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DRUG UTILIZATION IN CHILDREN WITH ASTHMA – METHODOLOGICAL APPROACHES AND PRACTICAL IMPLICATIONS

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Drug utilization in children with asthma – methodological approaches and practical implications

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ABSTRACT

There is limited research on drug utilization among children, despite them representing 20% of the total population in Europe. In the Priority Medicines report, the World Health Organization suggested that drug utilization in children is one of the priority areas in need of more attention, resources, and research. Asthma is the most common chronic disease in children, and asthma medications are one of the most commonly used drugs by children. Therefore, the overall aim of this thesis was to describe the drug utilization in children with asthma.

In studies I and II, questionnaire data from the population-based birth cohort BAMSE were combined with dispensing data from the Swedish Prescribed Drug Register. The concordance between the two data sources was investigated as well as the association between drug usage, patient characteristics, and asthma disease control. We showed that an 18-month time window is preferable when using dispensing data to study the use of asthma medications. Most adolescents with asthma reported use of asthma medications, but a considerable proportion were neither dispensed any drugs nor reported use of someone else's medications. Girls were less likely to achieve asthma control than boys.

In study III, the association between sibship and dispensing patterns of asthma medications in young children was studied. It was a register-based cohort study including all children born in Stockholm, Sweden 2006 – 2007. Sibling status was used as exposure, and incidence of dispensed asthma medications and persistence to therapy over time were used as outcomes. We found that children with siblings had different dispensing patterns of asthma medications compared to singletons regardless of family income and asthma diagnoses. After including the siblings' asthma medication and comparing with control children, the proportion of children with persistent medication increased which may indicate that siblings share asthma medications.

In study IV, we assessed the effect of the eliminated patient fee on the dispensing patterns of asthma medication in children. We used dispensing data two years before and after the intervention (January 1st, 2016) to measure prevalence, incidence, numbers of Defined Daily Doses (DDDs)/child, and persistence to drug treatment before and after the intervention. We found that the intervention had a modest effect on the dispensing patterns of asthma medication, nevertheless the volume dispensed per child increased, particularly in children with low socioeconomic status.

In conclusion, this thesis describes drug utilization in children with asthma. Four factors to consider when assessing the dispensing patterns of asthma medications were found to be important: sex, sibship, time window used in the register, and changes in the co-payment system. Different data sources of drug utilization will give different results. Dispensing data from pharmacies will underestimate drug use compared to data from self-reported (or parental-reported) use of asthma medications. Siblings share asthma medications, which may lead to an underestimation of drug use if only one of the siblings' asthma medications is included in the measurement of drug usage when using data on dispensed drugs.

SVENSK SAMMANFATTNING

Evidensen kring barns läkemedelsanvändning är begränsad trots att de utgör 20 % av populationen i Europa. Världshälsoorganisationen (WHO) föreslår att barns läkemedelsanvändning ska prioriteras genom ökad uppmärksamhet, ökade resurser och forskning. Den vanligaste kroniska sjukdomen bland barn är astma och därmed är astmaläkemedel en av de mest använda läkemedelsgrupperna. Det övergripande syftet med avhandlingen var därför att beskriva läkemedelsanvändningen bland barn med astma.

I studie I och II kombinerades enkätdata från BAMSE (barn födda i norra Stockholm 1994–96) med utköpsdata från Läkemedelsregistret. Samstämmigheten mellan de två datakällorna studerades samt sambandet mellan läkemedelsanvändning, patientens levnadsförhållande och hur välbehandlad astma barnet hade. Vi visade att ett 18-månaders tidsfönster är att föredra när man använder utköpsdata från apotek för att studera användningen av astmaläkemedel. De flesta ungdomar med astma rapporterade användning av astmaläkemedel, trots att en stor del av ungdomarna varken hade hämtat ut läkemedel på apotek eller använt någon annans astmaläkemedel under samma tid. Flickor var mer sällan välbehandlade i sin astma jämfört med pojkar.

I studie III undersöktes sambandet mellan syskonskap och utköpsmönster av astmamediciner bland yngre barn. Det var en registerbaserad kohortstudie som inkluderade alla barn som föttsi Stockholms län 2006–2007. Studien visade att barn med syskon har ett annat utköpsmönster av astmaläkemedel jämfört med ensambarn oavsett familjens inkomstnivå och förekomst av astmadiagnos. Efter att ha inkluderat syskonens astmamediciner och jämfört med kontrollbarn ökade andelen barn som fortsatte hämta ut sina mediciner, vilket kan indikera att syskon delar mediciner.

I studie IV undersöktes effekten av den svenska reformen om kostnadsfria läkemedel till barn på utköpsmönstret av astmaläkemedel. Vi använde utköpsdata två år före och efter reformen (som trädde i kraft den 1 januari 2016) för att mäta uttag av astmamediciner och en eventuell trendförändring före och efter interventionen. Studien visade att interventionen hade en begränsad effekt på utköpsmönstret av astmaläkemedel, men att volymen uthämtade läkemedel per barn ökade, speciellt bland barn från familjer med lägre socioekonomisk status.

Sammanfattningsvis har denna avhandling beskrivit läkemedelsanvändningen bland barn med astma. Fyra faktorer visade sig vara viktiga att beakta när man analyserar användningen av astmamediciner: kön, syskonskap, vilket tidsfönster som används i analyser av uthämtade läkemedel, och reformen om kostnadsfria läkemedel till barn. Olika datakällor för att beskriva läkemedelsanvändning kan vidare ge olika resultat. Utköpsdata från apotek underskattar läkemedelsanvändningen jämfört med självrapporterade (eller föräldrarapporterade) data över astmaläkemedel. Syskon delar astmamediciner med varandra, vilket gör att läkemedelsanvändningen underskattas om endast ett av syskonens astmaläkemedel inkluderas när man mäter läkemedelsanvändningen med utköpsdata.

LIST OF SCIENTIFIC PAPERS

I. **Dahlén E**, Almqvist C, Bergström A, Wettermark B, Kull I. Factors associated with concordance between parental-reported use and dispensed asthma drugs in adolescents: findings from the BAMSE birth cohort. *Pharmacoepidemiology and drug safety*, 2014, 23, 942-949. doi: 10.1002/pds.3662

II. **Dahlén E**, Wettermark B, Bergström A, Jonsson EW, Almqvist C, Kull I. Medicine use and disease control among adolescents with asthma. *Eur J Clin Pharmacol*, 2016, 72(3), 339-347. doi:10.1007/s00228-015-1993-x.

III. **Dahlén E**, Ekberg S, Lundholm C, Jonsson EW, Kull I, Wettermark B, Almqvist C. Sibship and dispensing patterns of asthma medication in young children- a population based study. *Submitted*

IV. **Dahlén E**, Komen J, Jonsson EW, Almqvist C, Kull I, Wettermark B. Effects of eliminated patient fee on the dispensing patterns of asthma medication in children- an interrupted time series analysis. *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

ATC-codes	Anatomical Therapeutic Chemical-codes
BAMSE	Children (Barn), Allergy, Milieu, Stockholm, Epidemiology
CI	Confidence Interval
DAG	Directed Acyclic Graph
DDD	Defined Daily Dose
DTC	Drug and Therapeutics Committee
EMA	European Medicines Agency
EU	European Union
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroid
ISPE	International Society for Pharmacoepidemiology
ITS	Interrupted time series
LABA	Long-acting β2-agonist
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
LTRA	Leukotriene receptor antagonist
MBR	Medical Birth Register
MGR	Multi-Generation Register
MPA	Medical Products Agency
NBHW	National Board of Health and Welfare
NPR	National Patient Register
OTC	Over the counter
PIN	Personal identity number
PPV	Positive Predictive Value
PD	Pharmacodynamics
PK	Pharmacokinetics
RCT	Randomized controlled trial
RR	Relative Risk
SABA	Short-acting β2-agonist
SPDR	Swedish Prescribed Drug Register
VAL	Administrative healthcare databases
WHO	World Health Organization

1 PREFACE

As a licensed pharmacist, I have a special interest in drug utilization. My commitment in the Drug and Therapeutic Committee's expert panel of Respiratory and Allergy Diseases deepened my interest in asthma medications and how they are used. In my work at the Stockholm County Council, I encountered the team at the prospective birth cohort BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiology). My knowledge of medications and the Swedish Prescribed Drug Register was requested in a BAMSE-project. In addition, I wanted to learn more about questionnaires and research methods. Altogether, this led me to set up a research plan and start my Ph.D. project.

This thesis is based on pharmacoepidemiology and drug utilization in children with asthma. Different data sources were combined and used along with a methodological discussion of its pros and cons. Children with asthma are a challenging group within drug utilization. The disease is intermittent, and dispensing patterns for children with asthma are irregular. It is also known that there is room for improvement in the management of children with asthma. Therefore, the focus of the thesis was on drug utilization in children with asthma using a methodological approach.

2 INTRODUCTION

2.1 PHARMACOEPIDEMIOLOGY AND DRUG UTILIZATION

2.1.1 Pharmacoepidemiology

Pharmacoepidemiology, the study of the uses and effects of drugs in well-defined populations, is a relatively new discipline [1]. It is the bridge between pharmacology and epidemiology. Pharmacology is the study of the effects of drugs and clinical pharmacology can be described as the study of the therapeutic effects of drugs in humans. Epidemiology is the distribution and determinants of diseases in populations. In pharmacoepidemiology, the research questions often come from clinical pharmacology and the methods used come from epidemiology (Figure 1). Both descriptive and analytical studies of drug utilization patterns are included [2, 3]. There are many different reasons as to why pharmacoepidemiologic studies are conducted e.g., to obtain information about drug safety, gain information needed to answer questions from a regulatory agency to scan for unknown and unsuspected drug effects, or to study the comparative effectiveness of the therapy in clinical practice. The benefits can be conceptualized into four different categories: regulatory, marketing, legal, and clinical [1].

Figure 1: Pharmacoepidemiology is the bridge between clinical pharmacology and epidemiology, where the research questions often originate from clinical pharmacology and the methods from epidemiology.

Current needs in pediatric pharmacoepidemiology were assessed in a survey given to members of the International Society for Pharmacoepidemiology (ISPE; [4]). More than half of the respondents reported an issue with limited sample sizes, especially when studying age sub-groups or specific genetic populations. Missing data were also problematic among the respondents, and three main areas were pointed out: lack of detailed medication information, inability to link to parental data, and lack of detailed information about age, especially for infants. In the Swedish setting, where national registers are available for research, most of the problems stated above are not shared in the Swedish register-based research. However, issues with sample sizes can be present, depending on the prevalence of exposures and outcomes.

2.1.2 Drug utilization research

Drug utilization research is defined as "an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes" [2]. Drug utilization and pharmacoepidemiology are closely related. The main difference between them is that pharmacoepidemiology focuses on the assessment of quantitative risks of drug treatment in cohorts of patients, while drug utilization focuses on the quantity and quality of drug use in different countries, regions, and settings as well as the explanatory factors behind these patterns. The distinction between the two fields has diminished over time, and the terms are sometimes used interchangeably. While clinical trials study the "absolute" efficacy of a drug under ideal conditions, drug utilization research and pharmacoepidemiology study the "real world" effectiveness of medications and attempt to identify and quantify risks, which are difficult to observe and assess in clinical trials. Drug utilization research also includes the assessment of appropriate drug use and expenditures linked to drugs [2]. Furthermore, drug utilization includes both *quantitative* and *qualitative* research. In quantitative methods, numeric data are used along with structured techniques to measure and explain observations. Associations and differences between specific variables may be studied. In qualitative methods, the goal is to get a deeper understanding of a research question and to develop concepts, which can help us to understand social phenomena in natural (rather than experimental) settings [5, 6].

2.2 STUDY DESIGNS USED IN DRUG UTILIZATION RESEARCH

Drug utilization studies can be conducted using a wide variety of study designs [2]. Different designs have their advantages and limitations; thus, researchers should select the most appropriate method to get answers to the questions they want to investigate. Not only will the methodology vary with the research questions, but practical considerations such as data availability, budget, and the knowledge of the researchers will also affect the choice of method.

Observational studies are conducted in a real-life situation, where the researcher is limited to the interpretation of data obtained from observations. This is in contrast with an experimental set-up, where the researcher is influencing (and often controlling) the factors under study. Observational studies may be either descriptive or analytical. Descriptive studies identify patterns or trends in drug utilization without having any comparison group. They often represent the first scientific studies conducted in a specific area. Such studies can be used to estimate disease prevalence, drug expenditures, or to assess the quality of drug prescribing or drug use. Analytical studies, on the other hand, are studies designed to reach a causal inference about hypothesized relationships. They aim to gain a deeper understanding of the explanatory factors behind patterns of drug prescribing, dispensing, and consumption. Case-control studies and cohort studies are analytical studies, both with a comparison group. Case-

control studies are those that compare cases with a disease with controls without a disease, looking for differences in previous exposures. Case-control studies are particularly useful when studying an outcome with multiple possible causes and when an outcome is rare, guaranteeing a sufficient number of cases. Cohort studies are studies that identify a defined population and follow the population over time, looking for differences in outcome. Cohort studies are generally used to compare exposed patients with unexposed patients, although they can also be used to compare one exposure to another. Moreover, cohort studies are suitable for studying rare exposures and multiple outcomes. In descriptive drug utilization studies, a cross-sectional or a longitudinal design can be used. A cross-sectional study is a snapshot of a population status, with respect to disease and/or exposure variables at a specific time point. It is important to acknowledge that since these studies lack information on whether the factor of interest precedes or follows the effect, they may not be used to draw any conclusions on the cause and effect. Cross-sectional studies are relatively inexpensive and easy to perform. In a longitudinal study, the variables are measured repeatedly to gain information over time, at different time points. These may be used to study trends in drug utilization, for example, if the prescribing of an inappropriate drug has changed over time [2].

One specific type of observational study is the ecological study design. In ecological studies, the link between exposure and outcome is measured on a population level, rather than on an individual level. In drug utilization studies, ecological studies can be used to compare dispensing data with, for example, morbidity data in a specific setting. Ecological studies are relatively simple to conduct, but they have limited benefit since the linkages found cannot directly be interpreted as associations at the individual level [2].

Experimental studies are studies in which the investigator controls the therapy that is to be received by the patient. The preferred study design is a randomized controlled trial (RCT), where the exposed and the non-exposed groups are randomly selected to the experimental factor studied. A parallel evaluation of the exposure in the exposed and the non-exposed group is performed to evaluate the effect of exposure. RCTs have the highest degree of evidence; however, the design is expensive, and a low number of participants may lead to a power problem (i.e., not enough participants to detect an effect size in a given setting) [1, 2]. Furthermore, the ideal setting in an RCT with a selected patient population is seldom representative of how the drug studied will be used in real-life, including adherence to medication, lifestyle factors, and comorbidity. Another type of experimental studies is the one with a quasi-experimental design. These studies have a before-after design, where the occurrence of an outcome is measured before and after a particular intervention is implemented [7]. Interrupted time series (ITS) design is the strongest quasiexperimental approach for evaluating longitudinal effects of interventions [2, 8].

2.3 DATA SOURCES IN DRUG UTILIZATION

There are three main sources of information on drug utilization patterns: medical records, dispensing/claims databases, and person-reported data (Table 1). In medical records, diagnoses are registered primarily for use in medical care. Often, medical records include important information on diagnosis, lab data, and other clinical information useful in drug utilization research. However, the uncertainty in the completeness of other physician's diagnosis is a weakness. Computerized databases have several important advantages when used in drug utilization research. These have the potential of including a large sample size, being relatively inexpensive because no manual data collection is needed, and there is no opportunity for recall or information bias from the patients [9]. On the other hand, medical records can lack information about confounders such as lifestyle factors, family history of diseases, and siblings use of medication. Furthermore, by definition, medical records only include illnesses severe enough to come to medical attention. Also, the selection of which diagnoses to include, and the coverage of medical records could be issues. Information about drugs from medical records reflects what is prescribed to the patient, which does not necessarily mean that the drug has been dispensed and used.

Dispensing databases have similar strengths as the medical records when used in research, including large sample size and being relatively inexpensive. A difference from the medical records is that the patient needs to go to a pharmacy and purchase the drug to be included in the dispensing database. Often, only drugs from the ambulatory care are included, with the consequence that drugs dispensed at hospitals will be excluded. Still, many drugs that are dispensed are not used. Data on actual use may be collected directly from a person, thus, providing more direct information. Furthermore, many dispensing data bases only include information about drugs dispensed within the reimbursement system. Another limitation is that they are sensitive to changes in prescription regulations and co-payment systems. These types of dispensing databases (often known as claims databases) are missing information about drugs that have been paid for out-of-pocket by the patients i.e., over the counter drugs (OTC-drugs).

Person-reported data such as questionnaires and interviews have the advantage of being primary data from the patient. It is possible to get information about the patient's experiences and attitudes, not recorded in the registers. In addition, information about OTC-drugs can be collected. On the other hand, it is time-consuming, and large-sample data collections are seldom possible [1, 2]. It is also known that parents and school children report symptoms and treatment of allergic diseases differently [10]. The school children report a higher prevalence of symptoms than parents.

Table 1: Data sources used in drug utilization research with advantages and limitations.

Data sources	Advantages	Limitations
Medical records	Information about diagnoses and lab data, large samples	Lack information about confounders, may be unstructured
Dispensing data	Large samples, low cost, drugs are purchased and not only prescribed	No information about drugs administrated at hospitals, OTC*, and confounders
Person-reported data (Questionnaires, Interviews)	Primary patient data, patient's own information, information about attitudes and experiences	Time-consuming, information- and recall bias, dependent on the patients and the researchers' knowledge

*OTC-drugs- over the counter drugs, sold directly to a consumer without a prescription.

2.4 DRUG USE IN CHILDREN AND ADOLESCENTS

2.4.1 Children are not small adults

Drug treatment in children is complex, and treating children is different from treating adults regarding several factors. Children are defined as all individuals between 0 and 17 years of age, ranging from a premature infant of ≤ 500 g to a fully-grown adolescent of ≥ 100 kg. The drug metabolism differs between the ages; therefore, the dose and dosage interval will vary between children even though the weight of the child is considered. Besides weight, children differ from adults in pharmacokinetics (PK) and/or pharmacodynamics (PD) in varying degrees, depending on the age of the child. The PK of a drug includes the processes of absorption, metabolism, distribution, and elimination, whereas the PD comprises the physiological and biological response to the administered drug and therefore may represent both efficacy and safety measures. The development of enzyme pathways (PK) and function and expression of receptors and proteins (PD) matures gradually during childhood [11-13].

2.4.2 Off-label and unlicensed drugs

When doctors prescribe drugs for children, they want these drugs to be effective and safe. However, most clinical trials exclude children in their design; therefore, drugs are used outside the terms of the products license, so called off-label [11, 14]. In Sweden, half of all children (age 0–17) were dispensed a drug in 2007, and 14% of the prescriptions were off-label [15]. Furthermore, at Swedish hospitals, 49% of all pediatric prescriptions were not documented for use in children (i.e., off-label drugs, unlicensed drugs, or extemporaneously prepared drugs) [16].

2.4.3 The most common drugs in children

Many children take drugs. A review of 128 drug utilization studies involving children from 32 countries found that the overall prevalence was 60%, ranging from 51–70% [17, 18]. The highest prevalence was seen in preschoolers, with a decrease in children over 6 years. However, in some countries, the peak prevalence of drug use was observed in children under the age of two, ranging from 75–90%. The most frequently used drugs were antibiotics, accounting for 20–33% of all prescriptions. Anti-asthmatics constituted the second most common drug (10–25%), followed by analgesics (10–16%). In a large cohort study in three European countries, anti-infective agents, dermatologicals and respiratory drugs were the most common drugs across all age categories [19]. Emollients, topical steroids, and anti-asthmatics had the highest prevalence of recurrent use. The prevalence in Swedish children was 46%, and the most common medications dispensed were antibiotics for systemic use (18.2%), asthma medications (9.5%), and cough suppressants (7.8%) [20].

2.4.4 Initiatives to improve drug use in children

In the Priority Medicines report, the World Health Organization (WHO) suggested that drug usage in children is one of the priority areas in need of more attention, resources, and research [14]. In 2006, the European Union (EU) introduced a Pediatric Regulation to improve the health of children in Europe. In the wake of this regulation, an EU project started at the European Medicines Agency (EMA) to improve the gap of knowledge in drug treatment among children and also to facilitate the process of conducting clinical trials in children [21]. In Sweden, the Medical Products Agency (MPA) is leading this work. ePed, an experienced- and evidenced-based database, was initiated in 2005 in Stockholm, Sweden to share information on how to administer drugs in children and to learn from the experiences and mistakes of others [22, 23]. Today, it is possible for all County Councils in Sweden to share the information in ePed.

2.4.5 Sharing of drugs

Sharing drugs is defined as the lending or borrowing of prescribed drugs, where the recipient is someone other than the person for whom the prescription was intended [24]. In a systematic review by Beyene et al., it was found that sharing of drugs was common [25]. The prevalence of lending drugs was between 6% and 23%, and the prevalence of borrowing was between 5% and 52%. More recent studies had a higher prevalence of borrowing and lending drugs, suggesting a general increase in self-medication with prescription drugs in recent years [26, 27]. The most common source of shared drugs was either a family member or a friend [28, 29]. The most commonly shared classes of drugs were analgesics, allergy medications, and antibiotics [24, 29-32]. Sharing of asthma medications has been addressed in a few studies [28-30, 33, 34], but only two studies have included sharing among children and adolescents [28, 29].

2.5 ASTHMA

2.5.1 Asthma disease

Asthma is the most common chronic disease in children, with a global prevalence of 14% among adolescents aged 13 – 14 years, ranging from 6 to 27% in different geographical areas [35]. In Europe, the prevalence among school children was 5 – 20% [14]. The disease is characterized by a chronic inflammation of the airways, with respiratory symptoms (wheezing, shortness of breath, and coughing), and expiratory airflow limitations, varying over time [36]. The characteristics of the disease vary across childhood. Infection-induced asthma is common among younger children (<6 years), especially during the first years of life. This disease is often episodic, and it can be difficult to determine when wheezing in younger children is asthma and when it is not.

Theoretically, asthma should be easier to diagnose in adolescents than in younger children, given fewer differential diagnoses and an easier approach when measuring lung function. However, it is distressful to observe that under-diagnosis and under-treatment are quite common in this age group [37, 38]. It is important to focus on the asthma care of adolescents and the need to improve their trust in health care. Asthma management among adolescents includes self-management of asthma medications (including knowing how to use the device), ensuring a good transition from pediatric healthcare to adult healthcare, and awareness of how the disease changes over time [37]. The social, psychological, and physical environment around the adolescent with asthma may all contribute to the asthma control.

2.5.2 Asthma control and medications

Asthma medications can be classified as controllers or relievers [36]. The controllers—inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRAs)—are used regularly on a long-term basis to keep asthma under clinical control. The relievers—beta-β-agonists—are used on an as-needed basis and act quickly to reverse bronchoconstriction and relieve the symptoms. The Global Initiative for Asthma (GINA) guidelines recommend a step-wise approach for drug treatment, to achieve symptom control and minimize future risks.

The definition of asthma control in GINA guidelines is:

- Daytime asthma symptoms less than twice a week,
- No nightly awakenings due to asthma,
- Reliever needed for symptom control no more than twice a week
- No limitation of activity due to asthma.

In accordance with the GINA guidelines, the Swedish Pediatric Society's Section for Allergy and the Swedish Medical Products Agency recommend a similar approach, based on the child's age and symptoms (Figure 2).

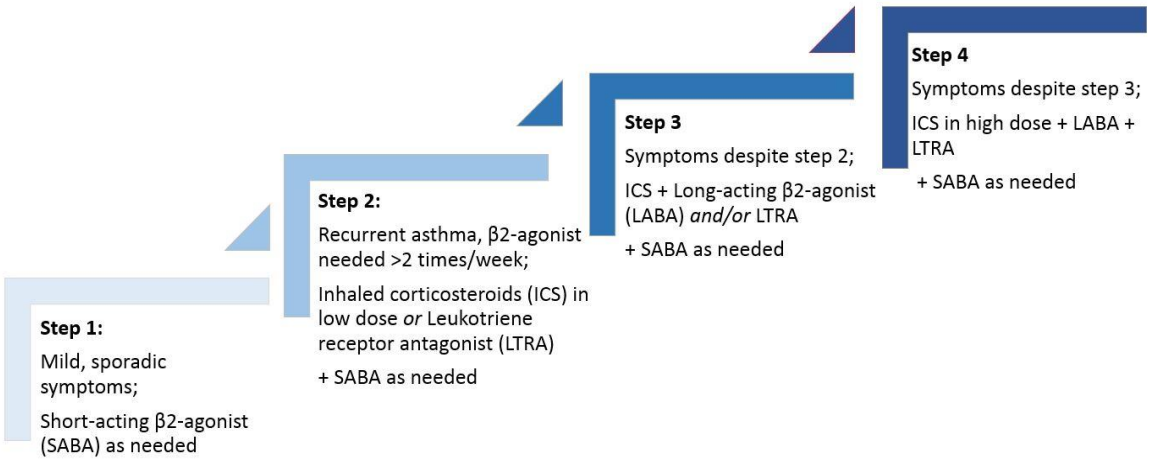


Figure 2: Pharmacological treatment of asthma for children >6 years, based on treatment guidelines from the Swedish Pediatric Society's Section of Allergy [39, 40].

If a child or adolescent does not achieve symptom control, it is important to evaluate the treatment before adding other drugs [41]. Is the inhaler technic correct and are the medications used as prescribed? If so, the next treatment step can be taken. In a review by Haughney et al., it was stated that 86% of the patients with asthma failed to use their device correctly on the first attempt [42]. After instructions, the percentage decreased to 76% on the second attempt, and 61% on the third attempt. In another review by Brocklebank et al., the mean percentage of patients who used their inhalers correctly was 65% for the dry powder inhalers [43]. The number of errors in inhaler use and inhalation technique has been

correlated with poorer asthma control in patients using ICS [44]. A demonstration of how the device works is generally thought to be essential for the patient to use the prescribed inhaler correctly. In a 24-week RCT of individualized asthma self-management education, adherence to ICS was improved in the intervention group compared with the control group [45]. It requires that healthcare professionals know how the different devices function. Education of healthcare professionals and patients is essential for positive patient outcomes. Thus, there is room for improvement in the healthcare of patients with asthma in Sweden [46, 47]. In the Stockholm County Council, the Drug and Therapeutics Committee (DTC) is essential when educating healthcare professionals in rational prescribing of drugs within the region. The DTC publishes an annual *Wise List* for recommended essential medications for common diseases in patients [48, 49]. The Wise List includes around 200 core medications for treatment in primary care and hospital care and another 100 complementary medications for treatment in specialized care. The overall adherence to the Wise List recommendations for core medications for all prescribers (primary and specialized care) is high (84% in 2015) [49].

2.6 ADHERENCE TO AND PERSISTENCE OF ASTHMA MEDICATIONS

2.6.1 The adherence process

Adherence is defined by the WHO as 'the extent to which a person's behavior corresponds with agreed recommendations from a healthcare provider' [50]. In drug utilization research, adherence to drugs is described as the process by which patients take their medications as prescribed [51, 52]. Adherence is further divided into 3 essential steps: *initiation*, *implementation*, and *persistence*. Initiation is 'when the patient takes the first dose of a prescribed drug'. Implementation is 'the extent to which a patient's actual dosage corresponds to the prescribed dosing regimen, from initiation until the last dose is taken.' Persistence is 'the time elapsed from initiation until eventual treatment discontinuation' (Figure 3).

Figure 3: The three steps of the adherence process: initiation (taking the first dose), implementation (the patient's actual dosage corresponds to the prescribed dosage regimen), and persistence (time from initiation until discontinuation of treatment).

Persistence can be measured in different ways, depending on the data available and preferences of the researcher [53, 54]. In an *anniversary* model, a patient is considered persistent for 1 year if a prescription is refilled within a specific interval (e.g., ±30 days) surrounding the anniversary of the prescription. In a *minimum refills* model, a patient is considered persistent with treatment if a specific minimum of prescriptions is dispensed per year. In a *refill sequence* model, persistence is measured as the interval between the date of the first prescription and the point at which an unacceptable gap between prescription refills occurs. In a *proportion of days covered* model, a patient is persistent if enough drugs to cover a specified proportion of days within a fixed interval are dispensed. In a *hybrid* model, persistence is measured as the interval between the initiation (date of the first prescription) and the point at which the patient would have had an insufficient supply of the available drugs to cover the days between prescription refills. Dispensing data are the golden standard when measuring persistence; however, questionnaire data, interviews, and medical records may also be used.

2.6.2 Adherence to and persistence of asthma medications among children

In most studies, dispensing data and/or medical record refills have been the main source of data for persistence studies [52]. Since the need for asthma medications can vary over time due to infections and or allergen exposure, there is no golden standard on how persistence should be measured in children with asthma. Øymar et al. measured the persistence among preschoolers as refilling the prescription of ICS each year [55]. They calculated the persistence of ICS after 5 years to 9 – 18%. In a review by Desai and Oppenheimer, it was concluded that non-adherence (not taking medications as agreed) among children with asthma was alarmingly high [56]. The adherence rate of ICS, on average, was under 50%, ranging from 30 to 70%. In a Dutch study of children aged 7 – 17 years, only half of the children used more than one puff of ICS per day, indicating non-adherence to ICS [57].

3 AIMS

The overall aim of this thesis was to describe the drug utilization in children with asthma. Different methods and data sources were used to gain further knowledge on methodological issues of importance for future research on drug utilization in children with asthma.

The thesis comprises four studies with the following aims:

• To investigate the concordance between register data on dispensed drugs and parental-reported use of asthma medication in adolescents. (*Study I*)

• To compare self-reported and register-based drug use in asthmatic adolescents. Furthermore, to investigate the association between drug use, patient characteristics, and degree of asthma control. (*Study II*)

• To assess the association between sibship and dispensing patterns of asthma medication in young children. The focus was on a) initiation of asthma medication, and b) differences in persistence of the drug therapy, taking sibship status, family income, diagnoses, and siblings' medications into account. (*Study III*)

• To assess the effect of the eliminated patient fee on the dispensing patterns of asthma medication among children. (*Study IV*)

4 MATERIAL AND METHODS

4.1 A SUMMARY OF THE STUDIES

Table 2: A summary of the studies included in the thesis.

Study	I	II	III	IV
Design	Cross-sectional	Cross-sectional	Cohort	Intervention
Study population	Adolescents whose parents answered the questionnaires in the 12-year follow-up in the BAMSE-study	Adolescents who answered the questionnaires in the 16-year follow-up in the BAMSE-study	Children born in Stockholm County 2006 – 2007	Children 0 – 17 years old in Stockholm County with a dispensed asthma medication from 2014–2017
Data source (s)	Longitudinal data from the BAMSE-study questionnaires from the baseline and the 12-year follow-up, the Swedish Prescribed Drug Register (SPDR)	Longitudinal data from the BAMSE-study questionnaires from the baseline and the 16-year follow-up, SPDR	The Medical Birth Register, the Multi-Generation Register, the Longitudinal Integration Database for Health Insurance and Labour Market Studies, the Cause of Death Register, SPDR, the National Patient Register, VAL	The administrative healthcare data bases of the Stockholm health care region (VAL)
Study period	2006 – 2008	2010 – 2012	2006 – 2014	2014 – 2017
Main factors analyzed	Concordance between parental-reported asthma medication use and dispensed asthma medication	Concordance between self-reported asthma medication use and dispensed asthma medication, asthma control	Dispensing patterns of asthma medication including sibling's medication	Dispensing patterns of asthma medication before and after the eliminated patient fee on January 1^{rst} 2016.
Statistical analyses	Sensitivity, Specificity, Positive predictive value, One sample t-test with finite population correction, McNemar's test, Logistic regression	Proportion test, Wilcoxon's rank sum test, Logistic regression	Cox Proportional Hazards Regression, Log-binomial regression, Likelihood ratio test	Absolute and relative differences, interrupted time series (ITS) analysis, Durbin-Watson statistics

4.2 THE SWEDISH HEALTHCARE SYSTEM

In Sweden, healthcare is publicly financed and accessible to all residents. Most residents are listed at a local Primary Healthcare Center (with a general practitioner), which is normally the first contact with healthcare. In Stockholm, children in need of seeing a pediatrician may consult a specialized clinic in ambulatory care. Primary care has a limited gate-keeping function in the Swedish healthcare system, i.e., patients may seek care directly from a specialist. In the Swedish healthcare system, the decision-making is decentralized in 21 elected county councils [58, 59].

Most prescription drugs are subsidized and included in the reimbursement system. According to the Swedish legislation, unless otherwise stated, all prescriptions are valid up to 1 year after they have been prescribed and may be repeatedly dispensed at the pharmacies until the total prescribed volume has been purchased [60]. A 3-month supply is the maximum amount that patients can be dispensed at each refill to get their prescribed drugs subsidized. In the Swedish reimbursement system, a high cost threshold system is applied for all inhabitants. During the period when *studies I – III* in the thesis were conducted, a maximum cost of 2,200 SEK (214 EUR) per patient was applied. All children in a family share the same high cost threshold i.e., a family with three children will only pay a maximum of 2,200 SEK for the children's dispensed prescription drugs included in the reimbursement system. As of January 1, 2016, all prescription drugs subsidized for children under the age of 18 years are free of charge [61]. The rationale behind the legal decision was to increase the access to medications regardless of social and financial conditions.

Sweden has unique opportunities for conducting register-based research. Existing national population-based registers include data on family, residence, education, work, hospitalizations, healthcare consumption, prescription drugs, and mortality. The registers are mandatory, and the coverage is almost complete. The personal identity number (PIN) is the common identifier across all registers [62]. The PIN can be used to link data between different registers and other data sources.

4.3 DATA SOURCES

4.3.1 National registers

The **Swedish Prescribed Drug Register (SPDR)** includes all prescribed drugs for the entire population, dispensed at Swedish pharmacies [63, 64]. The register has been available since July 2005 and includes patient-level data, with unique identifiers for over 99% of all prescriptions dispensed. The SPDR is held by the National Board of Health and Welfare (NBHW) and contains information about each person (sex, age, and PIN) as well as all drugs dispensed (Anatomical Therapeutic Chemical [ATC]-codes, date of prescribing and dispensing, and the number of packages, and doses). All dispensed prescription drugs are included in SPDR, regardless of whether the drugs were subsidized or not. In July 2010, the

legislation was changed and drug dispensing data for all citizens in each county council were also transferred to regional databases, thus enabling linkage with information in the regional healthcare databases of Stockholm (VAL; see chapter 4.3.2). Data from the SPDR were used in *studies I, II,* and *III*.

The **National Patient Register (NPR)** is held by the NBHW and consists of codes for diagnoses and procedures, on a national level [65]. The register covers hospitalizations since 1964 and outpatient visits to both public and private caregivers since 2001. However, diagnoses and procedures from primary care are not included. Data from NPR were used in *study III*.

The **Cause of Death Register** is held by the NBHW and contains information on all deaths since 1961 [66, 67]. All Swedish residents are covered, regardless of whether the death occurred in Sweden or abroad. Data from the Cause of Death Register were used in *study III*.

Since 1973, all pregnancies resulting in a delivery have been reported to the **Medical Birth Register (MBR)**, held by the NBHW [68]. The register contains information about the pregnancy, the delivery and the newborn. Data from the MBR were used in *study III*.

At Statistics Sweden, the **Multi-Generation Register (MGR)** has been kept since 2000 [69, 70]. This register links all Swedish residents to their parents, allowing for identification of family constellations, including identification of full- and half siblings. The coverage of the register has been complete since 1968. Data from the MGR were used in *study III*.

The **Longitudinal Integration Database for Health Insurance and Labour Market Studies** (**LISA**, by Swedish acronym; Statistics Sweden) includes information on employment, disposal income, education, and area of residence among other data for all individuals aged 16 years and above registered in Sweden [69]. The database has been updated yearly since 1990. Data from LISA were used in *study III*.

4.3.2 Regional registers

The administrative healthcare databases in Stockholm (so called VAL) are held by the Stockholm County Council [71-74]. VAL includes pseudonymized data on all healthcare contacts financed by the County Council. Data for primary care, specialized ambulatory care, and hospitalizations are all included, along with demographic data (sex, age, immigration, emigration, and death) and dispensed prescription drugs. Health care consumption including recorded diagnoses and procedures have been available since the 1980s for hospitalizations and specialized ambulatory care. Basic data from primary care have been available since 1998 and diagnoses since 2003.

Information on prescription drugs dispensed to inhabitants in Stockholm County has been available since July 2010. All dispensed drugs, regardless of reimbursement status, are included. Information on the drugs (ATC-codes, brand name, id-number, date of prescribing

and dispensing, and number of packages and doses), patients (age, sex, area of residence), and prescribers (specialty and workplace) are included. The information about dispensed prescription drugs in VAL is of the same data as in the national register, the SPDR. Data from VAL were used in *study IV*.

4.3.3 Questionnaire data - the BAMSE-study

The **BAMSE-study** (Children Allergy Milieu Stockholm Epidemiology Survey) is a prospective birth cohort including 4,089 children born in Stockholm, Sweden between 1994 and 1996 [75]. The participating families were recruited at child healthcare centers in predefined areas of Stockholm (Järfälla, Sundbyberg, Solna, and the northern part of the inner city of Stockholm). Of the 7,221 children born in the study area during the recruitment period, 5,488 were eligible according to the inclusion criteria (Figure 4). The final cohort consisted of 4,089 children (i.e., 75% of the eligible) whose parents answered a baseline questionnaire when the children were, on average, two months old. The families have been followed through questionnaires completed when the children were around 0, 1, 2, 4, 8, 12, and 16 years. Clinical examinations, including measuring of weight, height, and lung function as well as collecting blood samples were conducted around the time of answering the questionnaires at 0, 4, 8, and 16 years. The parents have been answering the questionnaires up to the 16-year follow-up. The adolescents have been answering the 12- and 16-year follow-up questionnaires, allowing for the possibility to compare the answers from parents and adolescents in the last follow-ups. The questionnaires contain information about each adolescent's health status, habits, use of drugs, and family history of asthma. The response rate has been high since the first follow-up and was 76% at the 16-year follow-up, ensuring a high internal validity. The BAMSE-study is ongoing, and data for the 24-year follow-up, including questionnaires and clinical examinations are being collected now.

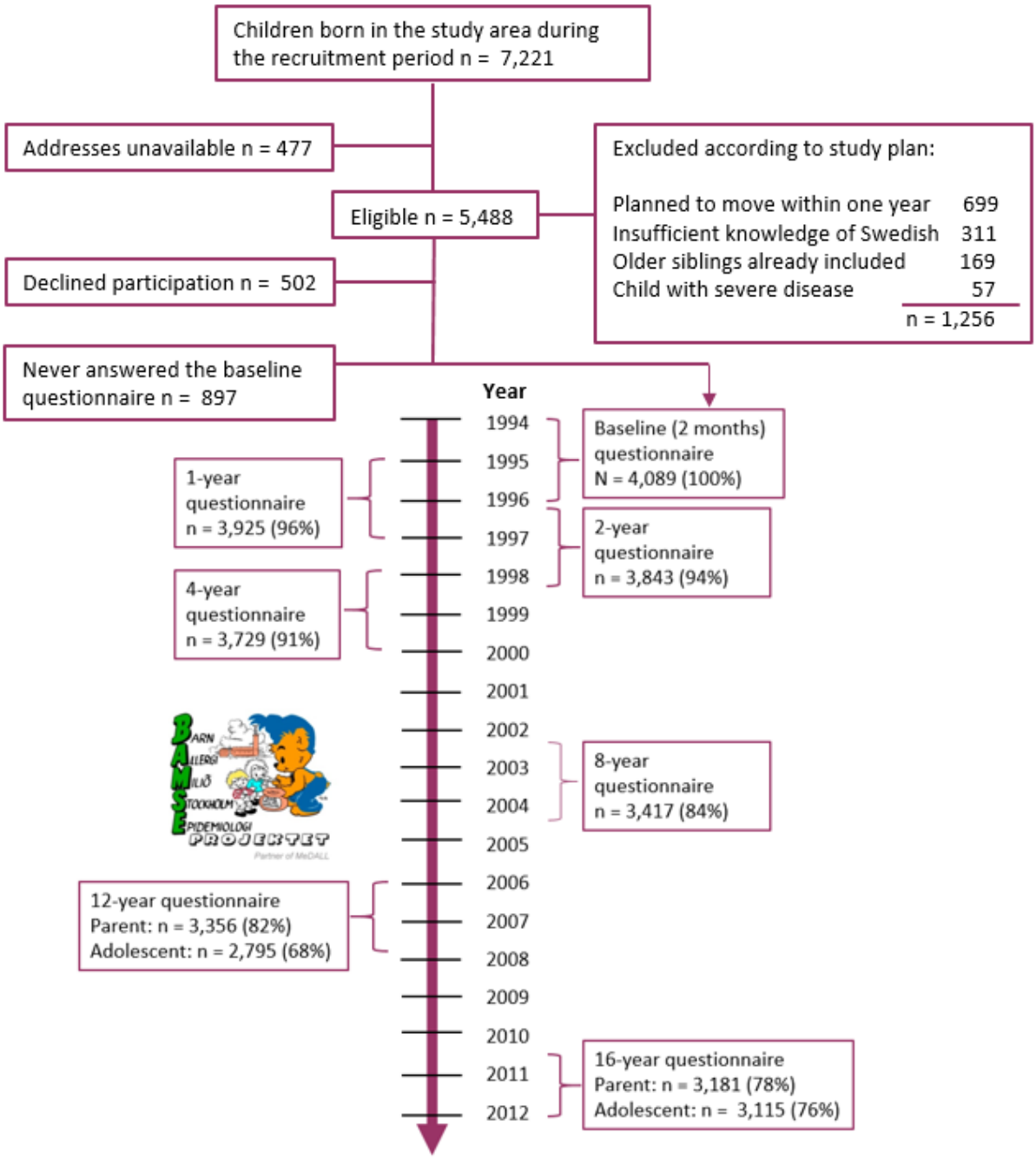


Figure 4: Flowchart of the recruitment and follow-up periods of the BAMSE birth cohort.

The BAMSE-study has contributed to over 200 scientific publications so far. Some of the findings are: family history and genetic factors affect the risk of developing asthma [76, 77]; breastfeeding during the first four months of life reduces the risk of developing asthma up to 8 years of age [78, 79]; and smoking during pregnancy is a risk factor for developing asthma [80]. Assessments of children with severe asthma, according to the WHO definition, have been done using data from the BAMSE-study, in combination with the SPDR [81].

4.4 STUDY DESIGNS AND POPULATIONS

In the thesis, three different study designs were used. A cross-sectional design was used in *studies I – II*, a cohort design in *study III*, and a quasi-experimental design (intervention) in *study IV*.

In *studies I* and *II*, parents of adolescents and adolescents answering the questionnaires (12- & 16- year, respectively) were included. Parental-reported and self-reported data on symptoms, diagnosis, and use of drugs were analyzed, along with the data on dispensed prescription drugs. Furthermore, baseline data on participant characteristics were included in both studies.

In *study III*, all children born in Stockholm County during 2006–2007 were included. Data on diagnoses, dispensed prescription drugs, emigration, death, and socioeconomic status were combined and analyzed. The study period ranged from January 1, 2006 to December 31, 2014.

In *study IV*, children 0–17 years in Stockholm County with dispensed asthma medication during 2014–12017 were included. Dispensing patterns before and after the eliminated patient fee were analyzed in relation to the socioeconomic status.

4.4.1 Measurements of asthma

Since there is not a single standard definition of asthma, it is critical to first define the measurements used in the studies. The focus of this thesis was to explore drug utilization in children with asthma. All four studies have measured asthma in one way or another, in different settings and populations (see table 2 in chapter 4.1 for details).

In *studies I – II*, the definition of asthma was based on a combination of reported symptoms of wheezing, doctor's diagnosis, and asthma medication use.

The definition of asthma medications from SPDR is identical in all four studies as follows (with ATC-codes [82]):

Short-acting β2-agonists, SABA (ATC R03AC02 + R03AC03)

Inhaled corticosteroids, ICS (R03BA)

Fixed combination of ICS and LABA (R03AK)

Leukotriene receptor antagonists, LTRAs (R03DC)

Long-acting β2-agonists, LABA (R03AC12 + R03AC13)

Any asthma medication, at least one of SABA, LABA, ICS, LTRA or a fixed combination of ICS + LABA.

Reported use of asthma medications was also used in studies I – II, categorized in the same way as described for the SPDR.

4.5 STATISTICAL METHODS

Standard statistical methods for epidemiological research were used in all four studies, which are summarized in Table 2 in Chapter 4.1. In this chapter, a description of how we applied and adapted some of these methods within this research project will be given.

4.5.1 Sensitivity, specificity, and positive predictive value

In *study I*, we wanted to see if some specific questions about asthma medication use in the 12-year follow-up questionnaire from the BAMSE-study could be replaced with data from the SPDR.

To do so, we used the measures of sensitivity, specificity, and positive predictive value (PPV) to calculate the agreement between the register and the questionnaire. Different time-windows in the SPDR were used to see how the agreement varied by time-window. We used the 12-year follow-up questionnaire from the BASME-study as the golden standard and calculated the measures as follows:

Measure of asthma medication use		Reported in the 12-year follow-up questionnaires	
		Yes	No
Dispensed at pharmacies (The Swedish Prescribed Drug Register)	Yes	A	B
	No	C	D

$$Sensitivity = \frac{A}{A + C}$$

$$Specificity = \frac{D}{B + D}$$

$$Positive\ predictive\ value = \frac{A}{A + B}$$

A low sensitivity implies that adolescents reported medication use without being dispensed any prescription drugs. These situations may occur if a too short time window in the register is used or if the adolescents are receiving the medications in other ways than the dispensed prescription drugs (borrowing medications from siblings or are dispensed medications abroad).

A low specificity implies that the adolescents are being dispensed prescribed drugs, but they do not report use of any medications. Reasons for non-adherence may be: forgetting to take the medication, lack of information on how to use the medication (technical problems with the device or miscommunication regarding the number of doses needed per day), or feeling uncomfortable in using the medication in front of others.

A low positive predicted value implies that dispensing data from the SPDR is not a good proxy for parental-reported drug use.

4.5.2 Cox Proportional Hazard Regression

Cox regression was used in *study III* to investigate the association between sibship and asthma medication. The age of the children was used as the underlying time scale and sibship was used as a time-varying exposure. The Cox model was adjusted for family income because it is a potential confounder for sibship and asthma medication. A child was censored when moving, upon death, or at the end of the follow-up, whichever occurred first. Due to non-proportional hazards, the time scale was split into below and above age 1, and an interaction term between age and sibling was included in the model.

4.5.3 Persistence models

The estimated proportion of children with persistent asthma controller medication was measured in *studies III – IV*.
In *study III*, the persistence models were explored and applied to the Swedish settings. Children with controller medication were included from the first date (first date ever) of dispensed controller medication. Persistence was defined with two different time windows, 4- and 18-months, using a refill sequence model [53]. The 4-month time window was selected based on the Swedish reimbursement system, where a prescription for medication for a chronic disease is normally refilled after 3 months. The 18-month time window was used based on our previous findings in *study I* [83]. To be classified as being persistent, the prescription had to be refilled within the defined time window (4- or 18-months; Figure 5).

In addition, siblings' controller medication was added in a separate persistence model, in which the child was classified as being persistent if the child or his/her sibling refilled the prescription within the defined time window (Figure 5). We called this model the *sibling* persistence model. However, adding another child's medication to the persistence evaluation

would automatically increase the persistence. Therefore, for comparison, we added controller medication from randomly selected siblings in the cohort to an unrelated control child's persistence model, in which the index child and the assigned control child's controller medication was included. A significant higher persistence in the sibling model compared to the unrelated control children model would suggest that siblings share medications.

A log-binomial regression model was used to estimate the effect of having siblings on the estimated proportion of children with persistent asthma medication after 1.5 years, expressed as relative risk (RR) with 95% CI. Both the 4-month and 18-month models were used. The models were adjusted for family income. Asthma diagnosis and parental asthma diagnosis were added to the model as interactions with sibship and tested with the Likelihood ratio test.

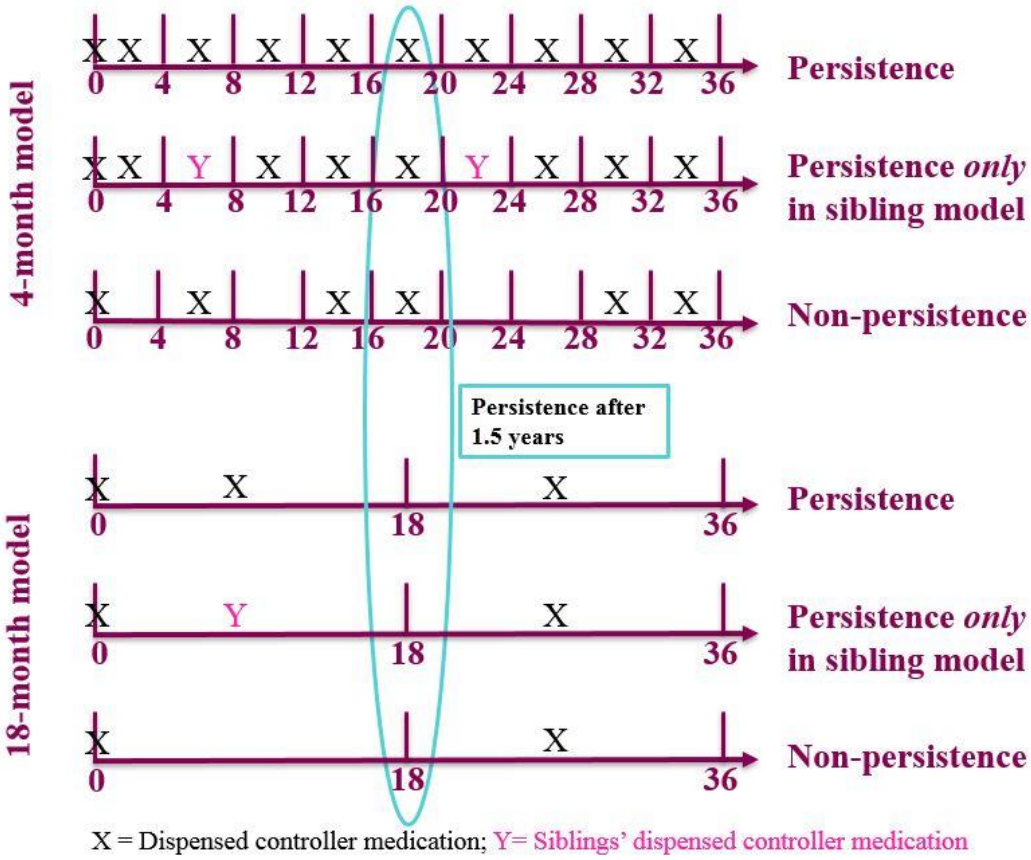


Figure 5: Persistence model for hypothetical children with two different time windows (4- and 18-months). Persistence was defined as refilling the prescription of controller medication (ICS, LTRA, or fixed combination) within the defined time window. Children with controller medication were included from the first date (first ever) of dispensed controller medication.

In *study IV*, we used the 18-month model (without siblings' medication) to estimate the proportion of children with persistence asthma controller medication. The persistence was measured in the uncontrolled before-and after comparison in sub-study (a).

4.5.4 Interrupted time series analysis

Interrupted time series (ITS) analysis was used in *study IV* to analyze the effect of the eliminated patient fee on the dispensing patterns of asthma medication in children. The ITS design is the strongest quasi-experimental design in interventional research [8, 84-86]. The outcomes were repeatedly measured each month to create a trend over time, starting from January 2014 and ending in December 2017. A pre- and post-intervention time frame of two years was created, giving an equal distribution of seasons and seasonal trends before and after the intervention. We used a segmented regression model to determine the direct effect (change in level) and the trend (change in slope) after the intervention (Figure 6). We checked for autocorrelation using the Durbin-Watson statistic and corrected for this where needed with an autoregressive term.

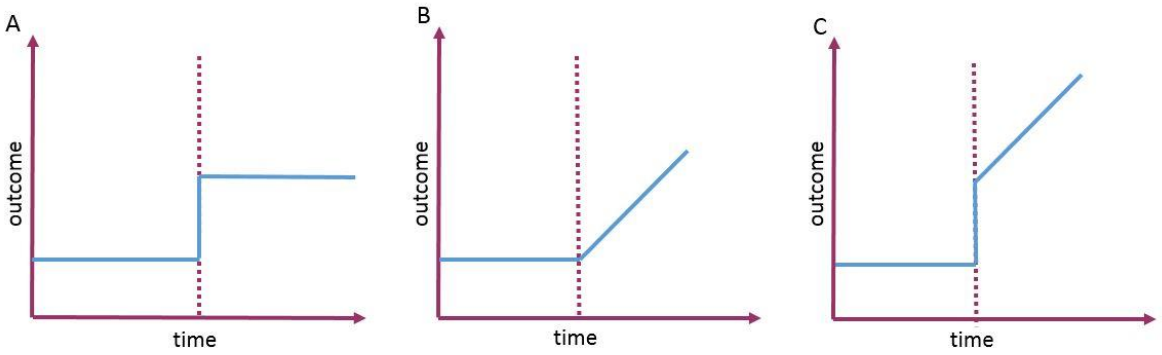


Figure 6: Interrupted time series models and the impact of an intervention (time point of intervention is the dotted line). Figure 6A illustrates a change in level, B a change in slope and C both a change in level and slope after the intervention.

5 ETHICAL CONSIDERATIONS

There are ongoing discussions about register-based research and how it should be conducted in Sweden and the rest of Europe [87]. However, in this section I will focus on the ethical considerations within my research project.

The studies within this thesis were approved by the Regional Ethical Review board in Stockholm, Sweden (*Studies I + II*: 2007/1634-31, 2010/0177-32, 2014/1804-32; *Studies III + IV*: 2015/1144-31, 2017/1356-32, 2018/1351-32). However, an ethical approval is not equated with being able to get data from a specific data provider [88]. Before handing over data to researchers, the data provider makes sure that you will handle the data in a secure way, as stated by the applicable law. The data provider also makes sure that no other Swedish laws will be violated before handing over the data to the researchers (such as the law of Public Access and Secrecy [89]).

5.1 DATA INTEGRITY

In all four studies, pseudonymized databases were used for the research. In such databases, the personal identity number (PIN) is encrypted with a specific database encryption key. The key makes it possible to update the database with new data but still maintain the integrity. Also, the key is managed by a third party ensuring that the researcher never encounters identifiable data.

The databases consist of information pertaining to many thousands of individuals, which will make it less likely to identify a specific individual. The data are aggregated before presenting any results, having the personal integrity in mind.

5.2 THE FOUR PRINCIPLES OF MEDICAL ETHICS

In this research project, the four principals of medical ethics have been considered [90]. First, the purpose of the research should be *beneficence*, i.e., for the benefit of others. The purpose of this thesis is good, namely, to improve drug utilization in children with asthma. We aimed to improve methods to analyze asthma medication use in children and to gain knowledge about their drug use. This can be beneficial for children, in general, and for the children included in each of the studies, in particular.

The second principle, respect for *autonomy*, is taken into consideration using *informed consent* (*studies I & II*). The BAMSE-study started just before the adolescents were born. Informed consent (written) was given by the parents when included in the study. At each follow-up, thereafter, the parents signed a consent form once again to allow data to be used for research. However, the adolescent did not give their own approval until the age of 12, when answering their own questionnaire for the first time. In *studies III* and *IV*, informed

consent was not obtained. These studies were pure large, register-based, studies with data from national and regional registers. Presenting data on asthma medication use among children in Stockholm before and after an intervention might seem like an invasion of privacy to some of the children included (or their parents). However, when performing large, register-based, epidemiological studies, it is not standard practice to obtain informed consent from all individuals included. When using pseudonymized register-based data on a large population e.g., all children born in Stockholm from 2006 – 2007, it is unlikely that the researcher will identify a specific individual.

Given that this doctoral project is not experimental, it is easier to fulfill the third principle of not harming (*non-maleficence*) the participants compared to experimental projects. On the other hand, it cannot be fully ruled out that none of the study participants were harmed. For example, the adolescents who were asked about their medication use might feel uncomfortable and mentally and/or psychologically harmed. In *studies III* and *IV,* data collection was not needed directly from the participants since the studies used only register-based data that had been previously collected for other purposes.

The last principle, *justice*, has also been considered, especially in the register-based study where all children born in Stockholm were included, regardless of the area of residence, the parents' socioeconomic status, where they received healthcare, or where they were dispensed drugs. The study specifically assessed the effect of the eliminated patient fee from a socioeconomic perspective. Children are often excluded from RCTs because of ethical and practical reasons. On the other hand, it is unethical to exclude children from research just because it is a 'tricky group of individuals.' In this thesis, children's use of asthma medication was investigated without (known) harm.

6 MAIN RESULTS AND DISCUSSION

6.1 THE PREVALENCE OF ASTHMA (I – IV)

The prevalence of asthma was calculated in all studies (*I – IV*), but the numbers varied due to different data sources, the age of the children and the definition of asthma. Table 3 provides a summary of the results.

Table 3: Prevalence of asthma in the four studies using different measurements.

Population	Drugs from SPDR[1]	Drugs from Questionnaires	Diagnosis from Questionnaires
Study I Adolescents 12 years	8.1%	10.7%	10.4%
Study II Adolescents 16 years	6.2%	8.2%	10.0%
Study III Children 0→6 years	23%	n/a	n/a
Study IV Children 0 – 17 years	11.9%; 13.0% [2]	n/a	n/a

[1] The Swedish Prescribed Drug Register

[2] The prevalence before and after the intervention January 1, 2016

The prevalence of asthma in *studies I* & *II* were within the range of documented prevalence between 5 – 20%, as described in a WHO report [14]. In the International Study of Asthma and Allergies in Childhood (ISAAC) study, the 12 months prevalence of wheezing in adolescents 13 – 14 years was 11.6% in Northern and Eastern Europe [35].

The definition of asthma medications from SPDR was identical in all four studies; however, since the age of the study population was different in all the studies, the prevalence varies. In *study IV*, the proportion of children with dispensed asthma medication was 11.9% two years before and 13.0% two years after the eliminated patient fee. In *studies I* and *II*, only adolescents were included which leads to a lower proportion. That could be both because of adolescents growing out of their asthma and because they are not getting their asthma medications dispensed regularly (non-adherence). Moreover, in *study III*, the study period was seven years compared to one to two years in the other studies. In general, we found that patient-reported data of asthma medications generated higher prevalence compared to register data. Overall, the prevalence of asthma medications among children ranged from 7% to 26% worldwide [17].

In the 16-year follow-up questionnaire of the BAMSE-study, 331 adolescents (10.0%) fulfilled the study definition of asthma (*study II*). Among them, most had recorded asthma medication use with at least one of the following methods: reported drug use in the last 12 months (82%), reported use of someone else's medication (10%), and dispensed asthma medication from pharmacies in the last 18 months (62%). The overlap between these groups is illustrated in a proportional Venn diagram (Figure 7).

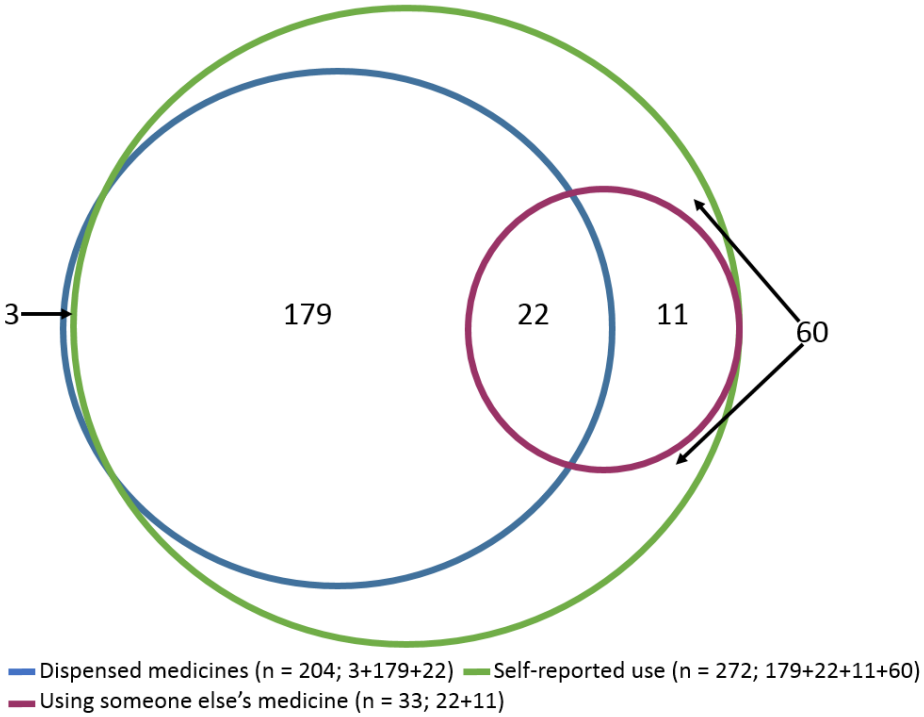


Figure 7: Proportional Venn diagram illustrating the use of drugs among adolescents with asthma, assessed with different methods. Among adolescents with asthma (n = 331), 83% (n = 275) had either self-reported use, were using someone else's medication, or were dispensed drugs.

In *study II*, we had the opportunity to assess drug utilization in three different ways to get more details about how adolescents with asthma are using their medications. We found that one out of ten adolescents with asthma used someone else's medication and half of them were not identified in a prescription register. To the best of our knowledge, this finding has not been shown before. It is evident, however, from other therapeutic areas (i.e., pain medication and allergy medication) that adolescents do borrow medications from others ([29, 91]; see also chapter 6.7).

6.2 CONCORDANCE BETWEEN REGISTER DATA AND QUESTIONNAIRES (I)

The concordance between the dispensing data in the register and the parental-reported drug use in the questionnaires (the 12-year follow-up from the BAMSE-study) was measured with different time windows in the register. The parental-reported prevalence of asthma

medications among the adolescents was 10.7% compared with 8.1% among adolescents with dispensed drugs during a 12-month period in the register (p-value <0.01). The sensitivity for the register was 0.65 with the 12-month time window and increased to 0.76 after extending the time window to 18 months when assessing dispensing history data (Figure 8). The specificity was high throughout the different time-windows (1.0 at 3 months and 0.97 at 24 months). The positive predicted value (PPV) was high at 3 months (0.9) and decreased when extending the time window in the register. After 18 months, the PPV started to decrease more rapidly, from 0.83 at 18 months to 0.76 at 24 months.

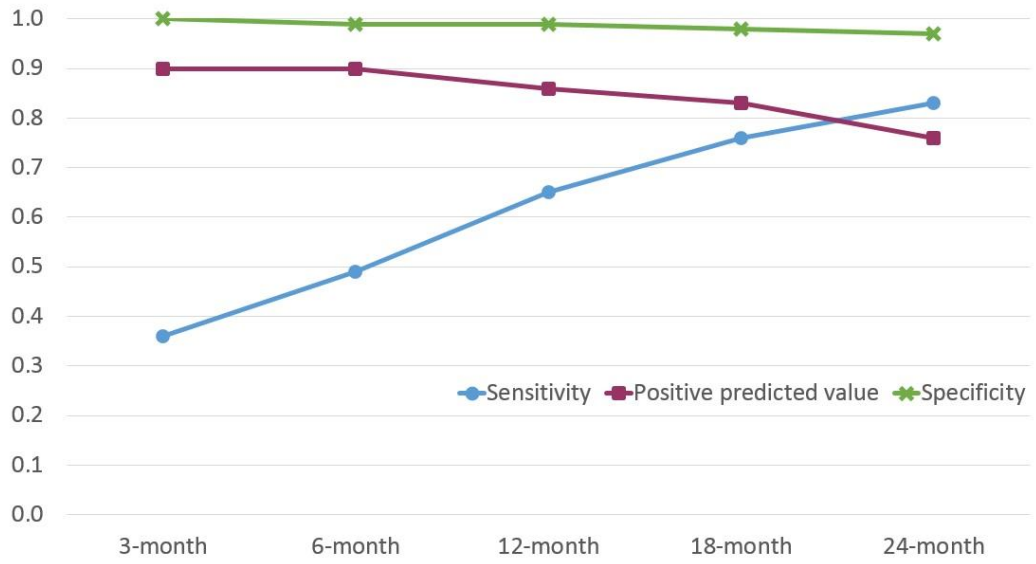


Figure 8: The concordance between dispensing data from the Swedish Prescribed Drug Register and questionnaire data from the 12-year follow-up of the BAMSE-study for asthma medications, using different time windows in the register.

The agreement between dispensing data and parental-reported drug use was lower in *study I* than in other studies, where sensitivities were found from 79% to 98% [92-95]. However, our study population was older than most of the others, which could explain our lower concordance. Parents of younger children are probably more involved in the administration of drugs than parents of adolescents. It is also known that non-adherence among children with asthma is common [37, 38]. The study conducted by Furu et al. had the same definition of asthma medications as *study I*; however, the other studies had a somewhat different definition, which might affect the concordance between the register data and the questionnaires. Also, we used parental-reported data from the questionnaires, as the golden standard because we assumed that reported drug use is closer to the truth than dispensing data from the register when assessing asthma medications. This was in contrast with other studies [92-94], which used the dispensing data as the reference.

6.3 ASTHMA CONTROL AMONG ADOLESCENTS (II)

Among adolescents with asthma in the 16-year follow-up questionnaire of the BAMSE-study, 53% had fully controlled asthma. This is in line with other findings. In a Danish study on young adults with asthma, 41% had controlled asthma [96]. Klok and colleagues found that 60% of preschool children with asthma had their disease under control [97]. The proportion of adolescents with asthma control in our study was higher among boys than girls, 75% vs. 41% (p-value <0.01). Adolescents with uncontrolled asthma reported using someone else's medications more often compared to adolescents with controlled asthma (14% vs. 6%; p-value = 0.02). Furthermore, adolescents with uncontrolled asthma were generally dispensed more drugs and in particular, higher doses of SABA. This might be surprising, knowing that pharmacological treatment may improve asthma control, but a higher dose of SABA may also indicate sub-optimal use of controller therapy. On the other hand, increased use of drugs may also indicate a more severe disease. Also, one of the criteria for uncontrolled asthma is using SABA more than twice a week. This was illustrated by the fact that all adolescents with severe asthma were in the uncontrolled group.

6.4 PERSISTENCE OF ASTHMA MEDICATIONS (III – IV)

The persistence of asthma controller medications among children differed largely with different time windows in *study III* (Table 4).

Table 4: The persistence of controller medications after 1.5 years with the different persistence models and time windows.

Persistence model	**4-month time window; % (95% CI)**	**18-month time window; % (95% CI)**
Standard model	7.2 (6.6 – 7.7)	64.5 (63.5 – 65.4)
Only children with a diagnosis of asthma	8.2 (7.5 – 9.0)	72.1 (71.3 – 73.1)
Sibling persistence model[1]	8.8 (8.2 – 9.4)	73.6 (72.6 – 74.5)
Control child model[2]	7.8 (7.3 – 8.4)	72.6 (71.7 – 73.6)

[1] Including both index children and siblings' controller medications; See chapter 4.5.3 for details.

[2] Including both index children and randomly selected unrelated control children's controller medications.

The reason for the discrepancy in persistence between the time windows, is most likely the irregular dispensing patterns for children with asthma. Since asthma in young children is often an intermittent disease, few children had their prescriptions refilled after four months. In accordance with *study II*, 18-months could be an optimal time window when analyzing dispensing patterns for asthma medication in the register data.

In concordance with *study III*, Øymar et al. found a low persistence of ICS among pre-school children [55]. Only 9 – 18% of the children in Norway were persistent (refilled a prescription of ICS every 12 months) after 5 years. Among children with intermittent asthma, admitted to the Children's Hospital of Michigan, Detroit, 25% lacked asthma medications [98]. This corresponds to our figure of 72% persistence among children with an asthma diagnosis, using the 18-month time window. In a Dutch study, 88% of the children (aged 7 – 17 years) were dispensed at least one ICS prescription drug during a 12-month period [57]. However, only half of them used more than one puff of ICS per day, an indication of non-adherence. This can also be an explanation for our results with low persistence using the 4-month time window and a substantial increase in persistence with the 18-month time window.

In *study IV*, the proportion of children with persistent controller medication was 48.3% before and 52.2% after the intervention using an 18-month time window. This study included all children 0 – 17 years, which could explain the lower proportion compared to *study III*. Also, in *study IV*, the persistence among girls was lower than in boys (50.1% and 53.6% respectively). These findings were also seen in the Norwegian study, where the proportion of children with persistent medication after one year was 49% in girls and 52% in boys [55]. Furthermore, the persistence was lowest among children with low socioeconomic status (46.0% before and 51.9% after the intervention).

6.5 CHILDREN ARE SHARING ASTHMA MEDICATIONS (II – III)

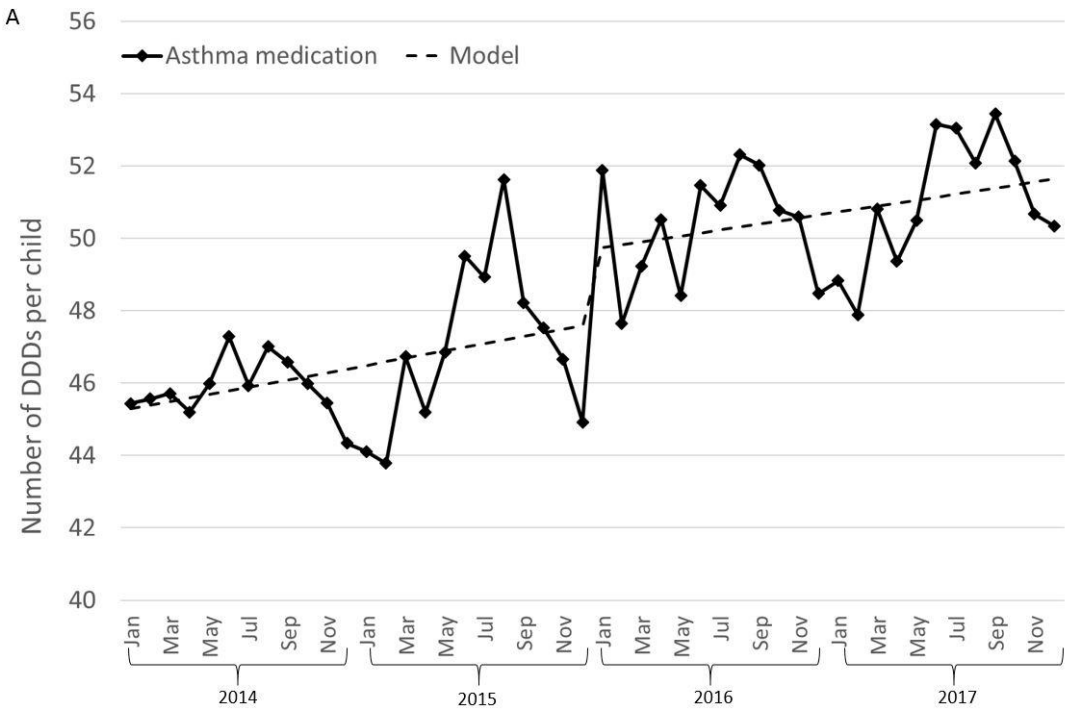
In *study II*, we found that 10% of the adolescents reported that they had used another person's asthma medication in the last 12 months. Among these adolescents, one out of three were not dispensed any asthma medications during the same period. To the best of our knowledge, sharing of asthma medications among adolescents has not been shown before. It is evident, however, from other therapeutic areas that adolescents borrow medications from others [29, 91]. In a study from the USA, one out of five adolescents shared medications, and in an Irish study, 26% of adolescents reported that they borrowed someone else's medication. The most common groups of drugs shared were allergy medications and painkillers.

Children with siblings had a lower persistence of asthma controller medication compared to children without siblings (p-value <0.01; *study III*). When including controller medication both from the index children and their siblings, the persistence after 1.5 years increased. The sibling model might be more complete and may suggest that the proportion of children with persistent asthma controller medication is not as low as previously shown [55, 56]. Moreover, the estimated proportion of children with persistent controller medication was lower for the

model including medication from an unrelated control child than that including medication from biological siblings, RR 0.89 (95% CI 0.81 – 0.98) with the 4-month time window. Altogether, this implies that siblings seem to be sharing asthma medication. With that knowledge, it becomes important that prescribers make sure that children with asthma have a sufficient supply of asthma medication available. In families where two or more siblings have asthma and potentially share the asthma medications, it is important to provide individual information (i.e., a treatment plan) about each child's management of asthma medication. An individual treatment plan can help prevent medical errors such as using an asthma device with a wrong strength or using the device less frequently than prescribed.

6.6 EFFECTS OF THE ELIMINATED PATIENT FEE (IV)

In January 2016, the legal decision to provide free medication to children (0 – 17 years) came into force [61]. The aim of *study IV* was to assess the effect of eliminated patient fee on the dispensing patterns of asthma medication. We found that the proportion of children with dispensed medication and the proportion of children who were initiated asthma therapy were not affected by the intervention. There was an increase in the dispensed volume related to the intervention, 3.4 more defined daily doses (DDDs)/child/month after the eliminated patient fee. This was most profound in children with low socioeconomic status (Figure 9).



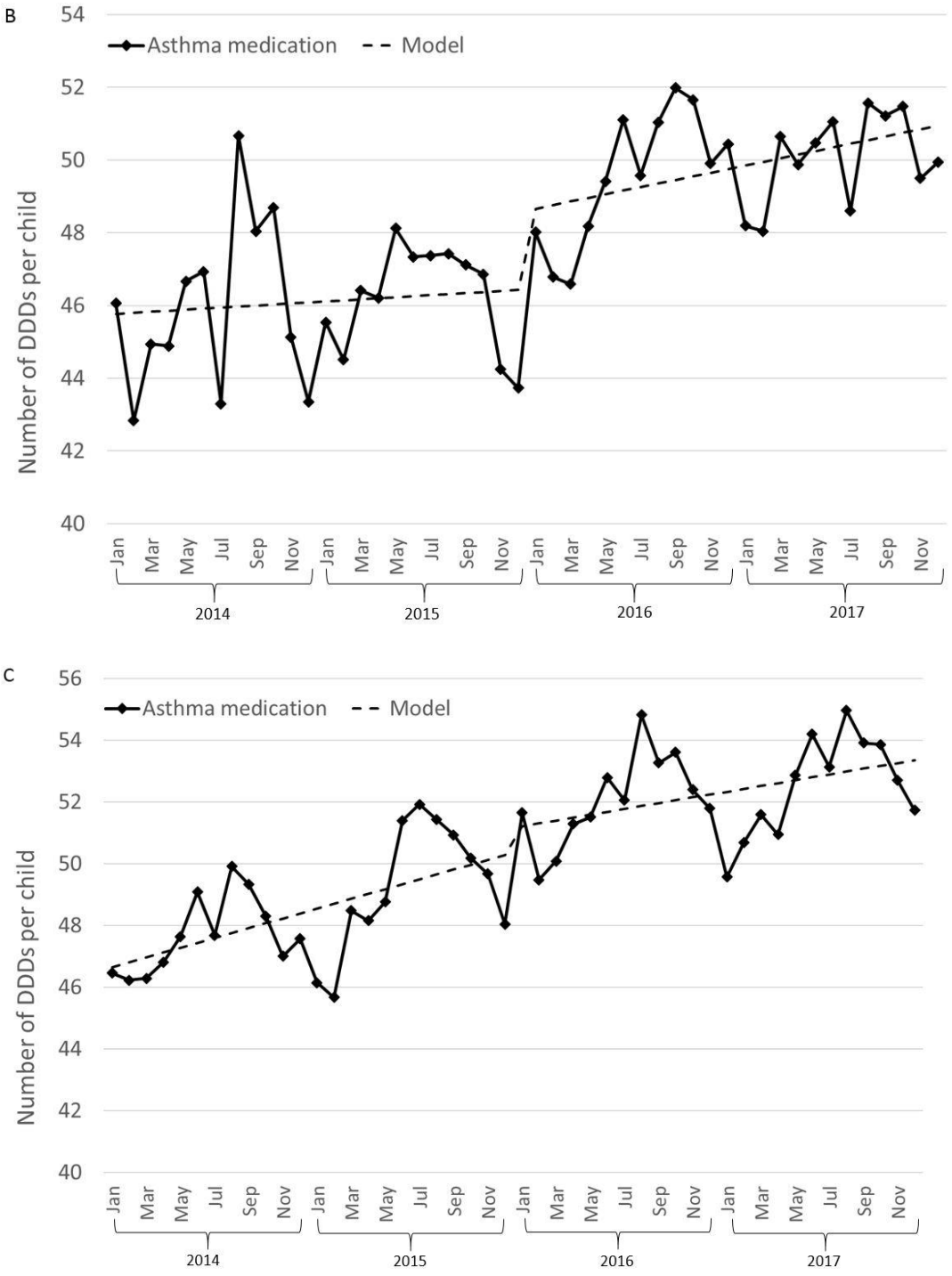


Figure 9: Segmented linear regression, interrupted by the eliminated patient fee, measured as the number of dispensed DDDs/child in children with low socioeconomic status (A), middle socioeconomic status (B) and high socioeconomic status (C).

Changes in the co-payment systems have previously been shown to affect the dispensing patterns of asthma medications [99, 100]. In American children 5 years and older, an increase in the cost-sharing for asthma medication resulted in a reduction in medication use (percentage of days covered by a prescription asthma medication; total expenditure on asthma medications) and higher rates of asthma hospitalizations [99]. Among U.S. citizens aged 12–64 years, even a small increase in the patient co-payment ($5) resulted in lower medication use and higher unintended use of healthcare services [100].

6.7 FACTORS TO CONSIDER WHEN ASSESSING THE DISPENSING PATTERNS OF ASTHMA MEDICATIONS (I – IV)

In general, asthma medications are not dispensed regularly among children. Within the scope of this thesis, the following four factors were found to be considered when assessing the dispensing patterns of asthma medication: sex, sibship, time window used in the register (estimated exposure of asthma medications), and change in the co-payment system.

The proportion of boys with fully controlled asthma is larger compared to girls (*study II*). Furthermore, the agreement between the parental-reported asthma medication use and dispensed asthma medications is higher among boys compared to girls (*study I*). The proportion of children with persistent controller medication is lower in girls compared to boys (*study IV*). This implies that girls with asthma need some extra attention when talking about asthma medication use and how important it is to remain on controller treatment.

Siblings also influence the dispensing patterns of asthma medications among children. The incidence rate of dispensed asthma medications in the first year of life was higher for children with siblings than for those without siblings. After one year of life, the incidence rate of dispensed asthma medications was lower for children with siblings than for singletons. Children with siblings had a lower persistence of asthma controller medications compared to those without. When combining the children's controller medication with their siblings' controller medication, the persistence increased, suggesting that they share the asthma medication (*study III*).

The estimated exposure of asthma medications may also vary depending on the time window used in the data bases. Since asthma in young children is an intermittent disease, few children had their prescription of asthma medication refilled four times a year (which is the standard for continuous pharmacological treatment in Sweden). Using a 6- or 12-month time window in the SPRD or other dispensing databases will underestimate the prevalence of asthma medication. An 18-month time window of dispensing data is preferable when studying dispensing patterns of asthma medications among Swedish children (*study I*).

Finally, a change in the co-payment system (an eliminated patient fee) can also affect the dispensing patterns of asthma medications in children (*study IV*). The total effect of the eliminated patient fee implemented in Sweden in January 2016 was limited, however the dispensed volume of medication (measured as DDDs/child) increased after the intervention. This was most profound in children with low socioeconomic status.

7 METHODOLOGICAL CONSIDERATIONS

7.1 VALIDITY IN DATA SOURCES

7.1.1 Registers

There are many advantages of using healthcare registers when conducting drug utilization studies. The large-scale databases, including data on healthcare visits and dispensed prescription drugs in an entire region (VAL) or dispensing data from a whole country (SPDR), provide a very cost-effective way of conducting pharmacoepidemiological studies [101, 102]. The registers describe the situation in routine care and not merely the controlled environment in a RCT. The VAL databases include diagnoses from primary care, which the national register (NPR) lacks. The information in NPR is well validated [65, 102, 103]. Örtqvist et al. concluded that doctors' recorded diagnosis of asthma in NPR was of high quality. They also found that dispensed asthma medications in SPDR can be used as a proxy when assessing asthma in children, especially if the child is 4.5-years-old or more [103]. The MBR is of high quality and includes 98% of all births in Sweden [68]. A high agreement between reported drug use in the MBR and dispensed drugs in the SPDR was seen for drugs used for chronic conditions but not for drugs used more occasionally [104]. The MGR has a full coverage of the Swedish population because the data is originated from the Swedish Population Register held by the Swedish Tax Agency. The LISA register includes information on registered income and education for all individuals in Sweden from 16 years of age.

However, there are also limitations with register data. To be included in a health register such as NPR, the person in question must have contacted a healthcare provider. We do not know for sure the quality of the recorded diagnosis in the registers. Another limitation is the lack of clinical data (e.g. spirometry data and lab data) and data on lifestyle factors. It is also important to acknowledge that a dispensed prescription drug is not necessarily the same as a used drug. Also, another person than the intended can use a dispensed drug, i.e., sharing of medications.

7.1.2 Questionnaires

Data from questionnaires are self-reported data, directly from the intended user or their parents (if parental-reported data). It is possible to ask a variety of questions to gain information on education, home environment, family constellations, lifestyle, diagnoses, drug use, and others. This information is never or only partly recorded in registers. The questionnaire data from BAMSE consist of rich information about the participating children, including data on socioeconomic status, quality of life, medical information (diagnoses and prescription drugs), and lifestyle (dietary information, smoking habits, and physical activity). The data were collected prospectively at each follow-up.

Some limitations with questionnaire data are also important to point out. The process of collecting data is time-consuming, and there is a risk of selection- and information bias. The quality of the data is dependent on the knowledge of the respondent and the researcher, which means that some important information can be lost.

7.2 STUDY DESIGN AND GENERALIZABILITY

Observational studies provide the possibility to study drug utilization in children from a different perspective than randomized controlled trials. These types of studies describe the real-life situation, where a perfect proportion of patients with persistent medication and 100% attendance at healthcare check-ups are non-existent.

The study populations in *studies I – II* have their origin in a population-based birth cohort with participants born during 1994 – 1996. The participating families were recruited from Child health care clinics in four predefined areas of Stockholm to include families living in different types of buildings and with different socioeconomic status (education and profession). The response rates during the follow-ups are comparatively high for questionnaire data, with 78% of the original cohort still remaining at 16 years of age. The findings from *studies I – II* may be generalized to pediatric populations in other urban settings. In *study III*, all children born from 2006 – 2007 in Stockholm County were selected. Participants were excluded if moving from Stockholm or upon death during the first year of life. In *study IV*, there was no selection of the population, other than being a child (age <18 years), being registered in Stockholm County, and having dispensed an asthma medication during 2014 – 2017. The children were included, regardless of their socioeconomic status, sex, and healthcare consumption.

All study populations within this thesis originated in Stockholm County. In general, inhabitants in Stockholm are younger and have a higher education level than inhabitants elsewhere in Sweden [105]. The availability of healthcare in Stockholm is high [106]. In addition, Stockholm has the highest proportion of inhabitants with dispensed antibiotics compared to the other County Councils (22% in Stockholm, 20% in Sweden as a total, and 15% in Västerbotten with the lowest proportion) [107]. However, all children in Sweden are included in the same reimbursement system for prescription drugs and there are no documented differences in dispensing histories of asthma medications among children in Stockholm compared to children in other parts of Sweden. The large-scale *studies III* and *IV*, including all children in a specific setting with high quality register-based linkages, increase the *generalizability* (external validity) of the findings. It is important, however, to acknowledge that there are differences in healthcare organizations across Sweden and that national guidelines may not be implemented likewise across regions, which might limit the generalizability of the findings to other settings.

In this thesis, different data sources were used in the analyses. Two of the studies, *I* [83] and *II* [108], applied record-linkage using data from questionnaires and a dispensing register. Such a linkage of data from different sources is a great strength to the thesis, since it may facilitate validation of both sources. The questionnaires contributed with clinical data and the patient perspective. The register contributed with total material (little missing data in variables and no non-responders).

7.3 ASPECTS THAT MAY AFFECT VALIDITY

The internal validity of a study can be affected by three types of biases: information bias, selection bias, and confounding [109].

7.3.1 Information bias (misclassification)

Information bias is a bias introduced to the study when assessing the exposure or the outcome [109]. The misclassification can be non-differential (a misclassification not related to other variables in the study) or differential (a misclassification that differs per other variables in the study).

In *study I*, we concluded that using a short time-window (12 months) in the SPDR could lead to a non-differential misclassification of asthma medications. In *study II*, an 18-month time-window was used to avoid that bias. There could also be a bias (most likely non-differential) in the reporting of smoking in the questionnaire data, where parents may underreport smoking during pregnancy. A non-differential underreporting of smoking during pregnancy has been seen in a Finish study [110].

In *study III*, there is no reason to suspect a misclassification of exposure (sibship) or outcome (dispensed asthma medications). In the before and after study (*study IV* a), no misclassification of outcomes was seen. In the ITS-analysis (*study IV* b*)*, the proportion of children initiated on asthma therapy is likely to be biased due to the monthly data, although a non-differential bias before and after the intervention is expected. A non-differential misclassification of socioeconomic status in study IV is expected. The aggregated measure of socioeconomic status was assessed based on the area of residence, which assumes that all inhabitants in the same area have the same socioeconomic status. The effect of the intervention across different socioeconomic categories may be diluted in our study due to the aggregated data.

7.3.2 Selection bias

Selection bias may occur when the study population at hand differ from the intended source population [109]. The misrepresentation of the source population in the study may lead to inaccurate conclusions.

In *studies I – II*, the study population originated from the BAMSE birth cohort. In the BAMSE cohort, there is at least a theoretical selection bias of participants, when only including children from four different areas. The family history for atopic diseases did not influence the willingness to participate in the BAMSE cohort, unlike lifestyle (as indicated by parental smoking) [75]. The response rate in a cohort study can also lead to selection bias. In the BAMSE-study, the response rates during the follow-ups were high (78% of the original cohort still remaining after 16 years of age); therefore, it is unlikely that any extensive selection bias is present.

In *study III*, the selection of participants was based on birth year. There is no reason to believe that children born during 2006 – 2007 differ in patient characteristics with children born in other nearby years. In *study IV*, all children (0 – 17 years) with dispensed asthma medication during 2014 and 2017 were included. Therefore, no selection bias is expected.

7.3.3 Confounding

Confounding is a situation in which the association between an exposure and an outcome is distorted by the presence of another variable, a *confounder* [109]. In epidemiological research, confounders and other variables connected with the exposure and outcome in one way or another can be summarized using causal diagrams known as *Directed Acyclic Graphs* (*DAGs;* Figure 10; [111]).

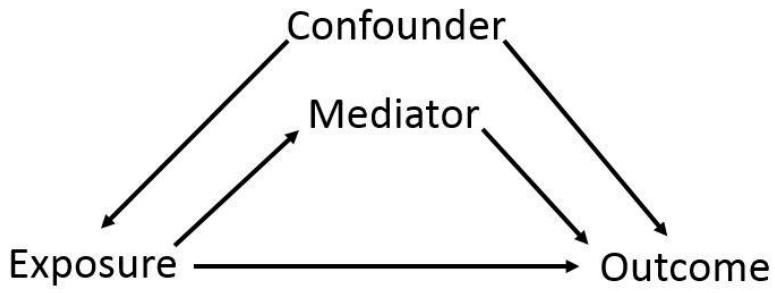


Figure 10: An illustration of concepts in causal inference from a Directed Acyclic Graph (DAG).

The thesis is based on population data from registers and questionnaire data. Therefore, no randomization or restrictions of data were done to minimize the confounding. Adjustments of potential confounders were made within the analyses in all studies.

In *studies I* and *II*, we decided to include variables as potential confounders in the logistic regression models based on previous knowledge from the literature and clinical experience. For example, we decided to include the male sex in *studies I – II*. Previous studies have reported a higher prevalence of asthma in boys compared to girls, as well as girls with asthma being undertreated with drugs [112-114]. Children living in more than one home could affect

both the concordance between parental-reported drug use and dispensed drugs and was therefore included in the logistic regression models. The asthma medication may be in the other home when needed, leading to another refill of prescription or not taking the medication when needed. Furthermore, family history of allergic disease was also included in the model as a confounder.

In *study III*, sibling was used as the exposure and dispensed asthma medication as the outcome. The cox-model was adjusted for family income, which may affect both the number of siblings in a family (family planning) and the incidence rates of asthma medication. In the log-binomial regression models with siblings and persistence to asthma medication after 1.5 years, the same confounder (family income) was used as in the Cox-model. In addition, asthma diagnosis and parental asthma diagnosis were included in the models as interaction terms (effect modifiers) with sibship.

In *study IV*, we analyzed the association between the intervention and a change in utilization patterns of asthma medication. ITS analysis was used in sub-study b, which is generally unaffected by typical confounders if constant over time. We assumed that all potential confounders were constant during the study period.

7.3.4 Methodological considerations in quasi-experimental studies

Study IV had a quasi-experimental design [2]. In sub-study (a), an uncontrolled before-and after design was used and in sub-study (b) an interrupted time series (ITS) design was used.

In the before-and after study, we measured the outcomes at baseline (before) and at follow-up (after) without any other control group. This design assumed that any observed changes in drug utilization was explained by the intervention, not taking secular trends or other factors into account. Consequently, uncontrolled before-and after studies are known to over-estimate the effects of interventions and the results of such studies need to be interpreted with caution [2].

ITS design is the strongest quasi-experimental design for evaluating the effects of interventions since it aims to determine if an intervention has a greater effect than the underlying trend. We created a pre- and post-intervention time frame of two years (24 data points), giving an equal distribution of seasons before and after the intervention. The assumption of independent observations was violated in this study (tested with Durbin-Watson statistics), which is often the case in ITS studies. Therefore, the models were adjusted for autocorrelation using an aggressive term. We decided not to include a control group in the ITS study which some other ITS studies have. The decision to provide free medications to children included all medication groups; therefore, no natural control group could be identified. Choosing adults' dispensing patterns of asthma medication as a control group would have been of limited value due to known differences in dispensing patterns of asthma medications and at least partly different phenotypes of asthma in children and adults. Finally,

there may have been factors other than the studied intervention that influenced the dispensing patterns of asthma medication in children during the study period (i.e., time-varying confounding). The updated national recommendations for asthma and chronic obstructive pulmonary disease were published in November 2015 [115], but their potential effect on the dispensing patterns of asthma medication would not be expected immediately afterwards [86]. On the other hand, a preliminary version of the national guidance was made public in 2014, which may have influenced the utilization patterns before they were finalized. However, there is no reason to believe that this resulted in a sudden change at the same point in time when the reimbursement change occurred.

8 CONCLUSIONS AND IMPLICATIONS

In this thesis, drug utilization patterns in children with asthma have been described and analyzed in relation to various patient characteristics, sibship, and a policy intervention. Different data sources and time periods for analyses were used, resulting in findings that may be of importance for researchers, physicians, policy makers, and patients. From the studies included in this thesis, we concluded that:

- When using data on dispensed prescription drugs to study asthma medication use in children, an 18-month time window is preferable. Due to irregular dispening patterns among children, a shorter assessment period may underestimate the prevalence of asthma medications. (*Study I*)

- Data on drug use from different data sources may lead to different estimations of drug exposure. Dispensing data from pharmacies may underestimate drug use compared to self-reported (or parental-reported) data from questionnaires on the use of asthma medications. On the other hand, self-reported data may overestimate drug use. Thus, it is valuable to use additional data sources when studying drug utilization in children with asthma. (*Study II*)

- Siblings share asthma medications, which may lead to underestimation of drug use in individual patients when using dispensing data from registers. Therefore, it may be useful to include siblings' medications in persistence models under such circumstances. Translated into a clinical implication, healthcare professionals seeing children with asthma should be aware of the possibility that medications are shared among siblings and make sure that each patient has a sufficient medical supply and an individual treatment plan. (*Study III*)

- The proportion of children with persistent controller medication is lower in girls compared with boys; girls are also less likely to achive asthma control. Therefore, in clinical practice, it seems that the attention directed toward girls with asthma needs to increase. (*Studies II & IV*)

- Interrupted time series analysis provides a more relevant evaluation of effects of changes in co-payment systems than a before-and-after approach. More carefully designed policy interventions building on robust baseline analyses are needed to reach desired effects. Such interventions should also be better targeted to patients in most need, e.g. those with low socioeconomic status. (*Study IV*)

9 FUTURE PERSPECTIVES

During the years of my research project, new questions have been raised. There are many potential areas for future research on drug utilization in children with asthma. Some specific topics of interest are:

- Study the adherence process of asthma medication, e.g, by using linkage of prescription data, dispensing data, and patient-reported data. It is important to explore where in the adherence process (initiation-implementation-persistence) non-adherence is present. Next step would be to identify explanatory factors which may be the target for interventions to increase the adherence of medications in children with asthma. The development of technical devices (including digital inhalers) may also offer new ways to measure and improve adherence.

- Design a study to further explore sharing of asthma medications in children, in relation to asthma control, utilization patterns of medications, severity of disease, and hospitalizations. This thesis has suggested that children with asthma share medications. We know that it may have an impact on dispensing patterns, but not how it effects the quality of life in children with asthma. Is the asthma control better or worse among children sharing asthma medications compared to children not sharing? Is there a potential for medication errors caused by, e.g. differences in dosages between siblings? Does children with severe asthma also share asthma medications? Is there an association between mediciation sharing and hospitalization rates?

- Conduct a qualitative study, i.e., focus groups discussions to investigate how adolescents with asthma are using their medications. This potentail study would be a great compliment when trying to reach a deeper understanding about adolescents with asthma. Both practical aspects of asthma medications including how simple and feasable they consider their devices are to manage, as well as attitudes towards their medications and the management of their disease would be of interest.

- It would be of great value to test and validate our persistence model in *study III* in different study populations. Asthma in younger children is more intermittent compare to asthma in school children. To test the robustness of the persistence model, it would be useful to study school children. Furthermore, it coud be of interest to adopt the model to other countries with other prescription regulations and reimbursement systems.

These proposed studies are feasible to do within the Swedish setting. Conducting cross-national studies on children's drug utilization, including persistence of asthma controller medications, would also be of great interest and importance for pediatric pharmacoepidemiology.

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