ASTHMA

EPIDEMIOLOGY, TREATMENT AND EXACERBATIONS

IN REAL LIFE

MARJOLEIN ENGELKES

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The work presented in this thesis was conducted at the Department of Medical Informatics and the Department of Pediatric Pulmonology of the Erasmus Medical Center, Rotterdam, the Netherlands.

The contribution of all the participating patients, physicians, pharmacists and staff of the IPCI database, the PHARMO Database Network and the EU-ADR alliance is greatly acknowledged.

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ASTHMA

EPIDEMIOLOGY, TREATMENT AND EXACERBATIONS IN REAL LIFE

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CONTENTS

1 GENERAL INTRODUCTION

INTRODUCTION

Asthma is a highly prevalent and chronic respiratory condition affecting 300 million people worldwide. [1] Asthma is a potentially serious chronic disease that imposes a substantial burden on patients, their families and the community. It causes disability by respiratory symptoms, exacerbations with sometimes urgent health resource utilization, reducing the patient's quality of life and may be fatal. [2] It is estimated that asthma accounted for about 345,000 deaths worldwide in 2010. [3] There is no cure for asthma, but it can generally be controlled through tailored stepwise treatment as described by asthma management guidelines. Despite available therapies, asthma control in clinical practice is suboptimal in real life and much lower than in clinical trials. To see developments in epidemiology and to understand the full burden of asthma, it is important to have up-to-date, real world data on treatment and exacerbations in population based cohorts. The computerization of medical care has largely facilitated this as they capture detailed and time stamped data on disease, population and medication use and reflect real life, which is essential to conduct these studies. In this thesis we focus on the epidemiology of asthma, asthma treatment and asthma control in daily practice and we used different Dutch and international electronic health care databases.

Symptoms and pathophysiology of asthma

Asthma is a chronic, episodic, heterogeneous disorder of the airways, characterized by wheezing, shortness of breath, chest tightness and cough that vary over time. Chronic airway inflammation is an important aspect of asthma pathophysiology. [2] Effector cells are eosinophils, neutrophils, CD4+ T-lymphocytes and mast cells that contribute to the pathophysiological changes. [2, 4] These changes include airway inflammation, intermittent (reversible) airflow obstruction, which is potentially reversible either spontaneously or with pharmacological intervention, bronchial hyperresponsiveness and airway wall remodelling. [2] Chronic inflammation, mucosal oedema due to increased vascular permeability, smooth muscle contraction and excessive mucus secretion contribute to airway obstruction. The smooth muscle cells cause exaggerated bronchoconstriction in response to a wide range of specific and non-specific stimuli, this is called 'bronchial hyperresponsiveness'. [5] In addition to the inflammatory response, characteristic structural changes, 'airway remodelling', are seen in the airways of asthma patients. [2, 6] In asthma the remodelling usually begins early and thickening of the airway wall may be present before asthma is diagnosed. [6]

Epidemiology of asthma

Asthma is a highly prevalent and chronic respiratory condition affecting 300 million people worldwide. [1] Data on prevalence of asthma has been described for various countries, based on data from cross-sectional studies. [7, 8] From these data was estimated that about 8.6% of the young adults experience asthma symptoms and 4.5% have been diagnosed with asthma and/

or are taking treatment for asthma. About 14% of the children worldwide suffer from asthma symptoms.

There are only few recent studies on the incidence and time trends of incidence and prevalence of asthma in children in Europe. Studies on incidence rates for asthma in children reported widely varying rates, ranging between 4.26 and 20.0 per 1000 per year. [9-24] The huge variation in incidence rates can be explained by differences in asthma definition, differences in the population being studied, geographical factors, differences in calendar time, and reliability of data sources. [25] Data on time trends in asthma prevalence and incidence are conflicting. [26]

Treatment of asthma

The most important goal in the treatment of asthma is to control symptoms and prevent exacerbations. Therapeutic targets are suppression of airway inflammation and relaxation of bronchial smooth muscle. Medication for asthma can be classified into the following two main categories; (1) reliever (rescue) medication, taken when needed, and acting quickly to reverse bronchoconstriction and (2) controller medications for daily maintenance treatment. Inhaled corticosteroids (ICS) are the controller treatment of first choice. Corticosteroids inhibit airway inflammation by inhibiting multiple components of the inflammatory cascade, including the production of prostaglandins and leukotrienes by their action of phospholipase. They also inhibit cytokine gene transcription and increase gene transcription of β-receptors thereby increasing the responsiveness to β_2-agonists. [27]

Other options for maintenance treatment are long-acting β_2-agonists (LABA) or leukotriene antagonists (LTRA). In asthma patients, LABAs should only be used in combination with ICS. When used in monotherapy, LABAs may mask underlying inflammation through symptom relief, as they do not control the inflammation. This increases the risk of severe asthma exacerbations and could eventually result in mortality. [27-30]

LTRAs inhibit the binding of leukotrienes at the receptor level and block the inflammatory effects of leukotrienes. [27, 29] LTRAs are effective for long-term control of mild to moderate asthma. [27, 28] Several evidence-based guidelines for asthma treatment have been published. These include the GINA guidelines, which recommend a step-wise approach for adjustments of controller therapy to achieve good symptom control and minimize future risk of exacerbations. [2, 31, 32] If asthma is not well controlled, treatment should be stepped up until control is achieved. In children 5 years or older, treatment of uncontrolled asthma on a low dose of ICS include addition of long-acting β_2-agonists (LABA) or leukotriene receptor antagonists (LTRA) or doubling the dose of ICS. (Figure 1) Adjustments in treatment should be done in a constant cycle of reviewing response, assessing symptoms and monitoring inhalation technique and adherence. It is not known how well guidelines are followed in real life.

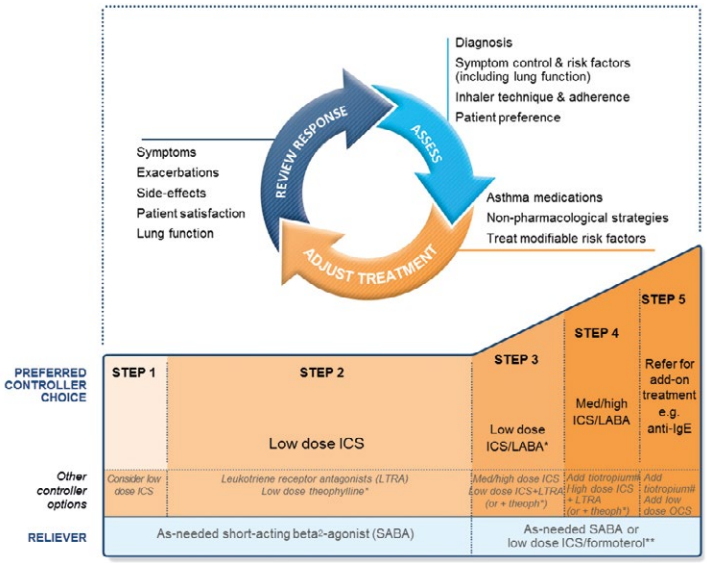

Figure 1. From the Global Strategy for Asthma Management and Prevention 2015, © Global Initiative for Asthma (GINA), all rights reserved.

* For children 6-11 years, theophylline is not recommended and preferred Step 3 is medium dose ICS
** For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
\# Tiotropium by soft-mist inhaler is indicated as add-on treatment for adults (≥18 years) with a history of exacerbations

Generic or brand medication

The expiration of the patent of brand inhalation medications, the ongoing pressure on the healthcare budget and preference policies have resulted in a growing market for generic inhalation medications. The preference policy favours the use of generic drugs as alternatives to more expensive brand-name products, substitution to generic can be done in the pharmacy independent of the physician's prescription, unless it is indicated that brand needs to be dispensed. [33] Before generic medications are marketed, demonstration of clinical bioequivalence is needed. As the drug delivery and intended action of orally inhaled drug products for local action, such as dry powder inhalers (DPI) do not rely on the systemic circulation, the bioequivalence cannot be demonstrated based on drug concentration in blood/plasma. [34] Therefore demonstration of bioequivalence of these products is more challenging. The EMA guideline on requirements for clinical documentation of orally inhaled products for asthma and COPD states that for inhalers with the same substance and required flow rate, similar in vitro performance is sufficient to show equivalence. [35] In vitro performance includes particle size distribution, fine particle fraction of emitted dose, flow rate dependency tested under validated circumstances.
Switching of inhalation therapy often coincides with a change of inhalation device. The choice of type of inhaler is based on patient characteristics (like age and inspiratory force), on the characteristics of the inhaler (like multidose/single dose, powder/aerosol) and patient

preference. [36] Each device requires a different inhalation manoeuvre, which needs to be carefully instructed. Unexpected change in inhaler device may lead to confusion, and incorrect use, which may lead to no or less drug inhaled.

In addition, there is evidence that generic substitution through changes in appearance (colour, size, appearance and packaging) has a negative impact on adherence and disease outcomes. [37-41] Therefore preference policy has raised concerns amongst respiratory health care providers, as it might increase exacerbations and therefore may have an opposite effect on health care budget. However, this has not been supported by real life data.

Adherence

Despite availability of treatment, many children with asthma do not achieve good symptom control. [42, 43] A major cause of uncontrolled asthma is suboptimal adherence to maintenance treatment. [44] Nonadherence is a worldwide problem, irrespective of age. Approximately 50% of adults and children on long-term controller therapy for asthma fail to take medications as directed at least part of the time. [45] Adherence to asthma treatment is commonly low, ranging between 30 to 70%. [2, 46-48] However, assessment of adherence is notoriously difficult. There are different ways to assess adherence. [49] One of these is the medication possession ratio (MPR), the ratio of the total days of supply to the number of days of follow-up per patient. The MPR can be calculated from prescription data or pharmacy dispensing data. MPR based on prescription data has disadvantages as it does not take dispensing, actual use or inhalation technique into account. It has been suggested that poor adherence to controller therapy increases the risk of exacerbations in children and adults, but literature on this topic is conflicting.

Asthma control and severe asthma exacerbations

Despite treatment, asthma exacerbations may occur due to inadequate treatment, or to nonresponse. [50] Clinical trials usually define a severe exacerbation according to the ATS/ERS guidelines as worsening of asthma symptoms which requires hospitalisation or emergency department visit or use of systemic corticosteroids. [51] Severe asthma exacerbations are associated with considerable morbidity and even mortality. Reported frequencies of asthma exacerbations in the literature vary by the definition of an asthma exacerbation, the studied patient population, the severity of asthma, degree of asthma control, and the data sources. Real life data on the incidence rates of asthma exacerbations and potential association with mortality are sparse. [52] Clearly, there is a need for more real life studies to assess the safety and effectiveness profile of inhalation medication for children with asthma in the real life setting which was the reason why we initiated the studies described in this thesis.

The objectives of our research were the following:

- To generate and evaluate automated case detection algorithms to identify children with asthma
- To describe the epidemiology and time trends of asthma in children
- To describe the incidence and risk factors of severe asthma exacerbations in children
- To describe overall mortality and mortality following asthma exacerbations in patients with asthma
- To describe the prescription/dispensing patterns and adherence of asthma controller therapy in children with asthma
- To examine dispensing patterns of brand and generic controller therapy and whether switching between brand and generic controller therapy influences adherence
- To study the association of switching between generic and brand inhalation medication and the risk of asthma exacerbations

Data sources

In this thesis we had access to the IPCI database [53, 54], the Dutch PHARMO Database Network [55] and the databases in the EU-ADR alliance. The EU-ADR alliance is a federated collaborative framework for drug safety studies, using six European population-based administrative and healthcare databases from Italy, the Netherlands, UK, Spain and Denmark. [56]

For most of our research questions we used data from the IPCI database. This database contains the electronic medical records of more than one million patients throughout the Netherlands. This database has the advantage of data on real life practice. Within this database we established the ESTATe cohort (Effectiveness and Safety of controller Therapy of Asthma Treatment in childrEn with asthma), children with asthma aged 5 and older between 2000 and 2012 were selected. For our research on use of generic and brand asthma drugs we used the PHARMO Database Network. This is a Dutch population-based patient centric data network including among other data, drug dispensing records from community pharmacies, hospital discharge records and GP records of more than two million individuals throughout the Netherlands. [55] For our research on the incidence of asthma exacerbations and mortality in patients with asthma, data from the database partners of the EU-ADR Alliance was used.

Outline of this thesis

To study the epidemiology of asthma in children, we identified a paediatric asthma cohort (ESTATe cohort) within the IPCI database. In **Chapter 2.1** we describe how this cohort was created by carefully exploring all medical records from potential asthma patients identified through "machine learning" techniques. In **Chapter 2.2** this validated dataset was used to describe the incidence, prevalence and trend of age at asthma diagnosis in 2000-2012. As data on the real life incidence of severe asthma exacerbation are rare we identified patients with frequent

exacerbations, and studied risk factors. In **Chapter 3.1** we describe asthma exacerbations and risk factors for frequent exacerbations in children with asthma. In **Chapter 3.2** mortality in patients with asthma and the risk of mortality following a severe asthma exacerbation was studied. In **Chapter 4.1** longitudinal prescription patterns and adherence to asthma medication are described, and characteristics of children with high adherence versus children with low adherence assessed. In **Chapter 4.2** we put our results on adherence into perspective, by performing a systematic review on the relationship between low adherence and risk of severe asthma exacerbations. In **Chapter 5** we report the prevalence of switching between generic and brand use of inhalation medications in **Chapter 5.1** and the association between switching and asthma exacerbations in **Chapter 5.2**. Finally, in **Chapter 6** we discuss the main findings of the studies included in this thesis and we provide suggestions for future research.

Chapter	Database	Outcome	Population
2.1	IPCI	Case detection for asthma	Children
2.2	IPCI	Incidence and prevalence of asthma	Children
3.1	IPCI	Incidence and risk factors of asthma exacerbations	Children
3.2	EU-ADR	Overall mortality and mortality following asthma exacerbations	Children and adults
4.1	IPCI	Prescription patterns and adherence of asthma controller therapy	Children
4.2	------	Medication adherence and the risk of severe asthma exacerbations- a systematic review	Children and adults
5.1	PHARMO	Dispensing patterns of brand and generic and switching of inhalation medication	Children and adults
5.2	PHARMO	Switching between generic and brand inhalation medication and the risk of asthma exacerbations	Children and adults

Authors' contributions

All authors contributed extensively to the work presented in this thesis. All chapters, except chapter 2.1 (Zubair Afzal) were drafted by Marjolein Engelkes. The data for all chapters except for chapter 2.1 (Zubair Afzal) and chapter 3.2 (Maria de Ridder) were analysed by Marjolein Engelkes. Nico van Blijderveen equally contributed to the analyses of chapter 5.1 and 5.2. Katia Verhamme, Hettie Janssens, Miriam Sturkenboom and Johan de Jongste jointly supervised the chapters. All co-authors critically revised the chapters.

REFERENCES

1. WHO. Chronic respiratory diseases.
2. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. . 2015.
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* Dec 15 2012;380(9859):2095-2128.
4. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet.* Sep 20 2008;372(9643):1107-1119.
5. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. *J Allergy Clin Immunol.* Sep 2011;128(3):451-462; quiz 463-454.
6. Jeffery PK. Remodeling in asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med.* Nov 15 2001;164(10 Pt 2):S28-38.
7. Lai CK, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax.* Jun 2009;64(6):476-483.
8. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health.* 2012;12:204.
9. Winer RA, Qin X, Harrington T, Moorman J, Zahran H. Asthma incidence among children and adults: findings from the Behavioral Risk Factor Surveillance system asthma call-back survey--United States, 2006-2008. *J Asthma.* Feb 2012;49(1):16-22.
10. Wendt JK, Symanski E, Du XL. Estimation of asthma incidence among low-income children in Texas: a novel approach using Medicaid claims data. *Am J Epidemiol.* Oct 15 2012;176(8):744-750.
11. Broms K, Norback D, Sundelin C, Eriksson M, Svardsudd K. A nationwide study of asthma incidence rate and its determinants in Swedish pre-school children. *Eur J Epidemiol.* Sep 2012;27(9):695-703.
12. Gommer AM (RIVM) PMR. Astma: prevalentie, incidentie en sterfte naar leeftijd en geslacht. *Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid.* 2011; <http://www.nationaalkompas.nl> Nationaal Kompas Volksgezondheid\Gezondheidstoestand\Ziekten en aandoeningen\Ademhalingswegen\Astma.
13. To T, Wang C, Guan J, McLimont S, Gershon AS. What is the lifetime risk of physician-diagnosed asthma in Ontario, Canada? *Am J Respir Crit Care Med.* Feb 15 2010;181(4):337-343.
14. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med.* Mar 2010;103(3):98-106.
15. Gershon AS, Guan J, Wang C, To T. Trends in asthma prevalence and incidence in Ontario, Canada, 1996-2005: a population study. *Am J Epidemiol.* Sep 15 2010;172(6):728-736.
16. Demir AU, Celikel S, Karakaya G, Kalyoncu AF. Asthma and allergic diseases in school children from 1992 to 2007 with incidence data. *J Asthma.* Dec 2010;47(10):1128-1135.
17. Punekar YS, Sheikh A. Establishing the incidence and prevalence of clinician-diagnosed allergic conditions in children and adolescents using routinely collected data from general practices. *Clin Exp Allergy.* Aug 2009;39(8):1209-1216.
18. Larsson M, Hagerhed-Engman L, Sigsgaard T, Janson S, Sundell J, Bornehag CG. Incidence rates of asthma, rhinitis and eczema symptoms and influential factors in young children in Sweden. *Acta Paediatr.* Sep 2008;97(9):1210-1215.
19. Burgess JA, Dharmage SC, Byrnes GB, et al. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. *J Allergy Clin Immunol.* Aug 2008;122(2):280-285.
20. Rudd RA, Moorman JE. Asthma incidence: data from the National Health Interview Survey, 1980-1996. *J Asthma.* Jan-Feb 2007;44(1):65-70.
21. Thomsen SF, Ulrik CS, Kyvik KO, et al. The incidence of asthma in young adults. *Chest.* Jun 2005;127(6):1928-1934.
22. Jaakkola JJ, Hwang BF, Jaakkola N. Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. *Environ Health Perspect.* Mar 2005;113(3):357-361.
23. Dik N, Tate RB, Manfreda J, Anthonisen NR. Risk of physician-diagnosed asthma in the first 6 years of life. *Chest.* Oct 2004;126(4):1147-1153.
24. Kujala V, Remes J, Latvala J, Jarvelin MR. Incidence of asthma in twelve thousand Finnish adults born in 1966. *Int J Occup Med Environ Health.* 2005;18(3):255-258.

25. Chawla J, Seear M, Zhang T, Smith A, Carleton B. Fifty years of pediatric asthma in developed countries: how reliable are the basic data sources? *Pediatr Pulmonol.* Mar 2012;47(3):211-219.
26. van Schayck CP, Smit HA. The prevalence of asthma in children: a reversing trend. *Eur Respir J.* Oct 2005;26(4):647-650.
27. Houglum JE. Asthma medications: basic pharmacology and use in the athlete. *J Athl Train.* Apr 2000;35(2):179-187.
28. Goeman DP, Jenkins CR, Crane MA, Bosnic-Anticevich SZ, Douglass JA. Unmet needs of older people with asthma: cross-sectional survey. *J Asthma.* Nov 2011;48(9):865-875.
29. BCFI. *Gecommentarieerd geneesmiddelen-repertorium 2014.* 27 ed2014.
30. Martinez FD. Safety of long-acting beta-agonists--an urgent need to clear the air. *The New England journal of medicine.* Dec 22 2005;353(25):2637-2639.
31. Bindels PJE VdGE, Grol MH, Van Hensbergen W, Steenkamer TA, Uijen JHJM, Burgers JS, Geijer RMM, Tuut MK. NHG-Standaard Astma bij kinderen(Derde herziening). *Huisarts Wet.* 2014;57(2):70-80. https://www.nhg.org/standaarden/volledig/nhg-standaard-astma-bij-kinderen Accessed 19-05-2014.
32. NVK. Richtlijn astma bij kinderen *Nederlandse Vereniging voor Kindergeneeskunde*2013.
33. ECLI. Voorzieningenrechter Rechtbank Breda. *BD2019* NL:RBBRE:2008:BD2019:188618 KG ZA 188608-188228. Available at: http://deeplink.rechtspraak.nl/uitspraak?id=ECLI:NL:RBBRE:2008:BD2019.
34. Lee SL, Adams WP, Li BV, Conner DP, Chowdhury BA, Yu LX. In vitro considerations to support bioequivalence of locally acting drugs in dry powder inhalers for lung diseases. *Aaps J.* Sep 2009;11(3):414-423.
35. Agency EM. *Guidelines on the requirements for clinical documentation for orally inhaled product (OIP) including requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and COPD in adults and for use in the treatment of asthma in children and adolescents.* . 2009.
36. Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J.* Jun 2011;37(6):1308-1331.
37. Balkrishnan R, Byerly WG, Camacho FT, Shrestha A, Anderson RT. Effect of prescription benefit changes on medical care utilization in a Medicare HMO population. *Am J Manag Care.* Nov 2001;7(11):1093-1100.
38. Godman B, Shrank W, Andersen M, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. *Expert Rev Pharmacoecon Outcomes Res.* Dec 2010;10(6):707-722.
39. Holmes DR, Jr., Becker JA, Granger CB, Limacher MC, Page RL, 2nd, Sila C. ACCF/AHA 2011 health policy statement on therapeutic interchange and substitution: a report of the American College of Cardiology Foundation Clinical Quality Committee. *J Am Coll Cardiol.* Sep 13 2011;58(12):1287-1307.
40. NIVEL. Gevolgen van preferentiebeleid en farmaceutische zorginkoop. 2015; http://www.nivel.nl/sites/default/files/bestanden/Rapport-gevolgen-preferentiebeleid-farmaceutische-inkoop.pdf. Accessed 11.13, 2015.
41. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med.* Feb 13 2006;166(3):332-337.
42. Fuhlbrigge AL, Guilbert T, Spahn J, Peden D, Davis K. The influence of variation in type and pattern of symptoms on assessment in pediatric asthma. *Pediatrics.* Aug 2006;118(2):619-625.
43. Gustafsson PM, Watson L, Davis KJ, Rabe KF. Poor asthma control in children: evidence from epidemiological surveys and implications for clinical practice. *Int J Clin Pract.* Mar 2006;60(3):321-334.
44. Drotar D, Bonner MS. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. *J Dev Behav Pediatr.* Dec 2009;30(6):574-582.
45. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest Med.* Sep 2012;33(3):405-417.
46. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. *Respirology.* Jun 2008;13(4):559-563.
47. McNally KA, Rohan J, Schluchter M, et al. Adherence to combined montelukast and fluticasone treatment in economically disadvantaged african american youth with asthma. *J Asthma.* Nov 2009;46(9):921-927.
48. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med.* Feb 1994;149(2 Pt 2):S69-76; discussion S77-68.
49. Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Ann. Pharmacother.* Jan 2009;43(1):36-44.

50. Blakeley JO, Evans DG, Adler J, et al. Consensus recommendations for current treatments and accelerating clinical trials for patients with neurofibromatosis type 2. *Am J Med Genet A.* Jan 2012;158A(1):24-41.

51. Reddel HK. Characterizing asthma phenotypes: predictors and outcomes at the extremes of asthma severity. *Respirology.* Aug 2009;14(6):778-780.

52. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: origin, effect, and prevention. *J Allergy Clin Immunol.* Dec 2011;128(6):1165-1174.

53. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med.* Nov 15 1993;119(10):1036-1041.

54. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med.* Dec 1999;38(4-5):339-344.

55. Herings RM. *PHARMO: a record linkage system for post- marketing surveillance of prescription drugs in The Netherlands.* . Utrecht, Utrecht 1993.

56. Coloma PM, Schuemie MJ, Trifiro G, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. *Pharmacoepidemiol Drug Saf.* Jan 2011;20(1):1-11.

2 EPIDEMIOLOGY OF ASTHMA

Chapter 2.1

Automatic generation of case-detection algorithms to identify children with asthma from large electronic health record databases

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ABSTRACT

AIMS Most electronic health record databases contain unstructured free-text narratives, which cannot be easily analysed. Case-detection algorithms are usually created manually and often rely only on using coded information such as International Classification of Diseases version 9 codes. We applied a machine-learning approach to generate and evaluate an automated case-detection algorithm that uses both free-text and coded information to identify asthma cases.

METHODS The Integrated Primary Care Information (IPCI) database was searched for potential asthma patients aged 5–18 years using a broad query on asthma-related codes, drugs, and free text. A training set of 5,032 patients was created by manually annotating the potential patients as definite, probable, or doubtful asthma cases or non-asthma cases. The rule-learning program RIPPER was then used to generate algorithms to distinguish cases from non-cases. An over-sampling method was used to balance the performance of the automated algorithm to meet our study requirements. Performance of the automated algorithm was evaluated against the manually annotated set.

RESULTS The selected algorithm yielded a positive predictive value (PPV) of 0.66, sensitivity of 0.98, and specificity of 0.95 when identifying only definite asthma cases; a PPV of 0.82, sensitivity of 0.96, and specificity of 0.90 when identifying both definite and probable asthma cases; and a PPV of 0.57, sensitivity of 0.95, and specificity of 0.67 for the scenario identifying definite, probable, and doubtful asthma cases.

CONCLUSIONS The automated algorithm shows good performance in detecting cases of asthma utilizing both free-text and coded data. This algorithm will facilitate large-scale studies of asthma in the IPCI database.

INTRODUCTION

Asthma is one of the most common chronic diseases of childhood globally. The main goal of asthma treatment is to achieve and maintain clinical control of the disease. Failing to control asthma can limit daily-life activities and can be fatal. In children, asthma is usually treated and maintained with low-dose inhaled corticosteroids (ICS). If asthma is not controlled, treatment is stepped up by either adding long-acting β_2-agonists (LABA) or a leukotriene receptor antagonist (LTRA) to low-dose ICS or increasing the dose of ICS until control is achieved. [1]

Safety concerns have been raised on the long-term toxicity of ICS, the risk of mortality, and asthma exacerbations with the use of LABAs in monotherapy and the risk of neuropsychiatric events and hepatotoxicity in children treated with LTRAs. [2–8] Randomized controlled trials (RCTs) on the efficacy and safety of these drugs in children are rare. In addition, the few trials conducted in children are often not designed to detect safety issues because of the limited sample size and short duration of follow-up. In general, observational studies are suited for research on drug safety because they usually have large sample size with long-term follow-up. Electronic medical records are valuable resources and are increasingly being used in epidemiological observational studies to detect safety issues. [9–15]

One of the challenges of using electronic medical records is to determine whether and when a medical outcome of interest has occurred. When coded information such as International Classification of Diseases version 9 (ICD-9) and Logical Observation Identifiers Names and Codes (LOINC) codes are available, outcomes are typically identified by searching for a combination of codes in the patient record. However, the recording of these codes can be incomplete and inaccurate, or the codes themselves might be ambiguous or have the wrong granularity for the research question at hand. It is therefore recommended that the performance of this search using codes is evaluated through manual chart review, where researchers often rely on the free-text narrative in the medical record. There are also databases where the coding is simply too incomplete. For example, in the Integrated Primary Care Information (IPCI) database [16], almost 60% of the record lines are narratives and do not contain coded information. These narratives may contain important information such as patient-reported symptoms, signs, or summaries of specialists' letters. In these databases, the search for outcomes is even more labor intensive. Usually, a broad text query is defined including all possible words and codes that might be relevant, and subsequently all narratives returned by the query are manually reviewed. With the increase in size of these databases, this practice is becoming prohibitively laborsome and expensive.

For this reason we used an alternative approach to identifying asthma cases, which uses the free-text narrative in an automated fashion. We apply a machine-learning approach to derive an automated case detection algorithm that uses both text and coded data if available. We not only show the performance of this algorithm in terms of positive predictive value (PPV), sensitivity and specificity, but also demonstrate how sensitivity and specificity can be tuned to best

meet the requirements of our study. We apply this approach to the Dutch IPCI database, but the same procedure to construct a case detection algorithm could be used on other databases, in other languages.

METHODS

Electronic medical record database

Data in this study were taken from the IPCI database. [16] The IPCI database is a longitudinal observational database of electronic medical records (EMRs) from Dutch general practitioners (GPs). The electronic records contain coded data and data on patient demographics, symptoms and diagnoses, clinical findings, referrals, laboratory findings, and hospitalization of more than 1.1 million patients. The IPCI database uses the International Classification of Primary Care (ICPC) [17] coding system. A list of ICPC codes related to asthma is presented in the Appendix. The cohort for the underlying study included children between age 5 and 18 that were present in the database between January 1, 2000 till January 31, 2012. A minimum registration period of six months was required to guarantee sufficient medical history data.

Clinical case definition

To create a labelled training set for machine-learning methods, we used a manually-defined clinical case definition. Patients were categorized into 'definite asthma', 'probable asthma', 'doubtful asthma', or 'no asthma' according to the following validation criteria.

For definite asthma patients, at least one entry in their medical record containing an asthma diagnosis confirmed by a specialist (paediatrician or pulmonologist) was required. For probable asthma patients, at least one entry should contain evidence of asthma diagnosed by the GP and there should be at least one more entry in the patient record suggestive of asthma (ICPC code, free text, lung function measurements, or use of specific bronchodilating drugs/anti-inflammatory drugs for the indication of asthma) within the next 12 months, or at least two additional entries in the patient record suggestive of asthma. For doubtful asthma patients, there should be at least one entry containing an indication of asthma without satisfying the criteria for a definite or probable asthma case. Patients with drug entries only (i.e., without evidence in ICPC code or free text) were considered non-asthma cases, as were patients with no indication of asthma in any entry of their patient record.

Training set for machine learning

We use machine learning methods to automatically learn case detection algorithms on the basis of a training set of entries, i.e., a set of positive and negative examples. To generate a training set for our machine-learning method, we first identified all potential asthma patients using a

broad automated search on ICPC asthma disease codes, asthma drug prescriptions, and free text. The broad query is presented in the Appendix. Because of the generic asthma-related keywords used in the broad query, many of the retrieved patients were likely not to have asthma. One medical doctor reviewed the entire medical record of the patients identified by the broad search strategy in random order for one month. A total of 5,032 patients were validated from 63,618 patients returned by the broad query. The doubtful patients were further reviewed by a senior medical doctor. Patients were labelled as definite asthma (n=308), probable asthma (n=1,133), doubtful asthma (n=160), or non-asthma (n=3,431). A patient's medical record consists of one or more entries, where each entry pertains to a patient visit, a letter from a specialist, prescribed drugs, and so on. The entries in the medical record of a patient were reviewed in chronological order and a patient was labelled positive whenever an asthma criterion (for definite, probable, and doubtful) was satisfied. The remaining entries in the medical record were not reviewed, and only the entries containing the indication of asthma were included in the training set as positive examples. If none of the entries of the patient record contained positive evidence of asthma, the patient was considered a negative case and one of the entries was randomly picked as a negative example in the training set.

To make the text in the entries better fit for machine learning approaches, we removed uninformative words (so-called stop words). Although some standard Dutch stop word lists are available [18], they are not entirely suitable for the clinical text because some of the words may have importance in the clinical context, e.g., 'op' (English 'on') could be an abbreviation of 'operation'. We therefore used a small stop word list, only containing 'en' (English 'and'), 'een' ('a'), 'de', and 'het' (both 'the').

All ATC codes related to respiratory drugs and starting with R03 (drugs for obstructive airway diseases) were replaced by a single keyword 'r03drug'. To remove negated and speculative assertions, we used the Dutch assertion filter proposed in [15], similar to NegEx. [19] Any words appearing between negation or speculation keywords and the end of sentence (demarked by a punctuation mark) were removed from the entry. All sentences containing an alternatives keyword were completely removed.

The text in the entries was converted to lower case and split into individual words. These individual words were treated as features for our machine-learning method (bag-of-words representation). Schuemie et al. [15] previously showed the advantage of using assertion filtering and bag-of-words representation on Dutch EMRs. For computational purposes, we reduced the number of features by chi-square feature selection. [20] A p-value of less than 0.05 was used as a feature selection criterion. Chi-square feature selection decreased the number of features in the data set by about a factor of 10 without affecting the performance of the classifiers but greatly reducing their training time.

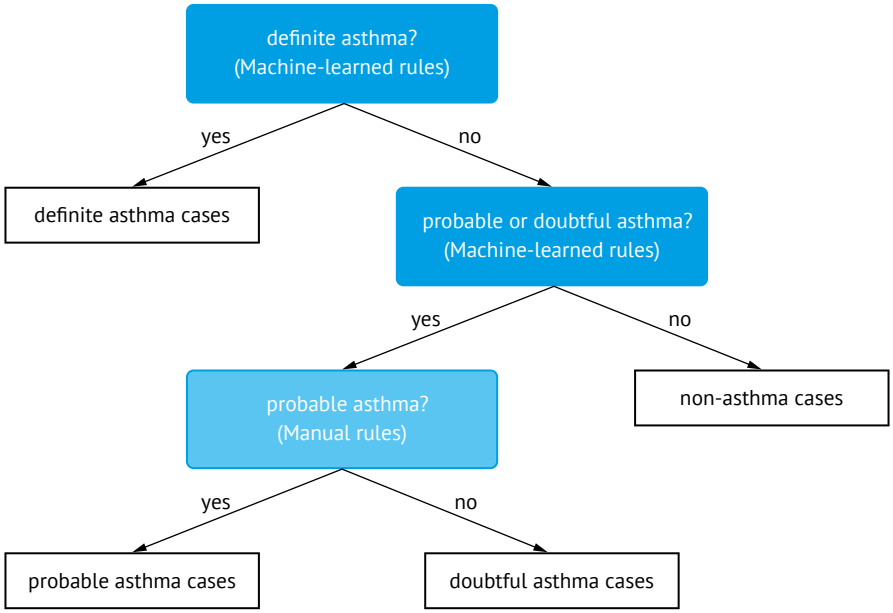

Figure 1 - Hierarchical classification scheme for asthma.

Automated generation of case definitions

Considering the hierarchical nature of the asthma labels (definite → probable → doubtful → non-asthma), we tackled the automated generation of case definitions as a hierarchical multi-class classification problem. [21–23] We followed an approach in which the hierarchy is structured as a decision tree and separate classifiers are built for the nodes in the tree (Figure 1).

We trained two machine-learning classifiers, one to separate definite cases from all other cases and the other to distinguish probable and doubtful asthma from non-asthma cases. The second classifier considered probable and doubtful cases as one (positive) group because the distinction between these cases is difficult to learn automatically. This distinction was made in a third classifier, which implemented two rules based on the manual case definition criteria: (1) if a patient had two positive asthma entries (according to the second classifier) within a period of 15 months and (2) one of the entries is not a medication/drug entry, the patient was considered a probable asthma case. A medication entry only contains prescription. The training set for the first, 'definite asthma' classifier consisted of the entries of the definite asthma patients as positive examples, and entries of the probable, doubtful, and non-asthma cases as negative examples. For the second, 'probable, doubtful, and non-asthma' classifier, we used the entries of the probable and doubtful cases as positive examples and the entries of the non-asthma cases as negative examples. The probable or doubtful asthma patients classified as definite asthma by the first classifier were removed from the training set of the second classifier, and the definite asthma patients missed by the first classifier were added as positive examples.

To shift the balance of sensitivity and specificity, we used a method called "over-sampling". Several over-sampling methods are described in a paper by Chawla. [24] Normally over-sampling is done by simply reusing the same examples multiple times, but Schuemie et al. [15] showed that using additional entries of non-cases could lead to an increased performance. Our over-sampling was focused on increasing the specificity of the classifiers. For a non-asthma patient, all entries were manually reviewed and no evidence of asthma was found. Although initially one entry was randomly selected for training the classifiers, the other entries can also be used as additional negative examples. We created a set of all these additional entries, and randomly sampled from this set to expand our training set. In total, we used 10 over-sampling percentages in the experiments. In each over-sampling run, a specified percentage of entries (of the original negative examples in the training set) from the additional entries set were added to the training set. The experiment without the over-sampling entries was considered a baseline.

Training and testing

The rule-learning algorithm RIPPER [25] was used on the training set to automatically generate rules for each of the asthma case definition. Schuemie et al. [15] evaluated several well-known machine-learning algorithms for the classification of EMRs in a similar experimental setting, and found RIPPER to be one of the best performing algorithms. RIPPER produces an ordered set of decision rules. The advantages of such machine-learning algorithms are their ability to produce output that is understandable by humans, their ease of use, and their applicability to a wide range of problems. [26] We used an implementation of the RIPPER algorithm called JRip, which is available in the open-source machine learning package Weka. [27]

We used five-fold cross-validation to evaluate our classifiers. Cross validation was done at the patient level (subject-level cross-validation [28]) i.e., the data set was randomly divided in five equally sized subsets of patients (folds). In five cross-validation runs, each time the entries pertaining to four folds were used as a training set and the entries of the remaining subset were used for testing. We used all entries of the patients in the test fold because in real-life situations we do not know the labels of the entries pertaining to the patients returned by the broad query. Cross-validation was used to obtain unbiased performance estimates of the classifiers, but all data was used to generate the final sets of rules.

We used PPV, sensitivity, and specificity as measures to evaluate the performance of the classifiers. PPV is defined as the fraction of positively identified cases that are true positive: number of true positives / (number of true positives + number of false positives). Sensitivity is defined as the true-positive rate: number of true positives / (number of true positives + number of false negatives), whereas specificity is the true-negative rate: number of true negatives / (number of true negatives + number of false positives).

RESULTS

We present results of the asthma classification using three different scenarios. Each can be used to meet the requirement of a particular study. In the first scenario (Figure 2), only definite asthma cases were considered relevant for the study. The probable and doubtful asthma cases were ignored. In the second scenario (Figure 3), the definite and probable asthma cases were considered relevant for the study. The definite and probable asthma cases were combined as positive asthma cases and doubtful cases were disregarded. In the third scenario (Figure 4), the definite, probable, and doubtful asthma cases were combined as positive asthma cases.

The sensitivity, specificity, and PPV of the classifiers using over-sampling and cross-validation methods for the three scenarios are presented in Figures 2-4.

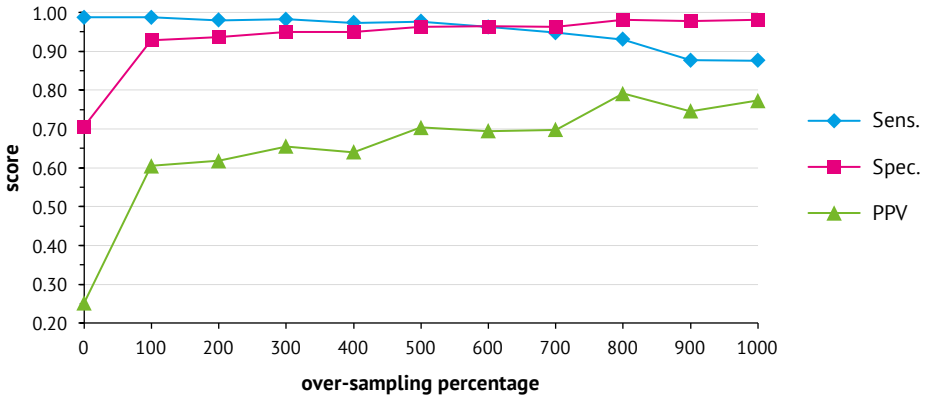

Figure 2 - Performance of the classifiers using cross-validation when only definite asthma cases were considered as positive asthma ignoring probable and doubtful cases.

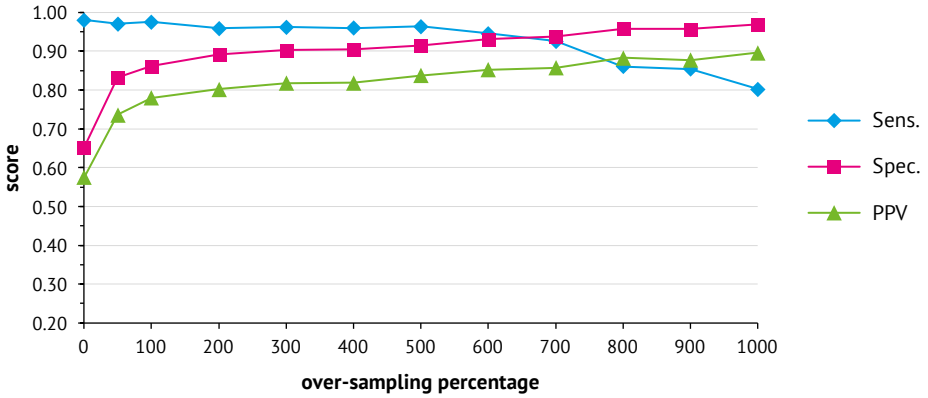

Figure 3 - Performance of the classifiers using cross-validation when definite and probable asthma cases were combined as positive asthma ignoring doubtful cases.

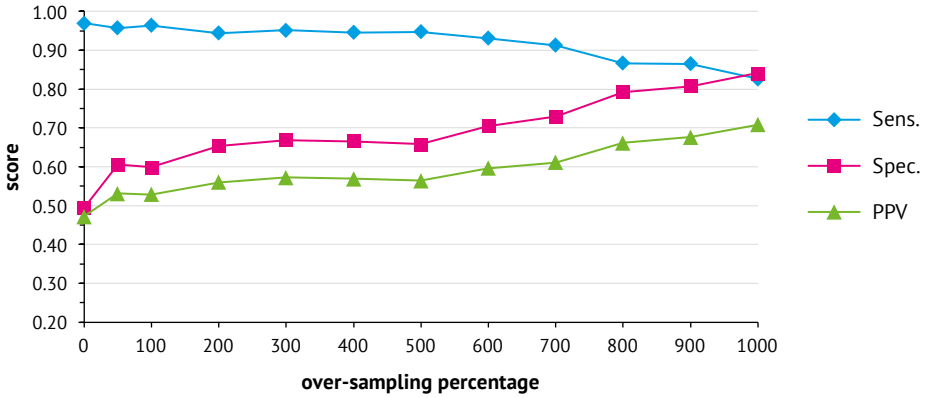

Figure 4 - Performance of the classifiers using cross-validation when definite, probable, and doubtful asthma cases were combined as positive asthma.

The first experiment with 0% over-sampling was considered as the baseline in our experiments. The classifiers showed consistent behaviour during the over-sampling experiments. The specificity and PPV gradually increased and sensitivity decreased as we increased the number of negative examples in the training set. For this particular study, we selected the model using 300% over-sampling as the final classification model because of its high sensitivity and specificity. A confusion matrix of the selected classification model is presented in Table 1. The confusion matrices for all over-sampling experiments using cross-validation are presented in the Appendix.

From 1,601 asthma cases (definite, probable, and doubtful), only 77 (5%) were misclassified as non-asthma cases. From 3,431 non-asthma cases, 1,137 (33%) were misclassified as asthma cases. The automatic case definition for definite asthma is shown in Table 2 and for probable and doubtful asthma in Table 3. Where necessary, the English translation of the terms is included between parentheses.

The term 'cmi' indicates an incoming communication (i.e., a letter) from a specialist or outpatient GP. There are codes to identify specialties in IPCI and the numbers '20' and '15' are used for paediatrics and pulmonology, respectively. Because specialists do not code events in their communications with GPs, none of the rules contains an ICPC or ATC code. The drugs 'flixotide', 'ventolin', and 'pulmicort' are used for obstructive airway diseases. The terms 'r96', '00' and '01' are part of the asthma ICPC codes 'R96.00' and 'R96.01'. Our pre-processing algorithm separated the codes as 'R96', '00', and '01' and because of the bag-of-words representation, these were treated as individual features. The term 's' is part of the 'SOEP' registration used by the GPs in the Netherlands. The 'S' in 'SOEP' stands for 'subjective', and refers to patient history and symptoms. Since the SOEP and ICPC codes can be entered by the GPs only, entries containing these terms indicate that these are GP entries. The keyword 'r03drug' marks the presence of an ATC code starting with R03, indicating a respiratory drug. The terms 'pulm', 'inh', and 'vag' are short for 'pulmonary', 'inhaler', and 'vesiculair ademgeruis' ('vesicular breath

Table 1 - Confusion matrix of the case detection algorithm generated with 300% over-sampling using cross-validation.

	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	228	47	29	4	308
Probable asthma	166	682	245	40	1133
Doubtful asthma	16	15	96	33	160
Non asthma	120	130	887	2294	3431
Total classified	530	874	1257	2371	5032

Table 2 - Automatically generated case detection rules for definite asthma.

1. "20" and "astma" → true
2. "cmi" and "astma" and not "00" and not "van" and not "s" → true
3. "cmi" and "flixotide" and not "ventolin" and not "medicatie" and "20" → true
4. "cmi" and "kindergeneeskunde" and "ventolin" and not "te" → true
5. "cmi" and "astma" and "15" → true
6. "cmi" and "20" and "pulmicort" → true
7. "cmi" and "longziekten" → true
8. DEFAULT → false

English translation and explanation of the terms	
cmi	Incoming letter from a specialist or an outpatient GP
van	"from", "of"
medicatie	"medication"
kindergeneeskunde	"pediatrics"
te	"too"
longziekten	"lung diseases", also used to refer to pulmonology
20	IPCI code that refers to pediatrics
15	IPCI code that refers to pulmonology
pulmicort	Drug name

sound)', respectively. The term 'diskus' indicates a type of dry powder inhaler. For the words 'van' (English 'from' or 'of') and 'te' (English 'too') we have no reasonable explanation why RIPPER found them useful. Almost all rules for probable and doubtful asthma classification contain a mixture of codes and free text.

To assess the impact of different types of information (codes, medications, free text) on classification performance, we compared the performance of our selected model (using 300% over-sampling), generated using all information in the medical records, with models that were generated using subsets of information (also using 300% over-sampling). The results in Table 4 show that the models that only used codes or codes and medications have much lower performance than the models that use free text. None of the models comes close to our selected model with regard to sensitivity, while specificity and PPV of the reference model is comparable to those of the other models using free text for scenarios 1 and 2.

Table 3 - Automatically generated case detection rules for probable and doubtful asthma.

1. "r03drug" and "r96" and not "01" → true	
2. "r03drug" and not "hoesten" and not "pulm" and "flixotide" → true	
3. "r03drug" and not "hoesten" and not "pulm" and not "piepende" and not "hoest" → true	
4. "astma" and "r96" → true	
5. "r03drug" and not "pulm" and "inh" → true	
6. "ventolin" and not "pulm" and "r96" → true	
7. "ventolin" and "astma" and not "vag" → true	
8. "r03drug" and not "piepen" and not "hoest" and "diskus" → true	
9. DEFAULT → false	
English translation and explanation of the terms	
r03drug	Respiratory drug with an ATC code starting with R03
r96	ICPC code for asthma
hoesten	"coughing"
piepende	"wheezing"
hoest	"cough"
piepen	"wheeze"
vag	Abbreviation of "vesiculair ademgeruis" ("vesicular breath sound")
inh	Short for "inhaler"
flixotide	Drug name
ventolin	Drug name

Table 4 - Performance of case detection algorithms that were generated using different combinations of information present in the electronic medical records.

	Scenario 1			Scenario 2			Scenario 3		
Information	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec	PPV
Codes	0.53	0.87	0.21	0.56	0.85	0.57	0.62	0.76	0.55
Codes+Medications	0.86	0.67	0.18	0.67	0.67	0.42	0.69	0.60	0.45
Free text	0.88	0.96	0.64	0.62	0.94	0.78	0.68	0.81	0.63
Free text+Codes	0.85	0.95	0.62	0.61	0.94	0.77	0.65	0.84	0.66
Free text+Medications	0.84	0.97	0.68	0.62	0.94	0.79	0.68	0.81	0.63
Free text+Codes+Medications	0.98	0.95	0.66	0.96	0.90	0.82	0.95	0.67	0.57

DISCUSSION

We created and evaluated an automated case detection algorithm to identify children with asthma within the IPCI database. The case detection algorithm was generated using a rule-learning algorithm which incorporated both information contained in the unstructured free-text and coded data in electronic medical records. We evaluated the automated algorithm in the context of three scenarios, and each scenario had different performance characteristics suitable for a different asthma study goal.

By using over-sampling techniques we could vary the performance of the resulting detection algorithm. By adding more negative examples of asthma cases, PPV and specificity increased, at the cost of decreased sensitivity (cf. Figures 2-4). Varying the amount of over-sampling allows researchers to generate a case detection algorithm suitable for a specific study. For example, when investigating incidence and prevalence, where the goal is to find the number of cases in a population in a given time period, a case detection algorithm with high sensitivity would be preferred. For our particular asthma study, we selected the algorithm with 300% over-sampling mainly because of both its high specificity and sensitivity. The selected case detection algorithm had a PPV of 0.66, sensitivity of 0.98 and specificity of 0.95 for the scenario when only definite cases were considered relevant for the study (cf. Figure 2), PPV of 0.82, sensitivity of 0.96, and specificity of 0.90 for the scenario when definite and probable asthma cases combined were considered relevant (cf. Figure 3), and PPV of 0.57, sensitivity of 0.95, and specificity of 0.67 for the scenario when definite, probable, and doubtful asthma cases were combined and considered relevant for the study (cf. Figure 4). Our experiments with subsets of information available in the medical record (codes, medications, free text) indicate that, overall, best classification performances are obtained with an algorithm that uses all information in the medical record.

Interestingly, none of the 7 rules in the case detection algorithm generated for definite asthma contains an ICPC code for asthma, i.e., R96, or any R03drug (cf. Table 2). The presence of the terms 'flixotide', 'ventolin', and 'pulmicort', which are all R03drugs, suggests that the specialists' letters do not (or not very often) contain ATC drug codes. The RIPPER algorithm was able to pick up both the terms used to indicate the specialty of pediatrics or a pediatrician in the IPCI database, i.e., 'kindergeneeskunde' and the IPCI database code '20'. Similarly, the algorithm also picked up both the terms used for the specialty of pulmonary diseases or a pulmonologist, i.e., 'longziekten' and the IPCI database code '15'. For probable and doubtful asthma cases, the algorithm picked up both the ICPC asthma code R96 and R03drug (cf. Table 3). The algorithm was also able to pick up specific drug names such as 'flixotide', 'ventolin', and 'pulmicort' and abbreviations such as 'inh' for 'inhaler' and 'vag' for 'vesiculair ademgeruis' (vesicular breath sound) used within the IPCI database. A comparison with the broad query (see Appendix) shows that the automated case definitions contain more specific keywords (and combinations) used within the database. This suggests that rules with database specific keywords are complicated to construct manually for use in the broad query.

There were some study limitations. The RIPPER algorithm used a training set of positive and negative examples of asthma cases from the IPCI database. The generated case detection algorithm is therefore specific to the IPCI database and it may not be applicable to other databases to detect asthma cases. A new training set is required to generate an automated case detection algorithm for a new EHR database. The automated case detection algorithm is applicable within the results of the broad query. Any asthma case initially missed by the broad query will

also be missed by the automated case detection algorithm. However, such asthma cases can potentially be identified by applying the automated case detection algorithm onto the complete EHR database, although we do not know how well this would work.

Usually the only way to extract or identify cases from the electronic health record databases is using codes such as ICPC or ICD-9 because the free-text narratives cannot be easily analysed. Recently, Flynn et al. [29] used free-text clinical reports to develop an algorithm using manual rules to identify ischaemic stroke and intracerebral haemorrhage. The approach we used in this study to generate a case detection algorithm to identify asthma patients has a number of advantages. Our approach not only used the structured information, as is usually done, but also took advantage of the free-text narratives present in the EHR database. Another advantage relates to patient confidentiality, which is a matter of concern when dealing with free-text in electronic health records. In our approach, once a model has been generated, cases can automatically be identified without need to anonymize data. We also demonstrated how sensitivity and specificity of the algorithms can be tuned to best meet the requirements of our study. An automatic case detection algorithm with high specificity can reduce the workload of manual annotation, by removing non-relevant records. Another advantage of automated case detection algorithm is that they can allow for more uniform and consistent annotations as compared to several manual annotators. Although the case detection algorithm for asthma discussed here is specific to the IPCI database, the approach used to generate the algorithm can be used in different databases.

In databases such as IPCI, manual review of all results of the broad query is currently mandatory in order to identify asthma cases. Using the automated algorithm described here, it is now feasible to automatically identify definite, probable, and doubtful asthma patients with acceptable performance, using both free-text narratives and coded information when available, allowing large scale epidemiology studies.

Acknowledgments

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REFERENCES

1. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1):143–78.
2. Wallerstedt SM, Brunlöf G, Sundström A, Eriksson AL. Montelukast and psychiatric disorders in children. *Pharmacoepidemiol Drug Saf*. 2009;18(9):858–864.
3. Cates CJ, Cates MJ. Regular treatment with formoterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev*. 2012;4:CD006923.
4. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev*. 2008;(3):CD006363.
5. Allen DB. Effects of inhaled steroids on growth, bone metabolism, and adrenal function. *Adv Pediatr*. 2006;53(1):101–110.
6. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. *Pediatrics*. 2008;122(1):e53–61.
7. Incecik F, Onlen Y, Sangun O, Akoglu S. Probable montelukast-induced hepatotoxicity in a pediatric patient: case report. *Ann Saudi Med*. 2007;27(6):462–463.
8. Sass DA, Chopra KB, Wu T. A case of montelukast-induced hepatotoxicity. *Am J Gastroenterol*. 2003;98(3):704–705.
9. Linder JA, Haas JS, Iyer A, et al. Secondary use of electronic health record data: spontaneous triggered adverse drug event reporting. *Pharmacoepidemiol Drug Saf*. 2010;19(12):1211–1215.
10. Norén GN, Hopstadius J, Bate A, Star K, Edwards IR. Temporal pattern discovery in longitudinal electronic patient records. *Data Min Knowl Discov*. 2009;20(3):361–387.
11. Boockvar KS, Livote EE, Goldstein N, Nebeker JR, Siu A, Fried T. Electronic health records and adverse drug events after patient transfer. *Qual Saf Health Care*. 2010;19(5):e16.
12. Persell SD, Dunne AP, Lloyd-Jones DM, Baker DW. Electronic health record-based cardiac risk assessment and identification of unmet preventive needs. *Med Care*. 2009;47(4):418–424.
13. Liao KP, Cai T, Gainer V, et al. Electronic medical records for discovery research in rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2010;62(8):1120–1127.
14. Allen-Dicker J, Klompas M. Comparison of electronic laboratory reports, administrative claims, and electronic health record data for acute viral hepatitis surveillance. *J Public Health Manag Pract*. 2012;18(3):209–214.
15. Schuemie MJ, Sen E, 't Jong GW, Soest EM, Sturkenboom MC, Kors JA. Automating classification of free-text electronic health records for epidemiological studies. *Pharmacoepidemiol Drug Saf*. 2012;21(6):651-658.
16. Vlug A, Van der Lei J, Mosseveld B, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med*. 1999;38(12):339–344.
17. Lamberts H, Wood M. ICPC: International Classification of Primary Care. Lamberts H, Wood M, eds. *Scand J Prim Health Care*. 1987;4(1):204.
18. Snowball stemmers. http://snowball.tartarus.org/.
19. Chapman WW, Bridewell W, Hanbury P, Cooper GF, Buchanan BG. A simple algorithm for identifying negated findings and diseases in discharge summaries. *J Biomed Inform*. 2001;34(5):301–310.
20. Setiono R. Chi2: feature selection and discretization of numeric attributes. In: *Proceedings of 7th IEEE International Conference on Tools with Artificial Intelligence*. IEEE Comput. Soc. Press; 1995:388–391.
21. Kiritchenko S, Matwin S, Nock R, Famili AF. Learning and evaluation in the presence of class hierarchies: Application to text categorization. Lamontagne L, Marchand M, eds. *Advances in Artificial Intelligence*. 2006;4013:395–406.
22. Costa E, Lorena A, Carvalho A, Freitas A, Holden N. Comparing several approaches for hierarchical classification of proteins with decision trees. *Advances in Bioinformatics and Computational Biology, Springer, Lecture Notes in Bioinformatics*. 2007;4643:126–137.
23. Metz J, Freitas AA, Monard MC, Cherman EA. A study on the selection of local training sets for hierarchical classification tasks. In: *Brazilian National Meeting on Artificial Intelligence (ENIA-2011)*.; 2011:572–583.
24. Chawla N V. Data Mining for Imbalanced Datasets: An Overview. In: Maimon O, Rokach L, eds. *Data Mining and Knowledge Discovery Handbook*. Boston, MA: Springer US; 2010:875–886.

25. Cohen WW. Fast Effective Rule Induction. In: Prieditis A, Russell S, eds. *Proceedings of the Twelfth International Conference on Machine Learning*. Morgan Kaufmann; 1995:115–123.

26. Geurts P, Irrthum A, Wehenkel L. Supervised learning with decision tree-based methods in computational and systems biology. *Mol Biosyst*. 2009;5(12):1593–1605.

27. Hall M, Frank E, Holmes G, Pfahringer B, Reutemann P, Witten IH. The WEKA data mining software. *ACM SIGKDD Explorations Newsletter*. 2009;11(1):10.

28. Adler W, Brenning A, Potapov S, Schmid M, Lausen B. Ensemble classification of paired data. *Comput Stat Data Anal*. 2011;55(5):1933–1941.

29. Flynn RW V, Macdonald TM, Schembri N, Murray GD, Doney ASF. Automated data capture from free-text radiology reports to enhance accuracy of hospital inpatient stroke codes. *Pharmacoepidemiol Drug Saf*. 2010;19(8):843–847.

SUPPLEMENTS

The following broad query was used to identify potential asthma patient:

"astma" OR
"asthma" OR
"wheez" OR
("piep" and not "piepen-" and not "geen" and not "niet") OR
"R96." OR
("kort" and "adem") OR
("dyspn" and not "dyspnoe-" and not "geen")

English translation and explanation of the terms	
wheez	Short for wheezing
piep	Short for piepen ("wheezing")
geen	"no"
niet	"not"
R96	ICPC code for asthma
kort	"short"

Confusion matrices of all over-sampling experiments using cross-validation

0%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	236	50	19	3	308
Probable asthma	326	630	155	22	1133
Doubtful asthma	39	22	75	24	160
Non asthma	705	212	820	1694	3431
Total classified	1306	914	1069	1743	5032

100%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	240	46	19	3	308
Probable asthma	184	711	211	27	1133
Doubtful asthma	16	15	102	27	160
Non asthma	157	177	1044	2053	3431
Total classified	597	949	1376	2110	5032

200%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	243	37	23	5	308
Probable asthma	197	646	247	43	1133
Doubtful asthma	16	10	93	41	160
Non asthma	150	127	911	2243	3431
Total classified	606	820	1274	2332	5032

300%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	228	47	29	4	308
Probable asthma	166	682	245	40	1133
Doubtful asthma	16	15	96	33	160
Non asthma	120	130	887	2294	3431
Total classified	530	874	1257	2371	5032

400%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	217	56	29	6	308
Probable asthma	146	696	250	41	1133
Doubtful asthma	10	11	99	40	160
Non asthma	122	125	900	2284	3431
Total classified	495	888	1278	2371	5032

500%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	207	65	31	5	308
Probable asthma	136	712	248	37	1133
Doubtful asthma	9	14	95	42	160
Non asthma	87	130	955	2259	3431
Total classified	439	921	1329	2343	5032

600%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	205	58	37	8	308
Probable asthma	141	654	285	53	1133
Doubtful asthma	10	10	91	49	160
Non asthma	90	93	828	2420	3431
Total classified	446	815	1241	2530	5032

700%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	220	45	31	12	308
Probable asthma	143	610	310	70	1133
Doubtful asthma	10	12	81	57	160
Non asthma	95	74	762	2500	3431
Total classified	468	741	1184	2639	5032

800%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	201	47	45	15	308
Probable asthma	101	580	316	136	1133
Doubtful asthma	8	6	84	62	160
Non asthma	53	70	588	2720	3431
Total classified	363	703	1033	2933	5032

900%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	185	52	45	26	308
Probable asthma	116	549	340	128	1133
Doubtful asthma	3	9	86	62	160
Non asthma	63	63	536	2769	3431
Total classified	367	673	1007	2985	5032

1000%	Definite asthma	Probable asthma	Doubtful asthma	Non asthma	Patients
Definite asthma	191	47	43	27	308
Probable asthma	112	471	374	176	1133
Doubtful asthma	4	4	77	75	160
Non asthma	56	39	450	2886	3431
Total classified	363	561	944	3164	5032

Table Coding systems used in IPCI

ICPC	translation
R96	Asthma
R96.01	Airway hyperresponsiveness
R96.02	Allergic asthma

Chapter 2.2

Time trends in the incidence, prevalence and age at diagnosis of asthma in children

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ABSTRACT

BACKGROUND Current knowledge on the prevalence of asthma is mainly based on cross sectional questionnaire data. Current population based data on the incidence of asthma in children are scarce.

AIMS To study the incidence, prevalence, and age at diagnosis of asthma in children in the Netherlands over the study period 2000-2012.

METHODS A population-based cohort study was conducted in the Integrated Primary Care Information database. The cohort consisted of 176,516 children (379,536 person-years (PY) of follow-up), aged 5-18 years between 2000-2012. All medical records of children with physician diagnosed asthma were validated. Incidence rates, annual percent change (APC) and prevalence for asthma were calculated. Influence of age and gender on incidence rates and change in age at diagnosis were studied.

RESULTS We identified an asthma cohort of 14,303 children with 35,181 PY. The overall incidence rate was 6.7/1000 PY (95% CI, 6.45-6.97). Until 2008 the incidence rate was significantly increasing (APC 5.79% (95% CI 1.43 to 10.34), from 2008 onwards a non-significant decrease was observed (APC -12.16 (95% CI -23.07 to 0.28). Incidence for girls was lower than for boys, this difference decreased with increasing age. ($p<0.001$) Overall, the age at diagnosis increased over calendar time and was lower for boys. (linear trend $p<0.001$)

CONCLUSIONS Our population-based cohort study observed an incidence rate of 6.7 per 1000 PY of physician diagnosed asthma in children in the Netherlands over 2000-2012. The asthma incidence rate was increasing until 2008. Further studies are needed to confirm the decrease in asthma incidence rate from 2008 onwards.

INTRODUCTION

Asthma is the most common chronic disease in children in the Western world and an increase in asthma prevalence has been shown in the developing world. [1] Although the prevalence of asthma has been described for various countries, these are mainly based on data from cross-sectional studies. [2, 3] The differences in study period, study population, asthma case definition and the reliability of the data sources result in highly differing trends within and between countries. [4] As a consequence of the lack of European longitudinal studies, there are only few recent studies on the incidence of asthma in children in Europe.

The most recent study on the incidence in asthma, performed in Canada using health administrative data, demonstrated a significant increase in incidence from 1992 to 2008 across multiple birth cohorts. [5] Data on the time trends in asthma prevalence and incidence are conflicting. [6] Some studies report an increase in asthma prevalence and incidence whereas other studies report a decline which might be attributed to earlier detection and treatment of children with asthma. [1, 7]

We investigated time-trends in the incidence, prevalence, and the age at diagnosis of physician-diagnosed asthma in children in the Netherlands by conducting a retrospective cohort study over a study period of 12 years, using a large general practitioners database containing the complete electronic medical records of more than 1 million patients.

METHODS

Setting

We conducted a retrospective population-based cohort study within the Integrated Primary Care Information database (IPCI), a longitudinal observational dynamic database which contains the complete electronic medical records of more than 450 GPs in the Netherlands. [8] In the Dutch health care system, patients are registered with a single GP who acts as a gatekeeper for secondary care. [9] Details of the database have been published elsewhere. [8, 10] Briefly, the database contains the complete electronic medical records of approximately 1,500,000 participants. These records contain anonymous longitudinal data on demographics, symptoms and diagnosis (coded and free text), referrals, laboratory findings, discharge letters, and drug prescriptions. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiological studies. [10] The scientific and ethical advisory board of the IPCI database approved the study.

Study cohort

The dynamic source population (n=176,516) comprised all children aged 5-18 years with a database history of at least twelve months. The study period was from 1st January 2000 to 1st January 2012. Follow-up started on 1st January 2000, or on the date on which the required 1 year of follow-up was obtained or on the date the age of 5 years was reached, whichever came last. Follow-up time of children below 5 or above 18 years of age during the study period was excluded from the study. All patients were followed from study entry until the end of the study period, or until leaving the GP practice, or death, or the day on which the patient turned 18 years, whichever occurred first.

Asthma Case identification and validation

All children who were 5-18 years old during the study period with physician diagnosed asthma were identified. First, all potential asthma cases were retrieved by a broad automated search on ICPC (international classification of Primary Care) asthma codes ("R96") and asthma-relevant free text. Asthma was defined as "definite" if diagnosed by a paediatrician. "Probable asthma" was defined as asthma diagnosed by the GP with at least 2 additional records/prescriptions of asthma medications in the 1 year following the initial diagnosis of asthma. A patient was labelled to have "possible asthma" in case of only 1 asthma record or inconsistency between records. Children were classified as not having asthma if the identified symptoms were not related to asthma or if the symptoms could be ascribed to other respiratory conditions (e.g. pneumonia, cystic fibrosis). If at any time during the follow-up asthma was diagnosed, the child was considered asthmatic from date of first diagnosis until the end of follow-up. As this broad automated search resulted in a high number of potential asthma cases (n=63,618), machine learning was used to facilitate the validation, as described in detail elsewhere. [11] The validity of this machine learning approach was reasonable good with a sensitivity of 95% and a specificity of 67% within the testset of 5032 manually annotated medical records. [11] For verification of the total asthma cohort, the medical records of all predicted definite asthma cases and 25% of probable asthma cases were manually reviewed by one of the authors, a medical doctor (ME). Manual review implied that the whole electronic medical chart of each case was reviewed, and searched for asthma diagnosis and asthma medication. If asthma diagnosis and/or asthma medication was observed, the case was categorized according to the predefined algorithm, as described above.

Patient characteristics / comorbidities

For all children the following comorbidities were extracted based on ICPC codes: allergic rhinitis, eczema, and conjunctivitis.

Statistical analysis

Descriptive analyses were used to describe the total cohort and asthma cohort. Chi square test was used to test the difference in comorbidities between subgroups.

Age- and gender-specific incidence rates were determined by dividing the total number of children newly diagnosed with asthma by the total number of person-years (PY) accumulated in the study population. Children were censored on the date of first diagnosis of asthma. Children with prevalent asthma did not contribute person-time to the denominator. Because of the dynamic nature of the population, the annual incidence was calculated per 1000 PY rather than per person. PYs were stratified by calendar year, age (assessed on the 1st January of each follow-up year), and gender. 95% confidence intervals (CI) around the incidence rates were estimated based on the Poisson distribution. [12]

Trends in incidence over time were assessed using Joinpoint Regression Software [13], for details see Kim et al. [14] Briefly, this method starts with a straight line, no joinpoints, to describe a trend over time and tests if the addition of 1 or more joinpoints identifies a significant change in the trend. We used Hudson's method for estimating joinpoints, which allows the joinpoints to occur anywhere between observations, while the alternative Grid search method only tests a discrete number of locations. [15, 16] In our data it is more realistic that the joinpoints may take any value within the observed data range. A maximum of two joinpoints was allowed for each analysis; this is the maximum feasible for 12 data points (2000-2012), as there should be a minimum of 4 datapoints between joinpoints. Trends were described by annual percent change (APC) and the corresponding 95% CI for each segment and an average annual percent change (AAPC) with 95% CI for the whole study period.

Poisson regression models were used to fit incidence rates over age categories adjusted for gender. Linear regression was used to analyse age at diagnosis over calendar time and by gender.

The asthma prevalence was calculated by dividing the number of patients already diagnosed with asthma at study entry by the total number of patients.

The cumulative asthma prevalence between 2000 and 2012 was calculated by dividing the number of children with prevalent asthma (of a certain age) by the total number of children of that age present in the study population on the first of January of each calendar year. The cumulative prevalence was calculated by age category with 95% CI on the basis of the Wilson score interval. [12] P-value of <0.05 was considered statistically significant. Analyses were conducted using SPSS for Windows version 20.0, Joinpoint Regression Program (Version 4.1.1.1), and Episheet. [12]

Table 1 - Baseline characteristics of the total cohort, asthma cohort and incident asthma cohort.

	Total Cohort			Incident cohort
	Non-asthma	Asthma (incident+prevalent)	P-value*	
Number of patients (n)	162,212	14,303		2,542
Gender Boys (%)	51%	59%	<0.001	53%
Eczema	14%	30%	<0.001	
Allergic rhinitis	8%	23%	<0.001	
Conjunctivitis	3%	8%	<0.001	
Specialist diagnosed asthma (n (%))	na	3,340 (23%)		558 (22%)
Age at asthma diagnosis (mean ± sd)		6.8 ± 4.6		11.0 ± 3.8

N = number, % = percentage, sd = standard deviation, na = not applicable

* P-value based on the Pearson Chi-square comparing the asthma and non-asthma cohorts.

RESULTS

The source population comprised 176,516 children with at least 1 year of valid history in the IPCI database. After a broad free text search, 63,518 potential cases of asthma were detected. Upon automated text validation, these were classified in 22,699 asthma cases (definite, probable and possible cases). After manual validation, the final asthma cohort consisted of 14,303 children (3,340 definite and 10,963 probable asthma cases) with 35,118 PY of follow-up. 2,542 children were classified as incident asthma cases, as those children were not yet diagnosed with asthma prior to study start.

Baseline characteristics of the final asthma cohort are described in Table 1. Briefly 3,340 children (23%) had specialist confirmed asthma and 58.7% were boys. Mean age at asthma diagnosis was 6.8 years (SD ± 4.6). Children with a diagnosis of asthma were more often diagnosed with eczema, rhinitis, or conjunctivitis than children without asthma. (all $p<0.001$)

Incidence and prevalence of asthma

Over the follow-up period of 12 years the overall incidence rate of asthma was 6.71 per 1000 PY (95% CI, 6.45-6.97) (Figure 1). Age specific incidence rates by gender are shown in Figure 2. The incidence rate of asthma was higher in boys than girls until the age of 13. After the age of 13, the gender difference reversed.

Joinpoint Regression selected a model with 1 join point. Until 2008 the incidence rate was increasing (APC 5.79% (95% CI 1.43 to 10.34) and from 2008 onwards a decreasing trend was observed. (APC -12.16 (95% CI -23.07 to 0.28) (Figure 3).

Poisson regression with age (categorical), gender and the interaction of age (continue) and gender as explanatory variables, showed that incidence rates for girls were lower than for boys, and this difference decreased with increasing age. (p for interaction <0.001)

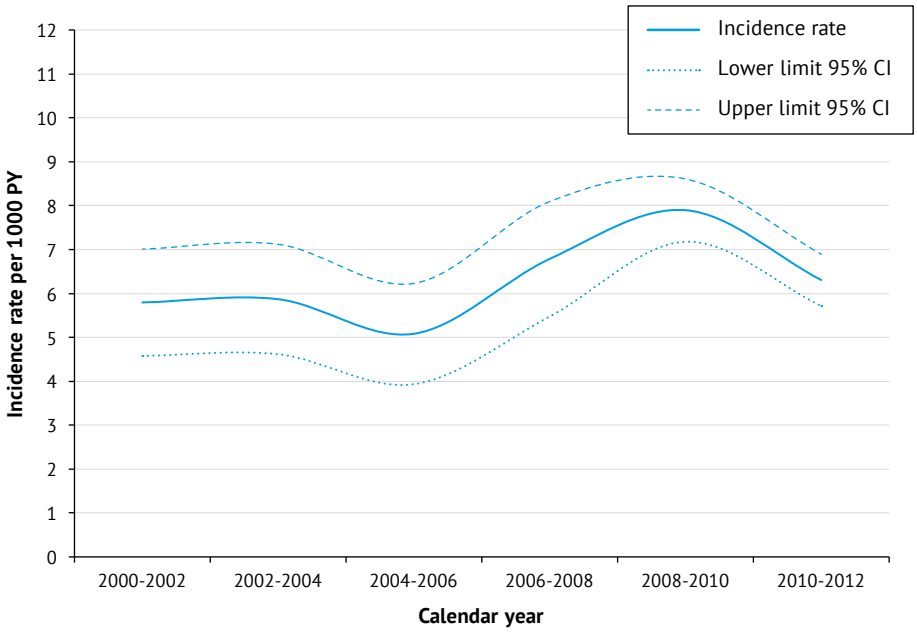

Figure 1 - Incidence rate of asthma in 2000-2012 in 5-18 year old children per 1000 PY.

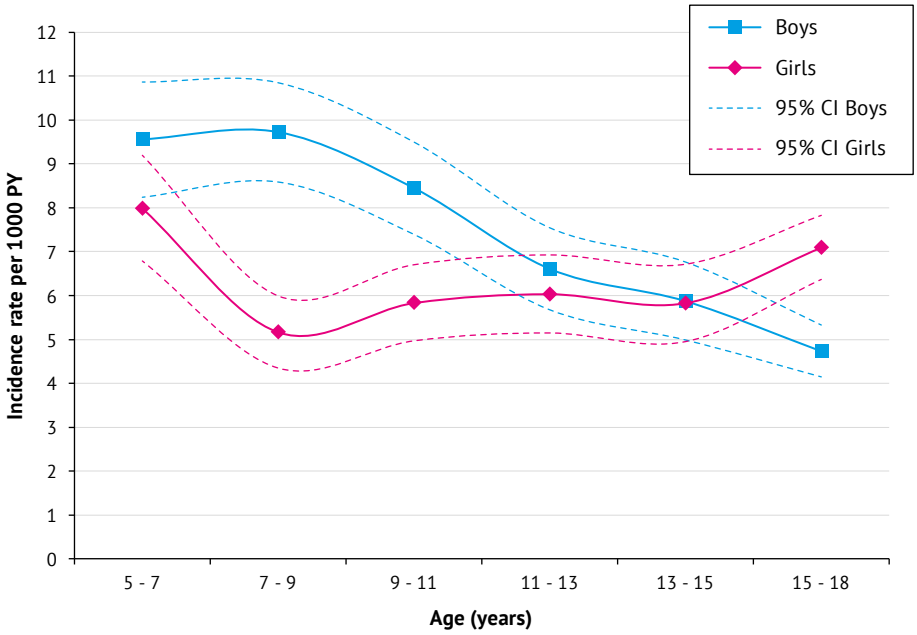

Figure 2 - Gender and age specific incidence rates of asthma in 5-18 year old children per 1000 PY in 2000-2012.

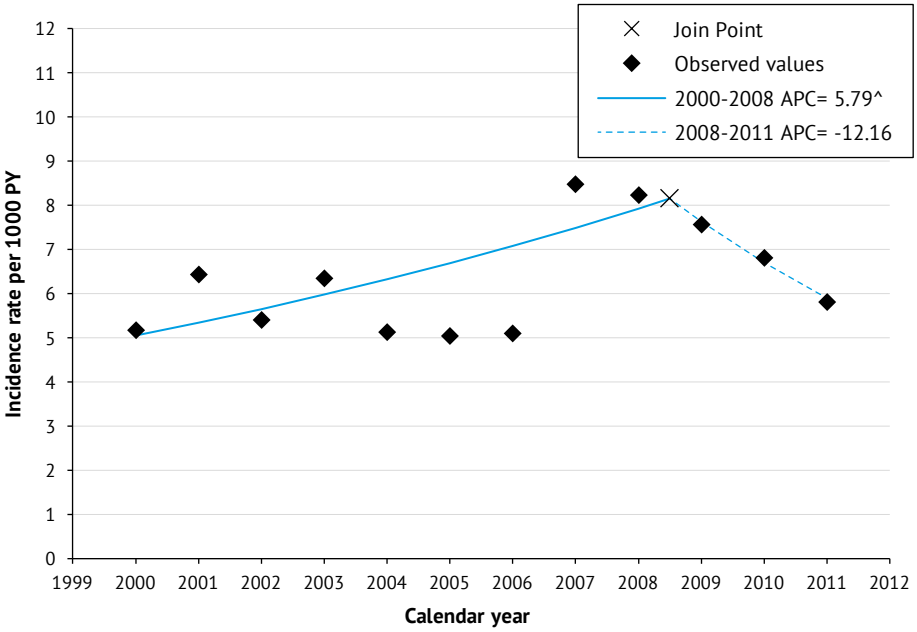

Figure 3 - Join point analysis: trends in the incidence rate of asthma in 2000-2012 in 5-18 year old children per 1000 PY.

The age at asthma diagnosis in children in the incident asthma cohort, over calendar years is shown in Figure 4. We observed that the age at diagnosis increased over calendar time, with increasing age at diagnosis with 0.12 year per calendar year (95% 0.07-0.17) (linear regression, $p<0.001$). Over the study period girls were on average 1.1 year (95% CI 0.82-1.40) older at time of asthma diagnosis than boys. ($p<0.001$)

The asthma prevalence at study start was 6.7% (95% CI 6.6-6.8). The cumulative prevalence of asthma was 8.1% (95% CI 8.0-8.2). The age-specific cumulative prevalence of asthma was higher in boys than in girls in all age categories.

DISCUSSION

This large longitudinal population based cohort study, covering a study period of 12 years, provides age- and gender-specific incidence rates as well as the prevalence of physician diagnosed asthma. The overall asthma incidence was 6.7 per 1000 PY, and increased significantly from 2000 to 2008 and decreased non-significantly after 2008.

Few studies have reported incidence rates for pediatric asthma in the general population. Of those studies that provide data on asthma incidence, the reported rates vary widely, ranging from 0.6 to 29.5 per 1000 persons for children and adults combined [17] and from 3.4 to 4.6 per 1000 PY for adults. [18] The huge variation in incidence rates can be explained by differences in asthma definition, differences in the population being studied, geographical factors,

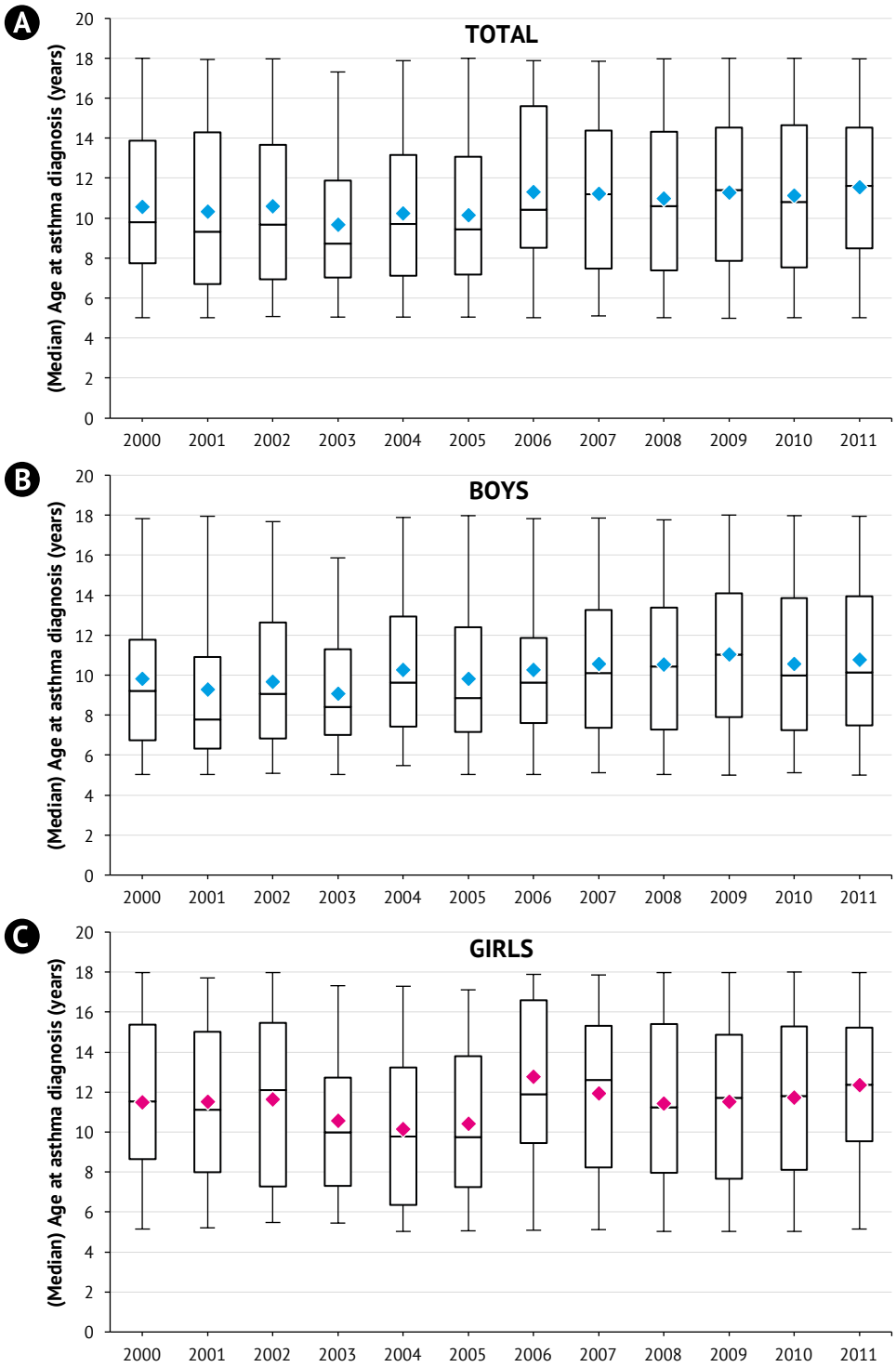

Figure 4 - Age at asthma diagnosis in 5-18 year old children in 2000-2012 for total (a) and for boys (b) and girls (c).
□ = 25th-75th percentile, ⊢⊣ = minimum-median-maximum, ◆ = mean

differences in calendar time, differences in study length and reliability of data sources. [4] The incidence rates as observed in our study are in line with the results from recent studies reporting asthma incidence rates in children ranging between 4.26 and 20.0 per 1000 per year. [19-34] (Online supplement Table 1)

Our asthma incidence rate is slightly lower than the asthma incidence rates of 9.23 (girls) and 13.46 (boys) per 1000 children aged 0-14 years as reported by the Dutch Ministry of Health. [22] However, their incidences rates in the age categories 5-9, 10-14, and 15-18 are in line with our data. The overall higher rates from the Ministry of Health probably reflect a higher asthma incidence rate in young children. In general, rates are higher in studies that include children below 5 years, possibly due to misclassification of viral wheezing, a common condition in these young children. [27, 20, 35]

Radhakrishnan et al. studied time trends in asthma incidence and reported an increase in asthma incidence from 1992 till 2008. [5] This increase in asthma incidence was confirmed in our study, but was no longer present after 2008.

The decrease after 2008 in incidence rate is not necessarily a true decline, but might reflect the impact of the revised Dutch national asthma guidelines in 2008, stating that infants and preschool children who wheeze are not necessary asthmatics, but may wheeze secondary to viral infections. [36] A diagnostic shift from 'asthma' to labels such as 'wheeze' or 'acute respiratory infection' is likely. [37]

Similar to other studies, we observed that the incidence of asthma was higher in girls than in boys after the age of 13. [22, 27]

More data are available in the literature on the prevalence of asthma than on incidence of asthma, but here again, large variations are reported because of differences in methodology. [1, 7, 38] Our prevalence was comparable with recent international studies, reporting prevalences of 7.3-8.4% in the USA [39] and 8% in the Netherlands. [40] In general, the asthma prevalence is higher in studies that used questionnaire data or prescription data, probably due to misclassification or diagnostic bias. [26, 30, 35, 41]

In 2010 a Dutch study reported that asthma was one of the diseases with the largest increase in prevalence. [42] Studies from Switzerland, Norway, Australia and the Netherlands showed that the rising trend in asthma prevalence might have come to an end. [6, 43-46] This decline in asthma prevalence has been partly attributed to earlier detection and treatment of children with asthma. [1, 7] However, in our study we could not confirm that age at asthma diagnosis decreased over time.

The main strengths of our study are the use of a large population based cohort with detailed information on symptoms, diagnosis, drug prescriptions and comorbidities over a study period of more than 10 years. This study design precluded selection bias due to non-responder or recall bias. In addition the potential of selection bias is unlikely as almost all inhabitants of the Netherlands are registered with one GP and data were collected as part of routine patient

care, irrespective of research questions. Patients with asthma were selected based on ICPC codes in combination with free text searches. We avoided misclassification by combining initial validation through machine learning with extensive manual validation according to a strict validation algorithm.

Our study has potential limitations as well. As mentioned above, we validated according to a predefined rigorous validation algorithm and used data from specialist referral letters to define "definite" cases of asthma. However, as not all GP computer systems track all specialist letters, we might have underestimated the actual asthma incidence and prevalence of specialist diagnosed asthma. Furthermore potential misclassification might be introduced by combining only definite and probable asthma cases, and discarding all possible cases. Possible cases were excluded from the analysis as asthma diagnosis was uncertain.

CONCLUSION

Our large population-based cohort study over 2000-2012 found an incidence rate of 6.7 per 1000 PY of physician diagnosed asthma in children in the Netherlands. The incidence rate was higher in boys than in girls up to the age of 13.

Asthma incidence rates increased until 2008, and showed a non-significant decrease from 2008 onwards. Further research is needed to confirm this decrease and to investigate possible explanations for this decrease.

REFERENCES

1. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy.* Feb 2010;65(2):152-167.
2. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax.* Sep 2007;62(9):758-766.
3. Janson C, Anto J, Burney P, et al. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. *Eur Respir J.* Sep 2001;18(3):598-611.
4. Chawla J, Seear M, Zhang T, Smith A, Carleton B. Fifty years of pediatric asthma in developed countries: how reliable are the basic data sources? *Pediatr Pulmonol.* Mar 2012;47(3):211-219.
5. Radhakrishnan DK, Dell SD, Guttmann A, Shariff SZ, Liu K, To T. Trends in the age of diagnosis of childhood asthma. *J Allergy Clin Immunol.* Jun 27 2014.
6. van Schayck CP, Smit HA. The prevalence of asthma in children: a reversing trend. *Eur Respir J.* Oct 2005;26(4):647-650.
7. von Hertzen L, Haahtela T. Signs of reversing trends in prevalence of asthma. *Allergy.* Mar 2005;60(3):283-292.
8. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med.* Nov 15 1993;119(10):1036-1041.
9. Schrijvers A. Health and health care in the Netherlands: a critical self assessment of Dutch experts in medical and health sciences. *Utrecht: De Tijdstroom.* 1997.
10. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods of information in medicine.* Dec 1999;38(4-5):339-344.
11. Afzal Z, Engelkes M, Verhamme KM, et al. Automatic generation of case-detection algorithms to identify children with asthma from large electronic health record databases. *Pharmacoepidemiol Drug Saf.* Aug 2013;22(8):826-833.
12. Rothman K, Greenland,S ,Lash T. *Modern epidemiology.* 3rd ed. New York2008.
13. *Joinpoint Regression Program* [computer program]. Version 4.1.1.1, October 2014: National Cancer Institute; 2014.
14. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Statistics in Medicine.* Feb 15 2000;19(3):335-351.
15. Hudson DJ. Segmented Curves Whose Join Points Have To Be Estimated. *J Am Stat Assoc.* 1966;61:1097-1129.
16. Yu BB, Barrett MJ, Kim HJ, Feuer EJ. Estimating joinpoints in continuous time scale for multiple change-point models. *Comput Stat Data An.* Feb 1 2007;51(5):2420-2427.
17. King ME, Mannino DM, Holguin F. Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med.* Jun 2004;46(2):97-110.
18. Eagan TM, Brogger JC, Eide GE, Bakke PS. The incidence of adult asthma: a review. *Int J Tuberc Lung Dis.* Jun 2005;9(6):603-612.
19. Winer RA, Qin X, Harrington T, Moorman J, Zahran H. Asthma incidence among children and adults: findings from the Behavioral Risk Factor Surveillance system asthma call-back survey--United States, 2006-2008. *J Asthma.* Feb 2012;49(1):16-22.
20. Wendt JK, Symanski E, Du XL. Estimation of asthma incidence among low-income children in Texas: a novel approach using Medicaid claims data. *Am J Epidemiol.* Oct 15 2012;176(8):744-750.
21. Broms K, Norback D, Sundelin C, Eriksson M, Svardsudd K. A nationwide study of asthma incidence rate and its determinants in Swedish pre-school children. *Eur J Epidemiol.* Sep 2012;27(9):695-703.
22. Gommer AM (RIVM) PMR. Astma: prevalentie, incidentie en sterfte naar leeftijd en geslacht. *Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid.* 2011; <http://www.nationaalkompas.nl> Nationaal Kompas Volksgezondheid\Gezondheidstoestand\Ziekten en aandoeningen\Ademhalingswegen\Astma.
23. To T, Wang C, Guan J, McLimont S, Gershon AS. What is the lifetime risk of physician-diagnosed asthma in Ontario, Canada? *Am J Respir Crit Care Med.* Feb 15 2010;181(4):337-343.
24. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med.* Mar 2010;103(3):98-106.
25. Gershon AS, Guan J, Wang C, To T. Trends in asthma prevalence and incidence in Ontario, Canada, 1996-2005: a population study. *Am J Epidemiol.* Sep 15 2010;172(6):728-736.

26. Demir AU, Celikel S, Karakaya G, Kalyoncu AF. Asthma and allergic diseases in school children from 1992 to 2007 with incidence data. *J Asthma.* Dec 2010;47(10):1128-1135.

27. Punekar YS, Sheikh A. Establishing the incidence and prevalence of clinician-diagnosed allergic conditions in children and adolescents using routinely collected data from general practices. *Clin Exp Allergy.* Aug 2009;39(8):1209-1216.

28. Larsson M, Hagerhed-Engman L, Sigsgaard T, Janson S, Sundell J, Bornehag CG. Incidence rates of asthma, rhinitis and eczema symptoms and influential factors in young children in Sweden. *Acta Paediatr.* Sep 2008;97(9):1210-1215.

29. Burgess JA, Dharmage SC, Byrnes GB, et al. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. *J Allergy Clin Immunol.* Aug 2008;122(2):280-285.

30. Rudd RA, Moorman JE. Asthma incidence: data from the National Health Interview Survey, 1980-1996. *J Asthma.* Jan-Feb 2007;44(1):65-70.

31. Thomsen SF, Ulrik CS, Kyvik KO, et al. The incidence of asthma in young adults. *Chest.* Jun 2005;127(6):1928-1934.

32. Jaakkola JJ, Hwang BF, Jaakkola N. Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. *Environ Health Perspect.* Mar 2005;113(3):357-361.

33. Dik N, Tate RB, Manfreda J, Anthonisen NR. Risk of physician-diagnosed asthma in the first 6 years of life. *Chest.* Oct 2004;126(4):1147-1153.

34. Kujala V, Remes J, Latvala J, Jarvelin MR. Incidence of asthma in twelve thousand Finnish adults born in 1966. *Int J Occup Med Environ Health.* 2005;18(3):255-258.

35. Karlstad O, Nafstad P, Tverdal A, Skurtveit S, Furu K. Prevalence, incidence and persistence of anti-asthma medication use in 2- to 29-year-olds: a nationwide prescription study. *Eur J Clin Pharmacol.* Apr 2010;66(4):399-406.

36. NVK. Richtlijn astma bij kinderen *Nederlandse Vereniging voor Kindergeneeskunde*2013.

37. Simpson CR, Lee AJ, Taylor MW, Helms PJ. Changing incidence of respiratory presentations in primary care fact or artefact? *Arch Dis Child.* Sep 2005;90(9):982-983.

38. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet.* Aug 26 2006;368(9537):733-743.

39. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief.* May 2012(94):1-8.

40. Willeboordse M, van den Bersselaar DL, van de Kant KD, Muris JW, van Schayck OC, Dompeling E. Sex Differences in the Relationship between Asthma and Overweight in Dutch Children: a Survey Study. *PLoS One.* 2013;8(10):e77574.

41. Gilliland FD, Berhane K, Islam T, et al. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol.* Sep 1 2003;158(5):406-415.

42. van der Lucht F PJ. Van gezond naar beter. Volksgezondheid Toekomst Verkenning 2010. Rijksinstituut voor Volksgezondheid en Milieu RIVM, CBS, Consument en Veiligheid, EUR (BMG, MGZ), GGD Nederland, NiDI, NIGZ, NIVEL, Prismant, RUG, Rutgers Nisso, SCP, STIVORO, TNO, Trimbos, UvA, Voedingscentrum.

43. Braun-Fahrlander C, Gassner M, Grize L, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J.* Mar 2004;23(3):407-413.

44. Furu K, Skurtveit S, Langhammer A, Nafstad P. Use of anti-asthmatic medications as a proxy for prevalence of asthma in children and adolescents in Norway: a nationwide prescription database analysis. *Eur J Clin Pharmacol.* Jul 2007;63(7):693-698.

45. Mommers M, Gielkens-Sijstermans C, Swaen GM, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax.* Feb 2005;60(2):97-99.

46. Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. *BMJ.* Feb 14 2004;328(7436):386-387.

SUPPLEMENTS

Online Table 1 - Overview of all published studies (that include children) regarding asthma incidence from 2004 onwards.

Author	Year	Data / Country / Age (years)	Number (cohort/cases)	Year of study	Incidence Estimate
Radhakrishnan et al.(5)	2014	Healthcare database Canada 0-8 years	1,059,511 cohort 201,958 asthma	1992-2008: 3 cohorts: each 8 year of follow-up	8 year cumulative incidence: 19.1%
Broms et al.(16)	2012	Questionnaires Sweden 1 and 6 years	4,255	2007: 5 year (cross sectional at age 1 and 6)	6-12/1000 year
Wendt et al.(15)	2012	Claim database Texas 1-17 years	2,164,463	2005-2007	overall: 4.26 per 100 PY 5-9y: 4.33 per 100 10-14y: 3.27 per 100 PY 15-17y: 2.92per 100 PY
Winer et al.(14)	2012	Questionnaires USA Children and adults	children/cases 164,327/ 592 adults/cases: 733,437/1,033	2006-2008	Adults: 3.8/1000 at risk Children: 12.5/1000 at risk
Gommer et al.(17)	2011	5 GP networks asthma codes Netherlands All ages	97,700 cases	2007	0-14 y:9.23-13.46 per 1000 15-64y: 3.96-5.98 per 1000
Demir et al.(21)	2010	Questionnaires Turkey 7-12 years	474/56 cases	1992-2007	0.9/100 children
To et al.(18)	2010	3 Healthcare databases Canada All ages	9,041,085 cohort /533,671 cases	1991-2007	Overall: 4.3/1000PY 0-9y: 16.2/1000PY 10-19y: 5.1/1000PY 40-59y: 2.9/1000 PY
Gershon et al.(20)	2010	healthcare database Canada All ages	12 million cohort, 975,000 cases	1996 and 2000 and 2004	overall 2004; 5.1 per 1000 PY 5-9y 10.9/1000py 10-14y: 5.6/1000py 15-39y: 2.9 PER 1000py
Simpson et al. (19)	2010	GP Database United Kingdom All ages	3 million cohort 333,294 cases	2001 and 2005	5-14y: 2001: 11.4 per 1000 PY 2005: 8.4 per 1000 PY
Punekar et al.(22)	2009	GP database United Kingdom 0-18 years	3,68 million cohort in 434 GP practice	1990-2008	13.6/1000
Burgess et al.(24)	2008	Questionnaires Tasmania 7-44 years	5,729 cohort	1974 and 1986 and 2004	4.37/1000
Larsson et al.(23)	2008	Questionnaires Sweden 0-6 years	4,779 cohort	2005	5 year incidence: 4.9% per year 1/100 children/year (1%) wheezing excluded: 0.6%
Rudd et al.(25)	2007	Questionnaires USA 0-18 years	16,000 cohort	1980-1996	9.6 per 1000 at risk in 1996
Jaakkoola et al.(27)	2005	Questionnaires Sweden 1-6 years	1,916 cohort	1991 and 1997	12.5/1000 PY
Thomsen et al.(26)	2005	Questionnaires Denmark 12-41 years	1,9349 cohort	Follow up 8 years	838 cases in 2002: Male: 4.5 per 1000 PY Female: 6.4 per 1000 PY
Kujala et al.(29)	2005	Prescription database Finland 15-38 years	11,946 cohort 466 cases	23 years (birthcohort)	15-20 years: 8.6-11.5/10000 PY at risk over 23 years
Dik et al.(28)		Administrative database USA 0-6 years	170,960 cohort	2004	0-2 years: 2.9% 5-6 years: 2% 14% cumulative incidence by the age of 6

3 ASTHMA CONTROL

Chapter 3.1

Incidence and risk factors of severe asthma exacerbations in children in primary care

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Under review: Respiratory Medicine.

ABSTRACT

BACKGROUND Real-life data on the incidence rates (IR) and risk factors of severe asthma exacerbations in children are sparse. We aimed to assess IR and risk factors of severe asthma exacerbations in children in real life.

METHODS We conducted a population-based cohort study using a Dutch GP database containing complete medical records of >1 million patients. All records of children with physician-diagnosed asthma aged 5-18 years between 2000-2012 were examined for exacerbations, defined as either hospitalization, emergency department visit or need of systemic steroids for asthma. IR was expressed as number of exacerbations per person year (PY).

RESULTS We identified 14,303 asthmatic children with 35,118 PY of follow-up and 732 exacerbations. The overall IR was 2.1/100 PY (95% CI 1.9-2.2), 4.1/100 PY (3.8-4.4) for children on asthma treatment. Re-exacerbation occurred in 2% (1.3-4.3) of patients within 1 month, in 25% (20.6-28.8) within 1 year. Predictors for (frequent) exacerbations were age, gender, specialist visits, ICS prescriptions and prior exacerbations (all $p<0.05$).

CONCLUSIONS The overall IR of severe asthma exacerbations was 4/100 PY in children on asthma treatment, highest in spring and fall. 25% of the patients with an exacerbation will experience a next exacerbation within 1 year. More severe asthma is a predictor of subsequent and future exacerbations.

INTRODUCTION

Asthma continues to be a public health concern due to its high prevalence in industrialized countries. [1, 2] Poor asthma control resulting from inadequate treatment or non-response to available treatments was associated with adverse long-term outcomes. [3] Asthma can usually be well controlled by treatment as described in asthma management guidelines. [4] A severe asthma exacerbation is defined as a hospitalisation or emergency department (ED) visit because of worsening asthma, or need of systemic corticosteroids because of asthma.[5] Reported frequencies of severe asthma exacerbations in the literature vary by the definition of an exacerbation, patient population, the severity of asthma, degree of asthma control, and the data source and incidence rates (IR) are sparse. [6] Most data on IR of severe asthma exacerbation derive from adults in clinical trials. These showed IRs ranging between 0.24-0.92/PY [7-11] and in cross-sectional data, IRs that ranged between 0.23-0.41/PY. [12, 13] As far as we know, only 4 studies investigated the rate of exacerbation in children, showing IR ranging from 0.04-0.64/PY. This broad range can be explained by differences in patient selection, sample size or study duration. [7, 14, 15] Asthma related hospitalization rates in asthmatic children ranged from 4-15% per year, depending on factors like age, sex, and asthma severity. [12, 16] The CAMP study observed an exacerbation-requiring-hospitalization-rate of 2.5/100 PY in children from 5-12 years of age with mild-to-moderate asthma. [17] Surveys in real-life indicated that the true incidence of severe asthma exacerbations may be higher than in clinical trials. [6] Insight in the real life incidence of severe asthma exacerbations and characteristics of children with frequent exacerbations is important to optimize management in those who are prone to exacerbations. Hence, the purpose of the present study was to evaluate the incidence of severe asthma exacerbations and to identify characteristics of children with severe asthma exacerbations over a 12 year period in a large cohort of children with physician-diagnosed asthma.

METHODS

We conducted a retrospective population-based cohort study within the Integrated Primary Care Information (IPCI) database, a longitudinal observational dynamic database containing the complete electronic medical records of more than 450 general practitioners (GPs) in the Netherlands. In the Dutch health care system, people are registered with a single GP who has a crucial role as a gatekeeper for and receiver of information from secondary care. [18] Details of the database have been published elsewhere. [19, 20] Briefly, the database contains the complete electronic medical records of approximately 1,500,000 patients, containing anonymous longitudinal data on demographics, symptoms and diagnosis in coded and free text, referrals, laboratory findings, discharge letters, and drug prescriptions. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiological studies. [20] The scientific and ethical advisory board of the IPCI

database approved the present study. (no 07/55 2011)

Asthma cohort

The dynamic source population (n=176,516) comprised all children aged 5-18 years with a database history of at least 12 months. The study period was from the 1st of January 2000 until the 1st of January 2012.

Within this population a cohort of children with asthma was identified. Asthma cases were retrieved by an automated search on both International Classification of Primary Care asthma codes [21] (ICPC code R96) and free text that was relevant to asthma. As this automated search resulted in a high number of potential asthma cases (n=63,618), we used machine learning to facilitate the validation, as described in detail elsewhere. [22] Asthma was defined as 'definite' if diagnosed by a paediatrician. 'Probable asthma' was defined as asthma diagnosed by the GP with at least 2 additional records of asthma diagnosis or prescriptions of asthma treatment in the 1 year following the initial diagnosis. To assess the validity of this approach, the medical records of 100% of predicted definite asthma cases and 25% of predicted probable asthma cases were manually reviewed by one of the authors.

Follow-up started on the latest of the following dates: start of study period, date on which the required 1 year of follow-up was obtained, the 5th birthday, or date of asthma diagnosis (for prevalent asthma cases, who had diagnosis before start of study period asthma diagnosis was not used as criterion). All patients were followed from study entry until the earliest of the following dates: end of the study period, transferring out of GP practice or age 18 years.

Severe asthma exacerbations

Severe asthma exacerbations were defined as any of the following; hospitalization, emergency department (ED) visit, or prescription of systemic corticosteroids for at least 3 days, all because of asthma. In case there were less than 7 days between two exacerbations, these were considered as one single exacerbation.

All potential exacerbations were identified in the electronic medical records and validated by a medical doctor (ME). To identify patients with ED visit or hospitalisation for reasons of asthma, the medical file was searched for asthma-specific disease codes in combination with information on hospitalisation, hospital referral and discharge letters. Use of systemic corticosteroids was retrieved from prescriptions via an automated search on the corresponding ATC codes. The indication of use was searched for in a window of 7 days before and 7 days after the prescription date.

Covariates

Covariates included age at study start, gender, age at time of exacerbation, eczema (yes/no), allergic rhinitis (yes/no), conjunctivitis (yes/no), number of respiratory infections, number of

prescriptions for any asthma medication, number of prescriptions for inhaled corticosteroids (ICS), number of specialist visits for asthma and number of prior severe asthma exacerbations. Baseline covariates were retrieved in the 365 days prior to cohort entry.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD). We used t-test, χ^2 test or Mann-Whitney test to compare baseline characteristics of children with and without exacerbations.

Rates of exacerbations

For each child the person time (in years, PY) of follow-up was stratified by calendar year, calendar month, gender and age (on January 1st of each year). Because of the dynamic nature of the population we used PY rather than persons. The incidence rate (IR) of exacerbations was calculated by dividing the number of exacerbations by the person time.

To assess seasonal effects, we compared monthly IRs in primary school (<13 years) and high school children (≥13 years of age) using Poisson regression.

IR for re-exacerbation was assessed in the following time-windows: 0-30, 0-90, 0-180 and 0-365 days after exacerbation, and in subsequent 90-day time-windows: 0-90, 90-180, 180-270 and 270-365 days. Cumulative incidences for re-exacerbation were calculated by multiplying the IR with the time duration.

Risk factors for exacerbations

Risk factors for exacerbations were estimated using Poisson regression. For the analysis of the total cohort, follow-up of each child was divided in episodes by year of age, the first episode started at the date of asthma diagnosis, or study entry whichever came last. For analysis of episodes after a previous exacerbation, start was at the first exacerbation or at study entry (for prevalent cases), whichever was last. Subsequent episodes started at each birthday. Covariates were retrieved during the 365 days prior to the start of each episode and could change over time for the different episodes. Analysis incorporated the potential effect of age, gender and interaction between age (quadratic) and gender.

As specialist visits because of asthma might be related to number of exacerbations, number of ICS prescriptions or number of asthma treatment prescriptions, analyses for these covariates were adjusted for number of specialist visits. Poisson regression analyses was repeated in the subgroup of patients with 1 or more exacerbations before or during follow-up.

Logistic regression was used to evaluate possible predictors of frequent exacerbations by comparing episodes with 2 versus <2 exacerbations per episode) (online Figure 1). A sensitivity analysis was done using ≥3 versus <3 exacerbations per episode.

Finally, a Cox regression was performed to determine risk factors for first exacerbation. For

this analysis, only time to first severe asthma exacerbation during follow-up was considered. P<0.05 was considered statistically significant. Analyses were conducted with SPSS 20.0 for Windows (SPSSinc Chicago).

RESULTS

The source population comprised 176,516 children aged 5-18 years. After validation the asthma cohort consisted of 14,303 asthmatic children with 35,118 PY of follow-up (median 2.33 PY). Baseline characteristics of the asthma cohort and cases with exacerbation (n=481) are described in Table 1. Cases had a total of 733 exacerbations during follow-up, the median number of exacerbations per patient was 1 (range 1-18). Detailed numbers of exacerbations and follow-up time of the cases are shown in online Table 1.

Table 1 - Baseline characteristics of the total asthma cohort and of the subgroups without and with exacerbation during follow-up.

Baseline characteristics (n,%) unless stated otherwise	**Total asthma cohort**	**≥1 exacerbation during FU**	**No exacerbation during FU**	**p-value***
Patients	14,303	481	13,822	
Gender (female)	5,903 (41)	196 (41)	5,707 (41)	ns
Age at cohort entry (years) (mean, sd)	10.5 (4.1)	10.1 (3.8)	10.5 (4.1)	0.016
Specialist diagnosed asthma	3,340 (23)	243 (51)	3,097 (22)	<0.001
Follow-up (years) (mean, sd)	2.46 (1.56)	1.17 (1.25)	2.44 (1.55)	<0.001
Prior to cohort entry:				
Conjunctivitis	821 (6)	26 (5)	759 (6)	ns
Eczema	3,852 (27)	159 (33)	3,693 (27)	0.002
Allergic rhinitis	2,541 (18)	77 (16)	2,464 (18)	ns
Exacerbations ever	1,868 (13)	481 (100)	1,387 (10)	<0.001
In 12 months prior to cohort entry:				
Exacerbations	415 (3)	129 (27)	286 (2)	<0.001
Paediatrician visits for asthma (yes/no)	816 (6)	71 (15)	745 (5)	<0.001
Prescription for asthma medication	9,275 (65)	410 (85)	8,865 (64)	<0.001
Children on ICS	5,547 (39)	262 (54)	5,285 (38)	<0.001
Children on LABA	292 (2)	27 (6)	265 (2)	<0.001
Children on LTRA	357 (3)	40 (8)	317 (2)	<0.001
Children on FDC-ICS/LABA	1,481 (10)	81 (17)	1,400 (10)	<0.001
Children on SABA	7,027 (49)	345 (72)	6,682 (48)	<0.001

N = number, % = percentage, sd = standard deviation, ns = not significant

* P-value based on the χ^2 or t-test comparing characteristics of the patients with no exacerbation during follow-up with patients with ≥1 exacerbation during follow-up.

The overall incidence rate of exacerbations was 2.1 per 100 PY (95%CI 1.9-2.2) and increased to 4.1 when restricted to children who did not only had a diagnosis of asthma but had also medications. (Figure 1) In both groups the rate was highest in the youngest and oldest children. ($p<0.001$ for quadratic term with age). The IR did not change over different years in the study period ($p=0.19$). (Figure 2) Significant seasonal effects ($p=0.005$ for calendar month) were observed with peaks in March-April and September-November, with highest rates (IR=2.8/100 PY) in November and lowest (IR=1.6/100 PY) in June. (Figure 3) The seasonal effect was not significantly different between pre-school or high-school aged children. (data not shown)

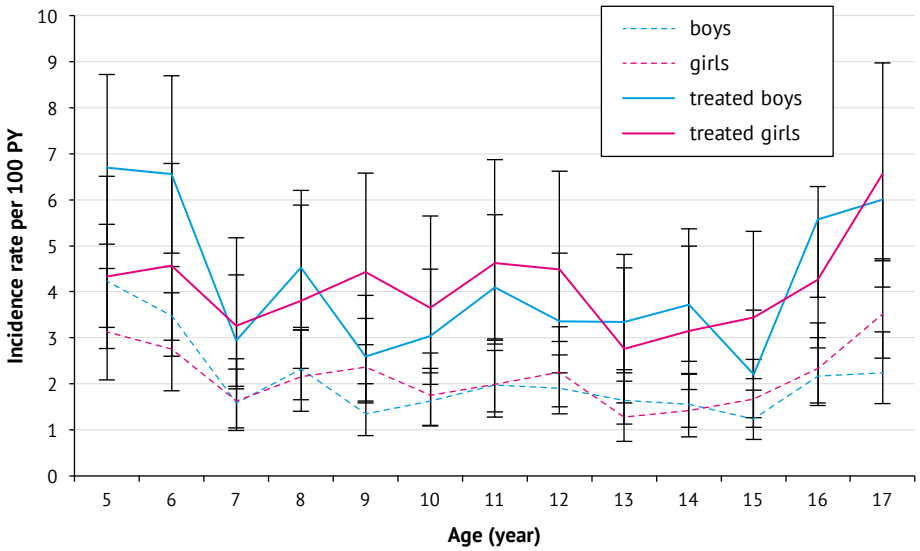


Figure 1 - IR for exacerbation by age and gender, all children and children on asthma treatment (≥1 prescription for asthma medication during follow-up).

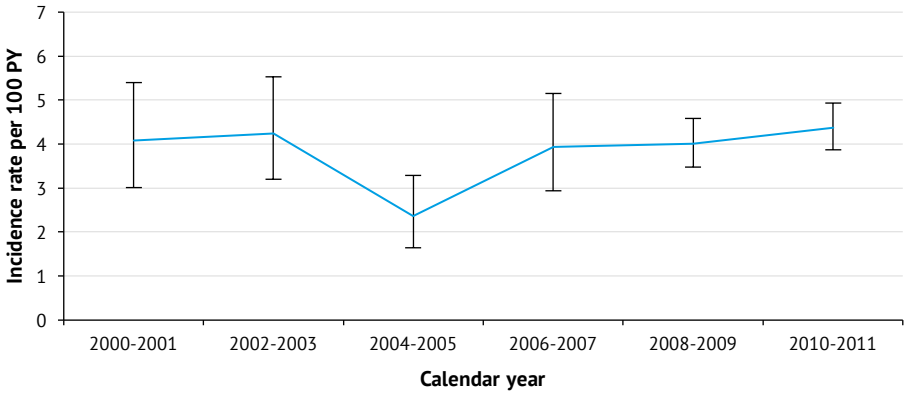


Figure 2 - Severe asthma exacerbation incidence rates for treated cohort by calendar year.

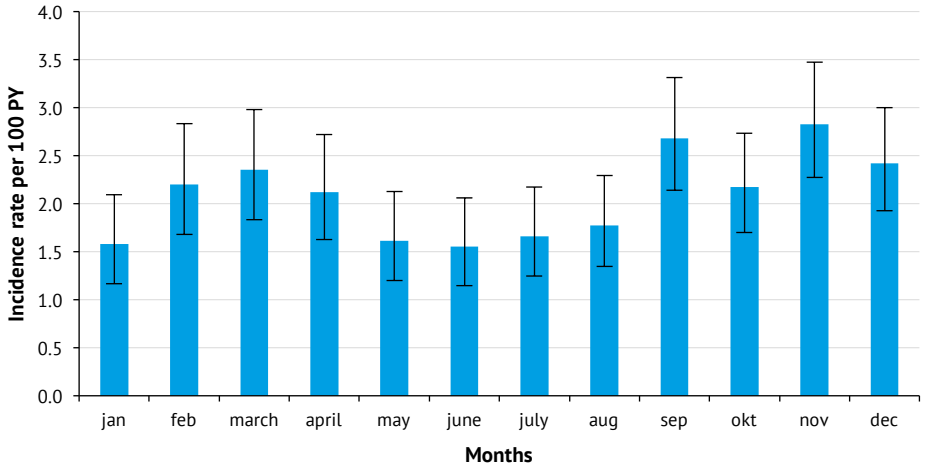


Figure 3 - Severe asthma exacerbation incidence rates by calendar month for the total asthma cohort.

Re-exacerbation

The incidence rate of re-exacerbation was constant over time. The cumulative incidence shows that within one year of a severe asthma exacerbation, 25% (95% CI 20.55-28.82) of the patients will have a new exacerbation. (Table 2)

Risk factors

Risk factors for severe asthma exacerbations estimated by Poisson regression analyses are shown in Table 3. Each Poisson model included age and age^2. As both gender and the interaction term between age and gender were not significant, we did not include these. Covariates that remained independent risk factors of exacerbations after adjustment for age were number of visits to the specialist, number of prescriptions of any asthma medication and specifically of ICS, and number of exacerbations in the previous year. No significant associations were observed with gender, eczema, allergic rhinitis, conjunctivitis, or respiratory infections. When repeating the Poisson regression analyses in only patients with exacerbations, the same risk factors as in the total cohort were found. (Table 3)

Factors that were associated with frequent exacerbation episodes estimated by logistic regression, were specialist visits, prescriptions of any asthma medication, prescriptions of ICS and exacerbations during the previous year. (Table 4)

Eczema, respiratory infections, specialist visits for asthma, exacerbations, and ICS prescriptions were significant predictors adjusted for gender and age and their interaction, when studying predictors of first exacerbation during follow-up using Cox-regression. Only the number of prior exacerbations and number of ICS prescriptions remained significant predictors after additional adjustment for number of visits to specialist. (Table 5)

Table 2 - Number of re-exacerbations, IR of asthma re-exacerbation (per PY) and cumulative incidence in percentage (%).

Time Window after exacerbation	Number of re-exacerbations	IR / PY	95% CI	Cumulative incidence (%)	95% CI
<30 days	12	0.31	0.16-0.54	2.5	1.31-4.34
<90 days	28	0.26	0.17-0.37	6.1	4.11-8.72
<180 days	53	0.26	0.20-0.34	12.1	9.39-15.44
<270 days	78	0.28	0.22-0.35	18.6	15.02-22.81
<365 days	99	0.28	0.23-0.34	24.7	20.55-28.82

Table 3 - Risk factors for severe asthma exacerbation for all episodes of the total asthma cohort and for episodes of children with ≥1 severe asthma exacerbation based on Poisson regression.

		Total asthma cohort			Children with ≥1 exacerbation ever	
Patients (n)			14,303			1,868
Episodes			46,423			5,940
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Basic model:						
Age	**0.67**	(0.48-0.92)	0.02	**0.72**	0.54-0.96	0.03
Age^2	**1.02**	(1.00-1.03)	0.02	**1.02**	1.00-1.03	0.03
Gender (male)*	1.02	(0.69-1.50)	0.94	0.86	0.59-1.26	0.44
Conjunctivitis*	1.36	0.70-2.65	0.37	1.15	0.62-2.14	0.66
Eczema*	0.76	0.42-1.36	0.35	0.68	0.39-1.18	0.17
Allergic rhinitis*	0.75	0.47-1.21	0.24	0.75	0.47-1.18	0.21
Respiratory infections (number)*	1.04	0.97-1.12	0.23	1.03	097-1.10	0.39
Specialist visits because of asthma*	**1.71**	1.39-2.10	<0.001	**1.25**	1.16-1.34	<0.001
Prior exacerbations*	**1.99**	1.40-2.83	<0.001	**1.60**	1.37-1.88	<0,001
*#	**2.39**	1.01-5.65	<0.05	**1.70**	1.27-2.27	<0.001
ICS prescriptions*	**1.25**	1.18-1.33	<0.001	**1.16**	1.09-1.22	<0.001
*#	**1.27**	1.20-1.34	<0.001	**1.17**	1.11-1.23	<0.001
Any asthma treatment*	**1.16**	1.12-1.19	<0,001	**1.10**	1.07-1.13	<0.001
*#	**1.16**	1.13-1.19	<0.001	**1.10**	1.07-1.13	<0.001

Variables in **bold** are statistically significant.

* = adjusted for age and age^2 # = additionally adjusted for specialist visits for asthma

Table 4 - Risk factors for frequent exacerbation episodes.

	<2 versus ≥2 exacerbations			<3 versus ≥3 exacerbations		
Episodes	5,801 versus 139			5,873 versus 67		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Basic model:						
Age	0.77	0.55-1.06	0.11	1.02	0.63-1.65	0.95
Age^2	1.01	1.00-1.03	0.11	1.00	0.98-1.02	0.89
Gender (female)*	1.06	0.70-1.61	0.80	1.07	0.58-1.96	0.83
Eczema*	0.65	0.30-1.39	0.27	0.90	0.37-2.16	0.81
Allergic rhinitis*	0.70	0.34-1.44	0.33	0.82	0.30-2.23	0.70
Respiratory infections*	0.99	0.89-1.10	0.81	1.05	0.93-1.20	0.41
Specialist visits because of asthma*	**1.31**	1.15-1.50	<0.001	**1.47**	1.28-1.69	<0.001
Exacerbations*	**2.11**	1.66-2.68	<0.001	**2.43**	1.84-3.23	<0.001
*#	**2.12**	1.57-2.87	<0.001	**2.31**	1.59-3.37	<0.001
ICS prescriptions *	**1.15**	1.08-1.24	<0.001	**1.21**	1.12-1.31	<0.001
*#	**1.16**	1.08-1.24	<0.001	**1.22**	1.12-1.32	<0.001
Any asthma treatment*	**1.11**	1.08-1.15	<0.001	**1.12**	1.08-1.17	<0.001
*#	**1.11**	1.08-1.15	<0.001	**1.12**	1.08-1.17	<0.001

Variables in **bold** are statistically significant.
* = adjusted for age and age^2, #= additionally adjusted for specialist visits for asthma

Table 5 - Risk factors for time until an exacerbation (Cox-regression).

	HR	**95% CI**	**p-value**
Gender (male)	**0.57**	0.33-0.96	0.04
Age	**0.97**	0.94-1.00	0.04
Age x gender	**1.06**	1.01-1.11	0.02
Variables retrieved prior to baseline:	**HR***	**95% CI**	**p-value**
Conjunctivitis *	0.94	0.63-1.39	0.75
Eczema *	**1.28**	1.06-1.55	0.01
Allergic rhinitis *	0.92	0.72-1.18	0.51
Respiratory infections within 1year prior to baseline *	**1.13**	1.05-1.21	<0.001
Specialist visits because of asthma within 1year prior to baseline *	**2.53**	2.24-2.85	<0.001
Exacerbations * within 1year prior to baseline	**4.04**	3.68-4.43	<0.001
*#	**3.65**	3.16-4.22	<0.001
ICS prescriptions within 1year prior to baseline *	**1.18**	1.14-1.23	<0.001
*#	**1.16**	1.11-1.21	<0.001

Variables in **bold** are statistically significant.
* = adjusted for age, gender and age x gender, HR = Hazard Ratio
*# = additional adjusted for specialist visits for asthma

DISCUSSION

This longitudinal population-based study covering 12 calendar years showed patterns, rates and risk factors of asthma exacerbations and demonstrated rates vary by season but are similar over the 12 calendar years, the most important risk factor/predictor of exacerbation is having a prior exacerbation. Patients with an exacerbation have 25% chance to have a subsequent exacerbation within a year.

Our incidence rates are consistent with the rates observed in the CAMP study [17] and study of Blais et al. [7] Zeiger et al. studied a cohort of children with persistent asthma and reported a threefold higher rate than we observed [15], this may be explained by their inclusion of only patients with severe asthma. The annual IR of exacerbation remained stable over time, which is in line with recent findings in a cohort of asthmatic adults, where the number of exacerbations per subject per year did not change between 2007 and 2011. [23] An earlier study showed a decrease in hospital admissions over time, however this study used data from 1990-2001. [24]

Our study confirms seasonal variability within a year with exacerbation peaks in spring and autumn. Exposure to pollen and other aeroallergens may account for the observed peaks. In September the increase was more obvious among children of kindergarten- and school age although the interaction with age was not significant. In other studies this September peak was related to the start of the school year. [6]

In the present study, the most important risk factors for severe asthma exacerbation and frequent exacerbations were prior exacerbation, which is in agreement with prior studies [9, 23, 25] Other risk factors of severe asthma exacerbation were the number of ICS prescriptions and the number of specialist visits, factors which we consider as proxy for asthma control.

The main strength of the present study is the size of the cohort with more than 14,000 children with asthma and the validation of the asthma diagnosis and asthma exacerbations which limits the risk of false positives. Selection bias was unlikely as almost all inhabitants of the Netherlands are registered with one GP and data are collected as part of routine patient care, irrespective of any research question. Still, as this is an observational study using data from electronic healthcare data, the risk of bias and/or confounding is substantial. As the IPCI database has no linkage with hospital admission- and discharge data, hospitalization and ED visits for asthma were retrieved either via disease-specific codes in combination with codes for hospitalization or via review of the discharge letters. This might underestimate exacerbations. Within the prescription file, information on the indication of prescribing of systemic corticosteroids was not always complete. If missing, we searched for asthma disease codes in a window of 7 days before or after the prescription date. Treatment information may be misclassified as the database captures prescribing data not dispensing data, patients can refill the drugs but may not actually take the drugs, and specialist initiated prescriptions may be missed if this is not captured in the records. This was probably minimal as the GP plays a gatekeeper role for patient care, implying that prescriptions as initiated by the specialist will often be continued by the GP. [26]

What is the clinical relevance of our findings?

This study showed that 4 out of 100 children on asthma treatment will have a severe asthma exacerbation when followed over 1 year. Furthermore, 25% of all children with an asthma exacerbation will have a next exacerbation within 1 year. In this study the IR of exacerbation was stable over time. The most important risk factors for exacerbations were prior exacerbations, which emphasizes the importance of close monitoring of children after a severe asthma exacerbation.

REFERENCES

1. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax.* Sep 2007;62(9):758-766.
2. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health.* Mar 19 2012;12(1):204.
3. Blakey JD, Wardlaw AJ. What is severe asthma? *Clin Exp Allergy.* May 2012;42(5):617-624.
4. Global Initiative For Asthma Global strategy for asthma management and prevention – updated 2012.: www.ginasthma.org. Accessed Last accessed 19 may 2014.
5. Reddel HK. Characterizing asthma phenotypes: predictors and outcomes at the extremes of asthma severity. *Respirology.* Aug 2009;14(6):778-780.
6. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: origin, effect, and prevention. *J Allergy Clin Immunol.* Dec 2011;128(6):1165-1174.
7. Blais L, Kettani FZ, Lemiere C, et al. Inhaled corticosteroids vs. leukotriene-receptor antagonists and asthma exacerbations in children. *Respir Med.* Jun 2011;105(6):846-855.
8. Kupczyk M, ten Brinke A, Sterk PJ, et al. Frequent exacerbators--a distinct phenotype of severe asthma. *Clin Exp Allergy.* Feb 2014;44(2):212-221.
9. Miller MK, Lee JH, Miller DP, Wenzel SE. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med.* Mar 2007;101(3):481-489.
10. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med.* Oct 15 2001;164(8 Pt 1):1392-1397.
11. Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med.* Nov 13 1997;337(20):1405-1411.
12. to T, dell S, dick P. Burden of childhood asthma: ICES investigative report. May 2004 http://www.ices.on.ca/file/ACF77.pdf. Accessed 5 may, 2015.
13. Zeiger RS, Schatz M, Li Q, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract.* Nov-Dec 2014;2(6):741-750.
14. Robroeks CM, van Vliet D, Jobsis Q, et al. Prediction of asthma exacerbations in children: results of a one-year prospective study. *Clin Exp Allergy.* May 2012;42(5):792-798.
15. Zeiger RS, Schatz M, Li Q, et al. The association of blood eosinophil counts to future asthma exacerbations in children with persistent asthma. *J Allergy Clin Immunol Pract.* Mar-Apr 2015;3(2):283-287 e284.
16. Millar WJ, Hill GB. Childhood asthma. *Health Rep.* Winter 1998;10(3):9-21 (ENG); 29-22 (FRE).
17. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med.* Oct 12 2000;343(15):1054-1063.
18. Schrijvers AJP. *Health and health care in the Netherlands. A critical Self-assessment by Dutch Experts i the Medical and Health Sciences.* Utrecht: De Tijdstroom; 1997.
19. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med.* Nov 15 1993;119(10):1036-1041.
20. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med.* Dec 1999;38(4-5):339-344.
21. Lamberts H, Wood M, Hofmans-Okkes IM. International primary care classifications: the effect of fifteen years of evolution. *FAM PRACT.* Sep 1992;9(3):330-339.
22. Afzal Z, Engelkes M, Verhamme KM, et al. Automatic generation of case-detection algorithms to identify children with asthma from large electronic health record databases. *Pharmacoepidemiol Drug Saf.* Aug 2013;22(8):826-833.
23. Schatz M, Meckley LM, Kim M, Stockwell BT, Castro M. Asthma exacerbation rates in adults are unchanged over a 5-year period despite high-intensity therapy. *J Allergy Clin Immunol Pract.* Sep-Oct 2014;2(5):570-574 e571.
24. MacFaul R. Trends in asthma hospitalisation: is this related to prevention inhaler usage? *Arch Dis Child.* Dec 2004;89(12):1158-1160.

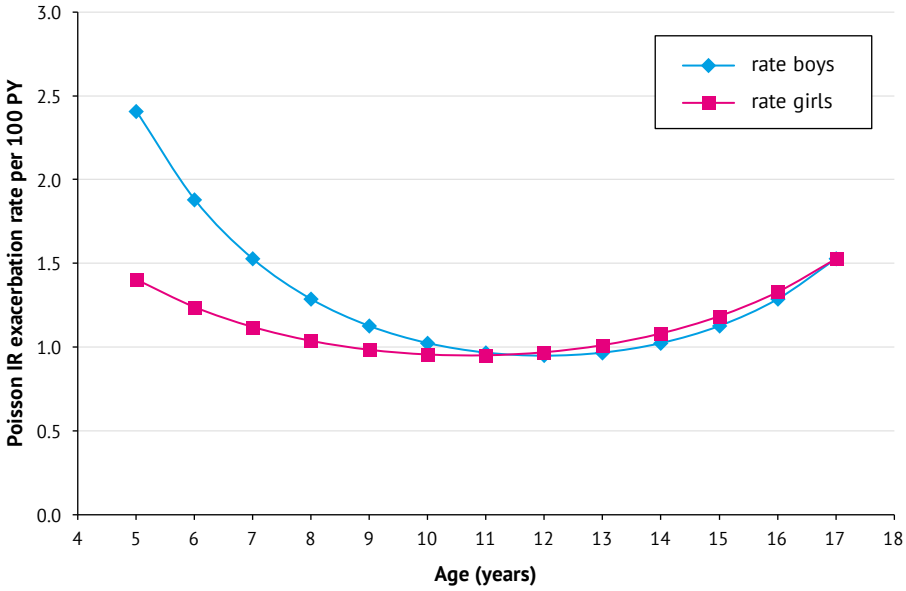
25. Al-ani S, Spigt M, Hofset P, Melbye H. Predictors of exacerbations of asthma and COPD during one year in primary care. *FAM PRACT.* Dec 2013;30(6):621-628.

26. de Vries CS, van Diepen NM, Tromp TF, de Jong-van den Berg LT. Auditing GPs' prescribing habits: cardiovascular prescribing frequently continues medication initiated by specialists. *Eur J Clin Pharmacol.* 1996;50(5):349-352.

SUPPLEMENTS

Online Table 1 - Number of exacerbations, follow-up time, cases and incidence rate per gender, per total asthma cohort and per patients with asthma treatment.

		All patients			Patients with treatment		
agecate-gory	**gender**	exacerba-tions (n)	Follow up time (days)	Incidence rate all	exacerba-tions (n)	Follow up time (days)	Incidence rate treated
5	1	55	474358	4.23	51	278318	6.69
5	2	26	303910	3.12	21	176770	4.34
6	1	49	514926	3.48	45	250565	6.56
6	2	26	344359	2.76	22	175976	4.57
7	1	24	552919	1.59	22	273825	2.93
7	2	17	380984	1.63	16	179198	3.26
8	1	37	582058	2.32	36	290184	4.53
8	2	23	390387	2.15	18	172814	3.80
9	1	22	595705	1.35	20	282048	2.59
9	2	26	400987	2.37	22	181475	4.43
10	1	27	603820	1.63	23	275847	3.05
10	2	19	397315	1.75	18	179945	3.65
11	1	34	628654	1.98	33	294192	4.10
11	2	22	404889	1.98	22	173729	4.63
12	1	34	651655	1.91	26	283131	3.35
12	2	26	421936	2.25	23	187145	4.49
13	1	30	667628	1.64	26	284234	3.34
13	2	15	426870	1.28	14	185000	2.76
14	1	28	655235	1.56	26	254869	3.73
14	2	17	439407	1.41	16	185714	3.15
15	1	21	619243	1.24	14	232191	2.20
15	2	20	437183	1.67	18	191178	3.44
16	1	34	571721	2.17	32	209881	5.57
16	2	28	437317	2.34	23	197101	4.26
17	1	32	520578	2.25	29	176360	6.01
17	2	41	426438	3.51	36	200443	6.56



Online Figure 1 - Association between age and incidence rate of exacerbations.

Chapter 3.2

Multinational multidatabase cohort study of mortality and risk factors for mortality in patients with asthma and severe asthma

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ABSTRACT

AIMS To assess the all-cause mortality, mortality following an exacerbation and risk factors for mortality in patients with asthma and severe asthma.

METHODS Asthma patients aged ≥5 years and with ≥1 year of follow-up were identified in six European electronic health record databases from the Netherlands, Italy, UK, Denmark and Spain in 2008-2013. Severe asthma was defined as use of high dose inhaled corticosteroids + controller therapy for >120 days. Exacerbations were defined as either emergency department (ED) visits, hospitalizations or systemic corticosteroid courses for asthma; severe exacerbations as ED-visits or hospitalizations. Risk factors for mortality were examined amongst adults with incident asthma only.

RESULTS The cohort consisted of 855,806 asthma patients; proportion of severe asthma ranged between 1.7-10.0% in the different databases (mean age 53.7-62.6 years; Pedianet: 9.3 years). All-cause mortality rates ranged between 6.0-12.8/1000 PY in asthma, and 16.0-33.4/1000 PY in severe asthma. In severe asthma, mortality in the 1st week following an exacerbation was 26.3-109.5/1000 PY compared to 57.9-239.4/1000 PY following severe exacerbations. Risk factors for mortality were age, comorbidity (COPD, diabetes, cerebrovascular disease or cancer), smoking and previous exacerbation. These risk factors were consistent in most databases.

CONCLUSIONS Mortality following an exacerbation is high, especially in patients with severe asthma, and in the first week following a severe exacerbation (up to 11%). Adult asthma patients with prior exacerbations, smoking, increasing age or comorbidity have an increased risk of mortality. Prevention of asthma exacerbations as well as smoking cessation are important to reduce associated mortality.

INTRODUCTION

Asthma is a highly prevalent and chronic respiratory condition affecting 300 million people worldwide. [1] Asthma is a major cause of disability, health resource utilization, and significantly reduces the patient's quality of life. [2] There is no cure for asthma, but it can generally be controlled through treatment as described by existing asthma management guidelines. [3] However, real world surveys among asthmatic patients indicate that the incidence of exacerbations is much higher than observed in clinical trials. [4] Asthma exacerbations are associated with increased healthcare costs, reductions in health related quality of life, and increased mortality. [5] In some countries, asthma related mortality has decreased over the last decade. [6, 7] Still, on a global scale it is estimated that asthma accounts for about 250,000 deaths per year. [1] GINA published in 2004 mortality estimates of 5.2 per 100,000 asthma patients aged 5-34 years in the United States, with wide variations across Europe (e.g. 1.6 per 100,000 in Finland and 9.3 per 100,000 in Denmark). [8]

There is growing evidence that patients with the asthma-COPD overlap syndrome (ACOS) have an increased risk of asthma exacerbations and hospitalization, and are at increased risk of mortality. [9,10] Commonly, this patient group is excluded from clinical trials, and therefore observational research is essential to study underlying COPD as risk factor for mortality in patients with asthma.

In this study we aimed to estimate all-cause and asthma related mortality, risk factors (including concurrent COPD) for mortality, and mortality following exacerbations, in patients with asthma and severe asthma, using one protocol and harmonized methods, across five different European countries.

METHODS

Design and setting

A retrospective cohort study was conducted using data from six European electronic health care databases: the Integrated Primary Care Information Project (IPCI) from the Netherlands, the Health Search Database (HSD) and Pedianet from Italy, Clinical Practice Research Datalink (CPRD) from the UK, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain and the Aarhus University Prescription Database (AUH) from Denmark. Detailed descriptions of these databases have been published before [11-16] and are available in the online supplement. All databases comprise detailed information on drug prescriptions or dispensing, outpatient diagnoses and hospitalizations, comorbidity and measurement data (e.g. lab results, spirometry, BMI). These databases contain information on mortality either through linkage with hospital data and death registries (AUH, SIDIAP and CPRD) or via information from discharge letters via GP (HSD, Pedianet and IPCI) or death records

registered by the GP. (CPRD, IPCI, Pedianet and SIDIAP) All participating databases comply with EU guidelines on the use of medical data for research and are registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) database. [17]

Cohort definition

A cohort of patients with asthma was defined in each database. To enter the cohort, patients needed to be at least 5 years old, with a minimum of 1-year database history and diagnose code of asthma. Asthma was defined as the presence of at least one asthma specific disease code (see online supplement) in combination with prescriptions/dispensing of asthma drugs within 3 months before or after an asthma disease code. Asthma drugs consisted of the following: inhaled corticosteroids (ICS), short-acting β_2-agonists (SABA), long-acting β_2-agonists (LABA), fixed combination of ICS+LABA, leukotriene modifier (LTRA), short-acting muscarinic antagonist (SAMA), fixed combination of SABA+SAMA, xanthines, systemic corticosteroids for the treatment of asthma and anti-IgE treatment. Information on drug use was retrieved by an ATC specific search from the drug prescription or drug dispensing records. Based on the asthma index date (first date of an asthma disease code at or after study entry), patients were categorized into prevalent or incident asthma.

Within the cohort of patients with asthma, a sub-cohort of patients with severe asthma was nested. According to international guidelines, severe asthma was defined as asthma which requires treatment with high dose ICS plus a second controller (and/or systemic corticosteroids). [3,18] Only those who fulfilled these criteria for a consecutive period of at least 120 days were included. For Pedianet, children were considered as having severe asthma based on criteria above, but without the extra requirement of use of at least 120 days, because only 1 patient fulfilled this extra requirement. The study period started at the first of January 2008 and ended 31st December 2013.

Follow-up

For each patient, cohort follow-up started from the maximum date of the following; start of study period, diagnosis of (severe) asthma, age of 5 years or after reaching a minimum of 365 days of database history. Further, to account for immortal time bias, follow-up in the severe asthma cohort started on day 120 of consecutive use of high dose ICS with additional controller therapy. [19] Follow-up ended when leaving the database, death or end of the study period whichever came first.

For the analysis of mortality following asthma exacerbations, follow-up ran from the date of an asthma exacerbation until the end of the respective time windows following an asthma exacerbation (7, 30, 90, 180 or 365 days), a next exacerbation, end of study period, or death, whichever date came first.

Outcome

In all databases, death and date of death are well documented. Information on cause of death was only systematically available for IPCI, AUH (available up to 2011) and Pedianet. Where available, cause of death was classified into "asthma related" or "non-asthma related death".

Covariates

"Asthma exacerbation" was defined as any of the following: acute use of systemic corticosteroids, ED visit or hospitalisation for an asthma exacerbation. [20] "Severe asthma exacerbations" were defined as ED visits or hospitalization for an asthma exacerbation.

The indication of corticosteroid use was retrieved from the prescription/description file or through an automated search on asthma or asthma exacerbation disease codes in a 7-day window before or after the prescription date. Continuous use of systemic corticosteroids, defined as consecutive use of 30 days or more, was not considered as an asthma exacerbation. If the time between 2 prescriptions of systemic corticosteroids was less than 2 weeks, this was considered as one asthma exacerbation.

In addition, we investigated the prevalence of the following comorbidities: atopy (allergic rhinitis, atopic eczema/dermatitis, chronic rhinosinusitis, or nasal polyposis), COPD; gastro-oesophageal reflux disease (GERD), depression and anxiety, overweight and obesity, diabetes mellitus, cardio- and cerebrovascular diseases and cancer. Smoking status was classified as "current smoker", "past smoker", "non-smoker" or "smoking status unknown". Comorbidities and smoking status were assessed at the start of follow-up (using information in the entire period prior, even before cohort entry) and at each exacerbation.

Analysis

Categorical data were presented in counts and proportions. For continuous data, the number of observations (n), mean, and standard deviation were presented.

The overall mortality rate was calculated by dividing the number of deaths by the respective number of person-years of follow-up. Mortality rates were calculated by gender and age category (5 to 12; 12≤18, 18≤25 and subsequent 10-year age categories). To account for differences in age distribution between databases, direct standardization was applied using the distribution of the largest population (CPRD) as the reference population. [21]

Mortality rates were calculated in predefined follow-up time windows (7, 14, 30, 90, and 365 days) following an asthma exacerbation.

Mortality rate ratios with 95% CI were obtained using Poisson regression comparing ACOS patients to patients without ACOS adjusted for age, gender, and smoking status. ACOS was defined as patients with asthma who also had a diagnosis of COPD (in their medical history or during follow-up). To elucidate on the potential confounding effect of COPD on mortality, posterior analysis were stratified by COPD status.

A meta-analysis was performed on the overall mortality rates estimated in the databases. Heterogeneity was quantified by the I^2 statistics. If I^2 was greater than 50% the random effect estimates were presented as the meta-analysis result and no pooling of data was done. If I^2 was less than or equal to 50%, then the fixed effect estimate was used for pooling and presented as the meta-analysis result. [22]

Furthermore, Kaplan-Meier curves for cumulative survival probability in the period after asthma exacerbation were calculated.

Risk factors of all-cause mortality in adult incident asthma patients, ie. without asthma diagnosis in their medical history, were assessed by means of univariate and multivariate Cox regression analyses, including all of the following covariates: age at asthma diagnosis, gender, smoking status, medical history (COPD, cancer, cardiovascular disease, cerebrovascular disease or diabetes mellitus) and two time-dependent covariates; time since previous exacerbation (classified in up to 30 days, 31 to 90 days, 91 to 365 days and more than 365 days) and asthma severity. Pooled results for the hazard ratios for time since exacerbation were obtained using multivariate meta-analysis. [23]

RESULTS

The source population comprised 16,259,085 individuals during the study period and the asthma cohort size was 855,806 patients. Within the total asthma cohort, 66,148 patients (7.7%) with severe asthma were identified. The percentage of severe asthma was similar across databases (6.0-8.7%) except for SIDIAP (1.7%) and Pedianet (1.7%). Baseline characteristics of the asthma cohorts are further described in Table 1, Table 2 and Online Table 1. Briefly, the mean age at start of follow-up was 7.2 years for Pedianet (a paediatric database), and ranged between 33.2-46.6 years for the other databases. In all databases, apart from Pedianet (36.1% females) and AUH (49.3% females), there was a preponderance of females (53.5-56.8%). This trend became stronger in patients with severe asthma (56.6-65.6% females). The prevalence of atopy (consisting of atopic eczema and/or allergic rhinitis) ranged between 11.3-36.7% and was not different in patients with severe asthma. The prevalence of chronic rhinosinusitis and nasal polyposis in patients with asthma ranged between 0.2%-8.6% and 0.4-2.3%, respectively, and increased in patients with severe asthma (0.7-13.0% and 0.8-5.5%, respectively). The prevalence of concurrent COPD ranged between 2.4-15.4% in all asthma patients and was higher in the subgroup of patients with severe asthma (11.2-36.5%).

In total, 24,537 deaths were observed during follow-up. Patient characteristics of patients who died are further described per database in Table 3. Asthma related death was reported in 2.4% of deaths in AUH, 0.4% in IPCI, 4.2% in SIDIAP, and 1.7% in CPRD. It should be noted that cause of death was not available in a substantial proportion in SIDIAP (57.9%) and CPRD (79.2%).

Table 1 - Baseline characteristics of asthma cohorts.

	IPCI n=116,281 (%)	AUH n=30,292 (%)	HSD n=48,463 (%)	CPRD n=551,165 (%)	SIDIAP n=101,341 (%)	PEDIANET n=8,264 (%)
Asthma						
- Prevalent	93,508 (80.4)	23,818 (78.6)	27,961 (57.7)	444,561 (80.7)	44,798 (44.2)	6,372 (77.1)
- Incident	22,773 (19.6)	6,474 (21.4)	20,502 (42.3)	106,604 (19.3)	56,543 (55.8)	1,892 (22.9)
Gender						
- Female	63,899 (54.9)	14,944 (49.3)	27,869 (57.5)	295,057 (53.5)	57,601 (56.8)	2,980 (36.1)
- Male	52,382 (45.0)	15,348 (50.7)	20,594 (42.5)	256,108 (46.5)	43,740 (43.2)	5,284 (63.9)
Age (mean, sd)	37.6 (22.9)	33.5 (25.0)	46.6 (20.2)	38.9 (22.7)	36.8 (24.4)	7.2 (2.5)
Smoking						
- Current*	14,567 (27.7)	160 (25.4)	6,784 (26.4)	97,047 (19.9)	13,856 (23.4)	
- Never*	24,981 (47.6)	262 (41.5)	14,451 (56.3)	243,782 (50.1)	37,459 (63.4)	
- Past*	12,975 (24.7)	209 (33.1)	4,447 (17.3)	146,716 (30.1)	7,781 (13.2)	
- Unknown	63,758 (54.8)	29,661 (97.9)	22,781 (47.0)	63,620 (11.5)	42,245 (41.7)	8,264 (100)
Atopy	36,682 (31.5)	3,441 (11.4)	8,202 (16.9)	202,272 (36.7)	21,741 (21.4)	1,990 (24.1)
Chronic rhinosinusitis	2,752 (2.4)	51 (0.2)	888 (1.8)	47,420 (8.6)	449 (0.4)	Nap
Nasal polyposis	421 (0.4)	253 (0.8)	504 (1.0)	12,675 (2.3)	996 (1.0)	Nap
COPD	11,121 (9.6)	4,126 (13.6)	7,476 (15.4)	33,010 (6.0)	2,433 (2.4)	Nap
GERD	6,490 (5.6)	837 (2.8)	5,561 (11.5)	42,980 (7.8)	1,681 (1.7)	146 (1.8)
Anxiety – depression	11,641 (10.0)	563 (1.9)	9,232 (19.0)	120,667 (21.9)	16,935 (16.7)	Nap
Diabetes mellitus	6,922 (5.9)	1,067 (3.5)	3,158 (6.5)	25,042 (4.5)	5,356 (5.3)	4 (0.0)
Cardiovascular disease	5,081 (4.4)	1,713 (5.7)	852 (1.8)	24,543 (4.5)	1,235 (1.2)	Nap
Cerebrovascular disease	2,554 (2.2)	801 (2.6)	1,242 (2.6)	10,311 (1.9)	1,237 (1.2)	Nap
Cancer	5,343 (4.6)	1,033 (3.4)	1,029 (2.1)	16,856 (3.1)	2,706 (2.7)	3 (0.0)
Obesity	25,977 (22.3)	1,938 (6.4)	9,662 (19.9)	279,620 (50.7)	48,827 (48.2)	3,977 (48.1)

* Percentage of patients for whom smoking is available, Nap = not applicable

Table 2 - Baseline characteristics of severe asthma cohorts.

	IPCI n=10,368 (%)	AUH n=3,020 (%)	HSD n=2,897 (%)	CPRD n=48,115 (%)	SIDIAP n=1,747 (%)	PEDIANET n=137 (%)
Asthma						
- Prevalent	9,607 (92.7)	2,691 (89,1)	2,681 (92.5)	45,486 (94.5)	1,287 (73.7)	131 (95.6)
- Incident	761 (7.3)	329 (10,9)	216 (7.5)	2,629 (5.5)	460 (26.3)	6 (4.4)
Gender						
- Female	6,147 (59.3)	1,735 (57.4)	1,641 (56.6)	28,280 (58.8)	1,146 (65.6)	34 (24.8)
- Male	4,221 (40.7)	1,285 (42.5)	1,256 (43.4)	19,835 (41.2)	601 (34.4)	103 (75.2)
Age (mean, sd)	53.7 (19.4)	53.9 (21.1)	58.2 (17.9)	58.7 (19.1)	62.6 (21.1)	9.3 (2.6)
Smoking						
- Current*	2,087 (28.5)	16 (22.8)	371 (22.1)	10,297 (21.6)	145 (10.3)	
- Never*	2,968 (42.9)	12 (17.1)	868 (51.7)	15,008 (31.5)	1,034 (73.1)	
- Past*	2,274 (28.6)	42 (60.0)	441 (26.2)	22,349 (46.9)	235 (16.6)	
- Unknown	3,039 (34.4)	2,950 (97.7)	1,217 (42.0)	461 (1.0)	333 (19.1)	137 (100)
Atopy	3,059 (30.0)	310 (10.3)	383 (13.2)	16,399 (34.1)	237 (13.6)	54 (39.4)
Chronic rhinosinusitis	397 (3.4)	20 (0.7)	78 (2.7)	6,238 (13.0)	14 (0.8)	Nap
Nasal polyposis	86 (0.6)	68 (2.2)	119 (4.1)	2,632 (5.5)	50 (2.9)	Nap
COPD	3,413 (23.7)	1,102 (36.5)	968 (33.4)	15,152 (31.5)	195 (11.2)	Nap
GERD	989 (8.8)	145 (4.8)	502 (17.3)	7,350 (15.3)	67 (3.8)	3 (2.2)
Anxiety – depression	1,585 (14.7)	94 (3.1)	700 (24.2)	16,806 (34.9)	386 (22.1)	Nap
Diabetes mellitus	1,286 (10.7)	217 (7.2)	327 (11.3)	5,195 (10.8)	268 (15.3)	Nap
Cardiovascular disease	1,000 (8.1)	382 (12.6)	80 (2.8)	6,067 (12.6)	78 (4.5)	Nap
Cerebrovascular disease	464 (3.7)	176 (5.8)	122 (4.2)	2,510 (5.2)	53 (3.0)	Nap
Cancer	848 (7.3)	226 (7.5)	137 (4.7)	3,346 (6.9)	136 (7.8)	Nap
Obesity	4,081 (35.0)	279 (9.2)	700 (24.2)	34,470 (71.6)	1,243 (71.1)	77 (56.2)

* Percentage of patients for whom smoking is available, Nap = not applicable

Table 3 - Characteristics of asthma patients who died.

	IPCI Number of deaths n (%)		AUH Number of deaths n (%)		HSD Number of deaths n (%)		CPRD Number of deaths n (%)		SIDIAP Number of deaths n (%)	
	asthma n=1,851 (%)	severe asthma n=451 (%)	asthma n=1,819 (%)	severe asthma n=469 (%)	asthma n=1,422 (%)	severe asthma n=192 (%)	asthma n=16,703 (%)	severe asthma n=4,874 (%)	asthma n=2,672 (%)	severe asthma n=156 (%)
Cause of Death										
- Asthma related*	6 (0.4)	4 (1.0)	29 (2.4)	7 (2.1)			58 (1.7)	32 (3.3)	47 (4.2)	3 (4.6)
- Other*	1,676 (99.6)	407 (99.0)	1,196 (97.6)	318 (97.8)			3412 (98.3)	939 (96.7)	1,077 (95.8)	62 (95.4)
- Unknown	169 (9.1)	40 (8.9)	594 (32.7)	144 (30.7)	1,422 (100.0)	192 (100.0)	13,233 (79.2)	3,903 (80.1)	1,548 (57.9)	91 (58.3)
Gender										
- Female	1,039 (56.1)	239 (53.0)	1,034 (56.8)	251 (53.5)	803 (56.5)	92 (47.9)	9,426 (56.4)	2,716 (55.7)	1,900 (71.1)	99 (63.5)
- Male	812 (43.9)	212 (47.0)	785 (43.2)	218 (46.5)	619 (43.5)	100 (52.1)	7,277 (43.6)	2,158 (44.3)	772 (28.9)	57 (36.5)
Smoking										
- Current*	395 (30.5)	126 (37.2)	85 (24.6)	15 (16.3)	153 (14.9)	24 (18.6)	2837 (17.0)	840 (17.24)	188 (7.9)	3 (2.1)
- Never*	423 (32.7)	85 (25.1)	64 (18.5)	12 (13.0)	556 (54.3)	49 (38.0)	4,284 (25.7)	936 (19.2)	1,880 (78.8)	119 (82.1)
- Past*	475 (36.7)	128 (37.7)	197 (56.9)	65 (70.6)	315 (30.8)	56 (43.4)	9,557 (57.3)	3,097 (63.5)	319 (13.4)	23 (15.9)
- unknown	558 (30.1)	112 (24.8)	1,473 (81.0)	377 (80.4)	398 (28.0)	63 (32.8)	25 (0.1)	1 (0.0)	285 (10.7)	11 (7.0)
Atopy	357 (19.3)	100 (22.2)	55 (3.0)	18 (3.8)	113 (7.8)	13 (6.8)	4,230 (25.3)	1,266 (26.0)	170 (6.4)	9 (5.8)
Chronic rhinosinusitis	48 (2.6)	13 (2.9)	4 (0.2)	3 (0.6)	27 (1.9)	1 (0.5)	2,086 (12.5)	672 (13.8)	10 (0.4)	1 (0.6)
Nasal polyposis	7 (0.4)	3 (0.7)	16 (0.9)	8 (1.7)	12 (0.8)	3 (1.6)	704 (4.2)	246 (5.0)	20 (0.7)	2 (1.3)
COPD	956 (51.6)	345 (76.5)	1,321 (72.6)	394 (84.0)	516 (36.3)	109 (56.8)	7,317 (43.8)	3,389 (69.5)	362 (13.5)	30 (19.2)
GERD	230 (12.4)	78 (17.3)	132 (7.3)	33 (7.0)	307 (21.6)	49 (25.5)	3,125 (18.7)	954 (19.6)	81 (3.0)	3 (1.9)
Anxiety – depression	342 (18.5)	106 (23.5)	270 (14.8)	60 (12.8)	486 (34.2)	69 (36.9)	5,971 (35.8)	1,823 (37.4)	794 (29.7)	36 (23.1)
Diabetes mellitus	494 (26.7)	128 (28.4)	355 (19.5)	88 (18.8)	357 (25.1)	60 (31.3)	3,479 (20.8)	991 (20.3)	752 (28.1)	54 (34.6)
Cardiovascular disease	517 (27.9)	138 (30.6)	591 (32.5)	165 (35.2)	122 (8.6)	24 (12.5)	4,963 (29.7)	1,506 (30.9)	279 (10.4)	18 (11.5)
Cerebrovascular disease	384 (20.7)	91 (20.2)	396 (21.8)	93 (19.8)	241 (16.9)	30 (15.6)	2,775 (16.6)	761 (15.6)	350 (13.1)	17 (10.9)
Cancer	700 (37.8)	157 (34.8)	608 (33.4)	152 (32.4)	365 (25.7)	53 (27.6)	5,606 (33.6)	1,443 (29.6)	734 (27.5)	33 (21.1)
Obesity	700 (37.8)	183 (40.6)	359 (19.7)	89 (19.0)	693 (48.7)	91 (47.4)	11,620 (69.6)	3,405 (69.9)	1,874 (70.1)	116 (74.4)

All characteristics measured at moment of death.

* Percentage of patients for whom cause of death/smoking is available

The overall age standardized mortality rates were 6.1/1000 PY in IPCI, 4.8/1000 PY in HSD, 6.3/1000 PY in SIDIAP, 7.8/1000 PY in CPRD and 13.2/1000 PY in AUH. No deaths were observed in Pedianet. (Table 4) The mortality rates were higher in patients with severe asthma (Table 5) and with increasing age. (online Table 2 and Figure 1). Heterogeneity of the mortality rates was substantial (I^2=97.5), which makes pooling of these rates meaningless. (online Figure 1)

The mortality rate in the first 7 days following any asthma exacerbation ranged between 14.6-88.4/1000 PY across databases. Mortality rates were highest in the first 7 days following severe asthma exacerbation and decreased thereafter. (Table 6 and Figure 2) Mortality rates were higher in patients with more severe asthma; however, this trend was less clear in SIDIAP and HSD.

From these mortality rates the cumulative incidences of death were calculated. (Table 6) Within 7 days following an asthma exacerbation, 0.0-0.2% of asthma patients and 0.1-0.2% of severe asthma patients died and this cumulative incidence increased to 0.1-0.3% in all asthma and 0.1-0.5% in severe asthma patients when only considering severe asthma exacerbations. Within 1 year following an asthma exacerbation, 0.9-3.1% of asthma patients and 1.7-4.9% of severe asthma patients had died and here again the cumulative incidence increased when considering severe asthma exacerbations only.

Mortality rates during cohort time in asthma patients were 1-3 fold higher in asthma patients with concomitant COPD compared to without COPD, irrespective of asthma severity. (Figure 3 and online Table 3). Mortality rates following an asthma exacerbations were also higher in ACOS patients; within 1 year following an asthma exacerbation, 1.0-5.0% of patients without COPD died, compared to 2.2-8.7% in ACOS patients. (online Table 4)

Risk factors for mortality

In the incident adult asthma patients (n=166,618) a previous asthma exacerbation was a risk factor for mortality in almost all databases, except for the AUH database. (online Table 5) In the multivariate analysis, age, previous exacerbations, smoking status, history of cancer, history of diabetes, and history of cerebrovascular disease were associated with exacerbations in most databases. (Table 7) History of COPD increased the risk of mortality up to 76% in IPCI, AUH, CPRD and SIDIAP. Current smoking increased the risk with 59-153% in IPCI, HSD, CPRD and SIDIAP. It should be noted that the smoking status of patients was often unknown.

Hazard ratios for the different periods after exacerbation are shown both per database and pooled. (Figure 4) The pooled HR_{adj} of dying for time since exacerbation decreased from 1.93 (95% CI 1.47-2.53) in the first 30 days after an exacerbation to 1.35 (95% CI 1.21-1.51) after 1 year.

Table 4 - Age standardized mortality rate (distribution of CPRD as reference population) (MR = number of deaths/1000 PY).

	Asthma		Severe asthma	
	Overall MR	Overall MR - Standardized	Overall MR	Overall MR - Standardized
IPCI	6.02	6.15	17.50	19.39
AUH	12.78	13.23	33.42	36.16
HSD	6.73	4.84	16.02	15.98
CPRD	7.76	7.76	27.49	27.49
SIDIAP	7.15	6.33	26.29	19.20

severe asthma = defined as asthma which requires treatment with high dose ICS and controller therapy for a consecutive period of at least 120 days

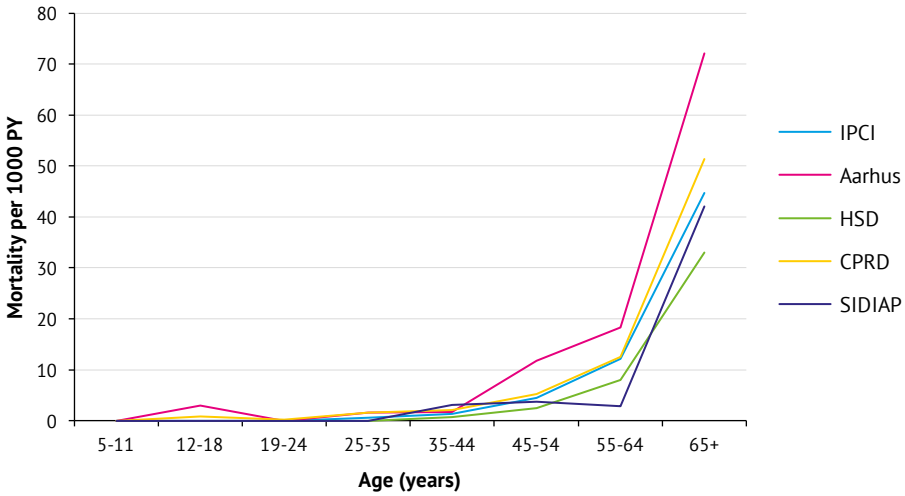


Figure 1 - Mortality rates by age category in patients with severe asthma.

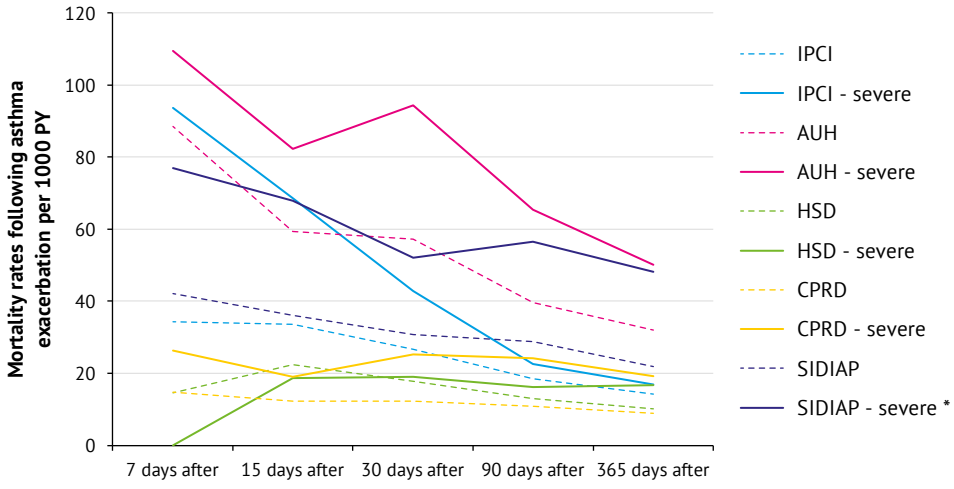


Figure 2 - Mortality rates following asthma exacerbation in the total asthma cohort and the severe asthma cohort.
* = severe definition without criterion of consecutive 120 days of high dose ICS

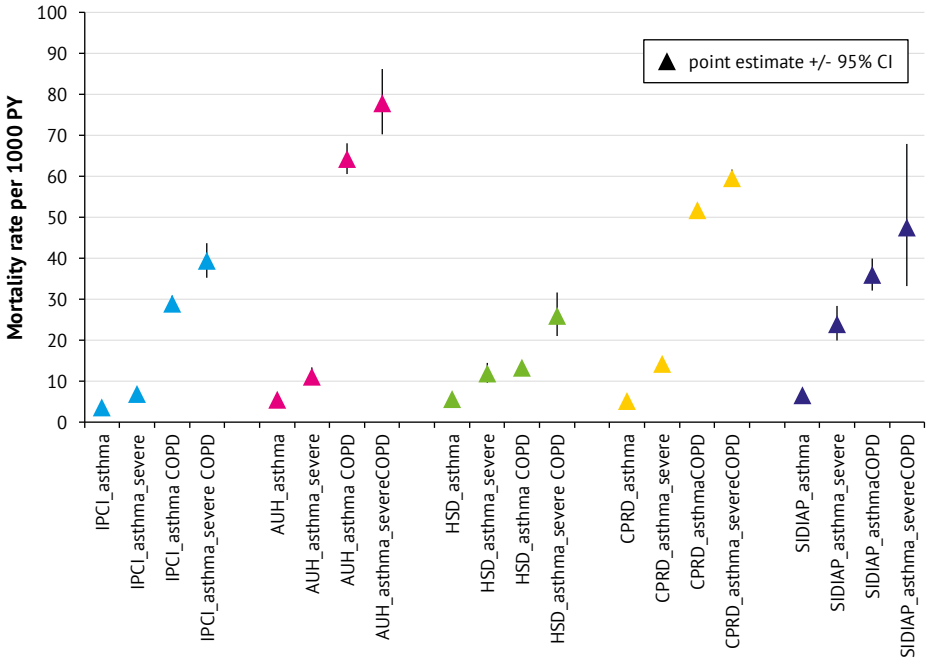


Figure 3 - Mortality rates in the total asthma cohort and the severe asthma cohort, stratified by history of COPD per database.

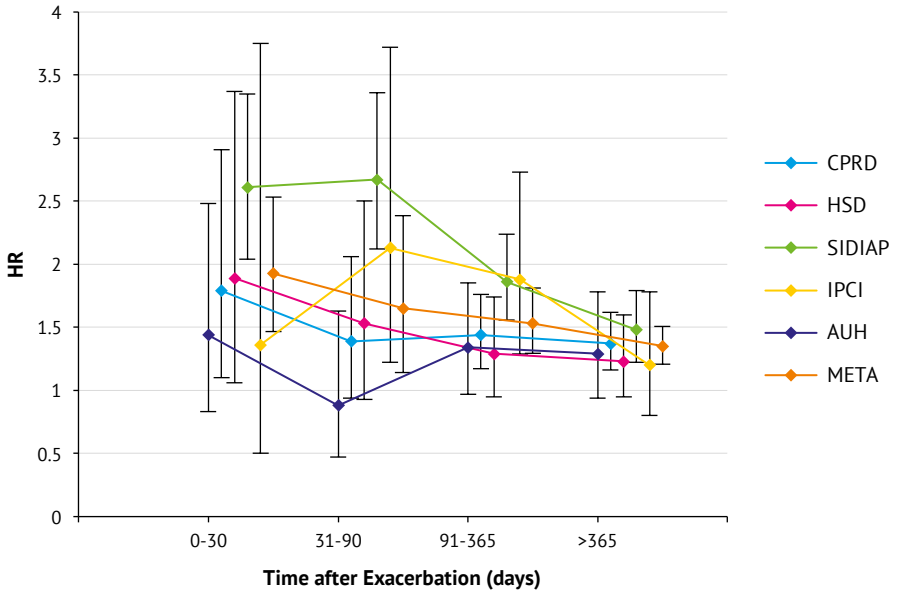


Figure 4 - Hazard ratios of mortality in incident adult asthmatic patients for time periods after exacerbation (0-30 days, 31-90, 91-365, >365 days after exacerbation).

* adjusted for gender, age at start, asthma severity, history of COPD, history of cancer, history of cardiovascular disease, history of cerebrovascular disease, history of diabetes mellitus and smoking.

Table 5 - Overall mortality rates (number of patients who died/1000 PY).

	Total asthma cohort			Severe asthma cohort		
	number of deaths	Mortality rate	95% CI	number of deaths	Mortality rate	95% CI
IPCI						
Overall	1,851	6.02	5.75-6.30	451	17.50	15.95-19.19
Female	1,039	6.18	5.81-6.56	239	15.73	13.85-17.85
Male	812	5.83	5.44-6.25	212	20.04	17.52-22.93
AUH						
Overall	1,819	12.78	12.20-13.38	469	33.42	30.53-36.59
Female	1,034	14.92	14.04-15.86	251	31.09	27.47-35.18
Male	785	10.74	10.01-11.52	218	36.59	32.04-41.78
HSD						
Overall	1,422	6.73	6.39-7.09	192	16.02	13.91-18.46
Female	803	6.70	6.25-7.18	92	13.62	11.10-16.71
Male	619	6.78	6.27-7.34	100	19.12	15.72-23.26
CPRD						
Overall	16,773	7.76	7.64-7.87	4,889	27.49	26.73-28.27
Female	9,458	8.22	8.06-8.39	2,724	26.00	25.04-26.99
Male	7,315	7.23	7.07-7.40	2,165	29.63	28.41-30.91
SIDIAP						
Overall	2,672	7.15	6.89-7.43	156	26.29	22.47-30.76
Female	1,900	8.89	8.49-9.29	99	25.27	20.75-30.77
Male	772	4.84	4.51-5.19	57	28.29	21.82-36.67

* 95% CI = 95% confidence interval

Table 6 - Mortality rate and cumulative incidence of mortality following asthma exacerbation for total asthma cohort and severe asthma cohort.

	IPCI			AUH			HSD			CPRD			SIDIAP		
ALL ASTHMA	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI	MR	CumInc	95% CI
mortality following asthma exacerbation (all exacerbations)															
< 7 days	34.37	0.1%	0.0-0.1	88.45	0.2%	0.1-0.3	14.62	0.0%	0.0-0.0	14.78	0.0%	0-0	42.06	0.1%	0.1-0.1
< 15 days	33.57	0.1%	0.1-0.2	59.29	0.2%	0.2-0.3	22.47	0.1%	0.1-0.1	12.19	0.1%	0-0.1	36.16	0.1%	0.1-0.2
< 30 days	26.69	0.2%	0.2-0.3	57.30	0.5%	0.4-0.6	17.82	0.1%	0.1-0.2	12.29	0.1%	0.1-0.1	30.74	0.3%	0.2-0.3
< 90 days	18.55	0.5%	0.4-0.6	39.67	1.0%	0.8-1.2	12.98	0.3%	0.3-0.4	10.82	0.3%	0.2-0.3	28.73	0.7%	0.6-0.8
< 365 days	14.25	1.4%	1.2-1.6	31.96	3.1%	2.8-3.5	10.09	1.0%	0.9-1.2	8.90	0.9%	0.8-1	21.78	2.2%	2.0-2.3
mortality following emergency department visit/hospitalisation															
< 7 days	61.62	0.1%	0.0-0.4	84.17	0.2%	0.1-0.4	0			46.64	0.1%	0.1-0.1	167.21	0.3%	0.2-0.5
< 15 days	38.75	0.2%	0.1-0.4	63.42	0.3%	0.1-0.5	0			34.89	0.1%	0.1-0.2	136.13	0.6%	0.4-0.8
< 30 days	34.82	0.3%	0.1-0.6	52.63	0.4%	0.3-0.7	0			29.85	0.2%	0.2-0.3	99.71	0.8%	0.6-1.0
< 90 days	21.52	0.5%	0.3-0.9	41.67	1.0%	0.7-1.5	0			21.81	0.5%	0.4-0.7	73.33	1.8%	1.5-2.1
< 365 days	11.31	1.1%	0.7-1.7	28.42	2.8%	2.2-3.5	0			15.48	1.5%	1.3-1.8	49.48	4.8%	4.3-5.4
SEVERE ASTHMA															
mortality following asthma exacerbation (all exacerbations)															
< 7 days	93.69	0.2%	0.1-0.3	109.47	0.2%	0.1-0.5	0			26.26	0.1%	0-0.1	42.89	0.1%	0.0-0.3
< 15 days	68.62	0.3%	0.2-0.5	82.20	0.3%	0.2-0.7	18.68	0.1%	0.0-0.3	19.10	0.1%	0-0.1	30.23	0.1%	0.0-0.4
< 30 days	42.76	0.4%	0.2-0.6	94.45	0.8%	0.5-1.2	18.96	0.2%	0.1-0.4	25.33	0.2%	0.2-0.3	25.71	0.2%	0.1-0.5
< 90 days	22.60	0.6%	0.4-0.8	65.44	1.6%	1.1-2.2	16.19	0.4%	0.2-0.8	24.20	0.6%	0.5-0.7	50.26	1.2%	0.8-1.9
< 365 days	16.81	1.7%	1.3-2.2	50.13	4.9%	3.9-6.1	16.7	1.7%	1.1-2.4	19.17	1.9%	1.7-2.1	48.10	4.7%	3.5-6.2
mortality following emergency department visit/hospitalisation															
< 7 days	166.40	0.3%	0.1-1.3	0			0			59.25	0.1%	0.0-0.3	239.43	0.5%	0.1-1.8
< 15 days	78.57	0.3%	0.1-1.3	69.39	0.3%	0.0-2.0	0			42.12	0.2%	0.1-0.4	113.89	0.5%	0.1-1.9
< 30 days	61.16	0.5%	0.2-1.5	71.43	0.6%	0.1-2.3	0			51.74	0.4%	0.3-0.7	92.30	0.8%	0.2-2.3
< 90 days	30.67	0.8%	0.3-2.0	92.65	2.3%	1.1-4.7	0			48.94	1.2%	0.9-1.7	144.01	3.5%	2.0-6.1
< 365 days	20.61	2.0%	1.0-4.0	50.03	4.9%	2.8-8.4	0			32.92	3.2%	2.6-4.0	99.91	9.5%	6.5-13.8

MR = mortality rate, CumInc = cumulative incidence, 95% CI = 95% confidence interval

Table 7 - Risk factors of mortality in incident asthma adult patients (multivariate analysis).

	IPCI				AUH				HSD				CPRD				SIDIAP			
Incident asthma patients (n)	17,913				5,022				18,951				81,772				42,960			
Deaths in 5 years (n)	269				376				498				1,415				1,231			
Parameter	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**
AgeStart	1.11	1.10	1.12	<.0001	1.09	1.08	1.10	<.0001	1.12	1.11	1.13	<.0001	1.10	1.09	1.10	<.0001	1.12	1.11	1.12	<.0001
Female gender	0.72	0.56	0.93	0.0104	0.85	0.69	1.04	0.1216	0.71	0.59	0.87	0.0009	0.91	0.82	1.02	0.0982	0.70	0.61	0.80	<.0001
No previous exacerbations	1	Ref			1	Ref			1	Ref			1	Ref			1	Ref		
30 days after exa	1.36	0.50	3.75	0.5488	1.44	0.83	2.48	0.1927	1.89	1.06	3.37	0.0304	1.79	1.10	2.91	0.0182	2.61	2.04	3.35	<.0001
31-90 days after	2.13	1.22	3.72	0.0081	0.88	0.47	1.63	0.6803	1.53	0.93	2.50	0.0926	1.39	0.94	2.06	0.1027	2.67	2.12	3.36	<.0001
91-365 days after	1.88	1.29	2.73	0.0010	1.34	0.97	1.85	0.0717	1.29	0.95	1.74	0.1055	1.44	1.17	1.76	0.0005	1.86	1.56	2.24	<.0001
>365 days after	1.20	0.80	1.78	0.3770	1.29	0.94	1.78	0.1165	1.23	0.95	1.60	0.1231	1.37	1.16	1.62	0.0002	1.48	1.22	1.79	<.0001
Exacerbations overall				0.0022				0.1565				0.0272				<.0001				<.0001
History of cancer	1.47	1.10	1.96	0.0094	1.39	1.06	1.83	0.0171	2.08	1.57	2.75	<.0001	1.87	1.62	2.15	<.0001	1.76	1.51	2.05	<.0001
History of COPD	1.68	1.29	2.19	0.0001	1.76	1.42	2.17	<.0001	0.84	0.68	1.04	0.1055	1.70	1.49	1.93	<.0001	1.33	1.12	1.58	0.0014
History of cardiovascular disease	1.12	0.84	1.49	0.4452	1.41	1.12	1.78	0.0030	1.34	0.97	1.86	0.0794	1.47	1.30	1.66	<.0001	1.41	1.15	1.73	0.0010
History of cerebrovascular disease	0.72	0.47	1.10	0.1318	1.55	1.19	2.03	0.0012	1.39	1.08	1.79	0.0107	1.55	1.32	1.82	<.0001	1.61	1.35	1.94	<.0001
History of diabetes mellitus	1.43	1.08	1.91	0.0133	1.81	1.38	2.38	<.0001	1.29	1.03	1.61	0.0236	1.58	1.39	1.81	<.0001	1.49	1.31	1.69	<.0001
Severe asthma	1.21	0.86	1.70	0.2703	1.17	0.85	1.61	0.3380	1.21	0.82	1.78	0.3459	1.38	1.19	1.60	<.0001	1.00	0.76	1.31	0.9828
Smoking never	1	Ref			1	Ref			1	Ref			1	Ref			1	Ref		
Smoking current	2.16	1.46	3.21	0.0001	0.81	0.20	3.25	0.7648	1.59	1.18	2.16	0.0027	2.53	2.16	2.97	<.0001	2.35	1.90	2.92	<.0001
Smoking past	1.23	0.85	1.76	0.2665	0.60	0.19	1.86	0.3751	1.01	0.77	1.34	0.9211	1.05	0.93	1.20	0.4154	1.17	0.96	1.43	0.1122
Smoking unknown	1.64	1.18	2.26	0.0030	1.37	0.61	3.10	0.4470	0.98	0.79	1.22	0.8661	1.86	0.77	4.51	0.1672	1.32	1.13	1.54	0.0004
Overall P				0.0004				0.1567				0.0126				<.0001				<.0001

DISCUSSION

In this study, we investigated overall mortality rates and mortality rates following an asthma exacerbation in 6 asthma cohorts from 5 European countries, using one protocol and harmonized methods. The overall age standardized mortality rate in patients with asthma ranged between 4.8-13.2/1000 PY per database, and increased in patients with severe asthma and with increasing age.

Mortality following exacerbations was the highest in the first week (14.6-88.4/1000 PY) after exacerbation and decreased thereafter, both in the different databases as well as in the pooled meta-analysis. The risk of dying within 1 week following an asthma exacerbation ranged across countries between 0.1% and 0.5%.

The WHO reported asthma related mortality in patients aged 5-34 years of age, ranging between 0-5/100,000 people with asthma in Italy and the UK and 5.1-10/100,000 people in Spain, The Netherlands and Denmark.[1] These mortality rates are lower than the overall mortality rates that we reported for these respective countries. However, we studied all-cause mortality in adult patients with asthma. In 2014, To et al. reported the results of a 10-year population study on asthma related mortality and all-cause mortality using data from the health administrative database from Ontario, Canada. The age and gender adjusted, all-cause mortality declined from 9.9/1000 in 1999 to 8.5/1000 in 2009 which is in line with the rates in our study. [24]

In 2006, Krishnan et al published US data on mortality following hospital admission for asthma and reported an in house mortality of 0.5%. [25] This estimate is comparable with the cumulative incidence of mortality of 0.1-0.5% within 7 days following asthma exacerbation in our European study. Similar results were recently described by Kaur et al. who reported that 1% of patients die in the hospital following admission for asthma exacerbation. [26] In 2013, age standardized mortality rates in 30 days following an admission for status asthmaticus in Denmark were published. [27] Between 2008-2011, the 30-day mortality rate was 1.5% which is in line with the 0.6% (95% CI 0.1-2.3) that we reported for Denmark. Although mortality following asthma exacerbation has already been studied, to our knowledge, we are the first to study previous asthma exacerbations as independent risk factor of mortality.

In our study, adjusted mortality rate ratios comparing patients with a history of COPD to patients without history of COPD were up to 2.8. A recent observational study by Yamauchi et al. compared in-hospital mortality in patients with asthma, COPD and ACOS. [28] The proportion of patients who died during hospitalization was 9.7% in patients with COPD, 2.3% in patients with ACOS and 1.2% in patients with asthma. Although our cumulative incidence (0.4 and 0.1%) is smaller than reported in this study by Yamauchi et al., our results confirm that COPD is an independent risk factor of mortality in patients with asthma.

As this is an observational study, using data from electronic health care databases, there is a possible risk of bias and/or confounding. First, for all electronic health care databases, it should be noted that the primary aim of data collection is patient management and not research. This

implies that only events that are deemed to be relevant to the patient's care are collected. Second, for those databases without linkage with hospital admission or discharge database (HSD and IPCI), severe asthma exacerbations were retrieved either via disease specific codes in combination with codes for hospitalization or via review of the discharge letters. Underestimation of severe asthma exacerbations is likely and plausible for HSD where incidence rates of severe asthma exacerbations are indeed very low. (data not shown)

For AUH and SIDIAP, dispensing data instead of prescription data were used, which reduced misclassification of exposure, however dosing information was missing. Therefore dosing was estimated based on the strength per device and the window between prescriptions. This method is susceptible to misclassification of severe asthma, that was based on at least 120 consecutive days with high dose ICS. This might explain the low proportion of severe asthma patients in SIDIAP.

The presence of asthma and underlying co-morbidity was assessed via disease specific codes only. Misclassification of asthma and co-morbidity is possible and might be differential between databases but it is unlikely that this resulted in an overestimation of the mortality rates. Mortality rates were higher for AUH compared to the other databases, which might be explained by the fact that AUH collects disease codes from hospital data (ambulatory or hospitalised) only, implying that asthma patients in AUH all required secondary or tertiary care and probably had more severe asthma.

The proportion of patients with underlying COPD was high, especially in patients with severe asthma, where 1 in 3 patients was diagnosed with COPD. ACOS is well described and we know that the proportion of patients with ACOS increases with age. [29, 30] It is also well-known that GPs are often unable to make a differential diagnosis between asthma and COPD. [31] As no manual validation of asthma or COPD was performed, there is a potential of misclassification of both asthma and COPD. This risk of misclassification is probably higher in older patients which could have affected our analysis on risk factors of mortality which was only conducted in patients with adult incident asthma to guarantee complete information on medical history of asthma exacerbations and complete follow-up from asthma diagnosis to mortality or end of study. Also, the pathogenesis and immunologic mechanisms are different in incident asthma patients compared to prevalent asthma patients. [32] Lack of asthma control, measured by means of asthma symptom scores, is an independent risk factor of asthma mortality. [33] Unfortunately, the databases that were used do not systematically collect information on asthma control.

The main outcome in this study was mortality, assessed either through direct linkage with death registries (CPRD, AUH and SIDIAP) or via information as collected by the GP. The overall mortality rates are comparable between databases (apart from AUH), suggesting that misclassification of the outcome is limited.

We studied risk factors for mortality in patients with asthma and investigated the effect of life style factors (smoking), asthma severity, previous asthma exacerbations and underlying

comorbidity. Current smoking was a major risk factor for mortality in most databases, which is a modifiable risk factor where clinicians and patients can make a difference.

In conclusion, our data demonstrate that mortality in patients with asthma, and especially severe asthma, is substantial and is highest in the first 7 days after hospitalisation for asthma exacerbation. Moreover, patients with a history of asthma exacerbation, increasing age and underlying comorbidity including COPD have an increased risk of mortality. Prevention of asthma exacerbations as well as smoking cessation are important to reduce associated mortality.

REFERENCES

1. WHO. Chronic respiratory diseases.
2. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health.* 2012;12:204.
3. GINA. Pocket guide for asthma management and prevention. 2014.
4. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: origin, effect, and prevention. *J Allergy Clin Immunol.* Dec 2011;128(6):1165-1174.
5. Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. *J Allergy Clin Immunol.* May 2012;129(5):1229-1235.
6. Rebuck AS. The global decline in asthma death rates: can we relax now? *Asia Pac Allergy.* Jul 2013;3(3):200-203.
7. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med.* Jul 2006;100(7):1139-1151.
8. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy.* May 2004;59(5):469-478.
9. Menezes AM, Montes de Oca M, Perez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest.* Feb 2014;145(2):297-304.
10. Lange P, Ulrik CS, Vestbo J. Mortality in adults with self-reported asthma. Copenhagen City Heart Study Group. *Lancet.* May 11 1996;347(9011):1285-1289.
11. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med.* Dec 1999;38(4-5):339-344.
12. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol.* 2010;2:273-279.
13. Cazzola M, Puxeddu E, Bettoncelli G, et al. The prevalence of asthma and COPD in Italy: a practice-based study. *Respir Med.* Mar 2011;105(3):386-391.
14. Cricelli C, Mazzaglia G, Samani F, et al. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med.* Sep 2003;25(3):254-257.
15. Gulliford MC, van Staa T, Dregan A, et al. Electronic Health Records for Intervention Research: A Cluster Randomized Trial to Reduce Antibiotic Prescribing in Primary Care (eCRT Study). *Ann Fam Med.* Jul 2014;12(4):344-351.
16. Sorensen HT, Larsen BO. A population-based Danish data resource with possible high validity in pharmacoepidemiological research. *J Med Syst.* Feb 1994;18(1):33-38.
17. Blake KV, Devries CS, Arlett P, Kurz X, Fitt H. Increasing scientific standards, independence and transparency in post-authorisation studies: the role of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. *Pharmacoepidemiol Drug Saf.* Jul 2012;21(7):690-696.
18. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* Feb 2014;43(2):343-373.
19. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol.* Feb 15 2008;167(4):492-499.
20. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* Jul 1 2009;180(1):59-99.
21. Curtin LR, Klein RJ. Direct standardization (age-adjusted death rates). *Healthy People 2000 Stat Notes.* Mar 1995(6):1-10.
22. Thorlund K, Imberger G, Johnston BC, et al. Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses. *PLoS One.* 2012;7(7):e39471.
23. Gasparrini A, Armstrong B, Kenward MG. Multivariate meta-analysis for non-linear and other multi-parameter associations. *Stat Med.* Dec 20 2012;31(29):3821-3839.
24. To T, Simatovic J, Zhu J, et al. Asthma deaths in a large provincial health system. A 10-year population-based study. *Ann Am Thorac Soc.* Oct 2014;11(8):1210-1217.

25. Krishnan V, Diette GB, Rand CS, et al. Mortality in patients hospitalized for asthma exacerbations in the United States. *Am J Respir Crit Care Med.* Sep 15 2006;174(6):633-638.
26. Kaur BP, Lahewala S, Arora S, et al. Asthma: Hospitalization Trends and Predictors of In-Hospital Mortality and Hospitalization Costs in the USA (2001-2010). *Int Arch Allergy Immunol.* 2015;168(2):71-78.
27. Strid JM, Gammelager H, Johansen MB, Tonnesen E, Christiansen CF. Hospitalization rate and 30-day mortality among patients with status asthmaticus in Denmark: a 16-year nationwide population-based cohort study. *Clin Epidemiol.* 2013;5:345-355.
28. Yamauchi Y, Yasunaga H, Matsui H, et al. Comparison of in-hospital mortality in patients with COPD, asthma and asthma-COPD overlap exacerbations. *Respirology.* Aug 2015;20(6):940-946.
29. van der Molen T. Co-morbidities of COPD in primary care: frequency, relation to COPD, and treatment consequences. *Prim Care Respir J.* Dec 2010;19(4):326-334.
30. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax.* Aug 2009;64(8):728-735.
31. Price D, Brusselle G. Challenges of COPD diagnosis. *Expert Opin Med Diagn.* Nov 2013;7(6):543-556.
32. Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. *Nat Med.* Aug 2013;19(8):977-979.
33. Omachi TA, Iribarren C, Sarkar U, et al. Risk factors for death in adults with severe asthma. *Ann Allergy Asthma Immunol.* Aug 2008;101(2):130-136.
34. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol.* 2015;7:449-490.
35. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol.* Aug 2014;29(8):541-549.
36. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). *Inform Prim Care.* 2011;19(3):135-145.

SUPPLEMENTS

Online Table 1 - Description of number of patients within the source population and the respective asthma cohorts.

	All	IPCI (NL)	AUH (DK)	CPRD (UK)	HSD (IT)	SIDIAP (SP)	Pedianet (IT)
Source population	16,259,085	1,500,645	1,235,036	7,024,124	1,158,349	5,225,243	115,688
Asthma	855,806	116,281	30,292	551,165	48,463	101,341	8,264
Prevalent	641,018 (74.9)	93,508 (80.4)	23,818 (78.6)	27,961 (57.7)	44,4561 (80.7)	44,798 (44.2)	6,372 (77.1)
Incident	214,788 (25.1)	22,773 (19.6)	6,474 (21.4)	20,502 (42.3)	106,604 (19.3)	56,543 (55.8)	1,892 (22.9)
Severe asthma	66,148	10,368	3,020	48,115	2,897	1,747	1
Percentage severe/ total (%)	7.7%	8.9%	10.0%	8.7%	6.0%	1.7%	0.0%

Online Table 2 - Overall mortality rates (number of patients who died/1000 PY).

	Asthma				Severe asthma			
	persons (n)	deaths (n)	MR	95% CI	persons (n)	deaths (n)	MR	95% CI
IPCI								
Overall	116,281	1,851	6.02	5.75-6.30	10,368	451	17.50	15.95-19.19
Female	63,899	1,039	6.18	5.81-6.56	6,147	239	15.73	13.85-17.85
Male	52,382	812	5.83	5.44-6.25	4,221	212	20.04	17.52-22.93
5-<12 years	20,214	1	0.02	0.00-0.17	201	0	Nap	Nap
12-<19 years	13,190	5	0.13	0.05-0.31	373	0	Nap	Nap
19-<25 years	8,734	10	0.41	0.22-0.76	353	0	Nap	Nap
25-<35 years	11,809	9	0.31	0.16-0.59	701	1	0.09	0.09-4.46
35-<45 years	16,070	30	0.73	0.51-1.05	1,378	4	0.48	0.48-3.44
45-<55 years	17,076	99	2.05	1.68-2.49	2,211	25	3.04	3.04-6.65
55-<65 years	13,490	251	6.49	5.73-7.34	2,153	67	9.56	9.56-15.44
≥65 years	15,698	1,446	31.82	30.22-33.51	2,998	354	40.24	40.24-49.56

severe asthma = defined as asthma which requires treatment with high dose ICS and controller therapy for a consecutive period of at least 120 days

Online Table 2 continued - Overall mortality rates (number of patients who died/1000 PY).

	Asthma				Severe asthma			
	persons (n)	deaths (n)	MR	95% CI	persons (n)	deaths (n)	MR	95% CI
AUH								
Overall	30,292	1,819	12.78	12.20-13.38	3,020	469	33.42	30.53-36.59
Female	14,944	1,034	14.92	14.04-15.86	1,735	251	31.09	27.47-35.18
Male	15,348	785	10.74	10.01-11.52	1,285	218	36.59	32.04-41.78
5-<12 years	8,989	5	0.17	0.07-0.41	157	0	Nap	Nap
12-<19 years	3,917	9	0.34	0.18-0.65	181	2	2.96	0.74-11.83
19-<25 years	1,619	9	0.85	0.44-1.63	90	0	Nap	Nap
25-<35 years	2,208	14	1.34	0.80-2.27	119	1	1.61	0.23-11.44
35-<45 years	2,882	23	1.70	1.13-2.55	288	2	1.76	0.44-7.02
45-<55 years	3,099	108	7.16	5.93-8.64	472	25	11.76	7.95-17.40
55-<65 years	3,170	211	14.09	12.31-16.13	663	57	18.32	14.13-23.75
≥65 years	4,408	1440	65.49	62.19-68.96	1050	382	72.09	65.21-79.69
HSD								
Overall	48,463	1,422	6.73	6.39-7.09	2,897	192	16.02	13.91-18.46
Female	27,869	803	6.70	6.25-7.18	1,641	92	13.62	11.10-16.71
Male	20,594	619	6.78	6.27-7.34	1,256	100	19.12	15.72-23.26
5-<12 years	552	0	0.00	0.00-0.00	5	0	Nap	Nap
12-<19 years	4,419	2	0.14	0.04-0.57	42	0	Nap	Nap
19-<25 years	3,666	5	0.27	0.11-0.66	87	0	Nap	Nap
25-<35 years	6,559	9	0.31	0.16-0.61	221	0	Nap	Nap
35-<45 years	8,662	24	0.65	0.43-0.96	344	1	0.75	0.11-5.34
45-<55 years	7,614	62	1.71	1.33-2.19	464	5	2.45	1.02-5.89
55-<65 years	6,619	114	3.89	3.24-4.68	548	18	8.04	5.06-12.76
≥65 years	10,372	1206	25.73	24.32-27.22	1,186	168	33.03	28.39-38.42

severe asthma = defined as asthma which requires treatment with high dose ICS and controller therapy for a consecutive period of at least 120 days

Online Table 2 continued - Overall mortality rates (number of patients who died/1000 PY).

	Asthma				Severe asthma			
	persons (n)	deaths (n)	MR	95% CI	persons (n)	deaths (n)	MR	95% CI
CPRD								
Overall	551,165	16,773	7.76	7.64-7.87	48,115	4,889	27.49	26.73-28.27
Female	295,057	9,458	8.22	8.06-8.39	28,280	2,724	26.00	25.04-26.99
Male	256,108	7,315	7.23	7.07-7.40	19,835	2,165	29.63	28.41-30.91
5-<12 years	66,259	13	0.08	0.04-0.13	920	0	Nap	Nap
12-<19 years	74,311	49	0.18	0.13-0.23	1,116	3	0.78	0.25-2.42
19-<25 years	53,017	74	0.34	0.27-0.42	1,159	1	0.25	0.04-1.81
25-<35 years	69,806	142	0.53	0.45-0.62	2,868	14	1.58	0.93-2.66
35-<45 years	74,205	317	1.18	1.06-1.32	5,033	33	2.07	1.47-2.91
45-<55 years	67,524	692	2.37	2.20-2.55	7,112	134	5.23	4.41-6.19
55-<65 years	59,490	1533	6.12	5.82-6.43	9,604	432	12.58	11.45-13.83
≥65 years	86,553	13953	33.92	33.36-34.49	20,303	4,272	51.42	49.90-52.99
CIDIAP								
Overall	10,1341	2,672	7.15	6.89-7.43	1,747	156	26.29	22.47-30.76
Female	57,601	1,900	8.89	8.49-9.29	1,146	99	25.27	20.75-30.77
Male	43,740	772	4.84	4.51-5.19	601	57	28.29	21.82-36.67
5-<12 years	22,846	8	0.14	0.07-0.28	118	0	Nap	Nap
12-<19 years	8,804	5	0.12	0.05-0.28	12	0	Nap	Nap
19-<25 years	5,745	13	0.50	0.29-0.89	9	1	0.00	0.00-0.00
25-<35 years	14,281	21	0.41	0.27-0.64	39	0	Nap	Nap
35-<45 years	13,653	53	0.98	0.75-1.28	111	0	Nap	Nap
45-<55 years	9,773	93	2.30	1.88-2.82	167	2	3.72	0.93-14.86
55-<65 years	9,163	139	4.00	3.39-4.73	310	3	2.91	0.94-9.01
≥65 years	17,076	2340	34.07	32.71-35.47	981	150	42.03	35.82-49.33

severe asthma = defined as asthma which requires treatment with high dose ICS and controller therapy for a consecutive period of at least 120 days

Online Table 3 - Crude and adjusted mortality rate ratio for history of COPD on mortality during cohort time.

	asthma		severe asthma	
	MRR crude (95% CI)	MRR adjusted (95% CI)	MRR crude (95% CI)	MRR adjusted (95% CI)
IPCI	8.18 (7.46-8.96)	1.84 (1.67-2.03)	5.76 (4.67-7.10)	2.23 (1.78-2.79)
AUH	11.91 (10.83-13.10)	2.81* (2.54-3.11)	7.04 (5.66-8.76)	3.48* (2.77-4.36)
HSD	2.37 (2.12-2.66)	1.04 (0.93-1.17)	2.18 (1.64-2.90)	1.13 (0.85-1.51)
CPRD	10.12 (9.81-10.44)	2.11 (2.04-2.19)	4.20 (3.97-4.46)	2.02 (1.90-2.15)
SIDIAP	5.56 (4.95-6.25)	1.50 (1.33-1.68)	2.00 (1.34-2.97)	1.43 (0.95-2.15)

Adjusted for age, gender and smoking status
* only adjusted for age and gender
MRR=mortality rate ratio, 95% CI=95% confidence interval.

Online Table 4 - Mortality rate (per 1000 PY) in the total asthma cohort and the severe asthma cohort stratified by COPD status.

	IPCI		AUH		HSD		CPRD		SIDIAP	
	MR	Cum Inc	MR	Cum Inc	MR	Cum Inc	MR	Cum Inc	MR	Cum Inc
mortality following asthma exacerbation (all exacerbations) – NO COPD										
< 7 days	46.94	0.1%	42.22	0.1%	0	0.0%	17.89	0.0%	26.74	0.1%
< 15 days	51.61	0.2%	19.78	0.1%	14.06	0.1%	12.62	0.1%	25.1	0.1%
< 30 days	30.29	0.2%	20.13	0.2%	14.26	0.1%	17.23	0.1%	25.44	0.2%
< 90 days	14.16	0.3%	21.94	0.5%	13.36	0.3%	14.21	0.3%	49.84	1.2%
< 365 days	10.24	1.0%	13.64	1.4%	13.83	1.4%	11.18	1.1%	51.45	5.0%
mortality following asthma exacerbation (all exacerbations) – COPD										
< 7 days	186.64	0.4%	181.9	0.3%	0	0.0%	59.97	0.1%	108.32	0.2%
< 15 days	102.35	0.4%	149.63	0.6%	27.82	0.1%	45.2	0.2%	51.12	0.2%
< 30 days	67.44	0.6%	175.4	1.4%	28.3	0.2%	58.01	0.5%	26.87	0.2%
< 90 days	39.37	1.0%	113.76	2.8%	22.01	0.5%	64.08	1.6%	52.16	1.3%
< 365 days	30.13	3.0%	91.56	8.7%	22.7	2.2%	50.23	4.9%	31.62	3.1%

Online Table 5 - Risk factors of mortality in incident asthma adult patients. (univariate analyses)

	IPCI				AUH				HSD				CPRD				SIDIAP			
Incident asthma patients (n)	17,913				5,022				18,951				81,772				42,960			
Deaths in 5 years (n)	269				376				498				1,415				1,231			
Parameter	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**	**HR**	**95%**	**CI**	**P**
AgeStart	1.12	1.10	1.13	<.0001	1.10	1.09	1.11	<.0001	1.12	1.11	1.12	<.0001	1.10	1.10	1.11	<.0001	1.12	1.11	1.13	<.0001
Female gender	0.82	0.65	1.05	0.1153	0.87	0.71	1.07	0.1750	0.84	0.70	1.00	0.0546	0.91	0.82	1.01	0.0840	1.26	1.12	1.42	0.0002
No previous exacerbations	1	Ref			1	Ref			1	Ref			1	Ref			1	Ref		
30 days after exa	2.66	0.97	7.31	0.0580	1.43	0.82	2.48	0.2047	2.04	1.15	3.63	0.0149	1.58	0.97	2.56	0.0652	5.87	4.58	7.54	<.0001
31-90 days after	4.12	2.36	7.17	<.0001	0.85	0.46	1.58	0.5995	1.61	0.98	2.62	0.0582	1.23	0.83	1.82	0.3090	5.18	4.11	6.53	<.0001
91-365 days after	3.39	2.34	4.90	<.0001	1.30	0.95	1.80	0.1052	1.31	0.97	1.78	0.0778	1.27	1.04	1.56	0.0194	3.24	2.70	3.88	<.0001
>365 days after	2.16	1.46	3.20	0.0001	1.14	0.83	1.57	0.4112	1.26	0.97	1.63	0.0861	1.17	0.99	1.39	0.0598	2.15	1.78	2.60	<.0001
Exacerbations overall				<.0001				0.3273				0.0138				0.0205				<.0001
Severe asthma	2.57	1.85	3.58	<.0001	1.51	1.10	2.07	0.0111	2.15	1.47	3.15	<.0001	3.42	2.97	3.94	<.0001	2.95	2.25	3.87	<.0001
History of cancer	4.74	3.58	6.29	<.0001	3.16	2.41	4.13	<.0001	5.16	3.93	6.77	<.0001	5.18	4.52	5.94	<.0001	5.48	4.71	6.37	<.0001
History of COPD	5.35	4.19	6.84	<.0001	4.82	3.94	5.91	<.0001	1.60	1.30	1.96	<.0001	6.35	5.64	7.16	<.0001	4.30	3.63	5.10	<.0001
History of cardiovascular disease	5.24	3.97	6.91	<.0001	3.88	3.11	4.83	<.0001	4.30	3.12	5.95	<.0001	6.38	5.67	7.18	<.0001	5.60	4.58	6.86	<.0001
History of cerebrovascular disease	3.45	2.27	5.25	<.0001	4.76	3.67	6.18	<.0001	5.35	4.18	6.84	<.0001	6.45	5.51	7.54	<.0001	7.84	6.55	9.37	<.0001
History of diabetes mellitus	3.74	2.83	4.94	<.0001	3.37	2.58	4.40	<.0001	3.11	2.50	3.87	<.0001	3.90	3.42	4.45	<.0001	4.43	3.90	5.03	<.0001
Smoking never	1	Ref			1	Ref			1	Ref			1	Ref			1	Ref		
Smoking current	1.24	0.85	1.81	0.2583	0.84	0.21	3.35	0.8015	0.60	0.45	0.81	0.0007	1.59	1.37	1.85	<.0001	0.34	0.28	0.42	<.0001
Smoking past	1.72	1.21	2.45	0.0025	1.14	0.37	3.54	0.8167	1.37	1.06	1.76	0.0160	2.06	1.82	2.33	<.0001	0.77	0.64	0.92	0.0044
Smoking unknown	1.02	0.74	1.41	0.8879	1.39	0.62	3.14	0.4231	0.68	0.56	0.84	0.0004	2.27	0.94	5.48	0.0687	0.53	0.46	0.62	<.0001
Smoking overall				0.0056				0.6659				<.0001				<.0001				<.0001

Online supplement: Description of databases

The Integrated Primary Care Information (IPCI) database is a Dutch database containing the complete medical record of more than 1.5 million patients provided by more than 450 GPs geographically spread over the Netherlands. [11] In the Netherlands, all citizens are registered with a GP practice which acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care. The International Classification of Primary Care (ICPC) is the coding system but diagnoses and complaints can also be entered as free text. Prescription data contain information on product name, quantity prescribed, dosage regimens, strength, indication and ATC codes.

The Health Search CSD Longitudinal Patient Database (HSD), is a longitudinal observational database that is representative of the Italian general population. HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.5 million patients) located throughout Italy. The database includes information on age, gender, patient and GP identification, which is linked to prescription information, clinical events and diagnoses and date of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision. Drug names are coded according to the ATC classification. [13, 14]

In 1998 Pedianet has been established in Italy to collect epidemiological information for clinical research from family paediatricians. Pedianet is a paediatric general practice research database that contains the clinical, demographic, prescription and outcome data of the children routinely seen by about 130 PCPs equally distributed throughout Italy (all Italian children aged less than six years are registered with a PCP as part of the country's national health service), and which has been used for various epidemiological and pharmacovigilance studies. The data are generated during routine patient care using common software, and are anonymously sent monthly to a centralised database for validation. The reasons for the contacts and diagnoses (free text or coded using the ICD-9 system) are recorded in the medical file, and the database also contains information about specialist referrals, procedures, hospitalisations, medical examinations, health status (according to the Guidelines of Health Supervision of the American Academy of Paediatrics), and centile diagrams.

Clinical Practice Research Datalink (CPRD) is a large validated computerized database of anonymized longitudinal medical records for primary care. Data comprise approximately 12 million patients with around 5.4 million of these being currently alive and registered from 680 primary care practices spread throughout the UK. The database contains the entire anonymized electronic medical record of each patient, including medical codes associated with consultations and referrals; details of all drugs prescribed; life style factors and laboratory tests. [15] Information on hospitalization is collected through linkage HES and information on mortality is retrieved through linkage with the Office of National Statistics (ONS) Mortality data.

The Aarhus University Prescription Database comprises clinical and prescription data from the Central Denmark Region and the North Denmark Region. It covers a total of 1.2 million inhabitants and is representative of the population of Denmark. [12] Data are available on demographics, life style factors, dispensing data, hospitalizations and procedures. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data are linked to the national registry [34] of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures to the to the Central Registration system [35] that records information on mortality and to the Danish Registry of Cause of death. [16]

The SIDIAP Database comprises the electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices. The SIDIAP data comprises the clinical and referral events (coded by ICD-10), demography information, prescription and dispensing, specialist referrals, life style factors, laboratory test results, and hospital admissions and their major outcomes. [36]

Online supplement: Asthma Disease codes

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma	J45*	493*	H33*	R96*
Asthma confirmed			102..00	
Extrinsic asthma with asthma attack			663d.00 663m.00	
Asthma severity			663V*	
Number of asthma exacerbations in past year			663y.00	
Emergency admission, asthma			8H2P.00	
Status asthmaticus	J46*			
Induced asthma			173A.00	
Asthma trigger			173c.00 173d.00 178*.00	
Asthma; emergency attendance since last visit			663m.00	
Asthma; emergency admission since last appointment			663d.00	
Asthma and exercise			663e.00 663e000 663e100 663f.00 663w.00 663x.00	
Asthma currently dormant			663h.00	
Asthma currently active			663j.00	
Asthma treatment compliance satisfactory			663n.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma treatment compliance unsatisfactory			663p.00	
Asthma disturbing sleep			663N.00 66YP.00 663N000 663N100 663N200 663O.00 663O000 66YP.00 66Yq.00 66Yr.00 66Ys.00	
Asthma limits activities			663P*	
Asthma daytime symptoms			663q.00	
Asthma not limiting activities			663Q.00	
Asthma causes night symptoms 1 to 2 times per month			663r.00	
Asthma never causes daytime symptoms			663s.00	
Asthma causes daytime symptoms 1-2/month			663t.00	
Asthma causes daytime symptoms 1-2/week			663u.00	
Asthma causes daytime symptoms			663v.00	
Asthma prophylactic medication used			663W.00	
Asthma medication review			8B3j.00	
Absence due to asthma			66YC.00 66Yu.00	
Health education about asthma			679J.*	
Asthma control			8793.00 8794.00 8795.00 8796.00 8797.00 8798.00	
Asthma quality indicators			9hA*.00	

Asthma exacerbation

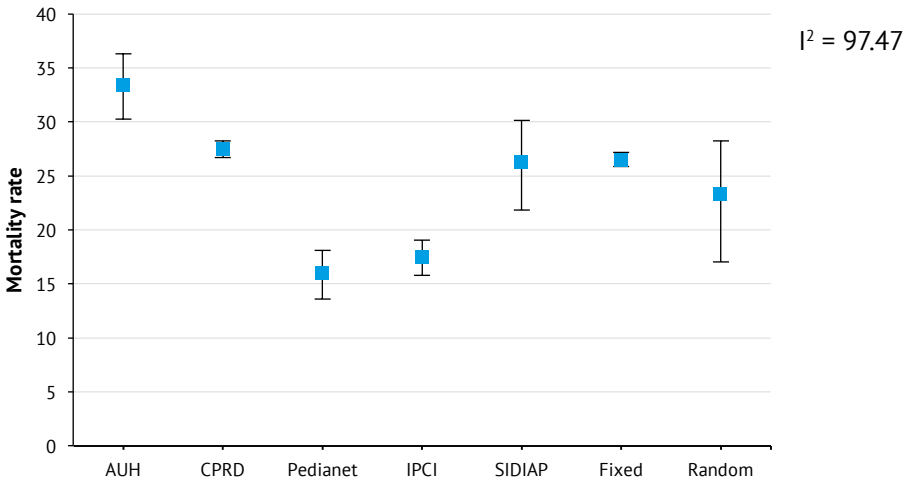
Definition of asthma

Asthma exacerbation was defined as the use of acute systemic corticosteroids, ER visit, or hospitalisation for reasons of asthma exacerbation. [21] To identify patients with a severe asthma exacerbation, defined as ER visit or hospitalisation for reasons of asthma, an automated search was done on codes specific for severe asthma exacerbation. In addition, the medical file was searched for asthma specific disease codes (thus not only asthma exacerbation codes) in combination with codes for hospitalisation. Hospitalization was retrieved either via linkage with hospital admission/discharge database (AUH, CPRD (→ HES)), combination of disease codes

with information from hospital referral (HSD, SIDIAP and IPCI) and discharge letters (SIDIAP and IPCI) or combination of disease codes with source codes (hospital discharge letters) (CPRD → for those patients where we do not have HES).

The following disease codes also did fit the criteria of asthma exacerbation:

Terms	ICD10	ICD9CM	Read Codes	ICPC
Emergency admission, asthma			8H2P.00	
Status asthmaticus	J46 J45.22 J45.32 J45.42 J45.52 J45.902	493.01 493.11 493.21 493.91	H33z000	
Severe asthma attack			H33z011	
Asthma accident and emergency attendance since last visit			663m.00	
Emergency asthma admission since last appointment			663d.00	



Online Figure 1 - Heterogeneity precluding pooling of the data on overall mortality rates.

4 ASTHMA TREATMENT

Chapter 4.1

Prescription patterns, adherence and characteristics of non-adherence in children with asthma in primary care

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ABSTRACT

BACKGROUND Adherence to treatment remains important for successful asthma management. Knowledge about asthma medication use and adherence in real-life offer opportunities to improve asthma treatment in children.

AIMS To describe prescription patterns, adherence and factors of adherence to drugs in children with asthma.

METHODS Population-based cohort study in a Dutch primary care database (IPCI), containing medical records of 176,516 children, aged 5-18 years, between 2000-2012. From asthma medication prescriptions, age, gender, seasonal and calendar year rates were calculated. Adherence was calculated using medication possession ratio (MPR) and ratio of controller-to-total-asthma-drug (CTT). Characteristics of children with high vs. low adherence were compared.

RESULTS The total asthma cohort (n=14,303; 35,181 person-years (PY) of follow-up) was mainly treated with short-acting β_2-agonists (SABA; 40users/100 PY) and inhaled corticosteroids (ICS;32/100 PY). Median MPR for ICS was 56%. Children with good adherence (Q4= MPR>87%) were younger at start of ICS, more often visited specialists and had more exacerbations during follow-up compared to children with low adherence (Q1=MPR<37%).

CONCLUSIONS In Dutch primary care children with asthma were mainly prescribed SABA, and ICS. Adherence to ICS was relatively low. Characteristics of children with good adherence were compatible with more severe asthma suggesting that adherence is driven by treatment-need or intensity of medical follow-up.

INTRODUCTION

Respiratory drugs are frequently prescribed in children. [1] According to the Global Initiative for Asthma (GINA), paediatric asthma can be treated with quick relievers, inhaled short-acting β_2-agonists (SABA) and/or controllers: inhaled corticosteroids (ICS) with or without concomitant use of long-acting β_2-agonists (LABA), or leukotriene receptor antagonists (LTRA). [2] Despite treatment, many children with asthma are not achieving good symptom control. A major cause of uncontrolled asthma is suboptimal adherence to maintenance treatment. [3] In practice, adherence to asthma treatment is commonly low, ranging between 30 to 70% [4-7], and lower in real life than in clinical trials. Improving adherence to ICS may reduce the burden of uncontrolled asthma resulting in fewer asthma-related emergency department visits and hospitalizations. [3, 8] Observational studies consistently show that asthma therapy is not always used in concordance with guidelines: massive consumption of SABAs and underuse of ICS has been reported. [9] Furthermore, some patients use LABA without concomitant ICS, whereas in asthma, LABAs are advised only in combination with ICS because LABAs might mask ongoing symptoms, do not treat the underlying inflammation and, when given alone, carry a possibly higher risk of death from asthma. [10-12] The extent to which LABA monotherapy actually occurs in children is unknown. Knowledge on the use of and adherence to asthma treatment in real life may offer opportunities to optimize asthma treatment in children by new adherence interventions. Therefore we investigated prescription patterns of asthma drugs and treatment adherence to asthma controller therapy, by conducting a cohort study using primary care data from a large database containing complete electronic medical records of more than 1 million patients.

METHODS

Setting

We conducted a population-based cohort study within the Integrated Primary Care Information database (IPCI), a longitudinal observational dynamic database containing the complete electronic records of >450 general practitioners (GPs) throughout the Netherlands. [13] In the Dutch healthcare system, patients are registered with a single GP who acts as a gatekeeper for secondary care. [14] Details of the database have been published elsewhere. [13, 15] Briefly, IPCI contains the complete electronic medical records of ±1,500,000 patients, containing anonymous longitudinal data on demographics, symptoms and diagnosis (coded and free text), referrals, laboratory findings, discharge letters, and prescriptions. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiological studies. [15] The scientific and ethical advisory board of IPCI approved this study (nr 07/55 2011).

Study cohort

The dynamic study cohort source population comprised all children aged 5-18 years with a database history of ≥12 months (n=176,516). The study period was from the first of January 2000 until the first of January 2012. Follow-up started on the first of January 2000, the date on which the required 1 year of follow-up was obtained, or on their 5th birthday, whichever came last. All patients were followed from study entry until the end of the study period, until they left the GP practice or until their 18th birthday, whichever occurred first.

Asthma Case identification and validation

All children who were 5-18 years old during the study period with physician diagnosed asthma were identified. First, all potential asthma cases were retrieved by an automated search on ICPC (International Classification of Primary Care) asthma codes ('R96') and free text relevant to asthma. Asthma was defined as "definite" if diagnosed by a paediatrician. "Probable" asthma was defined as asthma diagnosed by the GP with at least 2 additional records of asthma diagnoses or prescriptions of asthma medications in the 1 year following the initial diagnosis of asthma. If at any time during the follow-up asthma was diagnosed, the child was considered asthmatic from date of first diagnosis until the end of follow-up. As this broad automated search resulted in a high number of potential asthma cases (n=63,618), machine learning was used to facilitate the validation, as described in detail elsewhere. [16] The validity of this machine learning approach was reasonable good with a sensitivity of 95% and a specificity of 67% within the testset of 5,032 manually annotated medical records. [16] For verification of the total asthma cohort, the medical records of all predicted definite and 25% of probable asthma cases were manually reviewed by one of the authors (ME).

Prescriptions

To describe patterns of use, all prescriptions for asthma drugs were selected by ATC code R03. [17] These prescriptions were further categorized into SABA, LABA, SAMA, ICS, fixed combination of ICS+LABA (FDC-ICS/LABA), cromones, xanthines, or LTRA. (Detailed overview in online Table 1) Further analysis did not include SAMA, cromones or xanthines, due to low numbers. Detailed information on further categorization of type and dose of ICS, adapted from the GINA guidelines, is showed in online Table 2.

Annual user prevalence rates of asthma drugs were determined by the number of children that received ≥1 prescription of that drug in a given calendar year divided by the number of person-years in that calendar year. Annual user prevalence reflects the proportion of children that used a specific drug class in a specific year. If a child received prescriptions of 2 drug classes, this child contributed to both drug classes. If >1 prescription of the same drug was used in 1 year, this was only counted once in the numerator. Prevalence of use was stratified by calendar year, age (assessed on the 1st January of each follow-up year), and gender. 95% confidence

intervals (CI) around the prevalence were estimated based on the Poisson distribution. [18]
The overall month - and seasonal user rates over 2000-2012 were determined by the total number of children receiving ≥1 prescription of ICS or FDC-ICS/LABA in a given month (or season) summed for 2000-2011 divided by the number of person-months in that month (or season) summed for 2000-2011.
Among ICS users, the proportion of FDC-ICS/LABA prescriptions among the total ICS prescriptions was calculated per calendar year. Single ingredient LABA (SI-LABA) prescriptions were further classified as 'SI-LABA without ICS' or 'SI-LABA with ICS', either in 1 inhaler or in 2 separate inhalers.

Adherence

Adherence to asthma medication was assessed using both the medication possession ratio (MPR) and the controller to total ratio (CTT). The MPR for each class of controller medication was calculated by dividing the total number of days' supply of that medication prescribed by the total days of follow-up, multiplied by 100, and expressed as a percentage: MPR = (Days of drug supply / (follow-up (days))) x 100. Where days of drug supply equals the number of days that prescriptions should last based on the dosing instructions of the prescriber (Days of drug supply = number of doses in a prescription divided by the dosing frequency). The follow-up period was the interval between first and last prescription for that patient. MPR was truncated to 200 if MPR>200. MPR could be higher than 100% when there was overlap in prescriptions or in case patients use a higher dose (number of puffs/day) than originally prescribed.
Adherence assessed by CTT was defined as [prescriptions of controllers] divided by [prescriptions of controllers + relievers] as described by Schatz et al.[19] Patients with a ratio of ≥0.5 or higher were classified as high-ratio patients, and those with a ratio of <0.5 were classified as low-ratio patients.
To compare characteristics of high vs. low adherent children, we selected all children with ≥2 ICS prescriptions and at least 2 years of follow-up, follow-up was censored at 2 years. In these children, the ICS MPR was calculated and patient characteristics of the highest quartile (Q4) were compared to the lowest quartile (Q1).

Co variables

To analyse differences in adherent and non-adherent children, the following characteristics were collected: gender, age at start ICS/LABA, severe asthma exacerbation rate, specialist visit rate, number of infections during follow-up, and underlying comorbidity of eczema, conjunctivitis or allergic rhinitis. Asthma exacerbations were defined as emergency department visits or hospitalizations or oral corticosteroid prescriptions, all for asthma. Asthma exacerbations within 7 days after a previous exacerbation were counted as only 1 exacerbation.

Statistical analysis

Descriptive analyses were used to describe patient characteristics. Chi square test or Mann-Withney-U-tests or Poisson regression models were used to test the differences/rates in characteristics/rates between subgroups e.g. adherent and non-adherent groups, and SI-LABA vs. SI-LABA+SI-ICS groups. Kruskal-Wallis test was used to test differences between MPRs. Poisson regression models were used to fit annual ICS user rates over calendar time. A p-value of <0.05 was considered statistically significant. Analyses were conducted using SPSS for Windows version 20.0 (SPSS INC, Chicago, IL, USA) and Episheet. [18]

RESULTS

The source population comprised 176,516 children between 5-18 years during the study period. Upon automated text validation, these were classified in 16,139 asthma cases. After manual validation, the final asthma cohort consisted of 14,303 children (3,340 definite and 10,963 probable asthma cases according to the predefined algorithm as described above) with 35,118 PY of follow-up. Baseline characteristics of the asthma cohort are described in Table 1.

During 2000-2012 children with asthma mainly received prescriptions for SABA (38 users/100 PY) and ICS (31 users/100 PY). Detailed numbers are reported in online Table 3.

Asthma drug prescriptions were most frequent in the younger age categories with no differences between boys and girls up to the age of 13 years. From the age of 13 onwards, SABA, ICS and FDC-ICS/LABA were more prescribed to girls (Figure 1). Most children were prescribed Fluticasone propionate in low or middle dose, only 10% received a high dose. (online Table 4) With regard to type of device, most children between 5-8 years of age used an MDI to inhale ICS, more details are shown in online Table 5. Concomitant prescriptions of LTRA during ICS were observed in 216 children, during FDC ICS/LABA in 197 children and during LABA in 31 children (online Table 6). None of the GPs prescribed or continued Omaluzimab for a child in the asthma cohort.

Table 1 - Baseline characteristics for the total asthma cohort.

	Total asthma cohort - n (%)
Subjects (n)	14,303
Gender (male)	8,400 (59%)
Age at cohort entry (years)(mean, sd)	10.2 (4%)
Follow-up time after asthma diagnosis (years)(mean, sd)	2.5 (2%)
Eczema (till cohort entry)	3,852 (27%)
Allergic rhinitis (till cohort entry)	2,541 (18%)
Conjunctivitis (till cohort entry)	821 (6%)
Lower economic status (ever)	501 (4%)

n = number of subjects, sd = standard deviation

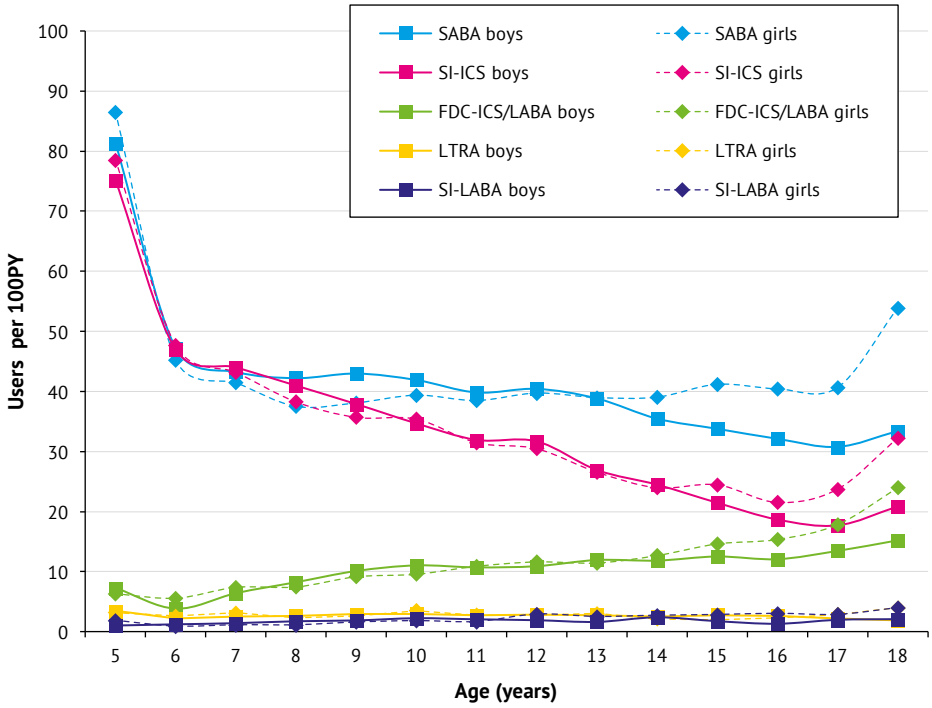


Figure 1 - Asthma drug use per 100 PY in the total asthma cohort by age (years) and gender.

We observed a seasonal pattern with more prescriptions for ICS during the winter and a peak in September, this pattern was observed in all calendar years and for the total study period. (online Figures 1 and 2) Poisson regression analyses showed that the proportion of ICS users decreased with increasing calendar time. ($p<0.001$) The use of SI-ICS decreased, while the proportion of FDC-ICS/LABA users increased over time from 2 users/100 PY in 2000 to 10 users/100 PY in 2011. (Figure 2)

The overall annual prevalence of LABA use was 27.8/100 PY of which the majority was FDC-ICS/LABA (24.3/100 PY). LABA was more prescribed to older children and to girls, especially after the age of 13 years. The prevalence of SI-LABA + SI-ICS (as 2 separate inhalers) was 2.9/100 PY and of SI-LABA use without concomitant ICS was 1.8/100 PY. (Figure 3) Use of SI-LABA decreased over time with prevalence rates of 1.44/100 PY (SI-LABA without ICS) and 1.52/100 PY (SI-LABA with ICS) in 2011. Of all children receiving SI-LABA (n=305), 122 children (40%) had no concomitant ICS use. They had less severe asthma, were older at the first LABA prescription (13.5 vs. 11.5 years, $p<0.001$), had fewer specialist visits and fewer severe asthma exacerbations compared to children with SI-LABA with ICS. (online Table 7)

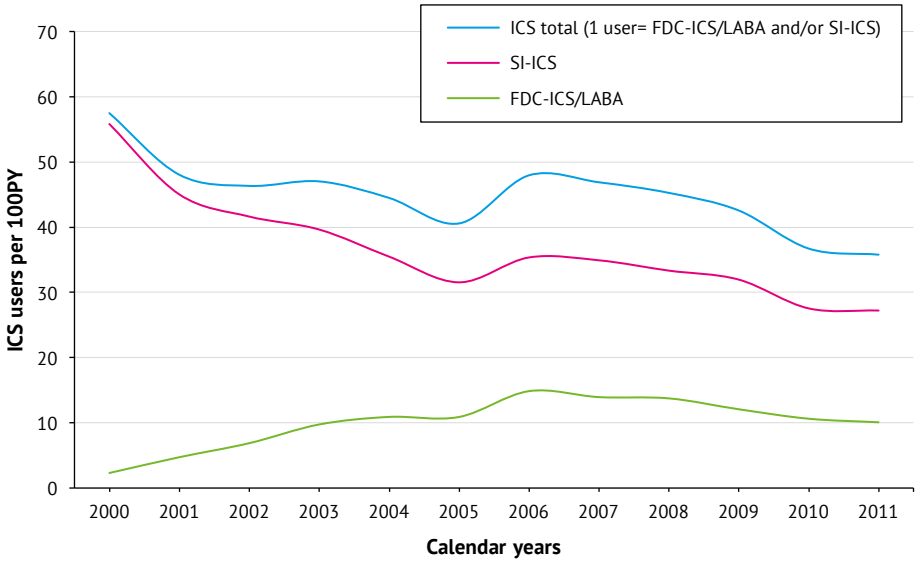


Figure 2 - Annual prevalence of total ICS use categorized into SI-ICS and FDC-ICS/LABA users per 100 PY in children with physician diagnosed asthma and treated during follow-up in 2000-2012.

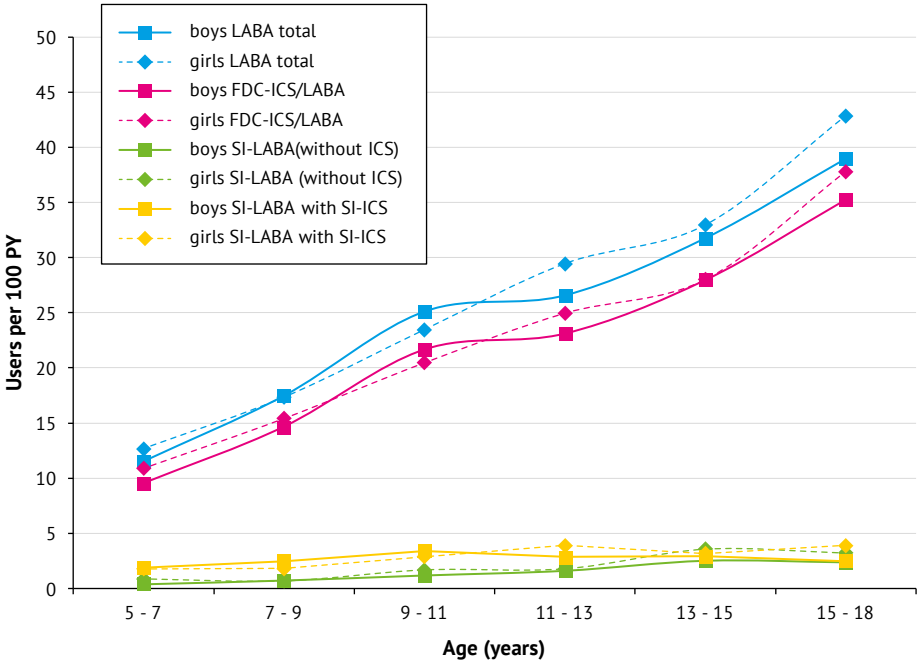


Figure 3 - All LABA users (SI-LABA without SI-ICS, SI-LABA with SI-ICS, and FDC- ICS/LABA) per 2 years of age stratified by gender, in children with physician diagnosed asthma and treated during follow-up.

Adherence

Median MPRs for LTRA, FDC-ICS/LABA, and ICS were significantly different, with MPRs 77.1, 61.3, and 56.0%, respectively. ($p<0.001$) (Figure 4) Good adherence (MPR>0.8) was observed in almost 46% of the LTRA users and in 34% of the FDC-ICS/LABA users. For ICS, only 33% of the users had good adherence (MPR≥0.8).

Univariate Poisson regression analyses of users with ≥2 prescriptions of ICS and 24 months of follow-up (n=2,397) showed that patients with a high MPR (Q4 MPR>87) were younger at start of ICS, had more specialist visits and more severe asthma exacerbations compared to patients with a low MPR (Q1 MPR<37). Differences were similar when comparing patients with MPR≥0.8 to MPR<0.8. (Table 2)

The CTT ratio was calculated for all patients using controllers and/or relievers. Sixty percent of the patients (n=5,519) had a high CTT ratio (CTT≥0.5) and used a mean of 5.0 controllers, whereas patients with a low CTT ratio used 1.5 controllers. Patients with a good adherence (CTT ratio>0.5) were younger at asthma diagnosis (χ^2, p=0.004) and at start of medication (p=0.009) compared to patients with a low CTT ratio.

DISCUSSION

This longitudinal, population based cohort study, covering a study period of 12 years, provides annual- and seasonal prescription patterns for asthma medication in children in the Netherlands. SABA and ICS were most frequently used, whereas SI-LABA was rarely prescribed and decreased over time. Adherence to asthma medications was suboptimal as only 31% of the ICS users had an MPR>0.8. Adherence to LTRA was significantly higher than to ICS, which may be due to the fact that this is oral medication, also 'steroid phobia' may play a role.

ICS was the most frequently prescribed controller medication. SI-ICS decreased over time, whereas the use of FDC-ICS increased. Only 1.8 users/100 PY received SI-LABA without concomitant ICS use, which is comparable to other studies. [20-22] SI-LABA as monotherapy does not comply with current national [23, 24] and international asthma guidelines. [25]

We observed seasonal patterns in ICS use, with the lowest rate in august and an increase in the winter. After checking our data, this coincides with severe asthma exacerbation patterns in this asthma cohort.

Overall, the prevalence of ICS prescriptions decreased over time. This might partly be caused by the fact that recent asthma guidelines advise to taper ICS to the minimum effective dose or to stop if possible. [25]

Adherence to controller medications was low, in line with recent literature. [26] Actual MPRs are probably even lower, as we only considered prescription data and not dispensing data, and even if all prescribed medication would be dispensed, not all dispensed medication would be actually (correctly) taken. It was emphasized by the European Respiratory Society Task Force

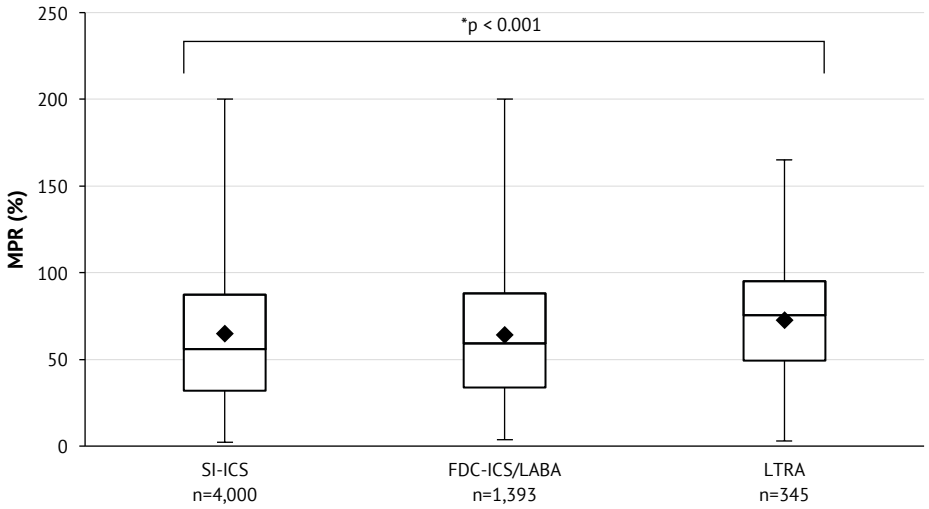


Figure 4 - Medication Possession Ratio (MPR) boxplot by drug.
□ = 25th-75th percentile, ⊢+⊣ = minimum-median-maximum, ◆ = mean

Table 2 - Characteristics of children with >1 ICS prescription and 24 months of follow-up comparing Q1 vs. Q4 MPR and MPR<0.8 vs. ≥0.8.

	MPR Q1 MPR<37	MPR Q4 MPR>87	p-value	MPR<0.8	MPR≥0.8	p-value
Number of patients (n)	599	598		1,659	738	
Gender (boys)	59%	56%	ns	60%	56%	ns
Age at start ICS (years, sd)	10.0 (3.4)	9.1 (3.4)	<0.001	9.5 (3.3)	9.1 (3.4)	0.001
Age at start asthma drug (years, sd)	7.9 (3.9)	7.0 (3.9)	<0.001	7.4 (3.8)	7.0 (3.9)	0.001
Eczema*	184 (31%)	212 (36%)	ns	552 (33%)	261 (35%)	ns
Allergic rhinitis*	159 (27%)	165 (28%)	ns	423 (26%)	208 (28%)	ns
Conjunctivitis*	56 (9%)	42 (7%)	ns	148 (9%)	54 (7%)	ns
Children with ≥1 specialist visits during follow-up	33 (6%)	91 (15%)	<0.001	152 (9%)	114 (15%)	<0.001
Children with exacerbation during follow-up	26 (4%)	42 (7%)	<0.05	80 (5%)	49 (7%)	ns
	rate/PY (95% CI)	**rate/PY** (95% CI)	**Poisson RR** (95% CI)	**p-value**	**rate/PY** (95% CI)	**rate/PY** (95% CI)	**Poisson RR** (95% CI)	**p-value**
Specialist visits during follow-up ^	0.04 (0.03-0.05)	0.12 (0.10-0.14)	1.50 (1.34-1.68)	<0.001	0.06 (0.06-0.07)	0.12 (0.10-0.14)	1.23 (1.15-1.31)	<0.001
Severe asthma exacerbations during follow-up^^	0.03 (0.04-0.06)	0.05 (0.02-0.04)	1.21 (1.05-1.40)	0.009	0.03 (0.03-0.04)	0.05 (0.04-0.06)	1.14 (1.03-1.26)	0.012

Ns = not significant, Sd = standard deviation, 95% CI = 95% confidence interval
* diagnosed prior to 1st ICS prescription
^ Specialist visit rate = number of visits to the specialist (for asthma) per person-year
^^ Exacerbation rate = number of severe asthma exacerbations (hospitalizations, ED visit or corticosteroid course for asthma) per person-year

that Correct inhaler technique is one of the prerequisites of successful asthma treatment and this inhalation technique should be taught, taught back and checked . [27] Internet based training offers possibilities to enhance correct inhalation techniques, e.g. the webpage ADMIT, this is a European place for information about obstructive pulmonary diseases and different treatment options with focus on inhalation therapy. Here patients as well as health care professionals can find various supports in order to achieve asthma control. Recently, a Dutch website on inhalation techniques in the Netherlands has been launched. [28]

The fact that the adherence in our study is relatively low might be due to the chosen methodology (=MPR) to assess adherence. Children might be adherent to ICS, stop due to few symptoms (but use rescue medication as needed) and be adherent to ICS again when symptoms return.

We performed a cluster analysis were we checked the timing of prescriptions. Four clusters were identified, but none of these clusters identified patients with periodic asthma (periodic prescribing at regular time intervals). Use of MPR to assess adherence might probably be too conservative in patients with periodic asthma. Future studies should investigate optimal adherence measures based on asthma phenotypes.

The low adherence to ICS can also be explained by the fact that in contrast to guidelines, many children use ICS as rescue medication, and that as a result of improper ICS prescribing, where patients are not asked to return for a follow-up visit, children who need long-term ICS therapy experience unmonitored discontinuation of therapy without corresponding order from their physician. [29]

Variations in adherence rates have been reported due to different study designs, adherence measures, and populations studied. [8] Characteristics of children with good adherence were compatible with more severe asthma, suggesting that adherence is driven by treatment need or intensity of medical follow-up. The design of our study was not suitable to investigate the association between adherence and exacerbations as we did not censor on severe asthma exacerbation.

Knowledge about asthma drug use and real life adherence may offer opportunities to optimize asthma treatment in children.

Promising results have been shown by targeting new adherence interventions, like speech recognition telephone calls, or by other e-health tools, or disease management programmes. [30-32]

Another opportunity to improve adherence is to enhance the promising pharmacist-led targeted interventions in patients with asthma. In the Netherlands, the pharmacist's role is shifting from a compounder, dispenser, and specialist of medication toward a patient-oriented healthcare professional. [33]

A recent published review presents seven national asthma programmes across Europe, including the asthma programme of the Netherlands. [34] A programme was defined as a well described activity, developing strategies to reduce asthma mortality and morbidity across Europe. Published data of the three evaluated programmes showed that, thanks to rigorous efforts, it is

possible to improve patients' quality of life and reduce hospitalisation, asthma mortality, sick leave and disability pensions. The direct and indirect costs, both for the individual patient and for society, can be significantly reduced.

The main strengths of our study are the large population based cohort with detailed information on prescriptions and comorbidities over a long study period. The design precluded selection bias due to non-responder or recall bias, and because patients were registered with one GP, where data were collected as part of routine patient care, irrespective of any research question. In addition, we were able to study age- and gender-specific asthma treatment patterns as the database captured all GP prescriptions with detailed information on dosage and duration. Limitations are the lack of dispensing data and actual drug intake. Our adherence rates might be underestimated as specialist prescribing is not routinely captured in the database. However, this bias is probably non-substantial as GPs play a central role in the care of patients and prescriptions initiated by the specialist are often continued by the GP. [35]

CONCLUSION

In Dutch primary care children with asthma were mainly prescribed SABA and ICS. ICS adherence was low, with only 31% of the patients having an MPR≥0.8. Characteristics of children with good adherence were suggestive of more severe asthma, and driven by treatment need or intensity of medical follow-up. These findings indicate that there is room for improvement of adherence to treatment, especially in children with milder forms of asthma.

REFERENCES

1. Sturkenboom MC, Verhamme KM, Nicolosi A, et al. Drug use in children: cohort study in three European countries. *BMJ.* 2008;337:a2245.
2. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J.* Jan 2008;31(1):143-178.
3. Drotar D, Bonner MS. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. *J Dev Behav Pediatr.* Dec 2009;30(6):574-582.
4. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. . 2015.
5. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med.* Feb 1994;149(2 Pt 2):S69-76; discussion S77-68.
6. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. *Respirology.* Jun 2008;13(4):559-563.
7. McNally KA, Rohan J, Schluchter M, et al. Adherence to combined montelukast and fluticasone treatment in economically disadvantaged african american youth with asthma. *J Asthma.* Nov 2009;46(9):921-927.
8. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J.* Feb 2015;45(2):396-407.
9. Gustafsson PM, Watson L, Davis KJ, Rabe KF. Poor asthma control in children: evidence from epidemiological surveys and implications for clinical practice. *Int J Clin Pract.* Mar 2006;60(3):321-334.
10. Gaist D, Hallas J, Hansen NC, Gram LF. Are young adults with asthma treated sufficiently with inhaled steroids? A population-based study of prescription data from 1991 and 1994. *Br J Clin Pharmacol.* Apr 1996;41(4):285-289.
11. Hallas J, Hansen NC. Individual utilization of anti-asthma medication by young adults: a prescription database analysis. *J Intern Med.* Jul 1993;234(1):65-70.
12. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest.* Jan 2006;129(1):15-26.
13. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med.* Nov 15 1993;119(10):1036-1041.
14. Schrijvers A. Health and health care in the Netherlands: a critical self assessment of Dutch experts in medical and health sciences. *Utrecht: De Tijdstroom.* 1997.
15. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med.* Dec 1999;38(4-5):339-344.
16. Afzal Z, Engelkes M, Verhamme KM, et al. Automatic generation of case-detection algorithms to identify children with asthma from large electronic health record databases. *Pharmacoepidemiol Drug Saf.* Aug 2013;22(8):826-833.
17. Hvidberg E, Andersen AH. [New classification of drugs. The Medical list and the Drug catalogue are introduced in Anatomical--Therapeutic--Chemical classification code (ACT-code) in 1981]. *Ugeskr Laeger.* Feb 4 1980;142(6):396-397.
18. Rothman K, Greenland,S ,Lash T. *Modern epidemiology.* 3rd ed. New York2008.
19. Schatz M, Zeiger RS, Vollmer WM, et al. The controller-to-total asthma medication ratio is associated with patient-centered as well as utilization outcomes. *Chest.* Jul 2006;130(1):43-50.
20. Klomp H, Lawson JA, Cockcroft DW, et al. Examining asthma quality of care using a population-based approach. *CMAJ.* Apr 8 2008;178(8):1013-1021.
21. Davidsen JR, Sondergaard J, Hallas J, Siersted HC, Lykkegaard J, Andersen M. Increased use of inhaled corticosteroids among young Danish adult asthmatics: an observational study. *Respir Med.* Dec 2010;104(12):1817-1824.
22. Arellano FM, Arana A, Wentworth CE, Vidaurre CF, Chipps BE. Prescription patterns for asthma medications in children and adolescents with health care insurance in the United States. *Pediatr Allergy Immunol.* Aug 2011;22(5):469-476.
23. Bindels PJE VdGE, Grol MH, Van Hensbergen W, Steenkamer TA, Uijen JHJM, Burgers JS, Geijer RMM, Tuut MK. NHG-Standaard Astma bij kinderen(Derde herziening). *Huisarts Wet.* 2014;57(2):70-80. https://www.nhg.org/standaarden/volledig/nhg-standaard-astma-bij-kinderen Accessed 19-05-2014.
24. NVK. Richtlijn astma bij kinderen (2013). In: Kindergeneeskunde NVv, ed2013: http://www.nvk.nl/tabid/1558/articleType/ArticleView/articleId/708/default.aspx.

25. Global Initiative For Asthma Global strategy for asthma management and prevention – updated 2012.: www.ginasthma.org. Accessed Last accessed 19 may 2014.
26. Elkout H, Helms PJ, Simpson CR, McLay JS. Adequate Levels of Adherence with Controller Medication Is Associated with Increased Use of Rescue Medication in Asthmatic Children. *PLoS One*. Jun 27 2012;7(6).
27. Pijnenburg MW, Baraldi E, Brand PL, et al. Monitoring asthma in children. *Eur Respir J*. Apr 2015;45(4):906-925.
28. Long Alliantie Nederland. www.inhalatorgebruik.nl. 2014.
29. Klok T, Kaptein AA, Duiverman E, Oldenhof FS, Brand PL. General practitioners' prescribing behaviour as a determinant of poor persistence with inhaled corticosteroids in children with respiratory symptoms: mixed methods study. *Bmj Open*. 2013;3(4).
30. Tran N, Coffman JM, Sumino K, Cabana MD. Patient reminder systems and asthma medication adherence: a systematic review. *J Asthma*. Jun 2014;51(5):536-543.
31. Mehring M, Donnachie E, Mutschler R, Hofmann F, Keller M, Schneider A. Disease management programs for patients with asthma in Germany: a longitudinal population-based study. *Respir Care*. Jul 2013;58(7):1170-1177.
32. Bender BG, Cvietusa PJ, Goodrich GK, et al. Pragmatic Trial of Health Care Technologies to Improve Adherence to Pediatric Asthma Treatment: A Randomized Clinical Trial. *JAMA Pediatr*. Feb 9 2015.
33. van Boven JF, Stuurman-Bieze AG, Hiddink EG, Postma MJ, Vegter S. Medication monitoring and optimization: a targeted pharmacist program for effective and cost-effective improvement of chronic therapy adherence. *J Manag Care Spec Pharm*. Aug 2014;20(8):786-792.
34. Selroos O, Kupczyk M, Kuna P, et al. National and regional asthma programmes in Europe. *EUR RESPIR REV*. Sep 2015;24(137):474-483.
35. de Vries CS, van Diepen NM, Tromp TF, de Jong-van den Berg LT. Auditing GPs' prescribing habits: cardiovascular prescribing frequently continues medication initiated by specialists. *Eur J Clin Pharmacol*. 1996;50(5):349-352.

SUPPLEMENTS

Online Table 1 - ATC codes grouped by drug class and drugname.

ATC code	Drug class	Drug
R03AC02	SABA	aerolin
R03AC02	SABA	airomir
R03AC02	SABA	salbutamol
R03AC02	SABA	ventolin
R03AC03	SABA	bricanyl
R03AC03	SABA	terbutaline
R03AC04	SABA	berotec
R03AC04	SABA	fenoterol
R03AC12	LABA	salmeterol
R03AC12	LABA	serevent
R03AC13	LABA	atimos
R03AC13	LABA	foradil
R03AC13	LABA	formoterol
R03AC13	LABA	oxis
R03AK03	fixb2atro	berodual
R03AK03	fixb2atro	fenoterol/ipratropium
R03AK04	fixb2atro	combivent
R03AK04	fixb2atro	salbutamol/ipratropium
R03AK06	FDC-ICS/LABA	salmeterol/fluticason
R03AK06	FDC-ICS/LABA	seretide
R03AK07	FDC-ICS/LABA	budesonide/formoterol
R03AK07	FDC-ICS/LABA	beclometason/formoterol
R03AK07	FDC-ICS/LABA	foster
R03AK07	FDC-ICS/LABA	symbicort
R03AK07	FDC-ICS/LABA	sinestic
R03BA01	ICS	aerobec
R03BA01	ICS	becloforte
R03BA01	ICS	beclometason
R03BA01	ICS	becotide
R03BA01	ICS	beclodin
R03BA01	ICS	qvar
R03BA02	ICS	budesonide
R03BA02	ICS	pulmicort
R03BA05	ICS	flixotide
R03BA05	ICS	fluticason
R03BA08	ICS	alvesco
R03BA08	ICS	ciclesonide
R03BB01	SAMA	atrovent
R03BB01	SAMA	ipratropium
R03BB01	SAMA	ipraxa
R03BB04	LAMA	spiriva
R03BB04	LAMA	tiotropium
R03BC01	cromones	cromoglicinezuur
R03BC01	cromones	lomudal
R03BC03	cromones	nedocromil
R03BC03	cromones	tilade
R03CC02	SABA	salbutamol
R03CC02	SABA	ventolin
R03CC03	SABA	terbutaline
R03DA04	xanthines	theofylline
R03DA04	xanthines	theolair
R03DC03	LTRA	montelukast
R03DC03	LTRA	singulair

Online Table 2 - Categorization of ICS doses into 'low', 'medium' and 'high' (adapted from GINA guidelines).

ICS	ATC (single)	ATC (fixed combination)	Children 5-11 years (dose in microgram)			Adults and adolescents (dose in microgram)		
			low	medium	high	low	medium	high
Beclomethasone dipropionate (HFA MDI)	R03BA01	R03AK08	50-100	>100-200	>200	100-200	>200-400	>400
Beclomethasone (DPI)	R03BA01	R03AK08	100-200	>200-400	>400	200-500	>500-1000	>1000
Budesonide (MDI)	R03BA02	Not available	100-200	>200-400	>400	200-400	>400-800	>800
Budesonide (DPI)	R03BA02	R03AK07	100-200	>200-400	>400	200-400	>400-800	>800
Budesonide (NEB)	R03BA02	Not available	250-500	>500-1000	>1000	500-1000	>1000-2000	>2000
Ciclesonide (HFA MDI)	R03BA08	Not available	80	>80-160	>160	80-160	>160-320	>320
Fluticasone propionate (DPI)	R03BA05	R03AK06, R03AK10, R03AK11	100-200	>200-400	>400	100-250	>250-500	>500
Fluticasone propionate (HFA MDI)	R03BA05	R03AK06, R03AK10, R03AK11	100-200	>200-500	>500	100-250	>250-500	>500
Fluticasone (NEB)	R03BA05	Not available	100-250	>250-500	>500	100-250	>250-500	>500

Online Table 3 - Prevalence of asthma drug use per 100 PY in the asthma cohort by age and gender.

	ICS		LTRA		SABA		LABA		FDC ICS/LABA	
Age	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
5	75.0	78.5	3.5	3.2	81.3	86.4	1.0	1.9	7.3	6.3
6	46.9	47.6	2.2	2.6	47.2	45.3	1.2	0.9	3.9	5.6
7	44.0	43.1	2.5	3.2	43.2	41.4	1.4	1.1	6.4	7.4
8	40.9	38.3	2.7	2.3	42.2	37.5	1.7	1.1	8.3	7.5
9	37.9	35.7	2.9	2.6	43.0	38.1	1.8	1.6	10.1	9.2
10	34.7	35.4	3.0	3.5	41.9	39.4	2.2	1.8	11.0	9.6
11	31.9	31.5	2.7	2.8	39.8	38.5	2.0	1.7	10.7	10.9
12	31.7	30.5	2.8	2.7	40.4	39.7	1.9	2.9	10.9	11.7
13	26.9	26.6	2.8	3.0	38.8	39.0	1.6	2.5	11.9	11.5
14	24.5	24.0	2.5	2.1	35.5	39.0	2.4	2.7	11.8	12.7
15	21.4	24.5	2.7	2.0	33.8	41.2	1.7	2.8	12.5	14.6
16	18.6	21.5	2.6	2.3	32.1	40.4	1.3	3.0	12.1	15.4
17	17.7	23.7	2.2	2.9	30.8	40.7	1.9	2.9	13.4	17.9
18	20.8	31.9	1.9	3.8	33.4	53.9	2.1	4.0	15.2	24.0

Online Table 4 - Categorization of number of children with prescriptions, and number of prescriptions for 'low', 'medium' and 'high' dose ICS.

ICS	ATC		Children 5-11 years (n) Dose				Children > 12 years (n) Dose				
			low	medium	high	Total children 5-11	low	medium	high	Total children >12	Total children 5-18
Beclomethasone dipropionate (MDI/DPI)	R03BA01 R03AK08	Pt	231	596	174		295	92	29	n.a.	
		Pres	533	1890	563	2986	777	233	69	1079	4065
		% pres	18	63	19		72	22	6		
Budesonide (MDI/DPI/NEB)	R03BA02 R03AK07	Pt	218	335	79		644	188	15		
		Pres	621	1043	193	1857	1833	453	26	2312	4169
		% pres	33	56	10		79	20	1		
Ciclesonide (MDI)	R03BA08	Pt	16	20	3		47	16	3		
		Pres	70	65	9	144	182	46	3	231	375
		% pres	49	45	6		79	20	1		
Fluticasone propionate (MDI/DPI/NEB)	R03BA05 R03AK06 R03AK10 R03AK11	Pt	1575	1919	399		1248	1342	242		
		Pres	5832	6536	1281	13649	3993	4373	719	9085	22734
		% pres	43	48	9		44	48	8		
TOTAL		Pres	7056	9534	2046	18636	6785	5105	817	12707	31343
		% pres	38	51	11		53	40	6		

* patients could belong to more than 1 age category during the study period.

Pt = patient, pres = prescription, % = percentage, n = number, ATC = atc code, ICS = inhaled corticosteroids, MDI = metered dose inhaler, DPI = dry powder inhaler, NEB = nebulizer

Online Table 5 - Categorization of children with prescriptions per device stratified by age category.

	Type Device ICS	Patients (n)	Prescription (n)	Proportion prescriptions per age category (%)
5-8 years	DPI	463	1,337	12
	MDI	2,674	9,407	87
	NEB	16	57	1
	total		10,801	
9-12 years	DPI	1,131	3,778	48
	MDI	1,449	4,015	51
	NEB	9	14	0
	total		7,807	
12-15 years	DPI	1,513	4,591	67
	MDI	859	2,215	32
	NEB	13	22	0
	Total		6,828	
15-18 years	DPI	1,537	4,736	80
	MDI	480	1,160	20
	NEB	5	11	0
	total		5,907	
total			**31,343**	

* patients could belong to more than 1 age category during the study period.
Pt = patient, % = percentage, n = number, ICS = inhaled corticosteroids, MDI = metered dose inhaler, DPI = dry powder inhaler, NEB = nebulizer

Online Table 6 - Number of patients with prescriptions per medication class and with prescriptions with concomitant use of LTRA.

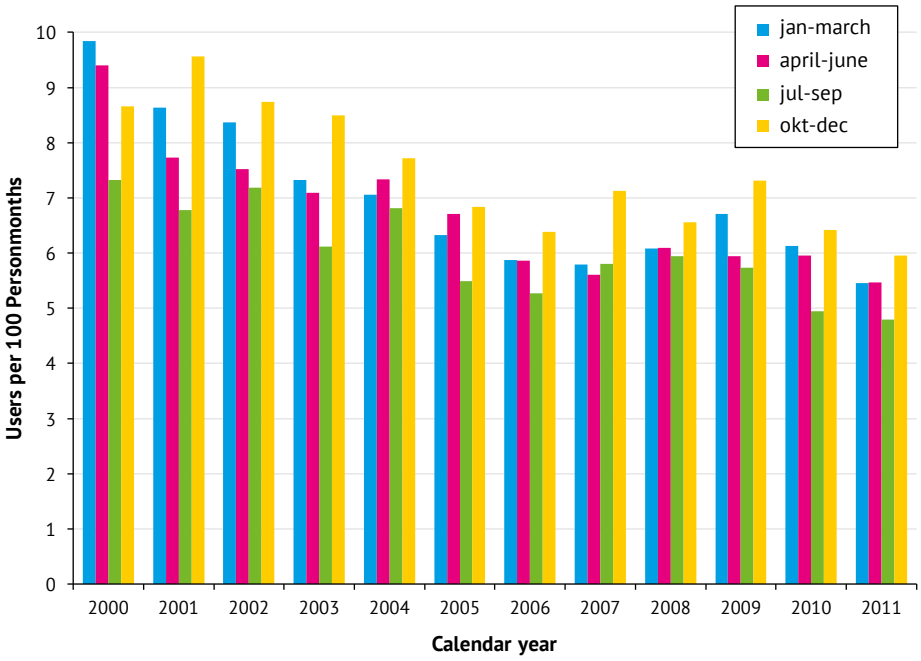
Drug (≥1 prescription during follow-up)	**Children** (number)
ICS	5,749
FDC-ICS/LABA	1,987
LTRA	507
LABA	386
SABA	7,544
Other asthma drugs (R03)	448
Concomitant drugs	
ICS+LTRA	216
FDC-ICS/LABA+LTRA	197
LABA+LTRA	31

ICS = inhaled corticosteroids, LTRA = leukotrienreceptorantagonist, FDC = fixed dose combination, LABA=long-acting β_2-agonist, SABA= short-acting β_2-agonist

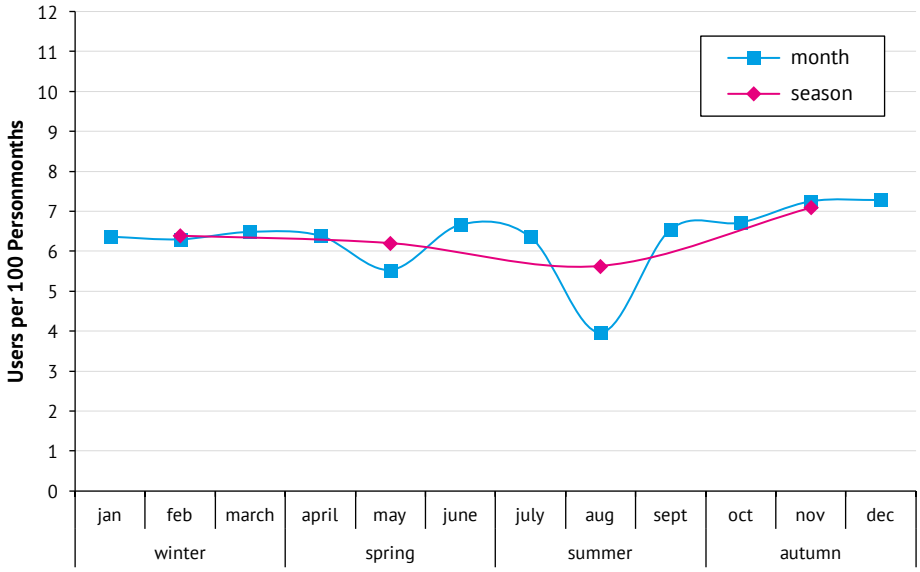
Online Table 7 - Children with SI-LABA; categorized in patients with and without concomitant SI- ICS.

	SI-LABA no SI-ICS	SI-LABA+SI-ICS	RR*	p-value Poisson
Number of patients (n)	122	183		X^2 p<0.001
Age first LABA prescription (years, sd)	13.5 (3.1)	11.5 (3.8)		X^2 ns
Gender (boys) (%)	47%	55%		
Specialist visit rate* till first LABA (rate/PY, 95% CI)	0.12 (0.07-0.19)	0.34 (0.25-0.54)	2.92 (1.60-5.31)	p<0.001
Specialist visit rate* after first LABA (rate/PY, 95% CI)	0.13 (0.09-0.18)	0.27 (0.23-0.33)	2.13 (1.42-3.20)	p<0.001
Exacerbation rate** till first LABA (rate/PY, 95% CI)	0.08 (0.04-0.15)	0.55 (0.43-0.69)	6.57 (3.40-12.72)	p<0.001
Exacerbation rate** after first LABA (rate/PY, 95% CI)	0.04 (0.02-0.07)	0.09 (0.07-0.12)	2.57 (1.21-5.50)	p=0.015

Ns = not significant, 95% CI = 95% confidence interval
Specialist visit rate* = number of visits to the specialist (for asthma) per person-year
Exacerbation rate** = number of severe asthma exacerbations (hospitalizations, ED visit or corticosteroid course for asthma) per person-year
* The total number of patients within the different asthma therapies is not equal to the number of patients receiving asthma therapy, as patients can use several therapies during follow-up.



Online Figure 1 - ICS (SI-ICS plus FDC-ICS/LABA) user rate per month (per 100 person months) per calendar year during the study period 2000-2012.



Online Figure 2 - Total ICS (SI-ICS plus FDC-ICS/LABA) user rate per month (per 100 person months) and per season during the study period 2000-2012.

Chapter 4.2

Medication adherence and the risk of severe asthma exacerbations - a systematic review

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ABSTRACT

BACKGROUND The benefits of drug therapy for asthma have been well established, but adherence to treatment is poor, and this might be associated with an increased risk of asthma exacerbations.

AIMS To review the literature on the association between adherence to asthma controller treatment and risk of severe asthma exacerbations in children and adults.

METHODS A systematic literature search in PUBMED, EMBASE and Web of Science from inception until January 2014 was performed. Studies were included if data on the association between medication adherence and severe asthma exacerbations were presented. Quality was assessed using a modified version of the Newcastle-Ottawa Scale.

RESULTS The search yielded 2,319 unique publications of which 23 met the inclusion criteria and underwent data extraction and quality scoring. High levels of heterogeneity across studies with regard to adherence and exacerbation measurements, designs and analysis precluded a formal meta-analysis. Although effect measures varied widely, good adherence was associated with fewer severe asthma exacerbations in high quality studies.

CONCLUSIONS Good adherence tended to be associated with lower risk of severe asthma exacerbations. Future studies should use standardized methodology to assess adherence and exacerbations, and should consider inhaler competence.

INTRODUCTION

Asthma is a chronic inflammatory airway disease with a high prevalence, around 10% in children and 5% in adults in Western countries. [1, 2] Asthma is a major cause of disability, health resource utilization, and reduces quality of life. [3] This is partly caused by asthma exacerbations which have a huge impact on patients and their families. To minimize asthma exacerbations, treatment should be stepwise adjusted, driven by the patient's asthma control level. [4] Asthma treatment includes daily use of a controller drug and as needed use of short-acting bronchodilators for quick symptom relief. [5] Adherence to treatment is essential to optimize the benefits of therapy. Poor adherence has been associated with outcomes like mortality [6], asthma symptoms [7], (in)direct costs of care [3] and quality of life. [8] In asthma, adherence to treatment tends to be poor with rates of less than 50% in children [9] and 30-70% in adults [4, 10, 11], depending on country, age, gender, and ethnicity. [12] These low adherence rates have been attributed to safety concerns about inhaled corticosteroids ("steroid phobia") by both the patients and the caregivers. [13] Indeed, use of ICS has been associated with growth impairment in children and other systemic adverse effects, such as an increased risk of pneumonia. [14] In addition, most ICS need to be administered twice daily, which increases the risk of poor adherence compared to once daily administration. [5] It has been suggested that poor adherence to ICS increases the risk of exacerbations. However, the literature on this topic is conflicting. With this systematic review, we aim to provide a critical appraisal of the literature examining the association between adherence to asthma controller therapy and the risk of severe asthma exacerbations in children and adults.

METHODS

Electronic searches

An extensive electronic literature search was conducted to identify all relevant articles, published from inception up to the 1st of January 2014, as indexed by PUBMED, Web of Science and EMBASE. (Supplementary data Table 1) Article reference lists were searched for additional potentially relevant articles.

Review criteria and data extraction

All original articles were considered, excluding case reports, audits, guidelines, editorials, management/implementation strategies, conference abstracts and study protocols. We excluded animal studies. No limits were set on study design, sample size, location, or follow-up. Eligible patient populations included both children and adults using asthma controller therapy; ICS, long-acting β_2-agonists (LABAs), or fixed combination therapies of LABA and ICS. Because of incomparability, we excluded studies that looked at leukotriene receptor antagonists or xanthines only.

Studies were included if they met the following 3 criteria;
(1) The exposure variable of interest was medication adherence to asthma controller therapy. Medication adherence is an umbrella term that encompasses both the concepts of compliance and persistence. Compliance is defined as the extent to which a patient acts in accordance with the prescribed interval and dosing regimen, and persistence, as the duration of time from initiation to discontinuation of therapy, according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). [15]
Only studies with objectively measured adherence, including electronic monitoring devices, pill counting, and prescription/refill data were included. Adherence measured through subjective measures, such as patient self-reports, questionnaires and physician's judgments were excluded as we considered these to be less reliable and not comparable to objective adherence measures.
(2). The outcome of interest was severe asthma exacerbation. According to the joined Global Initiative for asthma (GINA) [4], American Thoracic Society (ATS) [16] and European Respiratory Society (ERS) [17] asthma guidelines, this outcome was defined as "the occurrence of either an asthma-related hospitalization or visit to the emergency department (ED) or an urgent care facility, leading to treatment with systemic (oral, intramuscular, or intravenous) corticosteroids for at least 3 days".
(3) Evaluation of the association between adherence and exacerbations as primary or secondary endpoint.
The first author (ME) assessed the eligibility of studies from their titles and abstracts, excluding those that were not relevant. The full texts of eligible papers were assessed independently for eligibility by two authors (ME and KV) and data were extracted into a customized data extraction Excel form. Third party adjudication was foreseen in case of disagreement.

Assessment of methodological quality

All included studies underwent a formal evaluation according to the Newcastle Ottawa Scale (NOS), a set of criteria established and used in previous systematic reviews of observational studies [18, 19], that was modified for the purpose of this review.
All studies were independently rated by 2 reviewers (ME and KV), to assess the quality based on 5 parameters: overall design, selection of participants, exposure assessment, outcome ascertainment and control for extraneous factors. Each parameter received 0, 1, or 2 points. (Supplementary data Table 2). The total score represented the sum of all 5 parameters. This score was used as relative measure of data quality.

Data analysis

Pooling of studies was considered in case of adequate similarity, with respect to exacerbation definitions, adherence definitions, and methods to assess the relationship between adherence and exacerbations. In case of heterogeneity, the results of each study were reported individually.

RESULTS

Overview of the included studies

The search strategy identified 2,319 articles. Upon title and abstract review, 2,268 of these were excluded, mainly for the following reasons: lack of information on medication adherence, no severe asthma exacerbation or no evaluation of the relation between adherence and exacerbation (>1000), articles on intervention, management or implementation strategies (370), audit/guidelines (122), focus on other diseases (139), animal studies (106), cell biology/immunology (62), no original articles (40). A total of 23 articles were finally included in the review. (Figure 1)

Details of the 23 studies are shown in Table 1. Briefly, all 23 studies were published between 1993 and 2013. The sample sizes ranged from 24 to 97,743 individuals. [9, 20] Two studies were multicenter, 7 were single center and 14 were based on healthcare (pharmacy/insurance/claim) databases. Most studies were from the United States. The included studies mainly used a cohort design (n=19) with the remainder utilizing a cross-sectional (n=1) [9], case control (n=1) [21] or randomized design (n=2). [22, 23] Studies analysed adherence rates over a follow-up period ranging from 13 weeks (9) to 4 years. [23] Ten studies included only children, 7 both adults and children/adolescents and 6 studies only adults.

Measures of medication adherence

The assessment of medication adherence varied across studies. Most studies (n=11) used the Medication Possession Rate (MPR) as measure which is the number of days of medication supplied divided by the number of days between the first and the last refill. [24] Most studies chose a fixed time frame for the refill interval rather than using the last refill as the end point for the refill interval and did not exclude the last refill. MPR calculated across multiple refills is also called the continuous measure of adherence (CMA). In addition to the MPR, 2 studies also calculated a controller-to-total- ratio. [25, 26] Williams et al. used an unique method to calculate adherence, by calculating a moving 6-months-average ICS adherence for each day of follow-up. [27] Furthermore, 6 studies used number of (requested) refills in a certain period to assess adherence. Of the remaining studies, 3 used canister weighing/counting and 3 used electronic monitoring via a specific device.

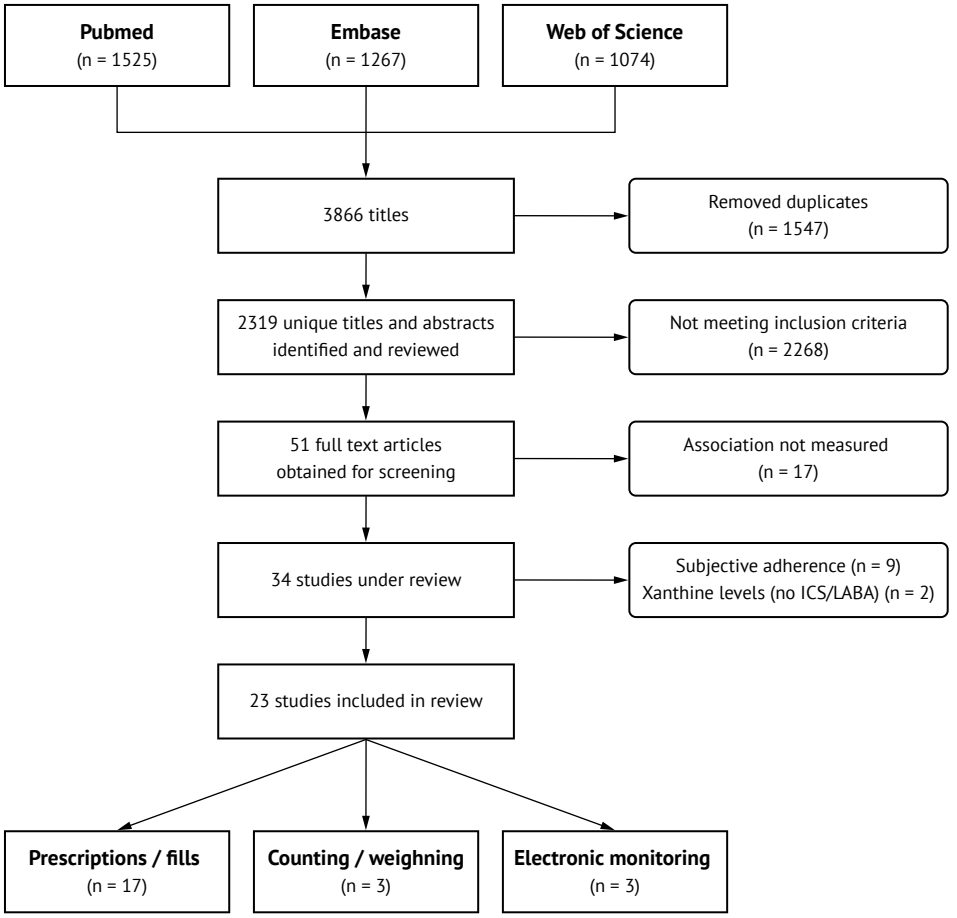

Figure 1 - PRISMA(63) flow diagram describing the steps for including studies in the review.

Measures of severe asthma exacerbations

Of the 23 studies using objective measures to assess adherence, 5 defined exacerbation as emergency department (ED) visit and/or hospitalization and/or OCS, 16 defined exacerbation as 2 out of 3 criteria. Five studies defined the need of OCS as a separate outcome. Only one study had need of OCS as the only outcome.

Asthma diagnosis

In 4 studies, the asthma diagnosis was based on physician diagnosis. In the remaining studies, diagnoses were based on disease codes (ICD-9) (n=9), disease codes and prescriptions (n=2), asthma controller therapy prescriptions (n=3), guidelines (n=4), or on study specific asthma definitions (n=1).

Table 1 - Characteristics of the 23 studies using objective measures to assess adherence.

Study	Design	Age (years)	Participants	Adherence measure	Adherence cutoff	Exacerbation measure	Estimates	Q
Refill data (MPR and prescriptions)								
Children								
Rust *et al.* 2013	Cohort	5 to 12	43,166	1. ICS PPDC 90days 2. ratio controller to total drugs	PPDC: ⩾50% or <50% Ratio: ⩾ 0.5 or <0.5	ED/Hosp	Exacerbation non adherent vs. adherent ratio: OR_{adj} ED: 1.21 (95% CI 1.14-1.27)I OR_{adj} Hosp: 1.70 (95% CI 1.45-1.98)	8
Camargo *et al.* 2007	Cohort	0 to 8	10,976	MPR ICS	Dichotomized at median MPR:0.08	Combined: Ed/ hosp visit	Exacerbation adherent vs. non adherent Budesonide HR_{adj} 0.32 (95% CI 0.19-0.68) Non-nebulised ICS HR_{adj} 0.25 (95% CI 0.13-0.47)	8
Bukstein *et al.* 2007	Cohort	0 to 4	11,407	Number prescription ICS	⩾2 vs. 1 prescription per 9 months before indexdate	Combined: ED/ hosp	Exacerbations: adherent vs. less adherent All controller therapy OR 0.80 (95% CI 0.59-1.10) ICS only: OR 0.60 (95% CI 0.37-0.99)	8
Bukstein *et al.* 2003	Randomized cohort	6 to 15	104	Filled prescription		ED/hosp/office visit/OCS	Adherent (⩾ 6) vs. non adherent (⩽5 fills) OCS: 26% adherent vs. 44%non adherent Montelukast users more adherent than Fluticasone users (p= 0.0003) No significant difference in Hosp/ED/office visits between mon-telukast/fluticasone groups.	7
Elkout *et al.* 2012	Cohort	children	3172	MPR ICS	Adequate MPR 80-120%	OCS	Adequate MPR (80-120%) was associated with higher risk of being prescribed OCS (ns) ICS only: OR_{adj} 1.02 (95% CI 1.00-1.04) LABA/ICS: OR_{adj} 1.12 (95% CI 0.58-2.11) LABA+ICS: OR_{adj} 1.43 (95% CI 0.75-2.71)	7
Herndon *et al.* 2012	Cohort	2 to 18	10,878	MPR ICS	3 MPR categories: 0-19%, 20-49%, >50%	ED/hosp	Higher adherence, less ED (p = 0.01): MPR ⩾ 0.50 vs.⩽ 0.19: ED: OR_{ad} 0.56 (95% CI 0.43-0.72) Hosp: OR_{adj} 0.96 (95% CI 0.67-1.36)	7
Adults								
Price *et al.* 2013	retrospective matched cohort study	12 to 80	30939	Beclomethason MPR and Ratio controller to total	4 MPR categories: <50%, 50-70%, 70-99%, >100%. Ratio: <0.5 or ⩾0.5	ED/hosp OCS	Higher exacerbation rates by better adherence to ICS.	9

Williams *et al.* 2011	Prospective asthma cohort	12 to 56	298	Moving CMA ICS	Per 25% increase MPR	Combined and ED/hosp/OCS	*Increase 25% adherence:* Combined outcome: HR_{adj} 0,89 (95% CI 0.81-0.97) p=0.009 OCS: HR_{adj} 0.90 (95% CI 0.80-1.0) p=0.043 ED: HR_{adj} 0.87 (95% CI 0.73-1.03) p=0.114 Hosp: HR_{adj} 0.99 (95% CI 0.65-1.51) p=0.971 *High (76-100% MPR) vs. low (0-25% MPR)* OR 0.58 (0.39-0.87)	8
Williams *et al.* 2004	Cohort	18 to 50	405	CMA CMG For ICS	Per 25% increase in CMA/CMG	Outpatient/ED/ hosp/OCS	Per 25% increase gap ED: RR_{adj} 1.25 (95% CI 0.84-1.85) OCS: RR_{adj} 1.26 (95% CI 0.95-1.67) Hosp: RR_{adj} 2.01 (95% CI 1.06-3.79) Per 25% increase CMA OCS: RR 0.75 (95% CI 0.58-0.97) Correlation Adherence CMA: ED: R -0,159, OCS: R -0.179,Hosp: -0.130 (ns)	8
Balkrishnan *et al.* 2000	Case-control	Older adults	751	Filled prescription ICS	0,1,2 refills in 2months before event	Combined: ED/ hosp	Exacerbation (referent=non adherent= 0 refills) OR_{adj} good (2 refills ICS): 0.62 (95% CI 0.42-0.90) OR_{adj} partial (1 refill ICS): 0.75 (95% CI 0.57-0.96)	8
Mattke *et al.* 2010	Cohort	0 to 65	12,476	MPR ICS	MPR quarters. Highest vs. lowest	Combined: ED/ hosp/ office	Lowest vs. highest adherence quarters Incidence of ED and hosp: not significantly different	8
Delea *et al.* 2008	Cohort	>=12	12907	MPR FCS	MPR quartiles per 3 months of follow-up.	ED/hosp or OCS	Per 25% increase mean adherence: ED/Hosp OR_{adj} 0,90 (95% CI 0,89-0,92) OCS: OR_{adj} 0.97(95% CI 0,94-0,996)	8
Stern *et al.* 2006	Cohort	6 to 99	97743	MPR all controllers		Combined ED/ hosp	75^{th} percentile MPR cut off vs. less adherent Exacerbation OR_{adj} 0.862 (95% CI 0.827-0.898)	8
McMahon *et al.* 2000	Cohort	12 to 45	4535	Days with ICS per 90 days.	0 days ICS 1-89 days 90 days	Combined: hosp+OCS And Hosp only	Combined exacerbation: 0 days adherent: OR_{adj} 0.77 (95% CI 0.44-1.35) 1-89 days adherent: OR_{adj} 1.02 (95% CI 0.60-1.73) Hosp: 0 days adherent: OR_{adj} 1.12 (95% CI 0.36-3.47) 1-89 days adherent: OR_{adj} 0.91 (95% CI 0.31-2.72)	7
Smith *et al.* 2009	Cohort	5 to 62	3013	MPR all controllers	MPR: 0-50%,50-80%, or>80%.	ED/Hosp	Risk of admission(ED/hosp) non adherent vs.: 50-80% adherent: OR 1.59 (95% CI 0.86-2.96) high adherent >80%: OR 2.11(95% CI 1.09-4.12)	7
Hyland *et al.* 2012	Cohort	adults	166	Prescription and records	> 75% recommended prescriptions	Combined: GP visit / ED/Hosp	Spearman correlation between asthma exacerbations and adherence was 0.21 (p=0.007)	6
Osman *et al.* 1999	Prospective cohort	adults	754	Requested prescription	Among pt with <7SABA: ⩽4 ICS vs 5-7ICS vs ⩾8ICS	Hosp/OCS	<7 SABA and <5 ICS versus 5-7ICS and >8 ICS: used few OCS (p=0.06) more hospital admissions (p<0.05)	5

Table 1 Continued - Characteristics of the 23 studies using objective measures to assess adherence.

Study	Design	Age (years)	Participants	Adherence measure	Adherence cutoff	Exacerbation measure	Estimates	Q
Electronical monitoring device (children only)								
Rohan *et al.* 2010	Prospective cohort	5 to 17	92	Electronical monitoring device ICS	Daily ICS use averaged over 5-day intervals.	Health care visits:(=ED/hosp/visit specialist)	Growth curve modeling: average healthcare related visits/year low adherent (1sd below mean): 0.76 moderate adherent:0.70 good adherent(1sd above mean): 0.65	6
McNally *et al.* 2009	Cohort	5 to 17	63 ICS+ LTRA users	Electronical monitoring device ICS adherence rate(=:mean percent prescribed)	Highest quartile: mean 0.62 vs. lowest quartile mean 0.20.	Healthcare utilization (=Hosp/ED/clinic visit)	Decline in fluticasone adherence was related to increased healthcare utilization: p<0.05 Rate of change in healthcare utilization related to fluticasone low vs. high adherence: R=-0.11 p=0.39 ns	6
Milgrom *et al.* 1996	Cross-sectional (4 visits)	8 to 12	24	Electronical monitoring device ICS and B-agonist	na	OCS	Mean adherence was 13.7% in cases vs. 68.2% in patients without OCS (P=0.008)	3
Weighing counting (w/c)								
Children								
Krishnan *et al.* 2012	Randomized controlled trial	5 to 12	140	w/c budesonide/placebo	na	ED/OCS	Treatment group–adherence4yrs interaction ED visits (yes vs. no); odds ratio -> p = 0.58 OCS (no. of courses/100 person years) p = 0.56	9
Lasmar *et al.* 2009	Prospective cohort	3 to 12	122	w/c beclomethoasone	na	Combined; asthma deterioration, OCS, ED, hosp	Adherence level 70,9% in group of patients without exacerbation vs. 44% in group of patients with exacerbations (p=0.004)	5
Adults								
Santos *et al.* 2008	Prospective cohort	>18	160	w/c ICS	Cut off point: 80% of prescribed dose administred	Exacerbation/ED	Adherent vs. non adherent: Exacerbation: 45.5% vs. 50% (ns) ED visits: 0.9±1.9 vs. 1.4±2.6 (p=0.2)	3

* Abbreviations: PPDC = proportion of prescribed days covered, ORadj = Odds Ratio adjusted, 95% CI = 95% confidence interval, p = p-value, ED = emergency department, Hosp = hospitalization, OCS = oral corticosteroids, HR = hazard ratio, ns = not significant, PY = person years, sd = standard deviation, vs. = versus, na = not applicable

MAIN RESULTS: adherence and exacerbations

Due to differences in design, exposure, outcome, cut-off values, assessments and definitions, studies differed substantially in effect magnitudes and this precluded a formal meta-analysis with pooling of results. We therefore report the findings separately for each type of objective adherence measure. The order of reporting within each category is based on quality score, indicated with the letter q. We separately reported results for children and adults. Details of the 23 studies included in the review are summarized in Table 1. The overall conclusions remained similar when papers with low quality (q≤6) were excluded.

An overview of the range of risk estimates, for those studies that reported risk estimates for the association between adherence and asthma exacerbation is shown in Figure 2 (for children) and Figure 3 (for adults).

Objective adherence measurements

To assess overall treatment adherence 17 studies used refill data, of these 11 used MPR measurements [20, 25-34] and 6 used number of prescription refills. [21, 22, 35-38] The remaining studies used either electronic monitoring devices (n=3) [9, 39, 40] or weighted canisters (n=3). [23, 41, 42]

The overall treatment adherence was low in pediatric and adult studies. In children, adherence measured as average MPR was only 20%-33.9% for ICS. [31, 40] Number of prescription fillings over the course of 1 year ranged from 4.7 to 5.5 times for fluticasone. [22, 38] In adults, MPR for ICS ranged between 15 [31, 32] and 54% [29].

Williams et al. demonstrated with a moving 6-months-average ICS adherence for each day of follow-up, that adherence to ICS medications began to increase just before the first asthma exacerbation, and continued to increase after the event. [27]

Association between exacerbation and objective adherence in paediatric studies (refill data)

Four out of 6 paediatric cohort studies using refill data reported that the risk of asthma exacerbation was 21-68% lower for children who were more adherent to their asthma controller medication compared to those who were less adherent. [25, 28, 31, 35] Rust et al. (q=8) observed this protective effect only if adherence was measured as controller to total ratio. In contrast, if adherence was measured as proportion of prescription days predicted (PPDC), lower PPDC was associated with lower ED/Hosp exacerbations. [25]

A previous study in 2003 by Bukstein et al. (q=7) found no significant differences between fluticasone and montelukast users (who were more adherent) in the frequency of asthma attacks requiring hospital admissions, acute office visits or ED-visits, but found a significant difference in the amount of OCS, which was higher for fluticasone than for montelukast. [22]

Finally, Elkout et al. (q=7) reported that the risk of being prescribed OCS in the year after first prescription of controller therapy was 2-43% higher in children with adequate MPR than those with inadequate MPR, although this difference was not statistically significant. [30]

Author	Q	N	outcome	adherence	OR	adherent vs non adherent
Rust et al.	8	43.166	hosp	Controller to total Ratio <0,5 or >0,5	0,59	
			ed	Controller to total Ratio <0,5 or >0,5	0,83	
Bukstein et al.	8	11.407	comb:ed/hosp	prescriptions: ⩾2 vs 1	0,60	
Camargo et al.	8	10.976	comb:ed/hosp	median MPR 0,08 is cut off	0,32	
Herndon et al.	7	18.456	hosp	MPR: >50% vs <19%	0,96	
			ed	MPR: >50% vs <19%	0,56	
Elkhout et al.	7	3.172	ocs	MPR: 80-120% vs less	1,02	

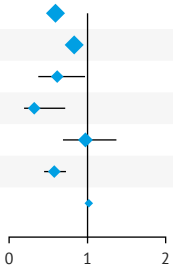

Figure 2 - Overview of pediatric studies publishing odds ratios (OR), sorted by quality score, number of participants and year published. (ctr = controller to total medication ratio, Comb = combined, ed = Emergency department visit for asthma, hosp = hospitalization for asthma, mpr = medication possession rate)

Author	Q	N	outcome	adherence	OR	adherent vs non adherent
Stern et al.	8	97.743	comb: ed/hosp	75th percentile vs less MPR	0,86	
Delea et al.	8	12.907	ocs	25%increase mean MPR	0,97	
			comb: ed/hosp	25%increase mean MPR	0,90	
Balkrishnan et al.	8	751	comb: ed/hosp	2 vs 0 refills	0,62	
Williams et al.	8	405	OCS	25% increase median cma	*RR 0.75	
Williams et al.	8	298	comb:ed/hosp/ocs	>75% vs <25% MPR	0,58	
McMahon et al.	7	4.535	hosp+ocs	90 vs 1-89 days adh	1,02	
			hosp	90 vs 1-89 days adh	0,91	
Smith et al.	7	3.013	comb: ed/hosp	>80% vs <50% MPR	0,47	

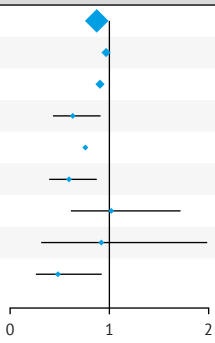

Figure 3 - Overview of adult studies publishing odds ratios (OR) or relative ratio (RR), sorted by quality score, number of participants and year published. (Comb = combined, perc = percentile, ed = Emergency department visit for asthma, hosp = hospitalization for asthma, mpr = medication possession rate, cma = cumulative medication availability, adh = adherence)

Association between exacerbation and objective adherence in adult studies (refill data)

Six out of 11 studies reporting on refills in adults showed that better adherence was associated with a reduced risk of severe asthma exacerbations. The 4 adult studies of good quality (q=8), reporting MPRs [20, 27, 29, 34] concluded that 25% increased adherence was associated with approximately 10% reduction of severe exacerbations. (HR_{adj} 0.89 [27], RR 0.75 [34], OR_{adj} 0.90 [29], OR_{adj} 0.86 [20])Similar associations were reported by Mattke et al. (q=8) for LTRA users but not for ICS users. [32] Interestingly Balkrishnan et al. (q=8) showed in ICS users a 40% decreased risk of an ED/hospitalization in adherent vs. non-adherent elderly patients with chronic pulmonary illnesses, including asthma. [21]

In contrast, five cohort studies (q=5-9) reported that the risk of OCS use and/or, hospitalization and/or ED visits increased with better adherence. [26, 33, 36-38]

Association between exacerbation and other measures of objective adherence

Three studies, 2 pediatric (q=5-9) and 1 adult (q=3) study, measured adherence by counting/weighing pills and canisters at the pharmacy or outpatient clinic. [23, 41, 42] Only one of these reported that adherence was associated with a reduced risk of asthma exacerbation. [41]

Three pediatric studies (q=3-6) measured adherence through electronic device monitoring, and all of these reported an association between low adherence and increased risk of severe asthma exacerbations; hospitalizations/ED visits [39, 40] or OCS [9].

Association between OCS courses and objective adherence

Seven studies, 3 paediatric and 4 adult studies, assessed adherence in relation to the need of an OCS course as a separate outcome. In 4 of these (q=7-8), the need of OCS courses was inversely related to the controller adherence rate, both in children [22] and adults. [22, 27, 29, 34] In the remaining 3 studies (q=7-9) this association was not significant in 1 paediatric study [23] and in 1 paediatric and 1 adult study an opposite, non-significant trend was observed. [30, 38]

DISCUSSION

To our knowledge, this is the first systematic review on the association between treatment adherence and severe asthma exacerbations. In the identified articles, we observed that low adherence was common. Despite heterogeneity amongst studies in terms of definitions of adherence and asthma exacerbations, the majority of the high quality studies consistently reported an association between low adherence and higher risk of severe asthma exacerbations, both in adults and children.

We identified important differences and limitations in the included studies. Firstly, the majority of studies were classified as moderate to low quality, largely because of flaws in the study methods, e.g. small sample sizes, which may compromise power, and cross sectional designs that are prone for bias. When excluding studies of poor or moderate quality (q<6) or excluding studies that used another design than cohort studies, the overall conclusion remained namely that good adherence was associated with fewer severe asthma exacerbations.

Secondly, included studies varied widely with regard to the definition of adherence. Indeed, there is no standardized method to measure adherence, and each measure has its own strengths and limitations. [11, 43, 44] Objective measures are considered to be more reliable and accurate than indirect measures. [11] Electronic device monitoring is usually considered the gold standard because of a detailed assessment of adherence patterns. Although it has the benefit to identify and exclude “dumping” (deliberate emptying of inhaler before study visits to conceal non-adherence) from analyses, unfortunately such monitoring is expensive and often prone to device failure. [11, 33]

The most cost-effective method to assess adherence is by self-report. However, the reliability of this method is questionable [45] as it is well known that patients over-report their adherence, [9, 11, 46] even in a clinical trial setting. [23] Hence self-report was not included in this study.

The majority of studies calculated the MPR, a common way to measure medication adherence from claims or pharmacy data and has been found to be useful and reasonably accurate. [47, 48] These data have the advantage to be easily accessible and inexpensive. [44] The drawback of these databases is that details about devices and day-to-day patterns of adherence are not always recorded. [11, 44]

In a pragmatic trial, patients are randomized within a real life setting which combines the sound methodology of RCT with daily practice enlarging the external validity of study results. This external validity is crucial for study investigating treatment adherence and associated factors. [49]

All methods have their sets of benefits and limitations. [50] It was suggested that the best design would probably be a combination of observational studies, pragmatic trials and RCTs, as all have advantages and drawbacks and they are not designed to answer the same questions. [51]

Furthermore, the number of prescriptions is highly influenced by the level of asthma control. Indeed, patients appear to self-titrate their medication, showing more adherence to therapy with worse level of control. [26] Additionally the number of prescriptions is also influenced by the quality and reliability of physicians prescribing. The best method to tease this out is by using a ratio of long-term controller to total asthma medications, in which the denominator and numerator increase with increasing severity, but the numerator is more specifically reflective of adherence to therapy. [25]

Even if studies used a common methodology to assess adherence, a wide variety in cut-off values to define "adherent patients" was observed. This arbitrary selection of adherence cut points is of considerable concern. Traditionally, medication adherence is dichotomized using a cut-off value (e.g. 80%) which is derived from studies in other chronic diseases, like HIV and hypertension [52], but not necessarily holds for asthma.

We noted heterogeneity in outcome definitions, despite international guidelines on the definitions and assessment of severe asthma exacerbations. [53] This might partly be explained by the data being used, e.g. pharmacy data not always have detailed information on disease codes and/or symptoms and diagnosis. As asthma is a difficult diagnosis, especially in children, risk of asthma misclassification, if based on prescription data only, is high.

It was quite remarkable that most studies did not attempt to measure whether and how medication was actually taken. This inhaler competence, the skill to inhale correctly, is particularly relevant for asthma medication as inhaling of drugs requires considerable skill and practice. [54] Even if medication is taken daily, deposition in the lungs will be low in case of incorrect inhalation technique. [55] Newer devices such as breath-actuated inhalers and smart nebulizers, that impose breathing patterns and record lung deposition, may partly overcome this problem, but

still require a high level of co-operation. Smart-nebulizers are expensive and the experience in children with asthma is limited. [56]

Still, all of these methods can overestimate adherence and there remains a number of complex issues affecting optimal medication use in children with asthma e.g. a lack of parental knowledge about asthma medications, parental beliefs and fears, and the child's self-image. (57)

Some of the studies were at risk of bias and/or did not adjust for potential confounders. There are limitations arising from the observational nature of the included studies. One important bias is the "healthy adherer effect", where healthier people are predisposed to follow medical advice, because they are more concerned about their health. Other biases in this type of research are recall bias and observer/investigator bias when using questionnaires. [58] Furthermore, misclassification of adherence caused by dumping or over-reporting might have contributed to an underestimation of the role of adherence in mediating the observed treatment effects.

"Asthma-severity" is an important confounder that is difficult to control for, as details on asthma severity are often lacking in database studies. Other potential confounders are environmental factors such as pollution or smoking habits of the parents.

Although the majority of papers of good quality indicated that higher levels of adherence were associated with a reduced risk of severe asthma exacerbations, this was not confirmed in all studies. Some studies even reported an inverse association between treatment adherence and risk of severe asthma exacerbations. This might be explained by the fact that the number of prescriptions was used as a proxy for adherence [33, 38], or because unusual cut off values for adherence were used. [37] Furthermore, there are a couple of general potential explanations for this inverse association. Treatment need is higher in patients with poorly controlled asthma, who are by definition at risk of asthma exacerbation. This higher need of treatment will result in increased prescription of asthma controller therapies with hence a higher MPR. [38, 45] Another explanation is self-titrating of medications; patients show more adherence to therapy with worse levels of control, thus positively influencing the MPR. [26] A third explanation could be the heterogeneity amongst asthma patients in treatment response; some patients reduce their prescribed controller medication without negative consequences [38] whereas other patients continue to have poor outcomes despite good adherence. [59] Additionally, there is no known dose of medication, or duration of treatment. Hence, the "low" adherence for some people may be adequate for them most of the time.

The main strengths of this review are the comprehensiveness of the searches and our standardized approach to study selection, data extraction and quality assessment.

However, our review has some limitations that need to be considered. Only published data was included, but the relatively small number of relevant publications suitable for this review warrants caution given the possibility of publication bias. Publication bias, is a type of error that may affect the results of a meta-analysis because studies with statistically significant positive findings are more likely to be published than studies with negative results. [60] However, given

the heterogeneity, inclusion of additional studies would have been unlikely to undermine our overall conclusion.

Overall, this review highlights the importance of adherence to prevent severe asthma exacerbations. This is in agreement with recent predictive models, which observed that improvements in medication adherence could lead to significant improvements in asthma outcomes. [61] It is clear that better studies about adherence treatments are needed but also more homogeneous outcomes and study design would be useful in order to reach conclusions.

For clinicians, it seems evident that efforts directed at improving, evaluating and measuring adherence should be a routine component of asthma care. [62] The recognition of non-adherence is an important first step towards optimal asthma control.

CONCLUSION

Despite the limitations, in this review the majority of the papers of good quality indicated that higher levels of adherence were associated with a reduced risk of severe asthma exacerbations. Adherence to asthma controller therapy was generally very low.

To further elucidate the association between adherence and risk of asthma exacerbations, there is a need for new, well designed real-life prospective studies, using consistent standardized measures for both treatment adherence (preferably electronic monitoring) and asthma exacerbations.

Future research should also include inhaler competence as it is an important confounder in the association of interest, and essential to disentangle the association between adherence and treatment outcomes.

REFERENCES

1. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007 Sep;62(9):758-66.
2. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012 Mar 19;12(1):204.
3. Bender BG, Rand C. Medication non-adherence and asthma treatment cost. Curr Opin Allergy Clin Immunol. 2004 Jun;4(3):191-5.
4. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008 Jan;31(1):143-78.
5. Choi TN, Westermann H, Sayles W, Mancuso CA, Charlson ME. Beliefs about asthma medications: patients perceive both benefits and drawbacks. *J Asthma*. 2008 Jun;45(5):409-14.
6. Harrison B, Stephenson P, Mohan G, Nasser S. An ongoing Confidential Enquiry into asthma deaths in the Eastern Region of the UK, 2001-2003. *Prim Care Respir J*. 2005 Dec;14(6):303-13.
7. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest*. 2006 Jul;130(1 Suppl):65S-72S.
8. Cote I, Farris K, Feeny D. Is adherence to drug treatment correlated with health-related quality of life? Qual Life Res. 2003 Sep;12(6):621-33.
9. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol*. 1996 Dec;98(6 Pt 1):1051-7.
10. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am*. 2005 Feb;25(1):107-30.
11. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med*. 1994 Feb;149(2 Pt 2):S69-76; discussion S7-8.
12. Williams LK, Joseph CL, Peterson EL, Wells K, Wang M, Chowdhry VK, et al. Patients with asthma who do not fill their inhaled corticosteroids: a study of primary nonadherence. *J Allergy Clin Immunol*. 2007 Nov;120(5):1153-9.
13. Chan PW, DeBruyne JA. Parental concern towards the use of inhaled therapy in children with chronic asthma. Pediatr Int. 2000 Oct;42(5):547-51.
14. Allen DB. Inhaled steroids for children: effects on growth, bone, and adrenal function. *Endocrinol Metab Clin North Am*. 2005 Sep;34(3):555-64, viii.
15. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007 Jan-Feb;10(1):3-12.
16. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009 Jul 1;180(1):59-99.
17. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. Eur Respir J. 2008 Sep;32(3):545-54.
18. Goodman M, Hays S. Asthma and swimming: a meta-analysis. *J Asthma*. 2008 Oct;45(8):639-47.
19. Wells GS, B.; O'Connell, D.; Petersen, J.; Welch, V.; Losos, M.; Tugwell, P. . The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in metaanalyses. : Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
20. Stern L, Berman J, Lumry W, Katz L, Wang L, Rosenblatt L, et al. Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data. *Ann Allergy Asthma Immunol*. 2006 Sep;97(3):402-8.
21. Balkrishnan R, Christensen DB. Inhaled corticosteroid nonadherence and immediate avoidable medical events in older adults with chronic pulmonary ailments. *J Asthma*. 2000;37(6):511-7.
22. Bukstein DA, Luskin AT, Bernstein A. "Real-world" effectiveness of daily controller medicine in children with mild persistent asthma. Ann Allergy Asthma Immunol. 2003 May;90(5):543-9.
23. Krishnan JA, Bender BG, Wamboldt FS, Szefler SJ, Adkinson NF, Jr., Zeiger RS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. *J Allergy Clin Immunol*. 2012 Jan;129(1):112-8.

24. Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Ann Pharmacother*. [Comparative Study Research Support, Non-U.S. Gov't]. 2009 Jan;43(1):36-44.

25. Rust G, Zhang S, Reynolds J. Inhaled corticosteroid adherence and emergency department utilization among Medicaid-enrolled children with asthma. *J Asthma*. 2013 Sep;50(7):769-75.

26. Price D, Thomas M, Haughney J, Lewis RA, Burden A, von Ziegenweidt J, et al. Real-life comparison of beclometasone dipropionate as an extrafine- or larger-particle formulation for asthma. *Respir Med*. 2013 Jul;107(7):987-1000.

27. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol*. 2011 Dec;128(6):1185-U500.

28. Camargo CA, Jr., Ramachandran S, Ryskina KL, Lewis BE, Legorreta AP. Association between common asthma therapies and recurrent asthma exacerbations in children enrolled in a state Medicaid plan. *Am J Health Syst Pharm*. 2007 May 15;64(10):1054-61.

29. Delea TE, Stanford RH, Hagiwara M, Stempel DA. Association between adherence with fixed dose combination fluticasone propionate/salmeterol on asthma outcomes and costs*. *Curr Med Res Opin*. 2008 Dec;24(12):3435-42.

30. Elkout H, Helms PJ, Simpson CR, McLay JS. Adequate Levels of Adherence with Controller Medication Is Associated with Increased Use of Rescue Medication in Asthmatic Children. *PLoS One*. 2012 Jun 27;7(6).

31. Herndon JB, Mattke S, Evans Cuellar A, Hong SY, Shenkman EA. Anti-inflammatory medication adherence, healthcare utilization and expenditures among Medicaid and children's health insurance program enrollees with asthma. *Pharmacoeconomics*. 2012 May;30(5):397-412.

32. Mattke S, Martorell F, Hong SY, Sharma P, Cuellar A, Lurie N. Anti-inflammatory medication adherence and cost and utilization of asthma care in a commercially insured population. *J Asthma*. 2010 Apr;47(3):323-9.

33. Smith K, Warholak T, Armstrong E, Leib M, Rehfeld R, Malone D. Evaluation of risk factors and health outcomes among persons with asthma. *J Asthma*. 2009 Apr;46(3):234-7.

34. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol*. 2004 Dec;114(6):1288-93.

35. Bukstein DA, Murphy KR, Katz LM, Ramachandran S, Doyle JJ, Stern LS. Outcomes among a young population of pediatric asthma patients using controller therapies: Results from a retrospective database analysis. Pediatr Asthma Allergy Immunol. 2007;20(4):211-21.

36. Hyland ME, Whalley B, Halpin DM, Greaves CJ, Seamark C, Blake S, et al. Frequency of non-asthma GP visits predicts asthma exacerbations: an observational study in general practice. *Prim Care Respir J*. 2012 Dec;21(4):405-11.

37. McMahon AD, Lipworth BJ, Davey PG, Morris AD, Macdonald TM. Continuity of prescribing with inhaled corticosteroids and control of asthma. Pharmacoepidemiol Drug Saf. 2000 Jul;9(4):293-303.

38. Osman LM, Friend JAR, Legge JS, Douglas JG. Requests for repeat medication prescriptions and frequency of acute episodes in asthma patients. *J Asthma*. 1999;36(5):449-57.

39. McNally KA, Rohan J, Schluchter M, Riekert KA, Vavrek P, Schmidt A, et al. Adherence to combined montelukast and fluticasone treatment in economically disadvantaged african american youth with asthma. J Asthma. 2009 Nov;46(9):921-7.

40. Rohan J, Drotar D, McNally K, Schluchter M, Riekert K, Vavrek P, et al. Adherence to pediatric asthma treatment in economically disadvantaged African-American children and adolescents: an application of growth curve analysis. *J Pediatr Psychol*. 2010;35(4):394-404.

41. Lasmar L, Camargos P, Champs NS, Fonseca MT, Fontes MJ, Ibiapina C, et al. Adherence rate to inhaled corticosteroids and their impact on asthma control. *Allergy*. 2009 May;64(5):784-9.

42. Santos Pde M, D'Oliveira A, Jr., Noblat Lde A, Machado AS, Noblat AC, Cruz AA. Predictors of adherence to treatment in patients with severe asthma treated at a referral center in Bahia, *Brazil. J Bras Pneumol*. 2008 Dec;34(12):995-1002.

43. Desai M, Oppenheimer JJ. Medication adherence in the asthmatic child and adolescent. Curr Allergy Asthma Rep. 2011 Dec;11(6):454-64.

44. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest* Med. 2012 Sep;33(3):405-17.

45. Riekert KA, Butz AM, Eggleston PA, Huss K, Winkelstein M, Rand CS. Caregiver-physician medication concordance and undertreatment of asthma among inner-city children. *Pediatrics*. 2003 Mar;111(3):e214-20.

46. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. *Am J Respir Crit Care Med*. 2004 Dec 15;170(12):1281-5.

47. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother.* [Research Support, N.I.H., Extramural]. 2006 Jul-Aug;40(7-8):1280-88.

48. Mattke S, Jain AK, Sloss EM, Hirscher R, Bergamo G, O'Leary JF. Effect of disease management on prescription drug treatment: what is the right quality measure? *Disease Management.* 2007 Apr;10(2):91-100.

49. Helms PJ. 'Real world' pragmatic clinical trials: what are they and what do they tell us? *Pediatr Allergy Immunol.* 2002 Feb;13(1):4-9.

50. Schmier JK, Leidy NK. The complexity of treatment adherence in adults with asthma: challenges and opportunities. *J Asthma.* 1998;35(6):455-72.

51. Bousquet J, Schunemann HJ, Zuberbier T, Bachert C, Baena-Cagnani CE, Bousquet PJ, et al. Development and implementation of guidelines in allergic rhinitis - an ARIA-GA2LEN paper. *Allergy.* 2010 Oct;65(10):1212-21.

52. Steiner JF, Earnest MA. The language of medication-taking. *ANN INTERN MED.* 2000 Jun 6;132(11):926-30.

53. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. J *Allergy Clin Immunol.* 2012 Mar;129(3 Suppl):S1-8.

54. Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C, Scheuch G, et al. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. *Respir Med.* 2013 Jan;107(1):37-46.

55. Newman SP. Scintigraphic assessment of therapeutic aerosols. Crit Rev Ther Drug Carrier Syst. 1993;10(1):65-109.

56. Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J.* 2011 Jun;37(6):1308-31.

57. Grover C, Armour C, Asperen PP, Moles R, Saini B. Medication use in children with asthma: not a child size problem. *J Asthma.* 2011 Dec;48(10):1085-103.

58. Dales RE, Cakmak S, Judek S, Dann T, Coates F, Brook JR, et al. Influence of outdoor aeroallergens on hospitalization for asthma in Canada. *J Allergy Clin Immunol.* 2004 Feb;113(2):303-6.

59. Smyth AR, Barbato A, Beydon N, Bisgaard H, de Boeck K, Brand P, et al. Respiratory medicines for children: current evidence, unlicensed use and research priorities. *Eur Respir J.* 2010 Feb;35(2):247-65.

60. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet.* 1991 Apr 13;337(8746):867-72.

61. Schlender A, Alperin PE, Grossman HL, Sutherland ER. Modeling the impact of increased adherence to asthma therapy. PLoS One. 2012;7(12):e51139.

62. Forno E, Celedon JC. Predicting asthma exacerbations in children. *Curr Opin Pulm Med.* 2012 Jan;18(1):63-9.

63. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009 Jul 21;6(7):e1000097.

SUPPLEMENTS

Online Table 1 - Search strategy per library.

PubMed :
(asthma*[tw] AND (exacerbat*[tw] OR oral corticosteroid*[tw] OR systemic corticosteroid*[tw] OR hospitali*[tw] OR acute[tw] OR emergen*[tw] OR attack*[tw])) AND (adheren*[tw] OR adhaeren*[tw] OR complian*[tw] OR cooperat*[tw] OR co-operat*[tw] OR nonadheren*[tw] OR nonadhaeren*[tw] OR noncomplian*[tw] OR noncooperat*[tw] OR concordance[tw])
EMbase: human, short survey/article/article in press
((asthma* AND (exacerbat* OR ((oral OR systemic) NEAR/1 corticosteroid*) OR hospitali* OR acute OR emergen* OR attack*)) AND (adheren* OR adhaeren* OR complian* OR cooperat* OR (co NEAR/1 operat*) OR nonadheren* OR non-adhaeren* OR noncomplian* OR noncooperat* OR concordance)):ti,ab,de
Web of Science: article
((asthma* AND (exacerbat* OR ((oral OR systemic) NEAR/1 corticosteroid*) OR hospitali* OR acute OR emergen* OR attack*)) AND (adheren* OR adhaeren* OR complian* OR cooperat* OR (co NEAR/1 operat*) OR nonadheren* OR non-adhaeren* OR noncomplian* OR noncooperat* OR concordance))

Online Table 2 - Quality criteria adapted from the NOS criteria (19).

	Points
1. Overall study design:	
Cross-sectional studies	0
Cohort & case-control studies, non-randomized experiments	1
Randomized trials or crossover experiments	2
2. Participant selection:	
Evidence of selection in study e.g. high loss to follow-up	0
Evidence of selection in setup study database, like database of specific insurance company, or a specific referral hospital.	1
Study with complete follow-up or studies with ≥80% participation and no evidence of selection.	2
3. Exposure assessment:	
Self-reports of adherence	0
Documented evidence (e.g. medical records)	1
Objective assessment of adherence (e.g. claims, refills, electronic monitoring)	2
4. Outcome ascertainment:	
Self-reports of exacerbations	0
Documented exacerbations (other than GINA; additional doctor visit/symptoms)	1
Documented exacerbations (e.g. GINA definition: OCS, ER, hospitalization)	2
5. Adjustment of results for confounding:	
No adjustment	0
Some adjustment	1
Detailed multivariate modeling, randomization or cross-over design or stratification or model fitting	2

5 PREFERENCE POLICY

Chapter 5.1

Brand versus generic inhalation medication use and frequency of switching in children and adults: a population-based cohort study

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Submitted.

ABSTRACT

BACKGROUND The expiration of the patent of brand inhalation medications and the ongoing pressure on the healthcare budget resulted in a growing market for generic inhalation medications. Switching between generic and brand medications often implies change of inhalation device, which might jeopardize adherence and inhalation technique, ultimately resulting in poor asthma control. Few data are available on the frequency of switching between generic and brand inhalation medications and between devices and the effect on adherence.

AIMS To study the frequency of brand and generic use, of switching between device and of switching between brand and generic inhalation medication as well as its effect on adherence.

METHODS Data from the Dutch PHARMO Database Network was used. All inhaled medications dispensed between 2003-2012 in patients aged ≥5 years were extracted. Switching was defined as either changing from brand to generic or vice versa, or change in device. Adherence to maintenance inhaled medication was calculated using the medication possession ratio (MPR) namely the sum of the days dispensed divided by treatment duration.

RESULTS The total cohort comprised 70,053 patients with 1,604,488 dispenses. The percentage of patients in the switching cohort (n=56,853) who switched between brand and generic inhalation medication was 5% per year. Of the patients using medication with possible switch in device, 5% per year switched between devices. Median MPRs over the first 12 months following the first brand or generic dispensing of maintenance medication were between 33 and 55%. MPR was higher in the first 12 months after switch to generic budesonide and beclomethasone, compared to the 12 months before switch. (59 vs 75% p=0.015, and 51 vs 59% p=0.011)

CONCLUSIONS Switching between brand and generic inhalation medication per calendar year was occurred in 5% of the patients. However generic dispensing is increasing. Switching between devices occurred in 5% and 16% of the patients used more than 1 device in 1 year. Adherence to both generic and brand inhalation medication was considerably low. The finding that there is no net negative impact on adherence in patients who switch from brand to generic is promising, however adherence was low. Further research of switching is needed to investigate potential clinical consequences on disease control.

INTRODUCTION

Asthma is a major problem with 334 million people having asthma worldwide. [1] In the Netherlands with a total population of 16,9 million, over half a million people are diagnosed with asthma. Asthma treatment requires individually tailored therapy and selection of the most appropriate treatment, which is dependent on both the choice of drugs and inhaler device. [2] Good inhalation techniques for proper use of these devices are crucial to obtain asthma control. To control healthcare costs, Dutch health authorities encouraged a preference policy by the health insurance companies which started in 2005, adopted as a law in 2008 but still causes a lot of debate. [2-4] The policy favours the use of generic drugs as alternatives to more expensive brand-name products, substitution to generic can be done in the pharmacy independent of the physician's prescription, unless it is indicated that brand needs to be dispensed.

Switching of inhalation therapy often coincides with a change of inhalation device. The choice of type of inhaler is based on patient characteristics (like age and inspiratory force), on the characteristics of the inhaler (like multidose/single dose, powder/aerosol) and patient preference. [5] Each device requires a different inhalation manoeuvre, which needs to be carefully instructed. Unexpected change in inhaler device may lead to confusion, and incorrect use, which may lead to no or less drug inhaled.

Before generic medications are marketed, demonstration of clinical bioequivalence is needed. As the drug delivery and intended action of orally inhaled drug products for local action, such as dry powder inhalers (DPI) do not rely on the systemic circulation, the bioequivalence cannot be demonstrated based on drug concentration in blood/plasma. [6] Therefore demonstration of bioequivalence of these products is more challenging. The guideline from the European Medicines Agency on requirements for clinical documentation of orally inhaled products for asthma and COPD states that for inhalers with the same substance and required flow rate, similar in vitro performance is sufficient to show equivalence. [7] In vitro performance includes particle size distribution, fine particle fraction of emitted dose, flow rate dependency tested under validated circumstances.

In other therapeutic domains, there are doubts about the bioequivalence of generic drugs. [8] In addition, there is evidence that generic substitution has a negative impact on adherence and disease control through changes in appearance (colour, size, and packaging). [9-12] In asthma and COPD the type of device is important as it is tailored to the patient's characteristics with respect to age, capability and inspiratory flow. [13] The change of inhalation device may increase confusion and mistakes in inhalation technique, and discourage appropriate use of the device. Few data were reported on the frequency of use and switching between generic and brand inhaled medication and whether generic substitution affects treatment adherence, in New-Zealand [14-16] and in the UK. [17, 18] Driven by the need to assure the quality of care, we need to understand the impact of switching between brand and generic inhalation medications.

In this study we aim to investigate the effects of preference policy by studying (1) the frequency

of use, and switching between generic and brand inhalation medication, and (2) of switching between devices and (3) to compare adherence before and after switching to generic inhalation medications in real life in the Netherlands.

METHODS

Setting

We conducted a population-based cohort study using data from the PHARMO Database Network (www.pharmo.nl). This population-based patient centric data network of healthcare databases combines data from different healthcare settings, including general practitioner (GP), in- and outpatient pharmacy and hospitals. It includes high quality and complete information linked on a patient level of, among other data, patient demographics, drug dispensing records from community pharmacies, hospital discharge records, and GP diagnoses of more than two million individuals throughout the Netherlands. [19] The Out-patient Pharmacy Database comprises detailed information on the dispensed package, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification as well as sales registry number. [20]

Study population

The dynamic study population comprised all patients aged 5 years or older, using inhaled medication for at least 1 year during the study period. Medication use was defined as at least 1 year between start of the first prescription and start of the last prescription. All patients were followed from study entry (1st of January 2003 or 5th birthday, whichever came last) until the end of the study period (1st of January 2013 or leaving the pharmacy, whichever occurred first. When restricted to only patients with asthma, (with a disease code for asthma (ICPC code 'R96') and without disease code for COPD (ICPC code 'R95) follow-up started on the date of disease code or on the 1st of January 2003, whichever was last.

Because switching is only possible with when a generic or other device is available, we constructed subcohort to study switching between brand-generic medications and the adherence before and after switch, as well as switching between devices.

Brand-generic cohort

From the study population, we identified all patients, who used inhalation medication for which generic substitutes were available at any time between 2003 and 2012. The information about availability of generic substitutes during the study period was retrieved from the medicines information bank from the Dutch Medicines Evaluation Board. [21] The inhalation medications for which generic substitutes were available included short-acting beta agonists (SABA),

shot acting muscarinic antagonists (SAMA) and inhaled corticosteroids (ICS), and long-acting beta agonists (LABA). (Table 1) If less than 0.5% of the total dispenses were generic dispenses, this ATC is not included in the generic analyses.

To calculate use of generic and brand medication and the frequency of switching per calendar year we selected only patients who had 1 year of follow-up and had at least 1 dispensing in that specific calendar year. Mixed use was defined as both generic and brand dispenses in 1 calendar year. Switch was defined as change from brand to generic brand dispensing or vice versa compared to the prior dispensing of a medication with the same ATC code in the previous 365 days, but not necessarily in the same calendar year. (Online Figure 1)

We categorized patients into 3 groups, 1. patients exclusively using brand name inhalation medication 2. patients exclusively using generics and 3. patients using both generic and brand medication in a specific calendar year. (=mixed users).

Device cohort

From the study population, we identified all patients who used inhalation medication for which different devices per ATC code were available between 2003 and 2012.

Table 1 - Overview of brand inhalation medication and generic substitute available between 2003 and 2012 per ATC code.

ATC code	Generic	Brand
R03BA02	Budesonide	Pulmicort®
R03BA01	Beclomethason	Aerobec®, Becotide®, Becloforte®, QVAR®
R03BB01	Ipratropium bromide	Atrovent®
R03AC13	Formoterol	Atimos®, Foradil®, Oxis®
R03AK04	Ipratropium/salbutamol	Combivent®
R03AC02	Salbutamol	Aerolin®, Aeromir®, Ventolin®

Table 2 - Overview of subcategories for all dry powder inhales (DPI) and pMDI (only beclomethasone) available between 2003-2012.

ATC code	Medication	DPI device
R03AC02	salbutamol, Ventolin®	Cyclocaps, diskus, novolizer, rotadisk
R03AC12	Serevent®, salmeterol	Diskus, rotadisk
R03AC13	Foradil®, formoterol, Oxis®	Clickhaler, cyclocaps, diskus, easyhaler, novolizer, turbuhaler
R03BA01	beclometason, Becotide®	Cyclocaps, rotadisk
R03BA02	budesonide, Pulmicort®	Clickhaler, cyclocaps, easyhaler, novolizer, turbuhaler
R03BA05	Flixotide®, Fluticason, Flutide®	Diskus, rotadisk
R03BB01	Atrovent®, ipratropium	Aerocaps, cyclocaps, inhalette
ATC code	**Medication**	**pMDI device**
R03BA01	Beclomethason, Becloforte®, Qvar®	Autohaler (breath-actuated), extrafine, becloforte, beclomethason

We classified the type of device per dispensing, into one of the following; pressurized metered dose inhalers (pMDI), dry powders inhalers (DPI), or nebulizers. Switching was defined as switch between devices with the same ATC code.

To gain more insight into switching within device groups, we classified the DPI into Clickhaler®, Cyclocaps®, Diskus®, Easyhaler®, Inhalette®, Novolizer®, Rotadisk®, and Turbuhaler®. For the pMDI's only beclomethasone (ATC code R03BA02) was subcategorized into Becotide®, Becloforte®, Extrafine® and Autohaler®. (Table 2)

Switching was defined as switch between devices with the same ATC code.

Adherence

Adherence was calculated for the three maintenance medications for which a generic substitute was available namely beclomethasone, budesonide, and formoterol. Adherence was calculated by using the medication possession rate (MPR). MPR was defined as the sum of the days for which inhalation medication was dispensed divided by the total number of days between the first and the last prescription plus the duration of the last prescription, multiplied by 100 and expressed as a percentage. A periodMPR was calculated in the 6 and 12 month period following the first dispense for patients exclusively on brand or generic. To compare adherence before and after switching, only patients for whom an MPR could be calculated both before and after switch were included, to control for patient characteristics. MPR in patients with a switch was calculated in the 6 and 12 months before and after the switch date. (online Figure 2) We excluded the switch dispense from this analysis as this would introduce differential overestimation of adherence in patients who switched. In case of multiple switching the follow-up time was censored at the next switch.

Statistical methods

Descriptive statistics were used where numbers are provided by counts and percentages. For continuous variables we provided medians and interquartile ranges (IQR).

To describe the use of generic and brand medication, we divided the number of users with only generic, or only brand, or brand and generic dispenses by the total number of users per specific calendar year.

To describe the switching patterns, in terms of generic or brand medication and also in terms of device, the prevalence of dispensing was calculated as percentage of users per calendar year, per ATC code and per device. We stratified by gender, frequency of use (1-3 versus >4 dispenses per year), and by age (5-18 vs ≥18).

In a sensitivity analysis we repeated the analysis in patients who have a disease code for asthma and do not have a disease code for COPD, follow-up started from the date of asthma diagnose.

To compare adherence before and after switch, we tested MPR differences by paired measurements with the Wilcoxon signed rank test.

All analyses were performed in SPSS version 21, SPSS Inc, Chicago. For difference in adherence we considered a p-value <0.05 as significant.

RESULTS

The total study population included 70,052 patients with a total of 1,604,488 dispenses of inhalation medication. Median age at cohort entry was 44.5 years (IQR 25.5-59.7), and 47% were men. 14,975 (21%) patients had a disease code for asthma, 9,328 (13%) had a disease code for COPD. 636 (1%) of all patients had both disease codes. At cohort entry 13,365 (19%) were children <18 years old. An overview of the cohorts is shown in Figure 1.

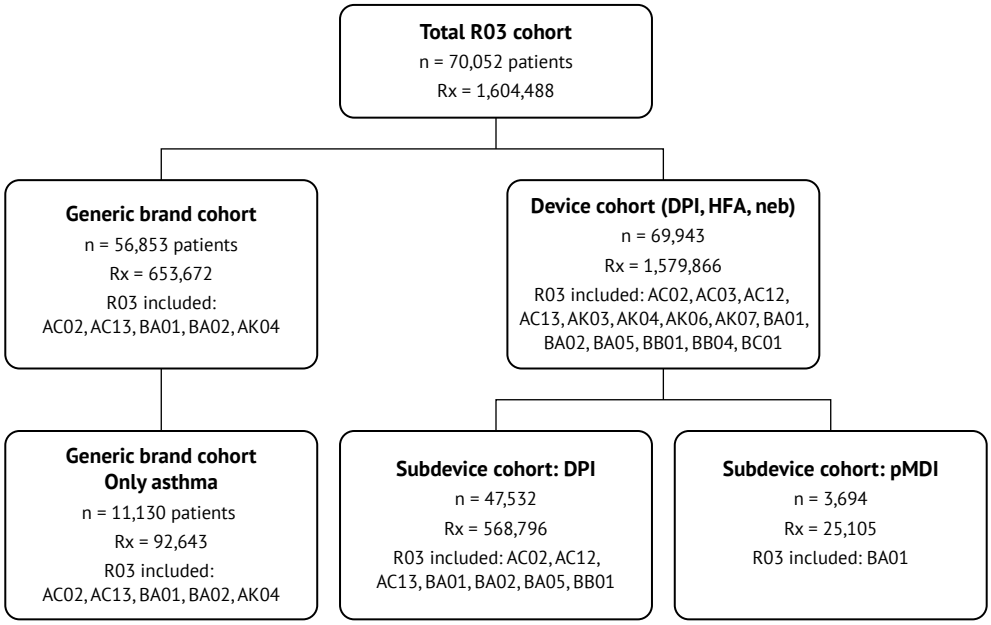


Figure 1 - Overview of the different cohorts.

Brand-generic switching

The brand-generic cohort, which was defined to estimate the prevalence of switching from brand to generic drugs and vice versa, consisted of 56,853 patients with 653,672 dispenses for which generic substitute was available. Of these 194,224 (29.7%) were generic dispenses. The highest generic dispensing rate was for Beclomethasone, 59% of the total beclomethasone dispenses from 2003-2013 were generics.

In all calendar years the number of users and the dispenses per calendar year were lower for girls than for boys. (13,260 total users with 26,410 dispenses for girls versus 19,668 total users with 39,965 dispenses for boys). For adults the number of dispense per year as well as the total

number of dispenses was higher for women compared to men (women: 96,216 total users total dispenses 305,270 versus men: total users 78,405 and total dispenses 262,531.) However, the patterns of generic, brand, mixed use and switching were similar for gender.

On average 10% of the patients in the brand generic cohort used both generic and brand inhaled medication (=mixed use), in all ATC codes, in one calendar year. (Figure 2). The proportion of generic users increased from 18% in 2003 to 31% in 2012.

Switching between brand and generic medication with the same ATC code was observed in 5% of the brand generic cohort per year, and remained stable over time. (Figure 3) We observed that the proportion of switching per ATC code was highest in salbutamol, with on average 6% of the salbutamol users switched in the study period. The pattern of switching in salbutamol over calendar year is shown in Figure 4. When studying beclomethasone (ATC=R03BA01), the switching percentage in beclomethasone (R03BA01) was highest in 2003 and 2004, both from brand to generic as from generic to brand, but dropped from 2005 onwards. (Figure 5). The number of generic dispenses increased in 2003 and 2004, but decreased thereafter. (online Figure 3)

The above results were similar when we restricted to patients with an asthma disease code (n=14,339). Absolute numbers were much lower.

All results were similar when stratified by use (high use (≥4 dispenses per calendar year) vs low use 1-3 dispenses per year). (data not shown)

Device switching

For patients within the device cohort (n=69,943) the use of pMDI, DPI and nebulizers is shown in Figure 6. In children most dispenses were pMDI's (49%), while in adults DPI were dispensed most frequently (73%). On average 16% of the adult users in the device cohort used more than 1 type of device per calendar year, in children this was 9%. On average 2% of the patients in the device cohort switched from device within 1 calendar year between 2003-2012. In adults switching was increasing over time, with most switches from DPI to pMDI. (Figure 7)

For patients within the subdevice cohort for DPI switching (n=47,532), on average 3% of the users switched between devices with the same ATC code per year. (Figure 8)

In patients in the beclomethasone subdevice cohort pMDI (n=3,694), on average 8% of the users switched. In 2003 and 2004 switching from becotide and becloforte to generic beclomethasone was most frequent. In September 2002 generic beclomethasone was licensed into the Dutch market, soon thereafter Becotide® en Becloforte® were off license.

Medication possession rate

The mean MPR was low for the 3 maintenance inhalation medications for which generic substitute was available namely, budesonide, beclomethasone and formoterol. The median MPR (IQR) for the first 12 months following the 1st dispense for patients exclusively on brand was

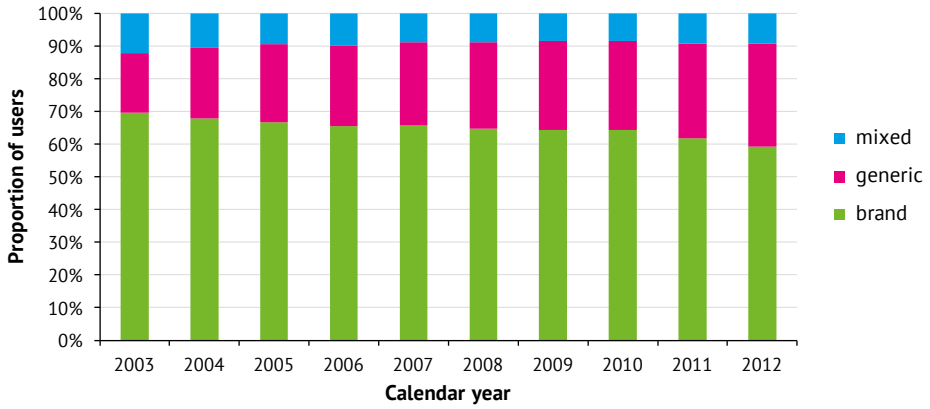


Figure 2 - Proportion of users with generic only, brand only, or mixed use, of all ATC codes within the brand-generic cohort, stratified by calendar year. Pct = percentage, Mpct = mixed use, gpct = generic user, bpct = brand user

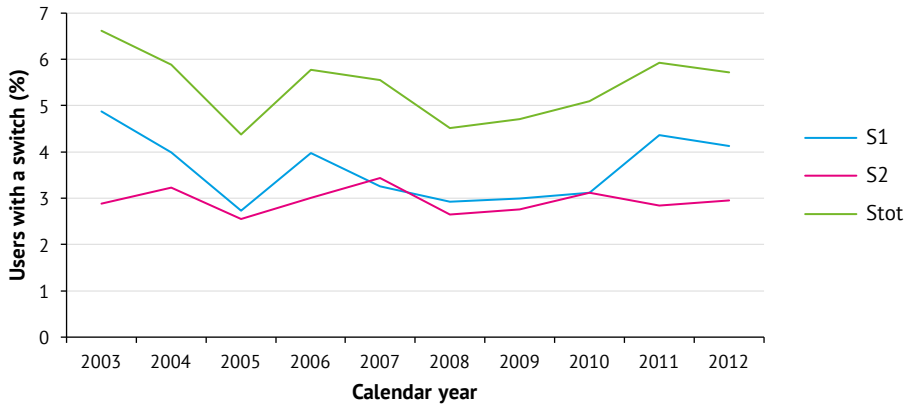


Figure 3 - Patients with ≥1 switch (with the same ATC code) per calendar year.
S1 = switch from brand to generic, S2 = switch from generic to brand, Stot = S1 and/or S2

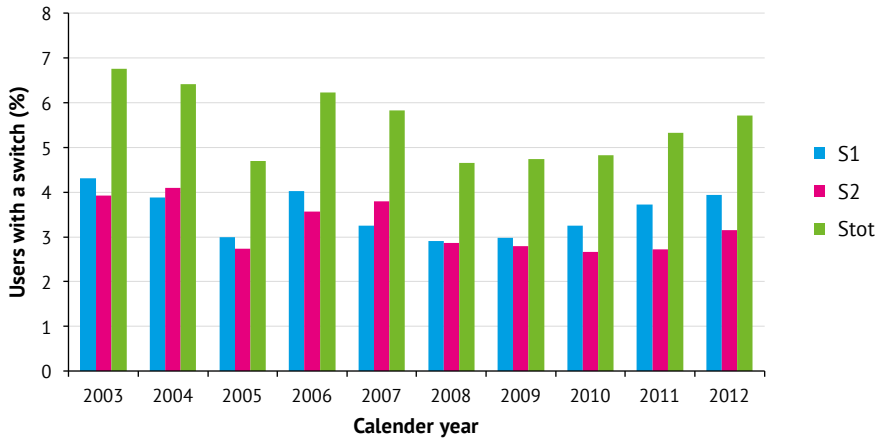


Figure 4 - Patients with ≥1 switch in salbutamol by calendar year.
S1 = switch from brand to generic, S2 = switch from generic to brand, Stot = S1 and/or S2

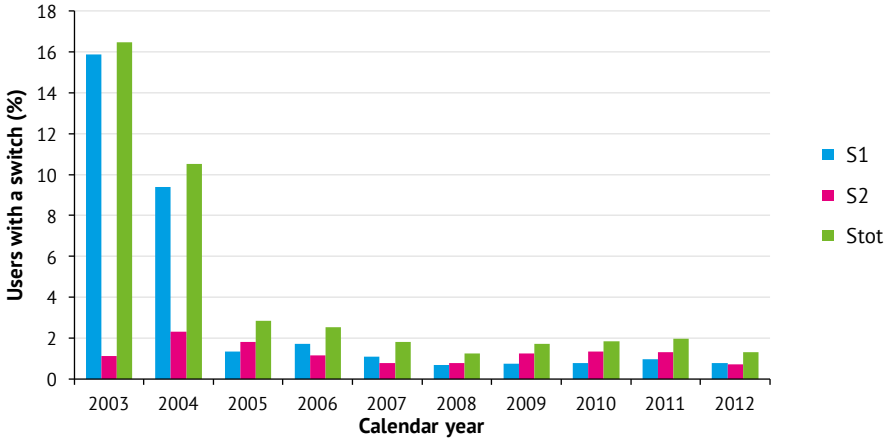


Figure 5 - Switching pattern for beclomethasone in the brand-generic cohort stratified by calendar year.
S1 = switch from brand to generic, S2 = switch from generic to brand, Stot = S1 and/or S2

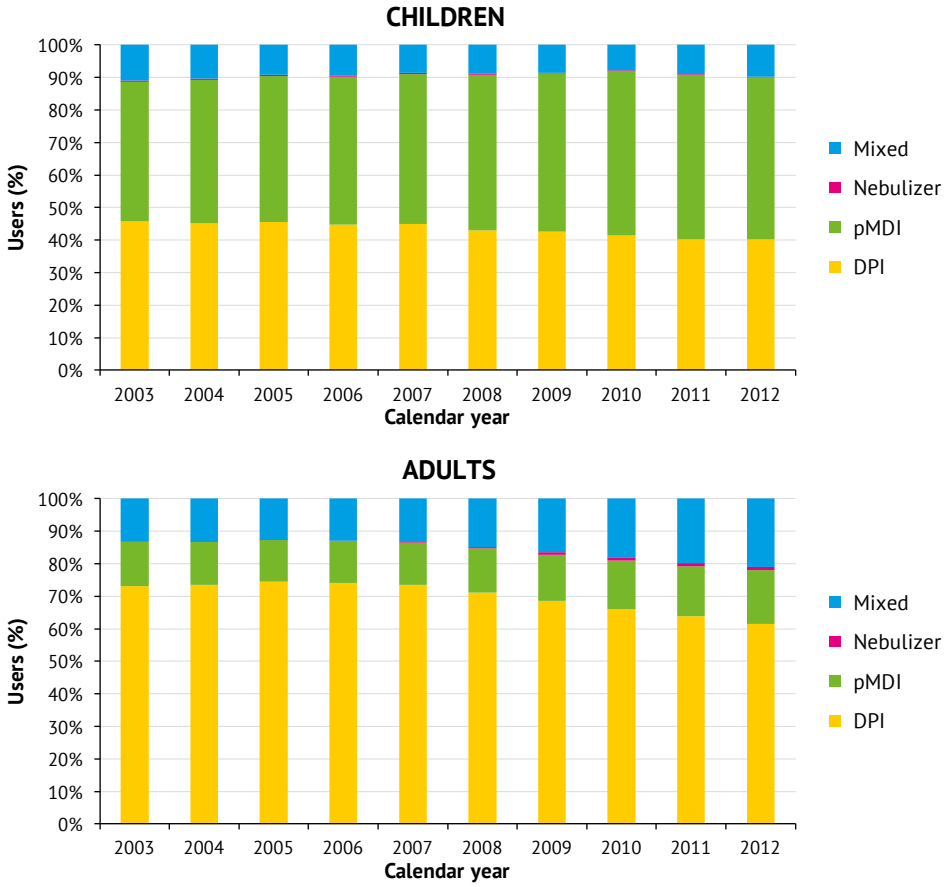


Figure 6 - Proportion of children and adults per device per calendar.
pMDI = Metered dose inhaler, DPI = dry powder inhaler

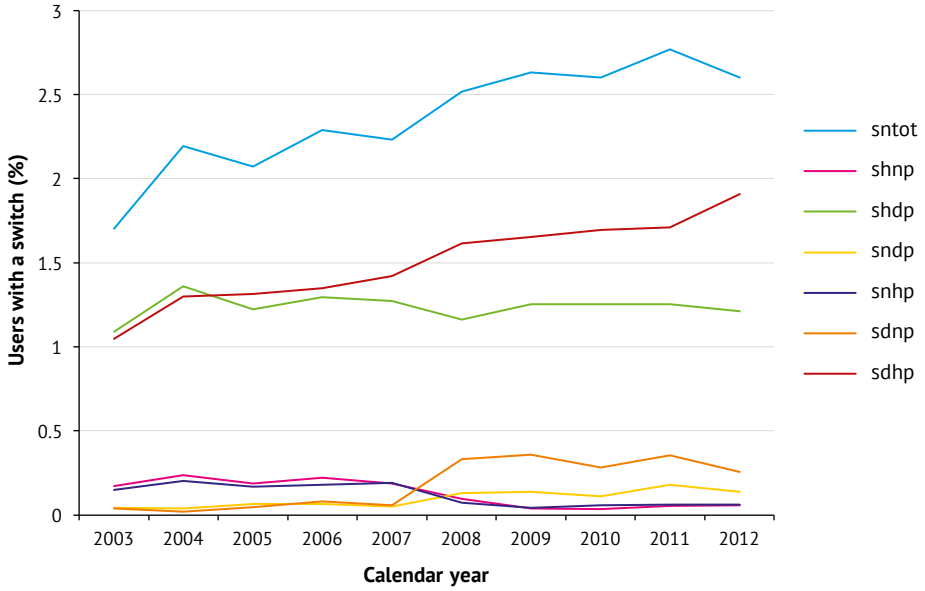


Figure 7 - Proportion of users with a switch in device per calendar year.
sntot = users with ≥1 switch, shnp = switch from pMDI to nebulizer, shdp = switch from pMDI to DPI, sndp = switch from nebulizer to DPI, snhp = switch from nebulizer to pMDI, sdnp = switch from DPI to nebulizer, sdhp = switch from DPI to pMDI

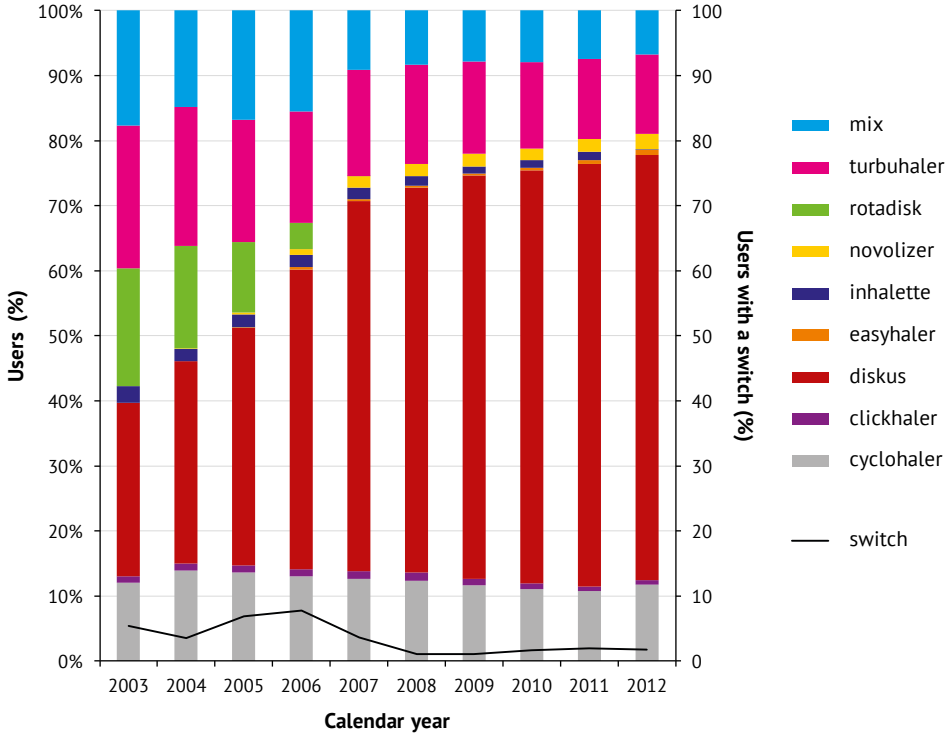


Figure 8 - mix = mixed use (>1 device), switch = users with ≥1 switch to another device with the same ATC code per calendar year

55% (41.1-82.2) for budesonide, 48% (27.4-68.5) for beclomethasone and 33% (23.4-49.3) for formoterol. The median MPR (IQR) for the first 12 months following the 1st dispense for patients exclusively on generic was 55% (41.1-82.2) for budesonide, 33% (16.4-57.0) for beclomethasone and 33% (21.9-49.32) for formoterol.

To control for patient characteristics, the analyses to compare adherence before and after switching was restricted to the same patients before and after switch with at least 6 or 12 months of follow-up before and after switch and at least 2 dispenses in each 6 or 12 months. Patients (n=102) who switched from brand to generic beclomethasone were more adherent in the first 12 months after switching compared to 12 months before switching (median MPR 55% (IQR 27.6-82.2) vs 41% (IQR 27.4-60.84) (Wilcoxon signed rank test p=0.015). Also, patients (n=77) who switched from brand to generic budesonide were more adherent to budesonide in the first 12 months after switching compared to 12 months before switching (median MPR 59 (IQR 41.1-97.4) vs 51% IQR (38.9-79.2), p=0.015). No differences in MPR before and after switch were observed in patients with dispensing of Formoterol. Numbers for switching from generic to brand were too low. Details are shown in Table 3.

DISCUSSION

In this study we provide population level data on the use of generic and brand inhalation medication and the frequency of switching between brand and generic inhalation medication and switching of inhalation device. In addition, we calculated adherence and investigated whether switching was associated with changes in adherence. Although use of generic medication increased over time. Very few patients switched from brand to generic or vice versa. Only 5% of patients in the brand generic cohort had 1 or more switches between brand and generic per year. We also observed that adherence to maintenance inhaled medication was low, and switching hardly affected adherence rates. 18% of all users had 2 or more different devices per calendar year.

Our results provide evidence that despite the preference policy patients continued to use brand medication. In some drug classes, e.g. in beclomethasone there was quite some switch away from generic to new brand inhaled medication This phenomenon was also observed by Fraser et al. [22] In our study it was observed that the use of brand beclomethasone increased and generics decreased when Qvar® (=beclomethasone pMDI delivered with ultrafine particles) came into the market [23] An extra caution needs to be taken regarding the switch of Qvar to generic beclomethasone pMDI. Whereas Qvar contains extra-fine particles with median aerodynamic particle size 1.1 µm, generic beclomethasone contains particles around 3.5 µm. This may have implications for the dose and efficacy. [24]

In addition the Becloforte and Becotide use decreased from 2004 onwards.

In line with previous research [25] adherence to both generic and brand inhalation medication

Table 3 - MPR of budesonide, beclomethasone, formoterol for the 6 and 12 months following the first generic or brand dispense, and for switchers both in the 6 and 12 months before the switch and 6 and 12 months after the switch.

	Budesonide						Beclomethasone						Formoterol					
R03BA01	n	mean mpr	median	SD	IQR	p-value	n	mean mpr	median	SD	IQR	p-value	n	mean mpr	median	SD	IQR	p-value
6 months following 1st dispensing																		
only generic	416	97.16	93.61	52.19	56.81-111.11		1416	64.03	65	45.71	25-90.56		166	57.05	50	24.54	33.33-66.67	
only brand	3778	86.23	83.33	34.64	55.56-111.11		1502	76.56	66.67	38.09	55-100		3952	54.1	50	30.37	33.33-66.67	
Switching 6 months, same people before and after switch																		
brand before switch	37	81.43	83.33	37.74	53.10-104.44		67	75.51	64.44	60.69	44.44-82.22		52	52.92	41.67	39.3	33.33-59.72	
generic after switch	37	103.32	94	42.11	73.61-128.33	p=0.038	67	68.69	65	41.1	25.00-100	p=0.82	52	53.51	50	24.32	33.33-66.39	p=0.14
generic before switch	23	76.55	65.22	41.75	47.22-103.89		44	66.5	57.5	38.85	31.81-94.45		13	63.8	50	50.47	22.50-95.83	
brand after switch	23	86.64	82.78	26.65	62.22-107.22	p=0.171	44	64.62	55.56	32.98	36.67-83.33	p=0.07	13	55.34	50	32.49	29.17-72.50	p=0.76
12 months following 1st dispensing																		
only generic	507	67.02	54.79	54.68	41.10-82.19		1697	43.22	32.88	36.26	16.44-57.00		187	39.72	32.88	23.39	21.92-49.32	
only brand	5151	62.07	54.79	32	41.10-82.19		1675	54.93	47.95	34.45	27.4-68.49		4447	47.35	32.88	27.48	23.56-49.32	
Switching 12 months, same people before and after switch																		
brand before switch	77	58.73	50.68	32.26	38.9-79.18		102	50.57	40.82	38.8	27.4-60.48		68	46.28	41.1	29.34	25.07-54.45	
generic after switch	77	74.81	59.45	41.83	41.10-97.40	p=0.02	102	59.42	54.79	37.02	27.6-82.19	p=0.01	68	41.29	32.88	23.74	24.66-48.84	p=0.15
generic before switch	28	57.91	46.44	51.8	25.69-71.92		57	45.45	38.36	28.86	25.61-55.34		19	43.82	32.88	29.75	28.77-41.10	
brand after switch	28	48.64	47.95	20.74	27.40-54.79	p=0.87	57	55.57	53.7	32.38	29.18-70.14	p=0.17	19	40.49	24.66	34.82	16.44-49.32	p=0.60

n = number of users
IQR = interquartile range
P = p value for Wilcoxon signed ranks test

within the first 12 months following the first dispense was low for beclomethasone, formoterol and budesonide with MPR ranging between 40-55%. From adherence studies on chronic medication, it is known that at initiation of medication most patients are adherent, but adherence decreases rapidly in the first 3–6 months. [26]

Some differences in adherence before and after switch were observed in users of budesonide and beclomethasone, where the median MPR was higher after switch to generics, but numbers were low (n=77 and n=102). In the Netherlands, generic substitution coincides with increased responsibilities of Dutch pharmacies with regard to educate patients about the reasons for generic substitution, the benefits of adherent drug use and correct use of inhalation device. [27] Patient education has been demonstrated to increase the acceptance of generic prescribing. [12] But the time needed to instruct a patient should be kept in mind, when substitution is a common policy.

Although the preference policy was implemented in 2005 for some medication and actively expanded by insurance companies to inhaled medications from 2008 onwards, it is still under debate. Currently, the Netherlands Pharmacovigilance Centre Lareb reported concerns on possible decreased efficacy of the generic salbutamol aerosol after the revision of the device. Besides some external changes, the formulation of the propellant changed as well.[28] Future research is needed to study the cost effectiveness of switching to this and other generic drugs.

We observed a low percentage of switching during our study period. Physicians might be reluctant to change from brand to generic in patients already on treatment and might preserve use of generic drugs in patients newly diagnosed with asthma.

Our study period was from 2003-2012, since 2012 new generic asthma drugs came into the market implying that the current proportion of generic medication use and the proportion of switching is probably higher than what we observed. [29]

This is an observational study: the limitations of which are well recognized and uses pharmacy database as primary data source, adding limitations; such as the fact that dispensing of a medicine does not equate actual use, nor guarantees a good inhalation technique. In addition, as the proportion of patients with a disease code for asthma (and without a code for COPD) was low, it is difficult to make a strong statement on the characteristics of the patients that were treated. Also, this database could not be used to investigate the indication of switching.

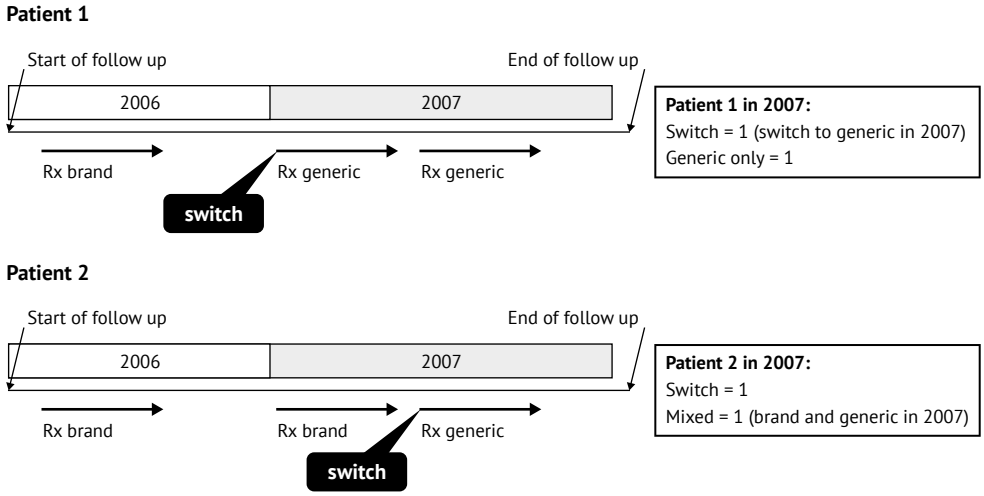
CONCLUSION

Generic dispensing in the Netherlands is increasing. Patients on inhaled medication have considerably low adherence rates and there was no net negative impact on adherence rates in patients who switched from brand to generic, which is promising. In near future with more generic drugs coming into the market, chance of switching is more likely. Further research on reasons of switching and potential impact on clinical outcomes is warranted.

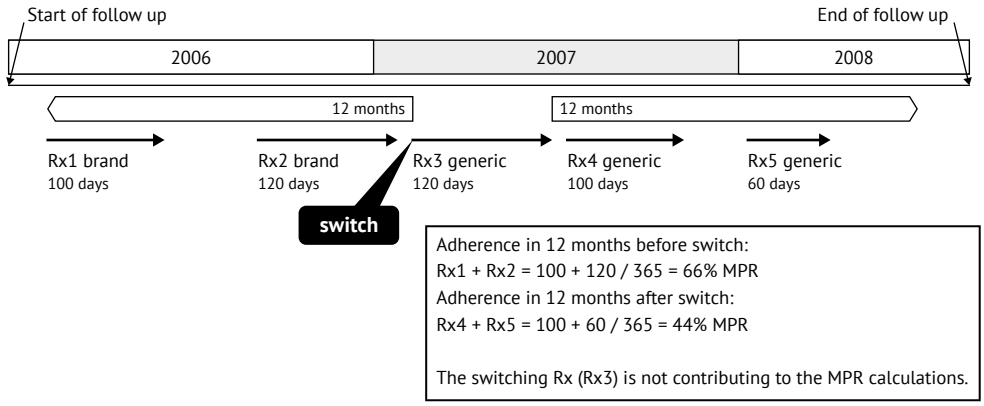
REFERENCES

1. *The Global Asthma Report 2014.* Auckland, Newzealand: Global Asthma Network;2014.
2. *Goed gebruik Inhalatiemedicatie astma en COPD.* Long Alliantie Nederland;2014.
3. ECLI. Voorzieningenrechter Rechtbank Breda. *BD2019* NL:RBBRE:2008:BD2019:188618 KG ZA 188608-188228. Available at: http://deeplink.rechtspraak.nl/uitspraak?id=ECLI:NL:RBBRE:2008:BD2019.
4. Schippers EI. Beantwoording kamervragen over de gevolgen van preferentiebeleid medicatie. 2012; https://www.rijksoverheid.nl/documenten/kamerstukken/2012/11/15/beantwoording-kamervragen-over-de-gevolgen-van-het-preferentiebeleid-medicatie
5. Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J.* Jun 2011;37(6):1308-1331.
6. Lee SL, Adams WP, Li BV, Conner DP, Chowdhury BA, Yu LX. In vitro considerations to support bioequivalence of locally acting drugs in dry powder inhalers for lung diseases. *Aaps J.* Sep 2009;11(3):414-423.
7. Agency EM. *Guidelines on the requirements for clinical documentation for orally inhaled product (OIP) including requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and COPD in adults and for use in the treatment of asthma in children and adolescents.* . 2009.
8. Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA.* Dec 3 2008;300(21):2514-2526.
9. Balkrishnan R, Byerly WG, Camacho FT, Shrestha A, Anderson RT. Effect of prescription benefit changes on medical care utilization in a Medicare HMO population. *Am J Manag Care.* Nov 2001;7(11):1093-1100.
10. Godman B, Shrank W, Andersen M, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. *Expert Rev Pharmacoecon Outcomes Res.* Dec 2010;10(6):707-722.
11. Holmes DR, Jr., Becker JA, Granger CB, Limacher MC, Page RL, 2nd, Sila C. ACCF/AHA 2011 health policy statement on therapeutic interchange and substitution: a report of the American College of Cardiology Foundation Clinical Quality Committee. *J Am Coll Cardiol.* Sep 13 2011;58(12):1287-1307.
12. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med.* Feb 13 2006;166(3):332-337.
13. Long Alliantie Nederland. www.inhalatorgebruik.nl. 2014.
14. Chang CL, Cooray M, Mills G, Hancox RJ. Is Salamol less effective than Ventolin? A randomised, blinded, crossover study in New Zealand. *N Z Med J.* 2007;120(1267):U2874.
15. Gillies J, Brown J, Byrnes C, Farrell A, Graham D. PHARMAC and Ventolin in New Zealand. *N Z Med J.* Aug 12 2005;118(1220):U1616.
16. Reti S. Ventolin to Salamol--a crossover study in New Zealand. *N Z Med J.* 2006;119(1244):U2276.
17. Doyle S, Lloyd A, Williams A, et al. What happens to patients who have their asthma device switched without their consent? *Prim Care Respir J.* Jun 2010;19(2):131-139.
18. Thomas M, Price D, Chrystyn H, Lloyd A, Williams AE, von Ziegenweidt J. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. *BMC Pulm Med.* 2009;9:1.
19. Herings RM. *PHARMO: a record linkage system for post- marketing surveillance of prescription drugs in The Netherlands.* . Utrecht, Utrecht 1993.
20. Hvidberg E, Andersen AH. [New classification of drugs. The Medical list and the Drug catalogue are introduced in Anatomical--Therapeutic--Chemical classification code (ACT-code) in 1981]. *Ugeskr Laeger.* Feb 4 1980;142(6):396-397.
21. medicines information bank. 2014. http://english.cbg-meb.nl/medicines-information-bank.
22. Fraser LA, Albaum JM, Tadrous M, Burden AM, Shariff SZ, Cadarette SM. Patterns of use for brand-name versus generic oral bisphosphonate drugs in Ontario over a 13-year period: a descriptive study. *CMAJ open.* Jan-Mar 2015;3(1):E91-96.
23. Geneesmiddelen informatie bank. 2015. www.geneesmiddeleninformatiebank.nl.
24. Busse WW, Brazinsky S, Jacobson K, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol.* Dec 1999;104(6):1215-1222.

25. Engelkes M JH, de Jongste JC, Sturkenboom MCJM, Verhamme KMC. Prescription patterns, adherence and characteristics of non-adherence in children with asthma in primary care. *Pediatr Allergy Immunol.* 2015.
26. Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. *BMJ.* Jul 29 1995;311(7000):293-295.
27. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Generic substitution of antihypertensive drugs: does it affect adherence? *Ann Pharmacother.* Jan 2006;40(1):15-20.
28. Decreased effectivity associated with the revised formulation of the salbutamol aerosol from Sandoz®. 2015; http://www.lareb.nl/Signalen/Signals_2015_Salbutamol_efficacy_lack.aspx.
29. NIVEL. Gevolgen van preferentiebeleid en farmaceutische zorginkoop. 2015; http://www.nivel.nl/sites/default/files/bestanden/Rapport-gevolgen-preferentiebeleid-farmaceutische-inkoop.pdf. Accessed 11.13, 2015.



Online Figure 1 - Patient 1 with a switch and Patient 2 with switch and mixed use.



Online Figure 2 - MPR calculations for patients with a switch, with 2 dispenses in 12 months before switch and 2 dispenses in 12 months after switch. The switching dispense is excluded from the MPR calculations.

Chapter 5.2

Switching between brand and generic inhaled medication and the risk of moderate to severe asthma exacerbations in patients with asthma - a case control study

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ABSTRACT

AIMS To study whether switching between generic and brand inhaled asthma medications or switching between inhalation devices affects the risk of moderate to severe asthma exacerbations.

METHODS We conducted two observational case-control studies nested in a cohort of asthma patients in data from the PHARMO Database Network between 2003 and 2013. Cases were patients ≥5 years of age with asthma who had a first moderate to severe asthma exacerbation, defined as need of systemic corticosteroids or requiring hospitalization for asthma (case-control set 1), or severe asthma exacerbation, defined as requiring hospitalization (case-control set 2). To each case, up to 10 controls were matched on age, gender, and index date. All dispensing of inhaled respiratory drugs were categorized into generic or brand use. At the index date, current or past exposure to generic or brand drugs was assessed. Switching was defined as either a change from brand to generic or vice versa, or as change in device. Switching was assessed during the 30 days or 1 year preceding the index date. Data were analysed using multivariate, conditional logistic regression.

RESULTS The first case-control set consisted of 3,796 cases. Current use of generic inhaled medication was associated with an increased risk of moderate to severe asthma exacerbations (OR_{adj} 1.33 (95% CI 1.20-1.47) most pronounced for β_2-agonists. Switching from brand to generic (or vice versa) salbutamol increased the risk of moderate to severe asthma exacerbations with 68%. (OR_{adj} 1.68 (95% CI 1.34-2.10), with highest risks in patients <18 and ≥45 years of age. (<18: OR_{adj} 1.95 (95% CI 1.16-3.27) and ≥45 OR_{adj} 2.14 (95% CI 1.51-3.03). The association with current use of generics was higher in the case control analysis on severe exacerbations (104 cases) (OR_{adj} 2.05 (95% CI 1.20-3.52). But no significance was reached when data were analysed by drug class or switching type.

CONCLUSIONS Our study showed that current use of generic inhaled β_2-agonists might be associated with an increased risk of exacerbations when compared to current use of brand β_2-agonists, in particular when switched between generic and brand. To elucidate whether this association is real, or confounded by lack of asthma control, we suggest to replicate our findings in more recent, international data, with detailed information on asthma control.

INTRODUCTION

Asthma is a major health problem with 334 million patients worldwide. [1] In the Netherlands with a total population of 16,9 million, half a million people are diagnosed with asthma. [2] Asthma treatment requires individually tailored therapy and selection of the most appropriate treatment is dependent on the choice of drugs and inhaler device. [3] Proper use of these devices is crucial to obtain asthma control. [3, 4] Asthma is a considerable burden on the healthcare budget: three brands of inhaled medication are in the top 10 of drugs with the highest expenses. [5] To control healthcare costs, Dutch health authorities encouraged a preference policy by the health insurance companies which started in 2005 and was adopted as law in 2008 but still causes a lot of debate. [3, 6, 7] This policy favours the use of generic drugs by the pharmacy independent of the physician's prescription.

Switching to generic often coincides with a change of inhaler. The choice of inhaler is based on patient characteristics, like age and inspiratory force, characteristics of the inhaler, like multi or single dose, powder or aerosol and patient preference. [8] Each inhaler requires a different inhalation manoeuvre, which needs to be carefully instructed.

Prior to registration of generic medications, demonstration of clinical bioequivalence is needed. As the effect of the inhaled drug do not depend on the systemic activity, bioequivalence cannot be demonstrated based on drug concentrations in blood. [9] The guidelines from the European Medicines Agency on requirements for clinical documentation of orally inhaled products for asthma and COPD states that for inhalers with the same substance and required flow rate, similar in vitro performance is sufficient to show equivalence. [10] In vitro performance includes particle size distribution, fine particle fraction of emitted dose, and flow rate dependency tested under validated circumstances. [10]

In other therapeutic domains, there are doubts about the bioequivalence of generic drugs. [11] In addition, there is evidence that substitution by generics has a negative impact on adherence and disease control through changes in appearance (colour, size, and packaging). [12-15]

Health care professionals are concerned about substitution of asthma drugs because it may have negative effects on disease control through lower adherence, and potential lack of efficacy in case of inappropriate use of inhalers. [3, 16] Indeed, data from a questionnaire study showed that patients, who switched asthma medication, experienced more often problems with use of the device (23% vs. 13%), were less likely to be adherent (55 vs. 68%) and were less likely to report being disease controlled (69 vs. 83%) compared to patients who did not switch. [17]

To assure the quality of care, we need to know the impact of switching between brand and generic inhalation medications. Therefore we investigated the association between the use of generic and brand drugs per drug class, including long-acting β_2-agonists (LABA), short-acting β_2-agonists, (SABA) and inhaled corticosteroids (ICS) switching between brand and generic and switching of the inhalers, and the risk of asthma exacerbations.

METHODS

Database

We conducted two nested case-control studies within a cohort of patients with asthma identified in a large population-based patient centric network of healthcare databases (the Dutch PHARMO Database Network (www.pharmo.nl). This combines data from different healthcare settings, including general practice (GP), in- and outpatient pharmacy and hospitals. It includes high-quality complete information linked on a patient level, including, patient demographics, drug dispensing records from community pharmacies, hospital discharge records, and GP diagnoses of more than two million individuals throughout the Netherlands. [18] The Out-patient Pharmacy Database comprises detailed information on dispensed package, prescriber, dispensing date, amount dispensed, and written dose instructions. The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification as well as sales registry number. [19] This study was approved by the independent compliance committee of the PHARMO institute.

Study design

The study cohort comprised all patients aged 5 years or older, diagnosed with asthma by the GP and using inhaled medication for at least 1 year. A patient was classified as having asthma from the date the asthma specific disease code (ICPC code='R96') was first recorded. Patients with a medical history of COPD were excluded. The study period was from the 1st of January 2003 until the 1st of January 2013. Follow-up started on the 1st of January 2003, the date of asthma diagnosis, the date on which the required 1year of inhalation therapy was obtained, or on the 5th birthday, whichever date occurred last. All patients were followed until their first exacerbation, until leaving the pharmacy, or at death or at the end of the study period, whichever occurred first.

Cases and controls

Within the study period, 15,289 asthma patients ≥5 years were identified and with at least 1 year of exposure to asthma drugs. Within this cohort, severe asthma exacerbations were identified by discharge diagnoses for asthma (ICD 9 code 493). In addition, moderate asthma exacerbations were identified by dispensing of systemic corticosteroids (ATC H02AB). We only considered the first asthma exacerbation during follow-up. The number of asthma exacerbations prior to the index date was considered as covariate.

Controls were selected through incidence density sampling and cases could function as control up to 1 month prior to the asthma exacerbation. To each case, we identified up to 10 controls matched on age, gender and index date. Two separate sets were generated, the first containing all cases with a first hospitalization or use of systemic corticosteroids, whichever was earliest, the second only cases with a first hospitalization.

Exposure

From the Out-patient Pharmacy Database, we selected all dispensing of inhaled medications (ATC 'R03'). From these we labelled drugs as either brand or generic based on drug name. (online Table 1) Information on the availability of generic substitutes during the study period was retrieved from the medicines information bank from the Dutch Medicines Evaluation Board [20] To control for differential prescribing, brand drugs for which no generic substitute was available were labelled as 'no generic available'. As we focused on patients with asthma, we classified only drugs that were included in current evidence- based treatment guidelines. [21] We classified the drugs into drug classes ICS, LABA and SABA. We did not perform stratified analyses on current use of other drugs (tiotropium, ipratropium, ipratropium+fenoterol, nedocromil or cromolyn sodium), because of their low prevalence.

For each dispensing, a legend duration was calculated based on the amount dispensed and the dosing instructions. Exposure at index date was categorized into 'current use', when the last dispensing covered the index date or ended less than 30 days prior to the index date, or 'past use'. Past use was further categorized into "recent past" use defined as 30 days up to 1 year before the index date and for switching "past use" was defined as longer than 1 year prior to the index date.

A switch was defined as a change between generic and brand within the same ATC level 7 code within 365 days of the previous dispensing. Switching was assessed in two time windows, 365 days prior to the index date or 30 days before the index date. (online Figure 1)

Switching of inhaler was defined as either switching within metered dose inhalers (pMDI) or within dry powder inhalers (DPI). (online Table 2)

Covariates

As covariates and potential risk factors of asthma exacerbation, we considered smoking history, obesity (BMI>30) or overweight (BMI between 27-30), anxiety/depression and gastro-oesophageal reflux disease (GERD), all assessed before the index date. Comorbidities were identified based on disease codes in the GP records. Concomitant drug use was assessed within 1-30 days prior to the index date for the following drug classes: antacids (ATC A02B), hypnotics or anxiolytics (ATC N05), antidepressants (N06), antihistaminic agents (R06A), antibiotics (J01) or nasal preparations (R01).

Statistical analysis

Descriptive statistics were used to provide numbers by counts and percentages. For continuous variables we calculated mean and standard deviation. Conditional logistic regression analysis was used to estimate associations. First a crude conditional logistic regression was conducted where matched odds ratios (OR) with corresponding 95% CI were provided. For the adjusted analyses, all factors with clinical relevance or associated with exacerbations in the univariate

analysis ($p<0.05$) were included.

Effect modification by calendar time, before and after 2008 as the preference policy became effective from 2008, and by age (per agegroup <18, 18-45 and ≥45 years) was investigated. Odds ratios were not provided in case of less than 3 exposed cases. All statistical analyses were conducted with the statistical software packages SPSS/PC 21.0 (SPSS Inc, Chicago, III).

RESULTS

We identified 3,796 cases with an exacerbation during follow-up. The median age of the cases was 48.7 (35.2-61.7) years. The characteristics of cases and controls are described in Table 1.

Risk factors for exacerbations were underlying comorbidities of anxiety/depression, obesity, overweight, GERD, obesity, smoking, and prior exacerbations. Concomitant use of antacids, hypnotics and sedatives/anxiolytics/antipsychotics/antidepressants, nasal preparations, antihistamines, and antibiotics were all associated with an increased risk of exacerbation.

A prior history of asthma exacerbation was the strongest risk factor of subsequent exacerbations. The use of antibiotics within 30 days before exacerbation was strongly associated with exacerbation. (Table 1)

Current use of generic asthma inhalation medication was associated with an increased risk of exacerbations (OR_{adj} 1.34 (95% CI 1.21-1.48) when considering all brand use, including brand for which no generic substitute was available, as reference category. (online Table 3) This risk remained when considering only brands for which a substitute was available as reference category. (OR_{adj} 1.33, 1.20-1.47). When splitting the drugs in individual drug classes, the risk tended to be higher for SABA and LABA and reduced for ICS, when adjusted for the other classes. For SABA this risk was mainly driven by the use of generic salbutamol.

Switching between brand and generic

In total, 145 cases (3.8%) switched between brand and generic compared to 690 controls (1.8%) (online Table 4). Switching was associated with an increased risk of exacerbations. (OR_{adj} 1.62, 1.34-1.97 Table 2) At the drug class level, the association was only significant for SABA (OR_{adj} 1.66, 1.32-2.08), while numbers for ICS and LABA were low. Switching was mainly reported for salbutamol, which was associated with an increased risk of 1.68 (95% CI 1.34-2.10). This was not modified by concomitant ICS use, interaction term of ICS and switching and risk of exacerbations ($p=0.121$).

Switching between devices was infrequent in the one year prior to the index date, in total 28 cases (0.7%) switched device compared to 227 controls (0.6%). (online Table 4) No association between inhaler switching and risk of exacerbations could be observed. (online Table 5)

Table 1 - Characteristics of moderate to severe asthma exacerbations and matched controls.

Moderate to severe exacerbations	cases n=3,796 (%)	controls n=37,367 (%)	matched OR* (95% CI)
Gender			
Male	1,451(38.2)	14,294(38.3)	
Female	2,345(61.8)	23,073(61.7)	
Age (median, IQR)	48.7(35.2-61.7)	48.3(35.1-61.1)	**nap**
Smoking	154(4.1)	1,064(2.8)	**1.47 (1.24-1.75)**
History of exacerbations			
Severe exacerbations (hospitalization)			
0	3,709(97.7)	37,071(99.2)	reference
1	62(1.6)	263(0.7)	**2.42 (1.83-3.21)**
2	17(0.4)	18(0.0)	**10.31 (5.25-20.23)**
>2	8(0.2)	15(0.0)	**5.33 (2.26-12.58)**
All exacerbations			
0	1,857(48.9)	26,802(71.7)	reference
1	773(20.4)	5,689(15.2)	**2.03 (1.85-2.22)**
2	393(10.4)	2,150(5.8)	**2.79 (2.48-3.15)**
>2	773(20.4)	2,717(7.3)	**4.40 (4.00-4.85)**
Co-morbidity			
Gastro oesophageal reflux disease	132(3.5)	994(2.7)	**1.34 (1.11-1.61)**
Psychological disease	455(12.0)	3,531(9.4)	**1.32 (1.19-1.47)**
Obesity	78(2.1)	580(1.6)	1.20 (0.96-1.49)
Overweight	90(2.4)	756(2.0)	**1.33 (1.05-1.70)**
Concomitant medication**			
Antacids	715(18.8)	4,379(11.7)	**1.84 (1.68-2.02)**
Antibiotics	678(17.9)	2,092(5.6)	**3.68 (3.35-4.05)**
Psycho-therapeutics	602(15.9)	3,891(10.4)	**1.58 (1.43-1.75)**
Nasal preparations	689(18.2)	4,596(12.3)	**1.61 (1.46-1.78)**
Antihistamines	530(14.0)	3522(9.4)	**1.59 (1.45-1.74)**

* matched on age, gender and index date
** measured at 1 to 30 days before index date, nap = not applicable

Table 2 - Association between use of inhalation medication by generic or brand, by generic, brand, and brand no generic available and by drug class (ICS, LABA and SABA) and moderate to severe asthma exacerbation.

Switch generic/brand in 1 year before index date	**cases** n=3,796 (%)	**controls** n=37,367 (%)	**matched OR** (95% CI)	**adjusted OR*** (95% CI)
ICS				
no switch and use in 1-365 days before index date	2,550 (67.2)	22,249 (59.5)	reference	reference
Switch and use in 1-365 days before index date	11 (0.3)	152 (0.4)	0.64 (0.35-1.19)	0.70 (0.37-1.30)
Use 1-365 days before index date of brand with no generic available	56 (1.5)	576 (1.5)	0.85 (0.65-1.13)	0.80 (0.60-1.07)
LABA				
no switch and use in 1-365 days before index date	345(9.1)	2,313(6.2)	reference	reference
Switch and use in 1-365 days before index date	4(0.1)	23(0.1)	1.26 (0.43-3.65)	1.43 (0.47-4.36)
Use 1-365 days before index date of brand with no generic available	5(0.1)	29(0.0)	1.21 (0.46-3.16)	1.02 (0.37-2.80)
SABA				
no switch and use in 1-365 days before index date	1,845 (48.6)	15,231 (40.8)	reference	reference
Switch and use in 1-365 days before index date	111 (2.9)	451 (1.2)	**2.01 (1.62-2.49)**	**1.66 (1.32-2.08)**
Use 1-365 days before index date of brand with no generic available	2 (0.1)	12 (0.0)	n.a.p	n.a.p
SABA salbutamol				
no switch and use in 1-365 days before index date	1,622 (42.7)	13,337 (35.7)	reference	reference
Switch and use in 1-365 days before index date	110 (2.9)	444 (1.2)	**2.01 (1.62-2.50)**	**1.68 (1.34-2.10)**
SABA terbutaline				
no switch and use in 1-365 days before index date	238 (6.3)	2,055 (5.5)	reference	reference
Switch and use in 1-365 days before index date	0 (0.0)	7 (0.0)	**n.a.p**	**n.a.p**
SABA salbutamol+ ipratropium				
no switch and use in 1-365 days before index date	33 (0.9)	109 (0.3)	reference	reference
Switch and use in 1-365 days before index date	1 (0.0)	0(0.0)	**n.a.p**	**n.a.p.**
Switch SABA generic/brand in 30 days before index date	**cases** n=3,796 (%)	**controls** n=37,367 (%)	**matched OR** (95% CI)	**adjusted OR*** (95% CI)
SABA all				
No switch and current use	1,293 (34.1)	7,917 (21.2)	reference	Reference
Switch and current use	8 (0.2)	16 (0.0)	**3.00 (1.28-7.03)**	**2.20 (0.90-5.37)**
Use 1-30 days before index date of brand with no generic available	1 (0.0)	3 (0.0)	Nap	nap
SABA salbutamol				
No switch and current use	1,121 (29.5)	6,732 (18.0)	reference	reference
Switch and current use	8 (0.2)	16 (0.0)	**2.94 (1.26-6.90)**	**2.17 (0.89-5.29)**

ICS = inhaled corticosteroids, LABA = long-acting β_2-agonists, SABA = short-acting β_2-agonists

* Adjusted for past use of respiratory drugs, current use of all other drug classes, smoking history, follow-up time, severe to moderate exacerbations, GERD, anxiety/depression, obesity, overweight prior to index date and concomitant medications; antacids use of hypnotics or anxiolytics, use of antidepressants, nasal preparations, antihistamines used in the 30 days before index date.

** all respiratory drugs = ICS, LABA, SABA, and other (= tiotropium, ipratropium, ipratropium+fenoterol, cromoglycaat and nedocromil)

Numbers of the different drug classes (ICS, LABA, SABA) are not adding up to total number of "all", as for each treatment class we started with selecting patients currently using a drug in that treatment class. One patient could be present in all treatment classes. Current use = 1-30 days before index date.

n.a.p.: not applicable as number of exposed cases lower than 3

Effect modification

Effect modification by calendar year was not observed. Effect modification by age was significant ($p<0.05$). No significant association was observed for current use of ICS, LABA or SABA separately, or numbers were very low. (online Table 6)

Switching salbutamol was associated with an increased risk of exacerbations for patients younger than 18 or older than 44 years. This association was stronger for switching within 30 days for patients older than 44 years, but numbers are low. (Table 3) Switching from brand to generic (or vice versa) LABA was associated with an increased risk of exacerbations for patients between 18 and 45 years of age, but numbers are very low.

The second case-control set was limited to cases with exacerbations leading to hospitalization. (n=104 cases, median age 35.7 years) The characteristics of cases and controls are described in Table 4. Risk factors were comparable to those of the first case-control set. A previous asthma exacerbation was the strongest risk factor for subsequent asthma exacerbations. ($OR_{matched}$ 12.76, 7.02-23.21)

Current use of generics, compared to brand inhalation medication with generic available, doubled the risk of severe asthma exacerbations. (OR_{adj} 2.05, 1.20-3.51). (Table 5). Numbers were too low for individual medication classes and no further associations were found. (Table 5 and online Table 7)

DISCUSSION

In this study we provide population level data on the association between use of brand or generic asthma drugs, switching between brand and generic drugs and switching of inhalers and the risk of asthma exacerbations in the Netherlands during a 10-year period. The risk of exacerbations was higher with generic asthma drugs and the strength of association increased for severe exacerbations. Switching in the year before the index date was associated with an increased risk of exacerbations, and it was most pronounced for SABA. The risk tended to be higher in children and in patients older than 44 years. It is unclear whether the association between switching and exacerbation risk is causal, or due to residual confounding by asthma severity or protophatic bias, i.e. prescription or switching because of first symptoms of an asthma exacerbation. Device competence may be particular important when switching therapy, in younger and older patients. If switching coincides with ineffective use of the drug, this could explain an increased risk of asthma exacerbation.

By our definition of switching, there might be a window of maximum 1 year between the indexdate and the start of the last dispense with a switch. This makes it unlikely that the association between switching and risk of exacerbation is causal. When we considered switches with start of the last dispense within 30 days prior to indexdate, the association became stronger, but we lacked power to reach statistical significance.

Table 3 - Association between switching between generic and brand salbutamol and moderate to severe asthma exacerbation by agegroup.

Switching Generic brand salbutamol 1 year	**cases** n=3,796 (%)	**controls** n=37,367 (%)	**matched OR** (95% CI)	**adjusted OR*** (95% CI)
Salbutamol				
<18				
No switch and use in 1-365 days before index date	229 (71.1)	1,633 (50.7)	reference	reference
Switch and use in 1-365 days before index date	24 (7.5)	83 (2.6)	**2.00 (1.24-3.23)**	**1.95 (1.16-3.27)**
18-45				
No switch and use in 1-365 days before index date	662 (52.2)	5,498 (43.6)	reference	reference
Switch and use in 1-365 days before index date	34 (2.7)	208 (1.7)	1.34 (0.92-1.95)	1.16 (0.79-1.72)
>45				
No switch and use in 1-365 days before index date	731 (33.2)	3,206 (28.8)	reference	reference
Switch and use in 1-365 days before index date	52 (2.4)	153 (0.7)	**2.79 (2.00-3.88)**	**2.14 (1.51-3.03)**
Switching Generic brand salbutamol 30 days	**cases n=3,796 (%)**	**controls** n=37,367 (%)	**matched OR** (95% CI)	**adjusted OR*** (95% CI)
Salbutamol				
<18				
No switch and use in 1-30 days before index date	178 (55.3)	807 (25.1)	reference	reference
Switch and use in 1-30 days before index date	2 (0.6)	3 (0.1)	Nap	Nap
18-45				
No switch and use in 1-30 days before index date	447 (35.2)	2,849 (22.6)	reference	reference
Switch and use in 1-30 days before index date	2 (0.2)	7 (0.1)	Nap	Nap
>45				
No switch and use in 1-30 days before index date	496 (22.5)	3,076 (14.3)	reference	reference
Switch and use in 1-30 days before index date	4 (0.2)	6 (0.0)	**2.87 (0.47-17.71)**	**2.27 (0.34-15.18)**

* Adjusted for past use and current use of other drug classes, follow-up, smoking, asthma exacerbations, GERD, anxiety/depression, obesity, overweight prior to index date and concomitant medications antacids use of hypnotics or anxiolytics, use of antidepressants, nasal preparations, antihistamines used in 30 days before index date. Current use = 1-30 days before index date. Past use = >30 days before index date.

Nap = not applicable as number of exposed cases lower than 3

** all respiratory drugs = ICS, LABA, SABA, and other (= tiotropium, ipratropium, ipratropium+fenoterol, cromoglycaat and nedocromil)

Table 4 - Characteristics of patients with severe exacerbations (asthma exacerbation requiring hospitalization) and matched controls.

Moderate exacerbations	**cases** n=104 (%)	**controls** n=1,040(%)	**matched OR*** (95% CI)
Gender			
- Male	43 (41.3)	430 (41.3)	
- Female	61 (58.7)	610 (58.7)	
Age (median ,IQR)	35.7 (9.7-56.8)	35.7 (9.7-56.0)	Nap
Smoking	4 (3.8)	18 (1.7)	
History of exacerbations	**cases** n=104 (%)	**controls** n=1,040(%)	**matched OR*** (95% CI)
Severe exacerbations (hospitalization)			
0	86 (82.7)	1,019 (98.0)	
1	9 (8.7)	18 (1.7)	**5.49 (2.42-12.45)**
2	4 (3.8)	3 (0.3)	nap
>2	5 (4.8)	0 (0.0)	nap
All exacerbations (hospitalization or OCS)			
0	28 (26.9)	640 (61.5)	
1	14 (13.5)	156 (15.0)	**2.49 (1.25-4.96)**
2	16 (15.4)	106 (10.2)	**4.57 (2.35-8.90)**
>2	46 (44.2)	138 (13.3)	**12.76 (7.02-23.21)**
Co-morbidity			
Gastro oesophageal reflux disease	5 (4.8)	21 (2.0)	2.53 (0.91-7.03)
Anxiety/depression/ psych	9 (8.7)	116 (11.2)	0.75 (0.36-1.54)
Obesity	1 (1.0)	28 (2.7)	nap
Overweight	3 (2.9)	23 (2.2)	nap
Concomitant medication**			
Antacids	24 (23.1)	128 (12.3)	**3.06 (1.77-5.30)**
Psycho-therapeutics	20 (19.2)	106 (10.2)	**3.07 (1.76-5.36)**
Nasal preparations	11 (10.6)	111 (10.7)	0.99 (0.55-1.78)
Antihistamines	13 (12.5)	97 (9.3)	1.29 (0.71-2.35)
Antibiotics	30 (28.8)	64 (6.2)	**7.34 (4.38-12.3)**

* matched on age, gender and index date

** use in the 1-30 days before the index date

Table 5 - Association between use of inhalation medication (generic/brand) and severe asthma exacerbation.

Generic/brand/brand no generic	**cases** n=104 (%)	**controls** n=1,040 (%)	**matched OR** (95% CI)	**adjusted OR*1** (95% CI)
Current use				
Brand	46 (44.2)	377 (36.3)	reference	reference
Generic	38 (36.5)	141 (13.6)	**2.22 (1.36-3.61)**	**2.05 (1.20-3.52)**
Brand no generic available	2 (1.9)	10 (1)	nap	nap
Past use				
Generic	7 (6.7)	207 (19.9)	**0.28 (0.13-0.65)**	**0.36 (0.15-0.87)**
Brand	11 (10.6)	301 (28.9)	**0.30 (0.15-0.59)**	**0.40 (0.19-0.82)**
Brand no generic available	0 (0)	4 (0.4)	**nap**	**nap**
Generic/brand ICS/LABA/SABA Current use	**cases** n=104 (%)	**controls** n=1,040 (%)	**matched OR** (95% CI)	**adjusted OR*2** (95% CI)
Current use of ICS				
Brand	44 (42.3)	333 (32)	reference	reference
Generic	3 (2.9)	13 (1.3)	1.66 (0.45-6.08)	1.66 (0.37-7.41)
Brand no generic available	2 (1.9)	12 (1.2)	nap	nap
Current use of LABA				
Brand	12 (11.5)	22 (2.1)	reference	reference
Generic	1 (1)	3 (0.3)	nap	nap
Brand no generic available	1 (1)	0 (0)	nap	nap
Currrent use of SABA				
Brand	26 (25)	139 (13.4)	reference	reference
Generic	32 (30.8)	120 (11.5)	1.50 (0.82-2.74)	1.59 (0.81-3.14)
Brand no generic available	2 (1.9)	7 (0.7)	nap	nap
Currrent use of salbutamol				
Brand	21 (20.2)	117 (11.2)	reference	Reference
Generic	32 (30.8)	120 (11.5)	1.56 (0.83-2.93)	1.63 (0.80-3.29)
Currrent use of salbutamol+ipratropium				
Brand	1 (1.0)	0 (0.0)	reference	Reference
Generic	0 (0.0)	0 (0.0)	nap	nap
Currrent use of terbutaline				
Brand	5 (4.8)	24 (2.3)	reference	Reference
Generic	0 (0.0)	0 (0.0)	nap	nap

*1 Adjusted for past use of all respiratory drugs**, smoking, follow-up, asthma exacerbations, GERD, anxiety/depression, obesity, overweight prior to index date and concomitant medications antacids use of hypnotics or anxiolytics, use of antidepressants, nasal preparations, antihistamines used in 30 days before index date. Current use = 1-30 days before index date. Past use = >30 days before index date.

*2 Additionally adjusted for current use of all other respiratory drugs**

** all respiratory drugs= ICS, LABA, SABA, and other (=tiotropium,ipratropium, ipratropium+fenoterol, cromoglicic acid and nedocromil)

Numbers of the different drug classes (ICS, LABA, SABA) are not adding up to total number of "all" as for each treatment class we started with selecting patients currently using a drug in that treatment class. One patient could be present in all treatment classes. Current use = 1-30 days before index date.

nap: not applicable as number of exposed cases lower than 3

Although the preference policy was implemented in 2005 and expanded in 2008, we observed a relatively low percentage of switching during our study period 2003-2012. Since 2012, new generic asthma drugs came on the market and the current proportion of switching may well be higher now than before 2012. [3] The fact that we did not observe many device switches is promising, and in line with the substitution guidelines in the Netherlands. [22]

Our findings on increased risk of generic salbutamol are in line with recent case reports on decreased efficacy of the generic salbutamol aerosol after the revision of the device that were reported to the Netherlands Pharmacovigilance Centre Lareb. Besides some external changes of the device, the formulation of the propellant was changed as well.[23] However these cases were reported in 2015 and our latest dispensing information is from 2012. Our data confirm a previous cross over study in 36 asthmatic adults from New Zealand in whom asthma stability was significantly worse with generic salamol compared to brand. [24] In contrast, other studies found no difference in FEV1 [25, 26] or doubtful clinical effect. [27]

We did not observe an association between the use of generic ICS and risk of asthma exacerbations, which is in line with an 8-week therapeutic equivalence study of brand and generic beclomethasone in adult asthmatic patients. [28]

The main strengths of this study are the large size (15,289 patients with asthma), the detailed information on comorbidity and life style factors, the access to dispensing rather than prescription data and the real life data, collected as part of routine patient care, which reinforces the external validity.

The limitations of an observational study are obvious. We used pharmacy data, implying that we only have information on dispensing and not on actual use nor inhalation technique. Diagnostic bias might have occurred as we did not validate comorbidities but relied on ICPC disease codes and hospital registration codes to identify asthma, exacerbations and comorbidities. We have no reason to assume that this bias would be differential, and if bias affected our results it would probably underestimate the studied associations. Smoking status was not systematically reported in all patients whereas we know that it is an important covariate in respiratory research. In addition, differential prescribing driven by factors such as asthma control, prescriber preferences and other unmeasured factors is likely. Unfortunately, we did not have access to the complete medical records of the patients which makes it difficult to assess why a certain drug was prescribed or switched. As we did not have information on GP practice, we could not match on GP practice to control for preferential prescribing.

In conclusion, dispensing of generic drugs was associated with an increased risk of exacerbations, when compared to brand drugs. Moreover, switching between brand and generic drugs was associated with an increased risk of exacerbations, especially for β_2-agonists, and in particular when the switch occurred within 1 month before the exacerbation. To elucidate whether this association is real, or confounded by lack of asthma control, we suggest replicating our findings taking asthma control into account.

REFERENCES

1. *The Global Asthma Report 2014*. Auckland, Newzealand: Global Asthma Network;2014.
2. Wijga AH, Smit, H.A., Poos, M.J.J.C. Hoe vaak komt astma voor, hoeveel mensen sterven eraan en neemt dit toe of af? . *Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid*. Bilthoven: RIVM, <http://www.nationaalkompas.nl> Nationaal Kompas Volksgezondheid\Gezondheidstoestand\Ziekten en aandoeningen\Ademhalingswegen\Astma; 2014.
3. *Goed gebruik Inhalatiemedicatie astma en COPD*: Long Alliantie Nederland;2014.
4. Schatz M. Predictors of asthma control: what can we modify? *Curr Opin Allergy Clin Immunol*. Jun 2012;12(3):263-268.
5. Kengetallen SF. Data en Feiten 20152015.
6. ECLI. Voorzieningenrechter Rechtbank Breda. *BD2019* NL:RBBRE:2008:BD2019:188618 KG ZA 188608-188228. Available at: http://deeplink.rechtspraak.nl/uitspraak?id=ECLI:NL:RBBRE:2008:BD2019.
7. Schippers EI. Beantwoording kamervragen over de gevolgen van preferentiebeleid medicatie. 2012; https://www.rijksoverheid.nl/documenten/kamerstukken/2012/11/15/beantwoording-kamervragen-over-de-gevolgen-van-het-preferentiebeleid-medicatie
8. Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J*. Jun 2011;37(6):1308-1331.
9. Lee SL, Adams WP, Li BV, Conner DP, Chowdhury BA, Yu LX. In vitro considerations to support bioequivalence of locally acting drugs in dry powder inhalers for lung diseases. *Aaps J*. Sep 2009;11(3):414-423.
10. Agency EM. *Guidelines on the requirements for clinical documentation for orally inhaled product (OIP) including requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and COPD in adults and for use in the treatment of asthma in children and adolescents*. 2009.
11. Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA*. Dec 3 2008;300(21):2514-2526.
12. Balkrishnan R, Byerly WG, Camacho FT, Shrestha A, Anderson RT. Effect of prescription benefit changes on medical care utilization in a Medicare HMO population. *Am J Manag Care*. Nov 2001;7(11):1093-1100.
13. Godman B, Shrank W, Andersen M, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. *Expert Rev Pharmacoecon Outcomes Res*. Dec 2010;10(6):707-722.
14. Holmes DR, Jr., Becker JA, Granger CB, Limacher MC, Page RL, 2nd, Sila C. ACCF/AHA 2011 health policy statement on therapeutic interchange and substitution: a report of the American College of Cardiology Foundation Clinical Quality Committee. *J Am Coll Cardiol*. Sep 13 2011;58(12):1287-1307.
15. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med*. Feb 13 2006;166(3):332-337.
16. Williams AE, Chrystyn H. Survey of pharmacists' attitudes towards interchangeable use of dry powder inhalers. *Pharm World Sci*. Jun 2007;29(3):221-227.
17. NIVEL. Gevolgen van preferentiebeleid en farmaceutische zorginkoop. 2015; http://www.nivel.nl/sites/default/files/bestanden/Rapport-gevolgen-preferentiebeleid-farmaceutische-inkoop.pdf. Accessed 11.13, 2015.
18. Herings RM. *PHARMO: a record linkage system for post- marketing surveillance of prescription drugs in The Netherlands*. . Utrecht, Utrecht 1993.
19. Hvidberg E, Andersen AH. [New classification of drugs. The Medical list and the Drug catalogue are introduced in Anatomical--Therapeutic--Chemical classification code (ACT-code) in 1981]. *Ugeskr Laeger*. Feb 4 1980;142(6):396-397.
20. medicines information bank. 2014. http://english.cbg-meb.nl/medicines-information-bank.
21. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. . 2015.
22. (KNMP). RDPA. Guideline for Generic Substitution. 2012; http://www.knmp.nl/downloads/producten-diensten/farmacotherapie/handleiding.geneesmiddelsubstitutie.engels.201202.pdf/view. Accessed 11.13, 2015.
23. Decreased effectivity associated with the revised formulation of the salbutamol aerosol from Sandoz®. 2015; http://www.lareb.nl/Signalen/Signals_2015_Salbutamol_efficacy_lack.aspx.
24. Reti S. Ventolin to Salamol--a crossover study in New Zealand. *N Z Med J*. 2006;119(1244):U2276.

25. Chang CL, Cooray M, Mills G, Hancox RJ. Is Salamol less effective than Ventolin? A randomised, blinded, crossover study in New Zealand. *N Z Med J.* 2007;120(1267):U2874.

26. Molise MC, Maffey AF, Ramos P, Rubinstein F. Original salbutamol versus similar salbutamol in children with asthma exacerbation: a randomized, controlled, double-blind study. *Archivos argentinos de pediatria.* Aug 2012;110(4):285-290.

27. Williamson IJ, Reid A, Monie RD, Fennerty AG, Rimmer EM. Generic inhaled salbutamol versus branded salbutamol. A randomised double-blind study. *Postgrad Med J.* Mar 1997;73(857):156-158.

28. Nell H, Louw CM, Cyster H, Williams Z, Bardin PG, Joubert JR. Therapeutic equivalence study of two formulations (innovator v. generic) of beclomethasone dipropionate in adult asthmatic patients. *S Afr Med J.* Jan 2001;91(1):51-56.

SUPPLEMENTS

Online Table 1 - Categories of inhalation medication with generic and brand.

Medication Class	ATC code	Generic name	Generic Available	Brand
SABA	R03AC02	Salbutamol	Yes	Aerolin®, Aeromir®, Ventolin®
SABA	R03AC03	Terbutaline	Yes	Bricanyl®
SABA	R03AC04	Fenoterol	No	Berotec®
LABA	R03AC12	Salmeterol	Yes	Serevent®
LABA	R03AC13	Formoterol	Yes	Atimos®, Foradil®, Oxis®
LABA	R03AC18	Indacaterol	No	Onbrez®, Hirobriz®
Other	R03AK03	Ipratropium + fenoterol	No	Berodual®
SABA	R03AK04	Salbutamol + ipratropium	Yes	Combivent®
ICS	R03AK06	Salmeterol + fluticasone	Yes	Viani®, Aliflus®, Seretide®
ICS	R03AK07	Beclomethasone + formoterol	Yes	Symbicort®, Assieme®, Flutiform® , Sinestic®, Foster®
ICS	R03BA01	Beclomethasone	Yes	Aerobec®, Becotide®, Becloforte®, QVAR®
ICS	R03BA02	Budesonide	Yes	Pulmicort®
ICS	R03BA05	Fluticason	Yes	Flixotide®, Flutide®
ICS	R03BA08	Ciclesonide	No	Alvesco®
Other	R03BB01	Ipratropium	Yes	Atrovent®
Other	R03BB04	Tiotropium	No	Spiriva®
Other	R03BC01	Cromoglicic acid	Yes	Lomudal®
Other	R03BC03	Nedocromil	No	Tilade®

ICS = inhaled corticosteroids, LABA = long-acting β_2-agonists, SABA = short-acting β_2-agonists

Online Table 2 - Categories of inhalation medication where switching between inhalation device is available.

ATC code	Generic name	Device	Device
R03AC02	Salbutamol	DPI	Cyclocaps, diskus, novolizer, rotadisk
R03AC02	Salbutamol	pMDI	Autohaler, ivax, mylan, redihaler, salbutamol, Ventolin, aerolin, airomir
R03AC12	Salmeterol	DPI	Diskus, rotadisk
R03AC13	Formoterol	DPI	Clickhaler, cyclocaps, diskus, easyhaler, novolizer, turbuhaler
R03AC13	Formoterol	pMDI	Aerolizer, atimos
R03AK07	Beclomethasone+formoterol	pMDI	Flutiform,foster,beclomethason
R03BA01	Budesonide	DPI	Cyclocaps, rotadisk
R03BA01	Budesonide	pMDI	Autohaler, extrafine, becloforte, beclomethason
R03BA02	Beclomethasone	DPI	Clickhaler, cyclocaps, easyhaler, novolizer, turbuhaler
R03BA02	Beclomethasone	pMDI	Pulmicort, budesonide
R03BA05	Fluticason	DPI	Diskus, rotadisk
R03BA05	Fluticason	pMDI	Flixotide,flutide
R03BB01	Ipratropium bromide	DPI	Cyclocaps, inhalette
R03BC01	Cromoglicic acid	pDMI	Lomudal, cromoglicaat

DPI = dry powder inhaler, pMDI = metered dose inhaler

Online Table 3 - Association between use of inhalation medication by generic or brand, by generic, brand, and brand no generic available and by drug class (ICS, LABA and SABA) and moderate to severe asthma exacerbation.

generic brand	cases n=3,796 (%)	controls n=37,367 (%)	matched OR (95% CI)	adjusted OR* (95% CI)
current use any*				
brand	1,914 (50.4)	14,821 (39.7)	reference	reference
generic	620 (16.3)	3,690 (9.9)	**1.30 (1.18-1.44)**	**1.34 (1.21-1.48)**
past use*				
generic	374 (9.9)	5,764 (15.4)	**0.50 (0.44-0.56)**	**0.59 (0.52-0.66)**
brand	888 (23.4)	13,092 (35)	**0.52 (0.48-0.57)**	**0.60 (0.55-0.66)**
Brand/Generic No generic available	**cases** n=3,796 (%)	**controls** n=37,367 (%)	**matched OR** (95% CI)	**adjusted OR*** (95% CI)
current use any*				
Brand	1,820 (47.9)	14,081 (37.7)	reference	reference
Generic	620 (16.3)	3,690 (9.9)	**1.3 (1.18-1.44)**	**1.33 (1.2-1.47)**
No generic available	94 (2.5)	740 (2)	0.96 (0.77-1.2)	0.86 (0.68-1.09)
Generic/brand ICS/LABA/SABA	**cases** n=3,796 (%)	**controls** n=37,367 (%)	**matched OR** (95% CI)	**adjusted OR*#** (95% CI)
Current use of ICS				
Brand	1,498 (39.5)	11,258 (30.1)	reference	reference
Generic	81 (2.1)	769 (2.1)	0.8 (0.63-1.01)	0.87 (0.68-1.11)
No generic available	45 (1.2)	441 (1.2)	0.78 (0.57-1.06)	0.71 (0.51-0.98)
Current use of LABA				
Brand	171 (4.5)	1,015 (2.7)	reference	reference
Generic	12 (0.3)	56 (0.1)	1.35 (0.71-2.58)	1.55 (0.78-3.07)
No generic available	2 (0.1)	13 (0)	nap	nap
Current use of SABA				
Brand	808 (21.3)	5,160 (13.8)	reference	reference
Generic	494 (13)	2,773 (7.4)	1.14 (1.01-1.29)	1.13 (0.99-1.28)
No generic available	1 (0)	3 (0)		
Current use of salbutamol				
Brand	641 (16.9)	3,976 (10.6)	reference	reference
Generic	489 (12.9)	2,772 (7.4)	1.10 (0.96-1.24)	1.10 (0.96-1.26)
Current use of terbutaline				
Brand	165 (4.3)	1,187 (3.2)	reference	reference
Generic	0 (0.0)	1 (0.0)	nap	nap
Current use of salbutamol+ipratropium				
Brand	18 (0.5)	74 (0.2)	reference	reference
Generic	5 (0.1)	0 (0.0)	nap	nap
Generic/brand no generic available	**cases** n=3,796 (%)	**controls** n=37,367 (%)	**matched OR** (95% CI)	**adjusted OR*** (95% CI)
past use**				
Generic	374 (9.9)	5,764 (15.4)	0.5 (0.44-0.56)	0.58 (0.52-0.66)
Brand	879 (23.2)	12,988 (34.8)	0.52 (0.48-0.57)	0.6 (0.55-0.65)
No generic available	9 (0.2)	104 (0.3)	0.68 (0.34-1.34)	0.71 (0.35-1.43)

* Adjusted for follow-up time, smoking, asthma exacerbations, GERD, anxiety/depression, obesity, overweight prior to index date and concomitant medications antacids use of hypnotics or anxiolytics, use of antidepressants, nasal preparations, antihistamines used in 30 days before index date. Current use = 1-30 days before index date. Past use = >30 days before index date.

Online Table 3 Continued - Association between use of inhalation medication by generic or brand, by generic, brand, and brand no generic available and by drug class (ICS, LABA and SABA) and moderate to severe asthma exacerbation.

Adjusted for past use of respiratory drugs and current use of all other respiratory drugs**
** all respiratory drugs = ICS, LABA, SABA, and other (= tiotropium,ipratropium, ipratropium+fenoterol and cromoglicic acid and nedocromil)
Numbers of the different groups are not adding up to total number of "all", as for each treatment class we started with selecting patients currently using a drug in that treatment class. One patient could be present in all treatment classes. Current use = 1-30 days before index date.

Online Table 4 - Patients with a switch from brand to generic (s1), from generic to brand (s2) or with switch in device, in 365 days before index date, and in 30 days before index date, categorized by drug class.

	Switch Generic Brand in 1 year before index date				Switch Generic Brand in 30 days before index date			
	Cases		Controls		Cases		Controls	
	(N)	%	(N)	%	(N)	%	(N)	%
s1_ics	7	0.2%	118	0.3%	1	0.0%	1	0.0%
s2_ics	7	0.2%	58	0.2%	0	0.0%	2	0.0%
s1_laba	4	0.1%	20	0.1%	0	0.0%	1	0.0%
s2_laba	0	0.0%	11	0.0%	0	0.0%	1	0.0%
s1_saba	72	1.9%	237	0.6%	4	0.1%	8	0.0%
s2_saba	56	1.5%	279	0.7%	5	0.1%	9	0.0%
s1_salbutamol	72	1.9%	233	0.6%	4	0.1%	8	0.0%
s2_salbutamol	56	1.5%	274	0.7%	5	0.1%	9	0.0%
s1_terbutaline	0		4	0.0%	0		0	
s2_terbutaline	0		5	0.0%	0		0	
s1_salbutamol + ipratropium	0		1	0.0%	0		0	
s2_salbutamol +ipratropium	0		0		0		0	
Total	145	2.4%	690	1.1%	10	0.3%	24	0.1%
	Switch Generic Brand in 1 year before index date				Switch Generic Brand in 30 days before index date			
	Cases		Controls		Cases		Controls	
	(N)	%	(N)	%	(N)	%	(N)	%
Total	28	0.7%	227	0.6%	2	0.1%	14	0.0%
ICS	15	0.4%	114	0.3%	1	0.0%	6	0.0%
LABA	1	0.0%	16	0.0%	0	0.0%	0	0.0%
SABA	10	0.3%	72	0.2%	1	0.0%	8	0.0%

S1 = switch from brand to generic. S2 = switch from generic to brand. ICS = inhaled corticosteroids, LABA = long-acting β_2-agonists, SABA = short-acting β_2-agonists. N = number, % is percentage of total patients
** Total switch is not adding up as the sum of saba, laba and ics as patients could switch more than once and switch was also possible in drugs not included in ics.laba or saba, namely ATC codes BB01, BB04, BC01, AK03 and BC02.

Online Table 5 - Association between switch in inhalation device switch and moderate to severe asthma exacerbation.

Switch device	cases n=3,796 (%)	controls n=37,367 (%)	matched OR (95% CI)	adjusted OR* (95% CI)
ICS				
no switch and use in 1-365 days before index date	2,731 (71.9)	23,546 (63.0)	reference	reference
Switch and use in 1-365 days before index date	15 (0.4)	114 (0.3)	1.11 (0.64-1.91)	1.11 (0.63-1.96)
Use 1-365 days before index date of drugs with no switch possibility	66 (1.7)	606 (1.6)	0.94 (0.73-1.22)	0.89 (0.68-1.16)
LABA				
no switch and use in 1-365 days before index date	382 (10.1)	2,445 (6.5)	reference	reference
Switch and use in 1-365 days before index date	1 (0)	16 (0.1)	nap	nap
Use 1-365 days before index date of drugs with no switch possibility	7 (0.2)	29 (0.1)	nap	nap
SABA				
no switch and use in 1-365 days before index date	1,807 (47.6)	14,192 (38.0)	reference	reference
Switch and use in 1-365 days before index date	10 (0.3)	72 (0.2)	1.13 (0.58-2.20)	0.96 (0.48-1.90)
Use 1-365 days before index date of drugs with no switch possibility	241 (6.3)	1,951 (5.0)	0.97 (0.84-1.12)	1.00 (0.86-1.16)

ICS = inhaled corticosteroids, LABA = long-acting β_2-agonists, SABA = short-acting β_2-agonists

* Adjusted for past use of respiratory drugs, current use of all other respiratory drugs**, smoking history, follow-up, severe to moderate exacerbations, GERD, anxiety/depression, obesity, overweight prior to index date and concomitant medications antacids use of hypnotics or anxiolytics, use of antidepressants, nasal preparations, antihistamines used in the 30 days before index date.

** all respiratory drugs = ICS, LABA, SABA, and other (=tiotropium,ipratropium, ipratropium+fenoterol, cromoglycaat and nedocromil)

Numbers of the different groups are not adding up to total number of "all", as for each treatment class we started with selecting patients currently using a drug in that treatment class. One patient could be present in all treatment classes. Current use = 1-30 days before index date.

nap: not applicable as number of exposed cases lower than 3

Online Table 6 - Association between use of inhalation medication by drug class and moderate to severe asthma exacerbation by agegroup <18, 18-45 and ⩾45 years.

Current use Brand/generic	cases n=3,796 (%)	controls n=37,367 (%)	matched OR (95% CI)	adjusted OR* (95% CI)
Current use of ICS				
<18	322	3,219		
brand	6 (1.9)	706 (21.9)	reference	reference
generic	142 (44.1)	46 (1.4)	0.70 (0.29-1.68)	1.04 (0.42-2.56)
brand without generic substitution	0 (0.0)	3 (0.1)	nap	nap
18-45	1,269	12,605		
brand	479 (37.7)	3,296 (26.1)	reference	reference
generic	51 (1.6)	5 (1.6)	0.60 (0.38-0.94)	0.67 (0.42-1.06)
brand without generic substitution	12 (0.9)	87 (0.7)	0.98 (0.53-1.80)	0.89 (0.47-1.68)
>45	2,205	21,543		
brand	877 (39.8)	7,256 (33.7)	reference	reference
generic	53 (2.4)	475 (2.2)	0.93 (0.70-1.25)	1.00 (0.74-1.35)
brand without generic substitution	33 (1.5)	351 (1.6)	0.78 (0.54-1.13)	0.71 (0.49-1.03)
Current use of LABA				
<18	322	3219		
brand	5 (1.6)	12 (0.4)	reference	reference
generic	0	0	nap	nap
brand without generic substitution	0	0	nap	nap
18-45	1,269	12,605		
brand	55 (4.3)	289 (2.3)	reference	reference
generic	3 (0.2)	4 (0.0)	3.93 (0.85-18.09)	**4.97 (1.04-23.68)**
brand without generic substitution	2 (0.2)	2 (0.0)	nap	nap
>45	2.205	21,543		
brand	111 (5.0)	714 (3.3)	reference	reference
generic	9 (0.4)	52 (0.2)	1.18 (0.56-2.46)	1.29 (0.60-2.80)
brand without generic substitution	0 (0.0)	11 (0.1)	nap	nap
Current use of SABA				
<18	322	3219		
brand	98 (30.4)	447 (13.9)	reference	reference
generic	94 (29.9)	437 (13.6)	1.00 (0.72-1.38)	1.14 (0.80-1.61)
brand without generic substitution	0	0	nap	nap
18-45	1,269	12,605		
brand	339 (26.7)	2,189 (17.4)	reference	reference
generic	169 (13.3)	1,116 (8.9)	0.97 (0.80-1.19)	1.03 (0.84-1.27)
brand without generic substitution	1 (0.1)	3 (0.0)	nap	nap
>45	2,205	21,543		
brand	371 (16.8)	2,425 (11.7)	reference	reference
generic	231 (10.5)	1,220 (5.7)	**1.27 (1.06-1.52)**	**1.20 (0.99-1.44)**
brand without generic substitution	0	0	nap	nap

* Adjusted for past use of all other drugs, current use of other drug classes, follow-up, smoking, asthma exacerbations, GERD, anxiety/depression, obesity, overweight prior to index date and concomitant medications antacids use of hypnotics or anxiolytics, use of antidepressants, nasal preparations, antihistamines used in 30 days before index date. Current use = 1-30 days before index date.

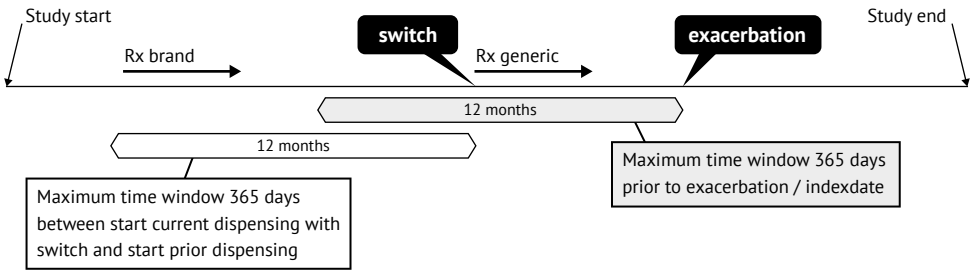
** all respiratory drugs = ICS, LABA, SABA, and other (= tiotropium, ipratropium, ipratropium+fenoterol, cromoglycaat and nedocromil)

nap = not applicable as number of exposed cases lower than 3

Online Table 7 - Association between generic and brand switch in inhalation medication and moderate to severe asthma exacerbation.

Switch generic/brand in 1 year before index date	cases n=104 (%)	controls n=1,040 (%)	matched OR (95% CI)	adjusted OR* (95% CI)
ICS				
no switch and use in 1-365 days before index date	70 (67.3)	628 (60.4)	reference	Reference
Switch and use in 1-365 days before index date	0 (0.0)	2 (0.2)	Nap	Nap
Use 1-365 days before index date of brand with no generic available	2 (1.9)	11 (1.1)	Nap	Nap
LABA				
no switch and use in 1-365 days before index date	17 (16.3)	54 (5.2)	reference	Reference
Switch and use in 1-365 days before index date	0 (0.0)	1 (0.0)	Nap	Nap
Use 1-365 days before index date of brand with no generic available	1 (1.0)	1 (0.1)	Nap	Nap
SABA				
no switch and use in 1-365 days before index date	72 (69.2)	483 (46.4)	reference	Reference
Switch and use in 1-365 days before index date	1 (1.0)	13 (1.2)	Nap	Nap
Use 1-365 days before index date of brand with no generic available	0(0.0)	1(0.1)	Nap	Nap

ICS = inhaled corticosteroids, LABA = long-acting β_2-agonists, SABA = short-acting β_2-agonists
* Adjusted for past use and current use of all other respiratory drugs and smoking history, follow-up time, severe to moderate exacerbations, GERD, anxiety/depression, obesity, overweight prior to index date and concomitant medications antacids use of hypnotics or anxiolytics, use of antidepressants, nasal preparations, antihistamines used in the 30 days before index date.
** all respiratory drugs = ICS, LABA, SABA, and other (= tiotropium, ipratropium, ipratropium+fenoterol, cromoglycaat and nedocromil)
Nap: not applicable as number of exposed cases lower than 3



Online Figure 1 - Switching between brand and generic medication (or vice versa). Figure shows the 3 criteria for switching (1) use of medication in 365 days before exacerbation and (2) switch in 365 days before exacerbation and (3) the window between the start of dispense with switch and start of the prior dispense is maximum 365 days.

6 GENERAL DISCUSSION

GENERAL DISCUSSION

Asthma is a highly prevalent and chronic respiratory condition. [1] According to the most recent comprehensive analysis of the WHO, an estimated 334 million people worldwide suffer from asthma. [2] Its prevalence has increased globally during the last decades according to results of the ISAAC questionnaires by 0.28% per year in the 13-14 year age group and 0.18% per year in the 6-7 year group. [3] However, there is some evidence that this increase came to an end, at least in Western Europe. [2, 3] Asthma is a chronic, episodic, heterogeneous disorder of the airways, characterized by wheezing, shortness of breath, chest tightness and cough that vary over time. This chronic airway inflammation is an important aspect of asthma pathophysiology, therefore asthma is most effectively treated with anti-inflammatory drugs, inhaled corticosteroids and leukotriene receptor antagonists, by inhibiting multiple components of the inflammatory cascade, including the production of prostaglandins and leukotrienes by their action of phospholipase. [4] Despite the proven efficacy of anti-inflammatory drugs in clinical trials, asthma control in clinical practice is suboptimal, as some asthmatics suffer from uncontrolled symptoms and exacerbations. [5] Several factors may contribute to this individual variation in treatment response, such as disease severity, co-morbidities, environmental factors, therapy adherence [6] and genetic factors. [7]

In this thesis we contributed to the knowledge on the epidemiology, medication use and disease outcome in patients with asthma using data from routinely electronic health care databases, reflecting real life.

In this chapter we discuss the main findings of this thesis and the methodological challenges that we encountered. In addition, we place the relevance of our findings and the potential implications in a broader context. Finally, some future perspectives of research with respect to epidemiology, treatment and outcomes of asthma are provided.

Main findings

Epidemiology of asthma

As a consequence of the lack of European longitudinal studies in children with asthma, data on the incidence of asthma in children in Europe are sparse. Using data from the Dutch general practice Integrated Primary Care Information database (IPCI), we identified 14,303 children with asthma, 2,542 were incident. The overall asthma prevalence at start study was 6.7% (95% CI 6.6-6.8%). The overall asthma incidence rate was 6.7 per 1000 person years (PY) (95% CI 6.45-6.97/1000 PY) with lower incidence rates for girls compared to boys. This gender difference in incidence became less obvious with increasing age. In IPCI the incidence rate increased significantly between 2000 and 2008 and tended to decrease after 2008. A recent study based on the '*National Health Interview Survey*' data from the US observed a decrease in asthma incidence in recent years. [8] However, data on the time trends in asthma incidence are conflicting. [9-11]

Asthma medication use in children

In the paediatric asthma cohort, we studied prescription patterns of asthma medication and medication adherence. SABA and ICS were most frequently prescribed, whereas LABA (as monotherapy) was rarely prescribed and the prevalence of LABA monotherapy decreased over time, which is in line with treatment guidelines that warn against LABA use as monotherapy. [1, 12] Treatment adherence is important, especially in chronic diseases like asthma. There are different ways to assess adherence, each with their own set of advantages and limitations. [13-15] In database research, the medication possession rate (MPR) is most commonly used. [16] Adherence to asthma medications in the paediatric asthma cohort was suboptimal as only 31% of the ICS users had an MPR>0.8. This low MPR falls within the MPR range that was reported in other studies. [17, 18, 19] In reality, MPRs are probably even lower, as we only considered prescription and not dispensing data. In addition, even if all prescribed medication would be dispensed, this would not guarantee that all dispensed medication is correctly taken. This low MPR however, reflects reality, where in contrast to current asthma guidelines, controller therapy is often taken on an as-needed basis driven by the patient's symptom control. [20] According to asthma guidelines, a follow-up visit is needed upon initiation of ICS or upon an increase of dose. However it is known that follow-up visits are not scheduled in all patients, putting patients at risk of unmonitored discontinuation of therapy and therefore lower MPR. [21] Another factor that may explain low adherence is that asthma in childhood is transient in some children which is reflected in transient medication use patterns. [22]

It is well known that adherence is influenced by many factors. [1] In our study, characteristics of children with good adherence suggested that these children were having more severe asthma. This good adherence was potentially driven by treatment need or tighter medical follow-up.

To put our findings in context to what has already been published and to study whether adherence has an impact on exacerbations in real life, we conducted a systematic review on asthma medication adherence and the risk of severe asthma exacerbations. (chapter 3.2) This review showed that there is large heterogeneity in adherence measures. In addition it reveals that despite heterogeneity amongst the studies, high quality studies, which used objective adherence measures, reported that good adherence to asthma drugs was associated with a reduced risk of severe asthma exacerbations.

Asthma Exacerbations

In spite of a wide choice of different asthma medications, asthma exacerbations may still occur due to a variety of reasons, like inadequate treatment, nonresponse, non-adherence or other triggers such as lower respiratory tract infections. [23] In our research, moderate to severe asthma exacerbations were defined according to the ATS/ERS guidelines as worsening of asthma symptoms which requires hospitalisation or emergency department visit or use of systemic corticosteroids. [24] Severe asthma exacerbations, hospitalisation or emergency department visit,

are associated with considerable morbidity and even mortality. [25] Little is known about the incidence of moderate to severe exacerbations, as data from RCTs are often underpowered in terms of sample size and follow-up. In the paediatric cohort from the IPCI database the overall incidence rate of moderate to severe asthma exacerbations was 2.1/100 PY (95% CI 1.9-2.2/100 PY) in the total asthma cohort and 4.1/100PY (95% CI 3.8-4.4/100 PY) in children who were on asthma treatment. (chapter 4.1) This is in line with the incidence rate observed in the CAMP study, a RCT in children with mild to moderate asthma who were treated with budesonide, nedocromil or placebo for 4-6 years. [26] In the CAMP study, the incidence rate of asthma exacerbations requiring hospitalisation was 2.5/100 PY in the budesonide group, 4.3/100 PY in the nedocromil group and 4.4/100 PY in the placebo group. In our study asthma re-exacerbation occurred in 2% (95% CI 1.3-4.3%) of all patients within 1 month, and in 25% (95% CI 20.6-28.8%) within 1 year and the risk remained constant over calendar time. Significant predictors for (frequent) exacerbations were age, gender, specialist visits, ICS prescriptions and prior exacerbations. Our data conform previous studies that also showed that prior exacerbations were an important risk factor for future exacerbations. [27-29] This emphasizes the importance of close monitoring of children after moderate to severe asthma exacerbations.

Mortality

As recent mortality rates in patients with asthma in Europe are sparse, we assessed all-cause mortality rates, mortality rates following severe asthma exacerbation and risk factors of mortality. (chapter 4.2) For this study, data from 6 European electronic healthcare databases were used, all members of the EU-ADR alliance. [30] The cohort consisted of 855,806 patients with asthma aged 5 years or older and the study period was from 2008 to 2013. The proportion of patients with severe asthma, defined as use of high dose ICS during 120 days, ranged between 1.7-10.0%, and all-cause mortality rate in this severe asthma cohort ranged between 16.0-33.4/1000 PY in the different databases. The mortality rate in the 1st week following a moderate to severe asthma exacerbation was 26.3-109.5/1000 PY. This mortality rate was twofold higher when restricting to severe asthma exacerbations (ED-visit/hospitalisation). (57.9-239.4/1000 PY). In most databases, risk factors of death in patients with asthma were increasing age, concomitant diseases (COPD, diabetes, cerebrovascular diseases, and cancer), smoking and underlying asthma severity. Prior moderate to severe asthma exacerbation was associated with a 76% increase in the risk of death. This finding underlines the importance of asthma control, as by preventing asthma exacerbations the risk of mortality may be reduced.

Preference policy

In Chapter 5.1 and 5.2 we studied the effects of the Dutch preference policy. This policy favours the use of generic drugs as alternatives to more expensive brand-name products. Before generic medications are marketed, demonstration of clinical bioequivalence is needed. As the drug delivery and intended action of orally inhaled drug products for local action, such as dry powder inhalers (DPI) do not rely on their effect in the systemic circulation, the bioequivalence cannot be demonstrated based on drug concentration in blood/plasma. [31] Therefore demonstration of bioequivalence of these products is more challenging. The guideline of the European Medicines Agency on requirements for clinical documentation of orally inhaled products for asthma and COPD states that for inhalers with the same substance and required flow rate, similar in vitro performance is sufficient to show equivalence. [32] In vitro performance includes particle size distribution, fine particle fraction of emitted dose and flow rate dependency tested under validated circumstances. [32] Health care professionals are concerned about generic substitution because fear of negative effects on disease control through non-adherence, and potentially lack of efficacy because of inappropriate use of inhalation devices.

Although generic substitution is widely implemented, it still remains to be answered whether generic use or switching influences persistence to long-term treatment and clinical outcomes. For this study we used data from the PHARMO Database Network, which links different sources of data (e.g. drug dispensing, hospital discharge diagnoses, and medical diagnosis and prescriptions of the GP) and includes information on 2 million residents in the Netherlands. First, we defined a population based cohort to study the prevalence of generic and brand use and switching between brand, generic inhalation medication and its effect on adherence. (chapter 5.1) The total cohort of patients who used inhalation medication for which a generic alternative was available, consisted of 56,853 patients. The annual proportion of patients who switched from generic to brand medication or vice versa was 5%. About 16% of all patients used more than 1 device in 1 calendar year. No net negative impact on adherence in patients who switch from brand to generic was observed, which is promising, however adherence remained low.

To investigate potential clinical consequences of use of generic inhalation medication and switching between generic and brand inhalation medication (or vice versa) on disease control we conducted two case control studies. (chapter 5.2) Cases were patients ≥5 years of age with asthma who had a first moderate to severe asthma exacerbation, defined as need of systemic corticosteroids or requiring hospitalization for asthma (case-control set 1), or severe asthma exacerbation, defined as requiring hospitalization (case-control set 2). To each case, up to 10 controls were matched on age, gender, and index date.

The first case-control set consisted of 3,796 cases. Current use of generic inhaled medication was associated with an increased risk of moderate to severe asthma exacerbations (OR_{adj} 1.33 (95% CI 1.20-1.47) Switching from brand to generic (or vice versa) salbutamol increased the risk of moderate to severe asthma exacerbations with 68%. (OR_{adj} 1.68 (95% CI 1.34-2.10),

with highest risks in patients <18 and ≥45 years of age. (<18: OR_{adj} 1.95 (95% CI 1.16-3.27) and ≥45 OR_{adj} 2.14 (95% CI 1.51-3.03). The association with current use of generics was higher in the case control analysis on severe exacerbations (104 cases) (OR_{adj} 2.05 (95% CI 1.20-3.52). But no significance was reached when data were analysed by drug class or switching type. This study showed that current use of generic inhaled β_2-agonists might be associated with a small increased risk of exacerbations when compared to current use of brand β_2-agonists, in particular when switched between generic and brand. However, it is unclear whether the association that was observed is causal. Unfortunately, we could not investigate the indication of switching in this database. In the asthma domain conflicting results with both protective as well as adverse effects of generic drug use were observed. [33-41] Another limitation was that our study period was from 2003-2012, a period in which the availability of generic respiratory drugs was still relatively low. Since 2012 new generic inhalation drugs came into the market implying that the current proportion of generic medication use and the proportion of switching should probably be higher than what we observed. [41]

Pharmaco-Genetics

There is evidence that genetic factors play a role in inter-individual differences in therapeutic responses to the common classes of asthma therapy such as β_2-agonists, corticosteroids, and leukotriene modifiers. [42] Unfortunately, it is difficult to conduct pharmaco-genetic research using the data from existing Dutch paediatric cohort studies, because only few children enrolled in these cohorts regularly used asthma medication. [43-45] Therefore, we are presently recruiting children with asthma to be included in a new paediatric cohort which will be used for future pharmacogenetics studies: the ESTATe -cohort. (www.estate-studie.nl) This ESTATe cohort has its origins in the IPCI asthma-cohort, which was used for many of our studies. Within the IPCI asthma cohort, we selected patients on asthma controller therapy and identified patients experiencing an asthma exacerbation as case. Each case was matched up to 4 controls on age, sex, general practice (GP) and asthma therapy. Patients were recruited via their GP and if they agreed to participate, they provided a saliva sample (for DNA extraction and genetic analysis) and completed a questionnaire including the Asthma Control Questionnaire. [46] As recruitment was more difficult than anticipated, we expanded the recruitment to patients in the PHARMO Database Network.

Until now 111 patients (cases and controls) provided a saliva sample and are included in the ESTATe cohort. We continue patient inclusion for the study, however we did not attain the foreseen sample size. Currently efforts are being made to combine our data with data from the PACMAN cohort [47] to guarantee sufficient power to conduct pharmaco-genetic studies on the association between genetic variability in treatment response and risk of asthma exacerbations. Eventually this data will be integrated with the Pharmacogenomics in Childhood Asthma consortium (PICA) [48], to guarantee enough power for genome wide association analyses in the future.

Methodological considerations

Different data sources for population based asthma research

All studies, except for the systematic review described in chapter 3.2 were conducted using data from electronic healthcare databases. For chapter 2.2, 3.1 and 4.1 we used the IPCI database, a general practitioner database containing the complete medical records of 1,5 million patients, with detailed information on patient characteristics, comorbidities and treatment. [49] One of the unique features of the IPCI database is that IPCI includes both structured and unstructured information, since much details are still described as narratives in the medical record. For some of the practices, referral and/or discharge letters were incorporated in the medical record. Previous research showed that IPCI is representative of the Dutch population with regard to age and gender. [50]

For chapter 5.1 and 5.2 the Dutch PHARMO Database Network (www.pharmo.nl) was used. This population-based patient centric data network combines data from different healthcare setting, including general practitioner (GP), in- and outpatient pharmacy and hospitals. It includes high quality and complete information linked on a patient level of, among other data, patient demographics, drug dispensing records from community pharmacies, hospital discharge records, and GP diagnoses of more than two million individuals throughout the Netherlands. [51] The PHARMO database was used to study the use of generic and brand inhalation medication because this database, in contrast to the IPCI database has data on dispensing data in addition to prescribing data and has the possibility to link to hospital data. Dispensing information was important, as pharmacists may substitute brand medications to generics or vice versa.

In chapter 4.2 we studied mortality rates following asthma exacerbations in Europe, therefore we used data from 6 different electronic healthcare databases which are managed or licensed by partners in the EU-ADR Alliance. The 6 databases were the Integrated Primary Care Information Project (IPCI) from the Netherlands, the Health Search Database (HSD) and Pedianet from Italy, the Clinical Practice Research Datalink (CPRD) from the UK, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain and the Aarhus University Prescription Database (AUH) from Denmark. Detailed description of these databases has been published before.[49, 52-56] All databases contain electronical medical records from primary care, apart from AUH which is a prescription database that links to the national registry. Each database has their own strengths and limitations in terms of sample size, dosing information, drug and disease coding systems, and the ability to link data.

Validation of asthma

For the studies described in chapter 2.2 and 4.1 we defined a population based paediatric asthma cohort in the IPCI database between 2000 and 2012. This cohort comprised all patients between 5-18 years of age, diagnosed with asthma. A patient was considered to have asthma

if diagnosed by the specialist, or in the presence of an asthma disease code in combination with at least two prescriptions of asthma drugs during follow-up. As the initial search returned over 60 thousand records, we used text mining for concept retrieval in the medical records, which was categorising subjects into "definite" or "probable" asthma cases, or patients without asthma based on machine learning techniques. (chapter 2.1) In order to train the machine a manually validated training set is needed. These techniques lead to a reduction of the false positives that are retrieved if only text strings are searched. Upon return of the machine classified asthma cases, manual validation was done for of 100% of the potential definite cases and 25% of the probable cases, as fully automated search would still lead to inclusion of false positives. The resulting prevalence at cohort entry was 6.8% which is in line with prevalences as reported in other studies. [3]

For the study in the EU-ADR alliance, the definition of patients with asthma was based on disease and medication codes, without manual validation. As each database had their own coding system (ICPC for IPCI; READ codes for HSD, ICD9 for Pedianet and HSD and ICD10 for AUH), a harmonisation of disease codes had to be conducted prior to data extraction. This harmonisation was done through use of the Unified Medical Language System. [57] A set of disease codes was created from disease concept mappings, which were then verified by the different databases prior to data extraction. Although some results were comparable between databases, i.e. mortality rates, differences were observed with regard to the incidence of moderate asthma exacerbations. The difference between databases in the incidence of moderate asthma exacerbations can be explained by different factors, for example by differences in coding systems or availability of data (i.e. indication of use missing in some of the databases). An earlier study on information on asthma drug use in Italy, UK and the Netherlands, clearly demonstrates the similarities and differences in prescription rates. [58] This study observed very heterogeneous prescription rates of systemic corticosteroids between countries, with user rates exceeding 10/100 PY in Italy, whereas user rates were five to eightfold lower in the UK and almost 20 fold lower in the Netherlands. Like in our study, the health care provider in the studied countries differed, with GP data from the UK and NL and family paediatrician data from Italy. However, we do not believe that this would hinder comparability between databases as the nature of the databases is the same. If there are differences between countries, this reflects differences in primary care prescribing behaviour and not in the type of data. This prescribing behaviour, reflecting the use of oral corticosteroids, might be explained by cultural differences. This was shown by Wahlstrom et al. where 100 physicians per country in 5 European countries, in the Netherlands, Germany, Sweden, Norway and the Slovak Republic, were asked to give their treatment decision for two sets of case simulations. One case on treatment of an exacerbation and one on adjustment of suboptimal maintenance treatment. When the decisions of all doctors of a country were pooled, they significantly differed in their recommendations concerning OCS prescriptions despite having been given similar case descriptions. [59]

Methodological challenges

The use of large real life databases was important for our research on asthma outcomes like severe asthma exacerbations and mortality as the incidence of these outcomes is relatively rare. Furthermore it gives the opportunity to study real life practice. However, observational research is prone for bias and-or confounding. Bias is generally categorized into selection bias and information bias. [60]

Selection bias, due to lack of participation or response in the study is probably minimal in these population based databases, as this does not require consent.

The bias which was probably most relevant to our research is *information bias.* Information bias might have resulted from our assessment of drug exposure, comorbidity and disease outcomes. With regard to assessment of drug exposure, information on drug dispensing was not available in some databases (IPCI, HSD, Pedianet, CPRD). This implies that prescriptions initiated by the specialist, or prescriptions during hospitalization might be missed. As the GP plays a gatekeeper role for patient care, prescriptions as initiated by the specialist will often be continued by the GP, which limits the amount of misclassification. [61] Additional misclassification of exposure relates to the fact that we did not have information on actual drug intake nor on correct use of the drugs.

Second, misclassification of outcomes and comorbidity is a concern in those studies where no manual validation of outcomes was done. Indeed, for those studies where other databases were used than IPCI, it was not possible to conduct a free text search followed by manual validation. Misclassification of outcomes like hospitalisation or ED visits for asthma exacerbation is a concern for those databases that do not automatically link to hospital data like IPCI, Pedianet and HSD. For those databases where linkage was not feasible, data on asthma exacerbations was indirectly retrieved either via disease-specific codes in combination with codes for hospitalization or via review of the discharge letters.

Finally, confounding is a concern in all observational research and could result in spurious associations. A confounding factor is a factor that is both associated with the exposure and with the outcome but that is not in the causal pathway. [62]

Important confounding factors in our research were asthma severity and smoking status. Asthma severity is a confounder because it is related to the exposure (choice of asthma drugs, driven by asthma control) and to the outcomes as patients with severe asthma are at risk of asthma exacerbations. Asthma severity scores are unfortunately not systematically recorded in the databases. Because of current treatment guidelines and GPs incentives to improve the quality of reporting, we observe an improvement with regard to registration of lung function data, smoking status and asthma symptom severity, nowadays. [63, 64]

Confounding can be controlled for either in the design of the study by restriction or matching or in the analysis through stratification or the use of multivariate techniques (e.g. multivariate logistic regression or proportional hazard analysis), and time-dependent covariables, which

ideally requires marginal structural modelling. [65]

In our research we applied several techniques like multivariate analysis, with time dependent variables in chapters 4.1 and 4.2 and matching on age, gender, practice and index date in chapters 5.1 and 5.2.

Although we tried to correct for confounders where available, unknown or unmeasured residual confounders might still have affected our associations.

Clinical implications and future research

The main aim of this study was to acquire real life data on the incidence and prevalence of asthma, treatment of asthma, asthma exacerbations and mortality.

In the studies as presented in this thesis, we showed that the asthma incidence seems to decline since 2008, but that asthma still imposes a significant burden on the population because of mortality and asthma exacerbations, implying the lack of adequate asthma control. Prior asthma exacerbations are the main risk factor for future exacerbations.

The ultimate goals of asthma treatment are to achieve and maintain clinical control, to identify potential risk factors for asthma exacerbations and enable the patient to lead a life without restrictions due to the disease. [1, 66] Asthma control will result in a reduction of morbidity and a reduction in health care costs. Possibly, lack of adherence to treatment or poor inhaler technique are the key factors for poor asthma control. Correct inhaler technique is necessary for adequate medication delivery, and should be clearly explained and well demonstrated, as we know that in real life patients make critical errors in using their inhaler. Preferably, therapy regimen and inhalation techniques should be taught and checked repeatedly during follow-up appointments to correct mistakes. [67] This is of particular importance in case of complex treatment regimens (use of more than one inhaler) or in case of switching from drug and/or device.

Pharmacists play a critical role in informing patients on the mode of action, correct device use and the importance of good adherence to reach sufficient asthma control. [68] Detecting and discussing non adherence through monitoring of refill prescription rates or by the use of electronic monitoring devices, increases awareness about adherence and correct medication use, with as ultimate goal to improve adherence and outcomes. [69]

Patients' (and parents') views and beliefs on the goals of treatment are essential in monitoring children with asthma. It is generally assumed that patients know whether their asthma is under control, however a recent online survey research suggested otherwise. [5] Underestimation of the symptoms may lead to inadequate treatment. Easy accessible attractive information on judgment of symptoms by smart phone applications or social media, might help children and their parents in symptom evaluation.

The burden of asthma on health care budget is considerable. Generic substitution of brand medications was implemented to reduce asthma health care costs. However some recent data suggest that generic substitution might increase the risk of asthma exacerbations. In September

2015 the Netherlands Pharmacovigilance Centre Lareb reported case reports on decreased efficacy of a generic salbutamol aerosol after the revision of the device. Besides some external changes, the formulation of the propellant was changed as well. [70] We also observed a small increased risk of asthma exacerbations for generic use of salbutamol. However the cases were reported to Lareb in 2015 and our latest dispensing information is till 2013. It remains questionable whether the association with increased risks of asthma exacerbations is real or confounded by other factors such as underlying asthma severity. We observed in our studies that substitution and device switch (which are not recommended) were low. We observed an association between use of generic salbutamol (and switching between generic and brand salbutamol (and vice versa)) and exacerbations, and not with ICS. Further studies should replicate these findings.

Directions for future research

First, as data on the incidence of asthma over time are conflicting, further research, preferably international population based incidence studies, are needed to find out how the pattern of asthma is changing by calendar time and age. Furthermore, most prevalence estimates outdated. Fortunately, the Global Asthma Network announced in their report in 2014 that it plans to continue worldwide studies to find out how the pattern of asthma is changing in children and adults. [2] To facilitate comparison of data, we strongly recommend that further efforts be taken to harmonize definitions of asthma when using electronic health care databases. In most of the prevalence and incidence studies of asthma in children, asthma is considered as a chronic disease whereas asthma can be intermittent and has the potential to change phenotype with age, growth and environmental exposures. [71] Since the prevalence is a resultant of the incidence and the duration of disease, it should be investigated how intermittent asthma affects the prevalence and incidence of asthma.

Second, we need to better understand how treatment adherence impact outcomes such as moderate to severe asthma exacerbations. Future studies should investigate optimal adherence measures based on asthma phenotypes, as MPR measures might be too conservative for patients with intermittent asthma. Ideally, not only treatment adherence but also inhalation techniques should be considered, although this is difficult to assess in electronic record database studies. Several studies on different strategies e.g. education, monitoring by pharmacists, electronical medical devices, to improve adherence already have been performed. [18] However real life studies are needed to demonstrate that these strategies not only lead to better adherence, but might also improve symptom control and prevent exacerbations. [72]

Third, we observed a possible association between switching between generic and brand SABA (or vice versa) and asthma exacerbations. In our study, data on asthma severity and reasons for switching were not available. This information is of utmost importance to disentangle whether switching occurred because of worsening of respiratory symptoms leading to asthma

exacerbations, or whether switching by itself results in poorer asthma control. The impact on clinical outcomes and the cost effectiveness of the preference policy by the Dutch health insurances should be investigated in newer data, as more generics are upcoming.

Fourth, to tailor treatment strategies, there is also need for better monitoring of asthma, and to detect poor control and risk of exacerbations. [73] Use of structured interviews incorporating objective symptom assessment might uncover unmet needs, and would detect poor control. In our research we characterised patients at risk of non-adherence, at risk of asthma exacerbations and at risk of mortality on population level. More individual characterisation, for example data on biomarkers i.e. exhaled breath condensate, may lead to better targeted treatment strategies. [72]

Finally, to reach the goal of individualized prescribing in asthma, more research into the variability of treatment response and knowledge of genetic influences on drug response is needed. [74] Characterisation of patients could be done at an individual level through pharmacogenetic research which may open the way for personalized medicine in children with asthma. Early recognition of patients who do not sufficiently respond to ICS treatment may reduce asthma-related outcomes. In future studies we hope to identify new loci through genome wide analysis of DNA collected in participants of the ESTATe study and the PACMAN study. [47] Findings will be replicated in databases of the PICA consortium. [48]

CONCLUSION

Asthma is a heterogeneous disease, with many risk factors. To some extent there is room for optimism, as the incidence of asthma tended to decrease and treatment guidelines were followed in general (e.g. LABA monotherapy is rare), however the burden of asthma with respect to mortality and exacerbations remains large, symptom control and adherence being suboptimal. The asthma outcomes are worse in real life than they could be and much worse than achieved in clinical trials. To improve these outcomes, future research should focus on prevention of exacerbation and improved symptom control. Therefore studies on strategies to ensure that patients are prescribed, receive and take appropriate treatments correctly, studies on optimizing adherence and studies on further characterizing patients at risk for exacerbations are warranted.

Hopefully the above mentioned directions for future research will lead to a personalized approach of patients with asthma improving their lives with better adherence and fewer asthma exacerbations.

REFERENCES

1. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. . 2015.
2. *The Global Asthma Report 2014.* Auckland, Newzealand: Global Asthma Network;2014.
3. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax.* Sep 2007;62(9):758-766.
4. Houglum JE. Asthma medications: basic pharmacology and use in the athlete. *J Athl Train.* Apr 2000;35(2):179-187.
5. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ primary care respiratory medicine.* 2014;24:14009.
6. Yawn BP. Factors accounting for asthma variability: achieving optimal symptom control for individual patients. *Prim Care Respir J.* Sep 2008;17(3):138-147.
7. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. *British medical bulletin.* 2000;56(4):1054-1070.
8. Akinbami LJ, Simon AE, Rossen LM. Changing Trends in Asthma Prevalence Among Children. *Pediatrics.* Dec 28 2015.
9. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy.* Feb 2010;65(2):152-167.
10. van Schayck CP, Smit HA. The prevalence of asthma in children: a reversing trend. *Eur Respir J.* Oct 2005;26(4):647-650.
11. von Hertzen L, Haahtela T. Signs of reversing trends in prevalence of asthma. *Allergy.* Mar 2005;60(3):283-292.
12. NVK. Richtlijn astma bij kinderen *Nederlandse Vereniging voor Kindergeneeskunde*2013.
13. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest Med.* Sep 2012;33(3):405-417.
14. Desai M, Oppenheimer JJ. Medication adherence in the asthmatic child and adolescent. *Curr Allergy Asthma Rep.* Dec 2011;11(6):454-464.
15. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med.* Feb 1994;149(2 Pt 2):S69-76; discussion S77-68.
16. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health.* Jan-Feb 2007;10(1):3-12.
17. Feehan M, Ranker L, Durante R, et al. Adherence to controller asthma medications: 6-month prevalence across a US community pharmacy chain. *J Clin Pharm Ther.* Aug 20 2015.
18. Sabaté E. *Adherence to long-term therapies: evidence for action.* Geneva, Switzerland: World Health Organization;2003.
19. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest.* Jul 2006;130(1 Suppl):65S-72S.
20. Chong J, Haran C, Chauhan BF, Asher I. Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. *Cochrane Database Syst Rev.* 2015;7:CD011032.
21. Klok T, Kaptein AA, Duiverman E, Oldenhof FS, Brand PL. General practitioners' prescribing behaviour as a determinant of poor persistence with inhaled corticosteroids in children with respiratory symptoms: mixed methods study. *Bmj Open.* 2013;3(4).
22. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med.* Jan 19 1995;332(3):133-138.
23. Blakeley JO, Evans DG, Adler J, et al. Consensus recommendations for current treatments and accelerating clinical trials for patients with neurofibromatosis type 2. *Am J Med Genet A.* Jan 2012;158A(1):24-41.
24. Reddel HK. Characterizing asthma phenotypes: predictors and outcomes at the extremes of asthma severity. *Respirology.* Aug 2009;14(6):778-780.
25. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* Dec 15 2012;380(9859):2163-2196.
26. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med.* Oct 12 2000;343(15):1054-1063.
27. Zeiger RS, Yegin A, Simons FE, et al. Evaluation of the National Heart, Lung, and Blood Institute guidelines impairment domain for classifying asthma control and predicting asthma exacerbations. *Ann Allergy Asthma Immunol.* Feb 2012;108(2):81-87.

28. Miller MK, Lee JH, Miller DP, Wenzel SE. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med*. Mar 2007;101(3):481-489.

29. Hasegawa K, Bittner JC, Nonas SA, et al. Children and Adults With Frequent Hospitalizations for Asthma Exacerbation, 2012-2013: A Multicenter Observational Study. *J Allergy Clin Immunol Pract*. Sep-Oct 2015;3(5):751-758 e751.

30. Coloma PM, Schuemie MJ, Trifiro G, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. *Pharmacoepidemiol Drug Saf*. Jan 2011;20(1):1-11.

31. Lee SL, Adams WP, Li BV, Conner DP, Chowdhury BA, Yu LX. In vitro considerations to support bioequivalence of locally acting drugs in dry powder inhalers for lung diseases. *Aaps J*. Sep 2009;11(3):414-423.

32. Agency EM. *Guidelines on the requirements for clinical documentation for orally inhaled product (OIP) including requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and COPD in adults and for use in the treatment of asthma in children and adolescents*. . 2009.

33. Doyle S, Lloyd A, Williams A, et al. What happens to patients who have their asthma device switched without their consent? *Prim Care Respir J*. Jun 2010;19(2):131-139.

34. Rathe J, Andersen M, Jarbol DE, dePont Christensen R, Hallas J, Sondergaard J. Generic switching and non-persistence among medicine users: a combined population-based questionnaire and register study. *PLoS One*. 2015;10(3):e0119688.

35. Thomas M, Price D, Chrystyn H, Lloyd A, Williams AE, von Ziegenweidt J. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. *BMC Pulm Med*. 2009;9:1.

36. Kesselheim AS, Bykov K, Avorn J, Tong A, Doherty M, Choudhry NK. Burden of changes in pill appearance for patients receiving generic cardiovascular medications after myocardial infarction: cohort and nested case-control studies. *ANN INTERN MED*. Jul 15 2014;161(2):96-103.

37. Roman B. Patients' attitudes towards generic substitution of oral atypical antipsychotics: a questionnaire-based survey in a hypothetical pharmacy setting. *CNS drugs*. Aug 2009;23(8):693-701.

38. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med*. Feb 13 2006;166(3):332-337.

39. Trusell H, Sundell KA. Effects of generic substitution on refill adherence to statin therapy: a nationwide population-based study. *BMC Health Serv Res*. 2014;14:626.

40. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Generic substitution of antihypertensive drugs: does it affect adherence? *Ann Pharmacother*. Jan 2006;40(1):15-20.

41. NIVEL. Gevolgen van preferentiebeleid en farmaceutische zorginkoop. 2015; http://www.nivel.nl/sites/default/files/bestanden/Rapport-gevolgen-preferentiebeleid-farmaceutische-inkoop.pdf. Accessed 11.13, 2015.

42. Tse SM, Tantisira K, Weiss ST. The pharmacogenetics and pharmacogenomics of asthma therapy. *The pharmacogenomics journal*. Dec 2011;11(6):383-392.

43. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol*. 2002;13 Suppl 15:55-60.

44. Eijkemans M, Mommers M, de Vries SI, et al. Asthmatic symptoms, physical activity, and overweight in young children: a cohort study. *Pediatrics*. Mar 2008;121(3):e666-672.

45. Katier N, Uiterwaal CS, de Jong BM, et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): rationale and design. *Eur J Epidemiol*. 2004;19(9):895-903.

46. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J*. Dec 2010;36(6):1410-1416.

47. Koster ES, Raaijmakers JA, Koppelman GH, et al. Pharmacogenetics of anti-inflammatory treatment in children with asthma: rationale and design of the PACMAN cohort. *Pharmacogenomics*. Aug 2009;10(8):1351-1361.

48. Pharmacogenomics in Childhood Asthma consortium *http://pica-consortium.org/* 2014; http://pica-consortium.org/.

49. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med*. Dec 1999;38(4-5):339-344.

50. Voordouw BC, Sturkenboom MC, Dieleman JP, Stijnen T, van der Lei J, Stricker BH. Annual influenza vaccination in community-dwelling elderly individuals and the risk of lower respiratory tract infections or pneumonia. *Arch Intern Med*. Oct 9 2006;166(18):1980-1985.

51. Herings RM. *PHARMO: a record linkage system for post- marketing surveillance of prescription drugs in The Netherlands*. . Utrecht, Utrecht 1993.

52. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol.* 2010;2:273-279.

53. Cazzola M, Puxeddu E, Bettoncelli G, et al. The prevalence of asthma and COPD in Italy: a practice-based study. *Respir Med.* Mar 2011;105(3):386-391.

54. Cricelli C, Mazzaglia G, Samani F, et al. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med.* Sep 2003;25(3):254-257.

55. Gulliford MC, van Staa T, Dregan A, et al. Electronic Health Records for Intervention Research: A Cluster Randomized Trial to Reduce Antibiotic Prescribing in Primary Care (eCRT Study). *Ann Fam Med.* Jul 2014;12(4):344-351.

56. Sorensen HT, Larsen BO. A population-based Danish data resource with possible high validity in pharmacoepidemiological research. *J Med Syst.* Feb 1994;18(1):33-38.

57. Bodenreider O. The Unified Medical Language System (UMLS): integrating biomedical terminology. *Nucleic Acids Res.* Jan 1 2004;32(Database issue):D267-270.

58. Sen EF, Verhamme KM, Neubert A, et al. Assessment of pediatric asthma drug use in three European countries; a TEDDY study. *Eur J Pediatr.* Jan 2011;170(1):81-92.

59. Wahlstrom R, Hummers-Pradier E, Lundborg CS, et al. Variations in asthma treatment in five European countries--judgement analysis of case simulations. *Fam Pract.* Oct 2002;19(5):452-460.

60. Rothman KJ, Lash TL, Greenland S. Dealing with biases. *Modern Epidemiology.* Vol 3. New York: Oxford University Press; 2012:148-164.

61. de Vries CS, van Diepen NM, Tromp TF, de Jong-van den Berg LT. Auditing GPs' prescribing habits: cardiovascular prescribing frequently continues medication initiated by specialists. *Eur J Clin Pharmacol.* 1996;50(5):349-352.

62. Miettinen O. Confounding and effect-modification. 1974. *Am J Epidemiol.* Jun 15 1995;141(12):1113-1116, discussion 1111-1112.

63. van Althuis TR, Bouma M. Overzicht en definitie van indicatoren voor asthma bij volwassenen in de huisartsenzorg. 2015;1.4. https://www.nhg.org/sites/default/files/content/nhg_org/uploads/ha-astma-indicatoren-v1.4-10feb15docx.pdf.

64. The NICE indicator Menu for the QOF. https://www.nice.org.uk/Standards-and-Indicators/QOFIndicators

65. de Keyser CE, Leening MJ, Romio SA, et al. Comparing a marginal structural model with a Cox proportional hazard model to estimate the effect of time-dependent drug use in observational studies: statin use for primary prevention of cardiovascular disease as an example from the Rotterdam Study. *Eur J Epidemiol.* Nov 2014;29(11):841-850.

66. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* Jul 1 2009;180(1):59-99.

67. Rottier BL, Eber E, Hedlin G, et al. Monitoring asthma in childhood: management-related issues. *Eur Respir Rev.* Jun 2015;24(136):194-203.

68. Hammerlein A, Muller U, Schulz M. Pharmacist-led intervention study to improve inhalation technique in asthma and COPD patients. *J Eval Clin Pract.* Feb 2011;17(1):61-70.

69. Gamble J, Stevenson M, Heaney LG. A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med.* Sep 2011;105(9):1308-1315.

70. Decreased effectivity associated with the revised formulation of the salbutamol aerosol from Sandoz®. 2015; http://www.lareb.nl/Signalen/Signals_2015_Salbutamol_efficacy_lack.aspx.

71. Rubin BK. Asthma myths, controversies, and dogma. *Paediatr Respir Rev.* Mar 2015;16(2):83-87.

72. Anderson WC, 3rd, Szefler SJ. New and future strategies to improve asthma control in children. *J Allergy Clin Immunol.* Oct 2015;136(4):848-859.

73. Pijnenburg MW, Baraldi E, Brand PL, et al. Monitoring asthma in children. *Eur Respir J.* Apr 2015;45(4):906-925.

74. maitland-van der Zee AH, Daly AK. *Pharmacogenetics and individualized therapy.* Canada: John Wiley & Sons; 2011.

7 SUMMARY SAMENVATTING

SUMMARY

In this thesis we focused on the epidemiology, treatment, exacerbations and mortality of asthma in daily practice. In addition we studied risk factors for non-adherence and asthma exacerbations. For this research, we used different Dutch and other European electronic health care databases.

Chapter 1 provides a brief overview of asthma and its aetiology and treatment. It also provides the aims of the performed studies and describes the outline of the thesis.

Chapter 2 describes the epidemiology of asthma. In **Chapter 2.1** we describe the selection of the paediatric asthma cohort (= ESTATe cohort: Effectiveness and Safety of controller Therapy of Asthma in the Treatment of childrEn with asthma) within the Integrated Primary Care Information (IPCI) database. This cohort was created by carefully exploring all medical records from potential asthma patients identified through "machine learning" techniques. The automated algorithm showed good performance in detecting potential cases of asthma utilizing both free-text and coded data, yielding a positive predictive value (PPV) of 0.82, sensitivity of 0.96, and specificity of 0.90 when identifying both definite and probable asthma cases. In **Chapter 2.2** we use this validated dataset of 14,303 children with asthma (35,118 patient years (PY) of follow-up) to describe the incidence, prevalence and trend of age at asthma diagnosis in 2000-2012. We showed that the incidence rate of physician diagnosed asthma was 6.7 per 1000 PY in children in the Netherlands. The incidence for girls was lower than for boys till puberty, after puberty this gender difference reversed. The asthma incidence rate increased until 2008, from 2008 onwards a non-significant decrease was observed. The cumulative prevalence of asthma was 8.1% (95% CI 8.0-8.2). The age-specific cumulative prevalence of asthma was higher in boys than in girls in all age categories.

In **Chapter 3.1** we describe the epidemiology and risk factors of asthma exacerbations. In the ESTATe cohort we identified 732 exacerbations. The overall incidence rate of asthma exacerbations was 2.1/100 PY, 4.1/100 PY for children on asthma treatment. A seasonal trend was observed with highest incidence rates in spring and fall. Asthma re-exacerbation occurred in 2% of patients within 1 month and in 25% within 1 year. Predictors for (frequent) asthma exacerbations were age, gender, specialist visits, inhaled corticosteroid (ICS) prescriptions and prior exacerbations, suggesting more severe asthma.

In **Chapter 3.2** we analyse the mortality in patients with asthma and the risk of mortality following a severe asthma exacerbation in 6 European electronic healthcare databases. The cohort consisted of 855,806 asthma patients. The all-cause mortality rate ranged between 4.8-13.2/1000 PY and in patients with severe asthma between 16.0-36.2/1000 PY for the different databases. Mortality in the 1st week following exacerbation was 26.3-109.5/1000 PY and was higher following an ED-visit/hospitalization (57.9-239.4/1000 PY). We studied risk factors for mortality in a subgroup of adult patients with incident asthma. Increasing age, concomitant

diseases (COPD, diabetes, cerebrovascular diseases and cancer), smoking, asthma severity and previous asthma exacerbations were associated with mortality in most databases.

In **Chapter 4.1** we describe treatment patters and adherence in patients with asthma. The ESTATe cohort was mainly treated with short-acting β_2-agonists (SABA; 40 users/100 PY) and ICS (32/100 PY). The adherence was low with a median medication possession rate (MPR) for ICS of 56%. Children with good adherence were younger at initiation of ICS treatment, more often visited specialists and had more exacerbations during follow-up compared to children with low adherence, suggesting that children with good adherence have more severe asthma.

Chapter 4.2 describes the results of a systematic review on the relationship between low adherence and risk of severe asthma exacerbations. We observed high levels of heterogeneity across studies with regard to adherence and exacerbation measurements, designs and analysis. Although effect measures varied widely, good adherence was associated with fewer severe asthma exacerbations in high quality studies.

In **Chapter 5** we report the prevalence and effectiveness of the Dutch preference policy of inhalation medications in the study period 2003-2012. **Chapter 5.1** shows that the occurrence of switching between brand and generic inhalation medication per calendar year was low, as it occurred only in 5% of the patients. Generic dispensing increased with calendar time. Switching between devices occurred in 5% of the patients who used an inhalation medication with an alternative device available. 16% of the patients used more than 1 device in 1 year. Adherence to both generic and brand inhalation medication was considerably low, with median MPRs over the first 12 months ranging between 33 and 55%. In **Chapter 5.2** we report that current generic use of β_2-agonists was associated with an increased risk of asthma exacerbations when compared to current use of brand inhaled β_2-agonists. This association was stronger when studying switching between generic and brand (or vice versa) inhaled β_2-agonists. This association was not observed for use of generic ICS nor for switching between brand and generic ICS.

Finally, in **Chapter 6** we discuss the main findings of the studies included in this thesis and the methodological aspects. In addition, we provide suggestions for future research.

SAMENVATTING

In dit proefschrift onderzochten we de epidemiologie, de behandeling, de incidentie van astma exacerbaties en mortaliteit bij patiënten met astma in de klinische praktijk. Bovendien werden de risico factoren van een lage therapietrouw, van astma exacerbaties en van mortaliteit bestudeerd. In dit onderzoek hebben we gebruik gemaakt van verschillende Nederlandse en andere Europese electronische patiëntendossier databases.

Hoofdstuk 1 geeft een kort overzicht over de etiologie en behandeling van astma. Het beschrijft ook de doelen van de uitgevoerde studies en de opzet van het proefschrift.
Hoofdstuk 2 beschrijft de epidemiologie van astma. In **hoofdstuk 2.1** beschrijven we de selectie van het pediatrische astma cohort (= ESTATe cohort; Effectiveness and Safety of controller Therapy of Asthma in the Treatment of childrEn with asthma) in de Integrated Primary Care Information (IPCI) database. Dit cohort werd samengesteld door het zorgvuldig bekijken van alle medische dossiers van potentiële astmapatiënten, die werden geïdentificeerd met behulp van "machine learning" technieken. Het geautomatiseerde algoritme, waarbij gebruik werd gemaakt van zowel vrije tekst als gecodeerde data, liet goede resultaten zien in het detecteren van potentiële cases. Dit algoritme had een positief voorspellende waarde van 0,82, een sensitiviteit van 0,96 en een specificiteit van 0,90, indien zowel zekere als mogelijke astma cases werden geïdentificeerd. In **hoofdstuk 2.2** werd de gevalideerde dataset van 14.303 kinderen met astma (totaal 35.118 persoonsjaren (PJ) follow-up) gebruikt om de trend in incidentie, prevalentie en leeftijd waarop de astma diagnose werd gesteld, te beschrijven tussen 2000 en 2012. De incidentie van dokter-gediagnosticeerd astma was 6,7 per 1000 PJ bij kinderen in Nederland. Deze incidentie was lager bij meisjes dan bij jongens vóór de pubertijd, na de pubertijd was dit verschil omgekeerd. De incidentie van astma nam toe tot 2008, en vanaf 2008 werd een niet significante afname geobserveerd. De cumulatieve prevalentie van astma was 8,1%. De leeftijd specifieke cumulatieve astma prevalentie was hoger bij jongens dan bij meisjes in alle leeftijd categorieën.
In **hoofdstuk 3.1** beschrijven we de epidemiologie en risico factoren van astma exacerbaties. In het ESTATe cohort identificeerden we 732 astma exacerbaties. De incidentie van astma exacerbaties was 2,1/100 PJ en was 4,1/100 PJ bij kinderen die tijdens follow-up astma medicatie kregen voorgeschreven. Een seizoen trend werd gezien, met hoogste incidenties in het voor- en najaar. Astma herexacerbaties traden op bij 2% van de patiënten binnen 1 maand na de exacerbatie en bij 25% binnen 1 jaar na de exacerbatie. Risicofactoren voor frequente astma exacerbaties zijn leeftijd, geslacht, specialist-bezoeken, voorschriften voor inhalatiecorticosteroïden (ICS) en eerdere astma exacerbaties.
In **hoofdstuk 3.2** analyseerden we de sterfte bij patiënten met astma alsook de risicofactoren op overlijden na een ernstige astma exacerbatie. Voor dit onderzoek maakten we gebruik van elektronische patiëntendossiers in 6 Europese databases. Het cohort bestond uit 855.806

astmapatiënten. De incidentie van overlijden varieerde tussen 4,8-13,2/1000 PJ in de verschillende databases. Deze incidentie was hoger bij patiënten met ernstig astma (16,0-36,2/1000 PY). Sterfte in de eerste week na een astma exacerbatie was 26,3-109,5/1000 PJ en was hoger na een ernstige astma exacerbatie (eerste hulp bezoek/ ziekenhuis opname) (57,9-239,4/1000 PJ). Risico factoren voor mortaliteit werden onderzocht in een subgroep van volwassenen met incident astma. Een oudere leeftijd, onderliggend lijden (COPD, diabetes, cerebro- en vasculaire ziekten en kanker), roken, ernst van astma, en eerdere astma exacerbaties waren geassocieerd met een verhoogd risico op overlijden in de meeste databases.

In **hoofdstuk 4.1** beschrijven we de behandelingspatronen en therapietrouw bij kinderen met astma. Voor dit onderzoek werd opnieuw gebruik gemaakt van het ESTATe cohort. Kinderen in dit cohort werden vooral behandeld met kortwerkende ß$_2$-agonisten (SABA; 40 gebruikers/100 PJ) en inhalatie corticosteroïden (ICS) (32/100 PJ). De therapietrouw aan ICS was laag met een mediane 'medication possession ratio' (MPR) van 56%. Kinderen met een goede therapietrouw aan ICS waren jonger bij de start van de ICS- behandeling, bezochten vaker een specialist en hadden vaker een astma exacerbatie tijdens follow-up, ten opzichte van kinderen met een slechtere therapietrouw. Dit suggereert dat kinderen met een goede therapietrouw een ernstigere vorm van astma hadden.

Hoofdstuk 4.2 vat de beschikbare literatuur tot 2012 samen met betrekking tot de relatie tussen therapietrouw en het risico op ernstige astma exacerbaties. We observeerden veel heterogeniteit in de publicaties met betrekking tot de definities van therapietrouw, astma exacerbaties, designs en analyses. Uit de studies met een goede kwaliteit blijkt dat een goede therapietrouw geassocieerd is met een lager risico op ernstige astma exacerbaties.

In **hoofdstuk 5** rapporteren we de prevalentie en doeltreffendheid van het Nederlandse preferentie beleid rond inhalatiemedicatie in de studieperiode 2003-2012. **Hoofdstuk 5.1** laat zien dat het switchen tussen merk en generieke inhalatiemedicatie weinig voorkomt, namelijk bij 5% van alle patiënten per kalenderjaar. Het aantal generieke afleveringen van inhalatiemedicatie nam toe in de tijd. Switchen tussen inhalatoren kwam voor bij 5% van de patiënten, die inhalatiemedicatie gebruikten waarvoor verschillende inhalatoren beschikbaar waren. 16% van alle patiënten gebruikten meer dan 1 inhalator in een kalenderjaar. Therapietrouw aan zowel generieke als merk inhalatiemedicatie was laag, met een mediane MPR gemeten over de eerste 12 maanden van 33 tot 55%. In **hoofdstuk 5.2** rapporteren we dat het huidig gebruik van generieke inhalatie β_2-agonisten geassocieerd is met een verhoogd risico op astma exacerbaties vergeleken met merk inhalatie β_2-agonisten. Deze associatie was sterker wanneer dit werd onderzocht bij patiënten die switchen tussen generieke en merk inhalatiemedicatie. Deze associatie werd niet gezien bij het gebruik van generieke ICS of switchen tussen generieke en merk ICS.

Tenslotte, bediscussiëren we in **hoofdstuk 6** de resultaten en de methodologische aspecten van de studies in dit proefschrift. We sluiten af met suggesties voor toekomstig onderzoek.

APPENDICES

LIST OF ABBREVIATIONS

ACOS	Asthma and COPD Overlap Syndrome
ACQ	Asthma Control Questionnaire
APC	Annual Percent Change
ATC	Anatomical Therapeutic Chemical classification system
ATS	American Thoracic Society
AUH	Aarhus University Prescription Database
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CTT	Control To Total drugs ratio
DPI	Dry Powder Inhaler
ED	Emergency Department
EHR	Electronic Healthcare Databases
EMA	European medicines agency
EMD	Electronic medical device
EMR	Electronic Medical Records
ERS	European Respiratory Society
FDC	Fixed Dose Combination
FEV1	Forced Expiration Volume in 1 second
GERD	Gastro Esophageal Reflux Disease
GINA	Global Initiative for Asthma
GP	General Practitioner
HR	Hazard Ratio
HSD	Health Search CSD longitudinal patient Database
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
ICS	Inhaled Corticosteroids
IPCI	Integrated Primary Care Information
IQR	Inter Quartile Range
IR	Incidence Rate
ISAAC	International Study of Asthma and Allergies in Childhood
LABA	Long-Acting β_2-Agonists
LAMA	Long-Acting Muscarinic Antagonists
LTRA	Leukotriene Receptor Antagonist
MPR	Medication Possession Rate
OCS	Oral CorticoSteroids

OR	Odds Ratio
pMDI	Metered Dose Inhaler
PPV	Positive Predictive Value
PY	Person Years
RCT	Randomized Controlled Trial
SABA	Short-Acting β_2-Agonists
SAMA	Short-Acting Muscarinic Antagonists
Sd	Standard Deviation
SI	Single Inhaler
SIDIAP	Sistema d'Informacio per al Desenvolupament de la Investigacio en Atencio Primaria
WHO	World Health Organization

LIST OF PUBLICATIONS

Manuscripts based on this thesis

2.1 Z Afzal, **M Engelkes**, KMC Verhamme, HM Janssens, MCJM Sturkenboom, JA Kors, MJ Schuemie. Automatic generation of case-detection algorithms to identify children with asthma from large electronic health record databases. *Pharmaco epidemiology and drug safety.* 2013 Aug;22(8):826-33.

2.2 **M Engelkes**, HM Janssens, JC de Jongste, MCJM Sturkenboom, KMC Verhamme. Time trends in the incidence, prevalence and age at diagnosis of asthma in children. *Pediatric allergy and immunology,* 2015 Jun; 26(4):367-74.

3.1 **M Engelkes**, HM Janssens, JC de Jongste, MCJM Sturkenboom, KMC Verhamme. Incidence and risk factors of severe asthma exacerbations in children – a population based cohort study. *(Under Review Respiratory Medicine)*

3.2 **M Engelkes**, HM Janssens, JC de Jongste, MCJM Sturkenboom, KMC Verhamme. Medication adherence and risk of severe exacerbations in asthma - a systematic review. *European Respiratory Journal* 2015 Feb;45(2):396-407.

4.1 **M Engelkes**, HM Janssens, JC de Jongste, MCJM Sturkenboom, KMC Verhamme. Prescription patterns and adherence in children with asthma – a population based study. *Pediatric allergy and immunology* 2016 Mar;27(2):201-208.

4.2 **M Engelkes**, MAJ de Ridder, E Svensson, K Berencsi, D Prieto-Alhambra, F Lapi, C Giaquinto, G Picelli, N Boudiaf, F Albers, S Cockle, E Bradford, R Suruki, P Rijnbeek, MCJM Sturkenboom, KMC Verhamme. Multinational, multi-database asthma cohort study to assess all-cause mortality following severe asthma exacerbations.*(submitted)*

5.1 **M Engelkes**, JC van Blijverveen, KMC Verhamme, JA Overbeek, JG Kuiper, RCM Herings, MCJM Sturkenboom, JC de Jongste, HM Janssens. Switching between brand and generic inhalation medication and the risk of moderate-to severe asthma exacerbations in patients with asthma - a case control study. *(submitted)*

5.2 **M Engelkes**, JC van Blijverveen, KMC Verhamme, JA Overbeek, JG Kuiper, RCM Herings, MCJM Sturkenboom, JC de Jongste, HM Janssens. Brand versus generic inhalation medication use and frequency of switching in children and adults: a population based cohort study. *(submitted)*

Other manuscripts

Engelkes M, de Ridder M, Svensson E, Berencsi K, Prieto-Alhambra D, Lapi F, Giaquinto C, Picelli G, Boudiaf N, Albers F, Cockle S, Bradford E, Suruki R, Rijnbeek P, Sturkenboom M, Verhamme K. Multinational, multi-database asthma cohort study to assess the incidence rate of severe asthma exacerbations. *(draft)*

Engelkes M, van Blijderveen J, Verhamme K, Overbeek JA, Kuiper JG, Herings RM, Sturkenboom M, de Jongste J, Janssens H. Prevalence of switching from brand to generic asthma medications. *Value Health, 2015 nov 18(7): A505-6.*

Warlé-van Herwaarden MF, Valkhoff VE, Herings RM, **Engelkes M**, van Blijderveen JC, Rodenburg EM, de Bie S, Alsma J, van de Steeg-Gompel C, Kramers C, Meyboom RH, Sturkenboom MC, De Smet PA. Quick assessment of drug-related admissions over time (QUADRAT study). *Pharmacoepidemiology and Drug Safety. 2015 May;24(5):495-503.*

Christmann V, Visser R, **Engelkes M**, de Grauw AM, van Goudoever JB, van Heijst AFJ. Yes, we can - achieve adequate early postnatal growth in preterm infants. *Acta Paediatrica. 2013 Dec;102(12):e530.*

Christmann V, Visser R, **Engelkes M**, de Grauw AM, van Goudoever JB, van Heijst AFJ. The enigma to achieve normal postnatal growth in preterm infants - using parenteral or enteral nutrition? *Acta Paediatrica. 2013 May;102(5);471-9.*

Heitink-Pollé KM, Pot DJ, **Engelkes M**, Bruin MC. Itracranial hemorrhage after high-dose methylprednisolone in a child with acute immune trombocytopenic purpura. Annals of Hematology. *2011 Nov;90(11):1361-3.*

PHD PORTFOLIO

Name	Marjolein Engelkes
Erasmus MC department	Medical Informatics and paediatrics, division respiratory medicine
Research School	NIHES
PhD period	2011-2016
Promotors	Prof. dr. M.C.J.M. Sturkenboom and prof. dr. J.C. de Jongste
Copromotoren	Dr. K.M.C. Verhamme and Dr. H.M. Janssens

PhD training	Year
Research Skills	
Master of Science, clinical epidemiology, Netherlands Institute of Health Sciences (NIHES), Rotterdam, The Netherlands	2011-2013
General courses and training	
Training for Upcoming leaders in paediatric Science (TULIPS) PhD curriculum	2013-2015
CPO mini symposiums (Erasmus MC)	2011, 2012, 2013, 2014
Research Integrity (Erasmus MC)	2013
English & Grant writing course (Erasmus MC)	2012
Basic course: Rules in Clinical Research (BROK) (Erasmus MC)	2012
Seminars and workshops	
Dag voor jonge onderzoekers (NVK)	2012, 2013, 2014
PhD day (Erasmus MC)	2011, 2012, 2013
Netherlands Respiratory Society symposium (NRS)	2012, 2013
Workshops VENA	2012-2015
Goed gebruik geneesmiddelen (Zonmw)	2013
(Inter) national conferences	
37th Nederlandse vereniging voor Kindergeneeskunde, Veldhoven, The Netherlands (2x SLAM session)	2015
Sophia Research Days- ErasmusMC Sophia, Rotterdam, The Netherlands (2x SLAM session)	2015
31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Boston, VS (2 poster presentations)	2015
25th European Respiratory Society, Amsterdam, The Netherlands (4 poster presentations)	2015
36th Nederlandse vereniging voor Kindergeneeskunde, Veldhoven, The Netherlands (SLAM session)	2014
24th European Respiratory Society, Münich, Germany (oral presentation with best pediatric asthma abstract award, and 1 poster presentation)	2014
30th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Taipei, Taiwan (1 poster presentation)	2014
23th European Respiratory Society, Barcelona, Spain (1 poster discussion, 1 poster presentation)	2013
29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada (2 poster presentations)	2013

PhD training	Year
(Inter) national conferences (continued)	
NRS Young Investigator Symposium, Utrecht, The Netherlands (poster)	2013
22nd European Respiratory Society, Vienna, Austria (poster presentation)	2012
28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Barcelona, Spain (oral presentation)	2012
36th 'Werkgroep epidemiologisch onderzoek Nederland' (WEON), Rotterdam, the Netherlands (poster presentation)	2012
29th Nederlandse vereniging voor Kindergeneeskunde, Veldhoven, The Netherlands (oral presentation)	2007
Grants and prizes	
Grant stichting astma bestrijding voor "Substitution policy project' 24.938 euro	2012
Best SLAM Session NVK 2014, 50 euro	2014
ERS grant for best abstract in Paediatric Respiratry Epidemiology, Munich, pediatric assembly, 2014, 1.250 euro	2014
Several travel grants for congress fees; Vereniging Trustfonds Erasmus Universiteit Rotterdam, longfonds, astmafonds, stichting astmabestrijding	2012-2015
Teaching activities	
Supervising and lecturing lung function to medical students	2014,2015
Supervising master thesis pharmacy student	2015
Other	
Weekly research meetings pediatric pulmonology	2011-2016
Weekly research meetings pharmaco-epidemiology/medical informatics	2011-2016
Bi-weekly research meetings medical informatics	2011-2016
RADAR meetings	2012-2014
Monthly Outpatient clinic pediatric pulmonology	2011-2015
Peer review of articles for scientific journals	2015-2016
Board of the Sophia Overzoekers Vertegenwoordiging (SOV)	2011-2014

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Marjolein

ABOUT THE AUTHOR

Marjolein Engelkes was born on September 16th 1983 in Sittard, the Netherlands. She received her Gymnasium degree at the College Sittard in Sittard in 2001. In this year, she started to study Psychology at the Radboud University in Nijmegen and received her bachelor degree in 2002. In 2002 she started medical school at the Radboud University Nijmegen. In this period she became interested in pediatrics, and her graduate research focused on early nutrition in preterm children (supervisors Liem and Christmann). After her final elective internship at the Pediatric ward at the Holy Hospital Techiman in Ghana, she obtained her medical degree at the end 2008. Thereafter she started working as a pediatric resident at the Gelre Hospital in Apeldoorn till 2010. In 2010 she started working at the Sophia Children's hospital in Rotterdam. After 1.5 years she started a PhD project under the supervision of prof. dr. Sturkenboom, dr. Verhamme, dr. Janssens en prof. dr. de Jongste, which has resulted in this thesis. During this project she had the chance to obtain her clinical epidemiology master, to follow the TULIPS PhD curriculum and to be a board member of the Sophia research board to organize the first Sophia research days. Marjolein is currently working as a pediatric resident at the Reinier de Graaf Hospital in Delft.

ASTHMA