Drug utilization and asthma control among young Danish adults with asthma

Analyses of trends and determinants

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THE THREE ORIGINALS PAPERS ARE

I: Increased use of inhaled corticosteroids among young Danish adult asthmatics: An observational study. Davidsen JR, Søndergaard J, Hallas J, Siersted HC, Lykkegaard J, Andersen M. *Respir Med* 2010;104:1817-24.

II: Impact of socioeconomic status on the use of inhaled corticosteroids in young adult asthmatics. Davidsen JR, Søndergaard J, Hallas J, Siersted HC, Knudsen TB, Lykkegaard J, Andersen M. *Respir Med* 2011;105:683-690.

III: Association between prescribing patterns of anti-asthmatic drugs and clinically uncontrolled asthma: A cross-sectional study. Davidsen JR, Hallas J, Søndergaard J, Christensen Rd, Siersted HC, Hansen MP, Knudsen TB, Lykkegaard J, Andersen M. Submitted for publication at the date of defence. Following published in a minor revised version (*Pulm Pharmacol Ther* 2011;24:647-53).

ABBREVIATIONS

ACQ: Asthma Control Questionnaire
ACT: Asthma Control Test
AHR: Airway Hyperresponsiveness
ATC: Anatomical-Therapeutic-Chemical System
CRN: Civil Registration Number
CI: Confidence Interval
COPD: Chronic Obstructive Pulmonary Disease
DDD: Defined Daily Dose
FDC: Fixed Dose Combination with inhaled LABA and ICS
FEV1: Forced Expiratory Volume in one second
FPAS: Funen County Patient Administrative System
GINA: Global Initiative for Asthma
IBA: Inhaled Beta-2-adrenoceptor Agonists
ICS: Inhaled Corticosteroids
ICS-FDC: Fixed dose combination inhalers with ICS and LABA
ICS-NC: ICS non-combination inhalers
LABA: Long Acting Beta-2-adrenoceptor Agonist
NAEPP: National Asthma Education and Prevention Program
OPED: Odense Pharmaco-Epidemiological Database
OR: Odds Ratio
QI: Quality Indicator
QoL: Quality of life
RMPS: Register of Medical Product Statistics
SABA: Short Acting Beta-2-adrenoceptor Agonist
SES: Socioeconomic Status
WHO: World Health Organisation

1 INTRODUCTION

Asthma is a common chronic inflammatory disorder of the airways with a wide variability in clinical presentation due to a substantial phenotypical heterogeneity [1,2]. Despite the availability of efficient pharmacological treatment and an increasing prevalence in the use of anti-asthmatic medication [3,4], the overall level of asthma control, e.g. minimisation of symptoms by adequate use of anti-asthmatic treatment, remains poor and falls far from the goals stipulated in international guidelines [5-7]. Pharmacological treatment, however, is only one cornerstone of asthma management and may be inadequate if non-pharmacological treatment is not instituted as well (e.g. establishment of a good patient-doctor relationship, identification and reduction of exposure to risk factors for deterioration, and patient education) [1,8,9].

Computerized files on drug prescription can be used to investigate, monitor and measure treatment quality for a number of diseases, including asthma [10-12]. The use of data extracted from population-based prescription registers allows longitudinal studies on trends and treatment patterns of anti-asthmatic drug use, but also analysis of factors associated with drug exposure by linkage to data from other health registers [11].

By use of prescription data, this thesis focuses on pharmacological asthma treatment and seeks to widen knowledge about trends in use of inhaled corticosteroids (ICS) and factors associated with ICS use in young Danish adult asthmatics, and furthermore, to determine whether certain prescribing patterns of anti-asthmatic medication are associated to clinical data on asthma control.

2 BACKGROUND

2.1 EPIDEMIOLOGY OF ASTHMA

Asthma is a common chronic disease affecting more than 300 million people worldwide [13], causing major health care prob-

lems with a huge financial burden, including a high number of disability-adjusted life years [13,14]. Asthma affects children, adults and elderly, with boys being more affected in childhood, shifting to more women than men after puberty [15], but also affects people of all race ethnicity and socioeconomic groups [1,16]. The mechanisms for development of asthma are complex and imperfectly understood [17]. Several genetic and environmental factors are, however, known to influence the risk of asthma either separately or interactively, e.g. genetic predisposition to atopy and airway hyperresponsiveness, and exposure to allergens, infections, smoke and pollutants [1].

Concurrently with atopic diseases as a whole the global prevalence of asthma has increased during the last three decades [18], with the highest prevalence being observed in westernised countries [13,19,20]. The increase has been explained by a more sedentary and indoor lifestyle giving rise to an increased exposure and sensitization to indoor triggers (e.g. moulds and dust mites) [21,22], but also leading to obesity, which is as a well-known independent risk factor of asthma [23]. Furthermore, the increased urbanisation and industrialisation have increased the exposure and sensitization to outdoor triggers (e.g. pollutants and pollens) [24]. An alternative explanation is the so-called hygiene hypothesis [25,26]. Although the prevalence seems to have reached a plateau in some countries [27,28], a recent study from Denmark demonstrated a continuing increase in asthma prevalence [29], supporting previous findings [30,31]. The prevalence of asthma in the general Danish population has been estimated to be approximately 10% among children and adolescents and 6-8% in adults [29,31-33].

2.2 WHAT IS ASTHMA?

Asthma has been described more than defined [34,35], and some of the difficulties in comparing results from epidemiological studies have been due to lack of consistency in the definition of asthma [36]. In current Global Initiative for Asthma (GINA) guidelines asthma is defined descriptively by a combination of clinical, physiological, and pathological characteristics: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cell elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly in night or in the early morning. These episodes are usually associated with wide-spread but variable airflow obstruction that is often reversible either spontaneously or with treatment" [1,37]. The clinical presentation of asthma, however, varies with respect to symptoms due to a substantial phenotypical heterogeneity (e.g. atopic, eosinofilic, exercise-induced, treatment resistant etc.) [2]. The phenomenon of increased responsiveness to stimuli, not causing symptoms in healthy individuals, is termed airway hyperresponsiveness (AHR) and is associated with reversible airway obstruction [1,38]. AHR and the pathological feature of chronic airway inflammation reflect the pharmacological treatment approach in terms of reliever and controller treatment [1].

2.3 PHARMACOLOGICAL TREATMENT

The pharmacological treatment of asthma is divided into short-term relievers and long-term controllers. Relievers are used on an as-needed-basis to relieve symptoms and reverse bronchoconstriction. Controllers are drugs used on a daily basis to keep asthma under long-term clinical control, mainly through anti-inflammatory properties [1,8,39]. Several drugs are available within each category (Figure 2), but due to the purpose of this thesis, a particular focus is put on inhaled beta-2-agonists (IBA) and ICS.

Inhaled beta-2-agonists

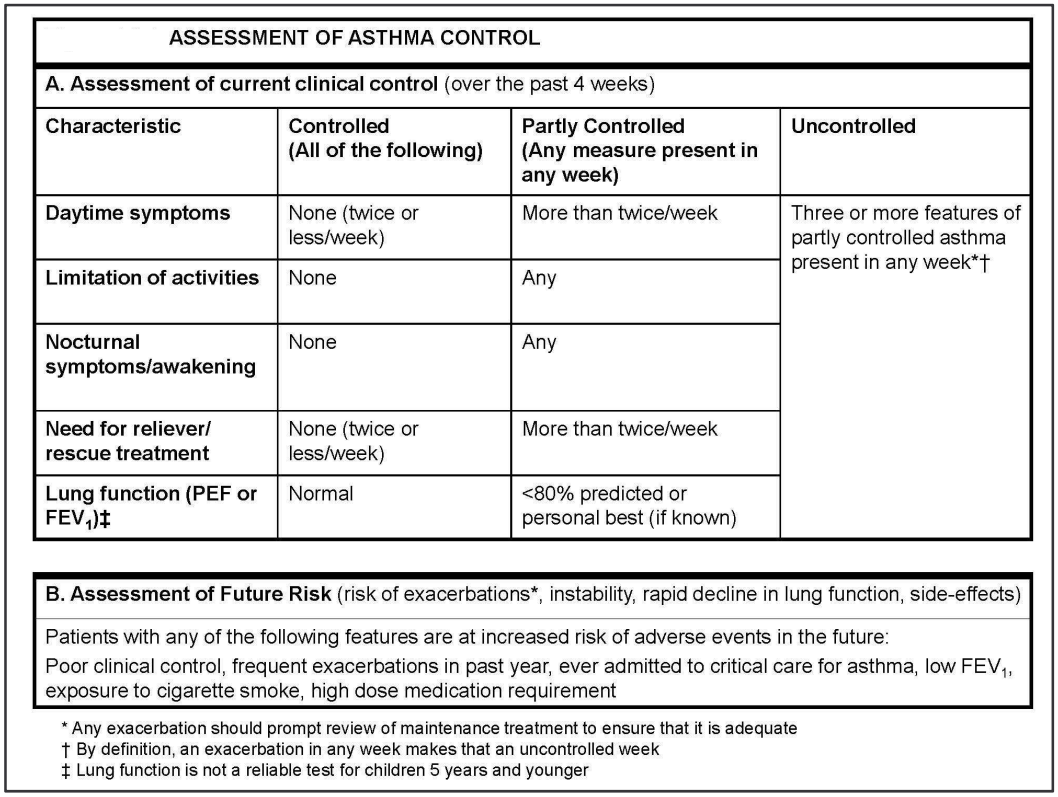
Ephedrine (an adrenergic agent) has been used as a bronchodilator for respiratory diseases in traditional Chinese medicine for more than 3000 years [40]. During the 1940-1960s different aerosolised formulations of other adrenergic agents were investigated as topical bronchodilators, but many had undesirable cardiac side effects due to beta-1-receptor activation [41,42]. In 1969 and 1970, the selective IBAs salbutamol (albuterol) [43] and terbutaline [44] were introduced, which still comprise some of the first-choice relievers today [1,8].

The bronchodilator effect of IBAs is mediated through binding to the beta-2-adrenergic receptor, located on the bronchial smooth muscle cells, leading to relaxation. The hereby lowered airway resistance entails reduction of asthmatic symptoms [45,46]. Other beneficial effects of IBA are increased mucociliary clearance, inhibition of mediator release from inflammatory cells, and reduced vascular permeability and oedema [47]. IBAs are classified into short-acting beta-2-agonists (SABA) and long-acting beta-2-agonists (LABA), according to their duration of action. However, to reflect their therapeutic relevance they are also classified into rapid and slow acting beta-2-agonists according to their onset of action (Table 1) [46].

	Duration of action	
Onset of action	**Short-acting beta-2-agonists** *(4-6 hours)*	**Long-acting beta-2-agonists** *(> 12 hours)*
Rapid-acting beta-2-agonists *(2-5 min)*	Terbutaline Salbutamol Fenoterol	Formoterol Indacaterol*
Slow-acting beta-2-agonists *(30 min)*		Salmeterol

Table 1
Available inhaled beta-2-agonists in Denmark.* Duration of action > 24 hours [48].

Rapid-acting beta-2-agonists (SABAs and formoterol) are the most effective bronchodilators to produce reversal of bronchoconstriction and thus recommended for quick relief of asthma symptoms [16,46]. When used on an as-needed-basis an increased use is a sign of deterioration [49]. LABAs are considered as controllers [1,8], but due to their modest anti-inflammatory activities on inflammatory cells [47], they are only recommended as an addition to patients inadequately controlled on ICS [1,8,46]. In combination with a daily regimen of ICS, LABAs have advantageous effects like improved lung function and fewer symptoms [50,51], and on exacerbations [52], which has led to development of fixed dose combination inhalers (FDCs) containing both LABA and ICS [53]. FDCs are as effective as the drugs given separately [54], but are an advantage to optimized adherence and ensure that LABAs are accompanied by ICS [55]. FDCs containing budesonide and formoterol are furthermore accepted for both controller and reliever treatment [1,49], and have shown improvements in symptoms and exacerbation rate compared to separate use of FDCs of budesonide and formoterol in combination with SABA reliever treatment [56,57]. However, adjustment of the LABA/ICS ratio may necessitate the use of more than one inhaler.



ASSESSMENT OF ASTHMA CONTROL

A. Assessment of current clinical control (over the past 4 weeks)

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week*†
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	<80% predicted or personal best (if known)	

B. Assessment of Future Risk (risk of exacerbations*, instability, rapid decline in lung function, side-effects)

Patients with any of the following features are at increased risk of adverse events in the future:

Poor clinical control, frequent exacerbations in past year, ever admitted to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medication requirement

* Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
† By definition, an exacerbation in any week makes that an uncontrolled week
‡ Lung function is not a reliable test for children 5 years and younger

Figure 1
Content from Global Strategy for Asthma Management and Prevention used with permission from the Global Initiative for Asthma (GINA), www.ginasthma.org.

Inhaled corticosteroids

The anti-inflammatory properties of oral corticosteroids have been used in asthma management since the1950s [58]. Though, to limit adverse effects from long-term systemic use, several attempts were made to develop corticosteroids for topical use in the airway system. The breakthrough that revolutionized asthma treatment came in 1972 when Brown and co-workers demonstrated beneficial effects of aerosol-inhaled beclomethasone diproprionate in chronic asthma patients [59]. Since then, additional preparations of ICS have been synthesized by a modification of hydrocortisone [60]. Currently, four types of ICS are available in Denmark; beclomethasone diproprionate, budesonide, fluticasone proprionate, and momentasone furoate [61]. They are currently the most effective anti-inflammatory drugs in asthma treatment, thus comprising the mainstay of asthma controller therapy and recommended as first-line treatment to all levels of persistent asthma in children and adults [1,8,62,63].

The activities of ICS occur through activation of glucocorticoid receptors localised in the cytosol of cells in the airway epithelium [64,65]. The overall anti-inflammatory effects of ICS occur from the inhibition of gene expression, synthesis, and release of inflammatory mediators resulting in a reduced activation, migration, and proliferation of inflammatory cells [63,64,66]. Further effects, relevant for asthma, are up-regulation of beta-2-adrenoreceptors on smooth muscle cells in the airways, inhibition of mucus secretion and plasma exudation, and decreased synthesis of arachidonic acid metabolites which are essential precursors of the inflammatory cytokine formation [63,64,66].

ICS do not cure asthma [16], but regular long-term treatment suppresses and controls airway inflammation, implying many beneficial clinical outcomes like improving quality of life, reducing asthmatic symptoms [67], airway hyperresponsiveness [68], lung function decline [69-71], and exacerbations [50], including hospitalisations [72]. These clinical benefits occur within weeks to months after initiation of ICS, but presuppose daily use [73]. If treatment is discontinued, symptoms will return to baseline within weeks, resulting in clinical deterioration [16]. This is important information regarding asthma education.

2.4 ASTHMA CONTROL: THE GOAL OF ASTHMA TREATMENT

Definition and classification

Guidelines on asthma have existed since the 1980s and constitute a valuable tool for clinicians as well as patients regarding appropriate diagnosis, management, and prevention of the disease [74]. In previous guidelines asthma was classified according to severity (intermittent asthma, and mild, moderate, and severe persistent asthma) based on symptoms and lung function [75,76]. As it became clear that asthma severity represented a non-static condition, changeable over time due to both the responsiveness to treatment and the severity of bronchial inflammation [37,77], this classification was criticized with regard to determining an individual treatment level at a single point in time [78]. Consequently, current GINA guidelines have replaced severity by level of control, classifying asthma into “controlled”, “partly controlled”, and “uncontrolled” using a composite measure of individual disease manifestations during the past week, and consisting of day and night symptoms, activity limitation, consumption of reliever treatment, and lung function measures [1] (Figure 1). However, the classification by severity is still accepted for research purposes and thus used implicitly in many studies 1. Furthermore, the latest National Asthma Education and Prevention

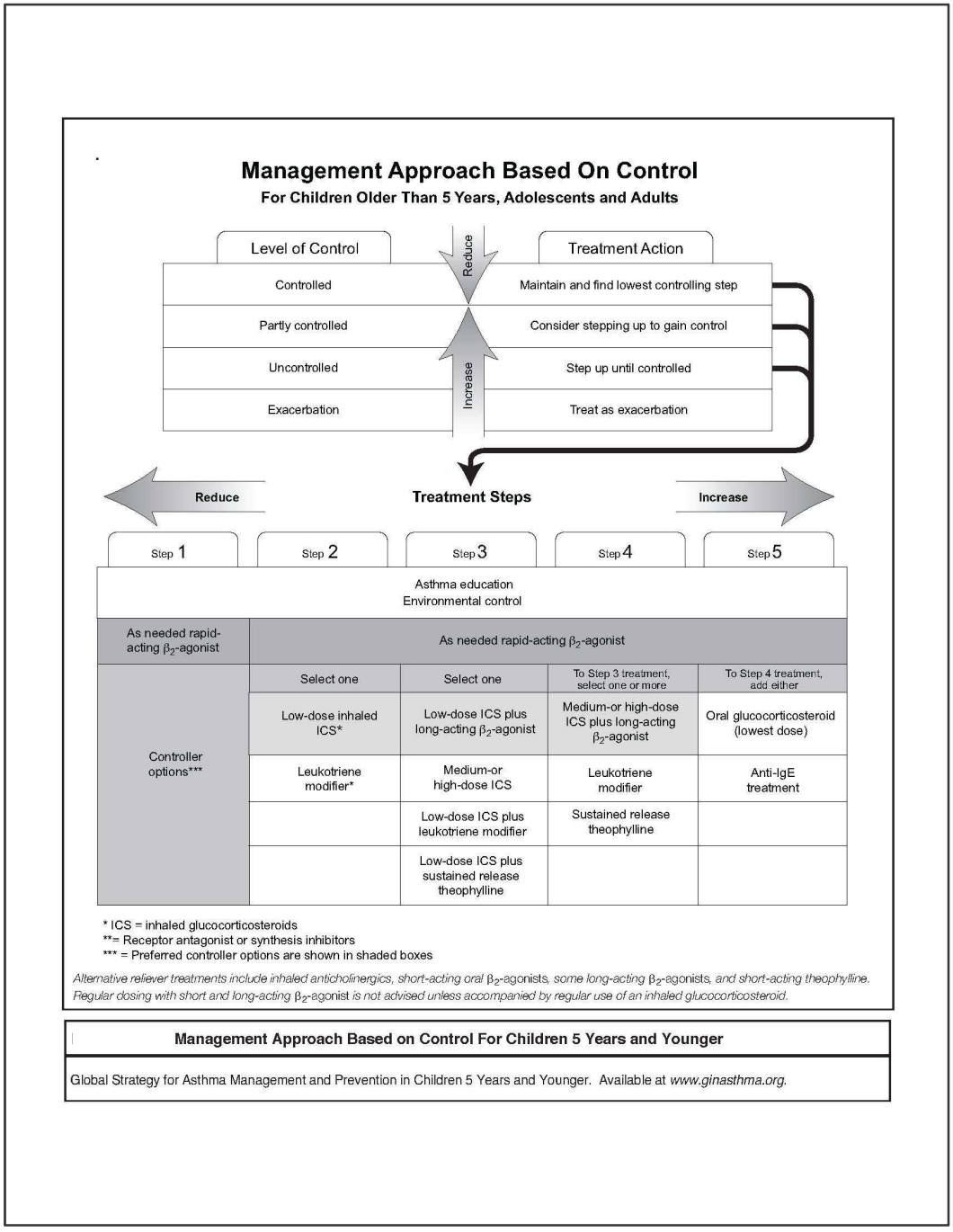


Figure 2
Content from Global Strategy for Asthma Management and Prevention used with permission from the Global Initiative for Asthma (GINA), www.ginasthma.org.

Program (NAEPP) guideline from 2007 still mentions assessment of asthma severity at the stage of diagnosis in order to determine initial treatment level [8].

The goal of successful treatment for all asthmatics is to achieve and maintain clinically well-controlled asthma [1,8], as current control is shown to reduce future risk of symptom instability and exacerbations [9]. Pharmacological achievement of asthma control can be obtained by using a stepwise approach [79]. At clinical evaluation, the current degree of asthma control is used to decide whether adjustment of an existing treatment level is recommended or should be initiated. A continued appearance of symptoms implies that the underlying airway inflammation may be inadequately controlled and indicates that treatment should be stepped-up [73]. An attempt to step-down treatment is recommended if clinical control has been maintained for at least three months [73]. The treatment steps based on achievement of clinical asthma control are illustrated in Figure 2.

2.5 ALREADY KNOWN ABOUT DRUG UTILIZATION AND ASTHMA CONTROL

Despite the availability of efficient pharmacological treatment, numerous observational studies report that the overall level of asthma control by adequate use of anti-asthmatic treatment remains poor and falls far from the goals stipulated in international guidelines [5-7]. Regardless of the varying methodology

used in the different studies, this conclusion appears unambiguous on a worldwide scale [80-82].

Inadequate controller treatment

Inadequate treatment involves over-, under- and no treatment, however, most focus has been due to under- and no treatment. European surveys from France, Italy, and Denmark have independently shown that the proportion of no treatment and undertreatment with ICS in populations of persistent asthmatics is approximately 35-84% and 48-86%, respectively [83-86]. This tendency has also been proved outside Europe. A national survey from United States found that almost 80% of the telephone interviewed asthmatics, including both children and adults, reported non-use of anti-inflammatory medication during the past month, applying to 74% of those having severe persistent asthma [87]. These results are consistent with recent findings from an Australian follow-up study in which 74% of the examined asthmatics used anti-inflammatory medication inadequately [88].

The reasons for inadequate use of ICS are multifarious and may result from a combination of several factors related to the patient, the health care professionals, but also to factors related to the health care system or society in general. On a patient level non-adherence to anti-asthmatic medication is a key element. Adherence is usually defined as "the extent to which the patients take their medication as prescribed by the physician" and involves an agreement between the patient and the prescriber, contrary to the term compliance [89,90]. Individual adherence rates to medication, reported as "the percentage of the prescribed dose of the medication actually taken by the individual over a specified period" [89], are typically considered adequate if constituting at least 80% or more [89]. This number also applies to anti-asthmatic treatment with ICS in order to obtain adequate asthma control [91]. Unfortunately, available evidence indicates low overall adherence rates to ICS prescribing varying from 20-78% [92-94] dependent on country, age, gender, race ethnicity, and underlying type of non-adherence, i.e. primary (the patient does not purchase prescribed ICS [95]), or secondary non-adherence (the patient stops or adjusts the prescribed ICS dosage [96]). There are several patient-related barriers associated with non-adherence to ICS use: Poor understanding of asthma and treatment (e.g. insufficient knowledge of trigger avoidance, of how to intervene a clinical deterioration, and distinction between reliever and controller treatment) [84,97], lack of motivation for behavioural change in proportion to medication use [98], improper beliefs and concerns about asthma and asthma medication [90], fear of medication side effects [96,99], and costs of medication [89,100]. Furthermore, an unfavourable patient-health care provider relationship resulting in communication failure [101] and deficient patient faith in the health care provider may also contribute to an inadequate level of ICS use [98].

On a health care provider level factors associated with inadequate ICS use involve irregular longitudinal assessment, poor knowledge of drug costs, and complexity of the asthma medication regimen prescribed [89,97,98]. Moreover, aspects like inappropriate patient education on asthma [98], and use of asthma management plans [102] should be mentioned, both of which imply that the patients possess deficient skills in how to initiate or adjust ICS appropriately in case of a deterioration [103]. Asthma specialists prescribe to a higher extent ICS compared to generalists [104], reflecting that a lower asthma knowledge level among health care providers has a negative impact on the adequacy of ICS use. This relation could be a consequence of non-adherence to asthma guidelines among health care providers, leading to an increased probability of inadequate treatment, handling of triggers, and comorbidity [84,105].

Factors within the health care system could also influence the overall inadequacy of ICS use. This could be due to an unequal and limited access to health care (e.g. due to fees at physicians or hospitals, and lack of health insurance), and changes in medication reimbursement rules [89,106]. Finally, it should be considered whether the notion of inadequate ICS use to some degree is based on incorrect assumptions. This aspect has been highlighted in a study aiming to develop and test quality indicators (QIs) based on prescription data as clinical surrogate measures of suboptimal asthma treatment. All the investigated QIs were found to be non-valid [107].

Inadequate asthma control

Inadequate treatment is closely associated with suboptimal asthma control [82,108]. Since the introduction of asthma guidelines the status of asthma control has been intensively investigated by use of epidemiological data. In 2000 the AIRE study by Rabe et al. reported striking findings as almost 95% of the population of young adult asthmatics from seven Western European countries were not well controlled according to guideline goals [5]. Subsequently, other large national and multinational surveys, including countries from Europe, Asia, and North America, have estimated the proportion of patients with uncontrolled asthma to be between 18-51% [7,80,103,109-111]. In a recent Danish survey Backer et al. found the proportion of uncontrolled asthmatics to be 61% [82].

Several factors are known to influence asthma control negatively, e.g. suboptimal treatment of concomitant diseases like rhinitis, sinusitis, and gastroesophageal reflux [112], environmental exposure to allergens [113,114], irritants (e.g. smoking [115] and pollutants [24]), respiratory infections [116], use of aspirin or aspirin like drugs [117], obesity [118], and pregnancy [119]. Thus, if such coexisting conditions are not handled appropriately, the patients are at higher risk of developing poor asthma control, involving increased symptoms and decreased quality of life (QoL). This underlines the importance of further diagnostics in patients who present with continuing poor asthma control despite ongoing controller treatment.

Disparity between use of reliever and controller treatment

An extensive use of reliever therapy can mask the inflammation of the asthmatic airways and lead patients to ignore symptoms, which is why this inappropriate treatment approach is pointed out as a risk factor for suboptimal asthma control [49,103]. However, a common problem in the observed low quality of anti-asthmatic treatment and asthma control seems to be an over-reliance on reliever therapy in favour of controller therapy [49,103]. Two major surveys have emphasized the fact that even in asthmatics with a frequent use of IBA, the consumption of ICS appears to be low [5,87]. This trend has also been found in pharmacoepidemiological studies using information from computerized files on anti-asthmatic drug prescription to investigate and measure the quality of asthma treatment [12,107,120-122]. In two such studies from Denmark it was observed that among young adult asthmatics with a massive daily use of IBA 20-35% were not prescribed ICS and only 10-20% received sufficient doses [12,120]. These disquieting observations unfortunately correspond to very recent findings based on Swedish and Canadian prescription data [121,122]. As some of the consequences of this improper use of anti-asthmatic medication are an increased number of exacerbations [50,123], lung function impairment

[69,70], and reduced QoL [67], attention to this problem is essential and emphasises e.g. the significance of educational support to the patients and a continuing longitudinal assessment of the disease.

Socioeconomic status and quality of asthma treatment

Socioeconomic status (SES) is a term frequently used to describe a person's social position [124]. Often social and economic factors like cohabitation status, ethnicity, education, occupation, and income are considered as either independent or composite key measures of SES [125]. However, as no strict international definition of SES is currently available a major challenge has been to compare results between studies [126].

During the past decade the impact of SES on the quality of pharmacotherapy has gained increased attention as it has become evident that subjects with low SES are at higher risk of being inadequately treated compared to subjects with high SES [127,128]. This relation also applies to asthma, e.g. illustrated by an increased and inappropriate over-reliance on reliever therapy among Canadian asthmatics with low SES compared to high SES [129]. Nevertheless, evidence for the association between SES and the quality of anti-asthmatic treatment with ICS is sparse and primarily based on small studies with conflicting results, e.g. showing both positive [130] and no associations [131] between low SES and non-adherence to controller treatment. Hence, knowledge to fully clarify a link between ICS use and SES is warranted and encourages further large-scale observational studies. Awareness of whether SES influences the quality of anti-asthmatic treatment is of clinical significance with respect to guiding health care professionals about which patients should have the most attention in order to secure adequate treatment and achieve asthma control.

Overall, the quality of asthma treatment and asthma control in general appears to be low. However, there is lack of longitudinal studies to elucidate whether the status and trend of ICS use have changed over time in consequence of new health care initiatives related to asthma treatment, e.g. new guidelines and introduction of anti-asthmatic drugs. In addition, enlarging knowledge on factors associated with ICS use and asthma control is still needed to improve identification of subjects at risk of being inadequately treated.

3 AIMS OF THE THESIS

The aims of the present studies were:

I. To investigate trends in use of ICS and factors associated with ICS use in young Danish adults with asthma during 1997-2006.

II. To investigate the associations between SES and anti-asthmatic treatment with ICS among young Danish adults with asthma during 1997-2005, and to investigate whether these associations were consistent over time.

III. To investigate whether prescribing patterns of anti-asthmatic drugs, in particular SABAs, were associated with clinically uncontrolled asthma.

Each of the above aims corresponds with one of the three papers upon which this thesis is based (Paper I, II, and III).

4 METHODS AND MATERIALS

4.1 SETTING AND DESIGN

The three studies were all conducted among young Danish adult users of anti-asthmatic drugs. Studies I and II were longitudinal studies based on repeated annual cross-sectional analyses on national register data during the respective observation periods. Study III was a cross-sectional study based on register and clinical data from a municipal cohort from Odense.

4.2 DATA SOURCES

Studies I and II

In Denmark a unique Civil Registration Number (CRN) is assigned to every Danish citizen which enables individual-based data linkage between different databases allowing register-based research on e.g. drug utilization of large and representative populations [11,132]. The Danish health care system is tax-financed and provides free access to hospitals and general practitioners. During hospital admission drugs are free of charge, whereas outpatient drug use is partially reimbursed according to the total costs of prescribed drugs per year [133]. The reimbursement percentage is higher, the higher the yearly individual reimbursable drug expenditure [134].

Statistics Denmark is a governmental institution collecting electronic records for a broad spectrum of statistical and scientific purposes in different registers. Since 1980 it has been possible to retrieve detailed longitudinal information at an individual level for the entire Danish population (5.27 million in 1997, 5.41 million in 2005, and 5.43 million in 2006) [135].

The Register of Medical Product Statistics

The Register of Medical Product Statistics (RMPS) is operated by the Danish Medicines Agency and serves as the Danish National Prescription Database 61. Data extraction and linkage are conducted through Statistics Denmark [135]. The information is collected from the Danish community pharmacies, hospital pharmacies, the Danish State Serum Institute (the National Central Laboratory of the Danish Health System) and the Danish Veterinary Laboratory (the Danish Veterinary Laboratory). RMPS comprises individual-based information on every medical product sold on prescription to outpatient use by Danish pharmacies since 1994, but does not contain individual-based information on inpatient drug use. Each prescription record includes the patient´s anonymous identifier, the identification code of the prescriber, the date of dispensing, the brand name, the manufacturer, quantity, form of the drug, code of reimbursement etc. Information on substances and quantities are classified according to World Health Organisation (WHO) anatomical-therapeutic-chemical (ATC) system and defined daily doses (DDD) methodology [136,137]. In brief, the ATC system classifies drugs into fourteen anatomical main groups and four subgroups according to the organ on which they act, therapeutic-, pharmacological- and chemical subgroup, and chemical substance. As an example, the ATC code composition for inhaled budesonide is R03BA02: R respiratory system, 03 drugs for obstructive airway diseases, B other drugs for obstructive airway diseases (inhalants), A glucocorticoids, and 02 budesonide. The DDD is only assigned for drugs with an ATC code and is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults [136]." The DDD provides a measure independent of price and dosage form (e.g. tablet strength), enabling researchers

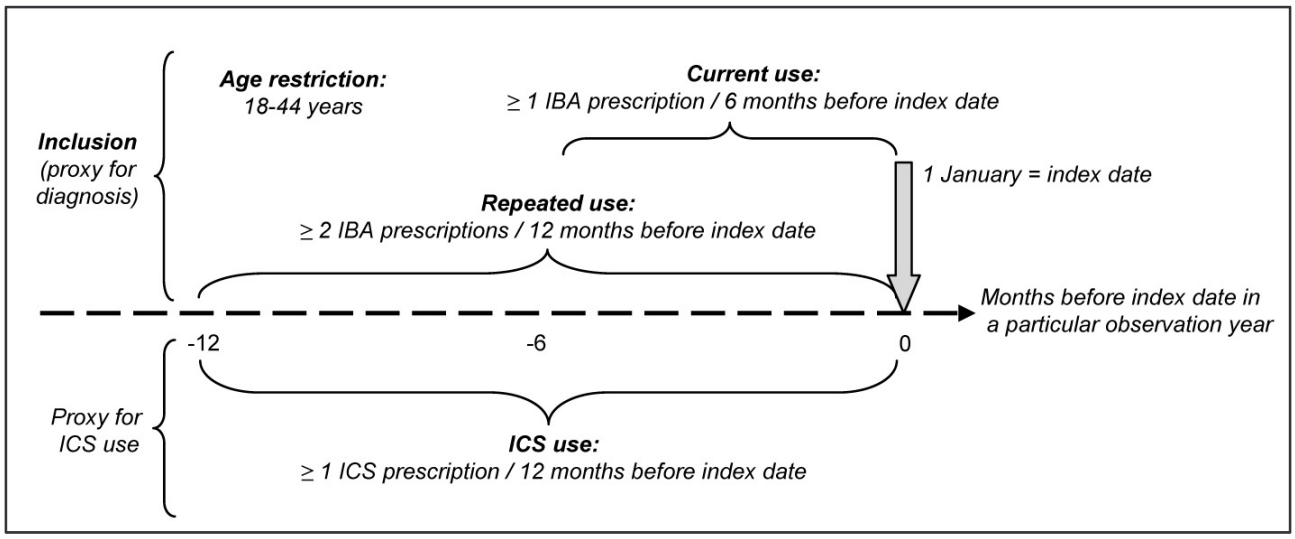


Figure 3
Inclusion criteria for studies I and II.

to assess trends in drug consumption and to conduct comparisons between populations. It should be emphasized that the DDD is not a dose recommendation, but a measure to aggregate drugs that have different potency [136].

Demographic and Socioeconomic Registers
Demographic and socioeconomic data were obtained from three different registers in Statistics Denmark. The Population Register contains demographic data on gender, year of birth, residence, and date of death, or of migrations. The Education Register contains data on the highest attained educational level. Data on individual income was obtained from the Register of Family and Income Statistics. These data come primarily from administrative registers (e.g. educational institutions and the Danish tax, customs and duties register (II)) [135].

Study III
Odense Pharmaco-Epidemiological Database (OPED)
Information on individual reimbursed drug dispensing in the County of Funen, Denmark (population 484 000 in 2009) has been recorded in OPED since 1990 and in the Region of Southern Denmark (population 1.2 million in 2009) since 1 January 2007. Each prescription record includes the same information as described in RMPS. Likewise, the substances and quantities are registered according to WHO's anatomical-therapeutic-chemical (ATC) system and defined daily doses (DDD) methodology [136,137]. Furthermore, individual inpatient drug use is not registered. The indication for treatment and the dosing instructions are not recorded. Drugs not reimbursed and therefore not recorded in the database are over-the-counter drugs and some non-reimbursed prescription drugs, mainly oral contraceptives, hypnotics, sedatives and some antibiotics, but also some intranasal drugs for rhinitis [132].

The Asthma Control Questionnaire (ACQ)
The ACQ is a validated seven-item questionnaire developed to measure individual asthma control during the previous week in clinical research studies as well as in clinical practice [138,139]. Items 1-5 cover questions on asthma symptoms and activity limitation, item 6 the use of short-acting beta-2-agonists (SABA), and item 7 is a measure of forced expiratory volume in one second (FEV1) in % of predicted. Each item is scored on a 7-point Likert scale from 0 to 6 (0=totally controlled, 6=severely uncontrolled) with the total ACQ score being the average of the questions. An ACQ score ≤ 0.75 and ≥ 1.50 is defined as having controlled and uncontrolled asthma, respectively [140]. An ACQ score between 0.75-1.50 has previously been defined as having partly controlled asthma [103]. We used the Danish version of ACQ, already translated by the MAPI Research Institute, with permission from the copyright owner.

4.3 STUDY POPULATIONS
In all three studies we used information on redeemed anti-asthmatic drug use from prescription databases to identify asthmatics. However, anti-asthmatics are not only used for asthma, but also for e.g. transient respiratory tract infections among small children, and for chronic obstructive pulmonary disease (COPD) among primarily the middle-aged and elderly. To avoid inclusion of subjects with use of anti-asthmatic drugs from diagnoses other than asthma we restricted age to 18-44 years.

Studies I and II
Identifying study subjects
In RPMS we identified all subjects who had redeemed drugs with ATC code R03 (drugs for obstructive airway diseases) during 1 January 1997 to 31 December 2006 (I) and during 1 January 1997 to 31 December 2005 (II). We used 1 January as index date in order to analyse annual cross sections of these populations. Thus, index dates were 1 January each year from 1998 and onwards in the respective observation periods. Data from RMPS were linked with demographic data by use of the anonymous person identifier, allowing us to include only subjects alive and resident in Denmark during the past year from index date.

Selection of study subjects
The annual group of asthma patients was defined for each index date as all subjects who fulfilled the following inclusion criteria: 1) age 18-44 years, 2) at least two redeemed prescriptions on IBA within 365 days before the index date, and 3) current IBA use defined as at least one redeemed prescription of IBA 180 days before the index date (Figure 3). A subject could be included on

multiple index dates, if he or she fulfilled the inclusion criteria. Hence, the annual group of eligible asthma patients was changeable since age, number of IBA prescriptions, and current IBA use at each index date influenced inclusion or exclusion that particular year. The study populations were N=106 757 in Study I and N= 97 665 in Study II.

Study III

Identification and selection of study subjects

In OPED we retrieved data on all subjects who had received prescribed drugs with ATC code R03 (drugs for obstructive airway diseases) between 1 December 2007 and 30 November 2008. Asthma patients were defined using similar inclusion criteria as in studies I and II: 1) age 18-44 years, 2) at least two redeemed prescriptions on inhaled beta-2 -agonists (IBA) 365 days before 30 November 2008, 3) current IBA use defined as at least one redeemed prescription on IBA 180 days before index date, and 4) alive and resident in the municipality of Odense, Denmark.

Recruitment and invitation

Name and address on the identified subjects (N=1435) as well as address of their general practitioners (GPs) were obtained from the regional patient administrative system [141]. Prior to inviting subjects for clinical assessment, the GPs were sent a list of the ones listed with their practice in order to exclude subjects that they did not find appropriate for any further contact (e.g. due to language problems or psychiatric diagnoses). Subjects not excluded by their GP (N=1308) were invited during 13 February and 22 April 2009. Non-responders were sent postal reminders 3-4 weeks after receiving the invitation letter. Responders had to answer two questions: "Have you ever had asthma?" and "was asthma diagnosed by a doctor?" Only responders answering "yes" to both questions were subsequently contacted by telephone to schedule an appointment for clinical attendance (N=421).

Clinical assessment

Flow chart for identification in OPED, recruitment, and clinical assessment is presented in Figure 4.

Responders who attended clinical examination were all clinically assessed between 1 April and 7 July 2009 by completion of the ACQ and performance of spirometry (N=365). The index date was defined as the date of clinical assessment. Instructions on how to complete the questionnaire and perform spirometry were given by two research nurses and Jesper Rømhild Davidsen at the Research Unit of Respiratory Medicine at Odense University Hospital, Denmark. Spirometry was performed on an IntraMedic, Micro Loop MK8 spirometer, in accordance with the European Respiratory Society (ERS) and American Thoracic Society (ATS) standards [142]. A total of 357 subjects were finally included.

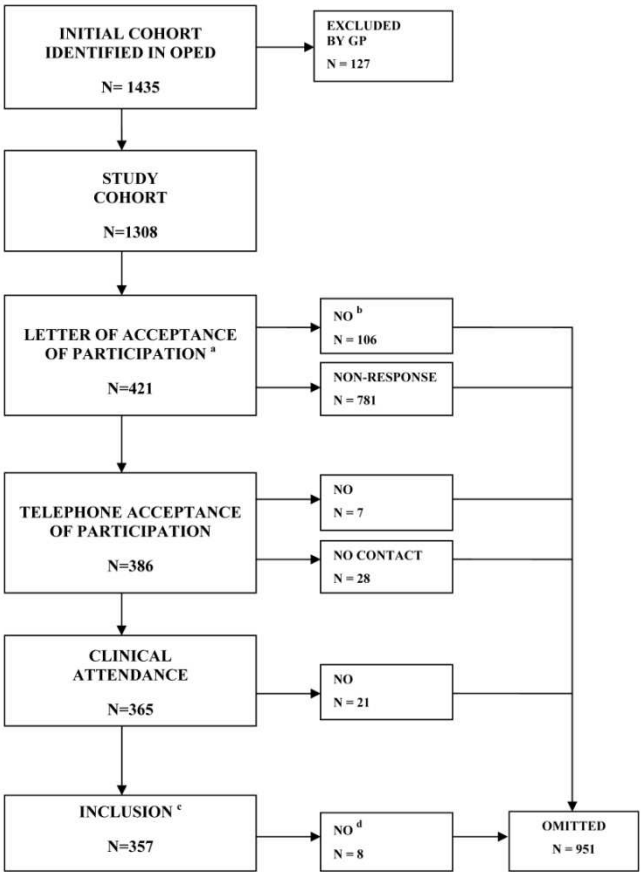


Figure 4

Patient flow for Study III.

a Letter of acceptance of participation and answering "yes" to both diagnostic questions on asthma.

b Eleven patients (10.4%) of the total 106 patients with non-acceptance of participation did not answer "yes" to both diagnostic questions on asthma.

c Sufficiently performed ACQ completion including spirometry.

d Insufficiently performed ACQ completion including spirometry (N=6) and language difficulties (N=2).

4.4 OUTCOME VARIABLES

Studies I and II

The outcome was use of ICS defined as at least one redeemed prescription of ICS during the year preceding the index date. Use of ICS referred both to ICS in non-combination inhalers (ATC R03BA01, R03BA02, R03BA03, R03BA05, and R03BA07), and fixed dose combination inhalers with ICS and LABA (FDCs) (ATC R03AK06 and R03AK07).

Study III

The outcome was clinically uncontrolled asthma defined as an individual ACQ score ≥ 1.50.

4.5 INDEPENDENT VARIABLES

Drug use variables (studies I, II and II)

Prevalent use of a particular drug was defined as having at least one redeemed prescription during the year preceding the defined index date. In Study III updated information on included subjects' anti-asthmatic drug use corresponding to the individual index dates was obtained from OPED.

In all three studies a proxy was used to define the study populations in which use of inhaled beta-2-agonist (IBA) was included. IBA referred to SABA (ATC R03AC02, R03AC03, R03AC04, and R03AC05), LABA (ATC R03AC12, and R03AC13), fixed dose combinations of SABA with anticholinergics (ATC R03AK03 and R03AK04), or fixed dose combinations of LABA with ICS (FDC) (ATC R03AK06 and R03AK07). In Study III SABA referred specifically to SABA (ATC R03AC02, R03AC03, R03AC04, and R03AC05), and combinations of SABA with anticholinergics (ATC R03AK03 and R03AK04). The LABA Indacaterol (ATC R03AC18) was first introduced in 2010 (main indication for COPD), thus not included in the three studies [143].

In studies I and II subjects were categorised according to their annual cumulative IBA use in DDD (1-99, 100-199, 200-399, and ≥ 400 DDD/year), whereas subjects in Study III were categorised according to annual cumulative use of SABA in DDD (0-99, 100-199, 200-399, and ≥ 400 DDD/year). Using inhaled terbutaline as an example, for which the DDD is 2.0 mg [137], a well-controlled asthma patient using less than two inhalations weekly according to GINA guidelines 1 corresponds to an annual use of 26-52 DDD when using a 0.5 mg inhaler device, and dependent on whether one or two inhalations are used at a time. In comparison, a person using more than 400 DDD/year would have an average use of at least 4.4 inhalations daily.

Other anti-asthmatic drugs included in all three studies were: Systemic glucocorticosteroids (ATC H02AB), leukotriene receptor antagonists (ATC R03DC), inhaled short-acting anticholinergics (ATC R03BB01 and R03BB02), oral beta-2-agonists (ATC R03CC), oral methylxanthines (ATC R03DA), and oral chromones (ATC R03BC). Also, we included drugs expected to be associated with some phenotypes of asthma. These were intranasal drugs for rhinitis (ATC R01A), and drugs for specific immune therapy (ATC V01). Omalizumab (Anti-IgE) (ATC R03DX) was not included as this drug category has restricted delivery to hospitals in Denmark [61]. Inhaled long-acting anticholinergics (ATC R03BB04) were not included in studies I and II, but in Study III. FDCs were considered both as IBA and ICS use.

Socioeconomic variables (Study II)

Education

Since 1981 individual-based information on education from administrative registers of educational institutions has been assembled in the Education Register of Statistics Denmark. On the basis of the population in Denmark of 1 January, an annual update is performed and coded according to highest attained educational level. The first two digits of this eight digit code describe one of the 12 main groups of educational level: 10 primary school, 15 secondary school, 20 high school, 25 business college, 30 basic vocational education, 35 vocational training, 39 continuing education of skilled workers, 40 short-length higher education, 50 medium-length higher education, 60 bachelor education, 65 long-length higher education, and 70 research education [135]. By use of these main group digits we categorized highest attained educational level into three groups: Basic school/high school (10-25: ~ 7-12 years of education), vocational training (30-39: ~ 10-12 years of education), and higher education (40-70: ~ ≥ 13 years of education). The lengths of education corresponding to this categorization are higher compared to other studies [127]. However, as we studied relatively young subjects, all born after 1953 and thus expected to have attended basic school (~ primary and secondary school) to a higher degree than those born before this year, this categorization, also used in previous publications [125], was considered reasonable. We excluded subjects for whom information on education was missing (2.1%).

Income

From the Danish Tax and Customs Administration (SKAT) annual individual-based information on income is collected in the Register of Family and Income Statistics. We used equivalent disposable income as economy measure, as this was thought to best represent the individual's economic capacity and thereby power to purchase medication [125]. Furthermore, using this variable enabled us to compare income between families of different sizes. Equivalent disposable income is defined as the disposable income for a single family member after taxation and adjusted for the number of family members, and calculated through the formula [135]:

$$\text{Equivalent disposable income} = \frac{\text{disposable income} \times 100}{(30 + (70 \times [\text{number of persons} \geq 18 \text{ years}]) + (50 \times [\text{number of persons} < 18 \text{ years}]))}$$

A person living alone or a person at least 18 years of age and living at home is defined as his/her "own" family. On the basis of quartiles of equivalent disposable income according to each year, we categorised subjects in low (1st quartile), medium (2nd and 3rd quartile), and high income (4th quartile) recipients [125]. Subjects for whom information on equivalent disposable income was missing (0.1%) were excluded. From 2006 the variable equivalent disposable income was based on data from registers which we did not have access to. In the following the term disposable income is used synonymously with equivalent disposable income.

Other independent variables (studies I, II and II)

In all three studies gender and age were included as independent variables. Age was stratified into three categories: 18-24 years, 25-34 years, and 35-44 years. Furthermore, calendar year was used in order to investigate time trends of ICS use in studies I and II.

4.6 STATISTICAL ANALYSIS

The distribution of gender, age and mean age was calculated for the three study populations in percentages.

Prevalence proportions

As a status measure of drug consumption at a given moment in time we estimated the prevalence proportion for use of particular anti-asthmatic drugs in all three studies. Prevalence proportion of use of a particular drug was estimated corresponding to the different index dates, with the numerator representing the number of the particular drug users and the denominator the number of included subjects (I, II, and III). Often prevalence proportion is referred to as prevalence [144]. In studies I and II the one year prevalences were calculated corresponding to each index date according to the annual groups of defined asthmatics fulfilling inclusion criteria. As an example from Study I 33 455 subjects were included in year 2000. Among these 21 584 were prevalent

ICS users giving rise to an overall one year prevalence of ICS use of approximately 64.4% (95% CI 63.8-64.9).

Logistic regression analysis

The main analysis used to estimate the associations between the outcome and independent variables was logistic regression. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were analysed by use of univariate (I, II, and III) and multivariate logistic regression models (I and II), respectively [145]. Regression analysis yields a regression model in which the outcome variable is expressed as a combination of the independent variable(s). Logistic regression analysis is used when analyzing binary outcome variables. In all three studies we used binary outcome measures defined as either the presence or absence of ICS use (I and II) or uncontrolled asthma (III).

The multivariate logistic regression models contained all independent variables applying to the specific study considering these as associated with the outcomes or potential confounders hereof. Testing for statistical interaction between exposure variables with particular focus on the outcome was performed by including the interaction term in the multivariate logistic regression models. As the same subject could be included on multiple index dates and thus occur in several cross-sectional analyses, we accounted for possible dependence of repeated measurements within subjects by adjusting for clustering using robust estimates in the multivariate logistic regression analyses [146] (I and II). Clustering was performed using the anonymous personal identifier. All analyses were performed using Stata Release, version 10.1 (I and III) and 11.0 (II) (StataCorp, College Station, TX, USA). A p-value < 0.05 was considered statistically significant in all studies.

4.7 CONTROLLING FOR CONFOUNDING

Confounding is a result of mixing effects between the exposure and an unknown or unaccounted confounding factor, a confounder, which leads to masking or distortion of the true relationship between exposure and outcome. A confounder is a factor associated with the exposure (but not a consequence of it) and with the outcome. Restriction, matching, and randomization are different methods used in the study design to control for both known and unknown confounders [147]. However, as these approaches were not applicable to our study designs we used other methods in the data analysis to control for confounding factors.

Stratification

We used stratification on gender, age, calendar year, and annual consumption of IBA (I and II) and SABA (III) in DDD/year. The intention of using stratification is to obtain unconfounded effect estimates of exposure on the outcome by subdividing data into smaller groups in which the confounding factor does not vary much or not at all [147].

Regression analysis

In mulitivariate regression models including more than one variable, variables are controlled for confounding simultaneously as the potential confounding of each included variable is unconfounded by the others (I and II) [147].

4.8 ANALYSES FOR INTERACTION

In statistics interaction describes a situation in which the simultaneous effect of two independent variables on a third (outcome variable) is not additive. In epidemiology the term effect measure modification is used, which refers to the effect of an independent variable (e.g. the exposure variable) on the outcome variable changing when simultaneous presence of another independent variable (the effect modifier) [147]. Most commonly statistical interaction is ascertained in the context of regression analyses.

Study I

A number of interactions between different independent variables on ICS use were tested by separate interaction analyses. Several interactions were found statistically significant, many of these were, however, clinically irrelevant. Only the interaction between gender and IBA use category was found to be clinically as well as statistically significant. In the final analysis, the ORs were adjusted for this interaction.

Study II

In a separate analysis testing for temporal trends for the association between ICS use and the socioeconomic variables we included the interaction term between calendar year and education, and the interaction between calendar year and disposable income in the multivariate logistic regression model. To analyse potential interactions between educational levels and disposable income, we stratified the multivariate logistic regression model by categories of highest attained educational level and disposable income, respectively.

Study III

Univariate logistic regression models were used to analyse associations between uncontrolled asthma and SABA use. To reveal whether interaction between different independent variables and SABA use had some potential impact on uncontrolled asthma, similar analyses stratified on gender, age category, and concomitant use of LABA and ICS, respectively, were performed. These did not lead to further suspicion, and thus no conventional interaction analyses were performed.

4.9 ETHICS

Studies I and II

Registry-based studies do not require an ethical approval in Denmark. Statistics Denmark and the Danish Medicines Agency gave permission to data access. Data was made available for further analysis with an anonymous but unique person identifier so that subjects could not be identified.

Study III

The local ethics committee of the Region of Southern Denmark (Project ID S-20080025) and the Multi Practice Committee under the Danish College of General Practitioners (Multipraksis-udvalget) approved the study. The Danish Data Protection Agency gave permission to data access (No. 2008-41-1895). Informed consent was obtained from each participant.

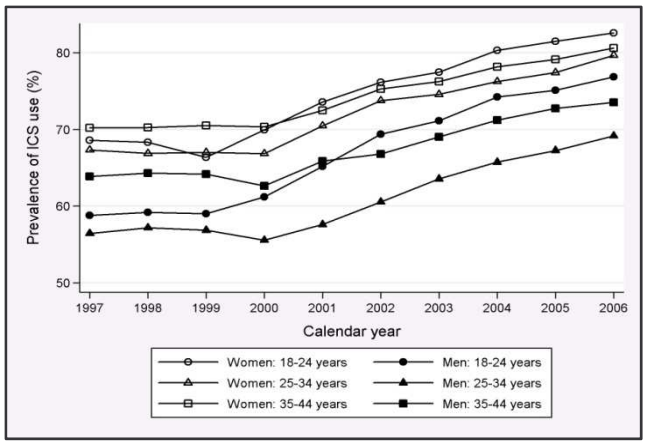


Figure 5
Prevalence of ICS use in different age categories stratified on gender each year during the observation period 1997-2006. Hollow symbols/solid symbols = women/men.

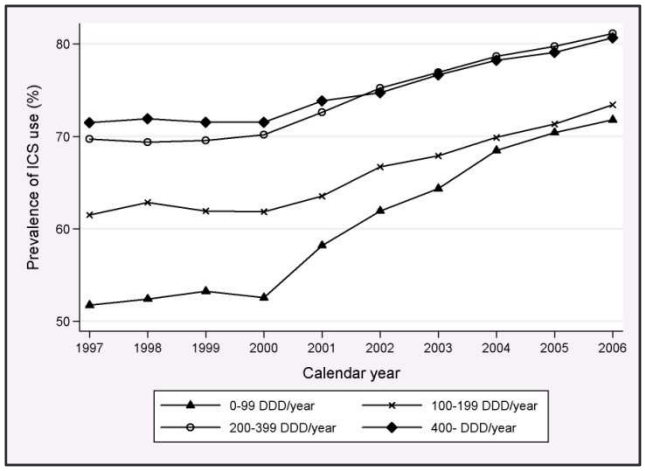


Figure 6
Prevalence of ICS use in different categories of IBA use each year during the observation period 1997-2006. IBA use in defined daily doses during 1 year (DDD/year).

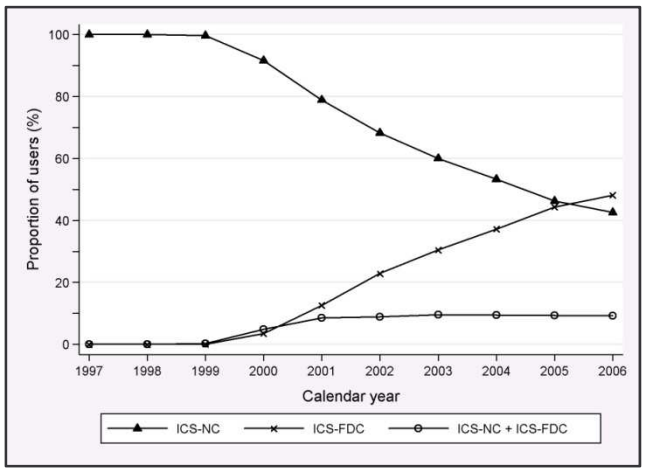


Figure 7
Proportion of ICS users categorised into users of only ICS non-combination inhalers (ICS-NC), users of only fixed dose combination inhalers with ICS and LABA (ICS-FDC), and users of both treatment options (ICS-NC + ICS-FDC) during the observation period 1997-2006.

5 RESULTS

5.1 INCREASED USE OF INHALED CORTICOSTEROIDS AMONG YOUNG DANISH ADULT ASTHMATICS: AN OBSERVATIONAL STUDY (STUDY I)

During 1997 to 2006, 106 757 users of anti-asthmatic drugs were identified in RMPS (Figure 3) of whom 77% were prescribed ICS. The overall one year prevalence of ICS use was constant during 1997-2000, approximately 64%, but increased gradually from 67% in 2001 to 77% in 2006. This trend also existed after stratifying on gender, age, and annual cumulative consumption of IBA (Figure 5 and 6). Figure 7 shows that the increasing one year prevalence in ICS use from 2001 occurred concurrently with a pronounced increase in the use of FDCs containing ICS and LABA, which in 2006 exceeded the proportion of ICS non-combination (ICS-NC) users corresponding to 42.6%.

This trend was confirmed in separate analyses showing an increased association between ICS use and calendar year from year 2001 (Table 2). Other factors associated with ICS use were high annual use of IBA, female gender, low age, use of leukotriene receptor antagonists, and drugs for rhinitis and specific immune therapy. Men seemed to be less responsive to IBA use, having consistently lower ORs in all IBA use categories compared to women.

5.2 IMPACT OF SOCIOECONOMIC STATUS ON THE USE OF INHALED CORTICOSTEROIDS IN YOUNG ADULT ASTHMATICS (STUDY II)

A total of 97 665 users of anti-asthmatic drugs met the inclusion criteria during 1997 to 2005. Table 3 shows that high levels of education and disposable income were independently associated with higher use of ICS, education demonstrating the strongest association, and that the impact of education and disposable income was more pronounced in 35-44 year-olds.

Figure 8 shows that for each year throughout the entire observation period higher education was a nearly constant factor associated with ICS use (ORs approximately 1.4-1.5), whereas high disposable income did not demonstrate any association before 2001, but with increasing ORs observed each year hereafter (ORs approximately 1.1-1.3).

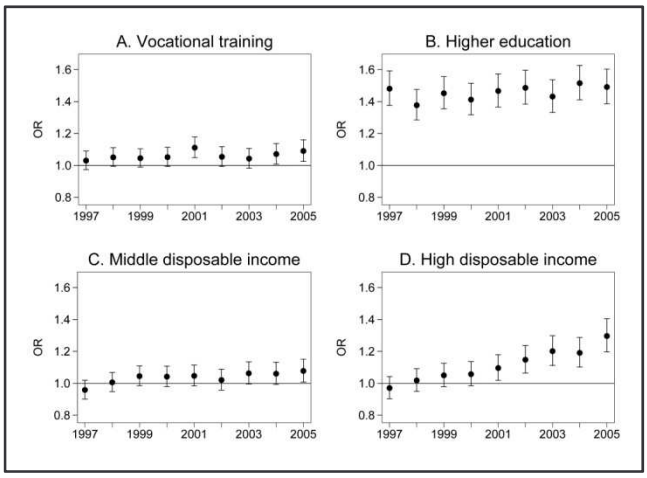


Figure 8
Trends in ORs for socioeconomic factors associated with ICS use for each year during the observation period for all subjects. A and B: Basic school/high school is used as reference, adjusted for disposable income, gender, age, IBA use, and ever use of specific anti-asthmatic drugs. C and D: Low disposable income is used as reference, adjusted for highest attained educational level, gender, age, IBA use, and ever use of specific anti-asthmatic drugs. OR = odds ratio.

Factors associated with ICS use		Prevalent users [a]	Crude [b]	Adjusted [b,c]
		N (%)	OR (95% CI)	OR (95% CI)
Year *	1997	33 819 (31.7)	1.00	1.00
	1998	35 335 (33.1)	1.01 (0.99 to 1.03)	1.00 (0.98 to 1.03)
	1999	35 554 (33.3)	1.00 (0.98 to 1.03)	0.98 (0.95 to 1.01)
	2000	33 445 (31.4)	1.00 (0.97 to 1.03)	0.98 (0.96 to 1.01)
	2001	33 687 (31.6)	1.14 (1.11 to 1.17)	1.12 (1.09 to 1.15)
	2002	34 519 (32.3)	1.29 (1.25 to 1.33)	1.26 (1.23 to 1.30)
	2003	35 035 (32.8)	1.40 (1.36 to 1.44)	1.39 (1.34 to 1.43)
	2004	36 463 (34.2)	1.56 (1.52 to 1.61)	1.56 (1.51 to 1.61)
	2005	35 819 (33.6)	1.68 (1.63 to 1.73)	1.66 (1.61 to 1.71)
	2006	36 394 (34.1)	1.83 (1.77 to 1.88)	1.81 (1.75 to 1.87)
Gender	Women		1.00	1.00
	Men		0.66 (0.64 to 0.68)	0.81 (0.78 to 0.85)
Age	18-24		1.00	1.00
(Years)	25-34		0.83 (0.81 to 0.86)	0.79 (0.76 to 0.81)
	35-44		1.06 (1.03 to 1.09)	0.92 (0.89 to 0.95)
IBA use, *women*	1-99		1.00	1.00
(DDD/year)	100-199		1.38 (1.34 to 1.43)	1.36 (1.32 to 1.41)
	200-399		2.38 (2.28 to 2.49)	2.30 (2.20 to 2.40)
	≥ 400		2.68 (2.53 to 2.84)	2.43 (2.30 to 2.58)
IBA use, *men*	1-99		1.00	1.00
(DDD/year)	100-199		1.21 (1.17 to 1.26)	1.22 (1.17 to 1.26)
	200-399		1.64 (1.57 to 1.71)	1.63 (1.56 to 1.70)
	≥ 400		1.62 (1.54 to 1.70)	1.57 (1.50 to 1.66)
Systemic glucocortico-	No		1.00	1.00
steroids	Yes	23 185 (21.72)	1.81 (1.75 to 1.87)	1.53 (1.47 to 1.58)
Leukotriene receptor antagonists	No		1.00	1.00
	Yes	7621 (7.14)	4.86 (4.47 to 5.27)	3.53 (3.25 to 3.84)
Intranasal drugs	No		1.00	1.00
for rhinitis	Yes	32 075 (30.04)	2.15 (2.09 to 2.22)	2.03 (1.97 to 2.09)
Drugs for specific	No		1.00	1.00
immune therapy	Yes	2866 (2.68)	2.67 (2.42 to 2.94)	2.32 (2.11 to 2.56)
Short-acting anticholinergics	No		1.00	1.00
	Yes	728 (0.68)	2.32 (1.87 to 2.88)	1.63 (1.30 to 2.04)
Oral beta-2-agonists	No		1.00	1.00
	Yes	5030 (4.71)	1.26 (1.18 to 1.36)	1.09 (1.02 to 1.18)
Methylxanthines	No		1.00	1.00
	Yes	2587 (2.42)	1.81 (1.62 to 2.01)	1.44 (1.29 to 1.61)
Chromones	No		1.00	1.00
	Yes	297 (0.28)	0.63 (0.48 to 0.83)	0.60 (0.45 to 0.78)

[a] For each calendar year the number of included subjects is presented in percentages of the total number of included subjects for the entire observation period (N=106 757). Number and percentages of users of specific anti-asthmatic drug categories are presented for the entire observation period.

[b] Lowest IBA use category for each gender, lowest age band, female gender, calendar year 1997, and non-use of specific anti-asthmatic drug categories were considered as references.

[c] Adjusted for IBA use categories, gender, interaction between IBA categories and gender, age categories, calendar years (time trend), and ever use of specific anti-asthmatic drug categories.

* Tests for time trends for 1997-2000 and 2001-2006 were p=0.189 and p<0.0001, respectively.

Abbreviations: IBA = inhaled beta-2-agonists. ICS = inhaled corticosteroids. OR = odds ratio. CI = confidence interval.

Table 2
Crude and adjusted odds ratios (ORs) for different factors associated with ICS use.

Table 4 shows that the impact of increasing disposable income on ICS use was most pronounced among lower educated subjects, OR 1.18 (95% CI 1.13-1.24). This finding agreed with an absolute difference in one year prevalence of ICS use between low and high SES groups of approximately 10% in 2005 for this age category (72.5% versus 81.4% for basic school/high school versus higher education, and 70.0% versus 79.6% for low versus high disposable income).

5.3 ASSOCIATION BETWEEN PRESCRIBING PATTERNS OF ANTI-ASTHMATIC DRUGS AND CLINICALLY UNCONTROLLED ASTHMA: A CROSS-SECTIONAL STUDY (STUDY III)

Of the 1435 subjects initially identified in OPED 357 were clinically examined, and among those 96 (26.9%) were classified as having uncontrolled asthma. Table 5 shows that clinically uncontrolled asthma was positively associated with SABA use, the association becoming stronger with higher annual quantity of SABA use. This trend persisted after stratifying for gender, age, and controller treatment with LABA or ICS (Table 6). Use of ICS protected against uncontrolled asthma, OR 0.51 (95% 0.27-0.94). This tendency also applied to LABA and leukotriene receptor antagonists, although not found statistically significant (Table 5). Figure 9 illustrates that subjects using ≥ 450 DDD/year of SABA were all uncontrolled, but that there was a substantial overlap in SABA use between controlled and uncontrolled subjects below this limit.

Factors associated with ICS use		All subjects* (N=97 665) OR (95% CI)	35-44 years* (N=49 317) OR (95% CI)
Year	1997	1.00	1.00
	1998	1.00 (0.98-1.03)	1.00 (0.96-1.04)
	1999	0.98 (0.96-1.01)	0.99 (0.95-1.04)
	2000	0.98 (0.96-1.01)	0.95 (0.91-1.00)
	2001	1.12 (1.08-1.15)	1.07 (1.02-1.13)
	2002	1.26 (1.22-1.30)	1.17 (1.12-1.23)
	2003	1.38 (1.34-1.42)	1.27 (1.21-1.34)
	2004	1.55 (1.50-1.60)	1.42 (1.35-1.49)
	2005	1.65 (1.60-1.70)	1.52 (1.44-1.60)
Highest attained educational level	Basic school/high school	1.00	1.00
	Vocational training	1.06 (1.02-1.09)	1.15 (1.10-1.20)
	Higher education	1.46 (1.40-1.51)	1.52 (1.44-1.60)
Disposable income	Low (1st quartile)	1.00	1.00
	Middle (2nd-3rd quartile)	1.03 (1.00-1.06)	1.15 (1.09-1.20)
	High (4th quartile)	1.10 (1.06-1.14)	1.24 (1.17-1.31)
Gender	Women	1.00	1.00
	Men	0.66 (0.64-0.68)	0.70 (0.67-0.73)
Age (Years)	18-24	1.00	
	25-34	0.71 (0.68-0.73)	
	35-44	0.83 (0.80-0.86)	
IBA use (DDD/year)	1-99	1.00	1.00
	100-199	1.33 (1.30-1.37)	1.44 (1.38-1.50)
	200-399	1.98 (1.92-2.05)	2.16 (2.06-2.27)
	≥ 400	2.02 (1.94-2.10)	2.21 (2.09-2.34)

* Adjusted for highest attained educational level, disposable income, gender, age, IBA use categories, and ever use of specific anti-asthmatic drug categories.
Abbreviations: IBA = inhaled beta-2-agonists. ICS = inhaled corticosteroids. OR = odds ratio. CI = confidence interval.

Table 3
Odds ratios for different factors associated with ICS use.

Highest attained educational level	Disposable income	OR (95% CI)
Basic/high school	Low	1.00
	Middle	1.04 (1.01-1.07)
	High	1.18 (1.13-1.24)
Vocational training	Low	1.00
	Middle	1.02 (0.97-1.09)
	High	1.09 (1.02-1.16)
Higher education	Low	1.00
	Middle	1.07 (0.99-1.16)
	High	1.06 (0.97-1.15)

Each stratum of highest attained educational level adjusted for gender, age, IBA use categories, and ever use of specific anti-asthmatic drug categories.
Abbreviations: IBA = inhaled beta-2-agonists, ICS = inhaled corticosteroids. OR = odds ratio. CI = confidence interval.

Table 4
Odds ratios for categories of disposable income associated with ICS use stratified on highest attained educational level.

Factors associated with uncontrolled asthma		Uncontrolled asthma N (%) [a]	Crude OR (95% CI) [b]
Gender	Women	52 (25.7)	1.00
	Men	44 (28.4)	1.14 (0.71 to 1.83)
Age	18-24	14 (20.0)	1.00
(Years)	25-34	36 (26.1)	1.41 (0.70 to 2.84)
	35-44	46 (30.9)	1.79 (0.90 to 3.53)
SABA use	0-99	48 (19.6)	1.00
(DDD/year)	100-199	19 (36.5)	2.36 (1.24 to 4.51)
	200-399	10 (29.4)	1.71 (0.77 to 3.81)
	≥ 400	19 (73.1)	11.14 (4.43 to 28.02)
LABA	No		1.00
	Yes	63 (24.6)	0.67 (0.41 to 1.11)
ICS	No		1.00
	Yes	77 (24.9)	0.51 (0.27 to 0.95)
Leukotriene receptor antagonists	No		1.00
	Yes	7 (20.6)	0.68 (0.29 to 1.62)
Oral glucocorticosteroids	No		1.00
	Yes	17 (37.8)	1.79 (0.93 to 3.45)
Long-acting anticholinergs	No		1.00
	Yes	4 (50.0)	2.79 (0.68 to 11.40)
Oral beta-2-agonists	No		1.00
	Yes	2 (50.0)	2.76 (0.38 to 19.83)
Methylxanthines	No		
	Yes	1 (100.0)	_ [c]

[a] Number and percentages of uncontrolled subjects in each stratum.

[b] Female gender, lowest age category, lowest SABA use category, and non-use of specific anti-asthmatic drug categories were considered as references.

[c] Not applicable.

Abbreviations: ACQ = Asthma Control Questionnaire. IBA = inhaled beta-2- agonists. SABA = short-acting beta-2-agonists. LABA = long-acting beta-2-agonists. ICS = inhaled corticosteroids. OR=odds ratio. CI = confidence interval.

Table 5
Associations between uncontrolled asthma, age, gender, and anti-asthmatic drug use.

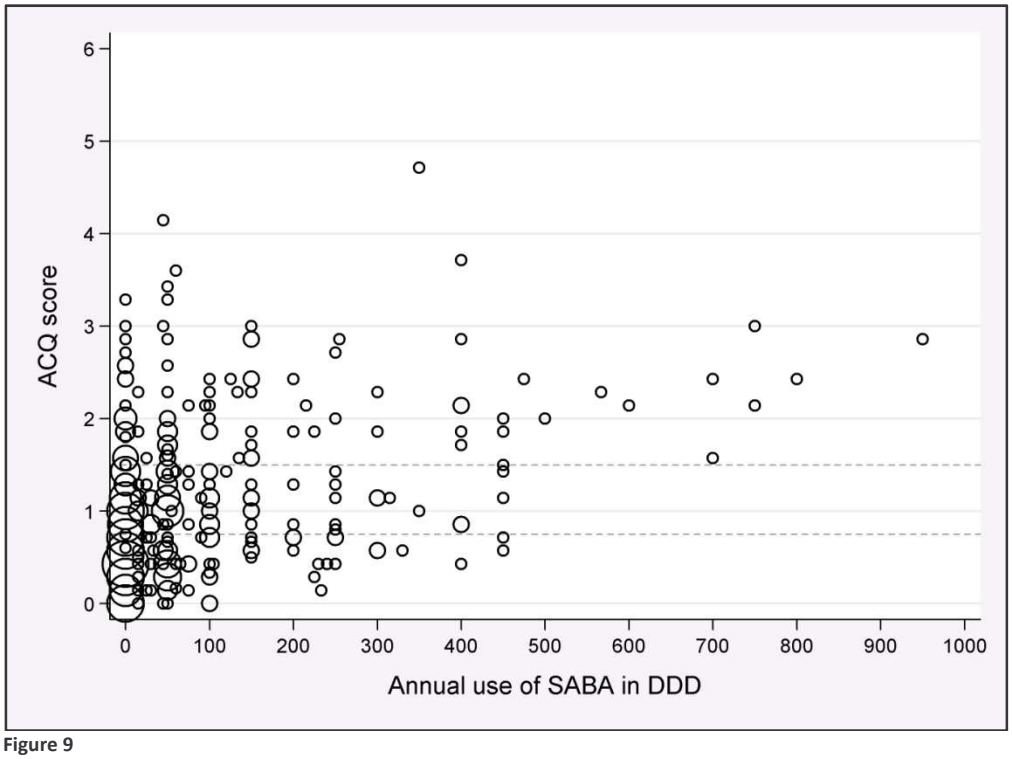


Figure 9
Distribution of ACQ scores according to individual annual use of SABA in DDD. Area of circles proportional to the number of subjects for each data point.

Factors associated with uncontrolled asthma	SABA use (DDD/year)	Total N [a]	Uncontrolled asthma N (%) [b]	Crude OR (95% CI) [c]
Women	0-99	151	30 (19.9)	1.00
	100-199	25	10 (40.0)	2.69 (1.10 to 6.58)
	200-399	17	5 (29.4)	1.68 (0.55 to 5.14)
	≥ 400	9	7 (77.8)	14.12 (2.79 to 71.44)
Men	0-99	94	18 (19.1)	1.00
	100-199	27	9 (33.3)	2.11 (0.82 to 5.46)
	200-399	17	5 (29.4)	1.76 (0.55 to 5.63)
	≥ 400	17	12 (70.6)	10.13 (3.17 to 32.42)
Age 18-24 years	0-99	55	7 (12.7)	1.00
	100-199	8	2 (25.0)	2.29 (0.38 to 13.64)
	200-399	5	3 (60.0)	10.29 (1.45 to 72.81)
	≥ 400	2	2 (100.0)	- [d]
Age 25-34 years	0-99	93	16 (17.2)	1.00
	100-199	20	8 (40.0)	3.21 (1.13 to 9.11)
	200-399	13	3 (23.1)	1.44 (0.36 to 5.84)
	≥ 400	12	9 (75.0)	14.44 (3.51 to 59.33)
Age 35-44 years	0-99	97	25 (26.0)	1.00
	100-199	24	9 (37.5)	1.73 (0.67 to 4.44)
	200-399	16	4 (25.0)	0.96 (0.28 to 3.25)
	≥ 400	12	8 (66.7)	5.76 (1.60 to 20.79)
Concomitant use of LABA	0-99	208	43 (20.7)	1.00
	100-199	25	8 (32.0)	1.81 (0.73 to 4.46)
	200-399	13	5 (38.5)	2.40 (0.75 to 7.70)
	≥ 400	10	7 (70.0)	8.95 (2.22 to 36.07)
No concomitant use of LABA	0-99	37	5 (13.5)	1.00
	100-199	27	11 (40.7)	4.40 (1.30 to 14.84)
	200-399	21	5 (23.8)	2.00 (0.50 to 7.93)
	≥ 400	16	12 (75.0)	19.20 (4.40 to 83.73)
Concomitant use of ICS	0-99	224	43 (19.2)	1.00
	100-199	40	13 (32.5)	2.03 (0.97 to 4.25)
	200-399	25	7 (28.0)	1.64 (0.64 to 4.17)
	≥ 400	20	14 (56.0)	9.82 (3.57 to 27.03)
No concomitant use of ICS	0-99	21	5 (23.8)	1.00
	100-199	12	6 (50.0)	3.20 (0.70 to 14.53)
	200-399	9	3 (33.3)	1.40 (0.29 to 8.86)
	≥ 400	6	5 (83.3)	16.00 (1.50 to 171.20)

[a] Number of subjects in each stratum.

[b] Number and percentages of uncontrolled subjects in each stratum.

[c] Lowest SABA use category was considered as reference.

[d] Not applicable.

Abbreviations: ACQ = Asthma Control Questionnaire. IBA = inhaled beta-2- agonists. SABA = short-acting beta-2-agonists. LABA = long-acting beta-2-agonists. ICS = inhaled corticosteroids. OR=odds ratio. CI = confidence interval.

Table 6
Associations between uncontrolled asthma and SABA use categories stratified on gender, age category, LABA use, and ICS use.

6 GENERAL DISCUSSION

6.1 MAIN FINDINGS

This thesis focused on trends in use of ICS and factors associated with ICS use among young Danish adults with asthma, and, furthermore, the association between prescribing patterns of anti-asthmatic medication and clinically uncontrolled asthma. The main findings are that 1) Treatment with ICS among young Danish asthmatics has increased since 2001, and this apparent improvement in ICS use was primarily due to the introduction of FDCs (I). 2) Approximately 20-30% of subjects with high annual consumption of IBA were not prescribed ICS indicating a room for improvement (I). 3) High levels of education and disposable income were positively associated with ICS use and most pronounced among 35-44 year-olds (II). 4) Higher education was more strongly associated with ICS use compared to high disposable income, which only became significant from 2001 (II). 5) Clinically uncontrolled asthma was closely associated with increasing use of SABA and existed irrespective of gender, age, and controller treatment with ICS and LABA (III). 6) The association between SABA use and uncontrolled asthma was not strong enough to allow firm conclusions for the individual asthma patient due to a substantial overlap in levels of SABA use among controlled and uncontrolled asthmatics (III).

6.2 STRENGTHS AND LIMITATIONS

Several noteworthy strengths and limitations need to be discussed in order to evaluate the internal validity (selection bias, information bias, and confounding) and external validity (generalisability) of the performed studies. These and other methodological issues are discussed in the following section.

Quality of the data sources

Register data

The main strength of all three studies is the population-based approach involving linkage of data from national and regional registers, allowing individual-based longitudinal study of drug utilization and factors associated hereby [11,132].

The prescription databases (RMPS and OPED) were the most important data sources in the investigation of anti-asthmatic drug utilization. Some drug utilization studies are limited by incomplete data on drugs. We used data from prescription databases, however, that cover all reimbursed prescriptions redeemed in Danish pharmacies (in OPED solely from pharmacies in the Region of Southern Denmark). To obtain reimbursement the pharmacies have an economic incentive to collect prescription data with as high accuracy as possible, securing a high level of data completeness [132,148]. The use of complete register data have minimized selection bias on drug exposure and avoided recall bias (information bias) concerning drug use.

Nevertheless, there are some weaknesses involved in using prescription data based on redeemed prescriptions. The distinction between physician prescribing and patient non-adherence by use of prescription data is difficult [149]. For example, a subject's drug dispense can be used as a proxy of physician's prescribing behaviour, but also as a proxy of prevalent drug use by the patient. Thus, if a patient fails to redeem a prescription (primary non-adherence) this may bias the interpretation of his physicians' prescribing behavior. However, one Danish study based on prescription data demonstrated that non-redemption rates appear to be low [150].

Another limitation of using prescription data is the uncertainty as to whether a purchased drug is actually being used by the patient (secondary non-adherence). If the purchased drugs are bought to family members or bought to be stored at several locations (e.g. in the car, boat, work, holiday home) in case of an urgent demand, this could be subject to misclassification of actual drug use resulting in an overestimation of the drug use prevalence, e.g. classifying subjects as heavy users of reliever therapy. Other shortcomings of using prescription data are discussed below.

We also used socioeconomic data from Statistics Denmark. These data are collected and updated annually from different administrative registers (tax-, labour market-, educational-, and social registers) and thus considered of generally high quality leading to an overall low probability of misclassification [135,151] (and personal communication with consultant Jørn Korsbø Petersen, Statistics Denmark).

Clinical data on asthma control

Several validated questionnaires are available to quantify the individual level of asthma control [152,153]. In clinical and research settings such instruments are essential in order to identify poorly controlled patients, who may require adjustment of current pharmacological treatment. In cross-sectional designs these instruments should possess strong discriminative properties to distinguish the level of asthma control [154]. These properties possess some of the most used instruments [73], the seven-item asthma control questionnaire (ACQ) [138,140], and the five-item asthma control test (ACT) [155,156]. Both questionnaires contain items on asthma symptoms, use of reliever therapy, and the ACQ furthermore involves measurement of lung function (FEV1). In addition, they both provide cut-points for identification of poorly controlled asthma, but a minimal important clinical difference has only been established for the ACQ [140]. As the ACQ also possesses strong evaluative properties, it excels in comparison to the ACT [153]. Accordingly, the use of ACQ was a strength of Study III. Prior to answering the ACQ items patients were given sufficient and comprehensive information by professional respiratory staff securing well-performed questionnaire completion and accomplishment of spirometry. This resulted in high response rate of between 96.9-100.0% for each of the seven items (N= 357), minimizing the possibility of missing data. In consequence we consider the clinical data obtained from ACQ as highly reliable.

Study design

A cross-sectional design was used in all three studies, which enabled us to appropriately analyse prevalence proportions for use of specific anti-asthmatic drugs (I and II), but also factors associated with their use (I, II, and III). Cross-sectional studies are limited by allowing only measurement of exposure and outcome variables at a certain point in time [144]. On the other hand, the cross-sectional design was the best suitable to answer our study aims and offered some advantages. By analyzing data sets from nine- (II) and ten- (I) year observation periods by repeated annual cross-sectional analyses, we were able to estimate a trend of ICS use in terms of one year point prevalences, but also to demonstrate a shift from use of ICS-NCs towards FDCs over time (I) (Figure 7). A further strength of this methodological approach was its ability to account for the changeable annual group of asthma patients by selecting these consistently at each index date using a composite of inclusion criteria as a proxy for the asthma diagnosis. These observations were not obtainable using a cohort design with follow-up. Unlike a cohort design, the cross-sectional design does not allow for study of incidence rates or causality, e.g. whether lack of asthma control was due to over-reliance of SABA or vice versa (III). However, this was beyond the scope of our studies. Another well-known limitation concerning cross-sectional studies is the possibility of introducing length-biased sampling, e.g. over-representation of cases with long disease duration as could be the case for asthma [144]. After all, due to the consistent inclusion of study subjects, we have no reason to believe that length-biased sampling has distorted the study results.

Selection bias

Asthma definition

An important limitation in using prescription data is lack of diagnosis and indication for treatment, which raises an important question: Are the included users of anti-asthmatic medication true asthmatics? We used a proxy for the asthma diagnosis based on a composite of different inclusion criteria corresponding to each of the index dates (Figure 3). As prevalent ICS use was of interest in all studies, ICS use could not be included in the proxy. Consequently, subjects were included according to redeemed prescriptions of IBA in combination with age restriction. We required at least two redeemed prescriptions of IBA per year, of which one should be redeemed within the past six months, presuming that these prescription patterns were reliable for subjects with a certain consistence in the asthma diagnosis. If only one IBA

prescription per year and older than 6 months was required, this may reflect only a temporary and non-trivial need for adjuvant bronchodilation in non-asthmatic indications like e.g. transient upper and lower respiratory tract infections [150,157]. Our proxy was, furthermore, supported by findings from a Dutch validation study in which at least two redeemed anti-asthmatic prescriptions (ATC code R03) per year corresponded to the asthma diagnosis with a sensitivity and positive predictive value of 0.71 and 0.79, respectively [158]. Furthermore, we chose one year observation intervals of drug exposure with the same index date to diminish potential influence of seasonal variation which could contribute to deterioration in asthma symptoms and lead to change in medication use.

Regarding studies I and II, a weakness of the "diagnostic" proxy was inclusion of subjects with more than trivial use of IBA and hence subjects more likely to have uncontrolled asthma. Consequently, this may have underestimated the size of the true annual group of young adult asthmatics due to avoidance of asthmatics with e.g. well-controlled asthma, and asthmatics characterised by low perception of symptoms, inducing a lower need of reliever therapy. However, in Study III the major purpose was examination of how uncontrolled asthma related to different strata of annual SABA use. Subjects were included on the basis of IBA, and questions confirming that they had physician diagnosed asthma [23,159]. Subsequently they were classified as either asthmatics with controlled or uncontrolled disease. Thus, the use of the register-based "diagnostic" proxy could not possibly be a source of selection bias per se in Study III. The reason why we continued including subjects on the basis of IBA instead of SABA in Study III was to relate the register-based findings from studies I and II to "real life" clinical data on asthma control.

Healthy volunteer bias (Study III)

This specific type of selection bias refers to different exposure and/or outcome characteristics among volunteers and non-volunteers in clinical studies, which is why each group may not be representative of the true population. For example, volunteers are assumed to be more health-conscious and therefore more likely to volunteer in studies offering clinical examination [144]. This phenomenon is also known from surveys in which results from responders are compared to non-responders [160]. Despite large variations in ACQ scores and SABA use among participants, the percentage of high annual SABA use was higher among non-participants, and we therefore need to consider healthy volunteer bias during the recruitment of study subjects in Study III.

In addition, 127 subjects of the initial cohort identified in OPED were excluded by their GPs and thus not included in the study cohort. As no further data analysis was possible for these subjects, it can only be speculated whether this procedure may have contributed to potential bias of our findings.

Information bias

Misclassification of ICS use (studies I and II)

At least one redeemed prescription of ICS the year preceding the index dates was used as an indicative of ICS use. This proxy has also been used in previous studies on anti-asthmatic drug use [3,12,120,122,150,158,161,162]. However, exposure to ICS is difficult to evaluate and may not be adequately reflected by this proxy leading to potential misclassification of regular ICS use. As we did not require current use or looked at the adequacy of the ICS amount we may have overestimated the annual number of prevalent ICS users which could have biased the study results in a too optimistic direction regarding one year prevalence proportions of ICS use (I). In a study of anti-asthmatic prescription patterns in children, a regular ICS use was defined as at least two prescriptions of ICS during one year [105]. Nevertheless, changing the ICS use threshold to at least two prescriptions within a year in Study II did not induce any substantial changes in the associations between education, disposable income and ICS use. This suggests that the proxy, after all, seems reliable as a surrogate measure of regular ICS use, which was the main purpose of studies I and II. Still, it is important to emphasize that the proxy did not possess the ability to distinguish between potential under- or over-treatment with ICS.

FDCs containing ICS and LABA were introduced on the Danish market in 1999 and 2001 [61], respectively. Prior to this subjects could use the two drugs concomitantly by two different prescriptions. As we aimed to estimate the overall ICS use (I) and associations between ICS use and different variables (I and II), we added prescriptions of ICS-NCs and FDCs under the same ICS heading allowing comparison of ICS use before and after FDC introduction. As one would expect that users of FDCs were representing a more uncontrolled degree of asthma compared to users of ICS-NCs, the joined ICS variable could have introduced some non-differential misclassification of ICS exposure leading to attenuation of the associations between ICS use and different factors associated with ICS use (I and II).

Misclassification of IBA and SABA use (studies I, II, and III)

Adjustment for the amount of IBA and SABA prescribed in categories according to cumulative consumption in DDD/year was intended to serve as a surrogate for the asthma severity, an approach which has also been used in previous studies [12,72,120]. However, as outlined current guidelines recommend subdivision of asthma severity by the intensity of treatment required to achieve asthma control [1]. As "treatment" does not only refer to IBA and SABA, but to all anti-asthmatic medication used at a certain point in time, non-differential misclassification could have appeared and consequently have lowered the strength of our associations.

Misclassification of anti-asthmatic drug use (Study III)

In Study III the assessment of individual anti-asthmatic drug use referred to redeemed prescriptions the year prior to the date of clinical examination, whereas ACQ referred to clinical symptoms during the past week. This may also have led to non-differential misclassification of asthma drug exposure, due to the different length of these time windows resulting in underestimated associations between uncontrolled asthma and anti-asthmatic drug use. Nevertheless, this did not affect the observed associations, quite the contrary.

Misclassification of drug use variables associated with the outcomes (studies I, II, and III)

Prescription data on purchased drugs were used as indirect proxies of their use. As already emphasized, data on redeemed prescriptions may not give an exact picture of actual use. In this way, valid information on real drug use would have been preferable, e.g. obtained by directly observed therapy or measurement of concentrations of a drug or its metabolite in blood or urine [89]. However, a major disadvantage to these approaches is that they are rather troublesome, expensive, and sensitive to the patient.

Misclassification of the socioeconomic variables (Study II)
Instead of using proxies based on aggregated information of different socioeconomic variables, we used two separate and individual-based measures of SES, disposable income and highest attained educational level, which diminished the potential of misclassification.
As the core variable of income we preferred using disposable income as this reflected what the individual subject could actually spend on medication costs. Besides adjustment for taxation and number of family members, disposable income was also adjusted for e.g. proceeds from savings/investments, housing and child benefits, and interest rates (personal communication with consultant Judith Zukunft, Statistics Denmark) [135]. This lowers the likelihood of misclassification compared to studies that use gross income [127,163], which is not adjusted for the aforementioned variables [135]. However, although the categorization of disposable income by quartiles has been used previously [125], it may not reflect the true income classification sufficiently. For example negative disposable income was observed in less than 0.8% of the included subjects, who may represent individuals that due to a newly started company were subject to initial negative interest rates secondary to raising large loans. Consequently, these would be categorised as low income subjects, which probably contradicts their real income classification. In spite of this, by categorizing subjects consistently according to their relative disposable income at each index date allowed comparison over time, but did also permit capturing the potential transition between the different income categories. In addition, it rendered the analyses less sensible to inflation, all of which strengthens our findings.
Highest attained educational level was the core variable used to categorize educational level. However, some continuing education and in-service training, e.g. refresher courses and extra courses required to obtain specific work-related skills, are not registered in educational registers. This may contribute to non-differential misclassification, as subjects classified as lower educated may be mixed with subjects having higher educational qualifications. On the contrary, misclassification of subjects as being higher educated than actually the case may be more unlikely. Even though our associations between ICS use and education may thus be attenuated, they still show an obvious tendency.

Confounding
Although, we used different methods to control for important patient-related factors and potential confounders associated with the outcomes, we still need to consider unmeasured or residual confounding as an explanation for our findings. A limitation of the studies was that the register-based approach did not allow controlling for other confounders that were not covered by the databases, e.g. smoking and obesity (body mass index > 30 kg/m2) etc. Lack of adjustment for these potential confounders may have distorted our results, as reflected below and exemplified by smoking and obesity.

Unmeasured confounders in studies I and II
Both smoking and obesity might be important confounders in the association between calendar year and ICS use, i.e. the trend in ICS use. Smoking is associated with uncontrolled asthma [115] due to a reduced anti-inflammatory effect of ICS [63]. The proportion of Danish smokers has decreased gradually since the 1970s [164,165], thus fewer smokers must be expected in our annual groups of asthmatics throughout the observation period. If we assume smokers use ICS more often than non-smokers in order to obtain the same anti-inflammatory effect, the effect of a decreasing smoking tendency alone would imply a negative trend in ICS use over time. If we were able to adjust for smoking the demonstrated positive trend in ICS use would have been even more pronounced and consequently the increasing trend of ICS may be underestimated.
On the other hand, an increasing prevalence of obesity has been demonstrated among young adult Danes over time [166]. Obesity is positively associated with uncontrolled asthma [167], and as obese asthmatics are less likely to achieve asthma control when using ICS compared to non-obese [168], asthma control among obese necessitates a higher ICS use. Thereby, we may have overestimated the trend of ICS use by not taking the obesity trend into account.

Unmeasured confounders in Study II
Could lack of confounder control for smoking and obesity have influenced the association between ICS use and SES? These characteristics appear more prevalent in subjects possessing low SES [169]. Thus, it may be presumed that the demand for ICS decreases with higher level of SES. However, due to lack of adjustment for these potential confounders the associations between ICS use and increasing SES may be underestimated, which only strengthens our findings of this gradient.

Unmeasured confounders in Study III
Study III aimed to prove a potential association between prescribing patterns and clinical data of uncontrolled asthma. Such knowledge would be of importance for the interpretation of findings in studies I and II. However, the associations in this study are more complex, and as smoking and obesity are not directly associated with use of SABA, they do not fulfil the criteria for being a confounder. Intuitively smoking is expected to relate to higher demand of SABA, but this would be through an intermediary step of uncontrolled asthma (smoking → uncontrolled asthma → ↑ SABA). After all, we are unable to entirely leave out a possible association between smoking and obesity with SABA use.

The above speculations are rather hypothetical and based on population-based information on smoking and obesity trends [164,166]. Whether these trends are applicable to our data is questioned and would require that the study populations were representative of the general Danish population per se. Without access to concrete information on potential confounders and their distribution in the study populations, it is still difficult to determine whether our results may be biased towards or away from the null hypothesis. Nevertheless, as we, to the extent possible, have made an immense effort to avoid bias, we do not consider the influence of potential unsolved residual confounding enough to make our findings unreliable.

6.3 GENERALISABILITY
Optimal generalisability would imply that the observations from the three studies could be extrapolated to other asthma populations. Our studies were restricted to subjects aged 18-44 years who had particular prescription patterns with more than trivial use of IBA. In Study III, the study population was, furthermore, restricted to subjects with residency in the municipality Odense. As already discussed in section 6.2, we may have precluded asthmatics with certain characteristics due to the selection on IBA use. Thus, it is likely that the included subjects represent patients with persistent asthma, and as these to a large extent are be-

lieved to have regular drug use consistent with inclusion criteria, we find it reasonable to generalize our findings to other populations of persistent asthmatics in this age category. Furthermore, we also consider the findings generalisable to such asthma populations in other countries with health care systems similar to the Danish one (e.g. drug prescribing, reimbursement rules etc.). Whether our findings are representative of other age groups is debatable. For example, presuming an overall lower length of education among the elderly may homogenize an older asthma population with respect to SES leading to an expected attenuation of the social gradient in ICS use (II). In conclusion, we find that the selected subjects reliably represent young Danish persistent asthmatics that are comparable with other asthma populations.

6.4 DISCUSSION OF STUDY RESULTS

Study I

In this large-scale observational study we found an almost constant one year prevalence of ICS use (1997-2000) before FDC introduction in 1999 and 2001 [61]. This contradicts previously reported findings from Europe and US in adults 3,4,12,104 and children [170] showing increasing trends of ICS use within this period. The disagreement, however, is very likely due to methodological differences between the studies and not least the extent of guideline integration between countries. Conversely, to our knowledge, this is the first longitudinal study to demonstrate the impact of FDC introduction on the overall increasing trend of ICS use from 2001 in a nationwide population of young adult asthmatics. As the proportion of FDCs on ICS use was consistent with findings from Sweden (48% Denmark in 2006, 46% in Sweden in 2007) [171] and also with a similar pattern observed among Danish children with asthma [105], we consider our findings reliable. It may be discussed whether the increasing trend in ICS use represents an overall increased tendency in disease severity. After all, as the rapid increase in ICS use appeared convergent with the introduction of FDCs, this explanation seemed more unlikely [105].

The increased association between ICS use and high annual IBA consumption corresponds with previous findings [172] and may reflect a well-known phenomenon in pharmacoepidemiology, confounding-by-severity [72]. Those subjects who have the most uncontrolled asthma (symptom severity) will have high IBA use and thus tend to use ICS more frequently. Their ICS use will lower their need for IBA, granted, but not to the level of those who have less uncontrolled asthma. Consistent with some [173], but not all studies on gender differences in ICS use [95,174,175] women were found to be more frequent than men to use ICS. This finding combined with men having consistently lower odds of ICS use in all IBA use strata compared to women may suggest that women have a lower threshold of symptom perception [15], but also being better educated and aware of their disease, thus knowing how to intervene against deterioration. Surprisingly, from 2001 the most pronounced increase in ICS use was seen in the low age category, opposing evidence of low age as a determinant of non-adherence [97,172]. This in combination with the largest increase in ICS use among low IBA use subjects could lead to the assumption that our results reflected change in physician prescribing behaviour, but also a decreased threshold of FDC prescribing due to an extensive marketing by the pharmaceutical industry [105].

Study II

Although several studies indicate that low SES is related to an increased prevalence and incidence of asthma [163,176-179] only limited evidence is available on the association between ICS use and SES in asthmatics. This longitudinal study, so far, is the first to explore this association in a nationwide population of young adult asthmatics. Even in a health care system that claims to ensure a high degree of equality in medical care, we found clear indications of a socioeconomic gradient in ICS use among young adult Danish asthmatics, as subjects possessing high SES were more likely to use ICS compared to low SES subjects. This association applied to both measures of SES, disposable income and educational level. In consequence of diverse definitions of SES, comparison to other studies is difficult [126]. Previous findings on this association are mainly based on educational level in small observational studies with few participants, but to some extent they agree with our results. Apter et al. showed that socioeconomic factors like less than 12 years of education and low household income were associated with non-adherence with ICS [130]. Using a combination of educational level and employment, de Vries et al. found low SES to be associated with poor asthma control which may reflect inadequate use of ICS [180]. Conversely, Janson et al. demonstrated that ICS adherence was associated with high income, but they were unable to demonstrate an association between ICS adherence and educational level [131].

Increasing age is an obvious prerequisite for achieving education. Hence, the relatively young age (18-44 years) of the included subjects may have influenced our results, and may explain that the fact that impact of education and income on ICS use was most pronounced among 35-44 year-olds who could be assumed to have finished their education and found their ultimate income level. High educational level may act as a proxy for cognitive skills, suggesting that higher educated subjects are more prone to transforming symptoms of uncontrolled asthma into ICS prescription [128,130]. Whereas higher education showed an almost constant association with ICS use each year throughout the observation period, an increasing association between ICS use and high disposable income was not observed before 2001. Furthermore, the association with ICS use was less pronounced among low income compared to among high income subjects. These findings could reflect involvement of other factors not accounted for in the analyses, e.g. implementation of changed drug copayment rules in 2000 which in brief implied full user payment for the first 500 DKK (~ 67 Euro in 2010) spent per year [134]. As costs of ICS are relatively high [61], these rules may have accentuated the barrier to purchase expensive inhalation medication for lower compared to higher income subjects, and thus be a potential explanation for these findings [89,100].

Study III

The observation that asthma patients on unbalanced high doses of reliever therapy were poorly controlled is well known from studies using solely clinical data [103] and prescription data [181]. Accordingly subjects with high annual reliever consumption in studies I and II, whether prescribed ICS or not, were more likely to possess uncontrolled asthma. However, the available data in these studies did not permit such deduction. Consequently, to clarify the reliability of this assumption according to “real life” asthma control, we examined the association between SABA prescribing and actual clinically assessed asthma control among 357 subjects initially selected by the same IBA criteria as in I and II. We found a clear link between increasing quantities of dispensed SABA and uncontrolled asthma, without any effect modification by gender, age, and controller treatment with LABA, or ICS. However, the results did not allow precise conclusions on an individual level due to large variations in both ACQ scores and

SABA use unless the annual SABA use was very high (≥ 450 DDD/year). The latter indicates that even though an increased possibility of ICS use was observed among subjects with a very high annual use of reliever therapy (≥ 400 DDD/year) (I and II), these were still more likely to possess uncontrolled asthma (III). Accordingly, a conventional clinical focus on the quality of asthma treatment is of continued importance to achieve adequate asthma control.

To our knowledge, this subject has only been handled sporadically in one study by complementing scores obtained from the Asthma Control Test (ACT) with pharmacy records [182]. Although purpose and methodology of this study differed substantially to ours, the highest proportion of clinically assessed uncontrolled asthma was found among patients being prescribed reliever therapy exclusively (60.9-82.4%) consistent with our observations.

6.5 INTERPRETATION OF STUDY RESULTS

Although we showed an increasing trend in ICS use, our observations still underline a substantial room for improvement in pharmacological asthma treatment (I). We found that subjects with a very high annual use of reliever therapy (≥ 450 DDD/year) were more likely to possess poor asthma control (III) and to use ICS (I and II). Combining these results suggests that despite an already existing ICS use, some high consumers of reliever therapy were still being exposed to under-treatment with ICS. However, approximately 20-30% were not prescribed ICS at all (I and II). Thereby, our findings add to previous evidence by demonstrating inadequate ICS use and asthma control in general populations of young adult asthmatics. Besides patient non-adherence, which was not investigated, this could be due to a continuing over-reliance on reliever therapy, as shown implicitly. Exemplified by inhaled terbutaline, for which the DDD is 2.0 mg [136], a heavy consumer using more than 450 DDD/year would have an average use of nearly 5 inhalations daily when using a 0.5 mg inhaler device. This clearly contradicts guideline recommendations [1]. As it appears, achievement of asthma control by adequate treatment the way it is stipulated in guidelines is a major challenge and emphasizes that asthma management is complex and dependent on various co-players. Nevertheless, as we believe to have accounted for patient-related factors in the study designs and analyses to the extent possible, it is more obvious that the demonstrated trends and associations with ICS use (I and II) reflected changes attributable to factors related to physicians, the health care system, or society as a whole. This also includes changes at different levels within each of these non-patient related factors, e.g. the constitution of general practices, change in physician prescribing behaviour, revised guidelines, introduction and extensive marketing of new anti-asthmatic drugs, change in medication reimbursement rules, constitution of outpatient clinics and hospital departments, but also a potential change in inflation and relative wealth. We demonstrated the impact of FDC introduction on the increasing trend of ICS use (I). However, due to the data available, we were not able to investigate the impact of the remaining non-patient related factors.

7 CONCLUSION

Answers to the aims of the thesis:

STUDY I

An annual increase in ICS use among young Danish adults with asthma since 2001 was found which occurred concurrently with the introduction and an increased use of FDCs. A high annual IBA use, female gender, and low age stood out as determinants of ICS use. Despite an apparent improvement in the overall use of ICS, still 20-30% of those subjects with a massive annual IBA consumption were not prescribed ICS, leaving a room for improvement.

STUDY II

We demonstrated that high levels of SES, measured by disposable income and highest attained educational level, were associated with a higher likelihood of ICS use. The effect of higher education on ICS use was almost constant throughout all observation years, whereas the effect of high disposable income did not become significant before 2001, with a continuous increase hereafter. It thus seems that other factors not accounted for in the analyses could have influenced the use of ICS.

STUDY III

An inverse relation between ICS use and uncontrolled asthma was found. Furthermore, we demonstrated a clear association between clinically uncontrolled asthma and anti-asthmatic prescribing of SABA, the association becoming stronger with higher annual quantity of SABA. This association, however, was not strong enough to apply to the individual asthma patient unless the level of SABA use was very high.

8 PERSPECTIVES

This thesis has contributed with findings giving rise to some clinical implications, but has also highlighted the lack of knowledge in certain areas, for which future research is merited.

- Approximately 2-3 out of 10 asthmatics with a very high annual consumption of reliever therapy did not use ICS (I and II) consistent with inadequate asthma control (III). This may suggest inefficient dissemination of guidelines, but also non-adherence to asthma controller treatment. Thus, in order to improve guideline implementation and adherence rates to anti-asthmatic treatment educational programmes on asthma and its treatment should be encouraged to both health care professionals and patients.
- Several factors were found to be inversely associated with ICS use and asthma control, e.g. male gender, older age, and low SES (I, II, and III). Furthermore, high consumption of reliever therapy was also associated with uncontrolled asthma (III). From a health care professional viewpoint such knowledge is imperative in order to identify subjects deserving special attention due to being at risk of poor asthma treatment and asthma control.

- We did not measure degree of adherence. To examine the individual course of ICS prescribing and adherence rates among e.g. high IBA consumers, a cohort design with individual follow-up would be preferred. This design would also enable investigating different patient-related interventions on ICS use, e.g. the effect of patient motivation and asthma education. Moreover, it would be possible to explore whether individual initiation/adjustment of ICS use had positive influence on rates of hospital admission and asthma mortality over time as reported in other countries.
- We demonstrated an association between ICS use and SES. However, the study design did not allow any causation to be elucidated. Overall, there is lack of research regarding potential causes for socioeconomic differences in anti-asthmatic treatment with ICS. In order to intervene to avoid such disparities it is important to recognize the reasons for their occurrence, why further research is warranted to uncover underlying mechanisms for this inequality (II).
- As income had some considerable influence on ICS use among lower educated subjects, this could indicate that cost of ICS is a barrier to its use for this subgroup (II). Thus, to reduce the possibility of non-adherence among subjects with lower educational level, it is important that the health care professional emphasizes to select the best possible option of ICS treatment, taking the price into consideration. In addition, reimbursement models should be designed to encourage patient adherence.
- It was possible to identify some uncontrolled asthmatics by looking at their drug use patterns (III). However, as the prescription data was insufficient to allow precise individual conclusions of asthma control in general, future studies should investigate if a combination of prescription data and clinical information (e.g. peak expiratory flow measurement, asthma diaries, and questionnaires on asthma symptoms) could be useful for assessing and optimizing asthma control. If so, such knowledge would be of significance as an asthma control monitoring tool in e.g. clinical telemedicine.
- We investigated individual anti-asthmatic drug use as determinants of uncontrolled asthma (III). However, other patient factors may be related to uncontrolled asthma, e.g. individual threshold of symptom perception, beliefs about medicine, and side effects. Further studies should focus on the extent of these issues. In a clinical setting such knowledge would be of importance when evaluating an actual treatment level, but also when providing information and education about the disease prior to treatment initiation.
- It is not known whether interventions based on individual prescription data are effective in improving individual asthma treatment and asthma control (e.g. feedback corresponding to prescribing patterns of anti-asthmatics). A randomized controlled trial would be the study design of choice to determine this question.

9 SUMMARY

This PhD thesis was performed during my employment at the Research Unit of General Practice in Odense, University of Southern Denmark. It comprises an overview of three papers, all published or submitted for publication in international peer-reviewed scientific journals.

Background: Observational studies have revealed inadequate use of inhaled corticosteroids (ICS) among asthmatics. However, only limited data exist on whether ICS usage has changed over time. In addition, improved knowledge is needed on factors associated with ICS use and asthma control in order to identify subjects at risk of being inadequately treated.

Aims: Among young adult Danish asthmatics we aimed:

- To investigate trends in ICS use and factors associated with ICS use during 1997-2006 (Study I).
- To investigate associations between socioeconomic status (education and income) and ICS use, and whether these associations were consistent over time during 1997-2005 (Study II).
- To investigate whether particular prescribing patterns of anti-asthmatic drugs were associated with clinically uncontrolled asthma (Study III).

Methods: Three studies were carried out among Danish users of anti-asthmatic drugs aged 18-44 years. Study I (N = 106 757) and Study II (N = 97 665) were longitudinal studies based on repeated annual cross-sectional analyses on national register data. Study III (N = 357) was a cross-sectional study based on register and clinical data from a municipal cohort from Odense, Denmark.

Results: Study I: We observed an annual increase in one year prevalence of ICS use from 67% in 2001 to 77% in 2006, occurring concurrently with the introduction of fixed dose combination therapy with ICS and inhaled long-acting beta-2-agonists. Still some 20-30% of subjects with a massive annual IBA consumption were not prescribed ICS. Factors associated with ICS use were high annual use of inhaled beta-2-agonists (IBA), female gender, age 18-24 years, use of leukotriene receptor antagonists, and use of drugs for rhinitis and specific immune therapy. Study II: High levels of education (OR 1.46, 95% CI 1.40-1.51) and income (OR 1.10, 95% CI 1.06-1.14) were found to be positively associated with ICS use with the most pronounced impact among 35-44 year-olds. Higher education showed an almost constant association with ICS use each year throughout the entire observation period, but high income did not demonstrate any statistically significant association with ICS use before 2001 (OR 1.10, 95% CI 1.02-1.18) with increasing ORs observed each year hereafter (OR 1.30, 95% CI 1.20-1.40 in 2005). Study III: A total of 96 of the clinically assessed subjects (26.9%) had uncontrolled asthma. An increasing association between uncontrolled asthma and an increasing annual quantity of inhaled short-acting beta-2-agonists (SABA) usage was demonstrated. Due to a substantial overlap in levels of SABA use among controlled and uncontrolled asthmatics this association was not strong enough to allow conclusions on individual asthma patients.

Conclusion: The results support previous findings by demonstrating a continuing inadequate use of ICS among young adult asthmatics with a consistent and high use of reliever therapy, which was associated with uncontrolled asthma. This apparent over-reliance on reliever therapy and possible non-adherence to ICS may indicate inefficient guideline implementation among patients and physicians, leaving room for further improvement. The clear indications of a socioeconomic gradient in ICS use further emphasizes that knowledge of patient-related factors associated with asthma treatment and asthma control is imperative for health care professionals to be able to identify subjects deserving special attention.

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