Children and asthma medication

When is that inhaler just a breath away?

Mira GP Zuidgeest

Mira GP Zuidgeest 2008

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When is that inhaler just a breath away?

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Children and asthma medication

When is that inhaler just a breath away?

Kinderen en astmamedicatie

Wie heeft de langste adem?

(met een samenvatting in het Nederlands)

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Mira Gerta Petra Zuidgeest
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Contents

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General introduction

I

I General introduction

BACKGROUND: MEDICINES FOR CHILDREN

For a long time the use of medicines in children has been a neglected field. Children are subject to many of the same diseases as adults, and consequently, they are often treated with the same medicines which are proven to be effective and safe in adults. However, the problems arising from this approach have been gaining more and more attention over the last years.[1-3] Several studies reported on how wide-spread unlicensed and off label drug use in children is in practice.[4-7] It has been found that as many as fifty percent or more of medicines used in children have never been studied in this population, but only in adults, and not necessarily for the same indication or disease.[8, 9] This does not mean that such medicines are not efficacious or are unsafe for children, but these observations clearly reflect the absence of data on medicines' use in children [5, 6, 10] and unlicensed and off label use of medicines has been associated with an increased risk of adverse drug reactions and prescription errors.[11, 12]

Over the last decade these findings have led to the awareness that extrapolating data from studies in adults to children is not sufficient enough to warrant efficacious and safe paediatric use of medicines and that the lack of knowledge on the use of medication in children leads to a suboptimal treatment and subjects children to unknown risks.[2, 13] This awareness was subsequently followed by developments within clinical, scientific and regulatory communities in order to address the need for more clinical and epidemiological research on medicines' use in children. On the regulatory site there has been a strong push to create new incentives for paediatric drug development both at the EMEA in Europe (the Paediatric Regulation) and the FDA in the US (the Best Pharmaceuticals for Children Act).[14-16] Although one may distinguish some differences between the two, they have in common the objective that regulatory systems should facilitate the development and availability of medicines for children aged 0 to 17 years, ensure that medicines for use in children are of high quality, ethically researched, and authorised appropriately, and improve the availability of information on the use of medicines

for children. This should be achieved by a creating both incentives for the industry to do research in children as well as obligations. Other initiatives arising from these developments include the foundation of national 'medicines for children research networks' (www.mcrn.nl/www.mcrn.org.uk).

In the context of creating a fruitful environment for paediatric drug development it has been widely acknowledged that bringing efficacious and safe therapy to children is not only a matter of developing new and better medicines. It also involves improving use of existing drugs in children, creating platforms for paediatric pharmacoepidemiology (e.g. TEDDY,[7] MCRN) and promoting accurate diagnosing. Particularly the latter has been identified as an immense challenge in paediatric medicine. A certain medicine can only be proven to be effective given a certain diagnosis. If there is no diagnosis then there is no evidence based medicine either. Just as a molecule no sooner becomes a medicine than when it receives an indication. Thus efficient and safe diagnostics are a first step in every medical-therapeutic scenario.

Diagnostic difficulties exist in many fields of paediatric medicine, e.g. epilepsy, respiratory disease, infections, behavioural and mental disorders. Additional difficulties in arriving at the correct diagnosis are created, because symptoms are often described by proxy by parents.[17] Moreover, the fact that children are still developing and therefore body functions and behaviour are changing over time makes diagnosing diseases in children particularly difficult. To assure that young patients receive the correct treatment for their disease according to current evidence and best practice, and to promote optimal treatment outcomes, it is crucial that (I) the diagnosis can be made with reasonable certainty and (II) there is sufficient evidence on which medications are efficacious and safe for this diagnosis and which is the preferred therapy.

When these criteria are not fulfilled it is very difficult to identify 'correctly' and 'incorrectly' treated patients and to evaluate treatment outcomes. However, the family of the child will expect a swift and adequate treatment, also without a full diagnostic picture. To evaluate medication use in such circumstances, one has to take the whole process of diagnosing and treatment changes over time into consideration, since it is likely that other factors, such as family and prescriber influences, will play a significant role in the process of arriving at a certain treatment scenario for a certain child.

TREATMENT WITH ASTHMA MEDICATION IN CHILDREN AS A LEARNING MODEL

In this thesis we aim to learn more about paediatric pharmacotherapy by focussing on treatment of children with asthma medication. Treatment of children with asthma medication is used as a learning model for paediatric pharmacoepidemiology.

An operational description of asthma in children is 'repeated attacks of airway obstruction and intermittent symptoms of increased airway responsiveness to triggering factors, such as exercise, allergen exposure and viral infections'. It is a common chronic disorder of the airways that involves an underlying inflammation.[18, 19] For most people the onset of asthma lies early in life and asthma is the most common chronic childhood disease in nearly all industrialised countries.[20, 21] The mean prevalence of wheeze and self-reported asthma for children in the EU25 is 12.3%.[22] In the Netherlands 4-12% of children aged 2-14 experience shortness of breath and 5 to 20% experience wheeze.[23, 24]

In children, experiencing asthmatics symptoms is not synonym to having asthma. A diagnosis of asthma is difficult to make in young children and 'not all that wheezes is asthma' is a statement only too true.[25-27] More and more voices are heard proposing to see asthma as a collective noun for several diseases with different patterns of illness and a different underlying pathogenesis.[28-30] A number of wheezing phenotypes have been identified, including transient wheezing and atopic asthma, based on factors such as age of first presentation with symptoms, persistence of symptoms and atopic status of the child.[18, 31, 32] These phenotypes most likely require a different therapeutic approach, but with the current diagnostic tools they can only be discriminated retrospectively.

In a search for objective measures to diagnose asthma and distinguish different phenotypes, many studies investigated the relationship between asthma and, among others, atopy (skin-prick tests or IgE based) or bronchial hyperresponsiveness (the tendency of the airways to narrow excessively in response to triggers that have little or no effect in normal individuals). Although in both cases the associations are well established, neither bronchial hyperresponsiveness nor atopy is restricted to children with asthma.[33-36]

Guidelines on diagnosis and treatment of asthmatic symptoms in childhood try to deal with these diagnostic issues. According to current insights, a diagnosis of asthma can be assessed more accurately with increasing age. Therefore different treatment recommendations are made for children below five to six years of age and older children. The guidelines advise physicians to base their decision for prophylactic treatment with inhaled corticosteroids (ICS) in young children on the presence or absence of certain factors related to persistence of asthmatic symptoms. These factors include severity of symptoms, triggers of symptoms, atopic characteristics of the child and a parental history of asthma.[18, 19, 37, 38] Use of short-acting beta2-agonists (SABA) to reduce symptoms during wheezing episodes is generally accepted in practice.[18] However, data on effectiveness of SABA in symptom reduction during viral wheeze and other respiratory morbidities that primarily occur in early childhood is conflicting.[39, 40] Also, in young children the response to a trial of asthma medication is widely used as a diagnostic tool to strengthen or reject the diagnosis of asthma.[18, 19, 37, 38] Recent findings that treatment with ICS does not seem to alter the course of the disease [41-43] caused a shift from prevention to symptom treatment. Previous studies describing actual use of asthma medication in children show ample variability in treatment patterns and raise concern about over- and under treatment both in children with and without doctor-diagnosed asthma.[44-51]

DATA SOURCES USED IN THIS THESIS

Two different data sources were used for the studies presented in this thesis. All studies in **Chapter 3** were performed within the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA study) and all studies in **Chapter 4** were performed within the second Dutch national survey of general practice (DNSGP-2).

The PIAMA study

The PIAMA study is a prospective birth cohort study among 3,963 Dutch children. The initial objectives of the PIAMA study were (I) to evaluate the effectiveness of allergen reduction measures for the prevention of asthma and mite allergy in children of allergic mothers, and (II) to investigate the natural history of childhood asthma and risk factors for asthma. Details of the study design have been published elsewhere.[52] Recruitment took place in 1996 - 1997. At eight years of age 3,653 children were still participating in the study. Data on respiratory and allergic symptoms, potential risk factors for asthma and allergy and demographic factors were collected by yearly postal questionnaires. At eight years of age several subgroups of the cohort underwent hospital-based medical examinations, blood sampling and lungfunction tests. Longitudinal data on medication use were collected at age eight through prescription data from community pharmacy records. Pharmacy information was received from community pharmacies for 2,004 children. For 777 children, these pharmacy data were complete from birth until age eight.

The DNSGP-2 study

The second Dutch national survey of general practice (DNSGP-2) is a nationwide survey, carried out in 2001 by the NIVEL (Netherlands Institute for Health Services Research) in cooperation with the National Institute for Public Health and the Environment (RIVM). The DNSGP-2 study has been described in detail elsewhere.[53, 54] In short, 195 general practitioners (GPs) in 104 practices serving approximately 400,000 patients registered all physician–patient contacts during 12 consecutive months. The participating GPs were representative of all Dutch GPs.[53] All practices within the DNSGP-2 made use of electronic medical records. The DNSGP-2 provides data on all diagnoses and prescriptions made by the GP. Every single health problem presented within a consultation was coded by the GP using the International Classification for Primary Care (ICPC).[55] Extra information on patient and GP characteristics was collected through questionnaires. In the Netherlands all non-institutionalised inhabitants are registered with a single general practice, with virtually no changes over time.

Objectives and outline of this thesis

The overall aim of this thesis is to gain more insight in the process of medicines' use in children by studying treatment with asthma medication as a learning model. The studies presented in this thesis encompass diagnostic difficulties in paediatric asthma, questions regarding effectiveness of medication, and challenges in evaluating medication use. To evaluate medication use in children, given diagnostic uncertainties, requires a comprehensive approach taking into account the whole process of prescribing and treatment changes over time, family and prescriber influences, but also the age of the child.

Chapter 2 addresses the general issues regarding medicines' use in children. This chapter originally appeared as a background paper to the WHO report 'Priority Medicines for Europe and the World' in 2004. In **Chapter 3**, the longitudinal development of treatment with asthma medication is addressed. To get a better comprehension of the extent of treatment of children with asthma medication and the patterns with age the treatment from birth to age eight is described and quantified in detail in *Chapter 3.1*. Since trial medication is common practice in young children with asthmatic symptoms, initiation of therapy does not imply that a child will continue using asthma medication. Therefore, in *Chapter 3.2* persistence of treatment in preschool children and possible determinants of this persistence, are addressed.
The relationship between treatment with asthma medication form birth to age eight and respiratory outcomes at age eight is examined retrospectively in *Chapter 3.3*. In **Chapter 4** we address the relationship between diagnosing and treating asthmatics in the context of family and prescriber influences.
In *Chapter 4.1* we describe the relationship between prescribing of asthma medication and doctor-diagnosed asthma in children aged 0-17.
Next we evaluate what other factors could play a role in prescribing of asthma medication to children by investigating how and to what degree prescribing of these medicines is influenced by child, family and physician characteristics in *Chapter 4.2*. The interactions between child, family and prescriber factors on treating young asthmatics either with reliever or maintenance therapy are examined in *Chapter 4.3*. Finally, **Chapter 5** provides an overall discussion about treatment with asthma medication in children, which can be regarded as a comprehensive learning case for medicines' use in children in general given diagnostic uncertainties, family and prescriber influences and treatment changes over time.

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Pharmaceuticals and children

2

2 Pharmaceuticals and children

Zuidgeest MGP, Willemen MJC, van den Anker JN

This chapter has been retrieved from the report: Priority Medicines for Europe and the World "A Public Health Approach to Innovation", Chapter 7.3; WHO; 2004. WHO/EMD/PAR/2004.7. Available from: http://mednet3.who.int/prioritymeds/background/children.doc.

SUMMARY

When looking at the size and nature of disease burden in the paediatric population, infectious diseases, asthma, mental disorders, and the genetic component of diseases are most important. This shows that children are subject to many of the same diseases as adults, and consequently are often treated with the same drugs. However, a large proportion of medicines used in children are not licensed ('unlicensed') for this age group or are prescribed outside the terms of the drug license ('off label'), which can place children at a direct risk of under- or overdosing and a delayed risk of long-term adverse effects. Data needed for effective and safe drug treatment in children cannot be linearly abstracted from adult data and specific research in children is necessary.

However, the obstacles of conducting research in children are numerous and include financial issues (small sales market), ethical issues (potential risks/discomfort for the child), scientific issues ('children' are a heterogeneous group) and practical issues (recruitment of a sufficient number of children, blood sampling). For obvious reasons there is still substantial resistance to the participation of children in research, however one may argue that off label and/or unlicensed drug use should be regarded as unethical treatment and may harm children even more. Moreover, it has been shown that clinical trials in children have resulted in significant improvements in their health care. Besides the lack of research in general, impediments to the development of a scientific basis for drug treatment in children are (I) the limited access to appropriate health care due to generic barriers and inherent barriers in the organisation of health care services (II) diagnostic dilemmas in children (III) attitudes towards disease and medication usage that impede the proper use of medicines and (IV) lack of knowledge on the pathophysiology and risk factors for diseases affecting children.

To reduce the burden of childhood diseases it is crucial that they are recognised as an important cause of morbidity, economic cost, and mortality world-wide. To ensure that children are treated with sufficiently evaluated and effective medicines, research into medicines for children needs to be improved. A first thing to accomplish this is to adjust the requirements and rules for paediatric research in children in Europe, with an obvious need for obligations. An important step has been made by the European Commission by adopting the proposal for the regulation on medicinal products for paediatric use on 28 September 2004. This proposal aims to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children. Other actions that need to be taken are (I) to better educate the medical community and the public about the rationale and benefits of trials and the potential dangers of using health-care interventions that have not been appropriately studied, with a special focus on the parents (II) to develop co-operation between institutions, thus improving clinical trials in children (III) to promote accurate diagnosis and treatment by training and educating public health officials, physicians and parents and by investigating the effectiveness of drugs in a daily life setting (IV) to improve the knowledge on the pathophysiology and risk factors for diseases affecting children, thus enabling existing therapies to be better targeted and facilitating the development of new treatment options (V) to ensure access to diagnostic and therapeutic options and (VI) to prevent progression of disease in adults by early detection and effective treatment in children.

INTRODUCTION

When it comes to pharmacotherapy, children cannot be regarded as small adults. Children do not only differ in pharmacokinetic and pharmacodynamic aspects, but also in adherence to therapy and other factors that influence the effectiveness and safety of medicine use. In spite of this, it is generally discerned that prescriptions for children are often written in the absence of sound scientific evidence.

Although all drugs on the market are subject to licensing procedures to ensure their quality, efficacy and safety, a large proportion of medicines

used in children are not licensed ('unlicensed') for this age group or are prescribed outside the terms of the drug license ('off label').[1] The drug licence, e.g. the Summary of Product Characteristics (SmPC), may contain statements such as 'no evidence for use in children'. This does not mean that the drug is unsafe for use in children but it clearly indicates the absence of data in children.[2, 3]

There are several reasons why specific drug research in children is necessary. Firstly, when medication is used unlicensed or off label, there are no data available on effectiveness, safety, dosage or toxicity. In these cases, physicians and pharmacists have to rely on their clinical experience or make educated guesses when making therapeutic decisions.[4] Very often such clinical decision-making is based on the extrapolation of empirical data in adults to expected data in children. This is done in spite of the fact that large differences exist between adults and children, and even among children themselves (e.g. a new-born infant is not comparable with a 16 year old teenager).[5, 6] Therefore, this extrapolation is often inappropriate; children have a different range of diseases, and metabolise medications differently, resulting in responses to treatment that are unpredictably different to adults.
For example, the adverse effects to medications such as thalidomide (phocomelia in the unborn child), tetracycline (staining of the teeth), chloramphenicol (the grey baby syndrome), and aspirin (Reye's syndrome in children with viral infections) are specific to children.[7]

Secondly, some diseases only occur in children (e.g. certain leukaemias, juvenile arthritis) and drugs for treatment must be investigated in children. Other diseases (e.g. asthma or psychiatric morbidities) may start in childhood and as they may continue into adult life, effective treatment at an early stage of the disease may be beneficial to the patient at a later stage in life.[8] Research in children is also necessary to establish the cause and natural history of diseases and thereby give insight into the possible preventive strategies for diseases which have important public health impacts (such as hypertension, obesity, diabetes mellitus, asthma and mental diseases).[9]

In the paediatric population (aged 0-17 years old) the percentages of off-label and unlicensed drug use are very high. Unlicensed drug use in children ranges between 25 and 50%, off label drug use ranges between 15 and 40%.[10, 11] The group in which off label or unlicensed drug use is most com-

mon are neonates. In neonatal intensive care units, 90% of babies receive an unlicensed or off label used drug. Antibiotics and vitamins are the most widely prescribed off label medicines in neonates.[12]
Because of the lack of paediatric licensing, there are only few paediatric formulations, and adult dosages have to be converted to appropriate paediatric dosages. Therefore, it is to be expected that unlicensed and off label drug use increases the risk of miscalculating doses and induces a higher rate of adverse drug reactions.[13, 14] Moreover, the intake of medicines is not a very pleasant experience for children and new or adapted formulations may ease administration and improve patient adherence to therapy (e.g. improving administration of methotrexate in juvenile arthritis). Formulations which are preferable in paediatric use are liquid preparations (e.g. suspensions, drops), tablets (dispersible or chewable), creams, ointments, nasal solutions and drops, ear- and eye drops and rectal preparations.[15]

WHAT IS THE SIZE AND NATURE OF THE DISEASE BURDEN?

Epidemiological trends

When looking at the size and nature of the disease burden in the paediatric population, one can distinguish two different categories. There are diseases that occur only in childhood and there are diseases that occur both in childhood and in adult life, including the chronic diseases that may arise at an early age and progress into adult life. The second category has a much greater impact on overall disease burden than the first.

The most important of the paediatric diseases is the group of infectious diseases, which is the leading cause of death in children world-wide, accounting for 63% of all mortality for this age group. Within the group of infectious diseases, six diseases cause 90% of all deaths. These six leading diseases are acute respiratory infections (including pneumonia and influenza), AIDS, diarrhoeal diseases, tuberculosis, malaria and measles.[16, 17] These infectious diseases are especially a problem in the developing world. Their prevalence and burden are much lower in Europe. Nevertheless, mainly due to the increased mobility of people around the world, in Europe there is still the risk of epidemics, which makes infectious diseases a global problem and necessitates awareness of the danger of infectious diseases everywhere.[17]

Of the respiratory conditions, particularly asthma, is one of the most common chronic diseases in the world, and is another disease that has great implications for disease burden in children. As opposed to the infectious diseases, the rate of asthma seems to be increasing as communities adopt western lifestyles and become urbanised.[18] The prevalence of this disease has been increasing in both children and adults in recent decades. It has been associated with an increase in atopic sensitisation and is paralleled by similar increases in other allergic disorders such as eczema and rhinitis. It is now estimated that as many as 300 million people of all ages, and all ethnic backgrounds, suffer from asthma and the burden of this disease to governments, health care systems, families and patients is increasing worldwide.[18]

In children, the prevalence of asthma symptoms varies between global populations from less than 2% to approximately 33% of the population, with the highest prevalence occurring in Australia, New Zealand and the UK.[19] Areas of low prevalence (1–7%) include Eastern Europe, China, and Indonesia. Furthermore, the prevalence appears to vary within countries. It is unclear why the variation in the prevalence of asthma is so large. One theory suggests that the greater understanding of hygiene and healthcare in the western world may lead to a different exposure to infection early in life. Consequently, this may render the immune system susceptible to an atopic response. Childhood respiratory disease, allergen exposure, dietary changes, and socio-economic differences may also play a role in the variation, as may ethnic origin.[20]

Paradoxically, lately there have been data from the United Kingdom showing a decline in asthma symptoms. Throughout the British Isles, the burden of self reported asthma and other allergic diseases among adolescents has changed substantially for the better in recent years. These trends correspond to those seen in the 10-14 year age group in hospital admissions, consultations with general practitioners, and parentally reported symptoms in the health survey for England. Just as it is not understood why the prevalence of symptoms of asthma has increased since the 1950s, it is unclear why asthma symptoms should now apparently be decreasing. The most likely explanation for the still seen paradoxical increase in prevalence of the label of asthma is that it is applied to increasingly milder disease.[21-23] One other key area that needs to be addressed when discussing disease burden in children, are the mental diseases. The awareness of the impact of mental

disorders has been growing in the last decades, but, in comparison with the more somatic morbidities, there is still limited attention for this group.[24] This is notwithstanding the fact that between 10 and 20% of the paediatric population seems to have one or more mental or behavioural problems.[25, 26] The total disease burden of mental disorders in paediatrics has not been fully elucidated yet, because there are many complexities in terms of defining diagnostic categories and health measurements, especially in children. Many of the disorders seen in children can be precursors of much more disabling disorders during later life.[24, 26] Mood disorders in children are a major risk factor for attempting and committing suicide.[27] It is estimated that in the age group 5-14 years old, the annual rate is 0.5 per 100,000 (girls) and 0.9 per 100,000 (boys). This rate is increasing up to 12.0 per 100,000 (girls) and 14.2 per 100,000 (boys) in the age group 15-24 years.[28] Mental disorders reduce health status and the quality of life, and have major impact on social life.[29] In countries with health systems that are not able to look after a patient, much of the care must be provided by family and friends. For them, the illness of the child causes also a burden of disease, because of the emotional involvement and thereby a decrease in their quality of life.[30] This burden of disease is also associated with the social stigma which exists in mental disorders.[30]

The growing recognition of the complexity of the genetic and molecular basis of disease is a subject, which is applicable to a substantial part of the diseases occurring in childhood. For the mentioned groups of respiratory and mental diseases there is a well-recognised genetically determined predisposition. But accumulating evidence now suggests that susceptibility to infections and disorders like haemolytic uremic syndrome may also be genetically determined. A study by McCandless *et al*. investigating the burden of genetic disease, found that, in a full-service paediatric inpatient facility, more than two thirds of admissions and 80% of the charges are attributable to diseases that have a recognised genetic component. Genetically determined diseases were almost evenly divided between those that have clear-cut genetic determinants (e.g. cystic fibrosis, sickle cell disease, congenital heart disease) and those for which there is a well-recognised genetically determined predisposition (e.g. asthma, diabetes, cancer).[31] Another study by Stevenson *et al*. recently found that malformations and genetic disorders are a substantial cause of mortality in a referral paediatric hospital. Many malformations have a genetic basis due to genetic, chromosomal, or multifactorial causation. In developed countries there has been a decrease in deaths from acquired causes, due to new advances in medicine, with a relative increase in deaths of genetic origin, making genetic disorders and malformations the leading cause of infant mortality in the US.[32] The aforementioned data show that genetic disorders are common and that genetic disorders and malformations have a significant impact on health care costs carried by society and individual families. However, the financial burden is not the only concern. Multiple hospitalisations and increased hospitalisation stays, in addition to increased mortality, likely cause anguishes and increase stress for the family involved. Therefore malformations and genetic disorders are important considerations in the health care of infants and children.[31, 32]

What are the current or likely future factors that have an impact on disease burden, and in what way do they affect this burden?

The important paediatric diseases mentioned above have a major health impact on the individual level. They reduce the health status of children and may result in decreased developmental achievements, permanent disability, or even death. This not only affects the young patients themselves, but also their families and relatives. Especially in developing countries, children have to support their families. If they cannot do that, this affects the family and even the community, which is affected by the loss of production of the children. This loss of productivity becomes a large economic burden.[21]

For chronic respiratory and acute infectious diseases, factors that influence disease burden are mostly in line of lifestyle changes. At the moment, most infectious diseases are still under control in the developed world (although current developments in the epidemiology of resistant bacterial and viral diseases may make this statement doubtful with respect to the future!) whereas social, economic and medical infrastructures in many developing countries are weak in terms of prevention of infectious diseases in children.[33] The fact that lifestyle and environmental factors are important determinants of paediatric disease burden is shown by data on asthma rates increasing as communities adopt western lifestyles and become urbanised. With the projected increase in the proportion of the world's population that is urban from 45% to 59% in 2025, there is likely to be a marked increase in the number of young asthmatics world-wide over the next two decades. It is estimated that there may be an additional 100 million persons of all ages with asthma by 2025.[18] This will most likely be accompanied by an increase in burden on all levels of society.

For the mental diseases, the nature and size of disease burden is already large and still increasing. One factor that contributes to this increase is the growing awareness of the existence of, often unrecognised and underdiagnosed, psychiatric and behavioural problems in children. This burden has been underestimated in the past, but nowadays people become more and more aware of the impact of mental disorders on a young patient's life.[34] Another reason for a probable increase in the burden of paediatric mental disorders during the next decades is the increasing involvement of children in traumatic experiences (e.g. war or orphanisation by HIV/AIDS[24]). In young patients with undertreated mental disorders, there are high rates of school drop-out, crime, unemployment, and suicide.[27, 28]

WHAT IS THE CONTROL STRATEGY?

To reduce the burden of childhood diseases there are some general issues that should be addressed. It is crucial for paediatric diseases to be recognised as an important cause of morbidity, economic cost, and mortality worldwide. The incidence and prevalence figures must be closely defined and monitored, as must the morbidity and mortality due to the disease throughout the world. What we have learned from childhood asthma is that a further identification of the environmental factors (including indoor and outdoor air pollution), which affect respiratory morbidity, with consecutive actions, is needed. Most visible in this respect is the promotion and implementation of anti-tobacco public health policies to reduce tobacco consumption.[18]

It is most important to protect children from being treated with insufficiently evaluated medicines, which could be regarded as unethical treatment, and to ensure that they are treated with utmost care using effective treatments options. A first thing to accomplish this is to improve research into medicines for children, thus reducing unlicensed and off label drug use.

Regulatory environment

There is a very important interface between the regulatory environment and paediatric drug research. The US Food and Drug Administration (FDA) has developed a number of initiatives to obtain more information on paediatric use of medicinal products. The Paediatric Labelling Rule in 1994 resulted

in 'The Best Pharmaceuticals for Children Act' (BPCA) in 2002.[13] This law, among other policy instruments, provides additional six months market exclusivity for companies that are willing to test their medication voluntarily in children. There are also important European initiatives in this direction, commissioned by the European Commission and the EMEA.[35]

In 1998, the Commission and the EMEA supported the need for international discussion on the performance of clinical trials in children and a European guideline has been in force since July 2002.[36] The goal of this guideline was to encourage and facilitate timely paediatric medicinal product development internationally.[37] A directive on Good Clinical Practice that was adopted in April 2001 takes into account some specific concerns on performing clinical trials in children, and in particular it lays down criteria for their protection in clinical trials.[38]

These European initiatives do not contain actual obligations and requirements, but mainly encourage the pharmaceutical industry to investigate drugs in children. Thus, a gap has occurred in paediatric medicine availability between Europe and the US. To reduce this gap the European Commission-Enterprise Directorate has proposed a European Legislative Initiative called 'Better Medicines for Children'.[36] This Initiative contains, among others, the following regulations: incentives for research, introduction of a period of data protection, creation of a specific fund that could be used to finance paediatric research, legal requirements for clinical trials, central database on off label uses, establishment of an EU scientific expert group, follow-up pharmacovigilance studies for high-risk products and creation of a pan-European network of clinical excellence for the performance of paediatric studies. [35]

Very recently, on 29 September 2004, which is two years after the initiation of the proposal, the European Commission adopted a proposal on medicinal products for paediatric use. It aims to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children. Key elements in the proposal are (I) a new expert committee, within the European Medicines Agency to assess and agree companies' testing plans, (II) a requirement at the time of marketing authorisation applications for data on the use of the medicine in children (III) a reward for studying medicines for children of 6-months extension to the supple-

mentary protection certificate, (IV) for off-patent medicines, ten-years of data protection for new studies awarded via a Paediatric Use Marketing Authorisation (P.U.M.A), (V) increased safety monitoring for children's medicines and compulsory submission by industry of existing studies in children, (VI) an EU inventory of the therapeutic needs of children and an EU network of investigators and trial centres to conduct the studies required and (VII) a system of free scientific advice for the industry, provided by the European Medicines Agency. The proposal will now be delivered to the Council and the European Parliament where it will go through the co-decision procedure. The earliest that the proposal is likely to become law is late 2006.[39, 40]

Accurate diagnosis and proper treatment

Accurate diagnosis and proper treatment are essential for reducing the burden of diseases in childhood. The WHO has set up the 'Integrated Management of Childhood Illness' (IMCI).[41] The goal is to reduce death, illness and disability in children under the age of five, by promoting accurate diagnosis and treatment. The three main strategies of IMCI are (I) improving case management skills of health-care staff, (II) improving overall health care and (III) improving family and community health practices.[41] This combined management strategy can be applied to all illnesses but seems especially suitable for paediatric infectious diseases.

For asthma, many guidelines for appropriate diagnosis and treatment have been developed and these could be used as a model for other paediatric illnesses as well.[19, 20] To manage and control asthma at the patient level, a six-part management program has been developed, which includes education for children and families to develop a partnership in asthma care, the assessment and monitoring of asthma severity, a plan for avoidance of exposure to risk factors.

An individual medication plan for long-term management and a plan to manage acute asthma attacks are being established according to age (infants and preschool children, school children and adolescents) and regular follow-up care is being provided. The goals are minimal or no symptoms, (including night-time symptoms), minimal asthma episodes or attacks, no emergency visits to physicians or hospitals, minimal need for reliever medication, no limitations on physical activities and exercise, nearly normal lung function and minimal or no side effects from medication.[19] To this aim,

further research into the causation of asthma, primary and secondary intervention strategies, and management programs is still necessary.[18]
This comprehensive system, successfully developed in the field of childhood asthma, provides many useful ingredients to be applied in other disease categories as well. For instance, in mental disorders in children, the burden of disease and the impact of the disease on a patient's life can be considerably reduced by accurate diagnosis and effective treatment. So far, however, there are no guidelines for the treatment of mental disorders in general. There are several topical guidelines for the specific mental disorders, e.g. depression [42, 43] and Attention Deficit/Hyperactivity Disorder.[44, 45]

Children with mental disorders experience a high impact on their social life, school performance and future perspectives. Therefore, it is really important to recognise the problems early on in order to prevent more harm.[24] The control strategy in mental disorders in children is to decrease the social stigma. Many patients and their parents are ashamed to tell about their problems and to ask for help.[29] By reducing these barriers, early intervention can prevent many problems.[24]

Improving access to preventive medicine

Another important issue related to drug use in children is how access to diagnostic and therapeutic options can be ensured. This question is particularly applicable to infectious diseases. Technologically speaking, for most infectious diseases there are suitable solutions available. However, when social, economic, and environmental circumstances do not facilitate access to such solutions, successful resolution of these problems cannot be achieved.[33]

Exemplary is the case for acute respiratory infections (ARIs, including pneumonia and influenza). Low-cost antibiotics can easily treat most ARIs. Another example is avoiding AIDS in children by preventing transmission of HIV during pregnancy and breast-feeding. Infectious diseases like diarrhoea can largely be prevented by good hygiene.

Measles, as one of the leading causes of mortality in infectious disease, can be prevented by timely vaccination.[17] The economic, political, and scientific factors, which limit the availability of such preventive medicine strategies should be identified and addressed more carefully.

Preventing progression of disease in adults by treating children: the asthma model

Epidemiological and natural history studies of asthma have found that, for most people who develop asthma, clinical manifestations of the disease occur in the early childhood years. Both asthma persistence and severity during early childhood predict disease persistence into later childhood and adulthood, at which point asthma remission is uncommon. Current pathogenesis paradigms suggest that early intervention, before serious pathologic changes to the lung occur, may lead to optimal outcomes. Early intervention might optimise lung growth and immune development, and mitigate asthma persistence and severity.[46]

Early management strategies for childhood asthma that can be used in this way are:

1. 'Early intervention' can be applied soon after clinical asthma has occurred, with the goals of reducing asthma symptoms and exacerbations safely, while mitigating immune pathogenic and aberrant repair processes to allow for normal lung growth and development to proceed.

2. 'Secondary prevention' strategies target at-risk infants and young children to prevent lung targeting of disease processes. Examples of at-risk children include those born prematurely or with early manifestations of atopy.

3. 'Primary prevention' aims to promote immune development in a manner that keeps pro-asthmatic immune responses from developing.[46]

This approach, which has been developed successfully in childhood asthma, could also be applicable to other diseases in children. However, there is a great gap between what has already been accomplished in childhood asthma and what still has to be accomplished in mental diseases. Treatment of children with mental disorders is still in its infancy, from a scientific, medical and economic perspective. Despite this, it would be important to treat such disorders appropriately because the percentage of mental disorders in adults that started in childhood is very high. Newman *et al*. showed that 73.8% of adults diagnosed at age 21 with a mental disorder, had a developmental history of, very often not recognised and undertreated, mental disorders.[47]

WHY DOES THE DISEASE BURDEN PERSIST?

Research in children

There are several reasons why it is not very attractive for pharmaceutical industries to develop specific paediatric medicines. Firstly, there are commercial problems. The market for paediatric medicines is by far not as large as the market for adult medicines, because the number of children that need medication is relatively small.[48] There are concerns that the differential obligation to carry out clinical studies on children in Europe as compared to the USA will result in a gap between Europe and the USA in paediatric medicine availability.[35] The proposal for the regulation on medicinal products for paediatric use, which was adopted by the European Commission just recently on 28 September 2004, is largely based on the regulations in the USA. Whether these regulations will be equally effective as the American BPCA and thereby reduce the gap between Europe and the USA has to be awaited.

Secondly, the only way to obtain medicines specifically licensed for paediatric populations is to do research in children. Clinical trials are widely accepted as the safest and most sensible way to improve knowledge of possible drug treatments for diseases in children. Nevertheless, in many countries there is still substantial resistance to the participation of children in clinical trials. In this context it is important to realise that the surroundings of clinical trials are much more controlled than they will ever be in case of unlicensed or off label drug use.[13, 49]

One can divide the obstacles of doing research in children into a set of categories, which, beside the commercial problems already mentioned, include ethical, scientific, and practical issues.

Ethical issues

The involvement of children in clinical trials represents a dilemma. There is a tension between the need to safeguard the health of an individual child and the obligation of society to facilitate research that will result in improved outcomes for children in the future. When considering trial participation, parents and paediatricians are usually more concerned about the risks and benefits for the individual child than any societal benefit.[7] Society wants to withhold children from the testing of new medicines for obvious reasons. On the other hand, one may argue that off label use and/or unlicensed drug

use may harm children even more.[49] The Declaration of Helsinki requires that treatment offered to the control group should be the current best standard treatment, and that those allocated to the experimental group receive a treatment proposed to be as good as or better than standard treatments. Hence, a well-designed randomised clinical trial (RCT) could arguably offer a patient the optimum treatment approach. Many reports show inclusion benefits for all trial participants, including children (the Hawthorn effect).[7]

Potential risks specific to children, that are not usually of concern when considering studies in adults, include discomfort, inconvenience, pain, fear, separation from parents or familiar surroundings, effects on growing or developing organs, and size or volume of biological samples.[7]
It has to be taken into account that children are a more vulnerable group than adults, because of possible long-term side-effects on growing or developing organs. A good example of this is the recent finding that early postnatal dexamethasone therapy should not be recommended for the routine prevention or treatment of chronic lung disease, because it leads to substantial adverse effects on neuromotor and cognitive function at school age.[50] However, this should not be a reason to exclude children from participating in trials, on the contrary, a well-conducted (multicentre) trial with a long-term follow-up is much more likely to detect long-term side effects than when using medicines off label or unlicensed.

Before participation of a child in a clinical trial, both parents and child must be fully informed. The information given must be adapted to the level of comprehension and intelligence of both parents and children.[51] In paediatric trials, consent is obtained by proxy from the child's parents or guardians. Parents are uncomfortable with this referred responsibility because of concerns about unknown or unexpected future side-effects and the possibility that the treatment their child receives might later be discovered to be ineffective or even harmful.[7] Whether parents give permission to include their child in a clinical trial can depend on several factors. It is likely that parents of children with a life-threatening disease may see the trial as the best hope and do not fully realise the risks.[49] Although it may seem reasonable to give compensation for the participation in the trial, the parents may be influenced by the offer of payments.[8, 49] It is widely accepted that children aged 7 years or older are judged to be capable to give assent for participation of a trial.[8, 49, 51] The assent or dissent given by the child, must be binding and be respected

by all parties, unless the research has potential therapeutic benefit in which case a child's dissent can be overridden.[8] In the US Code of Federal Regulations,[8, 52] clinical research in children is only allowed when the research qualifies for one of three risk-benefit categories (I) minimal risk (not greater than the risk in normal life), (II) greater than minimal risk, but presenting the prospect of direct benefit or (III) greater than minimal risk without the prospect of direct benefit but likely to produce generalisable knowledge about the subjects' disorder or condition.

An ethical issue of a different order concerns using placebo controls in clinical trials. In clinical trials with adults, this is a widely accepted approach, but in the case of children, it might be thought unethical.[48] Another related difficulty is the administration of a sub-therapeutic dose of the drug during pharmacokinetic dosage studies.[48]

Scientific issues [53, 54]
'Children' are a very heterogeneous group. Large differences exist between a new-born infant and a 16-year-old teenager. These differences include body size, composition, surface area, physiology, pharmacokinetics and pharmacodynamics. A division in age groups in order to create more homogeneous groups is widely accepted in research: neonates (< 1 month), infants (1 month to < 2 years), children (2 years to < 12 years), and adolescents (12 to < 18 years). Within these groups, the development and physiology are comparable, which adds to the statistical power of studies and makes the research easier.[15] On the other hand this division may decrease the generalisability of results.

Practical issues
For many reasons, it is difficult to recruit sufficient numbers of children for trials. As described above, the hesitation and objections of the parents are a major reason. They often do not want their children to participate in 'drug testing'.[8, 51] The balance of perceived benefits and barriers or risks of participation, and the importance of the study influences parents' willingness to participate.[7] Another important issue is that for many diseases, which occur in children, there is just a small number of children affected. Because of this small affected group, it is difficult to attain a reasonable sample size.[4] The recruitment of children for participating in clinical trials can be made more feasible through international, multi-centre trials.[55]

Another problem encountered in drug trials in children has to do with sampling of blood and/or other body fluids for measuring relevant biomarkers and the like. The small body size of a child may cause sampling problems, although micro-technologies are being increasingly improved. Children and their parents might find blood sampling traumatic.[9, 48, 55] Therefore, the number of blood samples taken in paediatric clinical trials must be kept to a minimum. When it is really necessary to sample blood, it is very important to comfort the child, thereby reducing the traumatic experience. It is also important to limit the complexity and duration of the testing and explain to the child and the parents what the procedures are and what the necessity of the test is.[13]

Health care system

There are many barriers to efficiently reducing the burden of diseases in childhood. They include generic barriers like poverty, poor education, poor infrastructure, and inherent barriers in the organisation of health care services in terms of geography, type of professional responding, education and training systems, public and private care and the tendency of care to be 'acute' rather than 'routine'.[18] There is limited access to appropriate health care for children.[33] In many countries, children do not have health care cost insurance and for many families, the costs are too high to be paid without insurance.[29]

This non-coverage of medical costs can lead to the choice not to consult a physician and in lack of treatment for children that need treatment. In the case of mental disorders, this can result in even worse problems, like criminal behaviour, early school drop-out, alcohol or drug abuse, violence and youth suicide.[24]

Another problem is the limited availability and use of medications including lack of basic medications from WHO or national essential drug lists, poor supply and distribution infrastructure, or costs. The burden of paediatric infectious diseases, in principle, should not exist because for many infectious diseases (e.g. pneumonia), there are very effective medications. The burden of infectious diseases persists because of the lack of access to medications in developing countries and because the low-income countries often do not have appropriate health care systems, making early intervention virtually impossible.[33]

Diagnostic dilemmas

Efficient and safe diagnostics are a first step in every medical-therapeutic scenario. This is particularly relevant in children where various problems may arise. In very young children for instance, differentially diagnosing asthma from other wheezing disorders remains a difficult task. For these children, wheezing is not only a central feature of chronic asthma but also of other, more transitory, respiratory conditions. The causes of wheezing in young children are quite heterogeneous, and only a minority (about 20%) of wheezing children will develop persistent atopic asthma. It is therefore important to make distinctions among wheezing syndromes, because the diagnosis affects treatment and disease outcome.[56] Guidelines tend to group all conditions together as if they are one uniform disease. Some childhood studies show infrequent episodic wheezing (often non-atopic asthma) being grossly overtreated. On the other hand, some cases of more severe asthma are underdiagnosed and undertreated.[57] However, although it is often possible to identify the future atopic individual fairly early in life, what we do not know is whether the child in question is going to develop asthma or not. At this stage, we do not have so far predictive markers that are clinically useful. It is important to identify individuals with chronic asthma because these are the undertreated patients.[58]

In childhood mental disorders there are problems with identifying and classifying affected children. In children it can be most difficult to distinguish between normal development and behaviour due to abnormal development. One important aspect here is that adult psychiatric diagnostics heavily rely on written and/or oral questionnaires. It is often difficult for children to describe and/or classify their mood or behavioural problems appropriately. When diagnosing mental disorders in children physicians are often dependent on people in the surroundings of the child (e.g. parents, teachers).[34] There are no good diagnostic tests to identify mental disorders in children. Therefore, it is likely that the prevalence of mental disorders is much higher than currently estimated.[29]

Attitude towards disease and medication usage

Attitudes towards diseases, medicines etc. may differ substantially between countries. In some countries and cultures, asthma has a low public health priority due to the importance of other respiratory illnesses such as tuberculosis and pneumonia and the lack of data on asthma morbidity and mortality.

The lack of symptom-based rather than disease-based approaches to the management of respiratory diseases including asthma can lead to under-treatment. Moreover, unsustainable generalisations across cultures and health care systems may impair implementation of therapeutic guidelines developed in high-income countries, in low and middle-income countries. In some regions a failure to adequately promote awareness of asthma is a barrier.[18] Besides that, patient barriers are very diverse and include cultural factors, lack of information, underuse of self-management, over-reliance on acute care and use of alternative unproven therapies.[18]

The greatest barrier in mental disorders is the social stigma of these diseases. Because of the social impact, many patients wait too long before they ask for help, while in an early intervention, it is often much easier to treat a disorder. The longer a patient goes untreated, the more difficult it often becomes to restore a patient to health in a swift and acceptable way. Also, if a patient talks about his complaints early, a break-through can be prevented more easily.[30] For asthma treatment some of the problems have to do with the cultural attitude towards drug delivery systems, e.g. inhalers. In children such delivery systems very often give rise to problems since there is a need for either coordinated action (which is difficult in the very young) or a bulky delivery system. Most current asthma guidelines are developed without direct involvement of patients or their parents.[57]

Incorrect intake of medicines can lead to serious problems; a good example of this is antibiotic resistance. In many countries, there is obvious overuse of antibiotics, also in children. This, combined with a poor adherence to the dosage regimes, contributes to the growing problem of drug resistance.[59] It is most important to make physicians and patients aware of the risks of poor adherence to antibiotic therapies.[60]

WHAT CAN BE LEARNT FROM PAST/CURRENT RESEARCH INTO PHARMACEUTICAL INTERVENTIONS FOR THESE CONDITIONS?

Research into children's medicine

For Europe, it is important to improve requirements and rules for paediatric research for pharmaceutical companies. The present guidelines are not obligatory and, as a result, there is still a lack of paediatric medications that have been properly evaluated. By harmonising the guidelines of EMEA and FDA to include obligations for specific research, it is very likely that the amount of drugs licensing in paediatrics will increase in Europe and the world. In short there is a need for obligations, not just recommendations. Europe has taken a big step forward in this direction by adopting the proposal for the regulation on medicinal products for paediatric use on 28 September 2004.

Clinical trials in children have resulted in significant improvements in their health care. A good example is childhood acute lymphoblastic leukaemia, in which the 5-year survival improved from 25% to more than 70% as a result of multicentre trials. Unfortunately, since there are few paediatric trials, the list of improvements in child health resulting from clinical trials is not long and is restricted to some childhood diseases, heavily clustering around cancer.[7] A good example of a result of the lack of paediatric research is the recent recommendation from the Committee for Proprietary Medicinal Products (CPMP, EMEA) not to use paroxetine in children and adolescents, as clinical trials have found paroxetine to be associated with an increased risk of suicidal behaviour and hostility. Moreover, the efficacy of paroxetine in children and adolescents has not been adequately demonstrated. The committee noted that paroxetine is not authorised in any EU Member State for use in children. The working mechanisms of all SSRIs are considered to be comparable. Therefore, it is likely that the recommendations made by EMEA also affect the use of other SSRIs.[61]

Proper use of medicines

When medicines for children are available, proper use of these medicines is critical. It is important to be aware of the discrepancies that exist between efficacy of a drug when tested in a tightly controlled setting and its effectiveness in a daily life setting. Again, paediatric asthma is a useful showcase here. Due to the heterogeneity of wheezing phenotypes in early childhood, limited compliance with long-term inhaler treatment and the intrinsic properties of inhaler devices, low effectiveness is to be expected when treating young wheezy infants and preschool children.[62]

Also, infectious diseases are still the leading cause of deaths in children, in spite of the availability of several suitable vaccines and treatments for

different infectious diseases. Most importantly, existing medications and vaccines must be used accurately. Current experiences show that it is crucial to train and educate public health officials, physicians and parents to use available vaccines and medications in the right way. Stimulating accurate use of antibiotics is also necessary to prevent the development of resistance.[59]

WHAT IS THE CURRENT 'PIPELINE' OF PRODUCTS THAT ARE TO BE USED FOR THIS PARTICULAR CONDITION?

Since being a child is not a 'condition' or disease, one cannot in general discuss products being in the pipeline for paediatric diseases. Therefore, like before, the 'pipeline' of products will be discussed separately for the different groups of diseases that are discussed in more detail in this paper. The only general subject one can refer to as 'being in the pipeline' for pharmaceuticals in children is the recent adoption of the proposal for the regulation on medicinal products for paediatric use by the European Commission, that will hopefully lead to more products registered for use in children.

There are various discrepancies between the number of products in the pipeline for a certain disease and the number that is also being tested for use in children. For instance, in 2004 there are at least eight drugs in the pipeline for the treatment of so-called 'attention deficit disorder' (ADHD). It is remarkable that for the specific use in paediatrics there are only two drugs in development. For the other mental disorders (depression, anxiety disorders), there are many drugs in the pipeline, but they are not specific for paediatric use.[63]

For acute respiratory infections (including pneumonia and influenza) there are some medicines also being investigated in children,but for HIV-infections there are only two drugs developed for use in children, while for use in adults, there is a very large number of drugs in the pipeline.[63] No paediatric drugs are in the pipeline for TB or malaria. For diarrhoea and measles there are no products in the pipeline at all.[63] There are several appropriate vaccines for measles available; for diarrhoea there are also some suitable treatments available. The need of development of new products is not that high, most important here is to distribute those effective vaccines and medications to the places where they are needed.

WHAT ARE THE OPPORTUNITIES FOR RESEARCH INTO NEW PHARMACEUTICAL INTERVENTIONS INCLUDING DELIVERY METHODS?

In general, early detection and treatment of childhood diseases may contribute to reducing the burden, not only in children but also with respect to adult disease burdens. For asthma increased understanding of risk factors should enable existing therapies to be better targeted, while facilitating the development of new treatment options.[20] The same goes for mental disorders and many other specific paediatric conditions.
For all mental disorders in paediatrics, there is a great lack of knowledge of pathophysiology and of effective and safe medications.[64] To improve drug development for children it is necessary to invest more in basic paediatric research, to improve participation of children in clinical trials and to enhance funding of the search of children-specific drug formulations. There is a great need for information on safety and efficacy of medication use in children, especially for the mental disorders with their high burden of disease (e.g. depression, anxiety disorders).[65]

In order to decrease infant mortality and better understand its impact on health care costs, resources and families, it is important to delineate the causes of infant mortality. This would allow for the development of better health intervention objectives designed to decrease morbidity and mortality, and to improve quality of life. Knowledge of the contribution of genetic disorders and birth defects in infant mortality is valuable in the evaluation of funding research in genetics. This information is also important for helping to develop health care strategies at paediatric hospitals and clinics for treatments and prevention of morbidity and mortality of genetic diseases and congenital malformations. Further research into their biological mechanisms will ideally lead to new developments in prevention and treatment. Ultimately, primary prevention of congenital defects would decrease the paediatric morbidity and death rate. Steps have already been taken to prevent some conditions including avoidance of teratogenic substances, preconceptional maternal folic acid/multivitamin administration, and preconceptional counselling. Trials in gene therapy for cystic fibrosis and urea cycle defects are ongoing. Hopefully, with technological advances and our current knowledge of the human genome, in future more effective treatments will be discovered. The integration of findings from genetic basic science and clinical research into the health care delivery will likely improve child health care.[32]

WHAT ARE THE GAPS BETWEEN CURRENT RESEARCH AND POTENTIAL RESEARCH ISSUES?

Research in general

There are three important notions when addressing research priorities related to drug treatment in children:

- Data needed for effective and safe drug treatment in children and adolescents cannot be linearly abstracted from adult data. Unlicensed and off label use of drugs in children are essentially 'regulatory' observations; these observations should be followed by specific paediatric clinical and pharmaceutical follow-up.

- There is increasing recognition that certain paediatric morbidity's are specific to childhood (e.g. neonatal respiratory problems, paediatric cancers); other conditions ask for more specific drug formulations and/or dosing schemes.

- Certain childhood morbidities are very often 'early signs' for severe and chronic adult diseases (e.g. wheezing/childhood asthma and chronic respiratory diseases later in life, childhood obesity and diabetes/cardiovascular problems, paediatric mental problems and severe adult psychiatric morbidity's). Accurate diagnosis and treatment at an early age are essential prevention strategies in order to reduce adult disease burden.

Conclusively it can be said that more research is needed into medicine use in children. However, when clinical trials are carried out in children, there are some important issues, which need to be considered. To make the experience of participating in research as comfortable as possible, much effort must be made to inform the child about the procedures, and to explain the reason of each intervention. To make the children (and the parents) feel more at ease and safe, it is important to recruit people who have experience with research in children. Central to ensuring the protection of children participating in trials, is the careful ethical review of research protocols at many levels by researchers, funding and scientific bodies, and research ethics committees. A review of the IRB (Institutional Review Board) system in the US shows that IRBs are under-resourced, over-burdened, and ill

prepared to handle the sheer volume and complexity of research that they are asked to review. Paediatric expertise and patient and family representation is often absent in the membership of IRBs. Another serious concern is the inconsistent interpretation of regulations and lack of education and training of IRB-members in common ethical principles and standards, particularly as they apply to children. There are fewer data on the European situation.[7] To ensure that research in children is ethical, research protocols have to be approved by a committee specialised in paediatric research, to ensure the best interest of the children. Governmental organisations, both national and international, can survey such paediatric research and support the drafting of research protocols. In that way, unethical research can be avoided and children are eventually served best.

An important concern in doing pharmaceutical research in children is that of possible long-term side-effects on growing or developing organs. Very little is known about long-term effects of (chronic) medication at a young age. This subject has already been mentioned discussing the ethical issues and it might seem contradictionary that possible long-term outcome can be both an ethical barrier for doing research in children and a gap between current and potential research. However, uncertainty about long-term effects of medication use should not be a reason to exclude children from participating in trials, because a well-conducted (multicentre) trial with a long-term follow-up is much more likely to detect long-term side effects than when using medicines off label or unlicensed. This situation changes when long-term side-effects are suspected from adult studies, such information might make research (but also unlicensed and off label use) in children unethical.

A specific issue that has to be addressed concerning paediatric research is the role of the parents. Already mentioned in this context is the informed consent; consent is obtained by proxy from the child's parents or guardians. Better education about the rationale and benefits of trials and the potential dangers of using health-care interventions that have not been appropriately studied [7] might increase their willingness to let their child participate.

However, parents can play a larger role in paediatric research. A good example of the influence parents can exercise is made by the VSOP (Dutch Genetic Alliance of Parent & Patient organisations), which is a Dutch co-operative effort of 60 national diagnosis bound parent and patient organisations, all

concerned with genetic and non-genetic congenital disorders. This organisation is involved in the reviewing of the draft regulation 'Medicinal products for Paediatric use' that is momentary under construction by the EMEA.

Pathophysiology of disease

Using childhood asthma as learning model, significant progress has been made by investing considerably in elucidating the basic mechanisms and pathophysiology of the disease. However, there is still a great gap in basic knowledge of the pathophysiology of mental disorders in children.[64]
If we attain an accurate understanding of these principles, more successful avenues for developing effective and safe medications will be opened.

For asthma the most important point is that no treatment has been shown to modify the natural history of the disease. Treatment can improve symptoms and quality of life, but it does not change whether the patients will continue to have mild, moderate or severe disease. The degree of lung function abnormality and the degree of bronchial hyperresponsiveness at the time of first presentation are all that will predict outcome of childhood asthma through to adulthood. This suggests that the basic roots of relevant pathology are established very early in a patient's life. So far we can control the symptoms but not the disease process.

A fundamental basic intervention that is going to switch off the process is the answer, but this has yet to be discovered.[57] To accomplish this it is important to try and understand the remodelling and inflammation process. The notion that inflammation somehow switches on the remodelling process should be avoided and instead a basic abnormality that drives both must be considered and examined. Secondly, the early life origins of asthma need to be studied. We ought to be able to identify the presymptomatic asthmatic to be able to 'switch things off' before they have started. This has to be the fundamental approach. Prevention is far better than attempts to treat established disease.[57] Next to research into the causation of asthma, the efficacy of primary and secondary intervention strategies, represent key priority areas in the field of asthma research.[18]

Proper use of medicines

Despite the fact that the infectious diseases are not a major problem in the developed world, it is important to realise that appropriate use of antibiotics is also necessary in the developed world to prevent an increasing resistance of antibiotics.[17] The increased migration of people in the past decades, causes an exchange of diseases and it is possible that infectious diseases could become more important in the next decade in the developed world.[17]

Better targeting of asthma pharmacotherapy, especially anti-inflammatory drugs, will become possible when the subgroup of recurrently wheezing children who have chronic airway inflammation and are likely to develop into asthmatics could be more easily identified. This is currently one of the 'hottest topics' in paediatric asthma research.[62] Several recommendations for future research into asthma treatment in children are:

- How do available interventions compare in safety and efficacy in both the short term and long term in the treatment of mild persistent asthma in children younger than 5 years of age?

- Do anticipated differences in adherence to medication regimens (for example, inhalation therapy vs. oral tablet dose therapy) translate into significant clinical differences in overall asthma control?

- Can response to various long-term-control medications be predicted prior to initiating treatment? Phenotype and genotype characterisations and definitions are needed to address this question.[66]

The problems in tracking and identifying children with mental disorders and the lack of good diagnostic tests to identify mental disorders in children make it likely that the prevalence of mental disorders is much higher than currently estimated.[29] Therefore it is important to study the true prevalence and burden of mental disorders in children.

This information can be a stimulant for industries in their decision to develop paediatric medications.[67] And again it needs to be stressed that the issue of mental health in children has been exposed to ample scientific and public discourse in the context of the effectiveness and safety of paediatric psychotropic drug use.[27] Among the public, parents and clinicians there are many uncertainties regarding the medical, ethical and societal aspects of children and adolescents taking medications on a daily basis without proper knowledge of the risks and benefits involved.[68, 69]

CONCLUSIONS

To reduce the burden of childhood it is crucial for paediatric diseases to be recognised as an important cause of morbidity, economic cost, and mortality world-wide. Children are subject to many of the same diseases as adults and are often treated with the same drugs. However, few drugs in use today have been studied and labelled for paediatric patients. Doses for children are often merely adjusted for their smaller weight, but there are many other differences in children that can affect how drugs act in the body. The lack of paediatric testing and labelling can place children at a direct risk of under- or overdosing and a delayed risk of long-term adverse effects. The lack of age-appropriate formulations, such as liquids or chewable tablets, can result in improper administration of drugs.

Drug companies do not often perform paediatric studies on drugs they intended to market to adults, primarily because, notwithstanding various governmental incentives, these drugs would provide little additional revenue from use in children. There seems to be little incentive for drug sponsors to conduct paediatric research on off-patent drugs. Patents have expired for many drugs that are widely used in children but lack paediatric information in their labelling. In this time of evidence-based medicine it is astonishing and unacceptable that children are so often treated with medicines not sufficiently evaluated for use in this vulnerable population. Therefore a first thing to accomplish is to improve research into medicines for children, thus reducing unlicensed and off label drug use.

Besides the lack of research in general, there are a number of known other impediments to the development of a scientific basis for drug treatment in children, including:

- The limited access to appropriate health care for children due to generic barriers and inherent barriers in the organisation of health care services.

- Diagnostic dilemmas, leading to under- and overtreatment.

- Attitudes towards disease and medication usage that impede the proper use of medicines and therefore the desired outcome.

- A lack of knowledge on the pathophysiology and risk factors for diseases affecting children.

To arrive at the desired state, namely a situation where drug treatment in children has at least the same quality as required for adults, the following actions must be taken:

- To improve requirements and rules for paediatric research in children in Europe, with an obvious need for obligations. Europe has taken a big step forward in this direction by adopting the proposal for the regulation on medicinal products for paediatric use on 28 September 2004.

- To better educate the medical community and the public about the rationale and benefits of trials and the potential dangers of using health-care interventions that have not been appropriately studied.[7]

- Structural external changes that would help improve clinical trials in children include the development of co-operation between institutions.[7]

- To stimulate the proper use of medicines by training and educating public health officials, physicians and parents and by investigating the effectiveness of drugs in a daily life setting.

- To improve the knowledge on the pathophysiology and risk factors for diseases affecting children, thus enabling existing therapies to be better targeted and facilitating the development of new treatment options.

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The PIAMA birth cohort: a longitudinal approach

3

ABSTRACT

Introduction
Although many studies evaluated the appropriateness of asthma medication use in children in a cross-sectional manner, very little is known about the longitudinal patterns of medication use. Since asthmatic symptoms, and thus treatment with asthma medication, in general precede the age at which a firm diagnosis of asthma can be made, evaluation of asthma medication use in young children profits from a longitudinal approach.

Methods
We complemented the data collection of the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study with information on asthma medication use through retrieval of pharmacy records and studied treatment with asthma medication in 777 children born in 1996-1997, for whom complete medication histories from birth up to age eight were available.

Results
280 (36%) children filled a first prescription for asthma medication before the age of eight, with 88% starting treatment before age five. Short-acting beta2-agonists (SABA) and inhaled corticosteroids (ICS) were the most used medication groups, 91.1% of all children initiating treatment received SABA and 61.1% ICS. Male gender was significantly associated with initiation of asthma medication.

Conclusions
Asthma medication is initiated in a very high percentage of children and mainly at an age at which an asthma diagnosis cannot yet be firmly established. The question remains whether all starters continue using asthma medication and what their health status is at an older age, when the diagnosis of asthma can be more firmly established.

3.1 Asthma therapy during the first 8 years of life: enrichment of the PIAMA study with medication data

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Submitted

INTRODUCTION

Due to diagnostic difficulties in young children with respiratory symptoms [1, 2] treatment with asthma medication is often initiated in children years before a firm diagnosis of asthma can be made. Only a minority of the children presenting with wheeze or other respiratory symptoms at a young age will develop persistent symptoms.[1, 3-5] Several cohort studies have been conducted to investigate the natural history of asthma, which led to the identification of a number of wheezing phenotypes, such as transient wheezing, nonatopic wheezing and atopic wheezing.[1, 4] Though these phenotypes require a different therapeutic approach, they can only be discriminated retrospectively and thus are of no direct use when deciding on treatment for these children. However, risk factors for persistence of symptoms were also identified. These risk factors were incorporated in guidelines on management of childhood asthma, which advise physicians to base initiation of long-term controller therapy on the presence or absence of these risk factors.[6-9] Also treatment of young children is often a therapeutic trial, where initial assessment and regular reassessment of the child's response to treatment and need for the given therapy is essential.[6-9] This is expected to lead to distinct treatment patterns in young children with asthmatic complaints. However, studies evaluating the appropriateness of asthma medication treatment in children are mainly cross-sectional [10-14] or focus on the group of children with persistent asthma or physician diagnosed asthma.[15-17]
It has not been investigated whether the guideline recommendations lead to differences in treatment between wheezing phenotypes nor what the actual treatment patterns are in young children with respiratory symptoms. These research questions require a longitudinal approach. In order to create a dataset in which these research questions can be answered, enrichment of the PIAMA birth cohort study with complete pharmacy data from birth until age eight took place. In this study we describe the formation of this dataset and show the first results, regarding prevalence and incidence of asthma medication use within the PIAMA study.

METHODS

Study design and study population

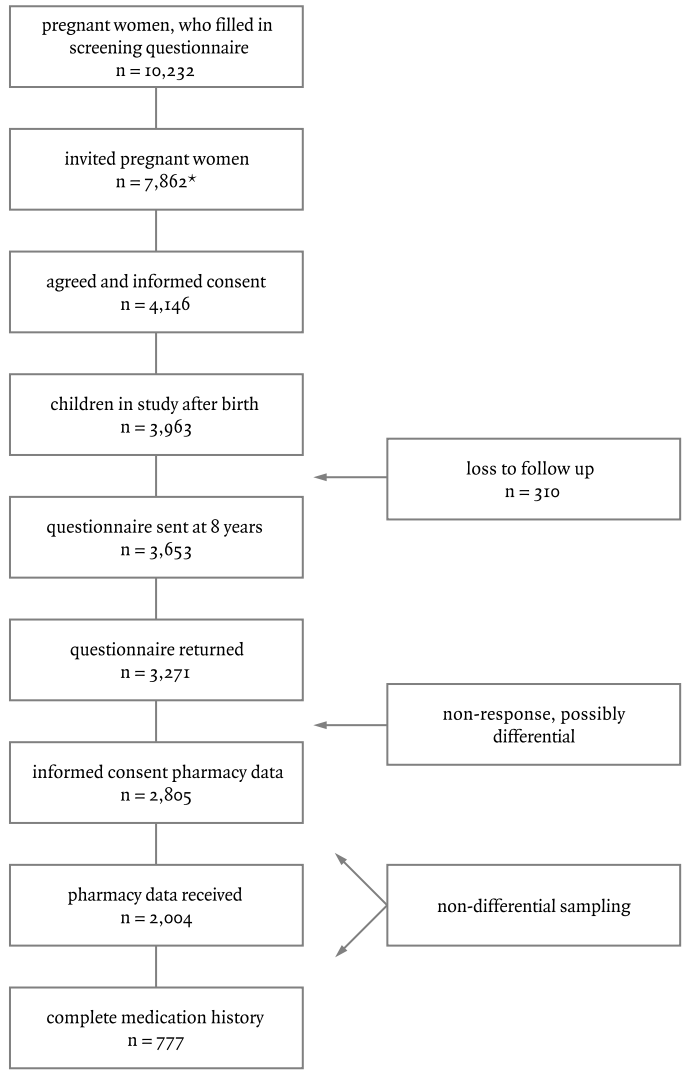
We studied 777 children born in 1996-1997 who participate in the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study, for whom complete medication histories up to age eight were available. The PIAMA study is a prospective birth cohort study among 3,963 Dutch children. Details of the study design have been published previously.[18] Recruitment took place in 1996 -1997. A screening questionnaire was distributed to 10,232 pregnant women visiting one of 52 prenatal clinics (Figure 1). Based on this screening 7,862 women were invited to participate in the study; 4,146 agreed and gave written informed consent. 183 participants were lost to follow-up before any data on the child had been obtained, therefore 3,963 newborn children started in the study. Data on respiratory and allergic symptoms, potential risk factors for asthma and allergy and demographic factors were collected by postal questionnaires. Questionnaires were sent to the participating parents during the last trimester of pregnancy, at the child's age of three months, at the age of one and annually thereafter.

Longitudinal data on medication retrieval have been collected at age eight through prescription data from community pharmacy records. In the annual questionnaire sent at age eight, parents were asked to sign written consent for retrieval of the medication history of their child from their community pharmacy. Informed consent was given in 2,805 of the 3,271 questionnaires returned at age eight. Pharmacy information was retrieved from community pharmacies for 2,004 children. For 777 children these pharmacy data were complete from birth until age eight. Medication histories were assumed to be complete if the first prescription of a family member was recorded before the child's date of birth, and the last prescription of the child or a family member was at least eight years after the date of birth. In the Netherlands, pharmacy records are virtually complete with regard to outpatient medication use.[19]

Medication use from birth up to age eight

All medicines with Anatomical Therapeutic Chemical (ATC) code R03 were considered to be asthma medication. This R03 group includes inhaled and oral short-acting beta2-agonists (SABA), inhaled long-acting beta2-agonists (LABA), inhaled corticosteroids (ICS), inhaled cromones, inhaled anticholinergics and montelukast.[20] The yearly prevalence was calculated for treatment with asthma medication in general and for specific medication groups, as was the overall prevalence during the first eight years of life. Combination preparations were calculated in both groups, to which the individual components belonged.

FIGURE 1 Flowchart study population



*2,779 atopic mothers and 5,083 non-atopic mothers

Based on the guidelines for treatment of asthma symptoms in children, in which separate recommendations are made for children below the age of five/six and older children and where the introduction of maintenance therapy with ICS is one of the most important decision moments [6-9] we defined four possible therapy groups: (I) children who never received asthma medication within the first eight years of life, (II) children who received a first prescription for asthma medication before age five but never received ICS within the first eight years of life, (III) children who received a first prescription for asthma medication before age five and received ICS at some point before age eight and (IV) children who received a first prescription for asthma medication between age five and eight. Initiation of any asthma medication or ICS between birth and age eight was analysed using Kaplan-Meier analyses. For the initiation of any asthma medication, subgroup analyses were performed for gender and parental asthma. Parental asthma was defined as at least one parent reporting to have (had) asthma. Oral corticosteroids (ATC code H02AB) were not classified as primary asthma treatment. Other medication groups of interest were antibiotics (all prescriptions with ATC code J01) and antihistamines (all prescriptions with ATC code R06). Antihistamines were further subdivided into medications mainly used for asthma and cough (deptropine and promethazine) and all other antihistamines, used for allergy.

RESULTS

Characteristics of the study population

A total of 777 children were included in this study. To define whether the non-response in retrieval of the pharmacy data led to differences in the composition of the study population compared to the original PIAMA population, three groups were compared with respect to basic child characteristics. This comparison between the group of children with complete pharmacy data (N = 777), the group for which informed consent was given (N = 2,805) and the population eligible for retrieval of pharmacy data, which was the total PIAMA population at age eight (3,271) is shown in Table 1. Our study population corresponded very well to the original PIAMA population with respect to gender, ethnicity, parental educational level, degree of urbanisation, parental asthma, and birth weight. No statistical significant differences in these characteristics were found between the three groups. Although the percentage of mothers who smoked during pregnancy seemed somewhat lower in our study population, this difference was not statistically significant. Children in our study population were primarily of Dutch origin (97.2%), 51.7% was male and 12.7% had at least one parent with reported asthma.

TABLE 1 Study population characteristics in relation to the original PIAMA cohort

	STUDY POPULATION (N = 777)	INFORMED CONSENT FOR PHARMACY DATA RETRIEVAL (N = 2,805)	ORIGINAL PIAMA STUDY POPULATION AT AGE 8 [a] (N = 3,271)
Gender, % male	51.7	50.9	51.5
Ethnicity, % Dutch [b]	97.2	95.1	94.9
Maternal educational level, % low [c]	21.2	21.2	21.5
Paternal educational level, % low [c]	25.7	24.4	24.6
Degree of urbanisation, mean (SD) [d]	3.2 (1.2)	2.9 (1.3)	2.9 (1.3)
Parental asthma, % [e]	12.7	13.7	13.5
Birth weight in g, mean (SD) [f]	3,532 (533)	3,517 (533)	3,524 (534)
Maternal smoking during pregnancy, % [g]	13.2	16.0	15.7

[a] *This is the eligible population for retrieval of medication history*

[b] *Based on both the country of birth of the mother and the self-reported ethnicity of the mother, if both Dutch*

[c] *Educational level: low = primary, lower vocational and lower general; intermediate/high = senior high school, intermediate and high vocational and university*

[d] *Degree of urbanisation: groups are defined based on the address density per km²: 1.>=2500, 2.1500-<2500, 3.1000-<1500, 4.500-<1000, 5.<500*

[e] *Father or mother or both reported to have (had) asthma*

[f] *Premature children were excluded from this group (n = 150 in the original PIAMA study population)*

[g] *Defined as any smoking by the mother during pregnancy after the fourth week of pregnancy*

Prevalence of asthma medication use

The prevalence of asthma medication use in the study population is shown in Table 2. 36% of all children received at least one prescription for asthma medication in the years from birth until age eight. When stratified by age, the prevalence was somewhat higher in the first years of life (varying around 12%) than at ages 5 to 7 (just above 10%). The relatively high overall prevalence compared to the yearly prevalences indicates that the group of children

receiving medication did not constitute of the exact same children, chronically using asthma medication throughout the years, but that in different years different children received asthma medication. When looking at specific medication groups, we found that SABA and ICS were the two most frequently prescribed medicine groups in our study population. The prevalence of SABA treatment steadily declined with age from 11.6% to 6.8%, whereas ICS therapy was lower in the first year of life (4.8%) and fluctuated from 6.4 to 8.8% from age one to seven. Anticholinergics were mainly used at a young age, with a decline in prevalence of 5.5% in the first year to almost nothing (0.1%) at age seven. Only few children received montelukast, cromones or theophylline. The LABA group was the sole asthma medication group to show a modest rise in prevalence with increasing age.

TABLE 2 Prevalence of asthma medication use within the study population (N = 777)

	AGE 0	1	2	3	4	5	6	7	0-7
Asthma medication	12.7	12.9	11.5	12.7	12.9	10.7	10.2	10.2	36.0
Medication groups									
SABA	11.6	10.6	9.5	9.3	9.9	7.3	7.0	6.8	32.8
ICS	4.8	6.4	7.2	8.8	7.9	8.0	7.9	7.0	22.0
LABA	0.3	0.3	0.3	0.5	0.6	0.5	1.0	1.2	2.8
Anticholinergics	5.5	4.0	2.8	2.2	2.1	1.2	0.5	0.1	11.2
Other [a]	0.3	0.1	0	0.1	0	0	0.3	0.3	1.0
Other medicines									
Oral corticosteroids	0.6	0.6	1.0	0.9	1.0	0.8	0.4	0	3.9
Antihistamines	20.9	18.0	10.0	8.6	11.7	7.5	5.9	7.6	48.3
deptropine and promethazine	18.0	13.1	5.8	5.0	6.8	2.6	1.7	2.3	35.8
all other	4.1	6.3	4.8	4.1	5.8	5.1	4.2	5.3	21.8
Antibiotics	30.6	39.1	34.4	28.6	33.2	23.6	17.0	17.9	81.7

[a] *Other = montelukast, cromones and/or theophylline*

SABA = short-acting beta2-agonist; ICS = inhaled corticosteroids; LABA = long-acting beta2-agonist

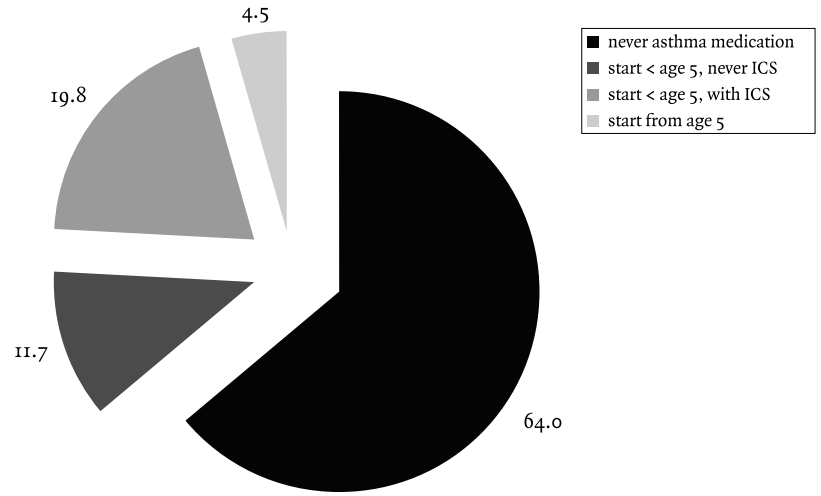
Other medicines

A majority of the children (81.7%) received at least one prescription for antibiotics in the first eight years of life. The high use of antihistamines at a young age can be explained by a high prevalence of deptropine and promethazine (18.0%, traditionally used for cough and asthma instead of allergy), which rapidly declines with age. The prevalence of use of all other antihistamines was fairly constant over the years. Oral corticosteroid use was low at all ages.

Asthma therapy groups

When dividing the children into the predefined therapy groups (Figure 2) we found that most children received a first prescription for asthma medication at a young age. 31.5% of the total study population received a first prescription before age five and 62.9% of these children received ICS at some point in time. Only 4.5% of the total study population received a first prescription for asthma medication between age five and eight.

FIGURE 2 A presentation of the most common asthma therapy groups



Time until first prescription

In Figure 3 the results from the Kaplan-Meier analysis are shown. Of the 280 children receiving a first prescription for asthma medication before age eight, 77.9% initiated this therapy within the first four years of life. We saw that for treatment with ICS 68.9% of children ever receiving ICS started treatment before age five. Initiation of asthma therapy was significantly associated with male gender (Figure 4), with 41.3% receiving asthma medication before age eight versus 26.6% of girls.

FIGURE 3 Start of asthma medication use during eight years of follow-up

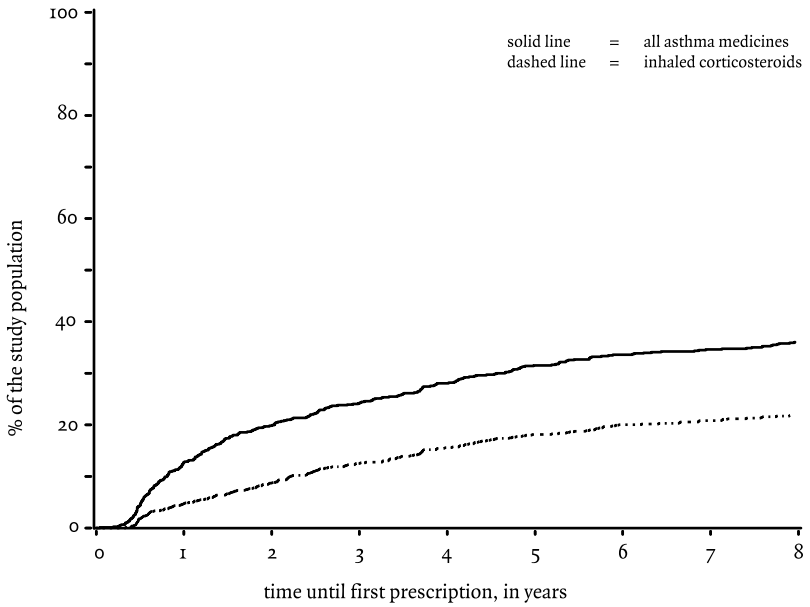
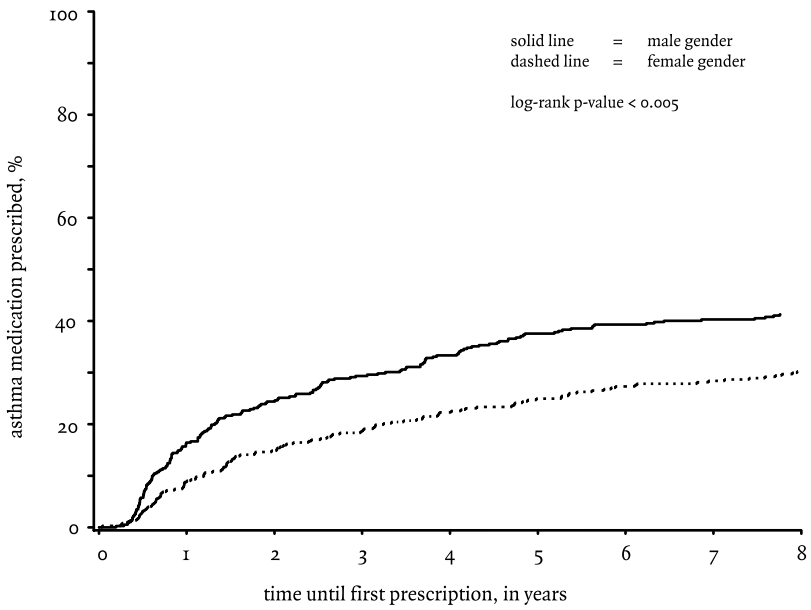
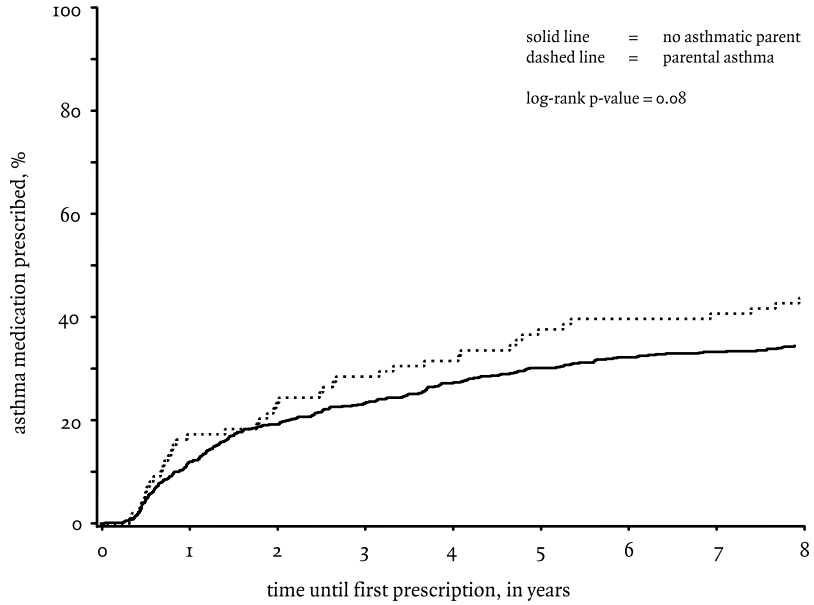


FIGURE 4 Difference in start of asthma medication use between gender



A similar trend, though not reaching significance, was found for children with an asthmatic parent (Figure 5), 43.9% of children initiated asthma medication versus 34.6% of children without parental asthma.

FIGURE 5 Difference in start of asthma medication use between children with and without at least one parent with asthma



DISCUSSION

In this study we showed the first results from the enrichment of the PIAMA birth cohort study with pharmacy data, collected with the aim to render insights into the longitudinal patterns of medication use in children from birth until age eight. Although we could not retrieve full medication histories for all children within the PIAMA cohort, no significant differences in basic child characteristics were found between our study population and the original PIAMA cohort, indicating that our study population is a good reflection of the population based PIAMA cohort.

The yearly prevalence of asthma medication treatment found in this study is in line with previous findings in the second Dutch national survey of general practice (DNSGP-2) where 11.7% of 0-2 year olds and 10.2% of 3-5 year olds received asthma medication.[21] The prevalence within 6-7 year old children is somewhat higher in this study (10.2%) than in the DNSGP-2 study (7.5% in 6-8 year old children). Our finding that SABA and ICS were the main asthma medication groups used in children is conform the guidelines.[6-9] 36% of children received a first prescription for asthma medication before the age of eight of which 88% before age five, which reflects the high burden of respiratory symptoms in young children reported in other studies. Bisgaard *et al.* reported a prevalence of asthma-like symptoms of 32% in children age one to five [22] and Martinez *et al.* reported 48.5% of children to have wheezed before the age of six.[4] This study shows that it is likely that many of these children receive treatment for their complaints.

The significant association between male gender and initiation of asthma therapy is conform previous findings in a population based cross-sectional study that showed that boys were more often treated with asthma medication and diagnosed as asthmatics [21] and can be explained by studies consistently reporting boys to have more wheeze and asthma than girls, while this pattern changes in adolescence.[23]

Both Goodman *et al.*[13] and Clavenna *et al.*[12] evaluated asthma medicine use cross-sectionally and showed that most children received only occasional prescriptions, presumably for mild illnesses and diseases other than asthma. With a longitudinal approach we will be able to evaluate whether the infrequent fills are within the group of transient wheezers. The difference in yearly and overall prevalence found in this study already shows that many children do not continue using asthma medication after a first prescription. In conclusion, our study showed that the enrichment of the PIAMA study with pharmacy data led to a study population which is a good reflection of the original PIAMA cohort. This data collection shows the high burden of treatment with asthma medication in children before age eight (36%) and provides opportunities to evaluate the appropriateness of this treatment in a longitudinal way.

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ABSTRACT

Introduction
In young children with asthmatic symptoms diagnostic difficulties lead to use of trials of asthma medication as a diagnostic tool. Our aim is to quantify the persistent use of asthma medication, initiated in the first year of life and identify determinants of this persistent use.

Methods
We identified 165 children within the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort who used asthma medication before the age of one. Persistent use was investigated during three years after the first prescription. A Cox regression analysis was performed to identify factors associated with persistent use.

Results
A total of 58.8% of children continued using asthma medication after the first prescription and 10.3% continued during three years. Children with doctor-diagnosed asthma (Hazard ratio of discontinuation (HR) = 0.64; 95% CI 0.45 to 0.91) or prescribed inhaled corticosteroids in the first year of life (HR of discontinuation = 0.59; 95% CI 0.40 to 0.86) were 1.6 to 1.7 times more likely to continue using asthma medication.

Conclusions
Persistence of asthma medication, prescribed in the first year of life is very low and is positively associated with doctor-diagnosed asthma and use of inhaled corticosteroids. Characterizing persistent users of asthma medication is important to understand prescribing of asthma medication in this age group.

3.2 Persistence of asthma medication use in preschool children

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INTRODUCTION

When a preschool child with symptoms suggestive of asthma presents at the physician's office, a diagnosis of asthma cannot be made with confidence.[1-4] It is well known that wheezing at a young age may not only be due to asthma but also to other, more transient, respiratory conditions.[2-6] Only a minority of wheezing children will develop persistent symptoms and will, therefore, be diagnosed as having asthma.[7-10] However, despite this diagnostic uncertainty, asthma medication is often prescribed to wheezing infants. Moreover, the response to asthma medication itself is widely used as a diagnostic tool to strengthen or reject the possible diagnosis of asthma.[3, 5, 11, 12]

The GINA guidelines state that 'a trial of asthma medication is probably the most confident way to make a diagnosis on asthma in children'.[11] The rationale behind the trial treatment is that young children with wheezing but no underlying asthmatic disease are expected not to respond to treatment and will therefore discontinue treatment after evaluation of the effect. It is not known how often infants initiating such trial treatment benefit from the asthma medication and, therefore, continue medication use.[13]

Notwithstanding the fact that asthmatic symptoms over time influence persistence of medication use, some patient characteristics, already known at start of asthma medication therapy, might be predictive of persistent asthma medication use in preschool children. If so, this could aid the decision whether or not to start a trial of asthma medication in a preschool child. The objective of this study is to quantify persistence of use of asthma medication in preschool children and identify possible determinants of persistence of use, which can be assessed at start of therapy.

METHODS

Study design and study population

For this study we identified 165 children from the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study, who received asthma medication before the age of one. The PIAMA study is a prospective birth cohort study among 3,963 children. The design of the PIAMA study has been described in detail elsewhere.[14] In short, the participating children were born between July 1996 and October 1997. They were recruited from the general population through prenatal healthcare clinics in three different regions of the Netherlands. Data on respiratory and allergic symptoms, potential risk factors for asthma and allergy and demographic factors were collected by postal questionnaires. Parents were sent a questionnaire during the last trimester of pregnancy, at the child's age of three months and annually thereafter. Longitudinal data on medication use have been collected at age four through prescription data from community pharmacy records. In The Netherlands, pharmacy records are virtually complete with regard to drugs dispensed to patients.[15]

Asthma medication and persistence of use

Medical drug prescriptions were registered according to the Anatomical Therapeutic Chemical (ATC) Classification system.[16] All medicines with ATC code R03 were considered to be asthma medication: inhaled or oral short-acting beta2-agonists (SABA), inhaled long-acting beta2-agonists (LABA), inhaled corticosteroids (ICS), inhaled cromones, anticholinergics and montelukast. Oral corticosteroids (H02AB) were not classified as primary asthma treatment. Persistence of use of asthma medication was investigated during a time-window of three years, using discontinuation rates.[17] The index date was defined as the date of the first prescription for asthma medication. Discontinuation of treatment was defined as the occurrence of a treatment gap of more than 365 days between one dispensing of asthma medication and a subsequent dispensing during the study time-window.

Time to discontinuation was calculated as the number of days from the index date to the date of the last dispensing before the gap of more than 365 days + a pre-specified time period of 90 days (which is the maximum duration of a single prescription in the Netherlands). A wide treatment gap of 365 days is chosen because we want to quantify the amount of children receiving an initial prescription for asthma medication without needing asthma medication regularly over the next couple of years and compare these children with the ones who might still have intermittent or seasonal complaints but do return to use of asthma medication at least once every year. If the aim had been to determine continuing availability of asthma medication the allowed treatment gap would have been much smaller.

Statistical analysis

Persistence of use was examined using survival analysis, the endpoint being discontinuation of asthma medication. The overall persistence of use was determined using Kaplan Meier analyses. Univariate and multivariate Cox regression models were used to calculate unadjusted and adjusted hazard ratios and 95% confidence intervals (CI) for discontinuation of asthma medication use. The hazard ratio is the effect of a variable on the hazard or risk of an event. In our study the hazard ratio is the ratio of the rates at which children are discontinuing asthma medication in the two compared groups. In terms of interpretation, a hazard ratio of 0.5 for boys would mean that at any point in time half as many boys are discontinuing asthma medication proportionally compared to girls. One has to keep in mind that a variable with a low hazard ratio gives proportional a low likelihood of discontinuation; such a variable is, therefore, a strong predictor of persistence of treatment. The following possible determinants of continuation of medication use were investigated, representing patient characteristics (gender, educational level of the parents), severity of symptoms (doctor-diagnosed asthma, prescribing of ICS, antibiotic use), familial predisposition (allergic status of family members, eczema of the child, use of other allergy medication) and environmental influences (smoke exposure, pet exposure, day care). Because doctor-diagnosed asthma and prescribing of ICS are expected to be related, an interaction term is added for these two variables. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

General characteristics of the study population of 165 children who started using asthma medication in their first year of life are shown in Table 1. Male gender was predominant, with 69.7% boys in our study population. More than half (56%) of the study population had at least one parent with

reported atopy (not shown in Table 1) and in 13% both parents were atopic. The most commonly used asthma medications were SABA, prescribed to more than 80% of the study population and use of ICS was seen in 40%. Almost 70% of the study population reported wheezing in the first year of life of which 30% also reported cough. Cough without wheeze was reported by 11% of the study population. The majority (57.6%) did not have parental-reported doctor-diagnosed asthma in the year asthma medication use was initiated.

TABLE 1 General characteristics of the study population: children receiving asthma medication in the 1st year of life

PATIENT CHARACTERISTICS	(N=165)		
Sex, % boys [b]	69.7	Smoke exposure in the home, % [c]	20.7
Mean age at end of follow-up, yrs (SD)	3.6 (0.2)	Pet exposure in the home, % [c]	46.7
Mother's educational level, % [c, f]		Day care, % [c]	33.3
low	23.0	Wheeze,% [c]	68.9
intermediate	44.2	Recurrent wheeze, % [c, h]	34.9
high	32.7	Dry cough at night, without cold, % [c]	40.4
Father's educational level, % [c, f]		Doctor-diagnosed asthma, % [c]	42.4
low	24.7	Doctor-diagnosed bronchitis, % [c]	52.8
intermediate	39.5	Lower respiratory tract infection(s), % [c, i]	56.9
high	35.8	Eczema, % [c]	23.3
Ethnicity, % Dutch [d]	94.6	Asthma medication, % [e, j]	100
Any other siblings, % [c]	70.9	Inhaled/oral beta2-agonists	82.4
Allergic sibling(s), % [c]	33.9	Inhaled corticosteroids	41.8
Allergic mother, % [a]	32.1	Parasympathicolytics	40.0
Allergic father, % [b]	37.5	Oral corticosteroids, % [e]	1.8
Parental asthma, % [a, b, g]	20.0	Antibiotics, % [e]	58.2
Mother smoking during pregnancy, % [b]	14.1	Other allergy medication, % [e, k]	50.9

[a] *Data collected from questionnaires at the time of pregnancy*

[b] *Data collected from questionnaires at the age of 3 months*

[c] *Data collected from questionnaires at the age of 1 year*

[d] *Data collected from questionnaires at the age of 2 years*

[e] *Data collected from the community pharmacy at the age of 4 years*

[f] *Educational level: low = primary, lower vocational and lower general; intermediate = /senior high school and intermediate vocational; high = higher vocational an university*

[g] *Father or mother or both reported to have (had) asthma*

[h] *Recurrent wheeze: >= 4 episodes wheeze*

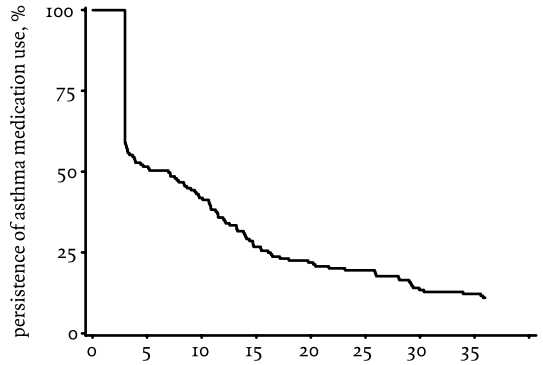
[i] *Lower respiratory tract infections: bronchitis, pneumonia and pertussis.*

[j] *Due to our selection criteria the use of asthma medication within the study population is 100%*

[k] *Nasal antiallergics, systemic antihistamines, topical corticosteroids and antiallergic eye preparations*

Overall persistence of asthma medication use was low, falling below 15% after three years of follow-up (Figure 1). Since 41.2% of the study population received a single prescription for asthma medication, a steep fall in persistence can be observed after approximately three months of treatment. After these three months, a steady decline in persistence was seen, becoming less steep around 16 months of follow-up and reaching the level of 10.3% at the end of follow-up.

FIGURE 1 Persistence of asthma medication use within the study population: children receiving asthma medication in the 1st year of life



Results from the univariate Cox regression analyses are shown in Table 2. Since the hazard ratios are for discontinuation of asthma medication, hazard ratios below 1.0 imply a higher persistence of asthma medication use. Most characteristics, including an allergic father, the use of antibiotics, eczema and pet exposure were not related to continuing use of asthma medication. Doctor-diagnosed asthma, prescribed ICS and the allergic status of the mother were significantly associated with persistent use of asthma medication. After adjusting for the other significant variables and gender (see Table 3) only doctor-diagnosed asthma and use of ICS remain significantly associated. Children with doctor-diagnosed asthma within the 1st year of life were 1.6 times more likely (hazard ratio of discontinuation = 0.64) to continue asthma medication than children without such a diagnosis.

TABLE 2 Univariate analyses of discontinuation of asthma medication use in relation to patient characteristics

	HR_{crude}	95% CI for the HR_{crude}	
		lower	upper
Sex, boys	0.74	0.52	1.04
Mother's educational level	1.03	0.83	1.27
Father's educational level	0.94	0.76	1.16
Doctor-diagnosed asthma	0.56*	0.38	0.76
Prescribed ICS	0.52*	0.37	0.73
Antibiotics	0.87	0.62	1.20
Allergic mother	0.67*	0.47	0.96
Allergic father	1.12	0.80	1.57
Allergic sibling(s)	0.82	0.58	1.16
Parental asthma	0.71	0.47	1.08
Eczema	1.08	0.96	1.23
Allergy medication	0.87	0.63	1.20
Smoke exposure in the home	1.17	0.99	1.38
Pet exposure in the home	0.99	0.72	1.37
Day care	1.16	0.83	1.63

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; ICS = inhaled corticosteroids

** Significant values $p < 0.05$*

The strongest determinant of persistence of use was a prescription for ICS in the first year of life, with a highly significant hazard ratio of discontinuation of 0.59, rendering children using ICS almost two times more likely to continue treatment than children not using these drugs. No interaction was found between the variables doctor-diagnosed asthma and inhaled corticosteroid use.

TABLE 3 Multivariate analyses of discontinuation of asthma medication use in relation to patient characteristics

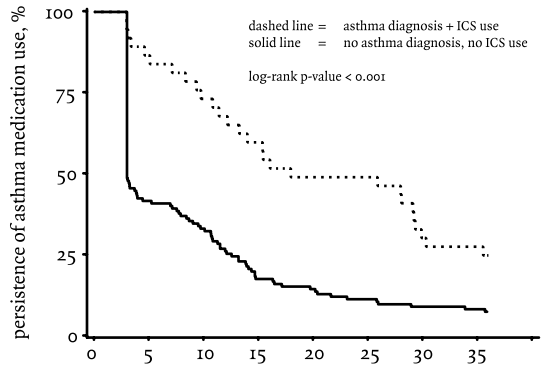
	HR_{adj}	95% CI for the HR_{adj}	
		lower	upper
Sex, boys	0.75	0.52	1.08
Doctor-diagnosed asthma	0.64*	0.45	0.91
Prescribed ICS	0.59*	0.40	0.86
Allergic mother	0.82	0.56	1.20

Definition of abbreviations: CI = confidence interval; HR_{adj} = the hazard ratio of the variable adjusted for all other variables in the model; ICS = inhaled corticosteroids

** Significant values $p < 0.05$*

Repeating the multivariate Cox regression, including three dummy variables for the possible combinations of the variables doctor-diagnosed asthma and inhaled corticosteroid use, rendered a significant adjusted hazard ratio of discontinuation of 0.34 (95% CI 0.25 to 0.63) for the group of children with both a diagnosis of asthma and use of ICS.

FIGURE 2 Difference in persistence between children with both an asthma diagnosis and a prescription for inhaled corticosteroids (ICS) and children without both diagnosis and ICS in the first year of life



The difference in persistence between children with both doctor-diagnosed asthma and a prescription for ICS and children without both, is visualised by a Kaplan Meier curve in figure 2. The main difference in persistence between the groups was due to a difference in discontinuation after the first prescription. After this steep fall, the declining trend runs parallel between the compared groups.

DISCUSSION

The study described here shows that 58.8% of children initiating asthma treatment before the age of one continue medication use after the first

prescription and only 10.3% is persistent after three years of follow-up. Children with doctor-diagnosed asthma and users of ICS in the first year of life were 1.6 to 1.7 times more likely to continue using asthma medication. When both diagnosed with asthma and receiving ICS, children were three times more likely to continue until the age of three. No other measures were significantly associated with persistence of asthma medication use.
Our results show that most of the time a trial of asthma medication in very young children does not lead to regular asthma medication use. Children who do become persistent asthma medication users could not be identified by objective measures that can be determined at start of therapy. Only the 'physician-decided' measures doctor-diagnosed asthma and prescribing of ICS are associated with persistent asthma medication use. The low persistence found in our study is consistent with the findings from previous studies that no valid criteria exist to prospectively identify children who will develop asthma within a group of wheezing children.[1, 2, 18-20] Moreover, a great proportion of those who wheezed in their first years of life did so for other reasons than asthma.[2-6]

However, other studies did find certain factors to be associated with persistent wheeze and asthma later in life, including early allergic sensitization,[1, 9, 18, 21, 22] atopic disease (such as rhinitis, eczema), eosinophilia,[19, 22, 23] female sex,[21] tobacco smoke exposure,[21, 22] a family history of asthma,[1, 9, 19, 22-25] early and/or severe wheezing.[18, 19, 25] Other characteristics, including pet or farm animal exposure,[18] day-care attendance or having older siblings [18, 26] and house-dust endotoxine [18] might reduce the risk of asthma. This association is not reflected in an association with persistent asthma medication use. Our results show that demographic characteristics, familial predisposition and environmental influences were not significantly associated with persistence of asthma medication use.

In contrast, we found that doctor-diagnosed asthma and prescribing of ICS were significantly associated with persistence of asthma medication use. As both these measures and the outcome, persistence of asthma medication use, are not objective measures but physician-based, care should be taken in interpreting these results. It is not unlikely that physicians are more inclined to continue medication use after diagnosing a child with asthma or prescribing ICS. Therefore, it is important that physicians check the necessity of continuing medication on a regular basis. In addition, restricting treatment to

the group of children with doctor-diagnosed asthma and use of ICS does not necessarily lead to better targeting of asthma medication, since a diagnosis of asthma is very difficult to make before the age of five and, if given, should be considered a working diagnosis.[11, 27, 28]

However, the low percentage of persistence in our study and the finding that one-third of the children in our study population does not report wheezing in the year that asthma medication is initiated raises the question whether overtreatment occurs, as has been reported in previous studies.[1, 2, 13, 23, 29, 30] Especially since recent evidence suggests that early ICS treatment has no effect on the natural history of asthma or wheeze later in childhood and that the beneficial effect during episodes of wheezing in preschool children is small to none existent.[20, 31, 32] Another study found no relation between responses to inhaled bronchodilators in infancy and asthma later in life, concluding that the presence or absence of a response to bronchodilators in early life cannot be used as a predictor of asthma.[33]

The current study has some limitations. First, we only have information on medication use for the first four years of life, hence the maximum follow-up of three years after start of asthma therapy. We do realise that the diagnostic and treatment problems do not disappear at the age of four. However, since already very few children remain persistent user after these three years we do not feel that the insight into persistent asthma medication use in this population would be much greater if we were able to add more years of follow-up. Second, in this study we cannot determine whether the persistence or discontinuation of medication is a just action. About one third of all children discontinuing medication reported asthmatic symptoms in the year after their medication was discontinued (data not shown). This could imply undertreatment, especially since a quarter of non-persistent children resumes medication use in year four. Third, parental reported doctor-diagnosed asthma might not be the true reflection of asthmatics. This has been shown to differ substantially from a diagnosis of asthma derived from the GPs clinical records in the sense that self-reported asthma renders many more 'asthmatics' than do the GP's records.[34]

In conclusion, we show that a treatment trial in most cases does not lead to regular use of asthma medication. Only 58.8% of children continue medication use after the initial prescription. With a three-year-persistence

of only 10.3% and the conflicting evidence on the benefit and diagnostic value of not only trials of ICS,[20, 31, 32, 35, 36] but also SABA [37] and anticholinergics [38] in children suffering from (transient) wheeze, there might be room for improvement in prescribing practice. It is important to identify which children should or should not be receiving asthma medication. However, our data showed that no objective measures, including a family history of asthma, eczema and smoke exposure, are associated with persistence of asthma medication use. These findings stress the need for objective tools to diagnose asthma at a young age.

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ABSTRACT

Introduction

As it is notoriously difficult to diagnose asthma in young children reliably, asthma treatment may be initiated before a more definite diagnosis can be made. The objective of this study was to compare the asthma medication prescription histories from birth until age eight of children with and without asthma at age eight.

Methods

We studied 775 children born in 1996-1997 who participated in the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study, for whom complete medication histories up to age eight and information on asthma status at age eight were available. We compared asthma medication prescription histories between (I) children never reporting asthmatic symptoms, without asthma at age eight, (II) children reporting asthmatic symptoms prior to age eight, but without asthma at this age and (III) children with asthma at age eight.

Results

Of 278 children to whom asthma medication had been prescribed at any time in the first eight years of life, 84 had asthma at age eight. Still, 82.4% of children with asthma at age eight received asthma medication in the prior years compared to 55.1% of children with transient asthmatic symptoms. The difference was stronger for receiving inhaled corticosteroids (ICS) with 69.6% of the children with asthma at age eight receiving these medicines and 31.9% of the children with transient asthmatic symptoms.
Children with asthma at age eight received asthma medication during significantly more years prior to age eight than children with transient symptoms (4.1 versus 2.1 years for all asthma medication; 3.1 versus 1.2 years for ICS), although they on average received their first prescription at a later age (3.0 versus 2.1 years). Children with transient symptoms received a last prescription for asthma medication at the average age of 3.7 while most children with asthma continued receiving medication up to the age of eight (average age of last prescription was 7.1)

Conclusions

Our study shows that asthma medication was frequently prescribed at an early age to children who at age eight did not have asthma. However, in children with asthma at age eight asthma medication was more often initiated. These children more often received ICS and were more likely to continue treatment up to age eight than children with prior asthmatic symptoms but no asthma at age eight. Some early distinction between children with transient early symptoms and children with asthma at a later age seems to be made.

3·3 Asthma medication from birth until the age of 8; a retrospective analysis on the differences in treatment between asthmatic and non-asthmatic children at age 8

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Submitted

INTRODUCTION

'Life can only be understood backwards; but it must be lived forwards' (Søren Kierkegaard, Danish philosopher 1813-1855) is a statement that particularly applies to treatment of asthmatic symptoms in children.
A firm diagnosis of asthma can not be made before the age of six and often even later,[1-3] but when a preschool child presents with respiratory symptoms that may be due to asthma it is no option to postpone treatment until that age. Although diagnostic tools are limited, physicians are recommended to base their decision for treatment on several factors related to asthma, including the age of onset of symptoms, severity of symptoms, triggers of symptoms, gender differences, atopic characteristics of the child and a parental history of asthma.[1-3]

The aim of this approach is to restrict the use of inhaled corticosteroids to those children most likely to have persistent asthma and thus minimise overtreatment.[3] This is important since many children present with wheeze that is transient in nature and does not lead to asthma with persistent symptoms.[4] The question is whether this leads to differences in treatment of wheezing between children who will turn out to be asthmatic compared to those in whom symptoms are transient.

The longitudinal design of our study enabled us to retrospectively distinguish children with transient symptoms from children who had asthma at age eight and evaluate whether there were differences in treatment of these children in the seven years prior to age eight. Besides asthma we used atopy (IgE measured sensitisation to inhalant allergens) and bronchial hyperresponsiveness (BHR) as outcomes at age eight because of the strong association of these objective measures with asthma.

METHODS

Study design and study population

We studied 775 children born in 1996-1997 who participate in the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study, for whom complete medication histories up to age eight and information on asthma status at age eight were available. The PIAMA study is a prospective birth cohort study among 3,963 Dutch children. Details of the study design have been published previously.[5]

Recruitment took place in 1996 -1997. A screening questionnaire was distributed to 10,232 pregnant women visiting one of 52 prenatal clinics. Based on this screening 7,862 women were invited to participate in the study; 4,146 agreed and gave written informed consent. 183 participants were lost to follow-up before any data on the child had been obtained, therefore 3,963 newborn children started in the study. Data on respiratory and allergic symptoms, potential risk factors for asthma and allergy and demographic factors were collected by postal questionnaires. Questionnaires were sent to the participating parents during the last trimester of pregnancy, at the child's age of three months, at the age of one and annually thereafter.

Longitudinal data on medication retrieval have been collected at age eight through prescription data from community pharmacy records. In the annual questionnaire sent at age eight, parents were asked to sign written consent for retrieval of the medication history of their child from their community pharmacy. Informed consent was given in 2,805 of the 3,271 questionnaires returned at age eight. Pharmacy information was retrieved from community pharmacies for 2,004 children. For 777 children these pharmacy data were complete from birth until age eight. Medication histories were assumed to be complete if the first prescription of a family member was recorded before the child's date of birth, and the last prescription of the child or a family member was at least eight years after the date of birth.

A comparison between the group of children with complete pharmacy data (N = 777), the group for which informed consent was given (N = 2,805) and the population eligible for retrieval of pharmacy data, which was the total PIAMA population at age eight (3,271) showed no significant differences in any of the general characteristics displayed in Table 1, nor in the percentage of children with asthma, atopy and bronchial hyperresponsiveness at age eight. In the Netherlands, pharmacy records are virtually complete with regard to outpatient medication use.[6]

Medication use from birth up to age eight

All medicines with Anatomical Therapeutic Chemical (ATC) code R03 were considered to be asthma medication: inhaled and oral short-acting beta2-agonists (SABA), inhaled long-acting beta2-agonists (LABA), inhaled corticosteroids (ICS), inhaled cromones, inhaled anticholinergics and montelukast.[7] Several measures of asthma medication treatment between birth and age eight were defined: a prescription ever for any asthma medication yes/no; a prescription ever for SABA and for ICS; cumulative exposure in years (operationalised as the number of years before age eight in which a child received at least one prescription for an asthma medicine) for any asthma medication, for SABA and for ICS; age at the time of both the first prescription (starting age) and the last prescription (stop age) for any asthma medication, SABA and ICS. Oral glucocorticoids (ATC code H02AB) were not classified as primary asthma treatment. Other medication groups of interest were antihistamines (all prescriptions with ATC code R06, including deptropine and promethazine) and antibiotics (all prescriptions with ATC code J01).

Asthma at age eight, questionnaire based

In the PIAMA study asthma at age eight was defined as at least one attack of wheeze, one episode of dyspnoea or a prescription for ICS in the last year, as reported by the parents in the annual questionnaire. Two of the 777 children lacking this information were excluded from the analyses. Parents were asked whether the child had at least one attack of wheeze in the last year in the questionnaires at age one to eight. Data on dyspnoea (at least one episode in the last year) were collected from three to eight years of age. Three groups were defined in this study based on these data: (I) children who never reported asthmatic symptoms prior to age eight and did not have asthma at age eight (reference group) (II) children reporting asthmatic symptoms prior to age eight, but without asthma at age eight (transient symptom group) and (III) children with asthma at age eight (asthma group).

Medical examination at age eight, assessing atopy and BHR

At eight years of age a subgroup of the study population (n =1,554), consisting of children of allergic mothers and a random sample of the children of

non-allergic mothers, was invited for a hospital-based medical examination where a blood sample was collected and the child performed lungfunction tests. Additionally, 1,964 children were invited for a short community-based medical examination or a home visit, in which case a blood sample was collected. The study protocol was approved by the medical ethics committees of the participating institutes and all parents gave written informed consent. In the collected blood samples at eight years of age, specific IgE was determined for the following common airborne allergens: house dust mite (Dermatophagoides pteronyssinus), cats, dogs, grass (Dactylis glomerata), birch, and Alternaria alternata. We defined a child to be atopic if a specific IgE of at least 0.70 IU/ml for at least one of the airborne allergens was present. In the children who participated in the hospital-based medical examination bronchial hyperresponsiveness (BHR) was determined according to the protocol of the European Community Respiratory Health Survey,[8] defined as a decrease of 20% in FEV1 at a cumulative dose of 0.61 mg methacholinebromide or below.

Statistical analyses

Initiation of any asthma medication or ICS in children between birth and age eight was analysed using Kaplan-Meier analyses, comparing children with asthma at age eight with all other children. Next, we calculated the Relative Risk (RR) of initiating asthma medication ever, receiving ICS ever, and receiving SABA ever during the first eight years of life, for the transient symptom and the asthma group compared to the reference group using binomial regression.[9] The same was done for subgroups of children for whom information on bronchial hyperresponsiveness (N = 219) and atopy (N = 443) was available. Since the aim of this study was to investigate whether the limited diagnostics tools available to physicians in children with asthma symptoms (such as severity of symptoms) lead to differences in treatment of asthmatics compared to non-asthmatics in the period before this diagnosis can be firmly established, we did not adjust for these variables

RESULTS

Within our study population 13% (N = 102) of the children satisfied the PIAMA definition for asthma at age eight, 36% (N = 276) reported asthmatic symptoms prior to age eight, but did not have asthma at age eight, and 51% (N = 397) never reported asthmatic symptoms nor had asthma at age eight. The characteristics of these groups are shown in Table 1. The groups differed with respect to gender, parental asthma, maternal smoking during pregnancy and use of medicines such as antihistamines and antibiotics. The relation with BHR and atopy of the child can also be found in this table.

TABLE 1 Characteristics of the study population (N = 775)

GENERAL CHARACTERISTICS	NEVER SYMPTOMS (N = 397)	TRANSIENT SYMPTOMS (N = 276)	ASTHMA AT AGE EIGHT (N = 102)
Gender, % male *	47.1	55.4	58.8
Ethnicity, % Dutch [a]	97.4	96.3	100
Maternal educational level, % low [b]	18.4	22.9	27.5
Paternal educational level, % low [b]	26.8	21.5	33.3
Degree of urbanisation, mean (SD)[c]	3.2 (1.2)	3.3 (1.2)	3.1 (1.2)
Parental asthma, % [d] *	9.9	13.9	20.8
Maternal smoking during pregnancy, % [e] *	10.2	16.1	16.7
Asthma related outcomes at age eight			
BHR at age eight (N = 219), % [f] *	34.5	40.3	64.1
Atopy at age eight (N = 443), % [g] *	25.2	24.7	66.7
Use of other medicines before age eight			
Antihistamines, % *	36.8	55.8	71.6
Oral corticosteroids, % *	1.3	3.6	14.7
Antibiotics, % *	76.8	86.6	88.2

[a] *Based on both the country of birth of the mother and the self-reported ethnicity of the mother, if both Dutch*

[b] *Educational level: low = primary, lower vocational and lower general; intermediate/high = senior high school, intermediate and high vocational and university*

[c] *Degree of urbanisation: groups are defined based on the address density per km2: 1.>=2500, 2.1500-<2500, 3.1000-<1500, 4.500-<1000, 5.<500*

[d] *Father or mother or both reported to have (had) asthma*

[e] *Defined as any smoking by the mother during pregnancy after the fourth week of pregnancy*

[f] *Bronchial hyperresponsiveness (BHR): determined according to the protocol of the ECRHS defined as a decrease of 20% in FEV1 at a cumulative dose of 0.61 mg methacholinebromide or below*

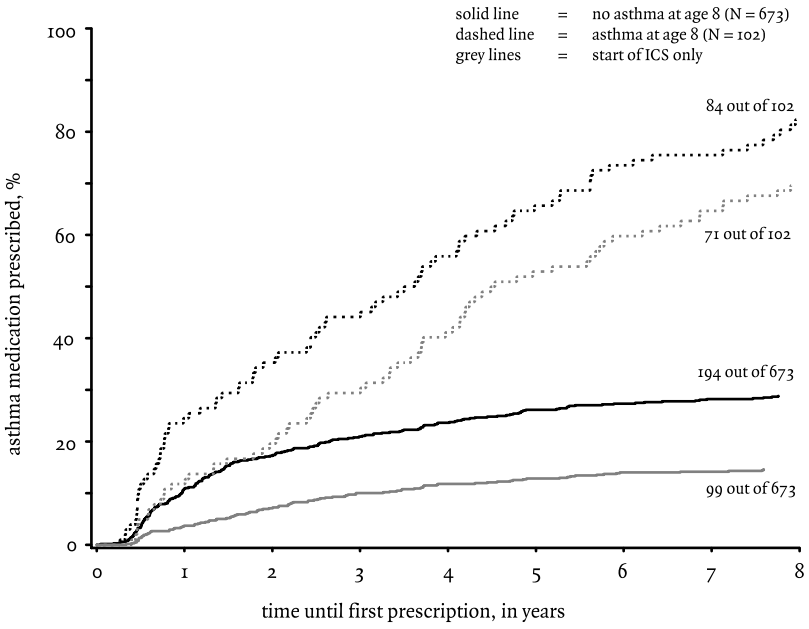
[g] *Defined as a specific IgE concentration of at least 0.70 IU/ml on at least one of the airborne allergens in blood sample collected at age eight*

* *Significant differences between groups, $p < 0.05$*

Figure 1 shows that children with asthma at age eight received both any asthma medication and ICS more often than children without asthma at age

eight (82.4% versus 28.7% for any medication; 69.6% versus 14.7% for ICS). Still, of the 278 children (36% of the study population) to whom a first prescription for asthma medication had been prescribed before age eight, only 84 had asthma at age eight.

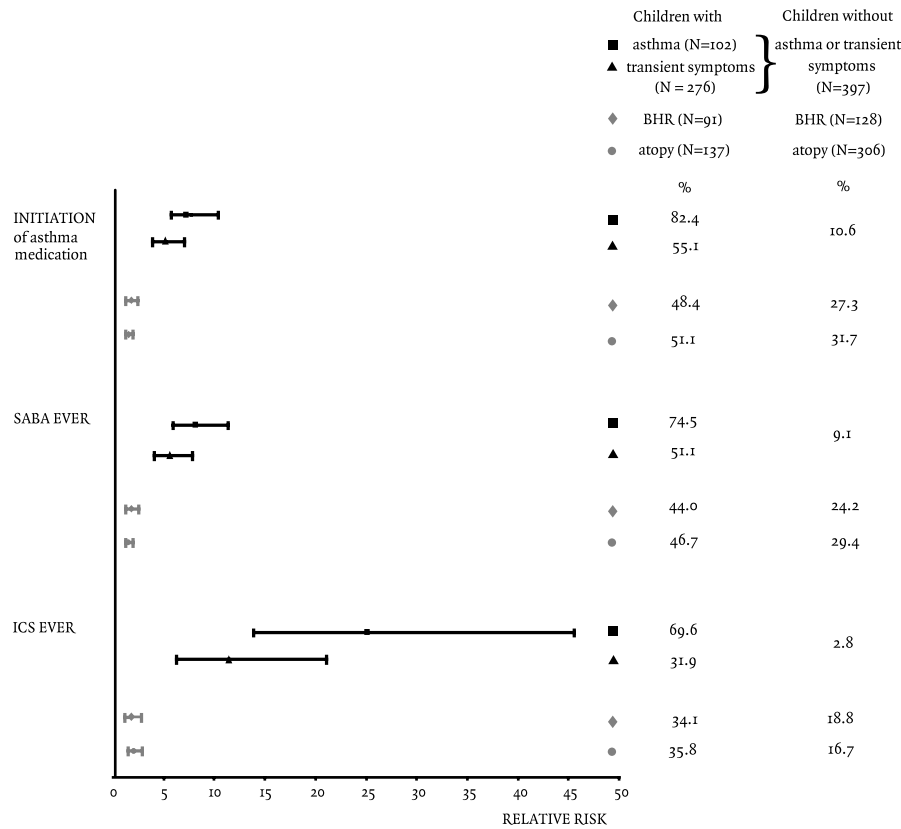
FIGURE 1 Difference in start of asthma medication treatment between children with and without asthma at age eight



After subdividing the group of children without asthma at age eight into the previously defined transient symptom and no symptom group, we found that children with transient asthmatic symptoms were five times more likely to receive asthma medication before age eight (RR = 5.2; 95% CI 3.8 to 7.1) than children without reported symptoms or asthma at age eight (Figure 2). For children with asthma at age eight this chance of receiving asthma medication was almost eight-fold higher (RR = 7.8; 95% CI 5.8 to 10.5). Both associations were stronger for receiving ICS (RR = 11.5; 95% CI 6.3 to 21.1 in children with transient asthmatic symptoms; RR = 25.1; 95% CI 13.8 to 45.6 in children with asthma at age eight). Thus 82.4% of children with asthma at age received asthma medication in the prior years compared to 55.1% of

children with transient asthmatic symptoms (RR = 1.5; 95% CI 1.3 to 1.7). The difference between these two groups was also stronger for receiving ICS with 69.6% of the children with asthma at age eight receiving these medicines versus 31.9% of the children with transient asthmatic symptoms (RR = 2.2; 95% CI 1.8 to 2.7). When comparing groups based on BHR and atopy the same associations were found, albeit less pronounced. The risk of receiving any asthma medicine before age eight was 1.7 (95% CI 1.2 to 2.5) for children with BHR compared to children without BHR and 1.6 (95% CI 1.3 to 2.0) for children with atopy compared to children without atopy.

FIGURE 2 The chance to receive asthma medication before age eight for children with different respiratory health outcomes at age eight



When looking more specifically at the onset and duration of treatment with asthma medication within the subgroup of children receiving asthma

medication (N = 278), we found several differences between the three defined respiratory health groups (Table 2). Children with asthma at age eight on average received their first prescription for asthma medication at a later age than children with transient symptoms (at a mean of 3.0 years versus 2.1 years). Still, they received asthma medication during significantly more years during the eight-year study period (4.1 years versus 2.1 for all asthma medication; 3.1 versus 1.2 years for ICS). Children with transient symptoms received a last prescription for asthma medication at the average age of 3.7 while most children with asthma continued receiving medication up until the age of eight (average age of last prescription was 7.1). The 42 children receiving asthma medication before age eight without ever reporting asthma symptoms, on average received asthma medication during 1.4 years and ICS during 0.3 year within the eight-year study period, which is less than in both other groups.

TABLE 2 Treatment characteristics for children within the three defined respiratory health groups

TREATMENT CHARACTERISTICS	NEVER SYMPTOMS (N = 42)	TRANSIENT SYMPTOMS (N = 152)	ASTHMA AT AGE EIGHT (N = 84)
Overall starting age, yrs (95% CI)	2.5 (1.8-3.2)	2.1 (1.8-2.3)	3.0 (2.5-3.5)
Starting age SABA, yrs (95% CI)	2.5 (1.7-3.3)	2.0 (1.7-2.3)	2.9 (2.4-3.4)
Starting age ICS, yrs (95% CI)	2.8 (1.8-3.9)	2.5 (2.1-2.9)	3.5 (3.0-4.0)
Overall cumulative exposure, yrs (95% CI) [a]	1.4 (1.2-1.6)	2.1 (1.9-2.3)	4.1 (3.7-4.5)
Cumulative exposure SABA, yrs (95% CI) [a]	1.1 (0.9-1.4)	1.7 (1.5-1.9)	3.0 (2.6-3.4)
Cumulative exposure ICS, yrs (95% CI) [a]	0.3 (0.1-0.5)	1.2 (0.9-1.4)	3.1 (2.6-3.5)
Overall stop age, yrs (95% CI) [b]	3.2 (2.5-3.9)	3.7 (3.4-4.1)	7.1 (6.8-7.4)
Stop age SABA, yrs (95% CI) [b]	3.2 (2.3-4.0)	3.3 (2.9-3.6)	6.5 (6.1-6.9)
Stop age ICS, yrs (95% CI) [b]	3.2 (2.0-4.5)	3.8 (3.4-4.3)	6.9 (6.6-7.3)

[a] *Cumulative exposure is operationalised as the number of years before age eight in which a child received at least one prescription for an asthma medicine*

[b] *The total medication history until age eight was evaluated. For calculation of the stop age, all children who did not stop treatment with asthma medication were given stop age eight*

DISCUSSION

The aim of our study was to investigate whether the limited diagnostic tools available in young children with asthmatic symptoms resulted in differences in treatment of these symptoms between children who will turn out to be

asthmatic compared to those in whom symptoms are transient. Our results show that this is indeed the case. Children with asthma at age eight compared to children with transient symptoms received asthma medication more often and during more years, though treatment was started at an older age. Our finding that 13% of the study population had asthma at age eight while 36% reported asthmatic symptoms prior to age eight, but did not have asthma at age eight is in line with findings from previous studies that the majority of preschool children with respiratory symptoms will outgrown these symptoms.[4, 10]

In the PIAMA study asthma at age eight was defined as at least one attack of wheeze, one episode of dyspnoea or a prescription for ICS in the last year, as reported by the parents in the annual questionnaire. In theory asthma could be defined at each age using this definition. However, it is well known that wheezing at a young age may not only be due to asthma but also to other, more transient, respiratory conditions.[11-16] Therefore, in this study the focus is on asthma at eight years of age, when asthma symptoms are less likely to be confused by symptoms due to other respiratory conditions.

We found that children with asthma at age eight had an almost eight-fold higher chance of receiving asthma medication than the control group. Still, 69.8% of all children in our study population who received a first prescription for asthma medication before age eight did not have asthma at age eight. This can be explained by the fact that the group of children reporting asthmatic symptoms in prior years, without asthma at age eight also had an increased chance of receiving asthma medication before age eight. This group with transient symptoms was almost three times larger than the group with asthma at age eight, so in absolute numbers, more children in this group will receive asthma medication.

The associations between asthma at age eight and treatment with asthma medication in the prior years are also observed for the endpoints BHR and atopy, albeit less pronounced. BHR is strongly related to asthma,[17] but many children without asthma at age eight also have BHR. One could argue that these children have undiagnosed asthma. However, the associations with asthma medication for children with BHR are significantly weaker than those found for asthma. This reasons against the previous argument and is in line with reports on high sensitivity but limited specificity of BHR for

asthma.[18] That the associations found between asthma at age eight and prior medication use are also seen for atopic status at age eight is conform results from studies reporting a relation between markers of allergic disease and asthma.[19, 20] However, not all atopic children have asthma which explains why the association between atopy and asthma medication is weaker.

The longitudinal nature of our data allowed us to take into account the onset and duration of treatment with asthma medication. We found that children with asthma received a first prescription for asthma medication at an older age, which is in line with several studies describing wheezing phenotypes.[4, 21] They showed that the largest part of children presenting with symptoms before age three had transient symptoms and children with onset at a later age more often had persistent symptoms.[4, 21] Children with transient symptoms also received a last prescription for asthma medication at the average age of 3.7 while most children with asthma continued receiving medication up until age eight.

In line with this we expected a higher duration of asthma treatment in the asthma group, because symptoms in this group tend to persist during childhood while non-asthmatics would lose the need for medication. Moreover, in children with transient symptoms, these symptoms could be due to other causes, in which case they would fail to respond to an initial trial treatment.[22] This is reflected in the finding that children with asthma at age eight received asthma medication during an average of four years in the eight year study period, while this was only two years for children with transient symptoms and 1.4 years for children who never reported symptoms. For SABA this difference is less pronounced, while the opposite is true for receiving ICS, with a difference of almost two years between children with asthma at age eight and children with transient symptoms. This could be a result of the accepted use of SABA to reduce symptoms during wheezing episodes in practice,[23] while especially the introduction of prophylactic treatment with ICS is recommended to be based on the presence of several factors related to asthma.[1-3]

The finding that 10.6% of children received asthma medication during an average of 1.4 years without ever reporting asthmatic symptoms is not easy to explain. Possibly the parents of these children failed to properly report symptoms. Another explanation could be that these children presented with cough, which is a very common symptom in childhood but can also be a

manifestation of asthma and is sometimes treated with asthma medication.[24] A possible limitation of this study is that the definition of asthma at age eight is based not only on symptoms but also on reported ICS use in the last 12 months. This could lead to an overestimation of the association between asthma at age eight and prior ICS use. However, in most children ICS treatment is initiated before age five and the relationship between receiving ICS at that age and reported ICS use at age eight is low. 17 of the 102 children with asthma at age eight fulfilled the definition for asthma solely due to reported ICS use at age eight. We performed two sensitivity analyses (see Appendix A of this thesis) in which we (I) excluded these 17 children or (II) defined these children as non-asthmatics at age eight and relocated them to the other two groups based on reported asthmatic symptoms from birth to age eight (15 to the transient symptom group and two to the never symptom group). Neither of these two approaches led to significant changes in the effect estimations presented in this manuscript.

Strengths of the present study are the longitudinal study design, with a follow up from birth until age eight and the completeness of the data with respect to patient characteristics. The availability of the entire medication history of the child and the combination of questionnaire based asthma at age eight with objective measures regarding atopy and BHR made it possible to retrospectively distinguish children with transient symptoms from children who had asthma at age eight and evaluate whether there were differences in treatment of these children from birth up to age eight. Because information on asthma medication was derived from community pharmacy records the probability of recall bias was eliminated.

In conclusion, our study shows that there is a substantial group of children starting asthma therapy at an early age and using ICS who turn out not to have asthma, atopy or BHR at age eight. However, children with asthma at age eight compared to children without asthma more often were treated with asthma medication, more often received ICS and were more likely to continue treatment up to age eight than children with prior asthmatic symptoms but no asthma at age eight.

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The DNSGP-2 study: identifying the role of the different actors

4

ABSTRACT

Introduction

In preschool children a diagnosis of asthma is not easily made and only a minority of wheezing children will develop persistent atopic asthma. According to the general consensus a diagnosis of asthma becomes more certain with increasing age. Therefore the congruence between asthma medication use and doctor-diagnosed asthma is expected to increase with age. The aim of this study is to evaluate the relationship between prescribing of asthma medication and doctor-diagnosed asthma in children age 0-17.

Methods

We studied all 74,580 children below 18 years of age, belonging to 95 GP practices within the second Dutch national survey of general practice (DNSGP-2), in which GPs registered all physician–patient contacts during the year 2001. Status on prescribing of asthma medication (at least one prescription for beta2-agonists, inhaled corticosteroids, cromones or montelukast) and doctor-diagnosed asthma (coded according to the International Classification of Primary Care) was determined.

Results

In total 7.5% of children received asthma medication and 4.1% had a diagnosis of asthma. Only 49% of all children receiving asthma medication was diagnosed as an asthmatic. Subgroup analyses on age, gender and therapy groups showed that the Positive Predictive Value (PPV) differed significantly between therapy groups only. The likelihood of having doctor-diagnosed asthma increased when a child received combination therapy of short-acting beta2-agonists and inhaled corticosteroids (PPV = 0.64) and with the number of prescriptions (3 prescriptions or more, PPV = 0.66). Both prescribing of asthma medication and doctor-diagnosed asthma declined with age but the congruence between the two measures did not increase with age.

Conclusions

In this study, less than half of all children receiving asthma medication had a registered diagnosis of asthma. Detailed subgroup analyses show that a diagnosis of asthma was present in at most 66%, even in groups of children treated intensively with asthma medication. Although age strongly influences the chance of being treated, remarkably, the congruence between prescribing of asthma medication and doctor-diagnosed asthma does not increase with age.

4.1 Prescription of respiratory medication without an asthma diagnosis in children: a population based study

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INTRODUCTION

Asthma is a chronic inflammatory disease, associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, shortness of breath and chest tightness.[1] Asthmatic complaints are relatively common in children.[1-3] The prevalence of asthma symptoms in children varies between global populations from less than 2% to approximately 33% of the population.[4] In the Netherlands in children from 2 to 15 years of age 4-12% experience shortness of breath and 5-20% experience chest wheezing. About 6,5% of 7-12 year olds has asthma.[5] Around one-third of all infants have one or more wheezing episodes in their first years of life.[2] There is substantial information, including guidelines, on how children with asthma symptoms should be treated, which kind of asthma medication should be used and which problems should be addressed.[1, 6, 7] However, studies describing actual use of asthma medication in children show ample variability in treatment patterns,[3, 8-12] and raise concern about over- and under treatment both in children with and without doctor-diagnosed asthma.[8, 10, 11, 13-16]

The interpretation of these findings differs with the age of the child. When a preschool child with asthmatic symptoms presents at the physician's office, a diagnosis of asthma is not easily made.[17-21] It is well known that wheezing at a young age may not only be due to asthma but also to other, more transient, respiratory conditions.[18-23] Different wheezing phenotypes have been described in children below the age of six of which transient early wheezing is the most common one counting for over 50% of wheezing children. This wheezing phenotype is often outgrown in the first three years of life and only a minority of wheezing children will develop persistent atopic asthma over time.[1, 24-26] Despite this uncertainty in diagnosis, asthma medication is often prescribed to wheezing infants. Moreover, the response to asthma medication itself is widely used as a diagnostic tool to strengthen or reject the possible diagnosis of asthma.[1, 6, 7, 19, 22]

According to current insights and diagnostics, the diagnosis of asthma can be assessed more accurately with increasing age. As can be deduced from both scientific literature and guidelines concerning treatment of children with asthmatic symptoms,[1, 6, 7, 27] the general consensus is that from the age of five to six years a diagnoses of asthma can be made with reasonable certainty. Therefore, theoretically, the congruence between use of asthma medication and doctor-diagnosed asthma is expected to increase with age.

However, previous studies have reported a mismatch between asthma medication use and a diagnosis of asthma.[28-31] Roberts *et al.* found that parents of 45.4% of children aged 0 to 17 receiving asthma medication, failed to report asthma.[28] And a study by Yeatts *et al.* showed a large group of undiagnosed frequent wheezers in children from 12 to 18 years of whom 12% used an inhaler in the past year.[30] In most of these studies the diagnosis of asthma was parental or self-reported, the study was not population based, a very specific age group was investigated or no extensive age group analysis has been performed. We feel that a better comprehension of the congruence between use of asthma medication and doctor-diagnosed asthma is useful to improve asthma medication use in children. Therefore the aim of this study is to evaluate the relationship between prescribing of asthma medication and a diagnosis of asthma, as found in the GPs clinical record, in children and adolescents aged 0-17.

METHODS

Setting and study population

This study has been conducted within the framework of the second Dutch national survey of general practice (DNSGP-2) which was carried out in 2001 by the NIVEL (Netherlands Institute for Health Services Research) and the National Institute for Public Health and the Environment (RIVM).[32, 33] The DNSGP-2 survey has been described in detail elsewhere.[32, 33] In short, 195 general practitioners (GPs) in 104 practices, registered all physician–patient contacts during 12 consecutive months. The participating GPs formed a representative sample of the total population of Dutch GPs according to age and sex of the GP, region, and location of the practice (rural/urban; deprived area); only the percentage of single-handed GP practices was smaller in the DNSGP-2 study. The total practice population consisted of 391,294 patients at the start of the survey. The population characteristics corresponded very well to the Dutch population as a whole with respect to age, sex, and the type of health insurance. The DNSGP-2 provides data on the nature and duration of GP-patient contacts, disease episodes, the diagnosis (coded using the International Classification of Primary Care [34]), the performed actions and all prescriptions made by the GP. In the Netherlands all non-institutionalised inhabitants are registered in a general practice. For the present study data from all 95 GP practices with adequate registration of physician-patient contacts and drug prescriptions was included. The study population consisted of all 74,580 children below the age of 18 years within these 95 practices.

Measurements and analysis

Asthma medication

Prescription drugs were registered by the GP according to the Anatomical Therapeutic Chemical (ATC) Classification system.[35] The following of these were considered to be asthma medication: inhaled short-acting beta2-agonists (SABA), oral short-acting beta2-agonists, inhaled long-acting beta2-agonists (LABA), inhaled corticosteroids (ICS), inhaled cromones, and montelukast. All children with at least one prescription for one of these medicine groups in the year 2001 were included in the study. Asthma medication users were further subdivided into four asthma therapy groups, which were most common in our study population: (I) monotherapy with SABA (inhaled or oral), (II) monotherapy with ICS, (III) combination therapy of these two medication groups (9.7% of the children in this group also received one or more other asthma medicines) and (IV) all other therapies. To be able to differentiate between one-time asthma medication users (where the medication itself might be used as a diagnostic tool to strengthen or reject the diagnosis of asthma) and the more chronic users we also made a subdivision into children with (I) only one prescription, (II) two prescriptions and (III) three or more prescriptions during the study period. All medications prescribed on the same day were considered to belong to one prescription.

Doctor-diagnosed asthma

During the study period GPs registered all contacts with their patients, including face-to-face consultations as well as telephone consultations and repeat prescriptions. Every single health problem presented within a consul-

tation was coded by the GP using the International Classification for Primary Care (ICPC).[34] When a patient presented two complaints within one consultation, these were coded as two separate (sub)consultations. Therefore it is known for every patient how often he or she contacted the GP and for which health problems. GPs were trained during an intensive course on coding practices and problems. In this study all children who, in the year under study, contacted the GP with a health problem subsequently coded as ICPC R96 (asthma) were considered to have doctor-diagnosed asthma.

Data analysis

To quantify the congruence between prescription of asthma medication and doctor-diagnosed asthma we determined Sensitivity and Positive Predictive Value (PPV) of asthma medication use as a predictor for doctor-diagnosed asthma. Based on the general consensus that from the age of five to six years a diagnosis of asthma can be made with reasonable certainty we divided the study population into two age groups: children below the age of six and children aged six years and older and analysed whether the found congruence changes. We repeated these analyses in subgroups of age, gender, asthma therapy and number of prescriptions. We also performed these analyses increasing the cut-off point for defining 'asthma medication use' from one to a minimum of two prescriptions, this way excluding possible trial medication. The results from these analyses are shown in Appendix 1. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

General characteristics of the study population are presented in Table 1. The study population was similar to the Dutch population with respect to gender and age groups. Prescription of asthma medication within our study population was 7.5% in the year 2001. In the same episode a diagnosis of asthma was present in the GPs' clinical record for 4.1% of the study population. Thus prescribing of asthma medication was twice as common as doctor-diagnosed asthma.

TABLE 1 Patient characteristics of the study population

		TOTAL STUDY POPULATION (74,580)		ASTHMA MEDICATION USERS (5,605)		CHILDREN WITH DOCTOR-DIAGNOSED ASTHMA (3,064)	
		N	%	N	%	N	%
Gender							
	Male	38,267	51.3	3,160	56.4	1,775	57.9
	Female	36,313	48.7	2,445	43.6	1,289	42.1
Age (years)							
	0-2	9,030	12.1	1,053	18.8	540	17.6
	3-5	12,690	17.0	1,300	23.2	689	22.5
	6-8	13,357	17.9	1,004	17.9	589	19.2
	9-11	13,521	18.1	853	15.2	490	16.0
	12-14	13,087	17.6	738	13.2	445	14.5
	15-17	12,895	17.3	657	11.7	311	10.2
Other respiratory problems							
	shortness of breath	367	0.5	240	4.3	101	3.3
	wheezing	176	0.2	144	2.6	46	1.5
	acute URTI*	6,307	8.5	1,122	20.0	530	17.3
	acute bronchitis/ bronchiolitis	2,269	3.0	1,002	17.9	406	13.3
	pneumonia	679	0.9	254	4.5	129	4.2
	allergic rhinitis	1,983	2.7	394	7.0	223	7.3
Number of contacts with GP							
	0	2,2784	30.5	240	4.3	0	0
	1-2	2,6725	35.8	1,314	23.4	658	21.5
	≥ 3	2,5071	33.6	4,051	72.3	2,406	78.5
Oral corticosteroid use		337	0.5	188	3.4	143	4.7
At least 1 parent with doctor-diagnosed asthma^		3,106	4.3	483	8.9	312	10.5

* *URTI=Upper Respiratory Tract Infection*

^ *Based on data from 96% of the study population due to missing values (N=71,712)*

An overview of the applied therapies, stratified by age groups is presented in Table 2. We see that prescription of asthma medication changed with age. The prescribing of asthma medication was highest in children age 0-2 years (11.7%) and steadily declined with rising age, to 5.1% in the group of 15-17 year old children. Although differences could be observed in the applied therapies, there were no obvious trends with age. Monotherapy with SABA and the combination of this drug with ICS were the most applied therapies in all age groups. Of all children receiving asthma medication 52.9% received medication on only one occasion.

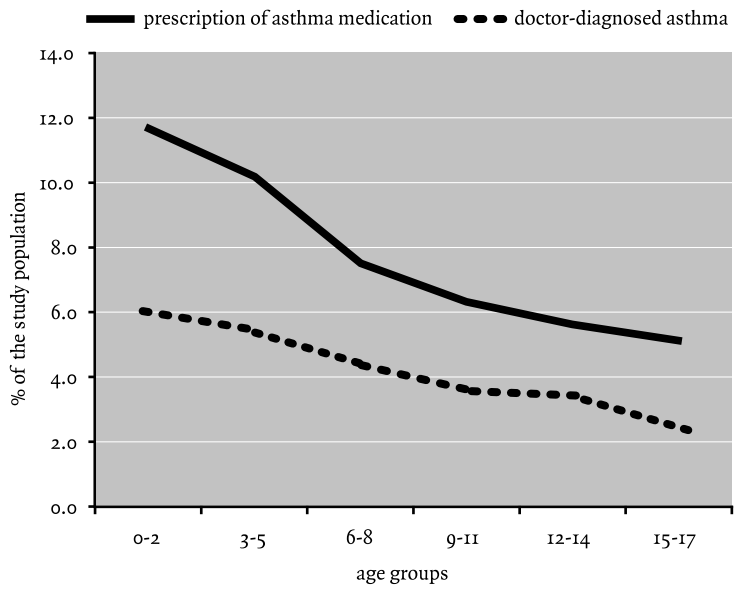
TABLE 2 Prescription of asthma medication by age group and type of medication

	AGE GROUPS						
	0-2	3-5	6-8	9-11	12-14	15-17	TOTAL
	N = 9,030	N = 12,690	N = 13,357	N = 13,521	N = 13,087	N = 12,895	N = 74,580
Prescription of asthma medication	11.7	10.2	7.5	6.3	5.6	5.1	7.5
Therapy groups, %							
SABA	36.9	24.9	28.0	32.2	40.4	40.5	32.7
ICS	19.5	22.9	23.1	20.5	16.3	19.6	20.7
SABA + ICS	35.0	45.3	43.4	40.0	36.7	30.9	39.4
Other medicines	8.6	7.0	5.5	7.3	6.6	9.0	7.2
1 prescription	58.1	52.5	48.3	52.3	52.6	53.7	52.9
2 prescriptions	20.2	21.1	21.9	21.0	19.7	20.2	20.8
≥ 3 prescriptions	21.7	26.5	29.8	26.7	27.8	26.0	26.3

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids

In Figure 1 we plotted the course of prescribing of asthma medication and doctor-diagnosed asthma with age. We found that both prescribing of asthma medication and doctor-diagnosed asthma declined with age.

FIGURE 1 The course of prescription of asthma medication and doctor-diagnosed asthma with age



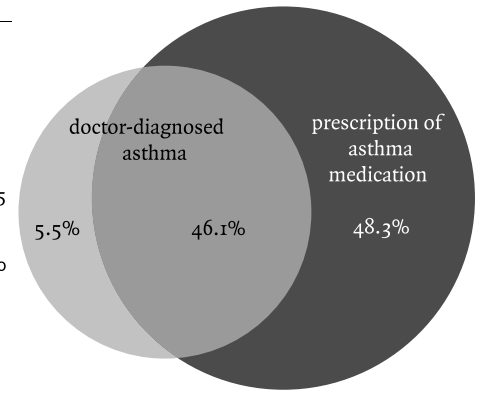
Initially prescribing of asthma medication seems to decline more rapidly with age than a diagnosis of asthma. Taking into account only the first three age groups one would expect the lines of prescribing and diagnosis to eventually cross each other. However, after age 6-8 the lines run virtually parallel, thus the gap between prescribing and diagnosing does not resolve. Moreover, approximately twice as many children received asthma medication than a diagnosis of asthma both in age group 0-2 and in age group 15-17.

The congruence between prescribing of asthma medication and doctor-diagnosed asthma for the overall study population is shown in two ways in Figure 2. The sensitivity shows that when selecting all asthma medication users, 89% of children with doctor-diagnosed asthma would be included in this selection. In other words, almost all children with doctor-diagnosed asthma were prescribed asthma medication. On the other hand, indicated by a PPV of 0.49, when selecting a child with asthma medication, this child would have doctor-diagnosed asthma in only 49% of the cases. Children receiving asthma medication without having doctor-diagnosed asthma had a registered diagnosis for other respiratory diseases (including acute upper respiratory tract infections, acute bronchitis, bronchiolitis and allergic rhinitis) or only a complaints diagnosis (including dyspnoea, wheezing and cough) during the registration period in respectively 45.4% and 21.9% of the cases.

FIGURE 2 Congruence between asthma medication use and doctor-diagnosed asthma within the total study population

		doctor-diagnosed asthma		
		Yes	No	Total
prescription of asthma medication	Yes	2,737	2,868	5,605
	No	327	68,648	68,975
	Total	3,064	71,516	74,580

Pearson's Chi - Square, P < .0001
positive predictive value (PPV) = 0.49
sensitivity =0.89



Based on the general consensus that from the age of five to six years a diagnosis of asthma can be made with reasonable clinical certainty, we divided

the study population into two age groups: children below the age of six and children aged six years and older. In Figure 1 we showed that there is an obvious age difference with respect to the number of children treated with asthma medication and diagnosed as being asthmatics. However, the congruence between these two measures does not differ between younger (< 6) and older children (≥ 6). Below six years of age 46% of the treated children had a diagnosis of asthma and in the older age group this was 51%.

Further subgroup analyses are shown in Table 3. Boys were more often treated with asthma medication and diagnosed with asthma than girls, but the PPV and sensitivity were similar. Between medication groups the PPV differed significantly: children on combination therapy were more likely to have doctor-diagnosed asthma. Also children who received asthma medication on more than one occasion had a greater chance of being diagnosed as asthmatics, with a PPV rising from 0.38 for children with one prescription to 0.66 for children with at least three prescriptions. The results from the analyses after changing our cut-off point for defining 'asthma medication use' from one to a minimum of two prescriptions are shown in Appendix 1.

TABLE 3 Subgroup analysis of the congruence between prescription of asthma medication and doctor-diagnosed asthma

	N	ASTHMA MEDICATION USE, %	DOCTOR-DIAGNOSED ASTHMA, %	PPV *	SENSITIVITY
Total population	74,580	7.5	4.1	0.49	0.89
Male	38,267	8.3	4.6	0.50	0.89
Female	36,312	6.7	3.5	0.47	0.90
< 6 yrs	21,720	10.8	5.7	0.46	0.88
≥ 6 yrs	52,860	6.2	3.5	0.51	0.90
SABA only		2.5	4.1	0.38	^
ICS only		1.6	4.1	0.42	
SABA + ICS		3.0	4.1	0.64	
1 prescription		4.0	4.1	0.38	^
2 prescriptions		1.6	4.1	0.54	
≥ 3 prescriptions		2.0	4.1	0.66	

** All Pearson's Chi-Square p-values < .0001*

^ The sensitivities for subgroups of asthma medication users are not shown, since they are highly dependent on the percentual contribution of the subgroups to the total group of asthma medication users and are therefore not very informative and, by definition, low

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids

Looking at gender differences we found that the difference between boys and girls lies mainly in the number of children treated with combination therapy and diagnosed with asthma (both higher in boys) but not in congruence between medication and diagnosis. Only the PPVs of ICS use only and of one prescription only were slightly higher in boys (0.45 and 0.40 respectively) than in girls (0.38 and 0.35 respectively).

Within the two age classes (<6 years and ≥ 6 years) separately, again no major differences in congruence were found between subgroups of gender, asthma therapy and number of prescriptions. The results for the older age group separately are shown in Appendix 1. The sensitivity remained high throughout the entire analyses, children with an asthma diagnosis received asthma medication in 87-91% of the cases. In children below the age of six gender differences were more pronounced. Girls this age were treated less than boys (4.5% versus 6.7%) and when treated, they were less likely to get diagnosed with asthma (PPV of 0.42 versus 0.49). In the older age group these gender differences were not present, 3.2% of girls was treated and 3.8% of boys and the PPVs were 0.50 and 0.51 respectively. This also shows that in boys the PPV was the same in both age groups (0.51) whereas this differed for girls (PPV 0.42 for girls <6 and 0.50 for girls ≥ 6). The lowest overall PPV found was for girls below six years of age. Within this group 58% of children with asthma medication did not have doctor-diagnosed asthma.

DISCUSSION

The congruence between asthma medication use and doctor-diagnosed asthma can be considered from two angles. One way is to determine whether all children with a diagnosis of asthma receive treatment. In our study an overall high sensitivity of 0.89 shows that indeed a high percentage of children diagnosed with asthma receive asthma medication. The other way, investigating whether children using asthma medication have an asthma diagnosis, we find that overall only 49% of all children receiving asthma medication has doctor-diagnosed asthma (i.e., 2,868 children receive asthma medication without a diagnosis of asthma). This discrepancy could be due to many factors, including over treatment, off label use, underdiagnosis and use of asthma medication as a diagnostic tool.

We hypothesised that the congruence between prescription of asthma medication and doctor-diagnosed asthma would increase with age. We expected to find more undiagnosed children and children with one prescription only in children using asthma medication below the age of six, because of diagnostic difficulties at this age and the use of medication as a diagnostic tool. Most children who wheeze at this age suffer from transient or self-limiting disease and might receive medication to lessen complaints but do not receive the label 'asthma'. From age six the diagnosis of asthma can be made with more certainty and the children receiving asthma medication are expected to be the 'real asthmatics' and thus have a matching diagnosis of asthma. We find that indeed both prescribing of asthma medication and doctor-diagnosed asthma are influenced by age. However, they both decline with rising age and the high sensitivity and low positive predictive value (PPV) found in the overall study population was consistent throughout the different age groups.

In subgroup analyses on gender and age we found only minor differences in PPV. The largest difference is between young girls (< 6 years) and older girls (≥ 6 years) with 42% versus 50% receiving treatment without a diagnosis of asthma. The PPV differs significantly between subgroups of therapy. Children on combination therapy have a much higher chance of having doctor-diagnosed asthma (PPV 0.64) than do children using SABA only (PPV 0.38). Also the number of prescriptions for asthma medication strongly influences the relationship with doctor-diagnosed asthma. However, the PPV never comes close to one, thus no matter which subgroup you select, there is always a substantial number of children present that is treated with asthma medication without being diagnosed as an asthmatic.

The number of children using asthma medication and the declining trend with age found in our study is consistent with results from other studies [11, 36] as is the number of children with doctor-diagnosed asthma.[37]

Recent guidelines state that the first two treatment steps to manage asthma for children age six and older are the following: start with inhaled SABA as needed and add low-dose ICS when symptoms are more frequent and/or worsen periodically. And although the evidence is not as strong in children age five years and younger, which precludes detailed treatment recommendations, these same two initial steps are recommended for this age group.[1, 6, 7] For the major part the therapies applied in our study population seem to

be in line with these guidelines. However, there is quite a large group of children receiving ICS without receiving a prescription for SABA in that same year. This could indicate that there is some overtreatment with ICS. Another explanation could be that children had very little need for reliever medication and still used SABA dispensed in the previous year. Indeed, although the guidelines state that reliever medication should always be provided for quick relief of symptoms, reducing or eliminating the need for reliever treatment is both an important goal and a measure of success of treatment.[1]

Our finding that 89% of children diagnosed with asthma receive asthma medication differs from other studies, in which many children with a diagnosis of asthma did not receive medication (ranging from 21.8 to 64.4%).[12, 28, 30, 31] However, these studies used parental-reported doctor-diagnosed asthma from questionnaire data, which have been shown to differ substantially from a diagnosis of asthma derived from the GPs clinical records in the sense that self-reported asthma renders many more 'asthmatics' than do the GP's records.[38] Despite this higher number of 'asthmatics' these studies do show similar results with respect to the percentage of children being treated without an asthma diagnosis. This percentage is lower than our finding (20.9%) in only one study, but comparable, ranging from 40.0% to 47.3%, in the other four studies.[3, 12, 28, 31, 39]

One previous study used medical and pharmacy claim data instead of questionnaire data and found that children receiving asthma medication without a diagnosis of asthma have considerable morbidity and health care utilisation. The authors conclude that better recognition of paediatric asthma is warranted.[29] Although this study was not population based (but made use of an administrative claims based dataset) and mainly focuses on the economic impact of undiagnosed children dispensed asthma medication, without detailed subgroup analyses, their finding that 40% of children used asthma medication without evidence of a documented doctor-diagnosed claim for asthma is in line with our own findings.

The current study has some limitations. First, we do not have information on specialist care. In the hypothetical case that a GP continues asthma medication initiated by a specialist without registering the diagnosis this would add to the group of children being treated without a diagnosis of asthma.

However, very few children in our study population were referred to a child lung physician (0.4% of children using asthma medication) or even to a paediatrician in general (5.4% of children using asthma medication). Second, in this study asthma diagnoses as registered by the GP are taken into account, and although often used as a gold standard in studies, this might not be the true reflection of asthmatics in the study population. Third, some overestimation of medication use might be present since not all prescribed medication is filled in the pharmacy. Since our interest lies in the relationship between the two GP based actions of diagnosing and prescribing (Does the GP base prescribing of medication on his decision whether or not to diagnose a child with asthma?), these last two limitations are of only relative importance to our study.

CONCLUSIONS

Several conclusions can be drawn from the work presented here. Firstly, less than half of all children prescribed asthma medication had a registered diagnosis of asthma. Secondly, detailed subgroup analyses show that a diagnosis of asthma is present in at most 66% of children; even in children treated extensively with asthma medication, such as children prescribed ICS or receiving asthma medication on at least three occasions within one year. Lastly, although age strongly influences the chance of being treated, remarkably, the congruence between prescribing of asthma medication and doctor-diagnosed asthma does not improve with age. Further research is needed to determine what causes this discrepancy and whether this is grounds for changing asthma medication use in children.

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appendix 1

TABLE 4 Subgroup analysis of the congruence between prescription of asthma medication and doctor-diagnosed asthma, with a cut-off for asthma medication use of at least 2 prescriptions

	N	ASTHMA MEDICATION USE, %	DOCTOR-DIAGNOSED ASTHMA, %	PPV*	SENSITIVITY
Total population	74,580	3.5	4.1	0.61	0.52
Male	38,267	4.0	4.6	0.61	0.52
Female	36,312	3.1	3.5	0.61	0.53
< 6 yrs	21,720	4.9	5.7	0.60	0.52
≥ 6 yrs	52,860	3.0	3.5	0.61	0.53
SABA only		0.5	4.1	0.44	^
ICS only		0.6	4.1	0.54	
SABA + ICS		2.2	4.1	0.67	

* All Pearson's Chi-Square p-values < .0001

^ The sensitivities for subgroups of asthma medication users are not shown, since they are highly dependent on the percentual contribution of the subgroups to the total group of asthma medication users and are therefore not very informative and, by definition, low

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids

TABLE 5 Subgroup analysis of the congruence between prescription of asthma medication and doctor-diagnosed asthma for children age 6 and older

	N	ASTHMA MEDICATION USE, %	DOCTOR-DIAGNOSED ASTHMA, %	PPV*	SENSITIVITY
Total population	52,860	6.2	3.5	0.51	0.90
Male	26,959	6.6	3.8	0.51	0.89
Female	25,902	5.7	3.2	0.50	0.91
SABA only		2.1	3.5	0.41	^
ICS only		1.2	3.5	0.40	
SABA + ICS		2.4	3.5	0.66	
1 prescription		3.2	3.5	0.41	^
2 prescriptions		1.3	3.5	0.55	
≥ 3 prescriptions		1.7	3.5	0.66	

* All Pearson's Chi-Square p-values < .0001

^ The sensitivities for subgroups of asthma medication users are not shown, since they are highly dependent on the percentual contribution of the subgroups to the total group of asthma medication users and are therefore not very informative and, by definition, low

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids

ABSTRACT

Introduction

Diagnosing children with asthmatic symptoms remains a challenge, particularly in preschool children. This creates space for variability in prescribing. The aim of this study is to investigate how and to what degree patient, family and physician characteristics influence prescribing of asthma medication in children.

Methods

Design: A multilevel population based study.
Setting: The second Dutch national survey of general practice (DNSGP-2), 2001.
Participants: 46,371 children aged 1-17 years belonging to 25,537 families registered with 109 general practitioners (GPs).
Main outcome measures: Prescribing of asthma medication, defined as at least one prescription for beta2-agonists, inhaled corticosteroids, cromones or montelukast during the one-year study period.
Analysis: A multilevel multivariate logistic regression analysis with three levels.

Results

On all three levels (child, family and GP) characteristics significantly associated with prescribing of asthma medication were identified.
The variance in prescribing between GPs was significantly higher in children below the age of six than in older children (95% CI 3.5 to 25.2% versus 2.4 to 13.4%; Chi-square = 7.3). Several diagnoses other than asthma and asthmatic complaints were strongly associated with prescribing of asthma medication, including bronchitis/bronchiolitis (OR 9.04; 95% CI 7.57 to 10.8) and cough (OR 6.51; 95% CI 5.68 to 7.47).

Conclusions

Our study shows a much higher variance in prescribing between GPs for children below the age of six compared to older children, which could be a direct result of the diagnostic complexities present in young children with asthmatic symptoms. Thus diagnostic gaps may lead to more physician driven prescribing irrespective of the clinical context.

4.2 What drives prescribing of asthma medication to children? A multilevel population based study

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INTRODUCTION

Asthma in children has been recognised as a major clinical and public health problem.[1, 2] Reported data on prevalence of asthma symptoms in children vary significantly, from 1 to more than 30 percent in different populations.[3] Despite all scientific and clinical progress, diagnosing and treating children with asthmatic symptoms remains a challenge.[4-6] Firstly, children often receive medication to reduce symptoms during wheezing episodes to prevent further exacerbations and to serve more or less as a diagnostic tool. However, at a young age valid diagnostic possibilities for asthma are still limited. Most children will eventually turn out to be transient wheezers, but there is a lack of objective diagnostic tools to distinguish these transient wheezers from the true asthmatics.[6] Secondly, the family of the child may play a role, for example with its specific help seeking behaviour [7] and genetic influence on disease susceptibility.[8] And last but not least, it is the treating physician who makes the decision whether or not to prescribe asthma medication to a certain child. To aid in this decision guidelines are available, rendering information on how children with asthmatic symptoms should be treated and which kind of asthma medication should be used.[9-11] There is general consensus that not earlier than from the age of five to six years a diagnosis of asthma can be made with reasonable certainty. Therefore different treatment recommendations are made for children below five to six years of age and older children.[9-11]

Thus, prescribing of asthma medication to children is a complex interplay between the child, the caregivers/parents of the child, and the treating physician. Given the absence of clear diagnostic guidance in children, particularly in preschool children, variability in prescribing is to be expected. As a result drug utilization studies describing actual use of asthma medicines in children show ample diversity in the applied therapies.[12-14] Other studies have reported a mismatch between asthma medication use and a diagnosis of

asthma.[15-17] A key question driven by these observations is whether this diversity seen in paediatric asthma therapy is mainly determined by the patient himself, the family or the treating physician. The attitude of the physician or preferences of the caregivers/parents could play a much larger role in the decision making process at a young age, when the diagnosis is uncertain, than at an older age, when the diagnosis of asthma can be more firmly established.
Therefore the aim of this study is to investigate how and to what degree prescribing of asthma medication in children is influenced by patient, family and physician characteristics. We will investigate to what extent variance in prescribing is associated with differences between children, how much variance can be attributed to the family and/or physician, and whether these variances differ for younger and older children.

METHODS

Setting and study population

In the Netherlands, children with asthmatic symptoms and morbidity are primarily seen by the physicians in general practice. Therefore, this study has been conducted within the framework of the second Dutch national survey of general practice (DNSGP-2). This nationwide survey was carried out in 2001 by the NIVEL (Netherlands Institute for Health Services Research) in co-operation with the National Institute for Public Health and the Environment (RIVM). Practices already participating in the Dutch National Information Network of General Practice (LINH) were invited to participate in this study because of their experience in the use of electronic medical records.
All practices within the DNSGP-2 made use of electronic medical records. The participating general practitioners (GPs) were representative of all Dutch GPs.[18] A pilot study also showed no differences in practice style between GPs participating in a registration network and those who are not.[19]
The DNSGP-2 survey has been described in detail elsewhere.[18, 20] In short, 195 GPs in 104 practices serving approximately 400,000 patients registered all physician–patient contacts during 12 consecutive months. The DNSGP-2 provides data on all diagnoses and prescriptions made by the GP.
Every single health problem presented within a consultation was coded by the GP using the International Classification for Primary Care (ICPC).[21]

Extra information on patient and GP characteristics was collected through questionnaires. In the Netherlands all non-institutionalised inhabitants are registered in a single general practice, with very little changes over time.
The DNSGP-2 survey was carried out according to Dutch legislation on privacy. The privacy regulation of the study was approved by the Dutch Data Protection Authority.

For the present study data from 72 GP practices were analyzed. The other practices were excluded for various reasons. Twenty practices were excluded because the information on which patient belongs to which individual GP was not available, ten because of incomplete data collection on morbidity items and two more practices were excluded due to lack of information on GP characteristics. The remaining 109 GPs within the 72 practices did not differ significantly from the total group of GPs participating in the DNSGP-2 except for a higher percentage of solo practices (due to our selection criterion including only patients which could be linked to a specific GP).
A total of 1,804 children (3.7%) who could not be linked to a single family were also excluded. Finally, the study population consisted of 46,371 children aged 1-17 years within 25,537 families, belonging to 109 GPs within 72 practices. Children, families and GPs seem to be representative for the Dutch situation on basic characteristics.[18, 20]

Measurements

Outcome variable: prescribing of asthma medication

Drug prescriptions were registered by the GP according to the Anatomical Therapeutic Chemical Classification (ATC) system.[22] The following of these were considered to be asthma medication: inhaled and oral short-acting beta2-agonists, inhaled long-acting beta2-agonists, inhaled corticosteroids, inhaled cromones and montelukast. We determined whether a child from the study population received at least one prescription for one of these medicine groups in the year under study (i.e. 2001), calling them 'children prescribed asthma medication'.

Child characteristics

On the level of the individual child the following variables were taken into account: age (categorised into children below the age of six and children aged six and older conform the guidelines); gender; the number of prescriptions a child received for antibiotics in the year under study;

the number of prescriptions a child received for oral glucocorticosteroids in the year under study; the number of contacts a child had with the GP in the year under study; whether a child had at least one referral for respiratory complaints/diseases or to a lung specialist in the year under study. Every single health problem presented within a consultation was coded by the GP using the International Classification for Primary Care (ICPC).[21] We included the following ICPC diagnoses of respiratory complaints and diseases as dichotomous variables: R02 (shortness of breath/dyspnoea), R03 (wheezing), R05 (cough), R74 (acute upper respiratory tract infection), R78 (acute bronchitis/bronchiolitis), R81 (pneumonia), R96 (asthma) and R97 (allergic rhinitis). Thus, if a child had at least one consultation coded with one of these ICPC codes then the dichotomous variable for that specific code for that child would be positive.

Family characteristics

On the family level the following variables were taken into account: ethnicity (whether one or both parents had a non-western cultural background based on the country of birth); the highest Social Economic Status (SES) of the parent(s) using the International Socio-Economic Index of Occupational Status (ISEI); and presence of parental asthma (at least one parent with a registered ICPC code R96 during the study period).

GP characteristics

On the GP level the following variables were taken into account: age; gender; practice type (single-handed versus group practice); degree of urbanization of practice location (as classified by Statistics Netherlands on a five-point scale); GP information system; whether the GP is a dispensing doctor (a doctor, authorised or required by the Health Authority to provide pharmaceutical services to his/her patients); whether the GP is full-time or part-time working in number of full-time equivalents (FTEs); workload of the GP (operationalised as the total number of patients divided by the number of FTEs per 1,000 patients); prescribing volume of the GP (operationalised as the average number of prescriptions issued per patient during one year); proportion of 0-17 year old per GP; and the proportion of children with an asthma diagnosis per GP. To display the GP characteristics (Table 4) we divided the GPs into two groups: those who prescribed asthma medication to the average % of children or less and those who prescribed above average (which, on the GP level is 7.4%) within their childhood patient population.

Statistical analyses

We performed a multilevel logistic regression analysis with three levels, namely children within families clustered within GPs. This enables us to study not only the influence of the child-, family- and GP characteristics on asthma medicine use in children simultaneously but also the variance in prescribing on the two higher levels. The variance at the level of the child was not determined since the outcome measure is dichotomous: a child either receives asthma medication or not.

The association between prescribing of asthma medication and the variables described above was first tested univariate for each variable. Only variables with a significant association ($p< 0.05$) with prescribing of asthma medication were included in the multivariate analysis. All variables which no longer showed a significant association in the multivariate analysis were excluded. A sensitivity analysis including all child characteristics irrespective of significance showed that including the non-significant variables did not alter the estimates for the significant variables. The child characteristics gender and all diagnoses of respiratory complaints and diseases were tested for an age-interaction.

The multivariate analysis was performed in several steps to differentiate between the influence of child, family and GP characteristics on the various estimates. Step 1, the empty model, gives the unexplained variance on the upper two levels (family and GP) without correcting for any differences that might exist in the population of children belonging to these families and these GPs. In step 2 we separated the variance in prescribing on the GP level and on the family level for children below the age of six and older children. On each level this renders a unique variance per age group and a covariance. If the covariance turns out to be much higher than the two unique variances at a certain level it is not meaningful to separate the variance for the two age groups at this level. In step 3 we added the child characteristics (including the age-interaction terms) to the model. This serves two purposes: (I) to make the populations seen by the GP and belonging to a family as similar as possible and (II) to determine which child characteristics are associated with prescribing of asthma medication. The variance in this model is the variance unexplained by the child characteristics introduced in the model. In step 4 we added the family characteristics to the model. In step 5 we added the GP characteristics to the model.

The variables included in the models presented here were rescaled by subtracting the mean, so that the intercepts represent prescribing of asthma medication to the average child. The percentage of children receiving asthma medication can be calculated by taking the inverse logit of the intercept. The association between characteristics on all three levels and prescribing of asthma medication is expressed using odds ratios (OR) and 95% confidence intervals (CI). The 95% confidence interval of prescribing of asthma medication at the GP level can be calculated for each age group using the sum of the unique variance of that age group and the covariance. All models were estimated using multilevel logistic regression, with PQL (penalised quasi-likelihood), 1st order and constrained level 1 variance (MLwiN 2.02).

RESULTS

Characteristics of the study population

Table 1 shows the characteristics of the study population on the level of the child and the results for the univariate analyses. During the year under study 7.3% of all children (N = 3,374) received asthma medication. All child characteristics were significantly associated with prescribing of asthma medication when tested univariately. An overview of the applied therapies, stratified by age groups is presented in Table 2. We see that prescribing of asthma medication declines with rising age. Short-acting beta2-agonists and inhaled corticosteroids were the most prescribed medicine groups at all ages.
The children within our study population belonged to 3,081 families (Table 3), thus in 12.1% of the families one or more children were prescribed asthma medication. The characteristics of the GPs can be found in Table 4.

TABLE 1 Child characteristics and results from the univariate analyses

CHILD CHARACTERISTICS	CHILDREN WITHOUT AN ASTHMA PRESCRIPTION (N = 42,997)	CHILDREN PRESCRIBED ASTHMA MEDICATION (N = 3,374)	OR (95% CI)
Mean age, year (SD;range)	9.1 (4.8;1-17)	7.7 (4.9;1-17)	0.94* (0.93-0.95)
Age < 6 years (%)	11,948 (25.8)	1,386 (41.1)	1.82* (1.69-1.96)
Gender, male (%)	21,798 (50.7)	1,922 (57.0)	1.29* (1.20-1.39)
N antibiotic prescriptions (SD;range)	0.2 (0.6;0-13)	0.6 (1.0;0-12)	1.85* (1.77-1.93)
N oral corticosteroid prescriptions (SD;range)	0.003 (0.11;0-12)	0.046 (0.26;0-5)	4.69* (3.59-6.12)
N contacts with GP (SD;range)	2.1 (2.6;0-35)	5.2 (4.0;0-34)	1.30* (1.29-1.31)
Children with zero contacts in registration year (%)	13,786 (32.1)	129 (3.8)	-
Referrals (%) [a]	93 (0.3)	94 (3.6)	13.0* (12.2-13.9)
Registered diseases and complaints [b]			
asthma (%)	227 (0.5)	1,739 (51.5)	260* (221-305)
shortness of breath/dyspnoea (%)	92 (0.2)	144 (4.3)	21.1* (15.9-28.1)
wheezing (%)	16 (0.0)	63 (1.9)	55.2* (30.7-99.2)
cough (%)	2,082 (4.8)	873 (25.9)	6.90* (6.26-7.59)
acute bronchitis/ bronchiolitis (%)	769 (1.8)	622 (18.4)	13.5* (11.9-15.3)
acute URTI (%)	3,267 (7.6)	674 (20.0)	3.06* (2.78-3.38)
pneumonia (%)	241 (0.6)	133 (3.9)	7.24* (5.74-9.15)
allergic rhinitis (%)	1,029 (2.4)	252 (7.5)	3.24* (2.78-3.77)

[a] *referrals for respiratory complaints/diseases or to a lung specialist*

[b] *dichotomous variables of the ICPC codes R02 (shortness of breath/dyspnoea), R03 (wheezing), R05 (cough), R74 (acute upper respiratory tract infection), R78 (acute bronchitis/bronchiolitis), R81 (pneumonia), R96 (asthma) and R97 (allergic rhinitis)*

* *Significant values* $p < 0.05$

SD = Standard Deviation; URTI = Upper Respiratory Tract Infection; OR = Odds Ratio; CI = Confidence Interval

TABLE 2 Prescription of asthma medication by age group and type of medication

	AGE GROUPS (IN YEARS)						
	1-2	3-5	6-8	9-11	12-14	15-17	TOTAL
	N = 5,293	N = 8,041	N = 8,335	N = 8,350	N = 8,196	N = 8,156	N = 46,371
All asthma medication, %	10.9	10.1	7.0	6.1	5.7	5.2	7.3
Medication groups, %							
SABA	8.0	7.0	4.9	4.5	4.5	3.6	5.3
ICS	5.9	7.0	4.8	4.0	3.2	3.0	4.5
LABA	0.1	0.3	0.5	0.7	0.6	0.6	0.5
Cromones	0.8	0.5	0.1	0.1	0.1	0.1	0.2
Montelukast	0.0	0.1	0.1	0.1	0.0	0.1	0.1
Therapy groups, % ^							
SABA	38.6	25.7	29.2	32.4	41.9	39.1	33.4
ICS	20.7	24.7	24.3	18.7	15.1	21.9	21.3
SABA + ICS	33.2	43.2	40.9	40.4	36.2	30.2	38.1
Other medicines	7.5	6.5	5.6	8.6	6.8	8.8	7.2

^ *Here we did not calculate the % of the total population but instead the % of the children using asthma medication of some sort. The therapy groups therefore add up to a 100%; The therapy groups are defined as follows:*

SABA = monotherapy with SABA; ICS = monotherapy with ICS; SABA + ICS = combination therapy of these two medication groups (10.3% of the children in this group also received one or more other asthma medicines, of which 82% LABA); Other medicines = all other therapies

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids; LABA = long-acting beta2-agonists

TABLE 3 Family characteristics and results from the univariate analyses

FAMILY CHARACTERISTICS	NO CHILD WITH ASTHMA MEDICATION WITHIN THE FAMILY (N=22,456)	AT LEAST 1 CHILD WITHIN THE FAMILY WITH AN ASTHMA PRESCRIPTION (N=3,081)	OR (95% CI)
One/both parents non-western cultural background (%) [a]	1,834 (10.6)	275 (11.1)	1.01 (0.87-1.17)
Mean SES highest (SD;range) [b]	50.4 (15.5;16-87)	49.5 (15.4;16-87)	1.00 (0.99-1.00)
Parental asthma (%) [c]	821 (3.7)	256 (8.3)	2.33* (1.90-2.85)

[a] *ethnicity based on the country of birth*

[b] *the highest Social Economic Status (SES) of the parent(s) using the International Socio-Economic Index of Occupational Status (ISEI)*

[c] *at least one parent with a registered ICPC code for asthma during the study period*

* *Significant values p < 0.05*

SD = Standard Deviation; OR = Odds Ratio; CI = Confidence Interval

TABLE 4 GP characteristics and results from the univariate analyses

GP CHARACTERISTICS	GPs WITH AVERAGE AND BELOW AVERAGE PRESCRIBING OF ASTHMA MEDICATION (N = 58) [a]	GPs PRESCRIBING ASTHMA MEDICATION ABOVE AVERAGE (N = 51) [a]	OR (95% CI)
Mean age (SD;range)	47.6 (5.7;36-59)	46.2 (6.2;33-56)	1.00 (0.99-1.01)
Gender, male (%)	50 (86.2)	37 (72.6)	0.83 (0.69-1.00)
Practice type, single-handed (%)	27 (46.6)	20 (39.2)	0.88 (0.75-1.02)
Urbanisation practice location (SD;range) [b]	2.8 (1.4;1-5)	3.1 (1.0;1-5)	1.03 (0.98-1.10)
Mean FTE (SD;range) [c]	0.91 (0.15;0.5-1.0)	0.88 (0.17;0.5-1.0)	0.79 (0.48-1.28)
Dispensing doctor (%) [d]	5 (8.6)	3 (5.9)	0.97 (0.73-1.29)
Workload (SD;range) [e]	2.8 (0.7;1.4-5.5)	2.6 (0.6;1.3-4.8)	0.89 (0.80-1.00)
Prescribing volume (SD;range) [f]	1.5 (0.5;0.05-2.7)	1.8 (0.5;0.9-3.2)	1.55* (1.38-1.75)
% of 0-17 year olds ≥ 25 (%) [g]	15 (25.9)	6 (11.8)	0.77* (0.64-0.93)
% children with an asthma diagnosis (SD;range)	3.5 (1.4;0.8-7.3)	5.4 (2.1;1.9-11.6)	1.10* (1.07-1.14)

[a] *to display the GP characteristics we divided the GPs into two groups: those who prescribed asthma medication to the average % of children or less and those who prescribed above average (which, on the GP level is 7.4%) within their childhood patient population*

[b] *degree of urbanization of practice location as classified by Statistics Netherlands on a five-point scale*

[c] *full-time or part-time working in number of FTEs*

[d] *a doctor, authorised or required by the Health Authority to provide pharmaceutical services to his/her patients*

[e] *operationalised as the total number of patients divided by the number of FTEs per 1000 patients*

[f] *operationalised as the average number of prescriptions issued per patient during one year*

[g] *variable indicating for which GPs 25% or more of their total patient population consists of children age 0-17*

* *Significant values p < 0.05*

SD = Standard Deviation; GP = General Practitioner; FTE = full-time equivalent;

OR = Odds Ratio; CI = Confidence Interval

The multivariate model

Table 5 shows the stepwise built multivariate multilevel logistic regression model. We found that in the empty model the variance on the family level (0.567) was much higher than the variance on the GP level (0.119).

TABLE 5 Multilevel logistic regression analyses with three levels: child, family and general practitioner

EXPLANATORY VARIABLES		EMPTY MODEL	MODEL 1 [a]	MODEL 2 [a,b]	MODEL 3 [a,b]
		Intercept (SE)	Intercept (SE)	Intercept (SE)	Intercept (SE)
	Age 1-17	-2.580 (0.039)			
	Age 1-5		-2.210 (0.054)	-3.629 (0.100)	-3.645 (0.091)
	Age 6-17		-2.779 (0.039)	-3.573 (0.071)	-3.605 (0.060)
				OR (95% CI)	OR (95% CI)
Gender, male				1.25 (1.13-1.39)	1.25 (1.13-1.39)
Shortness of breath/dyspnoea				20.7 (14.3-29.9)	20.2 (13.9-29.2)
Wheezing				51.5 (24.7-107)	49.7 (23.8-104)
Cough				6.51 (5.68-7.47)	6.46 (5.64-7.40)
Acute bronchitis/ bronchiolitis				9.04 (7.57-10.8)	8.91 (7.45-10.6)
Acute URTI				1.47 (1.26-1.72)	1.47 (1.26-1.72)
Pneumonia				2.10 (1.44-3.07)	2.11 (1.44-3.09)
Allergic rhinitis				2.12 (1.68-2.69)	2.10 (1.66-2.67)
N contacts with GP				1.10 (1.08-1.12)	1.10 (1.08-1.12)
Presence of parental asthma					1.74 (1.41-2.15)
Prescribing volume GP					1.99 (1.60-2.47)
% of 0-17 year olds ≥ 25 per GP					0.59 (0.44-0.78)
% children with an asthma diagnosis per GP					0.88 (0.83-0.93)
		Variance (SE) [c]	Variance (SE)	Variance (SE)	Variance (SE)
Between family variance		0.567 (0.071)	0.535 (0.071)	0.474 (0.112)	0.471 (0.111)
Between GP variance	Age 1-17	0.119 (0.022)			
	Age 1-5		0.209 (0.042)	0.751 (0.134)	0.547 (0.106)
	Age 6-17		0.097 (0.022)	0.384 (0.071)	0.214 (0.047)
	Covariance		0.118 (0.025)	0.479 (0.083)	0.284 (0.058)
		Correlations	Correlations	Correlations	Correlations
Correlation GP variances age groups [d]		-	0.83	0.89	0.83
ICC [e]	Age 1-17	0.17			
	Age 1-5		0.38	0.72	0.64
	Age 6-17		0.29	0.65	0.51

[a] *Model 1 (age groups), Model 2 (age groups, child characteristics), Model 3 (age groups, child characteristics, family characteristics, GP characteristics)*

[b] *In these models we corrected for the presence of an asthma diagnosis in the child (model 2: OR = 262; 95% CI 219 to 312; model 3: OR = 264; 95% CI 221 to 315)*

[c] *The variance at the lowest level (children) is not determined since the outcome is dichotomous*

[d] *This is the correlation between the variances of the two defined age groups on the GP level*

[e] *Intra Class Correlation between the two upper levels (families and GPs)*

The ICC is the relative contribution of the GP to the sum of the family and GP variance

SE = Standard Error; OR = Odds Ratio; CI = Confidence Interval; GP = General Practitioner; ICC = Intra Class Correlation

URTI = Upper Respiratory Tract Infection

Comparing two age groups

When separating the variance in prescribing on the GP level for children below the age of six and older children (Model 1) we found that the variance is significantly higher (Chi-square = 7.3) in younger children than in older children. This age influence was not found to be present on the family level; at this level the covariance was much higher than the two unique variances (model not shown). In children below the age of six 9.9% received asthma medication, in the older age group this was 5.8%. In young children the 95% CI of prescribing was 3.5 to 25.2% (95% of the GPs prescribe within this range) while this was 2.4 to 13.4% in the older age group. The correlation between the two age groups at the GP level was 0.83, indicating that GPs who tend to prescribe asthma medication to young children more often, also tend to do so for older children.

The association between child characteristics and prescribing

The next step was to add the child characteristics to the model (Model 2). In this model the correlation between the variances for the two age groups at the GP level increased to 0.89, but the unique variances were still significantly different (Chi-square = 9.5). Model 2 also shows that the different complaints and disease diagnoses were strongly related to prescribing of asthma medication. Children with diagnosed acute bronchitis/bronchiolitis were much more likely to receive asthma medication than the average child (OR 9.04; 95% CI 7.57 to 10.8), as were children experiencing shortness of breath (OR 20.7; 95% CI 14.3 to 29.9), wheezing (OR 51.5; 95% CI 24.7 to 107) or cough (OR 6.51; 95% CI 5.68 to 7.47). The number of antibiotic prescriptions, the number of oral corticosteroid prescriptions and referrals were no longer significantly associated with prescribing of asthma medication in the multivariate analyses. While children below the age of six years were more frequently prescribed asthma medication, no significant age-interactions were found for gender or any of the diagnoses. From the intercept in Model 2 we see that when correcting for child characteristics young children no longer had a higher chance of receiving asthma medication than older children.

Taking into account the family and GP characteristics

Model 3 is the final model and includes both the family and the GP characteristics. On the family level presence of parental asthma was the only variable significantly correlated to prescribing of asthma medication in the

univariate analyses (Table 3) and this association sustained in the multivariate model where we adjusted for asthma diagnosis of the child (OR 1.74; 95% CI 1.41 to 2.15). Adding family and GP characteristics did not have a significant impact on the associations of the child's characteristics. This final model shows that in older children about half of the unexplained variance on the two upper levels lays on the GP level and the other half on the family level (Intra Class Correlation = 0.51). In younger children however, the Intra Class Correlation was 0.64, thus more of the unexplained variance lies on the GP level in this age group. Further analysis of the GP characteristics showed that GPs who in general prescribe more medication (operationalised as the average number of prescriptions per patient per GP), prescribe more asthma medication as well (OR 1.99; 95% CI 1.60 to 2.47). GPs who serve a relatively large childhood patient population (operationalised as GPs for whom more than 25% of their total patient population consisted of children) were less likely to prescribe asthma medication to the average child (OR 0.59; 95% CI 0.44 to 0.78) as were GPs who had a higher percentage of children diagnosed with asthma within their patient population (OR 0.88; 95% CI 0.83 to 0.93).

DISCUSSION

Summary of the results

Our results show that a substantial part of children received asthma medication during the one-year study period (7.3%). Through studying the influence of the child, family and GP characteristics on prescribing of asthma medication simultaneously in a multilevel fashion, we found that on all three levels characteristics could be identified which were significantly associated with prescribing of asthma medication.

Comparing two age groups

Based on the assumption that a diagnosis of asthma can be made with more certainty from age six and onwards we expected more differences between GPs in prescribing of asthma medication to children below the age of six than in older children. Indeed, we found that the variance in prescribing between GPs was much higher in young children than in children six years and older. Only a small part of the difference in prescribing between these two age categories could be attributed to differences in child characteristics.

These findings are in line with the fact that, despite the ongoing search for better diagnostics of asthma in children, there is still a relevant diagnostic gap particularly in preschool children.[6, 23, 24] Such a gap provides ample opportunity for inter-physician variance in prescribing of asthma medication based on personal preferences and prescribing attitudes in general. Related to this aspect was the finding that the overall medication prescribing volume of the GP was positively associated with prescribing of asthma medication, irrespective of complaints and illnesses of the child.

Family influence

We also found that family influence on prescribing of asthma medication in children was substantial. These findings are in line with reports on genetic influence on disease susceptibility,[8] health seeking behaviour [7, 25] and the attitude of the caregivers/parents regarding medication use.[26] In our study we found that presence of parental asthma was positively associated with prescribing of asthma medication. Since guidelines concerning asthma treatment state that parental asthma status should be taken into account when evaluating asthmatic symptoms in children,[9-11] this finding is not unexpected. Moreover we found that every extra contact with the GP renders a 10% extra chance of receiving asthma medication, indicating that health seeking behaviour of the family has a relevant impact on the treatment of the child.

Respiratory morbidities other than asthma

As expected, we found that a diagnosis of asthma and typical asthmatic complaints such as wheezing were strongly associated with prescribing of asthma medication. However, our data showed that asthma medication was not only used to treat asthma and asthmatic complaints but also for other respiratory morbidities such as acute bronchitis and acute upper respiratory tract infections. These findings are in line with other studies showing a discrepancy between asthma medication use and asthma diagnosis [15, 16] and could indicate off label use and overtreatment. Studies evaluating the effectiveness of asthma medication for indications other than asthma are inconclusive.[27-30] The association between male gender and prescribing of asthma medication is in line with previous findings.[14, 31] Since none of the disease and complaints diagnoses showed a significant interaction with age we can conclude that GPs do not regard certain complaints or illnesses more or less important at a young age than at an older age when it comes to prescribing of asthma medication.

Limitations of the study

The current study has some limitations. First, the time relationship between the event of prescribing and the measurement of the independent variables was not evaluated. Also, we did not determine if and for how long use of asthma medication was continued. Second, the complaints and disease diagnoses are not absolute characteristics of the child. They are registered by the GP and are the result of an interplay between the child presenting with certain complaints and the interpretation of the GP. Also, possible differences in disease severity are not expressed in these dichotomised variables. Third, variables available to characterise GPs and families were limited. Model 3 shows how much of the variance is still unexplained after introducing the variables included in this model. Especially on the two higher levels, but also on the patient level, one could think of characteristics, not available in our study that might be associated with prescribing of asthma medication to children including cultural and environmental factors (e.g. particulate matter air pollution, indoor climate).

Strengths of the study

The strengths of this study are the large number of children in our study population, the representativeness of the sample and the fact that the data about diagnosing and prescribing are both derived directly from the GP's clinical records. Furthermore, inclusion of a wide array of variables that might be associated with prescribing of asthma medication in a multilevel analysis as present in this study surpasses by far that of most available studies to date. This enables us to identify important factors, associated with prescribing of asthma medication to children and their independent contribution to the variance in prescribing. The relatively large variances found at the GP and family level indicate a substantial influence of both GP and family on prescribing of asthma medication. As a consequence a substantial sample size of GPs and families will be required to cross-validate these findings elsewhere.

In conclusion

In conclusion, our study showed that all three evaluated parties (patient, family and GP) have a significant influence on prescribing of asthma medication in children. On the level of the child we found that prescribing of asthma medication was strongly related to asthma and asthmatic symptoms, but also to many other respiratory diseases. Also health-seeking behaviour, presence of parental asthma and the attitude and experience of the GP seemed to be associated with prescribing of asthma medication in children. We found a much higher variance in prescribing between GPs for children below the age of six compared to older children, which we consider to be a result of the diagnostic complexities present in especially preschool children with asthmatic symptoms. Diagnostics uncertainties may result in more physician and family driven prescribing irrespective of the clinical context, a feature not always in the interest of the child.

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ABSTRACT

Introduction

In a previous study we found that child, family and general practitioner (GP) all influence whether a child received asthma medication or not. However, several options are available within asthma treatment. In this study we investigated how and to what degree child, family and GP influence whether a child received reliever or maintenance therapy.

Methods

Design: A multilevel population based study
Setting: The second Dutch national survey of general practice (DNSGP-2), 2001.
Participants: 46,014 children aged 1-17 years belonging to 25,456 families registered with 109 GPs.
Outcome measure: The type of asthma treatment a child received based on all drug prescriptions within the one-year study period, either short-acting beta2-agonists (SABA only, reliever therapy) or SABA and inhaled corticosteroids (SABA/ICS, maintenance therapy).
Analyses: Multilevel multivariate regression analyses with three levels.

Results

Children with doctor-diagnosed asthma had a higher chance of receiving SABA/ICS ($OR_{SABA/ICS}$ = 2.13; 95% CI 1.79 to 2.54) while children with registered shortness of breath were more likely to receive SABA only ($OR_{SABA/ICS}$ = 0.38; 95% CI 0.26 to 0.57). All other registered respiratory symptoms and diseases were equally associated with prescribing of reliever and maintenance therapy. Every GP consultation rendered a 7% extra chance of receiving maintenance therapy (OR = 1.07; 95% CI 1.04 to 1.09). Differences between GPs in the percentage of children they treated with asthma medication increased for both treatment regimes when respiratory morbidities and GP consultations were taken into account.

Conclusions

In this study we found only few characteristics to be related specifically to the choice for reliever or maintenance therapy in a child. Most child and GP characteristics were equally related to both regimes, and thus to prescribing in general. Both prescribing of SABA only and SABA/ICS were significantly related to other respiratory morbidities than asthma. Large differences existed between GPs in the percentage of children receiving medication, regardless of the therapy regime, which could not be explained by the number of children with respiratory morbidities per GP. Taking into account registered respiratory morbidities only increased the differences between GPs. This indicates that the relation between diagnosing a child with a certain disease or symptom and prescribing of medication strongly differed between GPs.

4.3 What determines the choice for reliever or maintenance therapy? And do all general practitioners act alike?

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Submitted

INTRODUCTION

In a previous study (Chapter 4.2 of this thesis) we found that child, family and general practitioner (GP) all influenced whether a child received asthma medication or not. However, there are several treatment options for children with asthmatic symptoms. Both national and international guidelines recommend that treatment should be given in a stepwise approach according to the persistence, severity and/or frequency of symptoms.[1-4] The first step is to prescribe an inhaled short-acting beta2-agonist (SABA) as short-term reliever therapy for all patients with symptomatic asthma. The second step is to introduce maintenance therapy with inhaled corticosteroids (ICS). And if asthma is still not adequately controlled a third and fourth step, which include increasing the dose of ICS and initiating add-on therapy, are defined.

Although a diagnosis of asthma is difficult to make in young children,[5-7] the same treatment steps are recommended for children below 6 years of age.[1-4] Thus the use of SABA to reduce symptoms during wheezing episodes is generally accepted in practice.[1] However, physicians are recommended to base their decision on introducing maintenance treatment in young children on several factors related to asthma, including the age of onset of symptoms, severity of symptoms, triggers of symptoms, gender differences, atopic characteristics of the child and a parental history of asthma.[2-4]
Therefore, it is expected that children receiving SABA/ICS differ from children receiving SABA only with respect to disease severity. However, other child characteristics, such as current age of the child may play a role as well. Also, the family of the child might influence the treatment their child receives. Specific health seeking behaviour,[8] parental beliefs about the different medication groups [9, 10] and genetic influence on disease susceptibility [11] can all influence the physician's decision on what to prescribe. Also, in general, GPs have been found to prescribe different medications for the same diagnosis.[12]

In this study we investigated how and to what degree child, family and GP influence whether a child receives reliever therapy with SABA or maintenance therapy with SABA/ICS.

METHODS

Setting and study population

In the Netherlands children with asthmatic symptoms and morbidity are primarily seen by physicians in general practice. Therefore, this study has been conducted within the framework of the second Dutch national survey of general practice (DNSGP-2). This nationwide survey was carried out in 2001 by NIVEL (Netherlands Institute for Health Services Research) in cooperation with the National Institute for Public Health and the Environment (RIVM). The participating GPs were representative of all Dutch GPs.[13]
The DNSGP-2 survey has been described in detail elsewhere.[13, 14]
In short, 195 GPs in 104 practices serving approximately 400,000 patients registered all physician–patient contacts during 12 consecutive months.
The DNSGP-2 provides data on all diagnoses and prescriptions made by the GP. Every single health problem presented within a consultation was coded by the GP using the International Classification for Primary Care (ICPC).[15]
Extra information on patient and GP characteristics was collected through questionnaires. In the Netherlands all non-institutionalised inhabitants are registered in a single general practice, with very little changes over time.
The DNSGP-2 survey was carried out according to Dutch legislation on privacy. The privacy regulation of the study was approved by the Dutch Data Protection Authority.

For the present study data from 72 GP practices were analyzed. The other practices were excluded for various reasons. Twenty practices were excluded because the information on which patient belonged to which individual GP was not available, ten because of incomplete data collection on morbidity items and two more practices were excluded due to lack of information on GP characteristics. The remaining 109 GPs within the 72 practices did not differ significantly from the total group of GPs participating in the DNSGP-2 except for a higher percentage of solo practices (due to our selection criterion including only patients which could be linked to a specific GP). A total of 1,804 children (3.7%) who could not be linked to a single family were also excluded. Finally, the study population consisted of 46,371 children aged 1-17 years within 25,537 families, belonging to 109 GPs within 72 practices. Children, families and GPs seem to be representative for the Dutch situation on basic characteristics.[13, 14]

Measurements

Outcome variable: asthma therapy groups

Drug prescriptions were registered by the GP according to the Anatomical Therapeutic Chemical Classification (ATC) system.[16] The following of these were considered to be asthma medication: inhaled and oral short-acting beta2-agonists (SABA), inhaled long-acting beta2-agonists (LABA), inhaled corticosteroids (ICS), inhaled cromones, and montelukast.
The children within the study population were divided into therapy groups based on the prescribed asthma medication in the year under study. The therapy groups are based on the "NHG standaarden" (Dutch guidelines for GPs) of 1998 and 2006 [17, 18] and the guidelines for Dutch paediatric pulmonologists, [19] which use a stepwise treatment plan, comparable to other national and international guidelines.[1-4] Six groups were defined: (I) no asthma treatment (reference group), (II) monotherapy with SABA (SABA only, reliever therapy), (III) combination therapy of SABA and ICS (SABA/ICS, maintenance therapy), (IV) combination of SABA/ICS with add-on therapy of LABA and/or montelukast, (V) exacerbation treatment: one or more prescriptions for oral corticosteroids, within the group of children receiving asthma medication and (VI) all other (combinations of) asthma medication. Only the first three groups were further analysed in the multilevel regression models. The other groups (N = 357, 0.8% of the study population) were not included because of low numbers of children within these groups. Group III (SABA/ICS) also included children who in the year under study only received ICS (no SABA), based on the assumption that these children received SABA before the study period (since a well-controlled child will rarely need SABA and true monotherapy with ICS is rare).

Child, family and GP characteristics

All child, family and GP characteristics which in the previous study (Chapter 4.2 of this thesis) showed to have a relation to prescribing of asthma medication were included in the analysis.
Child characteristics: On the level of the individual child the following variables were taken into account: age (categorised into children below the

age of six and children aged six and older conform the guidelines); gender; the number GP consultations in the year under study. We included the following ICPC diagnoses of respiratory symptoms and diseases as dichotomous variables: R02 (shortness of breath/dyspnoea), R03 (wheezing), R05 (cough), R74 (acute upper respiratory tract infection), R78 (acute bronchitis/bronchiolitis), R81 (pneumonia), R96 (asthma) and R97 (allergic rhinitis). Family characteristics: On the family level presence of parental asthma (at least one parent with a registered ICPC code R96 during the study period) was taken into account. GP characteristics: On the GP level the following variables were taken into account: prescribing volume of the GP (operationalised as the average number of prescriptions issued per patient during one year); whether the proportion of 0-17 year old children per GP was more than 25% of the GPs total patient population; and the proportion of children with an asthma diagnosis per GP.

Statistical analyses

We performed a multilevel multinomial regression analysis comparing three groups:(I) no asthma treatment as the reference group, (II) monotherapy with SABA and (III) combination therapy of ICS and SABA. The multilevel multinomial regression analysis was thus performed on 46,014 children aged 1-17 years belonging to 25,456 families registered with 109 GPs. Three levels were included, children within families clustered within GPs. This enabled us to study not only the influence of the child-, family- and GP characteristics on prescribing of asthma medication in children simultaneously but also the variance in prescribing on the two higher levels.
The variance at the level of the child is set at $\pi^2/3$ because of the nominal character of the outcome.

The multivariate analysis was performed in several steps to differentiate between the influence of child, family and GP characteristics on the various estimates. Step 1, the empty model, gave the unexplained variance on the upper two levels (family and GP) for both therapy groups without correcting for any differences that might exist in the population of children belonging to these families and these GPs. On the GP level a unique variance per therapy group and a covariance could be estimated. On the family level the covariance has not been estimated because there were only 86 families in which children from both therapy groups were present. In step 2 we added the child characteristics to the model. This serves two purposes: (I) to make the

populations seen by the GP and belonging to a family as similar as possible and (II) to determine which child characteristics are associated with prescribing of SABA/ICS. The variance in this model is the variance unexplained by the child characteristics introduced in the model. In step 3 we added the family characteristics to the model. In step 4 we added the GP characteristics to the model.
A second multilevel logistic regression analysis was performed comparing the two therapy groups directly, with SABA only as the reference group and SABA/ICS as the outcome. The analysis was performed using the same characteristics and the same model building steps as described above.
This model shows which characteristics were related to whether a child received ICS on top of SABA in a group of children all receiving asthma medication. The variables included in the models presented here were rescaled by subtracting the mean, so that the intercepts represent prescribing of SABA or SABA/ICS to the average child. The percentage of children receiving either SABA or SABA/ICS can be calculated by taking the inverse logit of the intercept. The association between characteristics on all three levels and the two therapy groups is expressed using odds ratios (OR) and 95% confidence intervals (CI). The 95% confidence interval of prescribing at the GP level can be calculated for each therapy group using the sum of the unique variance of that therapy group and the covariance. The models including the three therapy groups were estimated using multilevel multinomial logistic regression, for unordered categories, with PQL (penalised quasi-likelihood), 1st order and constrained level 1 variance (MLwiN 2.02). The models including two therapy groups were estimated using multilevel logistic regression, with PQL, 2nd order and constrained level 1 variance (MLwiN 2.02).

RESULTS

Descriptive analyses

Study population characteristics are shown in Table 1 (child and family characteristics) and Table 2 (GP characteristics). During the year under study 7.3% of all children received asthma medication, mainly reliever therapy of SABA only (35.2% of all children receiving asthma medication, N = 1,188) and maintenance therapy of SABA/ICS (54.2% of all children receiving asthma medication, N = 1,829). These children were younger than children

not receiving asthma medication (> 40% younger than six years compared to 26% younger than six years). Children with asthma medication, especially those receiving oral corticosteroids, had higher consultation rates than children not receiving asthma medication (7.8 versus 2.1 GP consultations).

TABLE 1 Characteristics of the study population on the child and family level

	I REFERENCE: NO ASTHMA MEDICATION	II SABA ONLY	III SABA/ICS	IV SABA/ICS + LABA /MONTELUKAST	V ORAL CORTICOSTEROIDS	VI OTHER
Child level	(N = 42,997)	(N=1,188)	(N=1,829)	(N=184)	(N=126)	(N=47)
Mean age, year (SD;range)	9.1 (4.8;1-17)	7.8 (5.1;1-17)	7.3 (4.6;1-17)	10.7 (3.9;2-17)	8.4 (5.0;1-17)	10.4 (4.5;1-17)
Age < 6 years (%)	11,948 (25.8)	493 (41.5)	815 (44.6)	22 (12.0)	45 (35.7)	11 (23.4)
Gender, male (%)	21,798 (50.7)	664 (55.9)	1,045 (57.1)	111 (60.3)	81 (64.3)	21 (44.7)
N of GP consultations (SD;range)	2.1 (2.6;0-35)	4.5 (3.5;0-23)	5.4 (4.1;0-26)	5.6 (4.1;0-21)	7.8 (5.5;1-34)	4.9 (4.6;0-23)
Registered diseases and symptoms [a]						
asthma (%)	227 (0.5)	464 (39.1)	1,032 (56.4)	123 (66.9)	97 (77.0)	23 (48.9)
shortness of breath / dyspnoea (%)	92 (0.2)	76 (6.4)	55 (3.0)	7 (3.8)	6 (4.8)	0 (0)
wheezing (%)	16 (0.0)	25 (2.1)	35 (1.9)	2 (1.1)	1 (0.8)	0 (0)
cough (%)	2,082 (4.8)	301 (25.3)	503 (27.5)	35 (19.0)	29 (23.0)	5 (10.6)
acute bronchitis / bronchiolitis (%)	769 (1.8)	217 (18.3)	335 (18.3)	26 (14.1)	37 (29.4)	7 (14.9)
acute URTI (%)	3,267 (7.6)	231 (19.4)	380 (20.8)	22 (12.0)	37 (29.4)	4 (8.5)
pneumonia (%)	241 (0.6)	45 (3.8)	72 (3.9)	4 (2.2)	11 (8.7)	1 (2.1)
allergic rhinitis (%)	1,029 (2.4)	75 (6.3)	136 (7.4)	21 (11.4)	15 (11.9)	5 (10.6)
Family level [b]	(N=22,456)	(N=1,067)	(N=1,678)	(N=177)	(N=124)	(N=35)
Presence of parental asthma (%) [c]	821 (3.7)	85 (8.0)	135 (8.1)	21 (11.9)	12 (9.7)	3 (8.6)

[a] *Dichotomous variables of the ICPC codes R02 (shortness of breath/dyspnoea), R03 (wheezing), R05 (cough), R74 (acute upper respiratory tract infection), R78 (acute bronchitis/bronchiolitis), R81 (pneumonia), R96 (asthma) and R97 (allergic rhinitis)*

[b] *Definition of family groups: (i): reference group, if no child within the family received asthma medication; (ii): If at least one child in the family used SABA only and no child in the family belonged to treatment group III to V; (iii): If at least one child in the family belonged to the SABA/ICS group and no child in the family belonged to treatment group IV or V; (iv): If at least one child in the family belonged to the SABA/ICS + LABA/montelukast group and no child in the family belonged to group V; (v): If at least one child in the family belonged to the exacerbation group; (vi): The families in which all children using medication belonged to the 'other' group*

[c] *At least one parent with a registered ICPC code for asthma during the study period*

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids; LABA = long-acting beta2-agonists; SD = Standard Deviation; URTI = Upper Respiratory Tract Infection

All respiratory morbidities were more common in children with than in children without asthma medication. The percentage of children with an asthma diagnosis and allergic rhinitis rose with each add-on to the asthma therapy, while wheezing declined. Children receiving oral corticosteroids more often had acute bronchitis/bronchiolitis, upper respiratory tract infections and pneumonia. Parental asthma was more common in all therapy groups, but mainly in the group treated most extensively, with SABA/ICS + either LABA or montelukast.

TABLE 2 Characteristics of the study population on the GP level

GP CHARACTERISTIC	ALL GPs (N = 109)
Mean age (SD;range)	47.0 (6.0;33-59)
Gender, male (%)	87 (79.8)
Prescribing volume (SD;range) [a]	1.6 (0.5;0.05-3.2)
% of 0-17 year olds ≥ 25 (%) [b]	21 (19.3)
% children with an asthma diagnosis (SD;range)	4.4 (2.0;0.8-11.6)

[a] *Operationalised as the average number of prescriptions issued per patient during one year*

[b] *Variable indicating for which GPs 25% or more of their total patient population consisted of children age 0-17*

SD = Standard Deviation; GP = General Practitioner

Multilevel analysis comparing reliever and maintenance treatment to no treatment

The results from the multilevel multinomial regression analysis, investigating prescription of SABA only or SABA/ICS, with children not receiving asthma medication as the reference group, are shown in Table 3. The empty model shows that a substantial part of the prescribing variance was on the level of the family. This variance was slightly higher for the maintenance therapy, the Intra Class Correlation (ICC) was 16.3% compared to 10.4% for SABA only. The variance at the GP level was somewhat lower (ICC_{GP} = 6.5% for SABA and 5.7% for SABA/ICS), indicating that a smaller part of the variance in prescription of both therapy regimes was due to differences between GPs.

In model 1 child characteristics were added. We found that receiving either of the treatments was not age related. Boys had a higher chance of receiving medication, with a significant relation for maintenance therapy (OR = 1.16; 95% CI 1.04 to 1.59) and a similar, almost significant, trend for reliever therapy (OR = 1.11; 95% CI 0.99 to 1.24).

TABLE 3 Multilevel logistic regression analyses with three levels: child, family, general practitioner [a]

EXPLANATORY VARIABLES	EMPTY MODEL		MODEL 1 [b]		MODEL 2 [b]	
	SABA ONLY	SABA/ICS	SABA ONLY	SABA/ICS	SABA ONLY	SABA/ CS
	Intercept (SE)		Intercept (SE)		Intercept (SE)	
	-3.62 (0.05)	-3.22 (0.05)	-4.30 (0.09)	-4.25 (0.09)	-4.30 (0.08)	-4.25 (0.08)
			OR (95% CI)		OR (95% CI)	
Child characteristics						
Age, below six years			1.05 (0.93-1.19)	1.10 (0.98-1.23)	1.05 (0.93-1.19)	1.10 (0.98-1.24)
Gender, male			1.11 (0.99-1.24)	1.16 (1.04-1.29)	1.11 (0.99-1.24)	1.16 (1.04-1.29)
Asthma			129 (112-148)	258 (226-294)	128 (111-147)	253 (222-290)
Shortness of breath / dyspnoea			14.9 (10.9-20.5)	3.75 (2.68-5.26)	14.3 (10.4-19.6)	3.56 (2.53-5.00)
Wheezing			16.6 (9.94-27.7)	12.3 (7.36-20.4)	16.8 (10.0-28.0)	12.4 (7.43-20.7)
Cough			4.07 (3.52-4.69)	5.13 (4.48-5.88)	4.04 (3.50-4.67)	5.11 (4.46-5.86)
Acute bronchitis / bronchiolitis			5.52 (4.64-6.56)	4.89 (4.13-5.78)	5.41 (4.55-6.44)	4.81 (4.06-5.69)
Acute URTI			1.43 (1.22-1.68)	1.28 (1.10-1.49)	1.41 (1.20-1.66)	1.26 (1.08-1.47)
Pneumonia			3.41 (2.50-4.64)	2.48 (1.83-3.37)	3.27 (2.39-4.47)	2.39 (1.76-3.26)
Allergic rhinitis			1.86 (1.47-2.37)	1.93 (1.54-2.42)	1.86 (1.46-2.37)	1.93 (1.53-2.42)
N of GP consultations			1.05 (1.03-1.07)	1.10 (1.09-1.12)	1.05 (1.03-1.07)	1.10 (1.09-1.12)
Family characteristics						
Presence of parental asthma					1.22 (0.97-1.52)	1.17 (0.94-1.45)
GP characteristics						
Prescribing volume GP					2.17 (1.64-2.87)	1.88 (1.40-2.53)
% of 0-17 year olds ≥ 25 per GP					0.63 (0.44-0.90)	0.71 (0.49-1.03)
% children with an asthma diagnosis per GP					0.87 (0.81-0.94)	0.89 (0.82-0.96)
	Variance (SE) [b]		Variance (SE) [b]		Variance (SE) [b]	
Between family variance [c]	0.41 (0.17)	0.69 (0.12)	0.07 (0.06)	0.15 (0.06)	0.08 (0.06)	0.16 (0.06)
Between GP variance	0.20 (0.04)	0.18 (0.03)	0.68 (0.11)	0.68 (0.11)	0.45 (0.08)	0.52 (0.08)
Covariance	0.06 (0.03)		0.50 (0.09)		0.31 (0.06)	
	Correlations		Correlations		Correlations	
Correlation GP variances therapy groups [d]	0.31		0.73		0.64	
ICC for the family [e]	10.4	16.3	1.46	3.31	2.03	3.79
ICC for the GP [e]	6.50	5.71	25.9	25.5	18.3	19.4

[a] *Procedure used: first order PQL with constrained level 1 variance*

[b] *Model 1 (child characteristics), Model 2 (child characteristics, family characteristics, GP characteristics)*

[b] *Because we used nominal data the variance at the lowest level (children) is not determined but given by* $\pi^2/3$

[c] *On the family level the covariance between the two groups has not been estimated because there are only 86 families in which children from both groups are present*

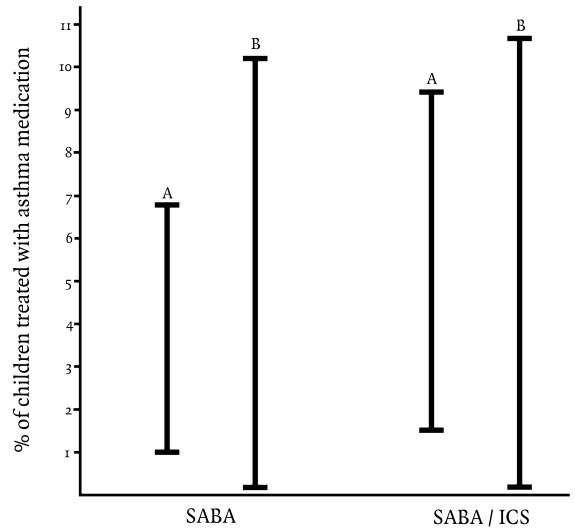
[d] *This is the correlation between the variances of the two defined therapy groups on the GP level*

[e] *Intra Class Correlation between the three levels. The ICC is the relative contribution of the specified level to the total variance*

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids; SE = Standard Error; OR = Odds Ratio; CI = Confidence Interval; GP = General Practitioner; URTI = Upper Respiratory Tract Infection

All respiratory diagnoses were significantly related to both therapy groups. Asthma and shortness of breath showed different strengths of the association with the two therapy groups, which is further investigated in the second multilevel regression analysis, comparing the two therapy groups directly with each other. The difference in prescribing volume between maintenance therapy and SABA only could largely be explained by a difference in the child characteristics (the intercepts for the two groups no longer differed in Model 1). Adding child characteristics (thus making the populations a GP sees more alike) had a profound effect on the variances at the two upper levels. The variance on the level of the family almost disappeared for both therapy groups, while the variance at the GP level showed an increase. The change in GP variation is shown in Figure 1. When correcting for the child characteristics some GPs prescribed SABA/ICS to only 0.2% while others prescribed to as much as 10.7% of their childhood patient population. The correlation between the two therapy groups at the GP level rose to 0.73, indicating that GPs who tended to prescribe one therapy more often, also tended to do so for the other therapy.

FIGURE 1 GP variation in the percentage of children they treat with asthma medication: the 95% prescribing range



A = observed; B = afer correcting for child characteristics

Taking into account the family and GP characteristics (Model 3) we found that parental asthma was not significantly related to either of the therapy strategies. With respect to the GP characteristics we found that GPs who had high overall prescription volumes also prescribed more asthma therapy (OR = 2.17; 95% CI 1.64 to 2.87 for SABA only and OR = 1.88; 95% CI 1.40 to 2.53 for SABA/ICS). GPs with a large childhood population (> 25% of their patients) were less likely to prescribe SABA only to the average child (OR = 0.63; 95% CI 0.44 to 0.90). A similar, albeit not significant, trend was seen for prescribing of SABA/ICS (OR = 0.71; 95% CI 0.49 to 1.03). The same holds for GPs with a higher percentage of asthma-diagnosed children within their patient population (OR = 0.87; 95% CI 0.81 to 0.94 for SABA only; OR = 0.89; 95% CI 0.82 to 0.96 for SABA/ICS). In this final model only a small part of the unexplained variance was at the family level (below 4% for both therapy groups) and a substantial part was due to differences between GPs (18% and 19% respectively).

Multilevel analysis to compare the two therapy groups directly

Table 4 shows that children with an asthma diagnosis had a two-fold higher chance of receiving SABA/ICS ($OR_{SABA/ICS}$ = 2.13; 85% CI 1.79 to 2.54) while children for whom the GP registered shortness of breath were almost three times more likely to receive SABA only ($OR_{SABA/ICS}$ = 0.38; 95% CI 0.26 to 0.57). Also every GP consultation rendered a 7% extra chance of receiving ICS on top of SABA ($OR_{SABA/ICS}$ = 1.07; 95% CI 1.04 to 1.09). The choice whether a child received SABA only or SABA/ICS was not related to the tested family and GP characteristics. However, a large part of the variance between these two therapy groups, unexplained by the characteristics in our model, was at the level of the GP (ICC_{GP} = 23.7%)

TABLE 4 A direct comparison of children receiving SABA/ ICS and children receiving SABA only (reference group) [a]

EXPLANATORY VARIABLES	EMPTY MODEL	MODEL 1 [b]	MODEL 2 [b]
	Intercept (SE)	Intercept (SE)	Intercept (SE)
	0.43 (0.07)	-0.06 (0.09)	-0.04 (0.09)
		OR (95% CI)	OR (95% CI)
Age, below six years		1.05 (0.88-1.25)	1.05 (0.88-1.25)
Gender, male		1.05 (0.90-1.24)	1.05 (0.90-1.24)
Asthma		2.13 (1.79-2.54)	2.10 (1.76-2.51)
Shortness of breath / dyspnoea		0.38 (0.26-0.57)	0.38 (0.26-0.57)
Wheezing		0.73 (0.41-1.28)	0.72 (0.41-1.28)
Cough		1.18 (0.96-1.43)	1.17 (0.96-1.43)
Acute bronchitis / bronchiolitis		1.01 (0.81-1.26)	1.00 (0.80-1.26)
Acute URTI		0.91 (0.73-1.13)	0.91 (0.73-1.13)
Pneumonia		0.89 (0.58-1.36)	0.89 (0.58-1.37)
Allergic rhinitis		1.03 (0.75-1.42)	1.03 (0.75-1.42)
N of GP consultations		1.07 (1.04-1.09)	1.07 (1.04-1.09)
Presence of parental asthma			0.98 (0.74-1.31)
Prescribing volume GP			0.80 (0.61-1.07)
% of 0-17 year olds ≥ 25 per GP			1.17 (0.83-1.67)
% children with an asthma diagnosis per GP			1.02 (0.95-1.10)
	Variance (SE) [c]	Variance (SE) [c]	Variance (SE) [c]
Between family variance	0.09 (0.11)	0.09 (0.12)	0.10 (0.12)
Between GP variance	0.32 (0.07)	0.35 (0.07)	0.34 (0.07)
	Correlations	Correlations	Correlations
ICC for the family [d]	6.33	6.40	6.75
ICC for the GP [d]	22.5	24.4	23.7

[a] *Procedure used: second order PQL with constrained level 1 variance*

[b] *Model 1 (child characteristics), Model 2 (child characteristics, family characteristics, GP characteristics)*

[c] *Because we used nominal data the variance at the lowest level (children) is not determined but given by* $\pi^2/3$

[d] *Intra Class Correlation (ICC) between the three levels (where the variance of the child level is given by* $\pi^2/3$*)*

The ICC is the relative contribution of the specified level to the total variance

SABA = short-acting beta2-agonists; ICS = inhaled corticosteroids; SE = Standard Error; OR = Odds Ratio; CI = Confidence Interval; GP = General Practitioner; URTI = Upper Respiratory Tract Infection

DISCUSSION

Our results show that the majority of children receiving asthma medication received SABA, either with or without ICS. Investigating the influence of child, family and GP factors on the probability of receiving SABA or SABA/

ICS (with not receiving any asthma treatment as the reference group) we found that all three investigated levels (child, family and GP) had an influence on prescribing of these two therapy strategies, although the variance seen at the family level could largely be explained by the child characteristics.

Family influence

Before correcting for child characteristics, a substantial part in the variance of prescribing of the two therapy strategies was on the family level. This is in line with a previous study from Chen *et al.* reporting differences in treatment of childhood asthma related to family structure.[20] The variance was slightly higher for SABA/ICS than for SABA only, which might be explained by the different beliefs within families regarding the two medication strategies, found in previous studies.[9, 10] Another explanation could be that the genetic component of asthma [11] leads to clustering of more severe asthmatic symptoms and thus of ICS use within families. In this study the family and child influences are difficult to separate because there are only few families in which children from both therapy groups are present. This could explain why family variance almost completely disappeared after correcting for child characteristics and why parental asthma (which we found to be associated with prescribing of asthma medication in general in a previous study) was not significantly associated to the therapy regimes investigated in this study. Also, table 1 shows that the percentage of parental asthma was especially high in the group of most extensively treated children and the oral corticosteroid group, which were not included in the multilevel analyses.

GP influence

The variance at the GP level shows to what extent one GP prescribed SABA or SABA/ICS more often than another GP. We expected that differences between GPs could partly be explained by a difference in respiratory morbidities in the patient populations they serve. However, we found that taking into account registered respiratory morbidities only increased the differences between GPs. These symptoms and disease diagnoses are, although present at the level of the child, not absolute characteristics of the child. They are registered by the GP and are the result of an interplay between the child presenting with certain symptoms and the interpretation of the GP. Our findings show that the relation between diagnosing a child with a certain disease or symptom and prescribing of medication differed between GPs. This entails that information on diagnoses is required when investigating GP variations in prescribing. We do not know whether this variance in prescribing is solely due to GP preferences or is a result of other factors such as a different response to regulations or the work-environment including peer influences.[21]

Comparing the two therapy groups directly

We found only few differences between prescribing of SABA only and SABA/ICS. Children with an asthma diagnosis were more likely to receive SABA/ICS while children with a diagnosis of shortness of breath more often received SABA only. This is in line with the guidelines [1-4] which recommend to base prescribing of maintenance therapy with ICS on certain factors related to persistence of asthmatic symptoms, thus trying to prevent overtreatment, whereas these reservations are not made for prescribing of SABA.

Although for both therapy groups the association with a diagnosis of asthma was by far the strongest, it needs to be stressed that the associations with the other respiratory morbidities were highly significant, even after correction for the diagnosis of asthma. Surprisingly, the strength of the associations with these other respiratory morbidities such as wheezing, cough and bronchitis did not differ between the two therapy groups. We expected more alternative diagnosing and off label use in the group treated with SABA only, because the use of SABA to reduce symptoms is generally accepted in practice [1] even though effectiveness in symptom reduction during viral wheeze and other respiratory morbidities such as acute bronchitis is not irrefutably proven.[22, 23] These findings, however, are in line with previous findings within this same dataset and findings from other researchers on the discrepancy between asthma medication treatment and an asthma diagnosis in children.[24-27] This can partly be explained by the fact that, despite the ongoing search for better diagnostics of asthma in children, a diagnosis of asthma is difficult to make, especially in preschool children.[1, 28, 29] These diagnostic difficulties, however, did not lead to a lower prescription of SABA/ICS below the age of six. We found that, when correcting for several symptom and disease diagnoses, children above the age of five did not receive maintenance therapy more often than younger children.

A child was more likely to receive regular maintenance therapy when he or she had more GP consultations. An explanation could be that the child had more serious symptoms and as a result both visited the GP more often and

also needed ICS. Or, regardless of the severity of the symptoms, this could be a result of the health seeking behaviour of the family [8] and the attitude of the caregivers/parents regarding medication use [30] influencing prescribing by the GP.

The current study has some limitations. First, the time relationship between the prescription and the measurement of the independent variables was not evaluated. Also, we did not determine if and for how long use of asthma medication was continued conform the therapy groups the children were assigned to. Second, possible differences in disease severity are not entirely expressed in the dichotomised variables for respiratory symptom and disease diagnoses. Third, variables available to characterise GPs and families were limited. Model 2 in Table 3 shows how much of the variance is still unexplained after introducing the variables included in this study. Especially on the two higher levels, but also on the patient level, one could think of characteristics, not available in our study that might be associated with the use of a specific asthma therapy including cultural and environmental factors.

The strengths of this study are the large number of children in our study, the representativeness of the sample and the fact that the data about diagnosing and prescribing are both derived directly from the GP's clinical records. Furthermore, the inclusion of a wide array of variables that might be associated with the two most common groups of asthma therapy in a multilevel fashion, allowed us to identify factors associated with both therapy regimes and their independent contributions to the variance in prescribing.

In conclusion, we found only few characteristics to be related specifically to the choice for reliever or maintenance therapy in a child. Most child and GP characteristics were equally related to both regimes, and thus to prescribing in general. Not only SABA but also prescribing of SABA/ICS was significantly related to other respiratory morbidities than asthma. We found large differences between GPs in the percentage of children receiving treatment for both therapy regimes. In contrast to what we expected, taking into account registered respiratory morbidities only increased the differences between GPs. This indicates that the relation between diagnosing a child with a certain disease or symptom and prescribing of medication strongly differed between GPs.

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General discussion

5

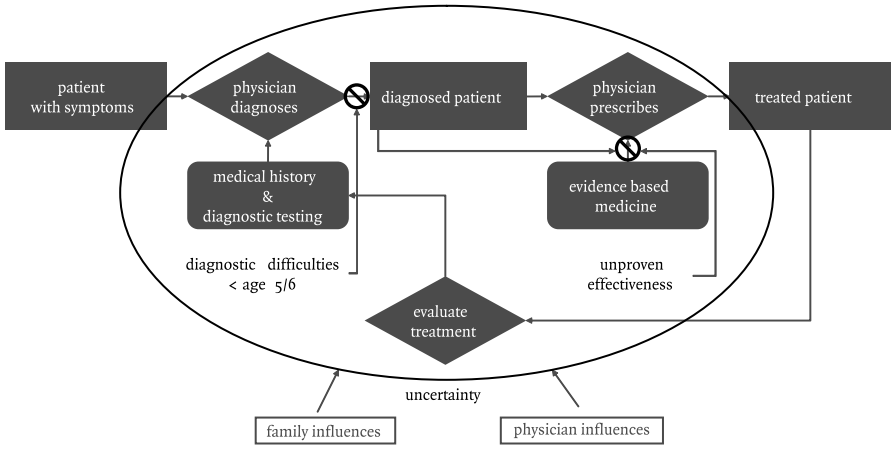
5 General discussion

INTRODUCTION

In this thesis we have studied a variety of aspects related to medicines' use in children with asthma as a learning model. We have addressed the challenges of treating children with respiratory symptoms in the context of uncertainty about diagnosis, prognosis, family and prescriber influences. Two different data platforms were linked to the project, i.e. the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study and the DNSGP-2 study (second Dutch national survey of general practice) providing opportunities to compare, to validate, and to fuel cross-cutting thinking.

In this final chapter we come to the synthesis, the weighing of the findings and the exploration of avenues for future research. As said in the introduction of this thesis, asthmatic symptoms are very common in childhood, but the evidence for the effectiveness and safety of asthma medication for the different respiratory morbidities that primarily occur in early childhood is still under debate.[1-3] To evaluate medication use in these circumstances one has to take the whole process of prescribing and treatment changes over time into consideration, since it is likely that, due to these uncertainties, factors like family and prescriber influences but also the age of the child, will play a larger role in the process of arriving at a certain treatment for a certain child.

We could thus summarise the process of treatment with asthma medication in children, including the obstacles, as follows:



In this thesis we set out to evaluate the treatment of children with asthma medication over time, establish the role of the different actors, and identify the challenges and gaps within this process.

MAIN FINDINGS

In Chapter 3.1 we evaluated the longitudinal patterns of asthma medication treatment in children followed from birth up to age eight within the PIAMA study. We found that asthma medication was often initiated in children, 36% received a first prescription for asthma medication during the first eight years of life, with 88% starting before age five and 61% receiving inhaled corticosteroids (ICS) at some point in time. Initiation of asthma therapy was significantly associated with male gender. The question remained whether all starters continued using asthma medication. We showed that for children who started asthma medication before their first birthday this was not the case (Chapter 3.2). In these children, persistence seemed to be very low, with only 58.8% continuing asthma medication after the first prescription and 10.3% continuing during three years of follow-up. Children with prescribed ICS or with doctor-diagnosed asthma in the first year of life were more likely to continue using asthma medication.

The relationship between prescribing of asthma medication and doctor-diagnosed asthma was investigated in more detail in Chapter 4.1. In the population based DNSGP-2 study 7.5% of children aged 0-17 received asthma medication but less than half (49%) of these children had a registered diagnosis of asthma. The likelihood of having doctor-diagnosed asthma increased to a maximum of 66% in children more extensively treated with asthma medication (ICS use, higher number of prescriptions). The congruence between prescribing of asthma medication and doctor-diagnosed asthma did not increase with age. In Chapter 4.2 we subsequently found that, after adjusting for an asthma diagnosis, other respiratory morbidities such as acute bronchitis, cough and pneumonia remained significantly related to prescribing of asthma medication, as did gender. In addition, a significant influence of the family and the general practitioner (GP) on prescribing of asthma medication was observed. In the DNSGP-2 study we divided children into two age groups, (I) children below the age of six and (II) children age 6-17, this conforms to the distinction made in the guidelines. We found that the variance in prescribing between GPs was significantly higher in children below the age of six than in older children (95% CI 3.5% to 25.2% versus 2.4% to 13.4%; Chi-square = 7.3).

Since there are different treatment options for asthmatic symptoms, in Chapter 4.3 we compared reliever therapy of short-acting beta2-agonists (SABA) only with maintenance therapy of SABA and ICS. We found that children with doctor-diagnosed asthma and children with more GP consultations had a higher chance of receiving SABA/ICS, while children with registered shortness of breath were more likely to receive SABA only. All other registered respiratory symptoms and diseases, such as acute bronchitis, were equally associated with prescribing of reliever and maintenance therapy. GP differences with respect to the percentage of children they treated with asthma medication increased for both treatment regimes when respiratory morbidities and GP consultations were taken into account. When relating longitudinal asthma medication use from birth to asthma outcomes at age eight within the PIAMA study (Chapter 3.3), we saw that asthma medication was frequently prescribed at an early age to children who at age eight did not have asthma. However, in children with asthma at age eight medication was more often initiated. These children more often received ICS and were more likely to continue treatment up to age eight than children with prior asthmatic symptoms but no asthma at age eight.

Methods

A major aim of this thesis was to contribute to the development of paediatric pharmacoepidemiology by using treatment with asthma medication in children as a learning model. We may conclude that this choice has given us a lot of learning opportunities. Studying treatment with asthma medication in children from different perspectives encompasses many clinical and epidemiological features. There is a need for longitudinal data, comprehensive data on baseline characteristics on a population level, information on family context, confirmed diagnoses of respiratory morbidities, biomarkers and prescription drug use over time. We tried to combine the best of two worlds in building appropriate data platforms to address a number of relevant research questions. On one hand, we used the strengths of a prospective birth cohort study, the PIAMA study, to study the development of treatment with asthma medication over time. On the other hand the opportunities of a population based study, the DNSGP-2 study, set in general practice were utilised.

The advantage of the PIAMA study compared to retrospective or cross-sectional studies is that data on exposure are collected prior to the development of the disease of interest. The exposure and reporting of the exposure are therefore not influenced by the presence of the disease. The development of treatment with asthma medication from birth until age eight could be evaluated in each child and the cumulative exposure to asthma medication over the years could be determined. Moreover, we were able to evaluate the association between asthma related health outcomes at age eight (current asthma, atopy, bronchial hyperresponsiveness (BHR)) and treatment with asthma medication in the years before. Also, the richness of baseline characteristics and the combination of data on respiratory symptoms and objective outcome measures, including atopy and BHR in the PIAMA study have been well received.

The opportunities provided by the DNSGP-2 study are its population base, the large number of children within the study, the representativeness of the sample and the fact that the data on diagnoses and prescriptions are both derived directly form the GP's clinical records. Furthermore, information was collected on patient, family and GP characteristics. This enabled us to identify important factors associated with prescribing of asthma medication

to children, not just on the level of the child but also on the family and GP level. The role of the different actors could be quantified by assessing the independent contribution to the variance in prescribing of asthma medication of family and GP using multilevel analyses.

Enrichment with pharmacy data

An important aspect of this thesis was the enrichment of the PIAMA study with data on asthma medication through prescription data from community pharmacy records. In the Netherlands, pharmacy records are virtually complete with regard to drugs dispensed to patients.[4] In the DNSGP-2 study, drug prescriptions were registered by the GP directly in the electronic medical record, according to the Anatomical Therapeutic Chemical Classification (ATC) system.[5] Although the use of prescribing data and pharmacy data is the accepted way to evaluate medication use, one has to keep in mind that this does not necessarily reflect the actual use in the home environment. Not all prescriptions are filled in the community pharmacy [6] and when a prescription is filled, adherence to the medication varies.[7-9] Of course it depends on the research question whether actual treatment in practice or intended treatment by the GP is the measure of interest. When evaluating the effectiveness of asthma medication in practice, actual use has to be known. However, in the DNSGP-2 studies in this thesis we wanted to investigate what determines prescribing of asthma medication and thus the therapy 'as intended' by the GP was of interest.

Asthma assessment

In the PIAMA study asthma at age eight is based on parental report of asthma symptoms and use of ICS in the preceding 12 months. In theory asthma can be defined at each age using this definition. However, wheezing at a young age may not only be due to asthma but also to other, more transient, respiratory conditions.[10-15] Therefore, the focus is on asthma at eight years of age, when asthma symptoms are less likely to be confused by symptoms due to other respiratory conditions. A sensitivity analysis was performed to determine the possible influence on our findings of the fact that ICS use at age eight (questionnaire based) is part of the asthma definition while ICS from birth until age eight (pharmacy record base) is part of the determinant (medication use). This analysis is shown in appendix A of this thesis. BHR and atopy (IgE based) were assessed because the associations between these two objective measures and asthma are well established.

However neither BHR nor atopy is synonym to asthma.[16-19] This can also be observed in our study in Chapter 3.3; atopy and BHR are both more common than asthma (based on respiratory symptoms and ICS use) at age eight. In the DNSGP-2 study, the asthma diagnosis as registered by the GP in the electronic medical record was used. Doctor-diagnosed asthma, although often used as a gold standard in studies, might not be the true reflection of asthmatics. It is well known that under- and overdiagnosing occurs,[20] especially in young children.[21] This was expressed in the high percentage of children receiving an asthma diagnosis in our dataset before the age of six. An asthma diagnosis in young children should probably be seen as a working diagnosis.

PERSPECTIVES FOR DIAGNOSIS AND TREATMENT OF CHILDHOOD ASTHMA

In order to place the findings from our studies on treatment with asthma medication in children in a broader perspective, we focussed on four domains: (I) the observed patterns of medication use, (II) the effect of age on treatment with asthma medication, (III) the relation with a diagnosis of asthma and other respiratory morbidities and (IV) the role of the different actors in the process of arriving at a certain treatment.

Patterns of medication use

The studies in this thesis show that many children initiated asthma medication, yet persistence of use was low and many children received only one prescription for asthma medication. Our finding that asthma medication was initiated in a high percentage of children below the age of eight is in line with studies reporting on the prevalence of asthmatic symptoms in children.[22] A study by Martinez *et al.* showed that at the age of six, 48.5% of children had shown symptoms of wheezing.[23] Also, the yearly prevalence of asthma medication treatment found in both the PIAMA and DNSGP-2 study corresponds to the prevalence reported in other studies.[24-26] As already mentioned, wheezing at a young age may not only be due to asthma but also to other, more transient, respiratory conditions.[10-15] Other studies could not find valid criteria to prospectively identify children who will develop asthma in a group of wheezing children.[2, 27, 28] This could explain both the low persistence we found in children who received asthma medication before their

first birthday and the finding that persistence of use was not related to objective measures such as eczema and a family history of asthma. Recently, an Asthma Predictive Index has been proposed which seemed valid in a subsequent clinical trial.[29, 30] This index identified several risk factors for developing persistent asthma among children younger than three years of age who had four or more episodes of wheezing during the previous year, including a parental history of asthma, a physician diagnosis of atopic dermatitis and evidence of sensitization to aeroallergens. If this knowledge is implemented in clinical practice, then future studies on persistence of medication use are likely to find as association between persistence of treatment and the above mentioned factors. The high percentage of children we found that received only one prescription for asthma medication is in line with the practice of trial treatment, as recommended in the guidelines, in which the response to asthma medication is used as a diagnostic tool to strengthen or reject the possible diagnosis of asthma.[1, 11, 12, 31]

The effect of age

In both populations studied in this thesis, treatment with asthma medication steadily declined with age. GPs differed with respect to the percentage of children they treated with asthma medication. We found this difference between GPs to be much larger for children below the age of six than in children age 6 to 17. Reliever therapy with SABA only and maintenance therapy with SABA and ICS were the most applied therapies in all age groups.
The declining trend of asthma medication treatment with age found in our studies is consistent with results from other studies.[25, 26] This also complies with the development of respiratory symptoms, with many transient wheezers at a young age who become symptom free later on in life.[23, 32] The higher variance in prescribing between GPs for children below the age of six could be explained by the higher uncertainty in diagnosing at this age.[3, 33, 34] However, this uncertainty is not reflected in a more conservative asthma therapy. The relative percentage of treated children receiving ICS is not lower in children below the age of six than in older children.

A diagnosis of asthma and other respiratory morbidities

Prescribing of asthma medication to children was often not accompanied by an asthma diagnosis. Children below the age of six received more treatment, but also got diagnosed with asthma more often. When correcting for an asthma diagnosis, other respiratory morbidities remained significantly

associated with prescribing of asthma medication. These associations were not influenced by age. Yet, a diagnosis of asthma was related to a higher persistence of asthma therapy and a more extensive treatment (ICS, number of prescriptions).

Our finding that, in children age 0 to 17, less than half of all children receiving asthma medication had a registered diagnosis of asthma (49%), is in line with the findings from previous studies reporting a mismatch between asthma medication use and a diagnosis of asthma.[35-41] This finding was anticipated in young children because of the diagnostic difficulties [3, 33, 34] and the generally accepted use of SABA to reduce symptoms during wheezing.[3] However, in contrast to our expectations, the congruence between prescribing of asthma medication and doctor-diagnosed asthma did not improve with age. In older children this discrepancy can not be explained as easily, since a diagnosis of asthma can be made with more certainty and the transient wheezers become asymptomatic.

When taking into account treatment characteristics, subgroup analyses showed that the likelihood of having doctor-diagnosed asthma did increase when a child received combination therapy of SABA and ICS and with the number of prescriptions. Since physicians are recommended to base both making a diagnosis of asthma and prescribing of prophylactic treatment with ICS on the presence or absence of certain factors, related to persistence of asthmatic symptoms such as severity of symptoms, triggers of symptoms atopic characteristics of the child and a parental history of asthma [1, 3, 31, 42] these findings are not surprising. Most likely this is the group of children with more severe symptoms. The finding that persistence of medication use is related to doctor-diagnosed asthma is probably related to this issue and needs further research.

Children with registered respiratory morbidities other than asthma and shortness of breath (such as acute bronchitis, cough and pneumonia) had a similar chance of receiving SABA/ICS as they had receiving SABA only. The significant relations found between other respiratory morbidities and prescribing of asthma medication are not surprising, given the results from other studies showing a discrepancy between asthma medication use and asthma diagnosis [36, 37] and they could indicate off label use and overtreatment. Studies evaluating the effectiveness of asthma medication for indications other than asthma are inconclusive.[28, 43-45] The results from the longitudinal analysis on asthma medication use from birth in relation to asthma outcomes at age eight reflect the same findings as described above. Asthma medication was frequently prescribed at an early age to children who at age eight did not have asthma, as shown in this thesis. Children may receive treatment for respiratory symptoms, while at that time it is not yet possible to predict which child will develop asthma.[2, 27, 28] Still, in children with asthma at age eight asthma medication was more often initiated in previous years. These children more often received ICS and received medication during more years, continuing treatment up to age eight, than children with prior symptoms but no asthma at age eight. This indicates that, although diagnostic possibilities are limited so far in young children, a certain distinction between future asthmatics and future non-asthmatics is already made at a young age.

The role of different actors

As described above, the age of the child and respiratory morbidities strongly influence treatment with asthma medication in children. In the introduction of this thesis we argued that uncertainties regarding diagnosing and treatment could lead to a more substantial role for other actors, such as the family and the GP. Indeed, a substantial influence of both family and GP was found on prescribing of asthma medication. Within the family we saw that parental asthma was positively associated with prescribing of asthma medication. This is in line with guidelines that state that parental asthma status should be taken into account when evaluating asthmatic symptoms in children.[31, 42, 46] The genetic influence on disease susceptibility plays a role in this recommendation.[47] We found that every extra GP consultation rendered a 10% extra chance of receiving asthma medication in general. The number of GP consultations was also positively associated with receiving ICS in particular. This could be a result of the health seeking behaviour of the family [48, 49] and the attitude of the caregivers/parents regarding medication use.[50] The finding that the variance in prescribing between GPs was much higher in young children than in children six years and older and how this could be explained by the diagnostic gap, particularly present for preschool children, has already been mentioned when discussing the effect of age in treatment with asthma medication. This finding shows how uncertainty in diagnosis provides opportunity for inter-physician variance in prescribing of asthma medication.

FINAL CONSIDERATIONS

In our studies we have addressed the knowledge gaps and complexities that are present in the process of diagnosing and treating children with respiratory symptoms and diseases. We have shown that treatment allocation, given the uncertainties about the right diagnosis, is a major challenge in medicine, particularly in childhood asthma. Our findings can be of direct benefit for clinical practice in two ways. First, by increasing awareness about risk groups for overtreatment and the influence of the different actors on prescribing of asthma medication. Second, seeing how many children initiate asthma medication and taking into account the often reversed timeline between diagnosis and treatment we believe that our findings stress the necessity of constantly re-evaluating the need for asthma medication in a child to prevent possible overtreatment. The strong association between an asthma diagnosis and the type, volume and duration of treatment with asthma medication is most likely related to the severity of symptoms of the child. But also it is not unlikely that physicians are more inclined to diagnose a child with asthma because they prescribe asthma medication and subsequently treat a child according to this 'label'.

There is a definite need for research into better diagnostic tools for asthma in children and into the effectiveness and safety of medication for treatment of symptoms due to different underlying respiratory morbidities. Another way forward could be achieved by finding a method to identify the individual child at risk of under- or overtreatment, based on characteristics already present when a child presents with wheezing for the first time. From the number of children that receive an asthma diagnosis before the age of six we deduce that asthma is often used as a working diagnosis.

Also, although effectiveness of asthma medication in other respiratory morbidities has not been irrefutably proven, there are studies that report a reduction of symptom burden.[43, 45] We found these other morbidities to be significantly related to prescribing of asthma medication after correcting for an asthma diagnosis. Therefore, we would recommend future researchers, who want to evaluate the appropriateness of asthma medication use, not to focus too much on an asthma diagnosis as a selection criterion for the study population or as the sole appropriate reason for treatment with asthma medication.

In the ideal situation we would be able to diagnose asthma with certainty from age zero and pharmaceutical research would be of such a level that we knew exactly which medicines were effective and safe in which situation. There is an ongoing search for ways of getting a better grip on the situation by means of improved diagnostics and by studying effectiveness of medication in subgroups of children. When it comes to treating asthmatic symptoms in children, Kierkegaard, unknowingly, summarised the challenges the best way possible: 'life can only be understood backward but it must be lived forwards' (Søren Kierkegaard, Danish philosopher 1813-1855). Therefore, we believe that analysing what happens in practice and which parties play which role is an essential step in achieving rational and optimal prescribing in this area.

Are our findings regarding the many children initiating asthma medication at a young age, the low persistence of use, the high variation between GPs seen in prescribing to young children and the number of children receiving medication without being diagnosed as an asthmatic troublesome? Not by definition. Given that symptoms are often transient, a diagnosis is difficult to make, the evidence for the effectiveness of asthma medicines for the various respiratory morbidities is conflicting and the practice of trial treatment as a diagnostic tool is considered good practice, these findings are not surprising. Although at all ages much more children are treated with asthma medication than have an asthma diagnosis, treatment is often not extensive (SABA only, only one prescription ever, treatment during only one year). Children who receive extensive treatment often do have or will receive an asthma diagnosis, we found hardly any undertreatment and the variation in prescribing between GPs declined with age. Asthma medication use in children is not as random as it may sometimes seem. This conclusion could not be drawn from the individual studies in this thesis, but only from the combined results of both a longitudinal and a multilevel approach. An important message also for the development for paediatric pharmacoepidemiology in other childhood diseases like epilepsy, infections and mental and psychiatric disorders.

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Summary

Summary

Medicines'use in children has been gaining more attention during recent years. Both governmental actions and initiatives arising from the field of paediatric medicine aim at improving medicines' use in children. In this thesis we aimed to gain more insight in the process of medicines' use in children by studying asthma medication as a learning model. Evaluation of treatment with asthma medication in children is challenging because of diagnostic difficulties in paediatric asthma and questions regarding effectiveness and safety of medication. It thus requires a comprehensive approach taking into account the whole process of prescribing and treatment changes over time and family and prescriber influences, as well as the age of the child.

In **Chapter 2** the general issues regarding medicines' use in children were addressed. This chapter originally appeared as a background paper to the WHO report 'Priority Medicines for Europe and the World' in 2004. Recommendations included adjustment of requirements and rules for paediatric research, education of public health professionals and parents to change the attitude towards paediatric research and promote accurate diagnosis and treatment, and facilitation of research into pathophysiology and risk factors for diseases affecting children, and into effectiveness of medicines in a daily life setting.

In **Chapter 3**, the longitudinal development of treatment with asthma medication has been addressed using data from the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study, complemented with pharmacy records on asthma medication use. Although many studies already evaluated the appropriateness of treament with asthma medication in children in a cross-sectional manner, very little is known about the longitudinal patterns of such medication. And since asthmatic symptoms, and thus treatment with asthma medication, in general precede the age at which a firm diagnosis of asthma can be made, evaluation of asthma medication in young children may benefit from a longitudinal approach.

First, in *Chapter 3.1*, the treatment of children with asthma medication from birth to age eight was described and quantified in detail to get a better comprehension of the extent of treatment and the patterns with age. This study showed that asthma medication was initiated in a very high percentage of children (36% filled a first prescription for asthma medication before the age of eight) and mainly at an age at which an asthma diagnosis cannot yet be firmly established (88% started before age five). However, in young children with asthmatic symptoms diagnostic difficulties lead to use of trials of asthma medication as a diagnostic tool. Thus initiation of therapy does not necessarily imply that a child will continue using asthma medication. Therefore, in *Chapter 3.2* persistence of asthma medication treatment was investigated during three years after the first prescription for all children who received a first prescription for asthma medication in the first year of life. A Cox regression analysis was performed to identify factors associated with persistent use. We found that 58.8% of children continued asthma medication after the first prescription and 10.3% continued during three years. Children with doctor-diagnosed asthma (Hazard ratio (HR) of discontinuation = 0.64; 95% CI 0.45 to 0.91) or prescribed inhaled corticosteroids (ICS) in the first year of life (HR of discontinuation = 0.59; 95% CI 0.40 to 0.86) were 1.6 to 1.7 times more likely to continue using asthma medication. In conclusion, persistence of asthma medication was very low in these children, and was positively associated with doctor-diagnosed asthma and use of ICS.

These studies showed that asthma treatment is often initiated before a more definite diagnosis can be made. The relationship between treatment with asthma medication from birth to age eight and respiratory outcomes at age eight was examined retrospectively in *Chapter 3.3*. We compared asthma medication prescription histories between (I) children never reporting asthmatic symptoms, without asthma at age eight, (II) children reporting asthmatic symptoms prior to age eight, but without asthma at this age and (III) children with asthma at age eight. We found that asthma medication was frequently prescribed at an early age to children who at age eight did not have asthma (194 of the 278 children receiving medication). However, in children with asthma at age eight medication was more often initiated than in children with transient asthmatic symptoms (82.4% versus 55.1%). Children with asthma at age eight more often received ICS (69.6% versus 31.9%), received asthma medication during significantly more years (4.1 versus 2.1 years for all asthma medication; 3.1 versus 1.2 years for ICS) and

were more likely to continue treatment up to age eight (last prescription at an average age of 7.1 versus 3.7) than children with prior asthmatic symptoms but no asthma at age eight. These results show that some early distinction between children with transient symptoms and children with asthma at a later age seems to be made.

We hypothesised that due to diagnostic difficulties and uncertainties regarding effectiveness and safety of medication in paediatric asthma, other factors including family and prescriber influences will play a significant role in the process of arriving at a certain treatment scenario for a particular child. In **Chapter 4** we addressed the relationship between diagnosing and treating asthmatic children in the context of family and prescriber influences in children below the age of 18, using data from the population based second Dutch national survey of general practice (DNSGP-2), in which general practitioners (GPs) registered all physician–patient contacts during the year 2001. First, the relationship between prescribing of asthma medication and doctor-diagnosed asthma was investigated in detail in *Chapter 4.1*. According to the general consensus a diagnosis of asthma becomes more certain with increasing age. Therefore the congruence between asthma medication use and doctor-diagnosed asthma was expected to increase with age. In total 7.5% of children received asthma medication but less than half (49%) of these children had a registered diagnosis of asthma. Subgroup analyses on age, gender and therapy groups showed that the Positive Predictive Value (PPV) differed significantly between therapy groups only. The likelihood of having doctor-diagnosed asthma increased to a maximum of 66% in children more extensively treated with asthma medication (ICS use, higher number of prescriptions). Although age strongly influenced the chance of being treated, remarkably, the congruence between prescribing of asthma medication and doctor-diagnosed asthma did not increase with age. Second, in *Chapter 4.2*, we evaluated which factors, besides a diagnosis of asthma, could play a role in prescribing of asthma medication to children by investigating how and to what extent prescribing of these medicines was influenced by child, family and GP characteristics. We performed a multilevel multivariate logistic regression analysis with three levels among 46,371 children belonging to 25,537 families registered with 109 GPs. In this study we divided children into two age groups, (I) children below the age of six and (II) children age 6-17, which conforms to the distinction made in clinical guidelines. We found that, after adjusting for an asthma diagnosis, other

respiratory morbidities such as acute bronchitis, cough and pneumonia remained significantly associated with prescribing of asthma medication, as did gender. In addition, a significant influence of the family and the GP on prescribing of asthma medication was observed. The variance in prescribing between GPs was significantly higher in children below the age of six than in older children (95% CI 3.5 to 25.2% versus 2.4 to 13.4%; Chi-square = 7.3), which could be a direct result of the diagnostic complexities present in young children with asthmatic symptoms. Thus diagnostic gaps may lead to more physician driven prescribing irrespective of the clinical context. And child, family and GP all influence whether a child received asthma medication or not. However, several options are available within asthma treatment. In *Chapter 4.3* the interactions between child, family and prescriber factors on treating young asthmatics either with reliever or maintenance therapy were examined. We determined whether the child received either short-acting beta2-agonists (SABA only, reliever therapy) or SABA and ICS (SABA/ICS, maintenance therapy), based on all drug prescriptions within the one-year study period. We found only few characteristics to be related specifically to the choice for reliever or maintenance therapy in a child. Children with doctor-diagnosed asthma had a higher chance of receiving SABA/ICS ($OR_{SABA/ICS}$ = 2.13; 85% CI 1.79 to 2.54) while children with registered shortness of breath were more likely to receive SABA only ($OR_{SABA/ICS}$ = 0.38; 95% CI 0.26 to 0.57). Every GP consultation rendered a 7% extra chance of receiving maintenance therapy ($OR_{SABA/ICS}$ = 1.07; 95% CI 1.04 to 1.09). All other child and GP characteristics were equally related to both regimes, and thus to prescribing in general. Both prescribing of SABA and SABA/ICS were significantly related to other respiratory morbidities than asthma. Large differences existed between GPs in the percentage of children to which they prescribed asthma medication, regardless of the therapy regime. This could not be explained by a difference in the number of children with respiratory morbidities per GP. Taking into account registered respiratory morbidities only increased the differences between GPs. This indicates that the relation between diagnosing a child with a certain disease or symptom and prescribing of medication strongly differed between GPs.

Chapter 5 provided a general discussion. The results of the individual studies were put into a broader perspective and clinical implications were discussed. Also, the advantages and limitations of the datasets and outcome measures used in this thesis were addressed. In conclusion, improvement of asthma medication therapy in children is warranted, but is highly dependent on better diagnostics and results from effectiveness studies. At the same time the combined findings of our studies show that, despite the extensive use of asthma medication, the low persistence and the high variance in prescribing, asthma medication use in children is not as random as it may seem sometimes.

Samenvatting

Samenvatting

Het gebruik van medicijnen bij kinderen staat de laatste jaren steeds meer in de belangstelling. Zowel vanuit de overheid als vanuit het veld van de kindergeneeskunde wordt getracht het medicijngebruik bij kinderen te verbeteren. Het beoogde doel van dit proefschrift is om meer inzicht te verschaffen in het proces van medicijngebruik bij kinderen door het gebruik van astmamedicatie te evaleren en dit te beschouwen als leermodel.
De evaluatie van het gebruik van astmamedicatie bij kinderen wordt bemoeilijkt door diagnostische problemen en onzekerheid betreffende de effectiviteit en veiligheid van de beschikbare medicijnen. Deze evaluatie behoeft dan ook een brede benadering, waarbij naast het gehele voorschrijf- en behandelproces door de tijd, ook de familie- en arts-invloeden en de leeftijd van het kind worden meegenomen.

In **Hoofdstuk 2** komen de algemene zaken betreffende medicijngebruik bij kinderen ter sprake. Dit hoofdstuk is oorspronkelijk verschenen als achtergrondartikel bij het WHO rapport 'Priority Medicines for Europe and the World' in 2004. Aanbevelingen zijn onder andere het aanpassen van de vereisten en regels voor pediatrisch onderzoek; het voorlichten van gezondheidszorgprofessionals en ouders om zo de houding ten opzichte van pediatrisch onderzoek te verbeteren en juiste diagnosestelling en behandeling te bevorderen; en het faciliteren van onderzoek naar de pathofysiologie en risicofactoren van ziektes die voorkomen bij kinderen en naar de effectiviteit van medicijnen in de dagelijkse praktijk.

Hoofdstuk 3 richt zich op de longitudinale aspecten van de behandeling van kinderen met astmamedicatie, waarbij gebruik werd gemaakt van data van de PIAMA (Preventie en Incidentie van Astma en Mijt Allergie) geboortecohortstudie, aangevuld met apotheekgegevens betreffende gebruik van astmamedicatie. Hoewel al in meerdere studies cross-sectioneel onderzocht is in hoeverre astmamedicijnen correct gebruikt worden bij kinderen, is er nog heel weinig bekend over de longitudinale patronen van zulk medicijngebruik.

Dit terwijl de evaluatie van het gebruik van astmamedicatie bij kinderen juist een longitudinale aanpak behoeft, aangezien astmatische symptomen, en dus ook de behandeling hiervan, over het algemeen voor het eerst optreden op een leeftijd waarop een astmadiagnose nog niet met zekerheid gesteld kan worden. In *Hoofdstuk 3.1* wordt de behandeling van kinderen met astmamedicatie vanaf de geboorte tot leeftijd acht gedetailleerd beschreven en gekwantificeerd met als doel een beter beeld te krijgen van de omvang van de behandeling en de leeftijdspatronen. Deze studie laat zien dat astmamedicatie bij een groot percentage kinderen geïnitieerd wordt(36% haalde een recept op voor astmamedicatie voordat ze acht jaar werden), voornamelijk op een leeftijd waarop een astmadiagnose nog niet met zekerheid te stellen is (88% startte voor leeftijd 5). Echter, bij jonge kinderen met astmatische symptomen wordt astmamedicatie vaak als proefbehandeling gebruikt om meer zekerheid over de diagnose te verschaffen. Initiatie van astmamedicatie impliceert dan ook niet noodzakelijkerwijs dat een kind het medicijngebruik zal voortzetten. In *Hoofdstuk 3.2* is om die reden de persistentie van behandeling met astmamedicatie onderzocht gedurende drie jaar na het eerste recept bij een groep kinderen die al in het eerste levensjaar een recept voor astmamedicatie kreeg. Er is een Cox-regressie-analyse uitgevoerd om factoren te identificeren die samenhangen met persistent gebruik. We vonden dat 58,8% van de kinderen medicatiegebruik voortzette na de eerste prescriptie en dat slechts 10,3% dit gedurende drie jaar deed. De kans dat kinderen met artsgediagnosticeerde astma (Hazard Ratio (HR) van discontinuering = 0,64; 95% CI 0,45 tot 0,91) of een recept voor inhalatiecorticosteroïden (ICS) in het eerste levensjaar (HR van discontinuering = 0,59; 95% CI 0,40 tot 0,86) het gebruik van astmamedicatie zouden voortzetten was 1,6 tot 1,7 keer groter. Concluderend zagen we dat persistentie van gebruik erg laag was in deze groep kinderen en positief geassocieerd was met artsgediagnosticeerde astma en het gebruik van ICS. Omdat deze studies lieten zien dat astmamedicatie vaak geïnitieerd wordt voordat een astmadiagnose met zekerheid gesteld kan worden, is in *Hoofdstuk 3.3* de relatie tussen de behandeling met astmamedicatie en respiratoire uitkomsten op leeftijd acht in retrospectief onderzocht. We hebben de astmamedicatiehistories vergeleken van (I) kinderen die nooit astmatische symptomen gerapporteerd hebben, zonder astma op leeftijd acht, (II) kinderen die op jongere leeftijd astmatische symptomen rapporteerden, maar geen astma hadden op leeftijd acht en (III) kinderen met astma op leeftijd acht. Er bleek veelvuldig astmamedicatie te worden voorgeschreven aan kinderen op jonge leeftijd, die op leeftijd acht geen astma

hadden (194 van de 278 kinderen die astmamedicatie kregen). Echter, medicatie werd vaker geïnitieerd bij kinderen met astma op leeftijd acht dan bij kinderen met voorbijgaande astmatische symptomen (82,4% versus 55,1%). Kinderen met astma op leeftijd acht kregen vaker ICS (69,6% versus 31,9%), kregen astmamedicatie gedurende significant meer jaren (4,1 versus 2,1 jaar voor alle astmamedicijnen; 3,1 versus 1,2 jaar voor ICS) en de behandeling werd vaker voortgezet tot leeftijd acht (gemiddelde leeftijd ten tijde van het laatste recept was 7,1 versus 3,7) dan bij kinderen die voorheen astmatische symptomen hadden maar geen astma op leeftijd acht. Deze resultaten laten zien dat er tot op zekere hoogte al op jonge leeftijd onderscheid wordt gemaakt tussen kinderen met voorbijgaande symptomen en kinderen met astma op latere leeftijd.

Onze hypothese was dat de diagnostische problemen en onzekerheden wat betreft effectiviteit en veiligheid van medicatie bij kinderen met astmatische symptomen ertoe konden leiden dat andere factoren zoals familie- en artsinvloeden een significante rol zouden gaan spelen bij het vaststellen van een bepaald behandelplan voor een bepaald kind. **In Hoofdstuk 4** is het verband tussen diagnosticeren en behandelen van astmatische kinderen onder de 18 jaar onderzocht binnen de context van mogelijke familie- en voorschrijver-invloeden. Hiervoor is gebruik gemaakt van data van de Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk (DNSGP-2), waarin huisartsen gedurende het jaar 2001 alle arts-patiënt contacten hebben geregistreerd. Eerst is in *Hoofdstuk 4.1* het verband tussen het voorschrijven van astmamedicatie en artsgediagnosticeerde astma gedetailleerd onderzocht. Volgens de algemeen geldende consensus wordt een astmadiagnose zekerder met de leeftijd. Om die reden werd verwacht dat de congruentie tussen het gebruik van astmamedicatie en artsgediagnosticeerde astma toe zou nemen met de leeftijd. In totaal ontving 7,5% van de kinderen astmamedicatie maar had minder dan de helft (49%) van deze kinderen een geregistreerde astmadiagnose. Subgroepanalyses op leeftijd, geslacht en therapiegroepen lieten zien dat de Positief Voorspellende Waarde (PPV) alleen significant verschilde tussen therapiegroepen. De waarschijnlijkheid dat een kind artsgediagnosticeerde astma had, steeg tot een maximum van 66% bij de kinderen die een uitgebreidere behandeling met astmamedicatie kregen (ICS gebruik, hoger aantal recepten). Hoewel de kans van het kind op het al dan niet behandeld worden met astmamedicatie sterk werd beïnvloed door de leeftijd, steeg de congruentie tussen het voorschrijven van astmamedi-

catie en artsgediagnosticeerde astma opvallend genoeg niet met de leeftijd. Vervolgens is in *Hoofdstuk 4.2* geëvalueerd welke factoren, afgezien van een astmadiagnose, een rol konden spelen bij het voorschrijven van astmamedicatie bij kinderen, door na te gaan hoe en in welke mate dit voorschrijven werd beïnvloed door kind-, familie- en huisarts-karakteristieken. Er is een multilevel multivariate logistische-regressie-analyse uitgevoerd met drie niveaus, onder 46,371 kinderen, behorend tot 25,537 families, ingeschreven bij 109 huisartsen. In deze studie werden de kinderen onderverdeeld in twee leeftijdsgroepen, conform het leeftijdsonderscheid gemaakt in klinische richtlijnen: (I) kinderen onder de leeftijd van zes jaar en (II) kinderen met leeftijd 6-17. We vonden dat, na correctie voor een astmadiagnose, andere respiratoire morbiditeiten zoals acute bronchitis, hoesten en longontsteking, evenals het geslacht van het kind, significant geassocieerd waren met het voorschrijven van astmamedicatie. Daarnaast werd er een significante invloed van de familie en de huisarts waargenomen op het voorschrijven van astmamedicatie. De variantie in voorschrijven tussen huisartsen was significant hoger bij kinderen onder de zes jaar dan bij oudere kinderen (95% CI 3,5 tot 25,2% versus 2,4 tot 13,4%; Chi-kwadraat = 7,3). Dit zou een direct gevolg kunnen zijn van de bemoeilijkte diagnostiek bij jonge kinderen met astmatische symptomen. Hiaten in de diagnostiek leiden mogelijk tot meer artsgedreven voorschrijven, ongeacht de klinische context. Dus kind, familie en huisarts beïnvloeden allen of een kind al dan niet astmamedicatie krijgt. Er zijn echter meerdere behandelmogelijkheden beschikbaar bij kinderen met astmatische klachten. In *Hoofdstuk 4.3* is onderzocht in hoeverre kenmerken van het kind, de familie en de huisarts samenhangen met de keuze voor aanvals- danwel onderhoudsbehandeling met astmamedicatie. Er is nagegaan of een kind kortwerkende beta2-agonisten (alleen SABA, aanvalsbehandeling) of SABA en ICS (SABA/ICS, onderhoudsbehandeling) ontving, gebaseerd op alle recepten gedurende de studieperiode van 1 jaar. Slechts enkele karakteristieken bleken specifiek geassocieerd te zijn met de keuze voor aanvals- danwel onderhoudsbehandeling. Kinderen met artsgediagnosticeerde astma hadden een grotere kans op het krijgen van SABA/ICS ($OR_{SABA/ICS}$ = 2,13; 85% CI 1,79 tot 2,54), terwijl kinderen waarbij benauwdheid geregistreerd werd vaker alleen SABA kregen ($OR_{SABA/ICS}$ = 0,38; 95% CI 0,26 tot 0,57). Met elk huisartsconsult steeg de kans op het krijgen van onderhoudsbehandeling met 7% (OR = 1,07; 95% CI 1,04 tot 1,09). Alle andere kind- en arts-karakteristieken waren uniform geassocieerd met beide behandelregimes en dus met voorschrijven in het algemeen. Zowel het voorschrijven van SABA als SABA/ICS bleek significant te associëren met andere respiratoire morbiditeiten dan astma. Er bestonden grote verschillen tussen huisartsen wat betreft het percentage kinderen waaraan ze astmamedicatie voorschreven, ongeacht het therapieregime. Deze verschillen konden niet verklaard worden door het aantal kinderen met respiratoire morbiditeiten per huisarts. Als rekening werd gehouden met de geregistreerde respiratoire morbiditeiten namen de verschillen tussen huisartsen alleen maar toe. Dit impliceert dat het verband tussen het diagnosticeren van een kind met een bepaalde aandoening of symptoom en het voorschrijven van astmamedicatie sterk verschilt per huisarts.

Hoofdstuk 5 voorziet in een algemene discussie. De resultaten van de individuele studies worden in een breder perspectief geplaatst en klinische implicaties worden besproken. Daarnaast worden de voordelen en de beperkingen van de gebruikte datasets en uitkomstmaten besproken. Concluderend is het van belang om behandeling van kinderen met astmamedicatie te verbeteren. De mogelijkheden tot verbetering zijn echter sterk afhankelijk van een vooruitgang wat betreft diagnostiek en de resultaten van effectiviteitstudies. Tegelijkertijd laten de gecombineerde resultaten van onze studies zien dat, ondanks het wijdverbreide gebruik van astmamedicatie, de lage persistentie en de hoge mate van variatie in voorschrijven, het gebruik van astmamedicatie bij kinderen minder willekeurig is dan soms het geval lijkt.

SENSITIVITY ANALYSIS PIAMA STUDY

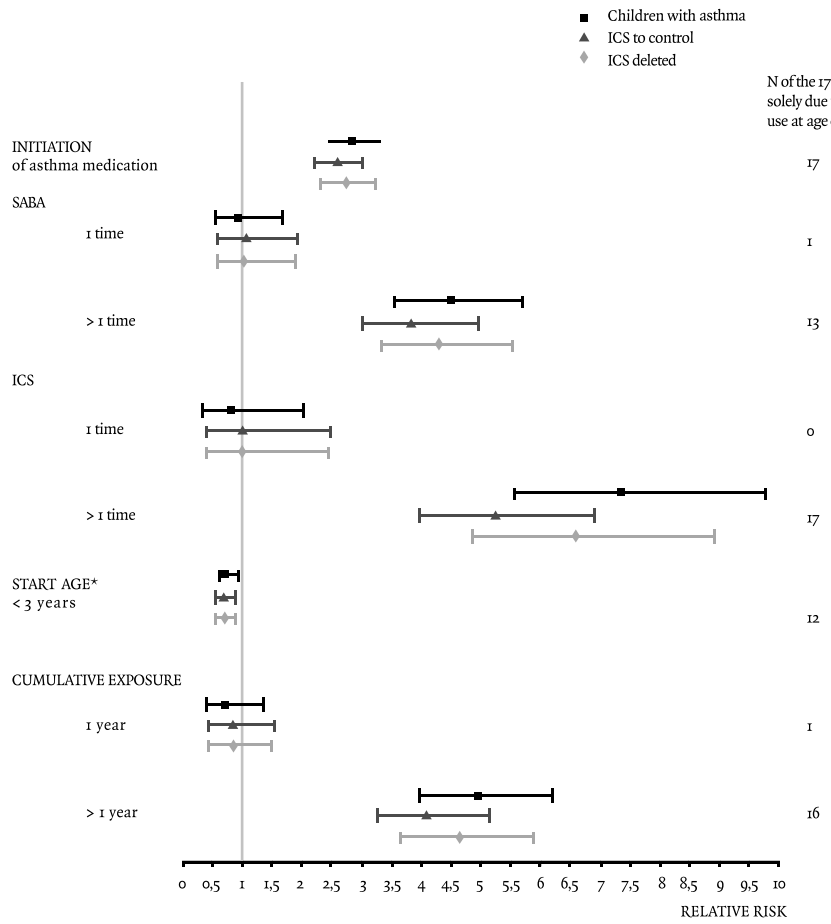
Purpose: This sensitivity analysis was performed to determine the possible influence on our findings of the fact that within the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study ICS use at age eight (questionnaire based) is part of the asthma definition while ICS from birth until age eight (pharmacy record based) is part of the determinant (medication use).

There are 17 children (of the 102 with asthma at age eight) who satisfy the asthma definition solely due to the fact that ICS use was reported at that age (no reporting of wheeze or shortness of breath in the same year).

Sensitivity analysis approach:
all 17 children have been moved to the group of non-asthmatic children
all 17 children have been removed from the study population

The results are shown in Figure 1. The estimates of the relative risks move somewhat (especially the one for > 1 time ICS) but the size and direction of the found effects do not change. When looking at the characteristics of the 17 children we see that they all initiated asthma medication and all used ICS more than once. 13 children started medication use before the age of three. Based on these findings we decided to use the formal PIAMA definition for asthma at age eight (in Chapter 3.3. of this thesis), since all the signs point to these children being a group of children with persistent symptoms.
It seems highly unlikely that children initiating medication at age three would still be using ICS at age eight just because they started once and not because of persistent symptoms.

FIGURE 1 Results of the sensitivity analysis: the chance to receive asthma medication before age eight for children with asthma at age eight compared to children without asthma at age eight



Dankwoord

Dankwoord

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Mira Zuidgeest was born on the 9th of February 1977 in Heerlen, the Netherlands. She completed secondary school in 1995 at 'Grotius College' in Heerlen. She studied pharmacy at Utrecht University, where she obtained her PharmD in 2003. During her studies she completed a research traineeship at the Faculty of Pharmaceutical Sciences of the University of Copenhagen in Denmark. After graduating she worked as a pharmacist at the Catharina Hospital, Eindhoven in the year 2003. December of that year she started the research described in this thesis at the Department of Pharmacoepidemiology and Pharmacotherapy at Utrecht University, in collaboration with the National Institute for Public Health and the Environment (RIVM), Centre for Prevention and Health Services Research. In 2008 she obtained her MSc in Epidemiology as a part of her PhD education-plan at the Julius Center, Utrecht University. Since March 2008 she fills a position at the NIVEL (Netherlands Institute for Health Services Research) as a researcher.