in mind that not only the physician, but also other health professionals around the patient influence the use of drugs. It should be possible to achieve better understanding of these influences by more systematically applying the three perspectives included in the concept of evidence-based medicine. Examples are patients preferences and values, the health professionals' clinical expertise and external clinical evidence from systematic research (1) (figure 4). Marketing of drugs may also influence the prescriber. It is important to try to understand how these three sources of knowledge interact with each other. More research is needed to obtain better insight into this area.

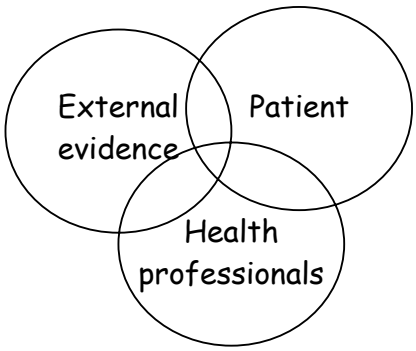


**Figure 4**. Interplay between patient, health professionals and external clinical evidence. Source: (1)

Our studies regarding regional variation indicate and highlight problems with adherence to guidelines. In study IV we studied adherence to two very clear national guidelines concerning the selection of patients who will benefit from addition of long-acting beta agonists and how to minimize safety problems with the same medication. Furthermore, doctors are generally recommended not to prescribe unselective beta-blockers to patients with asthma. We found an

unacceptable rate of only 33 to 58 percent adherence to these guidelines and quality measures in the counties.

Multiple reasons for poor adherence of the prescribers to guidelines have been studied (92). Guidelines implementation studies show that educational material alone brings about little or no effect on behavioral change among health professionals. Studies indicate that multifaceted intervention as audit and feed-back, reminders and local consensus processes have better effects (93). The paper by Grol et al. gives example of barriers to implementation of guidelines as organizational context (lack of reimbursement, lack of time), social context (usual routines, advocacy by drug companies) and professional context (self confidence in skills, inability to appraise evidence etc) (61). Little is known about optimal pharmaceutical treatment and care in primary care asthma patients. The studies that form the evidence base for treatment of asthma are usually performed in strictly selected patient groups, possibly with more severe asthma but less comorbidity, treated in chest clinics. If the guidelines are based on these types of studies, GPs may not find them applicable on their more heterogeneous patients and thus the implementation fails. It may also be that the required practical and personal resources are not present in the primary care setting.

In our study, poor adherence to guidelines was seen even in some counties where the DTCs are considered to be very active in the drug area (47). More effort must be put into describing, evaluating and analyzing the effects of DTCs recommendations. To use research and learn from studies in other disease areas and other cultures is important. Maybe the DTCs should focus more on how to implement guidelines, on follow up, incentives for GPs and information and education to the patients.

If variation in clinical practice occurs because of the health professionals' uncertainty or lack of knowledge this is an economic problem: variation suggests inappropriate care and welfare losses for the patient. Much of the Small Area Variation (SAV) research focuses on the socioeconomic characteristics of the population (60). For further research it would be very interesting to study the regional variations of pharmaceutical prescription costs in terms of these factors.

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men att ha roligt är en bra medicin.

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