Epidemiology of asthma drug use in children, adolescents and young adults in Norway

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Øystein Karlstad, October 2011

SUMMARY

Background

Asthma is one of the most common chronic diseases among children, adolescents and young adults. The use of drugs to treat asthma has not been widely investigated in the Norwegian population and there has been a lack of longitudinal data. Most studies have been conducted in confined age groups and geographic regions. The occurrence of additional health problems in the young population with asthma has important implications for the management of asthma and needs investigation. Asthma is a clinical diagnosis that is not easily captured in population-based studies and there is no agreement on a gold standard for measuring asthma in epidemiology. Prescription data on asthma drug use may be a useful proxy measure for identifying individuals with current asthma in the population.

Objectives

The main objectives of this thesis were to study issues related to asthma in the Norwegian population of children, adolescents and young adults. Three areas have been studied: Asthma drug use, asthma drug use as a proxy measure of asthma, and selected additional diseases and drug treatments occurring in individuals with asthma.

Materials and methods

This thesis rests on data from population-based databases and questionnaires: 1) The Norwegian Prescription Database, 2) The Norwegian Mother and Child cohort study questionnaire for seven years old participants, 3) The Youth Health Surveys in five counties, 4) The Population and Housing Census from 2001, and 5) The Central Population Register. Data on filled prescriptions from the Norwegian Prescription Database is the central source for information and provided the outcome variables in all papers of this thesis.

Main findings

Mother-reported use of asthma drugs in children had high validity, compared to prescription data of asthma drug use. Furthermore, the prescription data on asthma drugs corresponded well with maternal reports of current physician-diagnosed asthma, and few individuals with no reported asthma had filled prescriptions. Filled prescriptions were used as a proxy measure in the other papers in this thesis to identify individuals with current asthma in the study populations.

The prevalence and incidence of asthma drug use in the Norwegian population 2-29 years old was highest in preschool children and lowest in young adults. Males had higher levels than females at a young age, but this changed from about 15 years of age to higher levels in females. The persistence to asthma drugs over time was relatively low, with less than half of asthma drug users receiving drugs in three consecutive years. The type of asthma drugs used varied substantially by age but not by gender, and there were indications of suboptimal pharmacotherapy.

The occurrence of chronic diseases in individuals with asthma was assessed by utilizing diagnostic codes provided by physician on reimbursed prescriptions. Several diseases occurred more frequently in children, adolescents and young adults with asthma than in the Norwegian general population. A majority of the asthma population had one of the nine comorbid diseases examined, while few had more than one of the comorbidities. In another study, young adults with asthma were at an increased risk for initiating use of hypnotic drugs. The risk was highest among individuals who recently had received asthma drugs, indicating that they had currently active asthma disease.

Conclusions

The findings in this thesis indicate that prescription data may serve as a proxy for current asthma in the population. It is important to carefully consider the length of the capture period for prescription data and possible overlapping conditions treated with the same drugs in different age groups. The relatively low persistence to asthma drug use may reflect the variability of asthma within and between patients, and illustrate the challenges encountered in defining asthma in epidemiologic studies. Several diseases and drug treatments occurred more frequently in the asthma population. The presence of comorbidities may influence and complicate several aspects of asthma and both the causes and consequences of comorbidities need further investigation.

LIST OF PAPERS

The thesis is base on the following papers:

I. Furu K, Karlstad Ø, Skurtveit S, Håberg SE, Nafstad P, London SJ, Nystad W. High validity of mother-reported use of antiasthmatics among children: a comparison with a population-based prescription database. Journal of Clinical Epidemiology 2011;64:878-84. doi:10.1016/j.jclinepi.2010.10.014

II. Karlstad Ø, Nafstad P, Tverdal A, Skurtveit S, Furu K. Prevalence, incidence and persistence of anti-asthma medication use in 2- to 29-year-olds: a nationwide prescription study. European Journal of Clinical Pharmacology 2010;66:399-406. doi:10.1007/s00228-009-0749-x

III. Karlstad, Ø, Tverdal, A, Skurtveit, S, Nafstad, P, Furu, K. A prospective study of asthma and subsequent use of hypnotics in young adults. Pharmacoepidemiology and Drug Safety 2011;20:370-7. doi:10.1002/pds.2101

IV. Karlstad Ø, Nafstad P, Tverdal A, Skurtveit S, Furu K. Comorbidities in an asthma population 8-29 years old - a study from the Norwegian Prescription Database. Manuscript accepted for publication in Pharmacoepidemiology and Drug Safety, July 2011.

The papers will be referred to in the text by their Roman numerals.

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical classification system
CI	Confidence interval 95%
COPD	Chronic obstructive pulmonary disease
CPR	The Central Population Register
ECRHS	The European Community Respiratory Health Survey
FDC	Fixed dose combinations of β_2-agonists and corticosteroids, ATC code R03AK
GORD	Gastro-oesophageal reflux disease
HSCL-10	Hopkins Symptom Check List
IBA	Inhaled β_2-agonists, R03AC (includes both SABA and LABA)
ICD-10	The International Classification of Diseases, version 10
ICPC-2	The International Classification of Primary Care, version 2
ICS	Inhaled corticosteroids, ATC code R03BA
IRR	Incidence rate ratio
ISAAC	The International Study of Asthma and Allergy in Children
LABA	long-acting β_2-agonists, ATC code R03AC
LTRA	Leukotriene receptor antagonists, ATC code R03DC
MoBa	The Norwegian Mother and Child cohort study
NorPD	The Norwegian Prescription Database
PHC	The Population and Housing Census
RCT	randomized controlled trial
SABA	Short-acting β_2-agonists, ATC code R03AC
SMR	Standardized Morbidity Ratio
YHS	The Youth Health Surveys
Z-hypnotics	Benzodiazepine related hypnotics, ATC code N05CF

1 BACKGROUND

1.1 General introduction

Epidemiology is defined in several ways but a common definition is the study of the distribution and determinants of disease or illnesses in populations. Alternatively, it can be defined as the study of the distribution of health-related states and events in populations, thus also encompassing positive outcomes and physiologic states as well as diseases and illnesses (1). *Pharmacoepidemiology* is a branch under epidemiology and has been defined as "the study of the use of and the effects of drugs in large numbers of people" (2). It applies the methods of epidemiology on the content area of clinical pharmacology (the effect of drugs in humans) and aims to describe, explain and predict use and effects of drugs in a defined time, space and population. The major application area for pharmacoepidemiological principles is in post-marketing studies of drugs, where its main asset compared to the pre-marketing randomized controlled trials (RCTs) is the study size and "real life" setting. It may provide new information about rare adverse events or supplement information from RCTs about patients groups that have not been studied in RCTs such as children and pregnant women.

The increased availability of computerized databases containing medical care data, e.g. prescription data, has facilitated analyses of patient-level drug effects on a population-based scale. Such databases have been available and used for pharmacoepidemiological research in North America since the 1980s and included claims data used for reimbursement of health care costs (2). Databases have also been available in Europe, where some databases were developed specifically for research purposes. From January 2004, a research database containing prescription data covering the entire Norwegian population has been available, the Norwegian Prescription Database (NorPD) (3, 4). Before 2004, information about drug use in the entire Norwegian population was only available as sales statistics from pharmacies and wholesalers, i.e. not on an individual level. Therefore, NorPD gives opportunities to study patterns, determinants and consequences of drug use in the population. Furthermore, by using the unique person identity number assigned to all individuals living in Norway, information relevant to the study of drug use may be linked from other health registers, population surveys and biobanks (4).

This thesis focuses on aspects of the epidemiology of asthma drug use, and data from NorPD is the central source of information throughout. The field of pharmacoepidemiology is quite a new research field in Norway and very few population-based observational studies on the use of asthma drugs have been conducted. Inferences about the epidemiology of asthma disease may also be made from studies of asthma drug use, because the asthma drug treatment is intimately linked to asthma. Particularly in school-aged children, adolescents and young adults, there are few overlapping diseases that are treated with asthma drugs. There is some diagnostic and therapeutic overlap with Chronic obstructive pulmonary disease (COPD) in older adults and the studies in this thesis were confined to the population under 30 years of age. Diagnosis of asthma in preschool children is difficult due to unspecific symptoms but this group of children was also studied. There are some advantages of using NorPD data when studying a disease as varied in time, space and within patients as asthma; the data is routinely collected and updated regularly, and covers all age groups and geographical regions continuously. However, issues concerning definition and classification of asthma encountered in epidemiologic asthma research are still present, and these issues are discussed briefly in the following chapters.

1.2 Asthma

1.2.1 Definition, diagnosis and etiology

Asthma is a chronic, inflammatory disease of the airways characterized by recurrent reversible airflow obstruction. The pathogenesis involves several cells and mediators but has not been fully understood, and the definition of asthma is based on the functional consequences of asthma. The airway inflammation is associated with bronchial hyperresponsiveness to a variety of stimuli and causes symptoms such as recurring episodes of wheezing, breathlessness, chest tightness and cough (5). Asthma is a heterogeneous condition and there is great variability within and between individuals in terms of clinical expression, age at onset, and persistence of symptoms over time (6-9). Although it is regarded as a chronic disease, remission and later relapse of asthma during shorter or longer periods is a common feature. The persistence of asthma over time is correlated with the age of onset and there may be several phenotypes of asthma that have different risk factors, severity and long-term outcomes (7, 8, 10). There is increasing awareness of the heterogeneity of asthma but distinct subgroups based on objective criteria have not been identified yet (8, 11).

Asthma is a clinical diagnosis with no single characteristic or test that alone can identify asthma. The diagnosis is based on several components, such as symptom history, clinical examination, lung function tests, airway challenge tests, measurement of allergic status and exclusion of differential diagnoses. The clinical symptoms are variable and non-specific which complicates the diagnosis, particularly in preschoolers where asthma diagnosis is primarily one of exclusion of differential diagnoses (5, 12). Episodes of wheeze is common also in non-asthmatics at this age, e.g. during viral infections, while airflow limitation and inflammation is not easily assessed (12, 13). Middle-aged populations also have differential diagnoses, with COPD becoming a prominent cause of respiratory disease during the fifth decade of life (12).

The etiology of asthma is not fully understood and there is a multitude of suggested risk factors and triggers for asthma, some of which are both. These factors may be classified as host factors and environmental factors. Host factors include genetics, as well as obesity, gender and age. Environmental factors include allergens such as fungal spores and house dust mite, irritants, tobacco smoke and respiratory infections in early life. The "hygiene hypothesis" (14) and variants of this hypothesis suggested that exposure to certain allergens and infections in early life influence the development of the immune system and leads to reduced risk of allergic diseases including asthma. However, evidence supporting this hypothesis is inconclusive and other exposures in utero or early infancy have received increasing focus (15, 16).

1.2.2 Measuring asthma in epidemiological studies

An apparent increase in the occurrence of asthma has been reported during several decades in westernized countries while recent reports suggest that this increase has levelled off (17-20). It has been questioned whether the increase is due to a genuine increase in people suffering from asthma or if it is due to changes in how asthma is measured and perceived (10, 17, 19, 21, 22). Physicians may have changed their criteria for using the label asthma when patients present with respiratory symptoms, especially mild and transient cases (10, 17, 19, 21-25). Furthermore, an increased awareness in the general public and better access to care may have lead to increased perception of respiratory diseases. Regarding comparisons across countries, translation and interpretation of questionnaires on asthma symptoms can be challenging. For instance, the English word "wheeze" is often used in questionnaires but translation is difficult

(26). It has been observed in inter-country questionnaire studies that English-speaking countries report relatively high prevalence of asthma symptoms such as wheeze (27).

An inherent problem of asthma is that there is no single diagnostic test or criterion both necessary and sufficient to diagnose asthma. The diagnosis is based on factors not easily captured in epidemiological studies (e.g. patient history, clinical examination, exclusion of differential diagnosis), and it is therefore challenging to determine the occurrence of asthma in the population. There is currently no agreed upon gold standard for measuring asthma in epidemiological studies (28), and a multitude of definitions of asthma that are different in several domains have been used.

The *source of the data* in epidemiological studies of asthma may come from birth cohorts, census surveys in the general population, or registers such as hospital discharge databases, administrative data from physicians and prescription databases. These data sources have different *types of data* such as questionnaires, telephone or face-to-face interviews, or electronic records from databases. There are also differences in *who reports*, e.g. self-reports, parent-reports or physician reports. The *disease entity* that is measured is highly variable and includes asthma per se (no further specification), specific symptoms of asthma, confirmed doctor diagnosis, drug use for asthma, or physiologic measures (e.g. spirometry or bronchial hyperresponsiveness). However, physiologic measures are rarely available in large population studies. Furthermore, the *time frame* of the measure is important to consider in a time-varying disease such as asthma. The terms “ever” and “current” asthma are commonly used, the latter often operationalized as asthma during last 12 months.

Different combinations of these domains of asthma measures are used and has lead to a multitude of asthma definitions: One recent study reviewed the literature and found 60 different operational definitions in 122 papers on childhood asthma (29). The prevalence varied from 15% to 51% when some of the definitions were applied to an ongoing cohort study of 6-year old children (the children included were “at risk” of developing asthma, possibly explaining the high prevalence figures). Thus, the choice of outcome measure has high impact on the estimated occurrence of asthma and different measures do not identify the same set of individuals.

These issues may contribute to the substantial variability of reported occurrence of asthma in different studies and between countries. A possibly more pressing concern than determining the exact prevalence level in the population is to identify factors that cause asthma. Asthma is heterogeneous over time in the same individual, with remission and relapse of the clinical symptoms over shorter and longer periods (6, 30, 31). This makes it challenging to study risk factors, as the same individual may switch from being regarded as asthmatic to non-asthmatic depending on when the information is collected (28). Moreover, this variability may stem from both changes in exposure to triggers (e.g. seasonal allergy) and from factors inherent in the disease.

Self-reported asthma symptoms and/or doctor-diagnosed asthma are often used in population studies of asthma. However, this way of separating asthmatics from non-asthmatics is queried because of subjective symptom recognition and recall bias (21, 23, 24, 32). Questionnaire studies may also have problems with capturing seasonal variations in asthma, depending on the point in time questionnaires were filled in and the recall period used. Moreover, the generalizability of such studies to the general population may be compromised if the study is conducted only in a local population or narrow age groups.

An alternative method to identify asthmatics in the general population is to utilize data from administrative databases that routinely collect information on the use of health care services. One such data source is prescription registers. The drugs used for asthma are quite specifically used for asthma and the use of drugs to control asthma is a key component in asthma management (5). Thus, drug use could serve as a proxy measure of current asthma. International studies have shown the feasibility of drug prescriptions to identify individuals with asthma (33-36). Administrative registers like prescription databases have some advantages in that they include routinely collected data covering continuous time periods and are not collected on an ad hoc basis. The mandatory and automated capture of drug exposure and other variables diminishes selective reporting and participation, and facilitates the assessment of time sequence of events. Furthermore, these databases often have larger population size than studies dependent on the distribution of a large number of questionnaires. Among the limitations of administrative databases are that data are generated by a complex health care system and it may not always be transparent how the data come about. Furthermore, the collected information is not tailored to the research question.

1.2.3 Occurrence of asthma in the population

As delineated in the previous chapter, determining the occurrence of asthma in the population from published literature is difficult because of considerable variation in the applied definitions of asthma and representativeness of study populations. However, it is generally accepted that asthma is the most common chronic disease among children, and it is also common in the adolescent and adult population (37, 38). It has been estimated to affect as many as 300 million people globally (5).

Two major multi-center collaboration studies regarding asthma have been conducted in different countries: 1) The International Study of Asthma and Allergy in Children (ISAAC) among children and adolescents, and 2) the European Community Respiratory Health Survey (ECRHS) among adults. These studies use standardized questionnaires across countries and at several time points, and have reported large differences between countries in the asthma prevalence level and time trends (38-40). For instance, an ISAAC study reported prevalence of ever asthma ranging from about 2% to over 30%, with similar variations in reported current wheeze (40). The prevalence of asthma has been reported to be increasing globally during the last four decades of the 20th century (18). Some recent studies have reported a further increase while a leveling off or even a decrease in prevalence among children and young adults has been reported in some westernized countries (17, 18, 20, 40-42). This has also been observed in a repeat survey in Norway among 9-11 year olds, especially in girls (43).

There is a relatively large variability between Norwegian population-based studies in the reported prevalence of asthma between age groups, but also in the same age groups. In 4-5 year olds, the prevalence of current asthma has been reported to be 6.5% (44), while a cumulative prevalence of 8.7% and current prevalence of 7.7% has been reported (45). Among 10-year olds, a lifetime prevalence of 20% is reported (46), while current asthma has been reported in respectively 11% (46) and in 5.6% (47). Among adolescents, current asthma has been reported to be between 7 and 10 % (48) while in adults (15-70 years) a prevalence of ever doctor-diagnosed asthma has been reported in 7.6% of males and 10.7% of females (49). These studies were conducted during different time periods, and they were restricted to specific geographical areas and age groups, and they measured different disease entities and phrasings of questions, thus complicating comparisons.

1.2.4 Comorbidities of asthma

Comorbidity may be defined as the occurrence of one or more additional diseases in individuals who have an index disease (50). Asthma is a common disease in the young population and may co-occur (i.e. comorbid) with several diseases and illnesses. The extent and impact of comorbidities in asthmatics has received little attention compared to other chronic diseases like cardiovascular diseases and diabetes. This could in part be due to multimorbidity increasing with age while asthma is most prevalent in young populations (51). It is important to study comorbidities of asthma in the exploration of possible common causes or pathways for development of asthma and other diseases. Furthermore, the consequences of having comorbid diseases and its implications for asthma management are important to characterize. Comorbidities influence several aspects of asthma, such as detection and diagnosis, severity and changes in severity over time, and control of asthma symptoms (52-54). Additionally, the response to asthma therapy may be different and adherence to asthma therapy may decrease (55, 56). The use of health services is reported to be higher in asthmatics with comorbidities, and places an extra burden on the healthcare system and costs (57, 58). Identification and treatment of comorbidities is part of the core management of asthma, especially for more severe cases (5).

Associations between asthma and several conditions have been reported and some of the widely studied conditions are included in management guidelines for asthma. These include allergies, gastro-oesophageal reflux disease (GORD), and bacterial and viral respiratory tract infections (5, 59-61). The presence of allergy is even part of the definition of some proposed asthma phenotypes (61, 62). Other conditions linked to asthma include depression, anxiety and sleep problems (63, 64).

1.3 Treatment of asthma

1.3.1 Guidelines for management of asthma

Several national and international guidelines and expert reports have been compiled to guide physicians in the assessment and management of asthma (5, 65-68). Broadly speaking, guidelines adopt the same approach to asthma management (69). One of the most cited guidelines is the one issued by the Global Initiative for Asthma (GINA), which was launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute in the USA and the World Health Organization. The first report was issued in 1995 and was last updated in

2009 (5). Specific guidance for the management of asthma in preschool children has been published, due to issues concerning diagnosis and pharmacotherapy at this age (13, 68, 70).

Management of asthma includes several components such as monitoring of the disease, education of patients, control of environmental factors and pharmacotherapy. The medical treatment should follow a stepped care approach and the goal is to achieve and maintain control of asthma symptoms (5). Thus, step-up and down in therapy intensity by increasing doses and/or adding or changing type of asthma drugs is guided by the clinical control of asthma, while also taking into account the risk of adverse effects. The limited understanding of the etiology of asthma and identification of specific subgroups of asthma precludes the development of effective prevention strategies, and there is no affirmative evidence for interventions that modify the long-term course of asthma (5, 9, 16, 71-73).

1.3.2 Asthma drugs

The asthma drugs can broadly be classified as long-term controllers and quick-relief drugs but these categories are not mutually exclusive. The *controllers* have mainly anti-inflammatory effects while the relievers act mainly through bronchodilating effects (5, 74). Corticosteroids, with their multiplicity of anti-inflammatory properties, are the most effective controller drugs for the treatment of persistent asthma and have well-documented effect on clinical outcomes. Administration of glucocorticoids through inhalers is preferred over systemic administration as it gives higher local concentration of the drugs in the lung and lower risk of systemic side effects. Systemic administration is recommended for severe uncontrolled asthma and during acute exacerbations. Other controllers available in Norway are leukotriene receptor antagonists, long-acting β_2-agonists (LABA), cromones, xanthine derivatives (theophylline) and anti-IgE therapy (omalizumab) (75). These drugs are mainly used as add-on therapy if patients fail to achieve asthma control with inhaled corticosteroids, although leukotriene receptor antagonists may be used as the only controller drug (5, 75). LABA should be used only in combination with other controllers (e.g. corticosteroids) due to risk of serious adverse events during monotherapy (5, 75, 76). LABA is available as fixed-dose combination inhalers with corticosteroids as well as single component inhalers.

Relievers should be used as needed to relieve bronchoconstriction and all patients should have these available. They are generally not recommended as monotherapy except for individuals with mild, intermittent asthma (5, 67, 75). The most widely used relievers are inhaled short-

acting β_2-agonists (SABA). Other reliever drugs include anticholinergics and oral short-acting β_2-agonists.

1.3.3 Reimbursement scheme for drugs

All drugs used for asthma are covered by the national tax-supported public health service which all Norwegian citizens have unrestricted access to (77). Reimbursement should be granted only if the patient has a chronic condition where long term drug treatment is needed. "Long term" is operationalized as needing more than 3 months of regular or intermittent treatment during one year. Patients pay 38% of drug costs but no more than 520 NOK per 3 months treatment (2010). Furthermore, there is a ceiling for patient co-payment per year for reimbursed drugs, physician visits, outpatient visits and some other healthcare expenses (1840 NOK in 2010). There is no co-payment for children less than 16 years of age (12 years of age before 2010 and 7 years of age before 2006).

The system for general reimbursement of drugs is a "positive list" system, based on a list of diseases or conditions for which specified drugs can be reimbursed. The Norwegian Medical Products Agency maintains the list of drugs and corresponding diagnosis that is eligible for general reimbursement (78). If a drug or diagnosis has not been granted general reimbursement, physicians may apply on behalf of the patient for individual reimbursement of the drug treatment.

Physicians write a specific reimbursement code on prescriptions deemed eligible for general reimbursement. Earlier, the reimbursement codes were numbers that corresponded to specific diseases or disease groups, and asthma and COPD had the same number code. From July 2006, asthma and COPD were differentiated in the reimbursement system by assigning them different number codes. From March 2008, all number codes were substituted with codes from two diagnostic coding systems: The International Classification of Diseases version 10 (ICD-10) and the International Classification of Primary Care version 2 (ICPC-2). After a one-year transition period, all filled prescriptions with reimbursement were required to have diagnostic codes from 3 March 2009.

1.3.4 Occurrence of asthma drug use in the population

There are few Norwegian studies of the extent of asthma drug use in the general population. One study conducted in four Norwegian counties among 15-16 year olds during 2000-2002 found the self-reported asthma drug use during the previous four weeks to be 5.8% in males 7.0% in females (79). An ECRHS study in 14 countries among 20-48 year olds studied the prevalence of self-reported asthma drug use during the previous 12 months (80). In the Norwegian sample, the prevalence was 3.6% in the first survey (1990-1994) and 7.7% in the second survey (1998-2003). A prescription database study of the entire Norwegian population under 19 years of age estimated the one-year prevalence of different categories of asthma drug use during 2004 (81). 9.1% of the population used any drug for obstructive airways disease (Anatomical Therapeutic Chemical (ATC) code R03), while 5.4% of the population used inhaled asthma drugs (R03AC, R03AK, R03BA) that were reimbursed for use in asthma. The prevalence was 4.6% in girls and 6.2% in boys and the gender difference varied by age; a higher prevalence was observed in males during childhood, and shifted to a higher prevalence in females during adolescence.

The prevalence of asthma drug use in young adults has not been widely investigated in population-based studies. One Danish prescription study conducted in 1990-91 found a one-year prevalence of asthma drug use in 20-44 year olds to be 3.6% (82). The aforementioned ECRHS study in 20-48 year olds reported overall prevalence in all 14 countries of 6.8% (1990-1994) and 9.5% (1998-2003) (80). In children and adolescents, studies have been conducted in several European countries and the reported prevalence was highly variable and ranged from 4% to 26% (36, 83-85). However, some studies included all drugs used for obstructive airways disease (ATC code R03). Some of these drug classes may be used for other indications that asthma, such as unspecific respiratory tract symptoms and infections, especially in preschool children. Thus, there may be significant heterogeneity in the populations included in these studies.

2 AIMS OF THE STUDIES

The main objectives of this thesis were to study issues related to asthma in the Norwegian population of children, adolescents and young adults. Three areas were studied:

- Asthma drug use.
- Asthma drug use as a proxy measure for asthma.
- Additional diseases and drug treatments occurring in individuals with asthma.

The specific research questions to answer were:

1. Examine the validity of maternal reports of asthma drug use (paper I).
2. Examine the validity of dispensed asthma drugs as a proxy measure of asthma (paper I).
3. Study the gender- and age-specific annual prevalence and incidence and the persistence to asthma drug use (paper II).
4. Explore the type of asthma drugs used (paper II).
5. Examine whether young adults with asthma are at higher risk of initiating use of hypnotics (paper III).
6. Examine whether specific chronic conditions and antimicrobial treatment occur more frequently in asthmatics than in the general population (paper IV).

3 MATERIALS AND METHODS

3.1 Sources of data

The papers in this thesis are based on data from two population registers, one health survey one birth cohort study, and one population census: The Norwegian Prescription Database (NorPD) (paper I-IV); Data from a pilot questionnaire distributed to mothers of 7-year old children in the Norwegian Mother and Child (MoBa) cohort study (paper I); The Youth Health Surveys (YHS) from five Norwegian counties (paper III); The Population and Housing Census (PHC) conducted in 2001 (paper IV); The Central Population Register (CPR) (paper II, III and IV).

Data from NorPD served as the outcome variable in all papers and were linked at the individual level to the other data sources (paper I-IV). Data linkage was conducted by using the unique, encrypted 11-digit person identity number (PIN), assigned to all individuals residing in Norway (3, 86).

3.1.1 Norwegian Prescription Database (NorPD)

From 1st January 2004, it was mandatory for all Norwegian pharmacies to send electronic data on all dispensed drugs to the NorPD (in Norwegian: *Reseptregisteret*). NorPD is run and owned by the Institute of Public Health (3, 4, 87). Included in the database are dispensed drugs with and without reimbursement from prescribers of any occupation and specialty. I.e. NorPD includes drugs prescribed by specialists in secondary or tertiary care for use in the ambulatory care setting. Thus, NorPD covers dispensed drugs for the entire non-institutionalized population and data are stored on an individual patient level. Drugs delivered to nursing homes and to physicians for use in their own practice are included in NorPD as well, but these data are not on the patient level.

NorPD stores information about the *patient* (encrypted PIN, gender, age), the *prescriber* of the drug (encrypted prescriber identity number, specialty), the *pharmacy* dispensing the drug (pharmacy identifier, location) and information about the dispensed *drug* (date of dispensing, name and ATC code of drug, reimbursement status) (this is not an exhaustive variable list). All drugs in Norway are classified according to the Anatomical Therapeutic Chemical

classification system (ATC code) and these codes are used for identification of drugs and drug classes (88).

NorPD data were used in all papers (I-IV) of this thesis.

3.1.2 Norwegian Mother and Child Cohort Study (MoBa)

The MoBa cohort study (in Norwegian: D*en norske mor og barn-undersøkelsen*) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health and enrolled over 100,000 pregnancies during 1999-2008 (89, 90). Pregnant women from all over Norway were invited by mail to participate in connection with the routine ultrasound examination offered to all pregnant women at 17-18 weeks of gestation. A total of 38.5% of the women invited during 1999-2008 gave consent to participate (91). Mothers received three questionnaires during pregnancy while fathers received one. After birth, both mothers and fathers receive several questionnaires at specified ages of the child. Additional information about the MoBa study and questionnaires are available on the website of the Institute of Public Health (90). During March-June 2008 mothers of 3,394 children in MoBa who had reached 7 years of age received a pilot questionnaire, which included several questions regarding asthma and allergy (see questionnaire in appendix I).

The study in paper I rested on the pilot questionnaire.

3.1.3 Youth Health Surveys (YHS)

The population-based YHS (in Norwegian: *Ungdomsundersøkelsene*) were conducted during 2000-2005 in 6 of 19 Norwegian counties: Oslo 2000-2001; Hedmark 2001; Oppland 2002; Finnmark 2003; Nordland 2004; Troms 2002-2003 and 2005 (only in the main city Tromsø) (92). The YHS included questions on health, lifestyle, socioeconomic factors and living conditions (see questionnaire in appendix II). 10 years of school is compulsory in Norway and most students are 15-16 years of age at the time. All 10th grade students in each respective county were invited to fill in a self-administered questionnaire during two lessons in the spring term. A project assistant was present in each classroom to clear up possible misunderstandings and questionnaires were left at school to be completed by students not present. In Oslo, Oppland and Hedmark, questionnaires were sent to the home of those that did not respond during the course of the school year. In Troms and Finnmark, respectively

9.5% and 23% of the schools did not participate in the school-based survey and students received a postal questionnaire and one reminder instead. Both the mail survey and the school-based survey from these counties had lower participation rate than in the other counties (Troms 2002-2003; 81.7%, Finnmark 2003; 71.1%). The mean response rate in all six counties was 86.5%.

Paper III was based on the surveys conducted in five counties during 2000-2003 (15,436 individuals invited, 86% response rate).

3.1.4 Population and Housing Census (PHC)

The PHC (in Norwegian: *Folke- og boligtellingen*) consists of data from several administrative registers as well as data from a questionnaire sent to every family in Norway (93). The census has been conducted about every 10 years and it is mandatory to participate for all residents. The last census was conducted in 2001 and included all persons, also foreign citizens, considered resident in Norway on 3 November 2001 according to the Central Population Register (CPR).

Paper IV was based on the census conducted in 2001. Only variables from registers were utilized (encrypted PIN, date of birth and gender).

3.1.5 Central Population Register (CPR)

The CPR (in Norwegian: *Folkeregisteret*) is owned by the Norwegian Tax Administration while Statistics Norway maintain the register for research purposes. It includes continuously updated information about every person residing in Norway (94, 95). Information from the CPR used in the present thesis was the encrypted PIN and the date of death and emigration.

Aggregated data from CPR by gender and age groups on the number of people residing in Norway was retrieved from the website of Statistics Norway (paper II) (96). Individual level data files from CPR were used to determine if persons were alive (paper II-IV) and still residing in Norway (paper III and IV).

3.2 Definition of asthma drug use and asthma

The use of asthma drugs in the Norwegian population was examined in the present thesis by analyzing data on filled prescriptions from NorPD. In paper I, the congruence between asthma drug use as registered in NorPD and maternal reports of asthma drug use was examined. In paper II, the use of asthma drugs in the entire Norwegian population was examined by using NorPD data. As delineated in chapter 1.2.2, the use of asthma drugs is a core component in the management of asthma and may serve as a proxy measure of current, active asthma needing drug treatment. In paper I, the congruence of this proxy measure and maternally reported asthma was examined. In paper II-IV, the proxy measure was utilized to identify individuals with current asthma from the study populations.

The asthma drug classes to include in a proxy measure of asthma has been explored in a previous NorPD study among children and adolescents (81). In that study, inhaled asthma drugs were included: Short-acting (SABA) and long-acting (LABA) inhaled β_2-agonists; inhaled corticosteroids (ICS); and fixed dose combinations of β_2-agonists and corticosteroids (FDC). In paper I-IV of the present thesis, leukotriene receptor antagonists (LTRA) were also included in the proxy measure. LTRA has during the 2000s received increasing importance in asthma therapy, and may be used as the only controller drug instead of corticosteroids (5, 75). An increasing use of LTRA in Norway has been observed (87, 97). Thus, the most commonly used asthma drugs classes were included in the proxy and pooled together as one variable (see appendix IV for an overview of drug classes in ATC group R03 Obstructive airway diseases).

The asthma drug classes included in the proxy are the mainstay of asthma pharmacotherapy according to guidelines and treatment recommendations (5, 65, 67, 75). Other drugs registered in Norway with indication for use in asthma include anticholinergics, cromoglicic acid, xanthine derivatives (theophylline), anti-IgE therapy (omalizumab), and oral corticosteroids. Virtually all those who received these other asthma drug classes had also received at least one of the drugs in the proxy measure during the same year (paper II), i.e. these other asthma drugs were used as add-on therapy.

For paper II and IV, the definition of the proxy measure was further restricted by only including prescriptions with the specific reimbursement code for asthma. Thus, the reimbursement code was used as a substitute for diagnostic codes (see chapter 1.3.3 for details

about the reimbursement system). Except for these reimbursement codes, it is not mandatory for physicians to provide diagnostic information on prescriptions. Physicians may, together with the dosage information, provide information about the intended use of the drug and this is stored as a free text variable in NorPD.

3.3 Study populations

Table 1 summarizes the study populations and setting in paper I-IV.

Table 1: Study populations and setting

	Paper I	Paper II	Paper III	Paper IV
Study population source	MoBa pilot (birth cohort)	NorPD (prescription database)	YHS 2000-2003 (health survey)	NorPD[a] (prescription database)
Area covered	Norway	Norway	5 of 19 counties	Norway
Participation rate	61%[b]	Mandatory inclusion for all Norwegian residents	86%[c]	Mandatory inclusion for all Norwegian residents
Indivduals invited/included	MoBa children over 7 years of age	Idividuals filling prescriptions on asthma drugs[d]	All students in 10th grade in each county	Idividuals filling prescriptions on asthma drugs[d]
Study design	Validity	Crossectional and cohort	Cohort	Crossectional
Study population included in analysis	n=2,056	n=92,074[e]	n=10,164	n=37,060[f]
Outcome measured in period	During 2007-2008[g]	2005-2007	Janaury 2005 - July 2010	3 March 2009 - 2 March 2010
age during outcome period (yrs)	7-8	2-29	17-27[h]	8-29

Abbreviations: MoBa, Norwegian Mother and Child Cohort Study; NorPD, Norwegian Prescription Database; PHC, Population and Housing Census; YHS, Youth Health Surveys.

[a] The study population was identified from NorPD data for participants in the PHC conducted in 2001.

[b] On pilot questionnaire.

[c] 77% gave consent to data linkage.

[d] Only prescriptions with reimbursement for asthma were included.

[e] In 2007 (different study population in each 1-year cross-section).

[f] n=1,239,533 in the standard population (all PHC participants 29 years or less).

[g] During 1-year period prior to completion date of the MoBa questionnaire.

[h] 15-17 years old in the year of YHS participation (2000-2003).

Paper I

The study population was from the MoBa pilot questionnaire distributed to 3,394 mothers of 7-year old children in MoBa. 2,056 respondents (61%) were included in the analysis of validity.

Paper II

The study population included all individuals aged 2-29 years in Norway during 2005-2007 (n~= 1.7 million) who had filled at least one prescription for asthma drugs according to NorPD (n= 92,074 in 2007). Only prescriptions with reimbursement codes for asthma were included. Asthma drugs included were those defined as a proxy measure of asthma, see chapter 3.2. In the persistence analysis, 115 individuals who died during 2005-2007 were excluded.

Paper III

Participants from the YHS conducted during 2000-2003 in five Norwegian counties were included. The surveys from 2004-2005 were excluded to avoid overlapping time periods with NorPD data from 2004 onwards. 15,436 individuals were invited to participate and 13,309 (86%) responded to the questionnaire. 11,947 (77%) gave consent to link data with other registers, signed the consent form and were registered with valid person identity number, participation year and county. From this study population 1,783 individuals were excluded (see Figure I in paper III for details) and 10,164 participants without prior use of hypnotics were included in analysis.

Paper IV

The *standard population* included all persons who participated in the PHC in 2001 who were 29 years or less in 2009. The *study population* consisted of current asthmatics that were identified in the standard population by using the proxy measure for current asthma (see chapter 3.2). Included were those who had filled prescriptions for an asthma drug at least once in the year before and at least once in the year after the index date (3 March 2009). Only prescriptions with reimbursement codes for asthma were included.

3.4 Study design

Paper I

Data on filled prescriptions for asthma drugs during one year in NorPD were compared to maternal reports on questionnaires from MoBa regarding: 1) asthma drug use during the previous year; 2) the presence of ever asthma, current asthma and asthma diagnosis. The MoBa questionnaire was distributed during March-June 2008 to children who had reached 7 years of age. The mothers reported the date of questionnaire completion but for those with missing completion date, the return date of the questionnaire minus 5 days was used. Data from NorPD were extracted for the one-year and the three-year period prior to the completion date. Non-respondents to the MoBa questionnaire were also linked to NorPD data to assess the proportion among responders and non-responders filling prescriptions for asthma drugs.

Paper II

Use of asthma drugs as registered in the NorPD during 2005-2007 was studied. A combination of study designs was used. Prevalence, incidence and types of drugs used were analyzed as annual cross-sections among 2-29 year olds. The size of the source population (the age-specific Norwegian population) and the study population (asthma drug users) was therefore different for each annual cross-section. Persistence to drug use was examined as a cohort study of all asthma drug users in 2005 (i.e. prevalent users) that were followed during 2006 and 2007.

Paper III

A cohort study of hypnotic use among YHS participants (2000-2003) was conducted by record-linkage to NorPD data (January 2004 - July 2010). NorPD data from 2004 was used to define of the main independent variable (asthma), while NorPD data from January 2005 - July 2010 was used as outcome variable (hypnotic use). 10,164 individuals at risk of initiating (i.e. incident) hypnotic use during the outcome period were studied.

Paper IV

This was a one-year cross-sectional study of the occurrence of comorbidities among asthmatics participating in the PHC 2001. NorPD data were linked with PHC data and asthmatics were identified by filled prescriptions on asthma drugs. The outcome variable (presence of comorbidity, yes/no) was defined from reimbursement codes on filled prescriptions (ICD-10 or ICPC-2 codes) that corresponded to selected comorbidities during a

one-year period. The rate of occurrence of each comorbidity in the asthma population was compared to that in the standard population (all participants in PHC).

3.5 Outcome variables

The outcomes measured in paper I-IV were all defined by filled prescriptions in NorPD (Table 2). In paper I, maternal reports on questionnaire were also used.

Table 2: Summary of outcomes measured in paper I-IV.

Paper	Domain measured	Outcome measure	Definition	Variable type
I	Asthma drug use and asthma	Sensitivity and specificty	Filled prescription during a 1-year period[a]	Yes / no
			Maternal-reported asthma drug use during previous year[b]	Yes / no
			Maternal-reported ever, current and physician-diagnosed asthma	4 categories
II	Asthma drug use	Prevalence proportion	Filled prescription during calendar year	Yes / no
		Incidence proportion	Filled prescription during calendar year after a run-in period with no filled prescription[c]	Yes / no
		Persistence to treatment	Filled prescriptions in 3 consecutive calendar-years	Yes / no
		Drug types used	Filled prescription during calendar year	4 categories
III	Hypnotic use	Incidence proportion	Filled prescription during calendar year	Yes / no
		Incidence rate ratio	Number of filled prescriptions	Count
		Cumulative hazard	Time to event (filled prescription)	Continous
IV	Comorbidity	Standardized Morbidity Ratio[d]	Filled prescription with specific diagnostic code during a 1-year period	Yes / no

[a] During the 1-year period prior to the completion date of MoBa questionnaire. Also examined the 3-year period prior to the completion date.

[b] Also examined reports on open-ended questions about names of specific asthma drugs used.

[c] Filled prescription during calendar-year and no filled prescription in previous 3 calendar-years.

[d] Calculated separately for nine chronic diseases and for antimicrobial treatment.

Paper I

Use of asthma drugs as recorded in NorPD was compared with maternal reports about asthma drug use and asthma disease on the MoBa questionnaire. Included asthma drugs from NorPD

are given in chapter 3.2. Measures of validity were sensitivity and specificity. Positive predictive value and negative predictive values were also calculated. The MoBa questionnaire is included in appendix I.

Validity of maternal reports of asthma:

Maternal reports of asthma drug use in the MoBa questionnaire was compared to filled prescriptions on asthma drugs recorded in NorPD (reference standard). Use of asthma drugs in MoBa was defined by answers from mothers to the question "has the child used spray, inhaler or other medications for asthma during the past year?'' (yes/no). We examined the congruence between answers on this question and filled prescriptions in NorPD during the one-year and the three-year period prior to completion of the questionnaire. Maternal reports on open-ended questions about the name of asthma drugs used regularly or during attacks were also compared to NorPD data (salbutamol and fluticasone analyzed).

Validity of asthma drug prescriptions as a proxy for asthma:

Filled prescriptions for asthma drugs as a proxy measure of current asthma was compared to maternal reports of asthma disease in MoBa (reference standard). Asthma was defined in MoBa by mothers reporting on the question ''has the child ever experienced any of the following long-lasting illnesses or health problems?''. For each condition listed, the mothers ticked whether the child had ever experienced the condition, if the child still had the condition, and if a physician had verified it. Based on answers to these three questions we classified the participants into four mutually exclusive groups (see appendix III). NorPD data on prescriptions filled during the one-year and three-year period prior to completion of the MoBa questionnaire were used. Both children with and without filled prescriptions were included in the validity estimations.

Paper II

The outcome of interest was the use of any of the asthma drugs included in the proxy measure of current asthma, see chapter 3.2. Use of the asthma drugs was defined as filling prescriptions during 2005-2007. Four measures of drug use were calculated: two measures with the age-specific Norwegian population as denominator (prevalence and incidence proportions), and two measures with all prevalent asthma drug users during one year as denominator (persistence and type of asthma drug used).

Prevalence proportion:

Prevalence proportion was measured as a series of one-year cross-sections (2005-2007) where the nominator was individuals filling at least one prescription on asthma drugs during each year. The denominator was the gender- and age-specific Norwegian population in each year (midyear population). The prevalence proportion filling at least two prescriptions (on different dates) during the one-year periods was estimated as well.

Incidence proportion:

We estimated incidence proportion by counting new users in 2007. New users were persons with no filled prescriptions in 2004-2006 and with at least one prescription in 2007 (drug-free run-in period of 3 calendar years (98)). The denominator ("population at risk") was the gender- and age-specific Norwegian population as of 1 January 2007, minus individuals who had filled prescriptions during the previous 3-year period (2004–2006).

Persistence:

Persistence to treatment was assessed according to the minimum refill model (99). It was estimated as the proportion of the prevalent asthma drug users in 2005 being persistent to drug use the two subsequent years. The criterion for being categorized as "persistent" was: Filling at least one prescription in 2006 (1-year persistence), and at least one prescription in both 2006 and 2007 (2-year persistence).

Type of asthma drugs used:

Users of asthma drugs in each calendar year were classified by type of drug used. Individuals who received more than one type of asthma drug was assigned to the asthma drug group with the higher rank (i.e. groups were mutually exclusive): Inhaled β_2-agonists (IBA), inhaled corticosteroids (ICS), Fixed dose combinations of β_2-agonists and corticosteroids (FDC) and Leukotriene receptor antagonists (LTRA) (highest rank). The proportion of all prevalent users in each group was calculated.

Paper III

We studied initiation of hypnotic drugs use during January 2005–July 2010 among individuals without previous use of hypnotics (i.e. incident or new users). Hypnotic drugs were pooled together as one outcome variable and defined as: Benzodiazepines classified as hypnotics (ATC code N05CD), and the z-hypnotics zopiclone and zolpidem (N05CF). Three risk measures of the outcome were estimated.

Incidence proportion:

Incidence proportion was estimated as the proportion of the study population filling prescriptions during follow-up (dichotomous variable of 0 prescriptions versus 1 or more prescriptions).

Incidence rate ratio:

Incidence rate ratio was estimated with a count variable of number of prescriptions filled during follow-up. Recurring events were examined, i.e. individuals remained at risk of filling another prescription after their first prescription.

Cumulative hazard:

Cumulative hazard was estimated with all prescriptions filled on different dates included (multiple recurring events).

Paper IV

Diagnostic codes from reimbursed drug prescriptions registered in NorPD were used to define the outcome (comorbid diseases). The presence of a disease was defined as filling at least one reimbursed prescription with a diagnostic code during a 1-year period (confer chapter 1.3.3 for details on the reimbursement system). Nine chronic diseases were examined: Attention Deficit Hyperactivity Disorder (ADHD, denoted "hyperkinetic disorder" in ICD-10 and ICPC-2), epilepsy, migraine, mental illness, cardiovascular disease, diabetes (type 1 and 2), autoimmune disorders, gastro-oesophageal reflux disease (GORD) and allergy. See Table 1 in paper IV for details on diagnostic codes included. Outcome was measured by Standardized Morbidity Ratios (SMR).

To study the occurrence of antimicrobial treatment (normally not reimbursed), ATC codes on drugs dispensed were used instead of diagnostic codes. Antibacterials recommended in Norwegian guidelines(100) for use in upper and lower respiratory tract infections were included, as well as antivirals used for influenza virus infections. See Table 1 in paper IV for details on ATC codes included.

3.6 Strata and independent variables

Paper I

Stratified analysis was not performed but all children had turned 7 years of age the year before the MoBa questionnaires were distributed and completed.

Paper II

All four measures of asthma drug use were stratified by gender and one-year age groups. For presentation in tables, age groups were collapsed into five groups.

Paper III

Asthma was the main independent variable. In the YHS, participants were asked "have you, or have you had asthma" with answer alternatives yes or no. This information was combined with the proxy measure for current asthma, operationalized as filling at least one prescription on asthma drugs during 2004 (see chapter 3.2 for details). Hence, receiving asthma drugs in 2004 was used as a proxy measure of whether asthma was active (current) in the year prior to the start of follow-up. Individuals were classified into one of four asthma groups, see Figure 1 in paper III: 1) no asthma (reference group); 2) not active asthma; 3) active asthma recently developed; 4) still active asthma. Other independent variables that were adjusted for in incidence rate ratio estimation were self-reported on the YHS questionnaire: Age, gender, mental distress (Hopkins Symptom Check List (HSCL-10) mean score), eczema, smoking habits, alcohol consumption, and plans for education.

Paper IV

The proxy measure for current asthma (see chapter 3.2) was used to define the study population of current asthmatics and was compared to the general population. Results were stratified by gender and two age groups (8-19 years, 20-29 years).

3.7 Statistical analyses/methods

Data preparation and statistical analyses were performed by using Spss 14.0.1 and 17.0.1 and Stata SE 9.2 and 10.0 for Windows.

Paper I

95% confidence intervals were calculated for the validity measures by the continuity-corrected score interval method (101).

Paper II

Not applicable.

Paper III

The asthma groups were introduced as three dummy variables with the 'no asthma' group as reference in the incidence rate ratio and cumulative hazard estimation. *Incidence rate ratios* were estimated by negative binomial regression, which account for higher variance than expected in the Poisson model. In the adjusted model, mental distress (HSCL-10), eczema, education plans and gender were entered as dichotomous variables and smoking, alcohol consumption and age as continuous variables. *Cumulative hazard* estimates for asthma groups were constructed by using Anderson and Gill's method for defining time to event in recurrent events data, taking into account the dependency between recurring prescriptions filled by one individual (102).

Paper IV

The number of comorbidities occurring in the asthma population and in the general population was examined and presented as the proportion of the populations having respectively 0, 1, 2, 3, and 4 or more comorbidities. Associations of asthma with specific comorbidities were examined by calculating Standardized Morbidity Ratios (SMR). Standard rates for 1-year age-specific groups in the general population were calculated and applied to the asthma population separately for males and females. SMRs were calculated with 95% confidence intervals from the Poisson distribution. The magnitude of the SMRs are not directly comparable between the different genders and age groups, because they are compared to different standard populations.

3.8 Ethical considerations

The studies were endorsed by the Regional Committee for Medical Research Ethics and data linkage was approved by The Norwegian Data Inspectorate. The Research Council of Norway funded this work (project number 175314/v50).

4 SYNOPSIS OF PAPERS

4.1 Paper I

Furu K, Karlstad Ø, Skurtveit S, Håberg SE, Nafstad P, London SJ, Nystad W. High validity of mother-reported use of antiasthmatics among children: a comparison with a population-based prescription database. Journal of Clinical Epidemiology 2011;64:878-84.

Objectives

1. To examine the validity of maternal reports of asthma drug use on a questionnaire from the Norwegian Mother and Child cohort study (MoBa), and
2. To examine the validity of dispensed asthma drugs in the Norwegian Prescription Database (NorPD) as a proxy measure of asthma.

Materials and methods

Mothers of 2,056 7-year old children in MoBa responded to a pilot questionnaire (61% response rate). Data from NorPD was linked to both responders and non-responders of the questionnaire. NorPD data on dispensed asthma drugs served as reference standard for aim 1, while maternal reports of asthma in MoBa served as the reference standard for aim 2.

Results

- The one-year prevalence of having been dispensed asthma drugs in 2008 (NorPD) was 7.6% among responders and 7.9% among non-responders.

Aim 1:

- The sensitivity of the indication-specific MoBa question about *asthma drug use during the previous year* was 85%, compared to NorPD data on dispensed asthma drugs during same period (reference). The specificity was 97%.
- Among 61 children who had no dispensed drug in the previous year despite mother-reported use, 52% had been dispensed drugs 1-3 years ago.
- Open-ended questions about *names of asthma drugs used* had lower sensitivity (salbutamol 72%; fluticasone 74%) and higher specificity (salbutamol 98%; fluticasone 99%).

Aim 2:

- *Current asthma* was reported in 6.5% of children while c*urrent and physician-diagnosed asthma* was reported in 5.9% of children (MoBa).

- The sensitivity of dispensed asthma drugs during the previous year (NorPD) to identify children with *current and physician-diagnosed asthma* (MoBa) was 80%.
- The sensitivity was 55% for *current but not physician-diagnosed asthma*, and 18% for *asthma in the past*.
- Only 1.2% of children with *no reported asthma* had been dispensed asthma drugs in the preceding year.
- If the data extraction period for NorPD was extended from the previous year to previous three years, sensitivity increased and specificity decreased.

Conclusions

Mother-reported use of asthma drugs during the previous year among children was highly valid compared with records of dispensed drugs as reference standard. Prescription data on dispensed asthma drugs could be a useful proxy for identifying individuals with current asthma in the population.

4.2 Paper II

Karlstad Ø, Nafstad P, Tverdal A, Skurtveit S, Furu K. Prevalence, incidence and persistence of anti-asthma medication use in 2- to 29-year-olds: a nationwide prescription study. European Journal of Clinical Pharmacology 2010;66:399-406.

Objectives

To explore asthma drug use in the entire Norwegian population aged 2–29 years during 2005–2007 by examining: The gender- and age-specific annual prevalence and incidence of asthma drug use, and the proportion of asthma drug users persistent to treatment for 3 years, and the type of asthma drugs used.

Materials and methods

Data were retrieved from the Norwegian Prescription Database (NorPD) for all individuals 2–29 years old who received asthma drugs with reimbursement for asthma during 2005–2007.

Results

Prevalence and incidence:

- The annual prevalence was relatively stable during 2005-2007.
- Annual prevalence in 2007 of receiving drugs *once* was 5.9% (males) and 5.0% (females), while prevalence of receiving drugs at least *twice* was 3.4% (males) and 2.7% (females).
- Incidence of receiving asthma drugs in 2007, with three calendar years of drug-free run-in period, was 1.5% in both males and females. Incidences increased to 2.3% and 1.7% when the run-in period was shortened to one and two years, respectively.
- For both genders, the general trend by age was a decrease from the highest levels in 2-year olds to lowest levels in 20-29 year olds. During adolescence, an increase was observed among females that was not observed in males.
- Males had higher prevalence and incidence levels in the youngest age groups but levels for females surpassed males at 14-16 years of age.

Persistence to treatment:

- Among individuals who received asthma drugs in 2005, 61% also received drug in 2006, while 45% received drug in both 2006 and 2007.
- 10% received drug in 2005 and 2007 without receiving drug in the intervening year (2006).

Type of asthma drug used:

- The type of asthma drug received was substantially different by age but not by gender.

- A high share of preschool children were on ICS treatment (69%), shifting gradually to high shares on FDC (42%) or IBA monotherapy (35%) in 20-29 year olds.
- The share of all asthma drug users who did not receive any asthma controller drug (ICS, FDC or LTRA) increased from 14% in preschoolers to 35% in 20-29 year olds.
- 39% of LABA users in 2007 did not receive any inhaled corticosteroids (ICS or FDC) during the three preceding calendar years. These individuals constituted 1.5% of all asthma drug users in 2007.

Conclusions

Annual prevalence of asthma drug use in 2-29 year olds was stable during 2005–2007. The gender- and age-specific profile of prevalence and incidence correspond well with studies of asthma prevalence and incidence. Fewer than half the individuals filled prescriptions regularly over a 3-year period. The type of asthma drugs used was substantially different by age, with a gradual shift from ICS treatment in preschoolers to FDC or IBA monotherapy in older age groups.

4.3 Paper III

Øystein Karlstad, Aage Tverdal, Svetlana Skurtveit, Per Nafstad and Kari Furu. A prospective study of asthma and subsequent use of hypnotics in young adults. Pharmacoepidemiology and Drug Safety 2011;20:370-7.

Objectives/

To investigate whether young adults with asthma are at higher risk of initiating use of hypnotics.

Materials and methods

10,164 (86% response rate) 15-17 year olds from the Youth Health Surveys (YHS) with no previous use of hypnotics were linked to the Norwegian Prescription Database (NorPD). Four asthma groups were defined based on self-reported asthma (YHS) and asthma drug use (NorPD). The outcome was filling prescriptions on hypnotics during January 2005 – July 2010. Incidence proportions, Incidence rate ratios (IRR) and cumulative hazards were estimated. IRR was adjusted for potential confounders (illnesses, lifestyle and sociodemographic factors).

Results

- The incidence proportion was 6.1%, ranging from 5.7% in the no asthma group to 9.5% in active recently developed asthma group.
- The crude IRR was 1.35 (CI: 0.93–1.95) for not active asthma, 4.18 (1.83–9.55) for active recently developed asthma, and 1.63 (0.85–3.14) for still active asthma (no asthma group as reference).
- Adjusted IRR for active recently developed asthma group changed to 4.72 (2.07–10.75) while the other groups remained statistically not significant.
- Cumulative hazard functions were significantly different for the four groups, with highest hazard for the still active asthma group early on, but surpassed by the active recently developed asthma group after about 3 years of follow-up.
- Results were robust towards changes in study design and statistical methods.

Conclusions

In this prospective study of young adults in a general population setting, asthmatics had an increased risk of initiating hypnotic use. We observed a substantial differences in risk between asthma groups, with higher risk among asthmatics who recently received asthma drugs.

4.4 Paper IV

Karlstad Ø, Nafstad P, Tverdal A, Skurtveit S, Furu K. Comorbidities in an asthma population 8-29 years old - a study from the Norwegian Prescription Database. Manuscript accepted for publication in Pharmacoepidemiology and Drug Safety, July 2011.

Objectives

To examine occurrence of chronic diseases and antimicrobial treatment (comorbidities) in an asthma population 8-29 years old, compared to the occurrence in the Norwegian population.

Materials and methods

The asthma population was identified by dispensed asthma drugs in the Norwegian Prescription Database (NorPD). The occurrence of nine chronic diseases (comorbidities) was identified by received prescriptions with specific diagnostic codes (reimbursement codes) during one year: ADHD, epilepsy, migraine, mental illness, cardiovascular disease, diabetes, autoimmune disorders, GORD, allergy. Antibacterials for respiratory tract infections and antivirals were examined by drug class identification (ATC codes). Standardized Morbidity Ratio (SMR) for each comorbidity in the asthma population was calculated from the age-specific general population.

Results

- 59% of asthmatics had at least one of nine chronic comorbidities examined, compared to 18% in the general population.
- 6% of males and 8% of females had more than one of the chronic comorbidities.
- When antimicrobial treatment was included, 69% (male) and 71% (female) asthmatics had at least one comorbidity, compared to 30% and 34% in the general population.
- SMR estimates were consistently increased in both age groups and genders for all diseases except diabetes (range 0.9-1.4).
- Allergy and GORD had highest SMR (range 3.2-4.8) while the other comorbidities were in the range 1.2-2.5.

Conclusions

By using a nationwide prescription database containing diagnostic codes on reimbursed prescriptions, an excess occurrence of comorbidities in the young population of asthmatics was observed, compared to the general population of Norway. A majority of asthmatics had one comorbidity, while few had more than one.

5 DISCUSSION

5.1 General discussion

5.1.1 Use of asthma drugs

The prevalence of asthma drug use was stable during 2005-2007 among 2-29 year olds and was 5.5% in 2007 (paper II). For children and adolescents, our prevalence estimates are in the lower end compared to other studies: High levels (12-26%) have been reported in Italy and the USA (84, 103-105), while lower levels (4-8%) have been reported in the Netherlands, Denmark and the UK (36, 83, 85, 106, 107). In adults 20-29 years old, we found a stable prevalence during 2005-2007 that was 3.3% in males and 4.3% in females in 2007 (paper II). There are few studies among adults on the prevalence of asthma drug use. A Swedish study found a prevalence of 4.2% (males) and 5.9% (females) for any drug from ATC group R03 in 18-44 year olds in 2007 (108). A study from the European Community Respiratory Health Survey (ECRHS) reported a one-year prevalence of self-reported asthma drug use in Norwegians 20-48 year olds to be 3.6% (1990-1994), increasing to 7.7% (1998-2003) (80). The overall prevalence for all 14 countries of this ECRHS study was 6.8% (1990-1994) and 9.5% (1998-2003).

The aforementioned studies from different countries give crude numbers indicating which countries have higher and lower levels of asthma drug use. However, differences in age groups and definition of asthma drugs have great impact on the level of the prevalence estimates. For example, some studies included all drugs in ATC group R03 while other studies applied some reasoning to select specific respiratory drugs. Furthermore, some studies had access to diagnostic codes and confined populations to patients with physician-diagnosed asthma. Thus, it is likely that the study populations are heterogeneous.

The gender- and age-profile of asthma drug use in children and adolescents shows highest prevalence among the youngest age groups. Males had higher prevalence until adolescence, when an increase in prevalence is present in females and surpasses males from about 15-16 years onwards. The profile was stable during 2005-2007 (paper II) and the same pattern was also found in 2004 (81). Furthermore, the same profile emerges when including only persons who had two or more prescriptions, as when including persons who had one or more prescriptions (see appendix IV). This gender- and age-profile of asthma drug use has been

reported in Canada, the Netherlands and the UK, but not in Italy (84, 109, 110). These data on asthma drug corresponds well with studies of gender differences by age in the occurrence of asthma (48, 111-113).

5.1.2 Type of asthma drugs used

We studied the type of asthma drugs used by the Norwegian population 2-29 years of age in paper II. The assignment of asthma drug users to four mutually excluding drug groups may "preclude" some patterns of use. For example, inhaled corticosteroids (ICS) or fixed dose combinations of β_2-agonists and corticosteroids (FDC) may have been used in the leukotriene receptor antagonists (LTRA) group as well, and shares in the ICS and FDC groups should be regarded as the minimum using inhaled corticosteroids. Nonetheless, paper II gives and overview on asthma drug use of the entire young Norwegian population. The apparent use of inhaled long- and short-acting β_2-agonists (LABA and SABA) as monotherapy is discussed further below.

The safety of using LABA as monotherapy for asthma has been debated since the early 2000s (114-116). Regulatory agencies and guidelines state that LABA should only be used in combination with controller drugs like ICS (5, 75, 76). In paper II, we found that 39% of patients who received LABA during 2007 (1.5% of all asthma drug users) had not received any inhaled corticosteroids as controller drugs during 2005-2007. Taking use of LTRA into account only slightly reduced the share (38%, new unpublished data). Similar results to our finding have been reported for young adults in other countries; LABA monotherapy varied from 18-37% in Swedish counties, while it was reported in 26% and 11% of two American populations (108, 117, 118). The data in paper II are from 2007 and the use of controller drugs may have improved since then as the warnings from drug regulators intensified. Furthermore, the length and intensity of such monotherapy may be important but this was not investigated in our study. Further studies on the pattern and determinants of LABA monotherapy are warranted.

Another finding in paper II was the apparent use of SABA as monotherapy in a large share of adolescents and young adults: The share was 14% in preschoolers and increased to 35% in 20-29 year olds. This may reflect underuse of long-term controller drugs such as ICS. A few studies from Northern Europe have investigated SABA monotherapy and intensity of such use. Uijen et al. reported that 35% of 0-17 years olds on asthma therapy received SABA as

monotherapy (119). Davidsen et al. reported that nearly 20% of young adults with high consumption of inhaled β_2-agonists (IBA) did not receive ICS, with higher shares among low IBA consumers (120). Arnlind et al. reported uneven use of IBA (mostly SABA) among young adults, with a large share of doses being consumed by a small share of the patients (108). Paper II only gives crude data and SABA monotherapy is warranted in patients with mild, intermittent asthma (5). SABA may also have been used once as part of diagnosing respiratory complaints and some patients may have leftover controller drugs from previous years. A study of the intensity (doses and length of use) and determinants of SABA monotherapy is warranted, taking into account use of other asthma drugs. Furthermore, the intensity of SABA consumption may be used as a marker of asthma control in future studies (121, 122).

Our findings indicate that the pharmacotherapy of asthma may not be optimal, and could be due to concerns among patients or parents regarding long-term use of corticosteroids. Asthma therapy may be improved by educating patients on the safety, benefits and the place in therapy for the different asthma drug classes.

5.1.3 Reported asthma drug use compared to prescription data

Maternally reported asthma drug use in 7 year old children was studied for both an indication-specific drug question and for an open-ended question regarding the name of drugs (paper I). We found relatively high sensitivity (85%) and specificity (97%) for the indication-specific question, compared to filled prescriptions during the last year as reference standard. Furthermore, about half of the false positives had in fact received drug prescriptions, but did so 1 to 3 years ago. These children may have had intermittent asthma and had drugs left from earlier treatment episodes, with consequently no need to fill prescriptions during the last year. It may also represent some recall problems as to the exact time children used the drugs during the last 3 years. Our results correspond well with a Danish study among 6-8 year-olds reporting 92% sensitivity and 96% specificity (123). A previous study from the Norwegian Youth Health Surveys in 15-16 year olds reported a lower sensitivity (75%) on the asthma drug use question (124). This may be related to a lower adherence in adolescents, or differences in phrasing of questions and the age group that is reporting. On the open-ended questions regarding the names of the asthma drugs used we found lower sensitivity (range 72-74%) but high specificity (range 98-99%) compared to the indication-specific question. This is in accordance with published literature on phrasing of drug use questions (2).

5.1.4 Asthma drug use as a proxy measure for asthma

Administrative data on drug use may be utilized as a proxy measure of the occurrence of some diseases in the population. Generally, this is feasible if the drugs are used exclusively for one disease (specific) and that all diseased use drugs (sensitive). Insulin used by children with diabetes type 1 is probably the best example. We examined the validity of filled prescriptions on asthma drugs as a proxy measure of asthma in paper I. This proxy measure was utilized to identify current asthmatics in the study populations of paper II-IV.

There is no agreed upon gold standard for defining asthma in epidemiological studies (28). In paper I, maternal reports on a questionnaire regarding asthma in their children were used as reference standard (alloyed gold standard (2)). The children with no reports of asthma by their mothers were correctly identified by the proxy as not using asthma drugs in the previous year (1.2% received drugs) and the previous three years (3.7%, new unpublished data). The ability of the proxy measure to identify children with "current, physician-diagnosed asthma" was relatively high (sensitivity 80%) but may reflect some under-treatment. Alternatively, the capture period of one year in NorPD may be too short to capture all children deemed by their mothers to have current asthma, especially those with seasonal or intermittent asthma. This is supported by the improved sensitivity when increasing the length of the capture period (94% for three years). The proxy was less valid for identifying the two other categories of asthmatics ("current but not physician-diagnosed asthma" and "asthma in the past"). These two asthma groups are probably heterogeneous, with some individuals who should have received drugs and others that should not. Thus, a 100% match between questionnaire and prescription data was not expected. It is difficult to interpret the information that lies in mothers reporting "current but not physician-diagnosed asthma" and only 11 children were in this group. It could include some cases of mild asthma or cases still in the diagnostic process. For the group who had "asthma in the past", 18% had used drugs in the past year while 56% (new unpublished data) had used drugs in the past three years.

International studies have shown the feasibility of using databases with prescriptions as a proxy measure for asthma among children and adolescents (36, 107), and adults (34). Different cut-offs for the number of prescriptions received, length of capture period of prescriptions, and choice of asthma drugs to include in the proxy measure have been analyzed to identify the best-performing proxy measure. These studies used diagnosed asthma, retrieved from physicians, as a dichotomous reference standard. The best-performing proxy

measure using one year of prescription data had sensitivities between 63% and 95%, while specificities were between 87% and 99% (34, 36, 107). It is important to view these result in light of the differences in health care systems, reimbursement schemes and prescribing practices between countries. These factors influence how intimately linked asthma drug prescriptions is to the occurrence of asthma, and results may not be transferable to a Norwegian setting. In Norway, factors such as a well-developed government-financed healthcare system, a high rate of practicing physicians per inhabitants, and low co-payment for reimbursed drugs and physician visits (see chapter 1.3.3) should ensure that asthmatics have good access to asthma treatment.

Our validation study was carried out among mothers of 7-year old children, and the mothers' ability to report should not be substantially changed as children age. However, the proxy measure may not be transferable to all age groups. It is difficult to diagnose asthma in children less than 5 years of age because of variable and non-specific clinical symptoms, while airflow limitation and inflammation is difficult to assess (5, 12, 13). Asthma drugs are probably used during episodes of other respiratory complaints in preschool children who do not have asthma (106), or who have transient asthma complaints that will not persist into school age (7, 9). In adults, both an overlap in diagnosis and drug treatment with COPD will occur and the proxy measure may not be used above 40-50 years of age (12). The validity of this proxy measure is probably best in adolescents and young adults, because overlapping conditions are less prevalent and lung function testing as part of diagnosis is possible. Some mild cases are probably not captured by this proxy measure, as they are more difficult for physicians to detect, diagnose and subsequently prescribe drugs. However, the continuous data collection over several years may enable us to identify individuals who have long periods with remission of asthma (i.e. not used drugs for longer periods). A problem in asthma epidemiology is the transient nature of the disease in many patients, and there are no criteria for diagnosing the resolution of asthma. The same individual may switch from being regarded as asthmatic to nonasthmatic depending on when information is collected (28). Asthma should be regarded as a continuum rather than a dichotomy, and may be a syndrome arising from several pathways (125, 126). Thus, longer follow-up than one year is needed to separate cases of complete remission from cases in a temporary quiescent state. In the incidence and persistence analysis (paper II), 3-4 years of NorPD data was utilized. The results may reflect some of the variability of asthma disease, but a study using a longer follow-up period is desirable.

NorPD can identify current asthma that requires drug therapy in the population, given these restrictions on age. In paper I, the proxy measure using a one-year capture period performed best in identifying children with no reported asthma (specificity), while increasing the capture period to three years gave a good sensitivity. The definitions of the proxy measure can be varied depending on the focus of interest and will be a trade-off between high sensitivity and high specificity (32). Changes in the length of the capture period, drug classes included, and number of prescriptions required, may give different prevalence of asthma (127) and some advocate the use of positive predictive value to evaluate the proxy measure (107). For the NorPD data, it is possible to restrict the proxy measure by using reimbursement codes on prescriptions as a substitute for diagnosis. This has been done in a previous NorPD study (81) and was applied in paper II and IV.

The use of the question "ever asthma" in paper III could be problematic because of the variation in the disease activity and persistence of asthma over time. Sleep problems and use of hypnotic drugs (the outcome of the study) has been linked to the level of asthma control, i.e. currently active asthma. We therefore supplemented the questionnaire data with data on filled prescriptions for asthma drugs as an indication of whether asthma was currently active in the year prior to start of follow-up.

5.1.5 Comorbidities of asthma

In paper III and IV, we examined additional health problems and diseases requiring medical treatment that occurred in asthmatics in populations of children, adolescents and young adults.

Paper III showed a substantially higher risk of initiating hypnotic use in young adult asthmatics, especially in those who recently were in active asthma treatment. Results were robust towards the changes in design and statistical methods that we applied. The adjustment for covariates had little impact on risk estimates and may reflect that the measured covariates do not influence the effect of asthma group on risk of hypnotic use. Caution is warranted when interpreting this as covariates were measured a few years before the start of follow-up. This was during late adolescence, where changes in behaviors such as smoking and alcohol use occur in many individuals. The increased risk of hypnotic use could be a direct consequence of low asthma control, leading to more frequent or severe symptoms (e.g. nighttime symptoms). The level of control of asthma symptoms is related to both sleep

problems (63, 128, 129) and hypnotic use (130). It could also be a secondary effect of one of the many comorbidities observed in asthma populations (53, 131-133), which can have detrimental effects on sleep (e.g. allergy, depression and anxiety (53, 64, 128, 134-137)). We examined the occurrence of allergy, depression, anxiety as well as other chronic diseases among asthmatics in paper IV.

We found a higher occurrence of several chronic diseases among asthmatics in paper IV. This is the first study to examine asthma and comorbid diseases in the entire Norwegian population by using the diagnostic codes from NorPD. We studied chronic diseases that have been associated with asthma in previous population-based studies (53, 131-133) that were expected to be of some magnitude in this age group. Given the method for identifying comorbidities in this study, the diseases also had to have a relevant pharmacotherapy with reimbursement. A prerequisite for receiving reimbursement is that the physician deems the patient to have chronic disease (confer chapter 1.3.3). Thus, our measure of comorbidity will capture chronic diseases diagnosed by a physician, where the physician and the patient have chosen to treat with drugs in the ambulatory setting.

The observed associations may be due to causal pathways for development of disease, or be indirectly linked through common genetic and environmental factors. Some of the relations between asthma and comorbidities (allergy, GORD, infections) have been widely studied, and allergy may even be regarded as part of the asthma disease complex (atopic asthma phenotype). A multitude of possible biologic mechanisms could explain the observed associations. However, the process for developing asthma is not fully understood and there are few confirmed risk factors for asthma (9, 16, 73). Our study (paper IV) was cross-sectional, which precludes any inferences about the temporal sequence of developing asthma and comorbidities. Furthermore, the data and design is not suitable for making inferences about biology. A final observation regarding the results of paper IV is that many of the absolute differences are quite small and few had more than one of the comorbidities studied. This reflects the young and still relatively healthy population studied.

A contributing factor to the increased occurrence of additional health problems in asthmatics that was observed in paper III and IV could be detection bias (2); asthmatics visit physicians more often than their healthy peers and additional health problems come to the attention of the physician. Detection bias is less likely to be the case for more severe diseases such as diabetes

type 1. Furthermore, this bias may work the other way around in paper IV; mild, undiagnosed asthma may be more readily detected in persons who have other reasons for visiting physicians.

Another possible explanation is that asthmatics that are often in contact with their physician will likely be more aware of their illnesses and subsequently seek healthcare services. This relates to the issues on how to measure the occurrence of asthma and is not unique to studies based on healthcare service use. Self-reported asthma symptoms on questionnaires are commonly used in asthma epidemiology (21, 138). Reporting is influenced by the patients own perceptions and preferences, such as the threshold for reporting symptoms, seeking care and using drugs. For instance, psychosocial factors and mental illnesses like stress, depression and anxiety have been associated with asthma symptoms, but not necessarily with objective markers of asthma (e.g. lung function) or asthma diagnosis. These findings have been partly attributed to an increased perception of respiratory symptoms in patients with mental illnesses (135, 137, 139). Prescription data are objective in the sense that the individuals using drugs do not make deliberations on whether they have asthma symptoms. However, choosing to visit a physician and using the prescribed drugs rest on subjective judgments.

Prospective studies that can disentangle the temporal sequences of events may give new insight. Furthermore, studies of the consequences of comorbidities related to asthma outcomes are needed (52, 54). Comorbid diseases can lead to diagnostic difficulties, less control of symptoms, modulate the severity, and alter the response and adherence to asthma therapy (52-56). Use of hypnotics among individuals with asthma may be related to the level of asthma control and improvements in asthma management can make a difference, and the identification and treatment of comorbidities is part of the core management of asthma (5).

5.2 Methodological considerations

This chapter pertains to general considerations in epidemiologic research that is relevant to our studies. Specific methodological issues regarding the measures of asthma and asthma drug use have been discussed in chapter5.1.4.

The objective of epidemiological studies is to obtain an valid and precise estimate of the frequency of a disease/condition or of the effect of an exposure on the occurrence of a disease

(1). Furthermore, this estimate should be generalizable to a relevant target population. Thus, the study population should either be the target population itself, or at least experience effects similar to the target population. Errors that influence the estimate may be classified as random or systematic.

Random errors influence the precision of the estimate and may be represented by the width of the confidence limits around the point estimate. Random errors will generally diminish if the study population size is increased and studies using NorPD as population source are generally large. Thus, problems with random error were considered to be small when drawing the study population from NorPD. The Youth Health Surveys (paper III) are relatively large (~15,000 individuals invited). However, division of the study population by asthma groups yielded two small groups and will, together with the high number of zero counts (no filled prescriptions) in the outcome variable, contribute to less precise estimates in each group. The MoBa cohort study consists of more than 100,000 pregnancies but our study (paper I) was based on the children who had reached 7 years of age, thus constituting ~2000 respondents.

Systematic error tends to be a greater problem than random error in epidemiological studies. It influences the validity of the estimate by producing results that are consistently distorted in one direction, and the validity may be separated in two components: Internal validity of the inferences as they pertain to the source population, and external validity (generalizability) of inferences as they pertain to people outside the population (1). Three types of systematic errors in observational studies will be discussed in the following sections: Selection bias, information bias and confounding.

5.2.1 Selection bias

Selection bias is due to the procedures for selecting subjects to be included in the study and factors that may affect participation in the study. Thus, participants may not be representative of the source population because the occurrence of disease or the exposure-disease association is different in participants and non-participants (1). The age group examined in paper I-IV were under 30 years of age and the effect of selective survival of healthier individuals was considered negligible. Individuals who died (paper III and IV and persistence analysis in paper II) and emigrated (III and IV) were excluded from analysis because they did not have the chance to get the outcome. Relatively few individuals were excluded and then mainly due to emigration.

For NorPD, there is mandatory registration in the database, thereby covering all persons residing in Norway who fill prescriptions (no self-selection issues). Few individuals at this age are permanently residing in institutions and NorPD should therefore cover virtually all drug users in Norway. The study population in paper II was defined by NorPD data and selection bias was considered negligible with respect to asthma drug use. The population in paper IV was also defined by NorPD data but restricted to the individuals participating in the Population and Housing Census in 2001. This was a census in the entire population with mandatory participation and selection bias in paper IV was considered negligible. The representativeness of the individuals defined as asthmatics by our measures in paper I-IV has been discussed in chapter 5.1.4.

The MoBa cohort study (paper I) invited pregnant women from all over Norway to participate during 1999-2008, and the end of enrolment protocol released in 2010 (91) showed an overall participation rate of 38.5%. Nilsen et al. (140) studied the potential bias from self-selection in MoBa data from the period 2000-2006 (participation rate 43.5%), by comparing to all women giving birth in Norway. Nilsens study suggests that associations between exposures and outcomes were not biased but some prevalence estimates were. For example, the proportion of mothers that were smoking was lower in MoBa compared to total population, while prevalence of pregnancy complications and diseases were similar. Maternal asthma was about 4% in MoBa participants and in the total population (140). For the specific questionnaire used in paper I, the response rate was 61%. Self-selection in responding to this questionnaire was assessed by comparing prevalence of asthma drug use in the children between responders (7.6%) and non-responders (7.9%) as recorded in NorPD. The prevalence in the Norwegian population of 7-year olds was lower (6.9%). Selection bias is probably less important in studies of correspondence between two data sources (paper I) than in studies of prevalence of disease.

The Youth Health Surveys (paper III) invited all 10th grade students in each county and had a response rate of 86%, while 77% were possible to link with other register data. This is a relatively high participation rate, and may in part be attributed to questionnaires being filled out during school lessons. Students from some schools in Troms and Finnmark only received questionnaires by mail and had lower participation rate. However, also the school-based surveys in these counties had lower participation rates. In Oslo, Oppland and Hedmark,

reminders were sent to the home of non-responders. It is likely that no significant self-selection bias has occurred (internal validity). The counties surveyed were from different geographical areas of Norway and include both urban and rural areas. The study population should be fairly representative of the young population in Norway (external validity). The prevalence of asthma drug use in the study population and the Norwegian population of the same age was similar, and this is an indirect assessment of selection bias.

5.2.2 Information bias

Information bias pertains to the accuracy of the information collected for different variables, and is also called misclassification when discrete variables are used (1). When the misclassification of variables is similar for all individuals, it is called non-differential. When the misclassification of one variable is dependent on the actual value of another variable (e.g. more misclassification of outcome variable among non-exposed than exposed), it is called differential.

The use of drugs as registered in NorPD is central in all papers of this thesis. The terms fill or redeem prescriptions, receive or dispense drugs, have been interchangeably used with the term "drug use" throughout paper I-IV, and essentially mean filling a prescription at the pharmacy. Interpretation of "drug use" must take into account the possibility of received drugs not being used, or used at another time than it is received from the pharmacy. It seems less likely that drugs are not used if patients receive the same drugs on several occasions. Obtaining drug exposure data from databases such as NorPD eliminates recall bias (2). The electronic registration of data at the time of dispensing the drug as well as legislations and other incentives ensures high quality of registered data. Furthermore, NorPD captures all filled prescriptions to individuals in ambulatory care, regardless of reimbursement status, prescriber speciality or occupation (primary, secondary and tertiary care), or if patients move within the country. Asthma drugs (paper I-IV) and hypnotics (paper III) are prescription-only drugs and can be considered complete. Regarding paper IV, over-the-counter drugs are available for the treatment of allergy and GORD but patients have economic incentives to obtain a prescription and thereby receive reimbursement.

The self-reported data used in paper I and III relies on respondents correctly interpreting the questions, recalling the information precisely and willingness to disclose the correct information. Furthermore, questions need to formulated and presented in an unambiguous

manner on questionnaires. For questions on drug use, the time frame for recollection is important as participants have more difficulties recollecting drug use in distant past. Additionally, drug class-specific or indication-specific questions on drug use have been found to give more accurate reports than open-ended questions on the names of drugs used (2). In the validation study (paper I), the recall period was one year for the asthma drug use question and was found to have high validity. We observed the aforementioned difference between open-ended and indication-specific questions in paper I. In paper III, the covariates for the Incidence rate ratio (IRR) analysis were self-reported (except age and gender). There is a potential for selective reporting according to social desirability (e.g. smoking and alcohol consumption), while recall bias should be less pronounced as most covariates measured the current status. However, they were measured some time before start of follow-up, and may have changed before or during follow-up.

Possible detection bias in paper III and IV has been discussed in chapter 5.1.5.

5.2.3 Confounding

Confounding occurs when a secondary variable that is linked to both exposure and outcome distorts the estimate of effect, and may wholly or partially explain an observed association (1, 2). Possible confounding variables were adjusted for in paper III by using multivariable analysis in IRR estimation. Adjustments had little impact on the risk estimates. This may be due to changes in measured covariates between the baseline survey and the outcome period, or that the measured covariates do not influence the effect of asthma group on risk of hypnotic use. Stratification by gender (paper II and IV), stratification by age (II), and age standardization (paper IV) were performed to observe differences by gender and age.

6 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The prevalence of asthma drug use in the Norwegian population of children, adolescents and adults was relatively stable at about 5.5%, with higher rates in preschool children and lower rates in young adults. Both prevalence and incidence of drug use was higher in females from about 15 years of age. These data on asthma drug use corresponds well with the findings in epidemiological studies of asthma. We found good correspondence between reported asthma and asthma drug use registered in NorPD. Thus, NorPD could be a valuable proxy to identify active asthma diseases in the Norwegian population, given some restrictions on age groups and careful definition of the proxy measure.

The incidence and persistence analysis indicates that a large share of asthma drug users did not use their drugs continuously over years. This variability reflects the fluctuations of asthma disease over time, which complicates the definition of asthma in epidemiological research. Although several potential risk factors for asthma have been identified, efforts in epidemiology and other research fields on asthma have not been very successful in identifying causal factors for asthma development. Therefore, preventive measures remain illusive, and asthma pharmacotherapy is concentrated on controlling symptoms and not remission of the disease. Part of the problem in identifying risk factors seems to be how to define asthma in population studies, with great variability in definition, time frame and entities of the disease being measured. A strength of the NorPD data is the continuous and complete collection of high quality data and gives a new opportunity in Norway to follow individual patients' drug use over time. NorPD data could shed light on the natural history of asthma drug use, and the underlying disease, from childhood and into adulthood on a population-based scale by tracking patient cohorts over a longer time period. It would be interesting to further investigate whether there is a subgroup of patients that once they initiate drug use, need treatment consistently from childhood into adulthood.

This study has provided evidence of other diseases and health problems that are overrepresented in asthmatics in the Norwegian population. Several chronic diseases and antimicrobial treatment occurred more frequently in asthmatics, while the risk of initiating hypnotic use was higher in asthmatics. In due course, it will be possible to assess the time sequence of occurrence of asthma and the other chronic diseases that we have studied.

The study of asthma drugs used by the Norwegian population revealed some areas where there might be room for improvement in asthma care. The use of LABA as monotherapy is strongly discouraged, yet a large proportion seemed to use them as monotherapy. However, this situation may have improved in later years as drug regulators and other bodies have issued several warnings. The apparent use of SABA as monotherapy was high in the older age groups. This could be due to these individuals having mild, intermittent asthma where such treatment is warranted, or it could represent under-treatment with controller drugs. A more thorough analysis of this issue should focus on the intensity of such treatment. Furthermore, among those who receive controller drugs, intensive use of SABA could be an indicator of suboptimal asthma control. The quality of care in those who receive asthma therapy could be improved by e.g. education of the patients on benefits and harms of the different drugs.

To assess outcomes of asthma therapy, there is a need for outcome data. The Norwegian Patient Registry (NPR) with nationwide hospital inpatient diagnostic data can provide information on asthma outcomes and may be linked to NorPD data in future studies.

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TITLE PAGE

Comorbidities in an asthma population 8-29 years old
-a study from the Norwegian Prescription Database

Running head:
Comorbidities in an asthma population 8-29 years old

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Keywords:
Asthma, comorbidity, epidemiology, prescription database,

Key points:

- Comorbidities in asthmatics may influence asthma outcomes and have implications for disease management.
- Diagnostic codes on reimbursed drugs are available in NorPD from 2009 and may be used as surrogate measures of diseases in the population.
- An excess occurrence of nine chronic diseases was observed in the young population of asthmatics, compared to the general population of Norway of the same age.
- A majority of the asthma population had one of the comorbidities measured and few had more than one.

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ABSTRACT

Purpose:

To examine occurrence of chronic diseases and antimicrobial treatment in an asthma population 8-29 years old, compared to the general population.

Methods:

In this cross-sectional study, the asthma population was identified from the general population (retrieved from a census covering the entire Norwegian population) by using filled prescriptions on asthma drugs as a proxy measure of current asthma. The outcome was excess occurrence of specific diseases (comorbidity) among asthmatics, compared to the age-specific general population. Diseases were defined by filled prescriptions with specific diagnostic codes (ICPC-2 or ICD-10) during a 1-year period in the Norwegian Prescription Database. Nine chronic diseases were examined: ADHD, epilepsy, migraine, mental illness, cardiovascular disease, diabetes, autoimmune disorders, GORD, allergy. Additionally, antibacterials recommended for respiratory tract infections and antivirals were examined (defined by ATC codes). Standardized Morbidity Ratios (SMR) for each disease was calculated.

Results:

59% of the asthmatics had at least one of nine chronic diseases examined, compared to 18% in the general population. Few asthmatics had more than one additional chronic disease (6% of males, 8% of females). SMRs were increased for all diseases except diabetes, implying higher than expected occurrence of the specific diseases in asthmatics. This pattern was observed in both age groups (8-19 and 20-29 years) and genders. Allergy and GORD had highest SMR (range 3.2-4.8) while the other diseases were in the range 1.2-2.5.

Conclusions:

An excess occurrence of comorbidities was found in asthmatics. A majority of asthmatics had one additional chronic disease, and few had more than one.

INTRODUCTION

There is increasing recognition that co-occurrence of multiple chronic diseases is common also in children and has a significant impact on the overall health of patients.[1-3] The extent and impact of comorbidities in asthmatics has received little attention compared to other chronic diseases like cardiovascular diseases and diabetes, possibly because multimorbidity increases with age[1] while asthma is most prevalent in young populations.

From the societal point of view, health service use is higher in asthmatics with comorbidities and places an extra burden on the healthcare system.[4,5] At the patient level, comorbidities influence several aspects of asthma, such as detection and diagnosis, severity and control of asthma symptoms.[6-8] Identification and treatment of comorbidities is part of the core management of asthma, especially for more severe cases.[9] Associations between asthma and allergy, gastro-oesophageal reflux disease (GORD) and infections are well-established[9-12] while several other diseases have also been associated with asthma in population-based studies.[7,13-15] However, few studies include children and adolescents.

There is currently no systematic recording of diagnostic information in the Norwegian home-dwelling population. Thus, opportunities to study the occurrence of diseases in the population have been limited. However, a change in the reimbursement system for drugs may enable us to assess occurrence of diseases in the whole population. From March 2009, it became mandatory to provide the diagnostic code (ICPC-2 or ICD-10) of the treated medical condition on all reimbursed prescriptions. The Norwegian Prescription Database (NorPD)[16] is one of the first nationwide prescription databases to record this information. These codes may serve as surrogate measures of the diseases present among individuals in ambulatory care. The diseases studied in the present paper have been associated with asthma in previous population-based studies[7,13-15], are expected to be of some magnitude in this young population, drug treatment is central to the management of the disease, and drugs are reimbursable.

The aim of the present study was to examine the occurrence of specific types of chronic diseases and antimicrobial treatment in an actively treated asthma population of children,

adolescents and young adults, compared to the occurrence in the Norwegian general population of the same age.

MATERIALS AND METHODS

Data sources and study design

We conducted a cross-sectional study utilizing data from three datasets covering the entire Norwegian population. The datasets were linked by using the unique, encrypted 11-digit person identity number (PIN), assigned to all individuals residing in Norway.[16]

The latest *Population and Housing Census (PHC)* included all persons resident in Norway on 3rd November 2001 according to the Central Population Register (CPR).[17] The PHC provided a closed cohort of all Norwegians residents and variables used were the PIN, gender and birth year.

The *Central Population Register (CPR)* contains continuously updated data on every person residing in Norway.[18] The CPR provided information on date of death and emigration between the PHC in 2001 and the end of the study period.

The *Norwegian Prescription Database (NorPD)* stores electronic data on all filled prescriptions from Norwegian pharmacies since January 2004. Pharmacies are obliged to send the data, irrespective of reimbursement status of the dispensed drugs and the prescribers' specialty and occupation.[16] Thus, NorPD has complete coverage of drugs dispensed to the home-dwelling population. Variables from NorPD used in the present study were the PIN, date of dispensing drug, reimbursement code (diagnostic code from March 2009) and the Anatomical Therapeutic Chemical (ATC)[19] classification code of drugs.

Measure of comorbidities

Diagnostic codes from reimbursed drug prescriptions registered in NorPD were used to define the outcome (comorbidities).

Reimbursement scheme with diagnostic codes: Reimbursement of drug costs is a part of the national, tax-supported public health service which all Norwegians have unrestricted access to.[20] The drug reimbursement scheme is based on a list of conditions for which specified drugs can be reimbursed. Reimbursement should only be granted if the patient has a chronic condition where long term treatment is needed (at least 3 months of regular or intermittent treatment during a year). From March 2009, physicians were obliged to provide the diagnostic code of the condition being treated on prescriptions deemed eligible for reimbursement. Codes from either the International Classification of Diseases version 10 (ICD-10) or the International Classification of Primary Care version 2 (ICPC-2) can be used. The Norwegian Medicines Agency (NoMA) has defined about 20 additional codes for conditions that have no appropriate ICD-10 and/or ICPC-2 code, some of which has been included in our study (see comments in Table 1).

Occurrence of a comorbid disease: The presence of a comorbid chronic disease in an individual was defined as filling at least one reimbursed prescription with a diagnostic code during a 1-year period. These diagnostic codes were used as surrogate measure of disease. The following nine chronic diseases were examined: Attention Deficit Hyperactivity Disorder (ADHD, denoted "hyperkinetic disorder" in ICD-10 and ICPC-2), epilepsy, migraine, mental illness, cardiovascular disease, diabetes (type 1 and 2), autoimmune disorders, gastro-oesophageal reflux disease (GORD) and allergy (Table 1).

To study occurrence of antimicrobial treatment (normally not reimbursed), ATC codes on drugs dispensed were used instead of diagnostic codes (Table 1). Antibacterials recommended in Norwegian guidelines21 for use in upper and lower respiratory tract infections were included, as well as antivirals used for influenza virus infections.

Comorbidity may be defined as the occurrence of one or more additional diseases in individuals who have an index disease.[22] For brevity, the term "comorbidity" will be used in the present paper for the occurrence of any of the diseases also in the general population who do not necessarily have the index disease (asthma).

Index date and study period: From 3 March 2009, physicians were obliged to write diagnostic codes on all reimbursed prescriptions, and this date was therefore set as the index date. NorPD data on the outcome (comorbidity) for a 1-year period after the index date was retrieved for the Norwegian general population and for the study population of asthmatics.

Standard population: Norwegian general population

The standard population included all persons who participated in the PHC in 2001 and were under 30 years in 2009 (653,386 males, 620,453 females). Individuals who according to CPR data died or emigrated before the end of the study period (2 March 2010) were excluded (16,282 males, 18,024 females). Thus, 637,104 male and 602,429 female residents in Norway aged 8-29 years in 2009 comprised the standard population. Because the PHC was conducted in 2001, the lowest age class that could be studied was 8 years old.

Study population: Current asthmatics in the general population

The study population was all current asthmatics receiving drug treatment that could be identified in the standard population (20,207 males, 16,853 females). A proxy measure based on dispensed asthma drugs was used to identify this population, a measure described in previous NorPD studies.[23,24] Included were those who had filled prescription for an asthma drug at least once in the year before and at least once in the year after the index date. Only prescriptions with reimbursement codes for asthma were included. Asthma drugs were defined as inhaled β2-agonists (ATC code R03AC), inhaled glucocorticoids (R03BA), combination inhalers with β2-agonists and glucocorticoids (R03AK), and leukotriene receptor antagonists (R03DC).

Statistical methods

The number of comorbidities occurring in the asthma population and in the general population was examined as the proportion of the populations having respectively 0, 1, 2, 3, and 4 or more comorbidities (Table 2).

Associations of asthma with specific comorbidities were examined by calculating Standardized Morbidity Ratios (SMR) (Table 3). The occurrence of each disease (prevalence proportion) was calculated for 1-year age-specific groups in the general population and separately for males and females. From these prevalence proportions, Expected counts (E) in the asthma population were calculated, while Observed counts (O) were retrieved in the same manner as for the general population. The O/E ratio (SMR) was calculated with 95% confidence intervals from the Poisson distribution. Results were stratified by gender and age (8-19 years and 20-29 years). Note that the magnitude of the SMRs is not directly comparable

between the different genders and age groups, because they are compared to different standard populations.

The study was approved by the Norwegian Data Inspectorate, and the Regional Committee for Medical Research Ethics evaluated it.

RESULTS

Occurrence of nine chronic comorbidities was studied. 59% of male and female asthmatics had at least one of the comorbidities, compared to 18% of males and females in the general population (Table 2). Relatively few in the asthma population had more than one of these comorbidities (6% of males, 8% of females). When antimicrobial treatment was included, 69% of male and 71% of female asthmatics had at least one comorbidity, compared to 30% and 34% in the general population.

The occurrence of specific comorbidities in the asthma population is presented in Table 3. The prevalence proportion (O/n) of asthmatics having allergy was above 50% for all groups, while antibacterial treatment was also relatively prevalent in asthmatics (13-31%). The prevalence was higher in the oldest age group for all comorbidities except allergy in males, ADHD and antivirals. The largest percentage point difference in prevalence between the low and high age group were observed for migraine in females and for mental illness, as well as for the highly prevalent diseases (allergy, antimicrobials).

The SMR estimates generally showed an increased occurrence for all diseases, except diabetes (Table 3). This pattern was consistent in all gender and age groups and implies a higher than expected occurrence of the specific diseases in the asthma population compared to the gender- and age-specific general population. GORD and allergy had high SMRs (range 3.2-4.8). The other diseases were in the range 1.3-2.1, except for diabetes and ADHD which showed inconsistent patterns.

Diabetes was the only disease that did not have a consistent increased SMR for asthmatics, and was even below 1.0 for the youngest females. In an additional analysis, we only included the diagnostic codes that are more specific for diabetes type 1 (ICPC “T89 Insulin-dependent

diabetes mellitus", and ICD "E10 Diabetes mellitus type I"). This gave SMR of 1.3 [1.0-1.6] for youngest males and 1.1 [0.8-1.5] for the oldest males. For females, the numbers were respectively 0.8 [0.5-1.1] and 0.9 [0.6-1.3].

DISCUSSION

In this study of children, adolescents and young adults, we found that chronic diseases were present more often in asthmatics than in the general population. Likewise, use of specific antimicrobial treatments occurred more frequently among asthmatics. The present study is the first to examine asthma and comorbid diseases in the entire Norwegian population by using the diagnostic codes from NorPD. Our results obtained from diagnostic codes on prescriptions are essentially in line with studies that obtained diagnostic information from administrative data or self-reports. [7,13-15] However, most studies are in adults and few have reported age-stratified results.

Adams et al.[14] found associations of asthma and diabetes but not arthritis in adults 18-34 years old, but an association was present in older age groups. Cazzola et al.[13] reported hypertension, allergic rhinitis, diabetes, dyslipidemia, depression and GORD to be associated with asthma. Associations were generally weaker in 15-34 year olds compared to older adults except for allergic rhinitis, depression and diabetes. Prosser et al.[15] found asthma to be associated with a wide range of diseases in adults, including infections in the lower and upper respiratory tract, depression, hypertension, diabetes and certain autoimmune disorders. Zhang et al.[7] found associations with allergy, arthritis/rheumatism, hypertension, diabetes and mental illness in an adult population. Most chronic conditions were more prevalent in adults but allergies and mental illness were more frequent in 18-34 year olds.

In studies of specific diseases, anxiety and depression has been associated with asthma[25-27] and a bidirectional relationship has been suggested.[25] The association may be dependent on how asthma is defined.[28,29] Asthma has been found to be associated with migraine in adults.[30,31] In studies comparing epileptics to non-epileptics, an association with asthma has been reported.[32,33] ADHD and asthma are most prevalent in children and adolescents, and this is reflected in our data by ADHD being one of the more prevalent comorbidities of asthma. Associations with ADHD have been reported in the literature, including a NorPD study that

used ATC codes as proxy measures for diagnosis of both diseases.[34,35] Associations between diabetes and asthma has been found in several studies in adults. [7,13-15] Our data had a relatively few diabetes cases among asthmatics and did not show a consistent association. Of note is that a high proportion of participants in our young study population are expected to be type 1 diabetics, while studies among adults will be predominated by type 2 diabetics. For GORD, the absolute numbers (prevalence) is lower in asthmatics in our study than reported in the literature among children[11] and adults[12], possibly because it has not been diagnosed and subsequently treated with prescription drugs (over-the-counter drugs are also available). However, the strong relative association (SMR) is reported in other studies as well.[11,12] Links between asthma and allergies and respiratory infections are well known and receive much attention in asthma guidelines.[9,10] An association between asthma and antibacterials is difficult to disentangle from associations of asthma and infections themselves, and the present study was not designed for this purpose.

Our measure of comorbidity will capture chronic diseases diagnosed by a physician, where the physician and the patient have chosen to treat with drugs in the ambulatory setting. The study is cross-sectional and the temporal sequence events can not be determined. The associations observed may have several explanations and we will discuss three possibilities.

First, there may be a genuinely increased co-occurrence of other diseases in asthmatics. This may be due to a pathway where one problem is central to development of the other. For example, the comorbidity may be a risk factor for development of asthma, or for triggering asthma symptoms and increasing severity. The causal link may be reversed, in that asthma contributes to development of other diseases. Alternatively, asthma and comorbidities may be indirectly linked via common genetic and environmental factors for development of disease.

Second, there may be a higher detection rate of comorbidities in asthmatics, i.e. detection bias occurs.[36] This may be an issue in any epidemiologic study where health care service use is measured. Asthmatics do more often than their healthy peers visit physicians for monitoring of the disease and prescription renewals. Any additional health problems more easily come to the attention of physicians and a prescription for a drug may ensue. This may also go the opposite direction in that asthma is more easily detected in individuals who have other reasons for visiting a physician. This kind of bias is probably most pertinent in milder, intermittent cases of asthma, and for comorbidities with a high proportion of subclinical cases

that are not usually detected. An increased detection rate of diabetes and epilepsy seems less likely due to the severity of these diseases. Furthermore, our definition of the asthma population will have excluded some milder cases of asthma and individuals who tried asthma drugs only once as part of diagnosing respiratory complaints.

Third, some individuals may have a lower threshold for seeking healthcare services including drug treatment, and/or some physicians have a lower threshold for setting a diagnosis and prescribing drugs. Use of healthcare services may be a learned behavior where asthmatics who often are in contact with their physician will likely be more aware of their illnesses and may have learned to use, and possibly overuse, healthcare services. In support of the latter explanation are studies reporting a higher occurrence of a broad range of different conditions in asthmatics.[5,7,13-15] It would be interesting to find a "reference disease" that is not linked to asthma and study if there is an excess occurrence of this "reference disease".

The asthma drugs used to identify our asthma population are the mainstay of asthma pharmacotherapy[9] and are quite specifically used for asthma at this age. Largely all patients on anti-asthma treatment in Norway receive at least one of the included drugs[23] and a high validity of this measure was found in 7-year olds.[24] In the present study, we used a stricter criterion for defining the asthma population in that asthmatics had to fill at least two prescriptions and at least one year apart. Thus, the inception of asthma complaints took place before the 1-year study period and lasted for at least one year (persistently or episodes of asthma at least one year apart).

A limitation of the study is the cross-sectional design which unable us to determine a causal relationship between comorbidities and the occurrence of asthma. The recording of diagnostic codes has only recently been implemented but when more years of data are accumulated, long-term studies can be done to confirm our findings and to disentangle sequence of events. The time period of one year may be too short to capture some comorbidities, e.g. individuals with infrequent episodes of migraine may have long gaps between prescription refills. The length of study period is especially pertinent when studying a time-varying disease such as asthma where disease activity, and the use of asthma drugs,[23] is variable over shorter and longer time periods. A possible detection bias was discussed above. A further limitation is that for allergy and GORD, over-the-counter drugs without reimbursement are available. Some individuals may also have used non-reimbursed prescription drugs. This is probably

most relevant for migraine and mental illnesses, if the physician deems the disease as not chronic or not properly diagnosed yet. Patients have economic incentives for receiving their drugs on reimbursement but acquiring a prescription may be more convenient for asthmatics due to higher physician visit frequency.

One of the strengths of our study is that we use individual level data from three complete, nationwide datasets. NorPD captures all individuals receiving prescription drugs in the ambulatory care setting, including drugs prescribed by specialists in secondary and tertiary care. The universal healthcare system should ensure access to necessary healthcare services for all residents. Thus, we could examine the occurrence of a broad range of diseases in the Norwegian general population of the entire age range. The method for identifying chronic diseases is consistent between diseases and does not rest on subjective judgment by patients about their disease as in self-report studies, while recall bias is eliminated. However, the choice by patients and physicians to use drugs for a medical condition may be influenced by subjective judgments, as discussed above.

Comorbidities may influence and complicate several aspects of asthma, such as detection and diagnosis, severity and control of asthma symptoms.[6-8] Furthermore, the response to asthma therapy may be altered (e.g. obesity alter response to corticosteroids[37]) or adherence to asthma therapy decreases (e.g. depression[28,38]). The drugs used for the treatment of comorbid diseases can have detrimental effects on asthma (e.g. NSAIDs[9]).

In summary, by using a nationwide prescription database with diagnostic codes we have shown an excess occurrence of several chronic diseases in the young population of asthmatics, compared to the age-specific general population of Norway. 59% of the asthma population had at least one additional chronic disease, while relatively few had more than one additional disease.

Table 1: Comorbidities and corresponding diagnostic codes (ICPC-2 and ICD-10 codes) examined in the Norwegian Prescription Database (NorPD).

	Comorbidity	ICPC-2	ICD-10	Comment
Chronic diseases	Attention Deficit Hyperactivity Disorder (ADHD)[a]	P81	F90	a) Denoted as hyperkinetic disorder in ICPC and ICD coding systems.
	Epilepsy	N88	G40	
	Migraine	N89	G43	
	Mental illness -depression -anxiety	-74[b]; P74; P76	-74[b]; F41; F32	b) Reimbursement code for anxiety disorders, defined by NoMA (replaces ICPC and ICD codes).
	Cardiovascular disease -hypercholesterolaemia -hypertension	-26[c]; -27[c]; K86-87	-26[c]; -27[c]; I10-13; I15	c) Reimbursement codes for primary and secondary prevention of atherosclerotic disease, defined by NoMA (replaces ICPC and ICD codes).
	Diabetes[d] -type 1 -type 2	T89-90	E10-11; E13-14	d) ICPC codes do not distinguish between diabetes type 1 and 2.
	Autoimmune disorders -arthritis related diseases -systemic connective tissue disorders -ankylosing spondylitis -noninfective enteritis and colitis -psoriasis	L88; L99; D94; S91	M05-08; M13; M30-35; M45; K50-51; L40	
	Gastro-Oesophageal Reflux Disease (GORD)[e]	D84	K21	e) OTC drugs also on market but are not reimbursed.
	Allergy[f] -allergic rhinitis -allergic conjunctivitis -atopic dermatitis -urticaria	R97; F71; S87; S98	J30; H10.1[g]; L20; L50	f) OTC drugs also on market but are not reimbursed. g) NoMA specifies that only the 4th level code H10.1 is eligible for reimbursement.
antimicrobial treatment	Antibacterials[h] -upper and lower respiratory tract infections	ATC codes: J01AA02; J01CA04; J01CE02; J01FA		h) Drugs (ATC codes) recommended by guidelines[†] for treatment of upper and lower respiratory tract infections.
	Antivirals[i] -influenza virus infection	ATC codes: J05AH01; J05AH02		i) H1N1 influenza during study period. Pharmacists could write prescriptions and dipsense drugs according to set regulations, without consulting physicians.

Abbreviations: NoMA, Norwegian Medicines Agency; OTC, Over-the-counter-drugs (drugs sold without precription); ATC, Anatomical Therapeutic Chemical classification system for drugs; ICPC-2, International Classification of Primary Care, 2nd edition; ICD-10, International Statistical Classification of Diseases, 10th revision.

[†] Norwegian Directorate of Health. [Norwegian national guidelines for treatment with antibiotics in general practice]. 2008. Available from: http://www.helsebiblioteket.no/microsite/Antibiotikaretningslinjer (in Norwegian).

Table 2: Number of comorbid diseases occurring in the asthma population and the general population (8-29 years old) during a 1-year period.

	Males		Females	
Number of comorbidities	% of asthma population[a] (n=20,207)	% of general population (n=637,104)	% of asthma population[a] (n=16,853)	% of general population (n=602,429)
Chronic diseases[b]				
0	40.8	82.4	41.4	81.9
1	53.3	16.2	50.4	16.2
2	5.3	1.3	6.9	1.6
3	0.6	0.1	1.0	0.2
4+	0.1	0.0	0.2	0.0
Chronic diseases and antimicrobial treatment[c]				
0	30.7	70.2	29.1	66.4
1	48.2	24.3	44.6	26.3
2	17.3	4.8	20.0	6.1
3	3.3	0.6	5.2	1.0
4+	0.5	0.1	1.1	0.2

a) Not adjusted to the age-distribution of the general poulation.

b) 9 different comorbidities measured, see Table 1.

c) 11 different comorbidities measured, see Table 1.

Table 3: Standardized Morbidity Ratio (SMR) for occurrence of comorbid diseases in the asthma population (8-29 years old) during a 1-year period (Reference: Occurrence of diseases in the general population by gender and 1-year age specific groups).

	Males[a]					Females[b]				
Comorbidity[c]	Occurrence (O/n)	Observed count (O)	Expected count (E)	SMR (O/E)	[95% CI]	Occurrence (O/n)	Observed count (O)	Expected count (E)	SMR (O/E)	[95% CI]
8-19 years										
ADHD	4.0 %	585	469	1.2	[1.1 , 1.4]	2.2 %	223	129	1.7	[1.5 , 2.0]
Epilepsy	1.0 %	149	84	1.8	[1.5 , 2.1]	1.1 %	111	56	2.0	[1.6 , 2.4]
Migraine	0.9 %	133	76	1.7	[1.5 , 2.1]	2.0 %	203	118	1.7	[1.5 , 2.0]
Mental illness	0.4 %	65	39	1.7	[1.3 , 2.1]	0.9 %	90	67	1.3	[1.1 , 1.7]
Cardiovascular	0.1 %	20	13	1.5	[1.0 , 2.3]	0.2 %	21	12	1.8	[1.1 , 2.7]
Diabetes	0.6 %	83	62	1.3	[1.1 , 1.7]	0.4 %	37	43	0.9	[0.6 , 1.2]
Autoimmune	0.7 %	103	66	1.6	[1.3 , 1.9]	1.0 %	104	67	1.5	[1.3 , 1.9]
GORD	1.6 %	236	52	4.6	[4.0 , 5.2]	1.3 %	134	34	4.0	[3.3 , 4.7]
Allergy	56.1 %	8258	1 977	4.2	[4.1 , 4.3]	51.8 %	5274	1 098	4.8	[4.7 , 4.9]
Antibacterials[d]	13.8 %	2024	1 212	1.7	[1.6 , 1.7]	19.6 %	1994	1 212	1.6	[1.6 , 1.7]
Antivirals[d,e]	13.8 %	2033	986	2.1	[2.0 , 2.2]	13.1 %	1330	684	1.9	[1.8 , 2.1]
20-29 years										
ADHD	1.6 %	89	39	2.3	[1.8 , 2.8]	1.6 %	108	42	2.5	[2.1 , 3.1]
Epilepsy	1.3 %	69	39	1.8	[1.4 , 2.2]	1.4 %	93	49	1.9	[1.6 , 2.3]
Migraine	1.1 %	60	37	1.6	[1.3 , 2.1]	5.6 %	370	198	1.9	[1.7 , 2.1]
Mental illness	4.5 %	249	134	1.9	[1.6 , 2.1]	7.7 %	510	266	1.9	[1.8 , 2.1]
Cardiovascular	1.3 %	69	39	1.8	[1.4 , 2.2]	1.2 %	77	40	1.9	[1.5 , 2.4]
Diabetes	0.8 %	45	41	1.1	[0.8 , 1.5]	1.0 %	64	46	1.4	[1.1 , 1.8]
Autoimmune	1.9 %	104	80	1.3	[1.1 , 1.6]	2.8 %	188	121	1.5	[1.3 , 1.8]
GORD	3.3 %	179	56	3.2	[2.8 , 3.7]	2.7 %	183	52	3.5	[3.0 , 4.0]
Allergy	51.5 %	2831	591	4.8	[4.6 , 5.0]	55.9 %	3729	903	4.1	[4.0 , 4.3]
Antibacterials[d]	22.9 %	1259	777	1.6	[1.5 , 1.7]	31.7 %	2113	1 370	1.5	[1.5 , 1.6]
Antivirals[d,e]	9.7 %	534	251	2.1	[2.0 , 2.3]	11.1 %	739	389	1.9	[1.8 , 2.0]

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder (hyperkinetic disorder); GORD, Gastro-Oesophageal Reflux Disease.

a) Males n=20,207 (8-19 years n=14,709; 20-29 years n=5.498).

b) Females n=16,853 (8-19 years n=10,187; 20-29 years n=6,666).

c) Individuals that have more than one comorbidity is counted on each comorbidity (sum of observed counts (O) on all comorbidities does not equate to the study population size).

d) From ATC codes on drugs.

e) H1N1 influenza epidemic during the observed 1-year period.

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Appendix I

Pilot questionnaire for 7-year old children in the Norwegian Mother and Child Cohort Study (MoBa)

02/01/08

OBS!

Riv av dette arket og legg det i den vedlagte lille konvolutten og deretter i svarkonvolutten sammen med spørreskjemaet ditt.

Det hadde vært fint om du kunne gi oss din e-post adresse og mobiltelefonnummer slik at vi eventuelt kan kontakte dere igjen vedrørende Den norske mor og barn undersøkelsen.

Navn: .....

E-post adresse: .....

Mobiltelefonnummer: .....

Riv av arket og legg det i den vedlagte lille konvolutten og deretter i svarkonvolutten sammen med spørreskjemaet ditt.

02/01/08

den norske Mor & barn undersøkelsen

Spørreskjema 7, når barnet er ca 7 år

Skjemaet skal leses av en maskin. Det er derfor viktig at du legger vekt på følgende ved utfyllingen:

- I de små avkrysningsboksene setter du *et kryss* for det svaret som du mener passer best, slik: ☒
- Hvis du mener at du har satt kryss i feil boks, kan du rette det ved å fylle boksen helt, slik: ■

Oppgi dag, måned og år for utfylling av skjemaet — dag ☐☐ måned ☐☐ år ☐☐☐☐ *(skriv årstall med 4 tall, f.eks. 2008)*

Sykdom og helseplager

1. Har barnet eller har det noen gang hatt noen av følgende langvarige sykdommer eller helseproblemer?

	Ja	Hvis ja, hvor gammelt var barnet ved første tegn på sykdommen.	Hvis barnet er kvitt sykdommen, ved hvilken alder skjedde det?	Ja, har sykdommen fremdeles.	Sett kryss hvis sykdommen er diagnostisert av lege
1 Astma	☐	☐☐ år	☐☐ år	☐	☐
2 Allergi i øyne eller nese/høysnue	☐	☐☐ år	☐☐ år	☐	☐
3 Atopisk eksem/barneeksem	☐	☐☐ år	☐☐ år	☐	☐
4 Nedsatt hørsel	☐	☐☐ år	☐☐ år	☐	☐
5 Nedsatt syn	☐	☐☐ år	☐☐ år	☐	☐
6 Overvekt	☐	☐☐ år	☐☐ år	☐	☐
7 For liten vektøkning	☐	☐☐ år	☐☐ år	☐	☐
8 Søvnproblemer	☐	☐☐ år	☐☐ år	☐	☐
9 Reumatoid artritt/leddgikt	☐	☐☐ år	☐☐ år	☐	☐
10 Hjertefeil	☐	☐☐ år	☐☐ år	☐	☐
11 Crohns sykdom	☐	☐☐ år	☐☐ år	☐	☐
12 Ulcerøs collitt	☐	☐☐ år	☐☐ år	☐	☐
13 Kronisk utmattelsessyndrom (ME)	☐	☐☐ år	☐☐ år	☐	☐
14 Cøliaki	☐	☐☐ år	☐☐ år	☐	☐
15 Diabetes	☐	☐☐ år	☐☐ år	☐	☐
16 Epilepsi	☐	☐☐ år	☐☐ år	☐	☐
17 Cerebral parese	☐	☐☐ år	☐☐ år	☐	☐
18 Anemi (lav blodprosent)	☐	☐☐ år	☐☐ år	☐	☐

Forts. neste side

19 Kreft 02/01/08	☐		år		år	☐	☐
20 Forsinket motorisk utvikling	☐		år		år	☐	☐
21 Forsinket eller avvikende språkutvikling	☐		år		år	☐	☐
22 Hyperaktivitet/ADHD	☐		år		år	☐	☐
23 Autistiske trekk/autisme	☐		år		år	☐	☐
24 Asperger syndrom	☐		år		år	☐	☐
25 Atferdsproblemer (vanskelig og uregjerlig)	☐		år		år	☐	☐
26 Emosjonelle vansker/ (trist og engstelig)	☐		år		år	☐	☐
27 Allergi/intoleranse mot melk	☐		år		år	☐	☐
28 Allergi/intoleranse mot egg	☐		år		år	☐	☐
29 Allergi/intoleranse mot fisk	☐		år		år	☐	☐
30 Allergi/intoleranse mot andre matvarer	☐		år		år	☐	☐

Hvis ja, hvilke?
Rug ☐ Citrus frukter ☐ Hvete ☐ Soya ☐ Skalldyr ☐ Peanøtter ☐ Nøtter (andre enn peanøtter) ☐ Annet

2. Har barnet brukt medisin, spray, inhalator eller andre medikamenter for astma i løpet av det siste året?

☐ Nei
☐ Ja

3. Hvis ja, navn på medisin barnet bruker fast.....

4. Hvis ja, navn på medisin barnet bruker ved anfall.....

5. Hvis ja, når brukte barnet astmamedisiner sist?

☐ I går ☐ Siste 7 dager ☐ Siste måned ☐ Siste året

6. Har barnet noen gang hatt noen av følgende symptomer eller helseplager? Hvis ja, kryss av for i hvilken alder. Angi også hvor mange ganger barnet har vært plaget av dette de siste 12 måneder.

	Hatt symptomer Ja.	Hvis ja, ved hvilken alder Før 3 år	3-5 år	6-7år	Antall ganger siste 12 mnd?
1 Piping/hvesing i brystet	☐	☐	☐	☐	
2 Tetthet i brystet	☐	☐	☐	☐	
3 Nattlig hoste uten forkjølelse	☐	☐	☐	☐	
4 Tetthet/ piping i brystet under eller etter fysisk aktivitet	☐	☐	☐	☐	
5 Rennende nese uten forkjølelse	☐	☐	☐	☐	
6 Kløe/renning fra øyne uten forkjølelse	☐	☐	☐	☐	
7 Kløende utslett som har kommet og gått i minst 6 måneder	☐	☐	☐	☐	

Forts. neste side

02/01/08

8 Magesmerter	☐	☐	☐	☐		
9 Migrene	☐	☐	☐	☐		
10 Annen hodepine	☐	☐	☐	☐		
11 Oppkast/diaré	☐	☐	☐	☐		
12 Feberkramper	☐	☐	☐	☐		
13 Halsbetennelse	☐	☐	☐	☐		
14 Ørebetennelse	☐	☐	☐	☐		
15 Bronkitt	☐	☐	☐	☐		
16 Lungebetennelse	☐	☐	☐	☐		
17 Urinveisinfeksjon	☐	☐	☐	☐		
18 Bruddskader	☐	☐	☐	☐		
19 Andre skader	☐	☐	☐	☐		
20 Hjernehinnebetennelse/meningitt	☐	☐	☐	☐		
21 Andre symptomer eller sykdommer	☐	☐	☐	☐		

Beskriv hvilke.....

Levevaner og livsstil

7. Hvor mange dager har barnet vært borte fra skolen eller hatt avbrudd i lek eller fritidsaktivitet på grunn av sykdom?

Antall dager borte fra skolen siste 3 mnd. ☐☐ dager

Antall dager avbrudd i lek/fritidsaktivitet siste 3 mnd. ☐☐ dager

8. Utenom skoletid: Omtrent hvor mange timer per uke driver barnet fysisk aktivitet eller idrett (for eksempel sykling, turn, hopping på trampoline, ski, fotball o.l)?

	Mindre enn 1 time	1-2 timer	3-4 timer	5-7 timer	8-10 timer	11 timer eller mer
Sommer	☐	☐	☐	☐	☐	☐
Vinter	☐	☐	☐	☐	☐	☐

9. Utenom skoletid på en vanlig hverdag: Hvor mange timer per dag er barnet vanligvis utendørs?

Sommer ☐☐ timer

Vinter ☐☐ timer

10. Utenom skoletid på en vanlig hverdag: Hvor mange timer per dag bruker barnet vanligvis på TV, video, elektroniske spill, DVD eller PC?

	Mindre enn 1 time	1-2 timer	3-4 timer	5 timer el mer
Sommer	☐	☐	☐	☐
Vinter	☐	☐	☐	☐

11. Har barnet badet i et innendørs svømmebasseng i løpet av de siste 12 måneder?

☐ Nei

☐ Ja, av og til Antall timer per måned ☐☐

☐ Ja, ukentlig Antall timer per uke ☐☐

12. Hvor ofte kommer barnet seg til skolen ved hjelp av

	Aldri	Av og til	Vanligvis	Alltid
Å gå/sykle	☐	☐	☐	☐
Å bli kjørt	☐	☐	☐	☐
Med kollektivtransport	☐	☐	☐	☐

13. Hvor lang avstand er det mellom barnets bolig og skolen?

☐ Mindre enn 1 km ☐ 1-2 km ☐ 3-4 km ☐ Over 4 km

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14. Hvor mange timer sover barnet vanligvis i gjennomsnitt per natt på hverdager?

Antall timer ☐☐ +

15. Bor du sammen med barnets far?

☐ Nei
☐ Ja

16. Hvis nei, Hvor mye er barnet sammen med henholdsvis mor og far?

	Mor	Far
Mer enn halvparten av tiden	☐	☐
Omtrent halvparten av tiden	☐	☐
Mindre enn halvparten av tiden	☐	☐
Sjelden	☐	☐
Aldri	☐	☐

+

17. Hvordan er røykevanene i hjemmet nå for tiden?

	Deg selv	Din samboer/ektefelle
Røyker ikke	☐	☐
Røyker av og til	☐	☐
Røyker daglig	☐	☐
Hvis daglig, antall sigaretter	☐☐ per dag	☐☐ per dag
Hvis av og til, antall sigaretter	☐☐ per uke	☐☐ per uke

18. I løpet av det siste året, har vedfyring blitt brukt til oppvarming i boligen der barnet bor?

☐ Nei
☐ Ja

19. Hvis ja, er vedfyring hovedkilden til oppvarming i denne boligen?

☐ Nei
☐ Ja

20, Hvis ja, bruker dere en vedovn laget før 1997?

☐ Nei
☐ Ja

21. I løpet av det siste året har dere noen gang brukt åpen peis?

☐ Nei, aldri
☐ Ja, av og til
☐ Ja, ofte i vinterhalvåret
☐ Ja, daglig i vinterhalvåret

22. Brukte dere vedfyring i barnets hjem i perioden før barnet fylte 3 år?

☐ Nei
☐ Ja +

23. Er det dyr i barnets hjem?

☐ Nei
☐ Ja +

24. Hvis ja, hvilke?

☐ Hund ☐ Fugl
☐ Katt ☐ Annet
☐ Andre pelsdyr (marsvin, kanin o.l)

25. Er barnet i kontakt med gårdsdyr minst en gang i løpet av en uke?

☐ Nei
☐ Ja

26. Hvis ja, hvilke?

☐ Hest ☐ Gris ☐ Høner/fjærkre
☐ Sau/geit ☐ Storfe ☐ Annet

27. Hva er barnets høyde og vekt? Oppgi dato for målingen og kryss av for hvem som målte høyde og vekt.

Høyde ☐☐,☐ m Vekt ☐☐,☐ kg

Dato for måling ☐☐ dag ☐☐ måned ☐☐☐☐ år

Målt selv ☐ Målt av lege/helsesøster ☐

28. Hvor gammelt var barnet da hun/han fikk sin første melketann?

Antall måneder ☐☐ ☐ Husker ikke

29. Hvor gammelt var barnet da hun/han felte sin første melketann?

Antall år ☐☐ ☐ Husker ikke ☐ Har ikke felt ennå

30. Hvor ofte børstes barnets tenner (av barnet selv eller andre)?

☐ To ganger per dag eller oftere ☐ Av og til
☐ En gang per dag ☐ Aldri

31. Får barnet for tiden hjelp til å pusse tennene?

☐ Daglig ☐ Sjelden eller aldri
☐ Flere ganger i uken

32. Har barnet fått fyllinger i noen av tennene sine?

☐ Nei
☐ Ja

33. Bruker barnet fluortabletter?

☐ Nei ☐ Ja
☐ Av og til

Barnets kosthold

34. Hvor mange skiver brød/knekkebrød spiser barnet ditt vanligvis per dag?

Loff ☐☐ Antall skiver Lyst og mellomgrovt brød ☐☐ Antall skiver

Grovt brød ☐☐ Antall skiver Knekkebrød ☐☐ Antall skiver +

35. Hvor ofte spiser barnet ditt vanligvis følgende? Sett ett kryss for hver linje.

Pålegg og frokostblandinger	Aldri	1-3 ganger per mnd. eller sjeldnere	1-2 ganger per uke	3-4 ganger per uke	5-6 ganger per uke	1 gang per dag eller oftere
Ost (gul/brun), prim	☐	☐	☐	☐	☐	☐
Kjøttpålegg (servelat, skinke ol)	☐	☐	☐	☐	☐	☐
Fiskepålegg, inkl kaviar	☐	☐	☐	☐	☐	☐
Egg	☐	☐	☐	☐	☐	☐
Syltetøy/honning	☐	☐	☐	☐	☐	☐
Sjokolade- og nøttepålegg	☐	☐	☐	☐	☐	☐
Corn Flakes, Honey Corn, Frosties o.l.	☐	☐	☐	☐	☐	☐
Müsli/havregryn/frokostblanding	☐	☐	☐	☐	☐	☐
Yoghurt naturell	☐	☐	☐	☐	☐	☐
Fruktyoghurt/drikkeyoghurt	☐	☐	☐	☐	☐	☐

+ +

36. Hvor ofte drikker barnet ditt vanligvis følgende? (Sett ett kryss for hver drikke)

Drikke	Aldri	1-3 glass per mnd. eller sjeldnere	1-3 glass per uke	4-6 glass per uke	1-3 glass per dag	4 glass eller mer per dag
Helmelk (søt/sur)	☐	☐	☐	☐	☐	☐
Lett-/ekstra lettmelk/Skummet melk	☐	☐	☐	☐	☐	☐
Sjokolademelk	☐	☐	☐	☐	☐	☐
Biola/Culturamelk	☐	☐	☐	☐	☐	☐
Appelsinjuice, annen juice	☐	☐	☐	☐	☐	☐
Eplenektar / annen nektar	☐	☐	☐	☐	☐	☐
Saft med sukker	☐	☐	☐	☐	☐	☐
Saft kunstig søtet	☐	☐	☐	☐	☐	☐
Brus (Cola o.l.)	☐	☐	☐	☐	☐	☐
Brus kunstig søtet (Pepsi max o.l)	☐	☐	☐	☐	☐	☐
Vann	☐	☐	☐	☐	☐	☐

+

37. Hvor ofte spiser barnet ditt vanligvis disse matvarene/rettene? (Sett ett kryss for hver linje.)

Middagsmat	Aldri	1-3 ganger per mnd. eller sjeldnere	1-2 ganger per uke	3-4 ganger per uke	5-6 ganger per uke	1 gang per dag eller oftere
Fet fisk (laks, makrell, sild)	☐	☐	☐	☐	☐	☐
Annen fisk (torsk, sei o.l)	☐	☐	☐	☐	☐	☐
Fiskeboller/fiskepudding o.l.	☐	☐	☐	☐	☐	☐
Kylling/kalkun	☐	☐	☐	☐	☐	☐
Rent kjøtt	☐	☐	☐	☐	☐	☐
Pølser	☐	☐	☐	☐	☐	☐
Kjøttdeig, (hamburger o.l.)	☐	☐	☐	☐	☐	☐
Pizza	☐	☐	☐	☐	☐	☐
Pannekaker	☐	☐	☐	☐	☐	☐
Vegetarretter	☐	☐	☐	☐	☐	☐
Poteter	☐	☐	☐	☐	☐	☐
Ris, spagetti, pasta	☐	☐	☐	☐	☐	☐

+ +

38. Hvor ofte spiser barnet ditt vanligvis følgende? (Sett ett kryss for hver linje.)

Grønnsaker og frukt	Aldri	1-3 ganger per mnd. eller sjeldnere	1-2 ganger per uke	3-4 ganger per uke	5-6 ganger per uke	1 gang per dag eller oftere
Gulrot	☐	☐	☐	☐	☐	☐
Kålrot	☐	☐	☐	☐	☐	☐
Kål, blomkål, brokkoli	☐	☐	☐	☐	☐	☐
Spinat, grønne bønner	☐	☐	☐	☐	☐	☐
Erter	☐	☐	☐	☐	☐	☐
Andre grønnsaker	☐	☐	☐	☐	☐	☐
Appelsin, klementiner	☐	☐	☐	☐	☐	☐
Banan	☐	☐	☐	☐	☐	☐
Eple, pære	☐	☐	☐	☐	☐	☐
Druer, melon	☐	☐	☐	☐	☐	☐
Annen frisk frukt eller bær	☐	☐	☐	☐	☐	☐
Økologisk dyrket frukt eller grønnsaker	☐	☐	☐	☐	☐	☐

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39. Hvor ofte spiser barnet ditt vanligvis følgende? (Sett ett kryss for hver linje.)

Godteri og snacks	Aldri	1-3 ganger per mnd. eller sjeldnere	1-2 ganger per uke	3-4 ganger per uke	5-6 ganger per uke	1 gang per dag eller oftere
Boller/vafler/kaker	☐	☐	☐	☐	☐	☐
Is og melkedesserter	☐	☐	☐	☐	☐	☐
Sjokolade, sukkertøy/smågodt	☐	☐	☐	☐	☐	☐
Peanøtter	☐	☐	☐	☐	☐	☐
Potetchips o.l.	☐	☐	☐	☐	☐	☐

40. Hvor ofte spiser barnet ditt vanligvis følgende måltider sammen med familien? (Sett ett kryss for hver linje.)

	Aldri	1-3 ganger per mnd. eller sjeldnere	1-2 ganger per uke	3-4 ganger per uke	5-6 ganger per uke	Daglig
Frokost	☐	☐	☐	☐	☐	☐
Middag	☐	☐	☐	☐	☐	☐
Kveldsmat	☐	☐	☐	☐	☐	☐

41. Tar barnet ditt vanligvis følgende? (Sett ett kryss for hver linje.)

Kosttilskudd	Nei	Ja, av og til	Ja, daglig
Tran	☐	☐	☐
Andre fiskeoljer/omega-3	☐	☐	☐
Multivitamintilskudd	☐	☐	☐

Hvis ja, navn på multivitamintilskudd .....

Annet kosttilskudd	☐	☐	☐

Hvis ja, navn på annet kosttilskudd: .....

Kommentarer

Har du husket å fylle ut dato for utfylling av skjema på side 1?

Tusen takk for at dere fortsatt vil være med i Den norske mor og barn undersøkelsen!

Appendix II

Questionnaire from the Youth Health Surveys (YHS)

Etikett

U Helse-undersøkelsen

Dato for utfylling:
Dag Måned År

U1. EGEN HELSE

1.1 Hvordan er helsen din nå? *(Sett bare ett kryss)*

Dårlig ☐ 1 | Ikke helt god ☐ 2 | God ☐ 3 | Svært god ☐ 4

1.2 Har du, eller har du hatt? *(Sett ett kryss for hver linje)*

	JA	NEI
Astma	☐	☐
Høysnue (pollenallergi, allergisk reaksjon, rennende nese, svie i øynene)	☐	☐
Eksem	☐	☐
Diabetes (sukkersyke)	☐	☐

1.3 Har du de siste 12 mnd hatt? *(Sett ett kryss for hver linje)*

Ørebetennelse	☐	☐
Halsbetennelse *(minst 3 ganger)*	☐	☐
Bronkitt eller lungebetennelse	☐	☐
Psykisk plage som det er søkt hjelp for	☐	☐
Alvorlig skade eller sykdom	☐	☐

Hvis du svarte «JA»; hva slags alvorlig skade eller sykdom var dette:

_____

1.4 Har du følgende funksjonshemming? *(Sett ett kryss for hver linje)*

	Nei	Ja, litt	Ja, mye
Bevegelseshemming	☐	☐	☐
Nedsatt syn	☐	☐	☐
Nedsatt hørsel	☐	☐	☐

1.5 Har du i løpet av de siste 12 mnd flere ganger vært plaget med smerter i? *(Sett ett kryss for hver linje)*

	JA	NEI
Hode (hodepine, migrene e.l.)	☐	☐
Nakke/skuldre	☐	☐
Armer/ben/knær	☐	☐
Mage	☐	☐
Rygg	☐	☐

Hvis du svarte «NEI» på alle spørsmålene under 1.5: Hopp til U2

1.6 Har disse smertene ført til at du har vært hjemme fra skolen?

Oppgi også ca. antall skoledager de siste 12 mnd: *(Sett bare ett kryss)*

Nei ☐ 1 | Ja, 1-2 dager ☐ 2 | Ja, 3-5 dager ☐ 3 | Ja, 6-10 dager ☐ 4 | Ja, mer enn 10 dager ☐ 5

1.7 Har smertene ført til redusert aktivitet i fritida? ..... JA ☐ NEI ☐

U2. TANNHELSE

2.1 Mener du at du har bedre eller dårligere tenner enn andre ungdommer på din alder? *(Sett bare ett kryss)*

Bedre ☐ 1 | Som de fleste ☐ 2 | Dårligere ☐ 3 | Vet ikke ☐ 4

2.2 Bryr du deg om at du har fine tenner? *(Sett bare ett kryss)*

Ja, mye ☐ 1 | Ja, litt ☐ 2 | Nei ☐ 3

2.3 Hvor ofte pusser du tennene dine? *(Sett bare ett kryss)*

Flere ganger om dagen ☐ 1 | En gang om dagen ☐ 2 | Annenhver dag ☐ 3 | Sjeldnere enn annenhver dag ☐ 4

2.4 Har du hatt tannverk på grunn av hull? *(Sett eventuelt flere kryss)*

Ja, men før jeg begynte på skolen ☐ | Ja, etter at jeg begynte på skolen ☐ | Nei, aldri ☐ | Vet ikke ☐

U3. MOSJON OG FYSISK AKTIVITET

3.1 Utenom skoletid: Hvor mange ganger i uka driver du idrett/mosjon slik at du blir andpusten eller svett? ☐☐ *ganger pr. uke*

3.2 Omtrent hvor mange timer pr. uke bruker du på dette?

0 timer ☐ 1 | 1-2 timer ☐ 2 | 3-4 timer ☐ 3 | 5-7 timer ☐ 4 | 8-10 timer ☐ 5 | 11 timer eller mer ☐ 6

3.3 Driver du med konkurranseidrett? ..... JA ☐ NEI ☐
(Individuelt eller på lag)

3.4 Bruker du naturen (skog og mark) til turer?

	Aldri	Ja, mindre enn 1 gang i måneden	Ja, 1 gang i måneden eller mer
Sommer:	☐ 1	☐ 2	☐ 3
Vinter:	☐ 1	☐ 2	☐ 3

3.5 Utenom skoletid: Hvor mange timer pr. skoledag *(mandag til fredag)* **sitter du i gjennomsnitt foran TV, video og/eller PC (spill og internett)?**

Inntil 1 time ☐ 1 | 1-2 timer ☐ 2 | 3-5 timer ☐ 3 | Mer enn 5 timer ☐ 4

3.6 Hvordan kommer du deg normalt til skolen i sommerhalvåret? *(Sett bare ett kryss)*

Med buss/tog e.l. *(offentlig transport)* ..... ☐ 1
Med bil/moped ..... ☐ 2
På sykkel ..... ☐ 3
Til fots ..... ☐ 4

3.7 Hvor lang skolevei har du?

Mindre enn 2 km ☐ 1 | 2-4 km ☐ 2 | Over 4 km ☐ 3

Ikke skriv her: 1.3 *(skade)* ☐☐ 8.1 *(utdanning - annet)* ☐☐ 9.5 *(far født)* ☐☐☐☐ *(mor født)* ☐☐☐☐

9.7 *(far - yrke)* ☐☐☐☐ 9.7 *(mor - yrke)* ☐☐☐☐ 12.5 *(prevensjon)* ☐☐ 12.6 *(p-pille merke)* ☐☐

U4. RØYKING, RUSMIDLER OG DOP

4.1 Røyker du, eller har du røykt? *(Sett bare ett kryss)*

Nei, aldri ☐ 1 | Ja, men jeg har sluttet ☐ 2 | Ja, av og til ☐ 3 | Ja, hver dag ☐ 4

Hvis du har svart «NEI, ALDRI»; hopp til pkt. 4.3

4.2 Hvor gammel var du da du begynte å røyke? ☐☐ år

4.3 Bruker du eller har du brukt snus, skrå eller lignende? *(Sett bare ett kryss)*

Nei, aldri ☐ 1 | Ja, men jeg har sluttet ☐ 2 | Ja, av og til ☐ 3 | Ja, hver dag ☐ 4

4.4 Røyker noen av de du bor sammen med? *(Sett ett eller flere kryss)*

Ja, mor ☐ | Ja, far ☐ | Ja, søsken ☐ | Ja, andre ☐ | Nei ☐

	JA	NEI
4.5 Har du noen gang drukket alkohol? *(f.eks. alkoholholdig øl, rusbrus, vin, brennevin eller hjemmebrent)*	☐	☐

Hvis du svarte «NEI»; hopp til pkt. 4.8

4.6 Har du noen gang drukket så mye alkohol at du har vært beruset (full)? *(Sett bare ett kryss)*

Nei, aldri ☐ | Ja, en gang ☐ | Ja, 2-3 ganger ☐ | Ja, 4-10 ganger ☐ | Ja, mer enn 10 ganger ☐

4.7 Omtrent hvor ofte har du i løpet av det siste året drukket alkohol? *(Sett bare ett kryss)*
(Lettøl og alkoholfritt øl regnes ikke med)

4-7 ganger i uka ☐ 1 | 2-3 ganger i uka ☐ 2 | ca. 1 gang i uka ☐ 3 | 2-3 ganger pr. måned ☐ 4

Omtrent 1 gang i måneden ☐ 5 | Noen få ganger siste år ☐ 6 | Har ikke drukket alkohol siste år ☐ 7 | Har aldri drukket alkohol ☐ 8

4.8 Har du noen gang prøvd dopingmidler? *(Sett bare ett kryss)*

Nei, aldri ☐ 1 | Ja, en gang ☐ 2 | Ja, flere ganger ☐ 3 | Ja, jeg bruker det regelmessig ☐ 4

U5. MAT, DRIKKE OG SPISEVANER

5.1 Hvor ofte spiser du vanligvis disse matvarene?
(Sett ett kryss for hver linje)

	Sjelden /aldri	1-3 g. pr.mnd	1-3 g. pr.uke	4-6 g. pr.uke	1-2 g. pr.dag	3 g. el. mer pr.dag
Frukt, bær	☐	☐	☐	☐	☐	☐
Ost *(alle typer)*	☐	☐	☐	☐	☐	☐
Poteter	☐	☐	☐	☐	☐	☐
Kokte grønnsaker	☐	☐	☐	☐	☐	☐
Rå grønnsaker/salat	☐	☐	☐	☐	☐	☐
Feit fisk *(f.eks. laks, ørret, makrell, sild)*	☐	☐	☐	☐	☐	☐
Sjokolade/smågodt	☐	☐	☐	☐	☐	☐
Chips, potetgull	☐	☐	☐	☐	☐	☐
	1	2	3	4	5	6

U5. Mat, drikke og spisevaner (fortsettelse)

5.2 Hvor mye drikker du vanligvis av følgende?
(Sett ett kryss pr. linje)
(1/2 liter = 3 glass)

	Sjelden /aldri	1-6 glass pr.uke	1 glass pr.dag	2-3 glass pr.dag	4 glass el. mer pr.dag
Helmelk, kefir, yoghurt	☐	☐	☐	☐	☐
Lettmelk, cultura, lettyoghurt	☐	☐	☐	☐	☐
Skummet melk (sur/søt)	☐	☐	☐	☐	☐
Cola/brus med sukker	☐	☐	☐	☐	☐
Cola/brus «light»	☐	☐	☐	☐	☐
Fruktjuice	☐	☐	☐	☐	☐
Saft	☐	☐	☐	☐	☐
Vann	☐	☐	☐	☐	☐
	1	2	3	4	5

5.3 Hva slags fett bruker du oftest på brødet?
(Sett bare ett kryss)

Smør/hard margarin ☐ 1 | Myk/lett margarin ☐ 2 | Oljer ☐ 3 | Bruker ikke ☐ 4

5.4 Hvor ofte spiser du disse måltidene en vanlig uke?
(Sett ett kryss for hver linje)

	Sjelden /aldri	1-2 ganger pr.uke	3-4 ganger pr.uke	5-6 ganger pr.uke	Hver dag
Frokost	☐	☐	☐	☐	☐
Formiddagsmat/matpakke	☐	☐	☐	☐	☐
Middag	☐	☐	☐	☐	☐
	1	2	3	4	5

5.5 Hvor mye penger bruker du i uka på snop, snacks, cola/brus og gatekjøkkenmat? *(Sett bare ett kryss)*

0-25 kr ☐ 1 | 26-50 kr ☐ 2 | 51-100 kr ☐ 3 | 101-150 kr ☐ 4 | 151-200 kr ☐ 5 | over 200 kr ☐ 6

5.6 Bruker du følgende kosttilskudd:

	Ja, daglig	Iblant	Nei
Tran, trankapsler, fiskeoljekapsler?	☐	☐	☐
Vitamin- og/eller mineraltilskudd?	☐	☐	☐

5.7 Har du noen gang prøvd å slanke deg? *(Sett bare ett kryss)*

Nei, aldri ☐ 1 | Ja, tidligere ☐ 2 | Ja, nå ☐ 3 | Ja, hele tiden ☐ 4

Hvis du svarte «NEI, ALDRI»; hopp til pkt. 5.9:

5.8 Hva har du gjort for å slanke deg?
(Sett ett kryss for hver linje)

	Aldri	Sjelden	Ofte	Alltid
Jeg spiser mindre	☐	☐	☐	☐
Jeg faster	☐	☐	☐	☐
Jeg trener mer	☐	☐	☐	☐
Jeg kaster opp	☐	☐	☐	☐
Jeg bruker avføringspiller eller vanndrivende midler	☐	☐	☐	☐
Jeg tar mettende eller sult-dempende piller	☐	☐	☐	☐

5.9 Hva veide du sist du veide deg? ☐☐☐ *hele kg*

5.10 Hvor høy var du sist du målte deg? ☐☐☐ *hele cm*

5.11 Hva synes du om vekta di? *(Sett bare ett kryss)*

Vekta er OK ☐ 1 | Veier litt for mye ☐ 2 | Veier alt for mye ☐ 3 | Veier litt for lite ☐ 4 | Veier alt for lite ☐ 5

5.12 Jeg bryr meg mye om vekta mi. *(Sett bare ett kryss)*

Enig ☐ | Litt enig ☐ | Ikke enig ☐

5.13 Hvilken vekt ville du vært tilfreds med nå (din «trivselsvekt»)? ☐☐☐ *hele kg*

5.14 Har du noen gang vært til behandling for spiseforstyrrelser?

Nei ☐ 1 | Nei, men jeg burde vært ☐ 2 | Ja ☐ 3

U6. PÅKJENNINGER OG MESTRING

6.1 Under finner du en liste over ulike plager. Har du opplevd noe av dette den siste uken (til og med i dag)?
(Sett ett kryss for hver linje)

	Ikke plaget	Litt plaget	Ganske mye	Veldig mye
Plutselig frykt uten grunn	☐	☐	☐	☐
Føler deg redd eller engstelig	☐	☐	☐	☐
Matthet eller svimmelhet	☐	☐	☐	☐
Føler deg anspent eller oppjaget	☐	☐	☐	☐
Lett for å klandre deg selv	☐	☐	☐	☐
Søvnproblemer	☐	☐	☐	☐
Nedtrykt, tungsindig (trist)	☐	☐	☐	☐
Følelse av å være unyttig, lite verd	☐	☐	☐	☐
Følelse av at alt er et slit	☐	☐	☐	☐
Følelse av håpløshet mht. framtida	☐	☐	☐	☐
	1	2	3	4

6.2 Under finner du noen påstander.
(Sett ett kryss for hver linje)

	Helt galt	Nokså galt	Nokså riktig	Helt riktig
Jeg klarer alltid å løse vanskelige problemer hvis jeg prøver hardt nok	☐	☐	☐	☐
Hvis noen motarbeider meg, så kan jeg finne måter og veier for å få det som jeg vil	☐	☐	☐	☐
Hvis jeg har et problem og står helt fast, så finner jeg vanligvis en vei ut	☐	☐	☐	☐
Jeg føler meg trygg på at jeg ville kunne takle uventede hendelser på en effektiv måte	☐	☐	☐	☐
Jeg beholder roen når jeg møter vanskeligheter, fordi jeg stoler på mine evner til å mestre/få til ting	☐	☐	☐	☐
	1	2	3	4

6.3 Har du i løpet av de siste 12 mnd selv opplevd noe av følgende?
(Sett ett kryss for hver linje)

	JA	NEI
Foreldre (foresatte) har blitt arbeidsløse eller uføretrygdet	☐	☐
Alvorlig sykdom eller skade hos deg selv	☐	☐
Alvorlig sykdom eller skade hos noen som står deg nær	☐	☐
Dødsfall hos noen som sto deg nær	☐	☐
Seksuelle overgrep *(f.eks. blotting, beføling, ufrivillig samleie m.m.)*	☐	☐

6.4 Har du opplevd noe av følgende?
(Sett ett kryss for hver linje)

	Nei	Ja, av og til	Ja, ofte
Stort arbeidspress på skolen	☐	☐	☐
Stort press fra andre for å lykkes/ gjøre det bra på skolen	☐	☐	☐
Store vansker med å konsentrere deg i timen	☐	☐	☐
Store vansker med å forstå læreren når hun/han underviser	☐	☐	☐

6.5 Har fagpersonell sagt at du har eller har hatt lese- og skrivevansker. *(Sett bare ett kryss)*

Ja, store	Ja, middels	Ja, lette	Nei
☐ 1	☐ 2	☐ 3	☐ 4

6.6 Har du i løpet av de siste 12 mnd. opplevd problemer med mobbing på skolen/skoleveien?
(Sett bare ett kryss)

Aldri	Av og til	Omtrent en gang i uka	Flere ganger i uka
☐ 1	☐ 2	☐ 3	☐ 4

U7. BRUK AV HELSETJENESTER

7.1 Har du de siste 12 mnd. selv brukt?:
(Sett ett kryss for hver linje)

	Ingen ganger	1-3 ganger	4 ganger eller mer
Skolehelsetjenesten	☐	☐	☐
Helsestasjon for ungdom	☐	☐	☐
Vanlig lege (Allmennpraktiserende lege)	☐	☐	☐
PP-tjenesten	☐	☐	☐
Psykolog eller psykiater *(privat eller på poliklinikk)*	☐	☐	☐
Familierådgivning	☐	☐	☐
Annen spesialist *(privat eller på poliklinikk)*	☐	☐	☐
Legevakt *(privat eller offentlig)*	☐	☐	☐
Sykehusinnleggelse	☐	☐	☐
Sosialtjenesten i kommunen	☐	☐	☐
Fysioterapeut	☐	☐	☐
Tannlege/skoletannlege	☐	☐	☐
Alternativ behandler	☐	☐	☐

U8. UTDANNING OG UTDANNINGSPLANER

8.1 Hva er den høyeste utdanning du har tenkt å ta?
(Sett bare ett kryss)

- ☐ 1 Universitet eller høyskoleutdanning av høyere grad *(F.eks. lektor, advokat, sivilingeniør, tannlege, lege, psykolog, siviløkonom)*
- ☐ 2 Universitet eller høyskoleutdanning på mellomnivå *(F.eks. cand.mag., lærer, sosionom, sykepleier, politi, ingeniør, journalist)*
- ☐ 3 Videregående allmennfaglig/økonomisk administrative fag
- ☐ 4 Yrkesfaglig utdanning på videregående skole *(kokk, frisør, byggfag, elektrofag, helse- og sosialfag o.l.)*
- ☐ 5 Ett år på videregående skole
- ☐ 6 Annet: _____
- ☐ 7 Har ikke bestemt meg

8.2 Hvor mye egne penger brukte du siste uke? *kr*
(Småinnkjøp pluss større gjenstander som f.eks. musikkanlegg o.l.)

	JA	NEI
8.3 Har du lønnet arbeid i løpet av skoleåret?	☐	☐

Hvis du svarte «JA»:
Hvor mange timer i uka arbeider du? *ca.* ☐☐ *hele timer*
Hvor mye tjener du i gjennomsnitt pr. måned på dette arbeidet? *kr* ☐☐☐☐☐

8.4 Hvilken karakter fikk du siste gangen i karakterboken? *(Sett bare inn hele tallkarakterer)*

Matte	Norsk skriftlig	Engelsk	Samfunnsfag
☐	☐	☐	☐

U9. OPPVEKST OG TILHØRIGHET

9.1 Hvor lenge har du bodd i Norge? ☐☐ *hele år*

9.2 Hvor lenge har du bodd der du bor nå? ☐☐ *hele år*

9.3 Har du flyttet i løpet av de siste 5 årene? *(Sett bare ett kryss)*

Nei	Ja, en gang	Ja, 2-4 ganger	Ja, 5 ganger eller flere
☐ 1	☐ 2	☐ 3	☐ 4

9.4 Mine foreldre er: *(Sett bare ett kryss)*

Gift/samboere	Ugift	Skilt/separert	En eller begge er døde	Annet
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9.5 Hvor er dine foreldre født?

	Norge	Annet land	Hvilket land:
Far:	☐	☐	Far: _____
Mor:	☐	☐	Mor: _____

U9. Oppvekst og tilhørighet (fortsettelse)

9.6 Jeg tror vår familie, sett i forhold til andre i Norge, har:
(Sett bare ett kryss)

Dårlig råd ☐ 1 | Middels råd ☐ 2 | God råd ☐ 3 | Svært god råd ☐ 4

9.7 Er far og/eller mor i arbeid nå?

	Ja, heltid	Ja, deltid	Arbeidsløs/ trygdet	Hjemme-værende	Går på skole/ studerer	Død
Far:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
Mor:	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Hvis far og/eller mor er i arbeid, hvilket yrke har de?

Far: _____

Skriv kort hva han gjør på jobben:

_____

Mor: _____

Skriv kort hva hun gjør på jobben:

_____

U10. FAMILIE OG VENNER

10.1 Hvem bor du sammen med nå? *(Sett bare ett kryss)*
(Ta ikke med søsken og halvsøsken.)

Mor og far ☐ 1 | Bare mor ☐ 2 | Bare far ☐ 3 | Omtrent like mye hos mor og far ☐ 4

Mor el. far og ny samboer el. ektefelle ☐ 5 | Fosterforeldre ☐ 6 | Andre ☐ 7

10.2 Hvor mange søsken eller halvsøsken bor du sammen med? *Antall søsken* ☐☐

10.3 Hvor mange av disse er like gamle eller eldre enn deg? *Antall søsken* ☐☐

10.4 Når du tenker på familien din, vil du si at:
(Sett ett kryss for hver linje)

	Helt enig	Delvis enig	Delvis uenig	Helt uenig
Jeg føler meg knyttet til familien min	☐	☐	☐	☐
Jeg blir tatt på alvor i familien min	☐	☐	☐	☐
Familien legger vekt på mine meninger	☐	☐	☐	☐
Jeg betyr mye for familien min	☐	☐	☐	☐
Jeg kan regne med familien min når jeg trenger hjelp	☐ 1	☐ 2	☐ 3	☐ 4

10.5 Hvilket forhold har du til dine foreldre?
(Sett ett kryss for hver linje)

	Stemmer meget godt	Stemmer ganske godt	Stemmer ikke særlig godt	Stemmer ikke i det hele tatt
Foreldrene mine vet hvor jeg er og hva jeg gjør i helgene	☐	☐	☐	☐
Foreldrene mine vet hvor jeg er og hva jeg gjør på hverdagene	☐	☐	☐	☐
Foreldrene mine vet hvem jeg er sammen med i fritida	☐	☐	☐	☐
Foreldrene mine liker vennene jeg er sammen med på fritida	☐ 1	☐ 2	☐ 3	☐ 4

10.6 Når du tenker på vennene dine, vil du si at: *(Sett ett kryss for hver linje)*

	Helt enig	Delvis enig	Delvis uenig	Helt uenig
Jeg føler meg nært knyttet til vennene mine.	☐	☐	☐	☐
Vennene mine legger vekt på mine meninger.	☐	☐	☐	☐
Jeg kan bidra/være til støtte for vennene mine.	☐	☐	☐	☐
Jeg kan regne med vennene mine når jeg trenger hjelp.	☐ 1	☐ 2	☐ 3	☐ 4

10.7 Hvor mange personer utenfor din nære familie står deg så nær at du kan regne med å få hjelp hvis du:

Har personlige problemer *Antall personer* ☐☐

Har praktiske problemer *(f.eks. m/ skolearbeidet)* Antall personer ☐☐

10.8 Har du selv vært utsatt for vold (blitt slått, sparket e.l.) de siste 12 mnd.? *(Sett bare ett kryss)*

Aldri ☐ 1 | Ja, bare av ungdom ☐ 2 | Ja, bare av voksne ☐ 3 | Ja, av både ungdom og voksne ☐ 4

U11. SEKSUELL ADFERD OG PREVENSJON

	Ja, med en partner	Ja, med flere partnere	Nei
11.1 Har du noen gang hatt samleie?	☐	☐	☐

Hvis du svarte «NEI»; hopp til U12

11.2 Alder første gang? ..... Jeg var ☐☐ år

11.3 Brukte du/dere prevensjon ved siste samleie?

Nei ☐ 1 | Ja, kondom ☐ 2 | Ja, p-pille/p-sprøyte ☐ 3 | Ja, annet ☐ 4 | Vet ikke ☐ 5

	JA	NEI	Vet ikke
11.4 Har du noen gang blitt gravid/gjort ei jente gravid?	☐	☐	☐

Hvis du svarte «JA»;

Hvor gammel var du da dette skjedde? Jeg var ☐☐ år

	JA	NEI	Vet ikke
Ble det utført abort?	☐	☐	☐

U12. BRUK AV MEDISINER M.M

12.1 Hvor ofte har du i løpet av de 4 siste ukene brukt følgende medisiner? *(Sett ett kryss for hver linje)*
Med medisiner mener vi her medisiner kjøpt på apotek.
Kosttilskudd og vitaminer regnes ikke med her.

	Aldri	Daglig	Hver uke, men ikke daglig	Sjeldnere enn hver uke	Ikke brukt siste 4 uker
Smertestillende uten resept	☐	☐	☐	☐	☐
Smertestillende på resept	☐	☐	☐	☐	☐
Allergi-medisin	☐	☐	☐	☐	☐
Astma-medisin	☐	☐	☐	☐	☐
Sovemedisin	☐	☐	☐	☐	☐
Beroligende medisin	☐	☐	☐	☐	☐
Medisin mot depresjon	☐	☐	☐	☐	☐
Annen medisin på resept	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

12.2 Skriv navnet på medisinene som du har krysset av for ovenfor, og hva grunnen var til at du tok medisinene (sykdom eller symptom):
(Kryss av for hvor lenge du har brukt medisinen)

Navn på medisinen: *(ett navn pr. linje):*	Grunn til bruk av medisinen:	Hvor lenge har du brukt medisinen? Inntil 1 år	Ett år eller mer
		☐	☐
		☐	☐
		☐	☐

Dersom det ikke er nok plass her, kan du fortsette på eget ark som du legger ved.

SPØRSMÅL TIL JENTENE

	JA	NEI
12.3 Har du fått menstruasjon («mensen»)?	☐	☐

Hvis du svarte «NEI»; hopp til 12.5

12.4 Hvor gammel var du da du fikk din første menstruasjon?

Jeg var ☐☐ år

12.5 Bruker du, eller har du brukt:
(Sett ett kryss for hver linje)

	Nå	Før, men ikke nå	Aldri
P-pille/minipille/ p-sprøyte	☐	☐	☐
Annen prevensjon	☐	☐	☐

Hvilken type prevensjon?:

_____

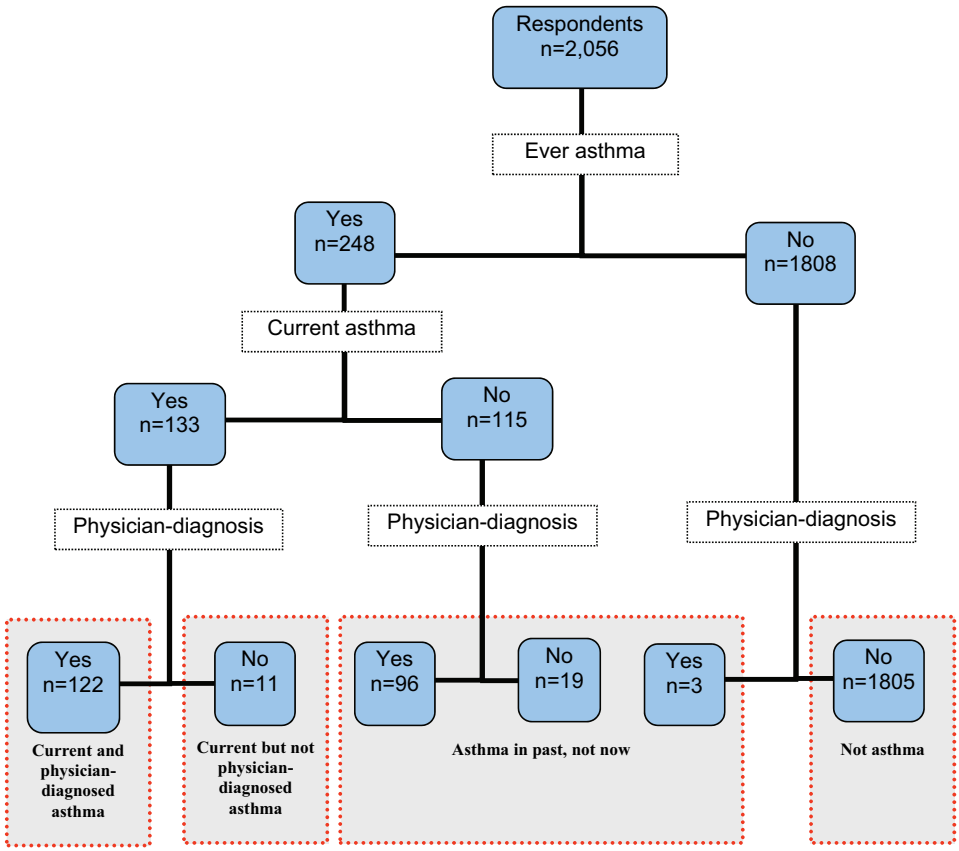
12.6 Til deg som bruker p-pille/minipille: Hvilket merke bruker du nå?:

_____

IE 000000-1024-1 - 5.000 - Beyer-Hecos 10.00

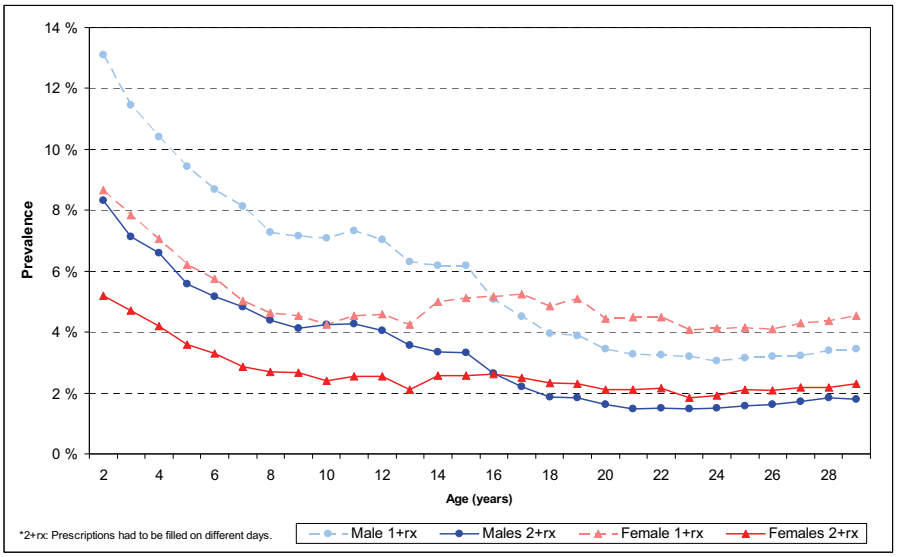
Appendix III

Asthma groups constructed from answers on the Norwegian Mother and Child cohort study (MoBa) pilot questionnaire for 7-year old children.



Appendix IV

Annual prevalence of filling at least 1 and at least 2* prescriptions (rx) for asthma drugs in 2007. Norwegian Prescription Database (NorPD).



Appendix V

Anatomical Therapeutic Chemical (ATC) classification codes of drugs for obstructive airway diseases (R03), including asthma drugs. 4th level ATC codes.

ATC code	Name
R	RESPIRATORY SYSTEM
R03	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R03A	ADRENERGICS, INHALANTS
R03AA	Alpha- and beta-adrenoreceptor agonists
R03AB*	Non-selective beta-adrenoreceptor agonists
R03AC	Selective beta-2-adrenoreceptor agonists
R03AH*	Combinations of adrenergics
R03AK	Adrenergics and other drugs for obstructive airway diseases
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
R03BA	Glucocorticoids
R03BB	Anticholinergics
R03BC	Antiallergic agents, excl. corticosteroids
R03BX*	Other drugs for obstructive airway diseases, inhalants
R03C	ADRENERGICS FOR SYSTEMIC USE
R03CA	Alpha- and beta-adrenoreceptor agonists
R03CB*	Non-selective beta-adrenoreceptor agonists
R03CC	Selective beta-2-adrenoreceptor agonists
R03CK*	Adrenergics and other drugs for obstructive airway diseases
R03D	OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R03DA	Xanthines
R03DB*	Xanthines and adrenergics
R03DC	Leukotriene receptor antagonists
R03DX	Other systemic drugs for obstructive airway diseases

* No sale registered in Norway according to statistics from wholesalers (97) and statistics from the Norwegian Prescription Database (87)