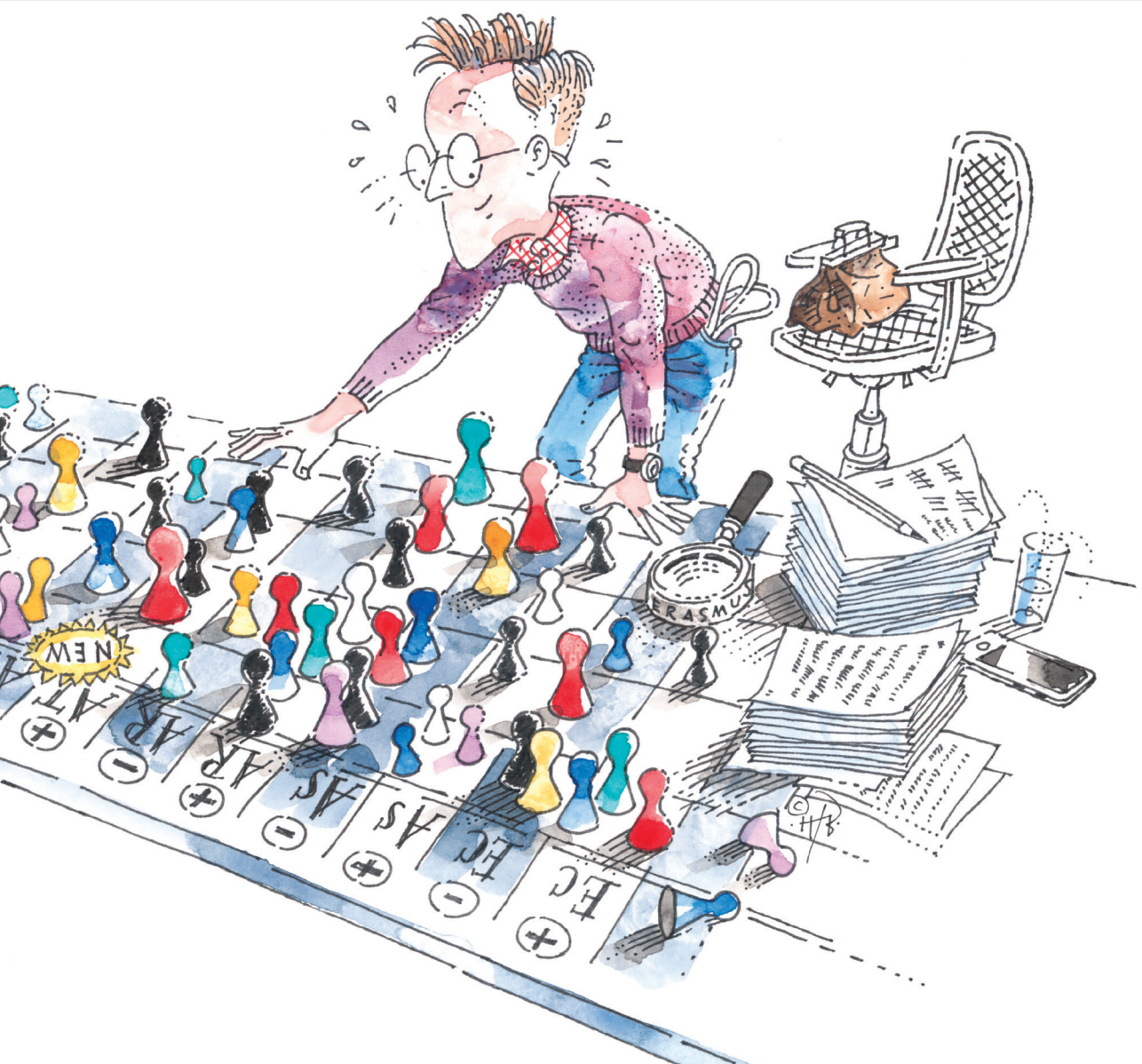
Atopic Children in General Practice

David H.J. Pols



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Eenheid in het nodige,
vrijheid in het onzekere,
in alles de liefde

~ De Dominis ~

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Chapter 1

General introduction

What are atopic disorders?

In this thesis the word 'atopic' refers to a predisposition toward developing a certain allergic hypersensitivity, which can result in the clinical diagnosis of atopic eczema (also called atopic dermatitis), asthma, or allergic rhinitis (also called allergic rhinoconjunctivitis, including hay fever). Although closely related to atopic disorders, food allergies are beyond the scope of this thesis.

Aetiology

Since atopic disorders have a complex aetiology, involving both genetic and environmental contributions, these children show a wide range of phenotypes. Some children only have one atopic disorder with mild symptoms, whereas others have all three atopic disorders with severe symptoms and everything in between. Atopic disorders can be associated with functional impairment in terms of activity limitation and reduced quality of life as compared to children who have no atopic disorder. Various environmental contributions have been proposed that could influence the development of atopic disorders, including pet ownership (1), traffic pollution (2, 3), household tobacco smoking (4), and diet (5). Even geo-climatic factors seem to correlate with the prevalence rates of atopic disorders (6). Based on twin studies, there is evidence that atopic disorders are (for a large part) genetically determined (7). Multiple genes (mainly genes involved in the T-helper 2 innate immune reaction) are associated with atopic disorders (8). Several other genes are specifically related to asthma (8) or related to atopic eczema (9).

Over time, some atopic patients develop all three atopic disorders, i.e. atopic eczema, asthma and allergic rhinitis. In the triad of events that include these three disorders, eczema is often the first disorder to evolve. A biologically plausible pathway to explain this cascade was proposed by Burgess et al. (10). As a result of a defective skin barrier in children with atopic eczema, an epicutaneous sensitisation to an allergen can take place resulting in T-helper type 2 memory cells; these cells can migrate to nasal and bronchial lymphoid tissue. When the airways become exposed to the same allergen, this might cause asthma and/or allergic rhinitis symptoms to evolve as a result of an exaggerated IgE-mediated immune response. In practice, the number of patients completing this classic 'atopic march' seems to vary considerably (11, 12). For example, some patients with asthma subsequently develop eczema (13). Furthermore, it has been shown that the atopic march can occur at any age (14), not just in childhood. It has been estimated that approximately one-third of patients with atopic eczema develop asthma (15, 16). Despite there being a clear temporal association and plausible biological mechanisms

to explain the atopic march, at this moment there is no definitive proof for such an association (17).

Epidemiology

Atopic disorders represent an important health problem in paediatric patients and create a serious burden on primary care resources as a result of frequent visits to the general practitioner (GP) (18). Acute upper airway infections (9.5%), middle ear infections (6.3%), warts (4.9%), asthma (4.3%), and atopic eczema (3.8%) represent the five most prevalent paediatric diseases diagnosed in Dutch general practice (19); in this list, allergic rhinitis (2.4%) is on the 12th place.
Also internationally the concern about these atopic disorders is demonstrated by the enormous participation in the International Study of Asthma and Allergies in Childhood (ISAAC) (6, 20). The ISAAC study showed globally one year prevalence rates in the open population for eczema, asthma and rhinoconjunctivitis in the 13-14 year-old age group of 7.3%, 14.1% and 14.6%, respectively. In the 6-7 year-old age group, the one year prevalence rates in the open population for eczema, asthma and rhinoconjunctivitis was 7.9%, 11.7% and 8.5%, respectively (6). In the Netherlands, the prevalence rates obtained in a study conducted in the open population and based on ISAAC questionnaires, demonstrated one-year prevalence rates for symptoms of eczema, asthma and rhinoconjunctivitis of 13.5%, 12.3% and 28.3%, respectively (21).

Natural course of atopic disorders

In Germany, Illy et al. studied the natural course of atopic eczema in a cohort of 1,314 children from the general population, until age 7 years (22). The prevalence increased to 21.5% at 2 years of age, but 43.2% were in complete remission by the age of 3 years.
Regarding asthma, Jenkins et al. screened 7-year-olds for this condition (23). The study was repeated 25 years later in a random sample (n=750); a quarter of those who had asthma as a child, reported asthma in adulthood. According to Sears, about half to two-thirds of the children with asthma will recover (24). An explanation for this observed recovery could be that viral infections are the main cause of wheeze before the age of 6 rather than allergic asthma. This is supported by data from a Dutch primary care study, which showed that for those children diagnosed with asthma between the age of 0-4 years, ≥ 60% were no longer known as such by the GP after 2 years and, after 10 years, 80% no longer carried this diagnosis (25). However, a different study, but based on the same Dutch primary care study,

demonstrated that when the same children were screened for asthma at a later age (10-23 years) 45% still had asthma (26), suggesting evidence for underdiagnosis. Finally, regarding allergic rhinitis, a prospective study on the course of allergic rhinitis in 738 individuals (with an average follow-up of 23 years) showed that in a majority of the adult patients the symptoms of allergic rhinitis reduce over the years (27). Another prospective study (n=257) on various forms of allergic rhinitis (confirmed by the presence of specific IgE to pollen, pets or dust mites), looked at the percentage of patients with complete remission of symptoms in a period of 8 years (28). This latter study found complete remission of symptoms in 12% of patients with pollen allergy, in 19% of patients with an allergy to pets, and in 38% of patients with house dust allergy.
In conclusion, an atopic disorder cannot be simply considered to be a chronic disorder in all initially affected patients.

Background of this thesis

Although atopic disorders in children represent an important health problem, epidemiological data from a general practice setting are scarce. Therefore, in the first part of this thesis, two systematic literature searches were conducted to examine available epidemiological data and compare two epidemiological sources (i.e. open population versus general practice). The knowledge obtained from these reviews was then used to acquire more reliable prevalence rates from an extensive and representative general practice database. In the second part of this thesis, different characteristics of atopic children in general practice were examined, focusing on comorbidity, medication use, and healthcare utilisation.

1. Different sources of epidemiological data

Epidemiological data are widely used to support GPs in their daily practice, e.g. as a guide to the management of patients in whom disease has already developed, and in creating strategies to prevent illness. Epidemiological data are also used by researchers to develop and prioritise research questions, and by policymakers to plan healthcare services and the workforce.
Two epidemiological sources are examined in more detail: i) epidemiological data obtained from the open population using health surveys, and ii) albeit with limited availability, epidemiological data obtained from general practice databases. Both sources provide valuable epidemiological data and are discussed further on.

Observed differences between the two epidemiological sources could in part be explained by the operational definitions used. The diagnosis of the three atopic disorders is not straightforward. Not all skin itching is atopic eczema, not all wheezing is asthma, and not all sniffing is allergic rhinitis. Therefore, diagnoses may differ between those based on the patient's own assessment and those based on the physician's assessment. Diagnoses may even differ between physicians and a patient over time (e.g. a simple itch may become atopic eczema, and a wheeze may become asthma). This can result in a wide variation of prevalence rates. Remarkably, these two sources have not yet been systematically compared. Learning more about potential differences may help policy-makers to optimise their strategies and help GPs to become more aware about the healthcare demands of atopic patients and the possible misclassification of allergic conditions in children. Furthermore, insight into differences in prevalence rates provides valuable knowledge for researchers that can be used to acquire more reliable prevalence rates from general practice databases.

1.a. Open population data

Although survey data provide useful information on the prevalence of self-reported symptoms of allergic disorders and the derived diagnosis (29), the accuracy of data obtained from surveys depends on various items, including the accuracy and knowledge of the responders, and the definitions used by the researcher (30). Another potential limitation is that questionnaires ask about symptoms, i.e. these symptoms could also be attributable to other diseases; a concern that is shared by others (31, 32). The International Study of Asthma and Allergies in Childhood (ISAAC) is the largest worldwide collaborative research project ever undertaken to investigate atopic eczema, asthma, and allergic rhinitis in the open population using a standardized questionnaire (33-35). The study involves more than 100 countries and nearly 2 million children. Nowadays, ISAAC provides most of the available survey data on atopic disorders in the open population regarding children. Results from the ISAAC studies are widely available and relatively easy to identify in online medical literature databases (36). Remarkably, non-ISAAC research groups (i.e. non-official ISAAC studies) have also published data using validated ISAAC questionnaires; however, the official ISAAC reviews do not include these latter data in their analyses. To what extent these data can be used as a valid alternative for the general practice setting is not known.

1.b. General practice data

In many countries, primary care professionals (e.g., family doctors/GPs) diagnose and treat atopic children. In the Netherlands, GPs are the gatekeeper of the healthcare system, are freely accessible, and use uniform coding systems for

recording the diagnosis, prescriptions and type of declared encounters. In principle, all non-institutionalised residents in the Netherlands are registered in a general practice, even if they do not visit the GP. Therefore, the electronic health records stored in primary care databases in the Netherlands contain valid information about the epidemiological denominator, making it an important source of epidemiological data (37). Furthermore, epidemiological data from primary care databases might be more specific (the prevalence is based on the assessment of a physician) and provide a better reflection of the true burden of disease in a general practice setting (38), as compared to data from the open population (29).
Unfortunately, the number of publications on the epidemiological study of atopic disorders in general practice databases is scarce and such studies are difficult to identify in online medical literature databases. The problem of identifying relevant publications lies in the complexity of identifying studies in a 'general practice setting' since the area of general practice is broad and difficult to define, mainly due to the different terminologies used. For example, the terms 'family medicine', 'general practice' and 'primary care' (amongst others), can be used to describe basically the same research setting. Developing an electronic search filter that could reliably identify studies conducted in a general practice setting from various online medical literature databases, would be an efficient way to address this problem. Unfortunately, all search filters that have been reported in the last couple of years lack adequate sensitivity (39-42). A well-validated search filter for general medicine with good sensitivity and specificity will support the development of systematic reviews and meta-analysis regarding general practice topics, such as developing a systematic review on epidemiological data of atopic disorders in children.

1.c. Retrieving valid prevalence rates from a general practice database
For the correct use of general practice databases, two problems need to be addressed for which the knowledge derived from the systematic reviews can become useful. First, how to address the expected variation between general practice databases? Part of this variation might be explained by the fact that GPs often work with a 'probability diagnosis' which inevitably creates a risk of misclassification, resulting in either over- or underestimation. Other possible explanations could be variation in the clinical knowledge and/or skills of the GP, and coding difficulties (i.e. when coding diseases in electronic health records). Second, some studies in a general practice setting have presented life-time cumulative prevalences for atopic disorders in children (43-46). The question arises as to what extent these *life-time* cumulative prevalences provide relevant information compared with *annual* point prevalences, knowing that these disorders are not always chronic and/or can have an intermittent course. Therefore, it would be valuable to determine a reliable strategy

(and thereby an epidemiological definition) for the analysis of raw data derived from general practice databases, addressing both aspects, to be able to calculate valid prevalence rates.

2. Characteristics of atopic disorders in general practice

Recently, the registration of diagnoses in Dutch general practice has been promoted by financial incentives, and both quality and quantity has much improved. Therefore, new research in large databases using recent data may provide valuable new insights into the epidemiology of atopic disorders, especially when using clear epidemiological definitions for atopic disorders. General practice databases contain a wealth of information. Not only can prevalence rates be derived more reliably from these databases, also valuable data on comorbidity and prescribed medications are available. To our knowledge, no study has investigated the complete range of potential comorbidities in atopic children in a general practice setting, nor the complete range of potentially prescribed medication. Healthcare utilisation can also be reliably examined using these databases.

2.a. Atopic disorders and comorbidity

Comorbidities are important for clinicians treating atopic patients, as they may be a marker of patients at risk of poor outcomes. Also, they may point to specific effective treatment options, and are important to researchers as possible confounding factors in clinical trials. Associations have been shown between atopic disorders and other diseases in children, but in different clinical settings (e.g. birth cohorts, hospitals, or paediatric clinics). Proven interrelations exist with (amongst others) diabetes (47-49), ADHD (50-52), autism (53-55), and obesity (56-58). According to other studies, the presence of some comorbidities may even influence the course of atopic disorders (59-63).

The following are highly relevant research questions regarding comorbidity: i) Are atopic children at increased risk for specific non-atopic symptoms or diseases that GPs should be aware of to reduce the risk of underdiagnosing relevant comorbidity? and ii) Are children with one atopic disorder at risk of being underdiagnosed for having another atopic disorder?

2.b. Atopic disorders and medication

Evidence-based medicine guidelines support Dutch GPs in the decision-making process when prescribing medication (64-66). According to these guidelines, the cornerstone for the treatment of atopic eczema in children are emollients and corticosteroid creams, prescribed in a stepwise approach (64). When anti-asthmatic

inhalation medication is needed, a GP will start with a short-acting beta agonist, followed by inhaled corticosteroids when indicated (65). For allergic rhinitis, treatment will depend on the severity of symptoms. Intermittent symptoms are often treated with local or oral antihistamines on demand, while moderate to severe symptoms will be treated with corticosteroid nasal sprays (66). How often these atopic-related prescriptions are also given to children that are not labelled/diagnosed with a specific atopic disorder has not been extensively studied and could reflect underdiagnosis or insufficient coding. Furthermore, to what extent these atopic children have a higher risk to receive more non-atopic related prescriptions has not yet been examined in primary care.
Two relevant research questions regarding prescriptions are: i) Which medications are prescribed by GPs for atopic disorders? and ii) What kind of other medications do atopic children receive?

2.c. Atopic disorders and healthcare utilisation
Finally, how do these prevalence rates correlate to healthcare utilisation in primary care? Learning more about the magnitude of the burden posed by atopic disorders in children on general practice resources would be of interest. This information is important epidemiologically for the planning of healthcare services and the workforce. Most studies on healthcare utilisation are limited to asthmatic children (67-69). However, a recent study in Denmark (birth cohort) evaluated healthcare utilisation in children with atopic eczema, asthma and allergic rhinitis, using health surveys (70). The number of additional consultations per year for eczema, asthma and for allergic rhinitis are 1.8, 2.5 and 1.2, respectively. A relevant research question regarding healthcare utilisation is to quantify the current health burden posed by atopic eczema, asthma and allergic rhinitis on general practice resources based on physician-diagnosed disorders.

Aim and outline of this thesis

The first part of this thesis focuses on obtaining valid prevalence rates of atopic disorders in children. **Chapter 2** presents the results of a systematic review (including a meta regression analysis) determining worldwide prevalence rates regarding children with atopic eczema, asthma, allergic rhinitis, and of having all three disorders, using data obtained from ISAAC questionnaires (including non-official ISAAC studies) and examining interrelationships between these disorders.
The aim of the study presented in **Chapter 3** was to develop and validate objective search filters, applicable in frequently-used online medical literature databases, to

identify studies that are conducted in, or apply to, or refer to family medicine and general practice settings. The efficiency of this filter is then examined by deploying it in the systematic review presented in **Chapter 4**; this review compares self-reported prevalence rates in the open population (ISAAC studies) with clinician-diagnosed prevalence rates of the three atopic disorders in general practice settings. The knowledge obtained from these reviews is then used to acquire more reliable prevalence rates from the extensive and representative NIVEL Primary Care Database. In **Chapter 5** four strategies are examined that can analyze raw data obtained from a general practice database in order to calculate valid prevalence rates.

In the second part of this thesis, different characteristics of atopic children in general practice are explored, focusing on comorbidity, medication use, and healthcare utilisation. First, in **Chapter 6** a total of 404 different symptoms and diseases, and their possible association with atopic disorders, are examined. In **Chapter 7** a total of 93 different medication groups were investigated for their possible association with atopic disorders. Then, in **Chapter 8** a study is presented that aimed to quantify the current primary healthcare burden posed by atopic eczema, asthma and allergic rhinitis on general practice resources. In **Chapter 9** the main results are discussed and recommendations are made for further research together with implications for clinical practice.

Finally, **Chapter 10** summarises the main results of this thesis in English.

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Chapter 2

Interrelationships between atopic disorders in children: a meta-analysis based on ISAAC questionnaires

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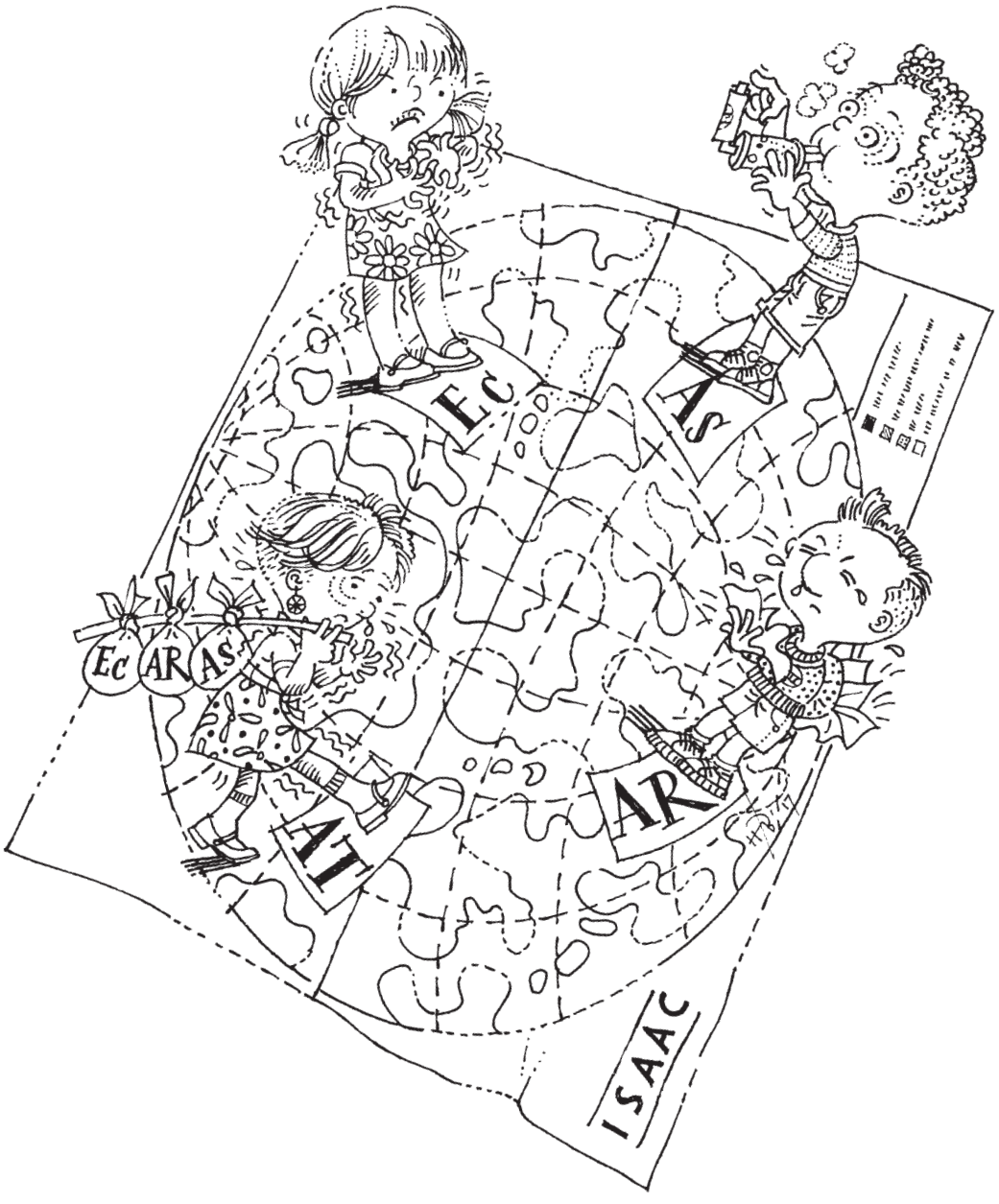


Abstract

Purpose: To study the prevalence and interrelationship between atopic eczema, asthma and allergic rhinitis using data obtained from ISAAC questionnaires.
Method: The Medline, Pubmed Publisher, EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register databases were systematically reviewed to evaluate epidemiological data of children with atopic disorders. To study these interrelationships, a new approach was used. Risk ratios were calculated, describing the risk of having two different atopic disorders when the child is known with one disorder.
Results: Included were 31 studies, covering a large number of surveyed children (n=1,430,329) in 102 countries. The calculated worldwide prevalence for atopic eczema, asthma and allergic rhinitis is 7.88% (95% CI: 7.88-7.89), 12.00% (95% CI: 11.99-12.00) and 12.66% (95% CI: 12.65-12.67), respectively. The observed prevalence [1.17% (95% CI: 1.17-1.17)] of having all three disorders is 9.8 times higher than could be expected by chance. For children with atopic eczema the calculated risk ratio of having the other two disorders is 4.24 (95% CI: 3.75-4.79), for children with asthma 5.41 (95% CI: 4.76-6.16), and for children with allergic rhinitis 6.20 (95% CI: 5.30-7.27). No studied confounders had a significant influence on these risk ratios.
Conclusions: Only a minority of children suffers from all three atopic disorders, however this co-occurrence is significantly higher than could be expected by chance and supports a close relationship of these disorders in children. The data of this meta-analysis supports the hypothesis that there could be a fourth distinct group of children with all three disorders. Researchers and clinicians might need to consider these children as a separate group with distinct characteristics regarding severity, causes, treatment or prognosis.

Background

Atopic eczema, asthma and allergic rhinitis are common atopic disorders among children, making it an important public health problem worldwide. The prevalences of these three disorders show variability at regional and even at country level (1-4). Despite this variability, there seems to be a close relationship between these disorders. In a triad of events that include atopic eczema, asthma and allergic rhinitis, eczema is often the first disorder to evolve. A biologically plausible pathway to explain this cascade was proposed by Burgess et al (5). As a result of a defective skin barrier in children with atopic eczema, an epicutaneous sensitization to an allergen can take place resulting in T-helper type 2 memory cells; these cells can migrate to nasal and bronchial lymphoid tissue. When the airways become exposed to the same allergen, this might cause asthma and/or allergic rhinitis symptoms to evolve. However, in practice, the number of patients following this classic 'atopic march' seems to vary considerably (6, 7), only partially explaining the interrelationships.

The International Study of Asthma and Allergies in Childhood (ISAAC) was established in 1991 and formally closed in December 2012. The ISAAC study was divided into three phases. The purpose was to assess the worldwide prevalence of atopic eczema, asthma and allergic rhinitis in children in the open population and to obtain possible risk factors that could influence these three disorders using a standardized questionnaire (8-10). This makes ISAAC a reliable data source to use when studying the interrelationship of atopic disorders in children aged 6-7 and 13-14 years. Although non-ISAAC research groups (i.e. non-official ISAAC studies) also published data using ISAAC questionnaires, the official ISAAC reviews do not include these latter data in their analyses.

The primary aim of this review is to calculate the worldwide prevalence in children of atopic eczema, asthma and allergic rhinitis, and of having all three disorders, using data obtained with ISAAC questionnaires and to examine interrelationships between these disorders using risk ratios. Risk ratios will describe the risk of having two different atopic disorders when the child is known with one disorder. A secondary aim is to analyze whether these risk ratios and prevalences are influenced by potential confounders such as study period, age, sex, continent, and use of the original English-language ISAAC questionnaire.

Method

Search strategy

An extensive literature search was performed in Medline (OvidSP), Pubmed Publisher, EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register. Two complementary search strategies were used for optimal article retrieval. The first strategy, focusing on the three atopic disorders, combined the following items: "Child" AND "Epidemiology" AND "Eczema" AND "Asthma" AND "Allergic rhinitis". The second strategy, focusing on ISAAC studies, used additional items and different Boolean operators: "Child" AND "Epidemiology" AND ("Eczema" OR "Asthma" OR "Allergic rhinitis") AND ("ISAAC" OR "International Study of Asthma and Allergies"). The full search strategies can be found in Appendix 1. Since ISAAC started in 1991, only full-text articles published after 1991 were considered; there was no language restriction. The search was completed on February 2, 2015. A reference check was made on all articles finally included.

Study selection

Studies (n>100) with a cross-sectional or cohort design, including youngsters aged 0-18 years, recruited in the open population (e.g. schools) were included. Studies using the ISAAC questionnaire, performed by both official and non-official ISAAC research groups, were included if the studies presented data on the prevalence of all three atopic disorders and their interrelationships.
One reviewer (EA) commenced the selection of studies, initially based on title and abstract. To check for any missed inclusions by the first reviewer, a random selection of 50% of the articles was independently checked by second reviewers (DP, JW, AB, NR, HM). This check showed that the first reviewer did not exclude any potentially relevant articles.
Of the abstracts selected, the full-text articles were retrieved. Two reviewers (EA and NR) independently performed the full-text selection using a standardized form based on the above-mentioned inclusion criteria. Studies were excluded if they only presented aggregated worldwide data, or when double inclusion of the data could not be ruled out. Disagreement was resolved in a consensus meeting or with the help of a third independent reviewer (DP). Authors of the studies were contacted regarding missing data.

Quality assessment

To minimize the risk of information bias, the quality of the included studies was assessed by two independent reviewers (DP and AB). Disagreement was resolved in a consensus meeting.

ISAAC used the same standardized method in ISAAC phase 1 and 3. Methodological differences between these phases were studied (11) and it was concluded that the ISAAC methodology was replicated to a high degree by the majority of the study centers. This showed that the ISAAC protocol is robust and that working in accordance with this protocol implied substantial generalizability. Any important violations of this protocol were, therefore, identified in order to assess quality (Table 1).

The present review includes only those articles that used the ISAAC questionnaires. This questionnaire has been translated into various languages by regional coordinators of ISAAC, using a consistent protocol that was evaluated by Ellwood et al. (12). Use of a validated questionnaire was also considered an important quality item and was part of the quality assessment (Table 1).

The above mentioned violations and the use of the original questionnaire or not could potentially influence the comparability of ISAAC and non-ISAAC studies. For this reason we performed a meta-regression analyses in order to evaluate if these violation would influence our outcomes (prevalence and RR).

Data extraction

Two reviewers (EA/JW and DP) independently extracted data from the included studies. A standardized digital form was used to record study design, participants, official ISAAC study or not, and outcome measures. In view of the outcome measures, the total number of participants and the number of participants with eczema (Ec), asthma (As), allergic rhinitis (AR) and of Ec+As, Ec+AR, As+AR and Ec+As+AR were extracted. These numbers were then entered in the Review Manager (RevMan) Computer program (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). This program provides risk ratios, 95% confidence intervals (CI) (using the Mantel-Haenszel test and random effects models) and the weight of every study. The extraction was limited to current symptoms (past 12 months) and data collected by written questionnaires. Study characteristics regarding gender, age, continent, validated (English) questionnaires, ISAAC/non-ISAAC study, number of participants, response rate, study period and ISAAC protocol violations were also collected. Data entry was additionally checked by two independent reviewers (AB, JW).

Table 1. Study characteristics and quality assessment

Article	ISAAC	No. analyzed*	Age range (years)	% Males	Response rate	Study year	Continent	English Question.	Violation protocols†
Ait-Khaled 2007 (13)‡	Yes	4,123	13-14	58.3	99.1	1996-1999	Africa	No	None
Asher 2001 (14)	Yes	18,569/19,023	6-7/13-14	50.6/46.7	91.2/92.6	1992-1993	Oceania	Yes	None
Austin 1999 (15)	Yes	27,507	12-14	49.2	85.9	1995	Europe	Yes	6
Bröms 2013 (16)	No	4,886	1-6	50,7	67,5	2002	Europe	No	1, 2, 3, 4, 6
Cibella 2011 (17)	No	2,150	10-17	49.2	87.8	2005-2006	Europe	No	2, 3, 6, 7
Civelek 2010 (18)	No	5,664	9-11	50.9	91.3	2005-2006	Europe	No	3
Duggan 2012 (19)	No	1,474/1,535	6-9	47.3/47.9	74.8/76.2	2002/2007	Europe	Yes	3, 6, 7
Eder 1998 (20)	Yes	3,672/3,371	6-8/12-15	51.0/51.0	88.2/85.1	1995	Europe	No	3, 6
Falade 2004 (21)	Yes	1,312	6-7	46.8	73.3	1995	Africa	Yes	6, 7
Futamura 2011 (22)	No	27,389	6-14	47.2	74.4	2005	Asia	No	3, 6
Ghaffari 2012 (23)	No	1,818	7-12	65.0	91.0	2010	Asia	No	3, 4, 5, 7
Hailu 2003 (24)	No	3,365	13-14	40.1	98.4	1997	Africa	No	None
Hong 2012 (25)	No	31,201	0-13	51.1	82.1	2010	Asia	No	3, 4, 5, 6
Janahi 2006 (26)	No	3,283	6-14	52.3	93.8	2003-2004	Asia	No	3, 5
Lamnisos 2013 (27)	No	4,569/5,587	7-8/13-14	50,0/49,8	56,8/68,1	2007-2009	Europe	No	2, 3, 6
Liao 2005 (28)	No	7,040	6-8	51.5	89.4	2002	Asia	No	3, 6
Liao 2009 (29)	No	4,622	6-8	53.2	79.1	2007	Asia	No	3, 6
Mallol 2012 (30)	Yes	388,453/796,368	6-7/13-14	50.3/49.3	–	2000-2003	World	Yes/No	6
Manning 1997 (31)	Yes	3,148	13-14	46.0	92.1	1995	Europe	Yes	None
Marinho 2007 (32)	No	815	5	54.7	67.3	1998-2002?	Europe	Yes	1, 2, 3, 5, 6, 7
Martin Fernández 2004 (33)	Yes	3,018	13-14	51.4	100.0	<2002?	Europe	No	None
Musharrafieh 2009 (34)	No	3,115	13-14	48.6	–	2005	Asia	No	2, 6
Nwaru 2013 (35)	No	2,448	5	53.0	93.0	2001-2009	Europe	No	1, 2, 3, 7
Rahimi Rad 2007 (36)	No	3,000	13-14	50.0	98.3	2002-2003	Asia	No	None
Rahimi Rad 2008(37)	No	2,999	6-7	48.4	94.4	2002-2003	Asia	No	7
Remes 1998 (38)	Yes	11,607	13-14	49.5	96.5	1994-1995	Europe	No	None
Robertson 1998 (39)	Yes	10,914/12,280	6-7/13-14	–	84.3/93.9	1993-1994	Oceania	Yes	6
Škvorc 2014 (40)	No	3,106	7-9	50,4	96,9	2005	Europe	No	3, 4
Wördemann 2006 (41)	No	398	5-13	48.0	100.0	2003-2004	North America	No	3, 4, 5, 7
Yao 2011 (42)	No	5,155	4-18	48.9	94.9	2007	Asia	No	3, 4, 5
Ziyab 2014 (43)	No	1,345	10	50,7	92,4	1999	Europe	Yes	1, 2, 3, 5, 7

* Number of patients available for analysis

† 1) Recruitment at schools; 2) All schools or randomly selected; 3) Age groups 6-7 and 13-14 years; 4) Use of validated questionnaires; 5) questionnaires completed by parents (< 12 years old) or by adolescents themselves (≥ 12 years old); 6) Participation >90%; 7) N ≥3000

‡ Only two centers were included (Benslimane, Morocco; Conakry, Guinea)

Statistical analyses

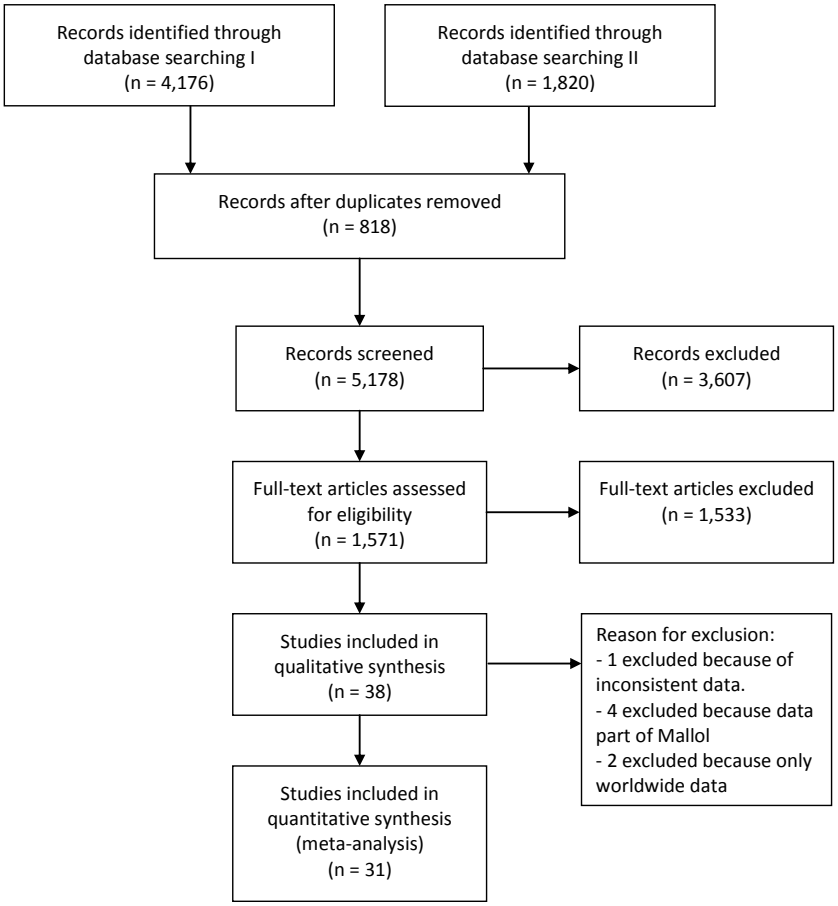
In order to calculate the mean prevalences, the studies were weighted for their number of participants. Risk ratios (RR) calculated by RevMan describe the risk of having two different atopic disorders when a child is known with one disorder. For example, if the RR for asthma is four, this would mean that a child with asthma has a fourfold risk of reporting atopic eczema and allergic rhinitis in contrast to a child without asthma. Heterogeneity (I^2) was assessed using a random effects model. For the study characteristics of this meta-analysis, a mixed-effects model was used for natural logarithm of the calculated RR for atopic eczema, asthma and allergic rhinitis and for the prevalence of atopic eczema, asthma and allergic rhinitis and having all three disorders. Initial models for these seven responses contained all covariates of interest as fixed effects: percentage of males, age, continent, ISAAC/non-ISAAC, number of participants, response rate, study period and the use of validated English questionnaires. The latter was chosen to explore the influence of using translations on the RR. Since not all studies provided data on the percentage of male participants and the response rate, and both variables did not have significant parameters in the complete case analysis, both variables were excluded from the models in order to be able to use all 57 studies for the meta regression. Some influential centers were removed from initial and final models using traditional measures: standardized residuals, DFFITS values, Cook's distance and hat values. All calculations were conducted in R with the metafor package (Wolfgang Viechtbauer (2010)). A p value of 0.01 was considered the limit of significance because of multiple testing (Bonferroni correction).

Results

Identification and selection of the literature

The combined search strategies resulted in 5,178 original abstracts. No articles were excluded because of language barriers but the majority (n=3,607; 69.7%) did not meet the inclusion criteria, mainly because these articles did not present data on all three disorders or because ISAAC questionnaires were not used. We retrieved 1,571 full-text articles for detailed evaluation. Of these, another 1,533 studies were not included, mainly because the studies did not use ISAAC questionnaires or because these articles did not present data on all three disorders. Finally 38 studies were initially included in this review for further analysis (2, 13-49) (Fig. 1).

Figure 1. Flow diagram for selection of studies identified in the systematic review.



Description and final selection of studies

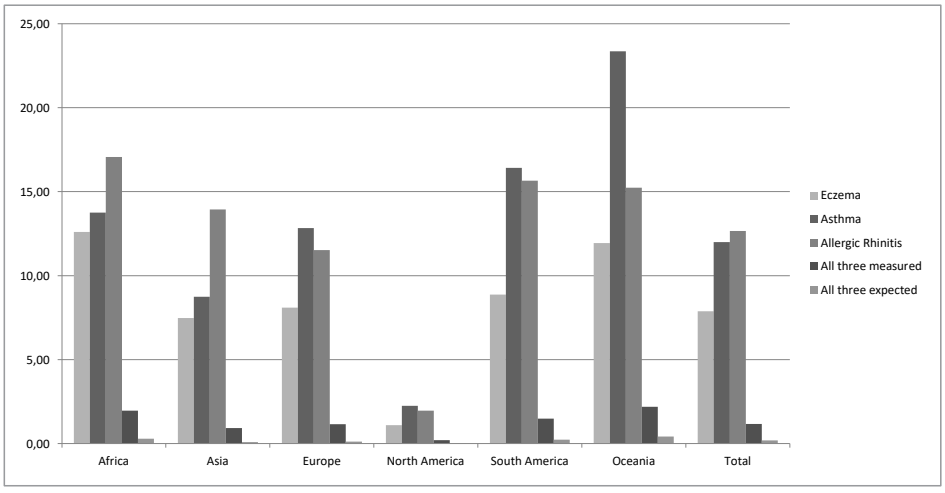
The ISAAC Phase 3 synthesis presented by Mallol et al. (30) covers a large number of surveyed children (n=1,184,821). Four of the included ISAAC studies (45-48) were excluded because it is assumed that the data from these studies were already included by Mallol et al. (30). The data presented by Song et al. (49) showed internal inconsistency and was therefore excluded. Furthermore, articles that only presented worldwide data (n=2) (44, 50) were not used for the final analysis. Finally, data from 31 studies were used, covering a large number of surveyed children (n=1,430,329) in 102 different countries. Table 1 presents descriptive characteristics of the studies, including the results of the quality assessment. All officially acknowledged ISAAC studies, with the exception of one (38), used the same

definition for atopic eczema, asthma and allergic rhinitis. Non-ISAAC studies varied considerably in the definitions they used for the disorders.

Overall and regional difference in prevalence of atopic manifestations

The calculated worldwide prevalence for atopic eczema, asthma and allergic rhinitis for children in the open population is 7.88% (95% CI: 7.88-7.89), 12.00% (95% CI: 11.99-12.00) and 12.66% (95% CI: 12.65-12.67), respectively. Figure 2 shows the prevalence per continent. None of the continents significantly influenced the worldwide prevalence of any one of the atopic disorders, neither did percentage of males, ISAAC/non-ISAAC, number of participants and the use of validated English questionnaires. There were significant negative associations between age and prevalence of eczema and between study period and prevalence of asthma. The worldwide observed prevalence of having all three disorders is 1.17% (95% CI: 1.17-1.17) and was not influenced by the above mentioned factors. If there would be no interrelationship at all between the three disorders, the expected worldwide prevalence of having all three disorders is only 0.12% (12.00%*7.89%*12.66%)). In the present review, the observed prevalence is 9.8 times higher than could be expected by chance, suggesting a close relationship between these disorders in children. It is remarkable that the prevalence of 'all three expected' is relatively consistent between the six continents (Fig. 2).

Figure 2. Prevalence (%) of the atopic disorders per continent.



Interrelationship between the atopic manifestations

Calculated RR for children with atopic eczema, asthma and allergic rhinitis are presented in the Forest plots (Figs. 3-5). If possible, the Forest plots provide a subdivision per article by continent and age. The overall RR for patients having atopic eczema to also suffer from asthma and rhinitis is 4.24 (95% CI: 3.75-4.79). For patients with asthma the RR is 5.41 (95% CI:4.76-6.16) and for allergic rhinitis the RR is 6.20 (95% CI: 5.30-7.27). These risk ratios show a clear relationship of the three disorders. Additional analyses to examine whether RRs were influenced by covariates (percentage of males, age, continent, official ISAAC/non-ISAAC study, number of participants, response rate, study period and the use of validated English questionnaires) showed no significant effect on the calculated RR.
There is substantial heterogeneity (I^2= 97-98%) between these studies. Subanalyses performed for different subgroups (percentage of males, age, continent, ISAAC/non-ISAAC, number of participants, response rate, study period) showed no major change in heterogeneity.

Figure 3. Forest plot of risk ratios for atopic eczema

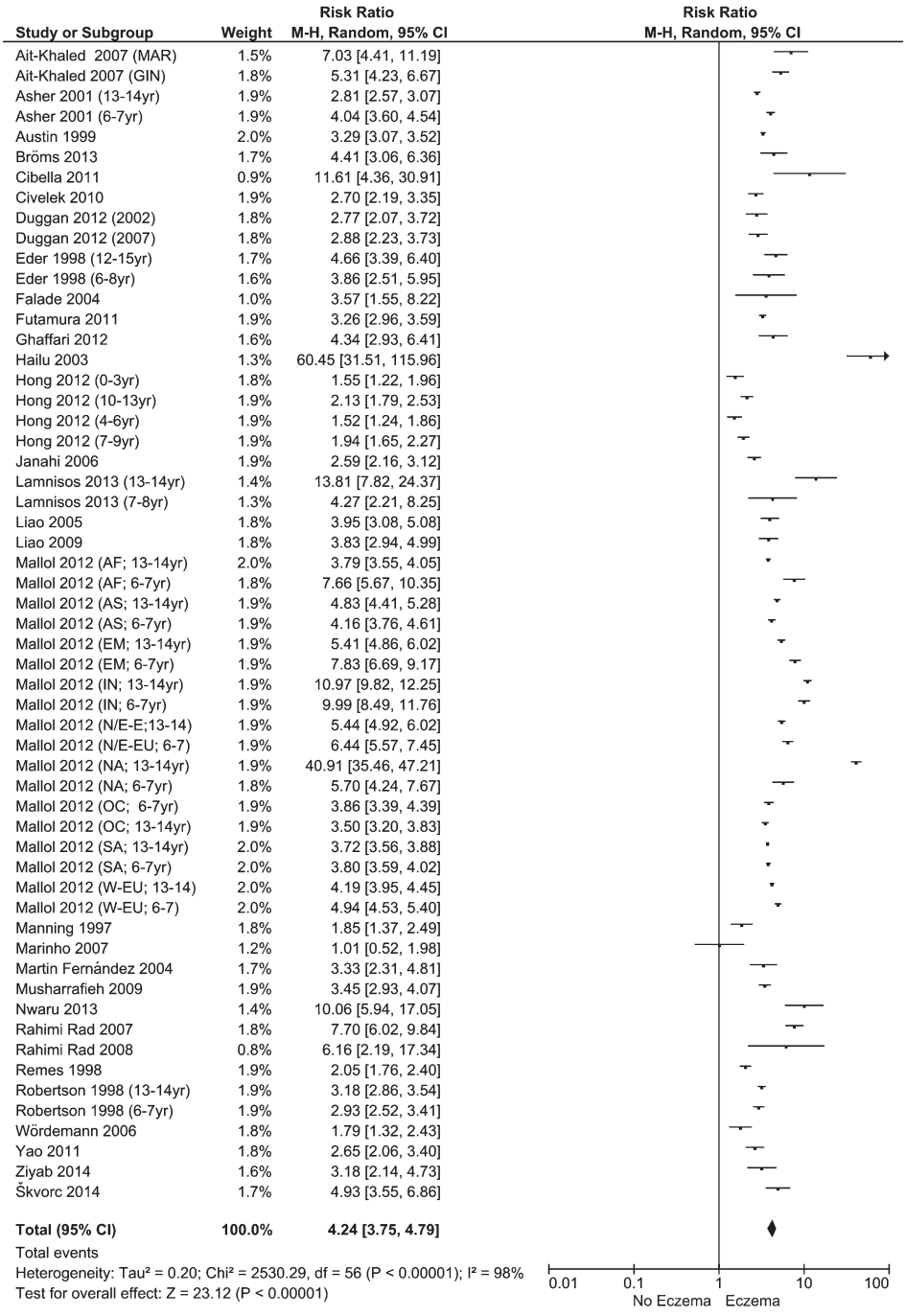


Figure 4. Forest plot of risk ratios for asthma

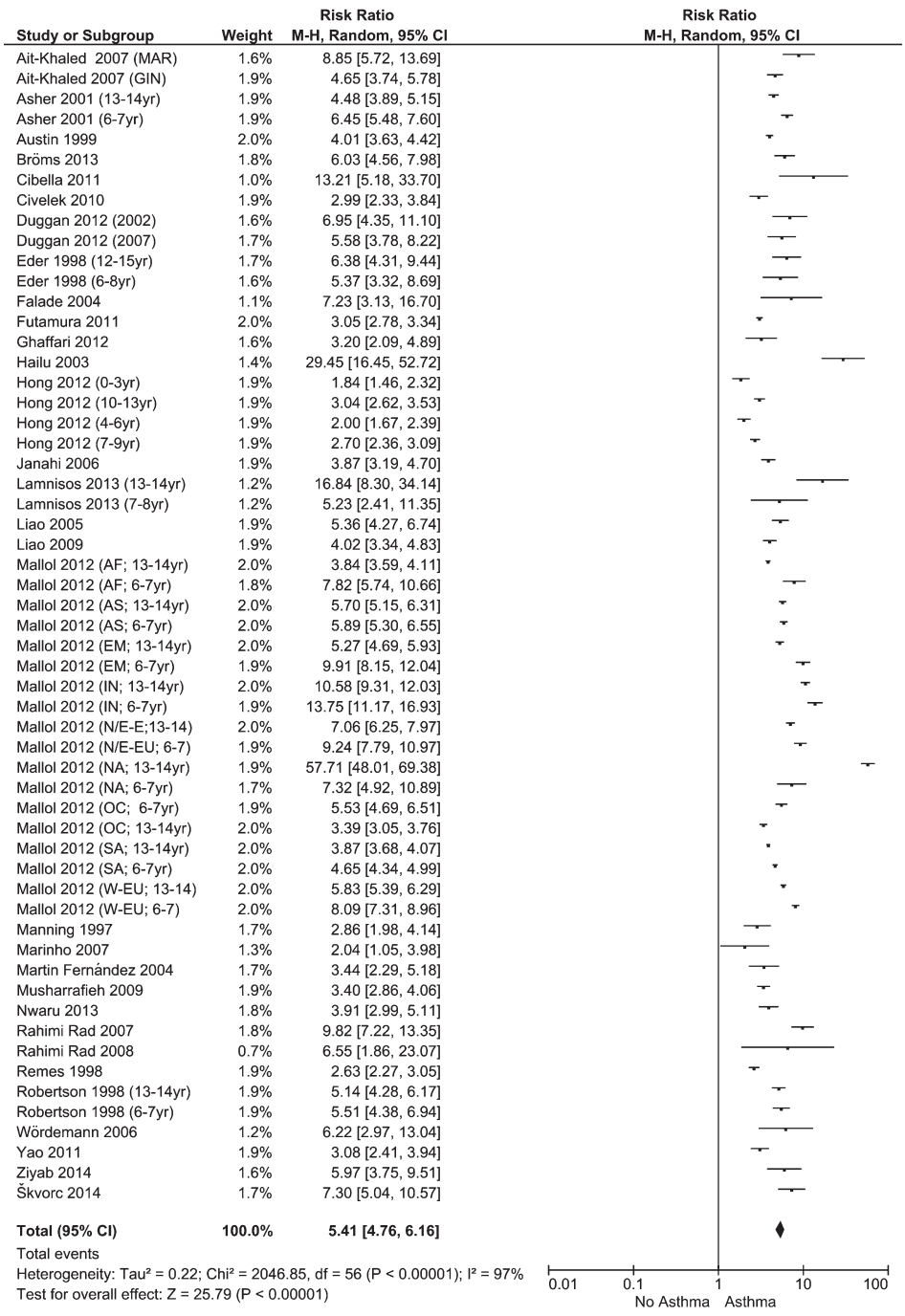
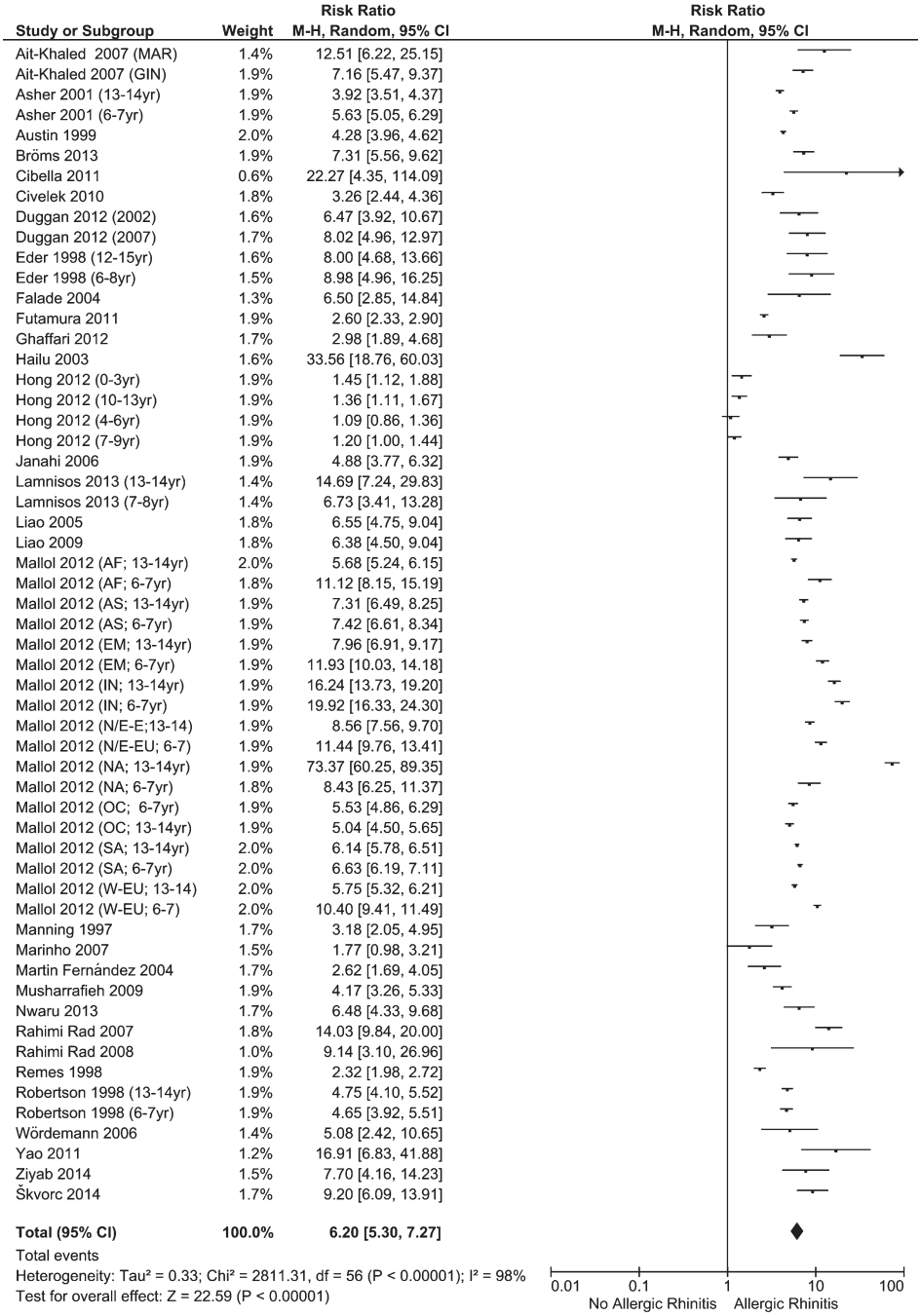


Figure 5. Forest plot of risk ratios for allergic rhinitis



Discussion

A comprehensive literature search retrieved data from 102 different countries, making this one of the largest meta-analysis of atopic eczema, asthma and allergic rhinitis ever conducted. The calculated worldwide prevalence for atopic eczema, asthma and allergic rhinitis for children in the open population is 7.9%, 12.0% and 12.7%, respectively. Overall this prevalence is higher than that presented earlier by Mallol et al (30). None of the individual continents had a significant influenced on the worldwide prevalence of one of the atopic disorders.

In this review, the observed prevalence of having all three disorders is 1.17% (95% CI: 1.17-1.17). This co-occurrence is substantially higher than could be expected by chance, based on the individual prevalence of each disorder (0.12%). This supports the hypothesis that there could be a fourth distinct group of children with all three disorders. A new and different way of looking at the interrelationships is by calculating RRs; the RRs presented in this review, describe the risk of having the other two atopic disorders when a child is known with one disorder. The RRs ranged from 4.24–6.20 and were not significantly influenced by any of the confounders investigated. Since all RR were > 1, this implies that the observed co-occurrence is not based on chance, but suggest a clear relationship between the disorders. Remarkably, the RR of atopic eczema is low compared with the other two disorders; this might be because we used prevalence data based on having complaints in the past 12 months and not on lifetime prevalences. On average, atopic eczema is seen in children at a younger age than those studied in this review, thereby resulting in a lower RR. This study also showed a significant decline in the prevalence of asthma when a child becomes older.

The wide variation in the prevalence of atopic disorders (1-4) has received considerable attention. Possible causes of these variations include (amongst others): genetics, use of paracetamol, use of antibiotics, breastfeeding, diet, body mass index, living in a rural area, and air pollution. However, none of these proposed factors fully explains this wide variation. Remarkably, when looking at the prevalence of having all three disorders, this wide variation does not occur to the same extent. In the present study, the limited degree of overlap between the three conditions (1.17%) was very similar to that reported by others (30, 50). Asher et al. (44) even showed that this overlap has been relatively consistent over a period of seven years; for 6-7 year olds this overlap increased from 0.8% to 1.0% and for the 13-14 year olds the overlap increased from 1.1% to 1.3%. This consistency in prevalence also suggests that a fourth group of children with atopic disorders might exist. In addition to the three regularly described groups of children with atopic eczema, asthma or allergic rhinitis, there seems to be a fourth distinct group of children with

all three disorders, that may show distinct characteristics regarding severity, causes, treatment or prognosis.

We suggest to add another chapter to the already impressive ISAAC study, focusing on this potentially distinct fourth group of children with all three manifestations. Is this group distinctive due to severity of symptoms? Does this group have a different genotype? Does this group need a different pharmacological approach? Does this group have a different prognosis? Which factors influence this group?

This meta-analysis has some limitations. First, one reviewer selected the studies based on title and abstract. Despite a random check of 50% of the retrieved articles showing concordance, we assumed that no relevant articles were missed. However, the full-text selection was done by two independent reviewers. In our review there was no limitation for any language and (where possible) authors were contacted for missing data.

When conducting a large multicenter international cross-sectional study, there is always a risk of potential limitations. Clear examples include language problems, cultural differences, environmental aspects, different healthcare systems, etc. Either an overestimation or an underestimation might be found. Another concern is the possible overestimation of the prevalence of the three atopic disorders. Although the questionnaires asked about symptoms, the symptoms could well be attributable to other diseases; this concern is shared by others (28, 46, 48, 51). Furthermore, Cane et al. (52) showed that the conceptual understanding of 'wheeze' differs between reporting parents and epidemiology definitions. Finally, different research groups used different definitions for the atopic disorders; this could have influenced our results.

The high level of heterogeneity that we found suggests that the included studies differ significantly from each other. However, this can be explained by the large number of participants in each study. Because the studies have such large populations, the CIs will be very small. Even small differences will result in statistical heterogeneity, but not in clinical heterogeneity.

This meta analyses supports the hypothesis that these three atopic disorders are clearly related. A biological plausible pathway for these relationships can be found in the atopic march theory. However, the obtained data in this meta-analysis does not allow to quantify the effect of this atopic march theory. This is due to two limitations. The first limitation relates to the cross sectional methods used. We have no follow-up data available for an individual child. The second one is that we limited our data inclusion to symptoms within the previous year (year prevalence). Using year-prevalences instead of life-time prevalences could result in an underestimation of the prevalences. Atopic dermatitis often goes into a clinical remission, but the atopic phenotype persists. The same applies to asthma. For example, when establishing the

prevalence at the age of e.g. 12 years, the child may answer no, but in fact might still have an atopic phenotype.

Conclusions

We studied the prevalence and interrelationships between atopic eczema, asthma and allergic rhinitis in children using data obtained from ISAAC questionnaires. The interrelationships were studied using risk ratios, adjusted for potential confounders. Our meta-analysis has shown that the prevalence of children with a co-occurrence of atopic eczema, asthma and allergic rhinitis was low, but significantly higher than could be expected by chance. The prevalence of having all three atopic disorders was remarkably consistent in all continents. This study supports the hypothesis that there might be a forth distinct group of children with all three disorders, in contrast to the traditional classification of children with atopic eczema or asthma or allergic rhinitis. Researchers and clinicians might need to consider this forth group as a separate group of children with their own characteristics.

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Appendix 1

Search string ONE contained the following specific terms:

For Embase

(asthma/exp OR wheezing/de OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) AND (eczema/de OR 'atopic dermatitis'/de OR (eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) AND (rhinitis/exp OR conjunctivitis/exp OR (rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti) AND (Epidemiology/exp OR 'epidemiological data'/exp OR epidemiology:lnk OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

For Medline via OvidSP

(exp asthma/ OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper ADJ (responsiv* OR sensitiv*))).ab,ti.) AND (exp Dermatitis, Atopic/ OR exp Eczema/ OR Eczem*.ab,ti. OR (atopic ADJ3 dermatit*).ab,ti.) AND (exp Rhinitis/ OR exp Conjunctivitis/ OR (rhinit* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen ADJ3 Allerg*) OR Pollinos* OR hayfever* OR hay fever*).ab,ti.) AND (exp Epidemiologic Studies/ OR exp Epidemiologic Factors/ OR epidemiology.xs. OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case ADJ3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR odds ratio* OR etiol* OR aetiol* OR natural histor* OR predict* OR prognos* OR outcome* OR course*).ab,ti.) AND (exp child/ OR exp infant/ OR (infan* OR newborn* OR new born* OR baby OR babies OR neonat* OR perinat* OR postnat* OR child* OR kid? OR toddler* OR teen* OR boy? OR girl? OR minor? OR underag* OR (under ADJ2 ag?) OR juvenil* OR youth? OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatric* OR

peadiatric* OR school* OR preschool* OR highschool* OR suckling*).ab,ti. OR ((adoles*.ab,ti. OR adolescent/) NOT exp adult/))

For PubMed publisher

(asthma[mh] OR (asthma*[tiab] OR wheez*[tiab] OR hyperresponsiv*[tiab] OR hypersensit*[tiab] OR hyper responsiv*[tiab] OR hyper sensitiv*[tiab])) AND (Dermatitis, Atopic[mh] OR Eczema[mh] OR Eczem*[tiab] OR (atopic AND dermatit*[tiab])) AND (Rhinitis[mh] OR Conjunctivitis[mh] OR (rhinit*[tiab] OR rhinoconjunctivit*[tiab] OR conjunctivit*[tiab] OR (Pollen AND Allerg*[tiab]) OR Pollinos*[tiab] OR hayfever*[tiab] OR hay fever*[tiab])) AND (Epidemiologic Studies[mh] OR Epidemiologic Factors[mh] OR epidemiology[sh] OR (prevalenc*[tiab] OR inciden*[tiab] OR trend*[tiab] OR associat*[tiab] OR comorbid*[tiab] OR relat*[tiab] OR correlat*[tiab] OR (case AND (control*[tiab] OR comparison OR referent)) OR epidemiolog*[tiab] OR cohort*[tiab] OR risk*[tiab] OR caus*[tiab] OR odds ratio*[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR natural histor*[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome*[tiab] OR course*[tiab])) AND (child[mh] OR infant[mh] OR (infan*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby OR babies OR neonat*[tiab] OR perinat*[tiab] OR postnat*[tiab] OR child*[tiab] OR kid* OR toddler*[tiab] OR teen*[tiab] OR boy* OR girl* OR minor* OR underag*[tiab] OR under ag* OR juvenil*[tiab] OR youth* OR kindergar*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepuberty*[tiab] OR pediatric*[tiab] OR peadiatric*[tiab] OR school*[tiab] OR preschool*[tiab] OR highschool*[tiab] OR suckling*[tiab]) OR ((adoles*[tiab] OR adolescent[mh]) NOT adult[mh])) AND publisher[sb]

For Cochrane

((asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) AND ((eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) AND ((rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti) AND ((prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

For Google scholar

asthma eczema rhinitis prevalence | incidence | epidemiology | cohort | risk | etiology | prognosis | outcome adolescents | infants | children | newborns "family | general | primary physician | practice | doctor | care"

Search string TWO contained the following specific terms:

For Embase

((asthma/exp OR wheezing/de OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) OR (eczema/de OR 'atopic dermatitis'/de OR (eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) OR (rhinitis/exp OR conjunctivitis/exp OR (rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti)) AND (Epidemiology/exp OR 'epidemiological data'/exp OR epidemiology:lnk OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti) AND (Isaac OR 'Asthma and Allergies in Childhood' OR 'Asthma and Allergy in Childhood'):de,ab,ti

For Medline via OvidSP

((exp asthma/ OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper ADJ (responsiv* OR sensitiv*))).ab,ti.) OR (exp Dermatitis, Atopic/ OR exp Eczema/ OR Eczem*.ab,ti. OR (atopic ADJ3 dermatit*).ab,ti.) OR (exp Rhinitis/ OR exp Conjunctivitis/ OR (rhinit* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen ADJ3 Allerg*) OR Pollinos* OR hayfever* OR hay fever*).ab,ti.)) AND (exp Epidemiologic Studies/ OR exp Epidemiologic Factors/ OR epidemiology.xs. OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case ADJ3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR odds ratio* OR etiol* OR aetiol* OR natural histor* OR predict* OR prognos* OR outcome* OR course*).ab,ti.) AND (exp child/ OR exp infant/ OR (infan* OR newborn* OR new born* OR baby OR babies OR neonat* OR

perinat* OR postnat* OR child* OR kid? OR toddler* OR teen* OR boy? OR girl? OR minor? OR underag* OR (under ADJ2 ag?) OR juvenil* OR youth? OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatric* OR peadiatric* OR school* OR preschool* OR highschool* OR suckling*).ab,ti. OR ((adoles*.ab,ti. OR adolescent/) NOT exp adult/)) AND (Isaac OR "Asthma and Allergies in Childhood" OR "Asthma and Allergy in Childhood").ab,ti.

For Pubmed publisher

((asthma[mh] OR (asthma*[tiab] OR wheez*[tiab] OR hyperresponsiv*[tiab] OR hypersensit*[tiab] OR (hyper responsiv*[tiab] OR hypersensitiv*[tiab])) OR (Dermatitis, Atopic[mh] OR Eczema[mh] OR Eczem*[tiab] OR (atopic AND dermatit*[tiab])) OR (Rhinitis[mh] OR Conjunctivitis[mh] OR (rhinit*[tiab] OR rhinoconjunctivit*[tiab] OR conjunctivit*[tiab] OR (Pollen AND Allerg*[tiab]) OR Pollinos*[tiab] OR hayfever*[tiab] OR hay fever*[tiab]))) AND (Epidemiologic Studies[mh] OR Epidemiologic Factors[mh] OR epidemiology[sh] OR (prevalenc*[tiab] OR inciden*[tiab] OR trend*[tiab] OR associat*[tiab] OR comorbid*[tiab] OR relat*[tiab] OR correlat*[tiab] OR (case AND (control*[tiab] OR comparison OR referent)) OR epidemiolog*[tiab] OR cohort*[tiab] OR risk*[tiab] OR caus*[tiab] OR odds ratio*[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR natural histor*[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome*[tiab] OR course*[tiab])) AND (child[mh] OR infant[mh] OR (infan*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby OR babies OR neonat*[tiab] OR perinat*[tiab] OR postnat*[tiab] OR child*[tiab] OR kid* OR toddler*[tiab] OR teen*[tiab] OR boy* OR girl* OR minor* OR underag*[tiab] OR (under ag*) OR juvenil*[tiab] OR youth* OR kindergar*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepuberty*[tiab] OR pediatric*[tiab] OR peadiatric*[tiab] OR school*[tiab] OR preschool*[tiab] OR highschool*[tiab] OR suckling*[tiab]) OR ((adoles*[tiab] OR adolescent[mh]) NOT adult[mh])) AND (Isaac OR "Asthma and Allergies in Childhood" OR "Asthma and Allergy in Childhood") AND publisher[sb]

For Cochrane

(((asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) OR ((eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) OR ((rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti)) AND ((prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND

((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti) AND (Isaac OR 'Asthma and Allergies in Childhood' OR 'Asthma and Allergy in Childhood'):ab,ti

For Google scholar

Asthma | wheezing|hyperresponsive | hypersensitivity | eczema | "atopic dermatitis" | rhinitis | conjunctivitis | "Pollen Allergy | allergies" | Pollinos | "hay fever" | hayfever prevalence | incidence | comorbidity | comorbidities | epidemiology | epidemiological infants | children Isaac

Chapter 3

Development and validation of search filters to identify articles on family medicine in online medical databases

David H.J. Pols, Wichor M. Bramer, Patrick J.E. Bindels, Floris A. van de Laar, Arthur M. Bohnen

Ann Fam Med. 2015; 13(4): 364-6 (published as 'Research Brief')

Abstract

Purpose: Physicians and researchers in the field of family medicine often need to find relevant articles in online medical databases. Because a search filter may help improve the efficiency of such searches, we aimed to develop and validate search filters to identify studies in the field of family medicine/general practice.
Method: To develop a search filter for family medicine, a precise definition was obtained which allows to classify articles as 'relevant' or 'irrelevant' to family medicine. This definition allowed to create a reference standard set of articles. Using specialized software, filter candidate terms and phrases were derived from this reference standard. Using these candidate terms and phrases, an optimal sensitive and an optimal specific filter were created. Finally, two filters were validated on two external validation sets.
Results: The sensitive filter has a sensitivity of 96.8% with an adequate specificity of 74.9%. The specific filter has a specificity of 97.4% with an adequate sensitivity of 90.3%
Conclusions: Two well-validated search filters were developed for family medicine with good sensitivity and specificity. Both filters can be applied in daily practice by family physicians and researchers. The quality of these filters is good when compared with other search filters applied in different scientific fields.

Background

Although many physicians use online medical databases to obtain biomedical information for clinical practice (1-3), the enormous volume and diversity of the available literature makes this a challenging process. Lack of time and skills, as well as a clear preference for asking an expert colleague or consulting a print source, are considered as barriers to the use of online databases (4, 5). A specific search filter might enhance the retrieval of relevant articles at the point of care by the physician. On the other hand, researchers in the field of family medicine completing a systematic review, will need a 'sensitive' search tool in order not to miss relevant articles. Electronic search filters, both sensitive and specific, can be used to improve the overall efficiency of a literature search. Search filters are strings of keywords and/or text words connected with Boolean operators (e.g. AND, OR, NOT). These topic-specific keywords can be found in the title or abstract of an article, or in the subject headings assigned to it. However, the indexing of these articles with subject headings is often inconsistent. The area of family medicine is particularly broad and difficult to define, mainly due to the different terminologies used. For example, the terms 'family medicine', 'general practice' and 'primary care' (amongst others), can be used to describe basically the same field.

Therefore, there is a need for a validated 'family medicine' search filter to support both family physicians and researchers. These filters should apply to the most frequently-used databases, e.g. PubMed, Ovid Medline, Embase and Cochrane.

To our knowledge, four filters have been developed for family medicine. Although the PHC Search Filter (6) can be considered specific, it was not designed to be comprehensive regarding what it retrieves. Jelercic et al. (7), Glanville et al. (8) and Gill et al. (9) also created search filters, but they also lack good sensitivity.

The present study was conducted to develop and validate objective search filters, applicable in frequently-used databases, to identify studies that are conducted in, or apply to, or refer to family medicine and general practice settings.

Method

Definition of family medicine

To develop an efficient and objective search filter, a clear definition of relevance to family medicine/general practice (FM/GP) is needed. WONCA Europe provides a consensus statement in which they define the discipline of FM/GP (10). Based on a short questionnaire that was sent to colleagues worldwide using the e-mail list of

the Cochrane Primary Healthcare Field, we learned that this definition was shared by many. However, the respondents indicated that two additional aspects should be taken into account. First, an inpatient hospital setting should explicitly be excluded. Second, one should be aware of the difference between 'primary care' and 'FM/GP'. Primary care was often regarded by the respondents as an umbrella term, that includes FM/GP, but could also include (amongst others) midwives, psychologists and physiotherapists. Based on an analysis of the submitted answers to the questionnaire, the WONCA definition was shortened as followed:
General practice/family medicine is the frontline of health care. It is a place where a patient can go without referral. This specifically trained physician can be consulted for acute and chronic health-related matters. Family medicine is considered to be out-of-hospital (together with the emergency department) care.
Relevance to general practice referred to any research article that explicitly indicated it was completed in a FM/GP setting as defined by WONCA, excluding inpatient hospital care and focusing specifically on FM/GP. Research articles that have 'FM/GP' as their research domain were also considered relevant (e.g. research on the efficiency of GPs).

Development of reference standard

Using Scopus, a list of 160 journals (in order of relevance for family medicine) was compiled. Five journals with a high rating (top 20) and five journals with a low rating

Table 1. Journal titles randomly selected from Scopus.

Rank in Scopus	Journal title	Hits on FM/GP* in Scopus	Hits in 2009 in PubMed	With an abstract	Included in the reference standard
2	British Journal of Family Medicine	5309	246	97 (39%)	63
3	Journal of Family Practice	3712	170	78 (46%)	44
5	American Family Physician	3404	260	104 (40%)	73
10	Canadian Family Physician	2669	264	89 (34%)	58
12	Family Practice	2288	119	112 (94%)	77
108	Age and Ageing	391	213	117 (55%)	79
121	Journal of Clinical Psychiatry	371	373	272 (73%)	188
128	Palliative Medicine	363	129	109 (84%)	73
144	Emergency Medicine Journal	305	367	217 (59%)	146
148	Intensive Care Medicine	280	415	303 (73%)	199
Total			**2556**	**1498**	**1000**

* FM: family medicine; GP: general practice

were randomly taken from this list (Table 1). From the obtained list of journals, 1000 articles published in the randomly selected year 2009, with abstracts and MeSH terms, were randomly selected. These articles were imported in EndNote X5 and anonymized, showing only the titles, abstracts and keywords to the reviewers. Two independent reviewers (DP and FvdL) classified the articles as being relevant or irrelevant to family medicine using the shortened definition based on the WONCA definition. If the anonymized information was not sufficient for a classification, all bibliographic data or even the full text was provided. Articles that refer to family medicine were tagged 'positives'. From this reference standard, two random sets were derived: a term identification set containing 1/3 of the reference standard and a development set containing 2/3 of the reference standard.

Generating a list of potentially useful terms

Using specialized software (PubReMiner (11) and AntConc (12)) candidate filter terms and phrases were derived in the term identification set from the bibliographic information of positive articles based on frequency of occurrence. Each retrieved term (MeSH term, text word or text phrase) was subsequently combined with various PubMed field codes ([mh]; [mh:noexp]; [mj]; [mj:noexp]; [sh]; [all fields]; [ad]; [tw]; [tiab]; [ti]). We included candidate filter terms for further analysis if that term retrieved at least 5% of the positive articles. Furthermore, the ratio between the percentage of positive articles containing the term and the percentage of negative articles containing the term had to be ≥ 1, and this ratio had to be significant (Chi-square test: $p<0.05$).

Creating and validating a sensitive and specific filter

With a list of candidate terms and phrases retrieved during the process described above, optimal search filters were created in the development set. The sensitive filter was created by sorting the search terms by accuracy. One by one, the items were meticulously added to the filter, whilst monitoring its performance. When an added term did not contribute to the overall accuracy of the filter, the item was excluded. The specific filter, with a target specificity of at least 95%, was created by discarding all search terms that had a specificity of ≤ 95%. Search terms that scored a specificity of 100% formed the basis of the filter. The remaining search terms were then sorted by accuracy, and were added one by one to the existing filter. When an added term did not contribute to the overall accuracy of the filter, the item was excluded.
The obtained filters were then validated in different validation sets (see below), calculating sensitivity and specificity. Finally, all the false negatives from different validation sets, missed by the sensitive filter, were manually screened by two

independent reviewers (DP and AB) to identify unique extra terms that could be added to the sensitive filter in order to improve its performance. These terms were then tested on both development and validation sets and included if they improved the overall accuracy of the sensitive filter.

Development of validation sets

In addition to the reference standard, two external validation sets were created. The first was created during the screening process of a family medicine relevant systematic review on atopic disorders in children (review standard) (13). The search for this review was not limited to family medicine, but all the references found for this review were also scored by two independent reviewers (DP and E. van Alphen) to classify articles as being relevant or irrelevant to family medicine. Relevance to general practice referred to any research article that explicitly indicated it was completed in a FM/GP setting as defined for the reference standard.
The second validation set was created by sending an e-mail to the list of the Cochrane Primary Healthcare Field (questionnaire standard). In this e-mail the participant was asked to send a reference of an article that they considered to be relevant for 'primary care', in particular for family medicine. These 500 references are considered to be positives. The negatives were collected from a random sample of articles from PubMed that were manually reviewed by two independent reviewers (FvdL and D. Al Rashad), creating 1,000 negatives.

Results

Creating and validating the filters

A total of 126 terms and phrases were considered as candidate filter terms. The original sensitive filter that was constructed missed a total of 35 'positives' in both the reference set and in the two validation sets. Manual evaluation of these 35 false negative references led to our decision to add three more terms to the sensitive filter to increase its performance, i.e. 'GP' 'GPs' and 'general pract*' were added; this substantially improved the filter.
Table 2 shows the strings of the sensitive and specific filters that were constructed using this methodology, including the translation for use in different search engines. Table 3 presents the results of a comparison between the performance of our filters and that of other published search filters (6-9). In the validation process the sensitive filter had an overall sensitivity of 96.8% (range 95.4-100%), with an adequate overall specificity of 74.9% (range 69.2-89.5%). For the specific filter

Table 2. The filters translated for different interfaces.

	Pubmed	Ovid (Medline/ Embase)	Embase.com	Cochrane
Sensitive filter	("family"[all fields] OR physician*[all fields] OR practice*[tw] OR "primary care"[all fields] OR "Primary Health Care"[mh] OR primary[tw] OR general pract*[tiab] OR gp[tiab] OR gps[tiab])	(family.af. OR physician$. af. OR practice$.mp. OR primary care.af. OR exp Primary Health Care/ OR primary.mp. OR general pract$.af. OR gp.tw. OR gps.tw.)	(family OR physician* OR practice*:de,it,lnk,ab,ti OR 'primary care' OR 'Primary Health Care'/exp OR primary:de,it,lnk,ab,ti OR (general NEXT/1 pract*) OR gp:ab,ti OR gps:ab,ti)	("family" OR physician* OR practice*:ti,ab,kw,pt OR "primary care" OR [mh "Primary Health Care"] OR "primary":ti,ab,kw,pt OR general pract*:ab,ti OR "gp":ab,ti OR "gps":ab,ti)
Specific filter	("Primary Health Care"[mh] OR "primary care"[all fields] OR "Physicians, Family"[mh] OR general pract*[all fields] OR "family"[ad] OR family pract*[all fields] OR family physician*[tw])	(exp Primary Health Care/ OR primary care. af. OR exp Physicians, Family/ OR general pract$.af. OR family.in. OR family pract$.af. OR family physician$.mp.)	('Primary Health Care'/ exp OR 'primary care' OR (general NEXT/1 pract*) OR family:ad OR (family NEXT/1 pract*) OR (family NEXT/1 physician*): de,it,Ink,ab,ti)	([mh "Primary Health Care"] OR "primary care" OR [mh "Physicians, Family"] OR general pract* OR family pract* OR family physician*:ti,ab,kw,pt)

the overall specificity was 97.4% (range 94.8-99.3%), with an adequate overall sensitivity of 90.3% (83.9-96.0%). Both the sensitive and the specific filters perform better compared to other recently published filters on the same topic (6-9). In table 4 the performance of our filters is compared to a combination of relevant Mesh terms (General Practice[Mesh] OR General Practitioners [Mesh] OR Physicians, Family [Mesh] OR physicians, primary care [mh]), i.e. a strategy used by many physicians in daily practice. Furthermore, the filter was tested against five search strategies used for general practice relevant Cochrane Reviews (14-18).

Discussion

Two well-validated search filters were created for family medicine, both with good sensitivity and specificity.

Our specific filter was developed to help family physicians find answers to clinical questions at the point of care when time is limited. The specific filter provides the physician with references that are relevant, but with a small risk of missing articles. If an answer to the question is not found using the specific filter, use of the sensitive filter could be the next step.

Our sensitive filter can also be used by researchers conducting a systematic review. The sensitive filter provides considerable efficiency. For example, we constructed a search string for a systematic review on atopic disorders in children through which 3,972 publications were found. If our sensitive filter had been applied, the number

Table 3. Performance of our search filters compared with that of other published filters

Used standard		Sensitive filter	Specific filter	PHCRIS (6)	Jeleric (7)	Glanville (8)	Gill (9) (high sens)	Gill (9) (balanced)	Gill (9) (high spec)
Review	**Sensitivity**	100%	90.7%	81.4%	46.5%	95.3%	95.3%	93.0%	88.4%
	Specificity	69.2%	97.9%	99.0%	94.4%	77.0%	61.0%	99.1%	99.5%
Reference	**Sensitivity**	95.4%	83.9%	65.9%	78.0%	84.3%	85.9%	68.9%	57.0%
	Specificity	69.5%	94.8%	96.3%	89.4%	89.4%	47.6%	96.7%	98.6%
Questionnaire	**Sensitivity**	97.4%	96.0%	81.4%	87.4%	97.0%	96.2%	92.2%	78.0%
	Specificity	89.5%	99.3%	99.0%	97.8%	96.1%	84.9%	99.4%	99.8%
Overall	**Sensitivity**	96.8%	90.3%	80.8%	81.9%	92.3%	91.9%	83.7%	70.9%
	Specificity	74.9%	97.4%	98.3%	94.3%	83.6%	65.0%	98.7%	99.4%

Table 4 Performance of our search filters compared with that of other search strategies

Used standard		Sensitive filter	Specific filter	Relevant Mesh	Cochrane 1 (14)	Cochrane 2 (15)	Cochrane 3 (16)	Cochrane 4 (17)	Cochrane 5 (18)
Review	**Sensitivity**	100%	90.7%	44.2%	91.1%	88.9%	88.9%	88.9%	71.1%
	Specificity	69.2%	97.9%	99.8%	99.0%	95.7%	93.1%	98.5%	96.4%
Reference	**Sensitivity**	95.4%	83.9%	56.7%	68.9%	70.2%	71.1%	68.5%	66.6%
	Specificity	69.5%	94.8%	99.9%	98.0%	88.4%	90.8%	96.4%	70.9%
Questionnaire	**Sensitivity**	97.4%	96.0%	75.8%	92.4%	92.8%	93.0%	92.0%	86.6%
	Specificity	89.5%	99.3%	99.7%	99.4%	97.5%	97.8%	99.3%	95.6%
Overall	**Sensitivity**	96.8%	90.3%	67.1%	84.1%	84.0%	84.3%	83.1%	74.8%
	Specificity	74.9%	97.4%	99.7%	98.8%	93.9%	93.9%	98.1%	87.6%

of relevant articles could have been limited to 1,478. In this example, no relevant articles were missed. Comparing our sensitive filter to the 'common practice' of search strategies used when conducting, for example, Cochrane systematic reviews, all tested literature searches showed a lack of good sensitivity (see online supplementary materials). Thus, it can be assumed that relevant references were missed in these reviews which might have been found when applying our sensitive search filter.

The present filters do not use the Boolean operators AND or NOT, but combined single search terms and phrases in an OR relationship. However, in our methodology, 'phrases' were already separately identified as combination of words in an AND matter that could potentially discriminate between FM/GP-relevant or not. For example 'primary health care' was identified in this way. These three words are combined in an AND matter, but the quotes also demand it to be in this specific order. Using an objective method, the developed filters did not always end up with phrases that one would expect, like 'family physician'. However, our objective method suggested the single words 'family' and 'physician' to be more distinctive. Finally, using NOT would imply a substantial risk of excluding relevant articles and was therefore rejected.

There are two important arguments for manually improving the sensitive filter. In order for this methodology to create a completely objective filter without manual improvement, it was estimated that about 30,000 articles had to be scored. Manually evaluating the false negatives overcomes the use of a relatively small 'reference standard'. Furthermore, in order for AntConc to find phrases, the 126 candidate filter terms were used. Words like 'general' and 'practice' did not meet the requirements for inclusion in the list of candidate filter terms, because the words themselves are not specific enough.

Translating the search strategies developed for PubMed to the syntax of the other databases (Ovid, Embase and Cochrane), carries a small risk of losing some sensitivity and specificity. Ideally, one would use the candidate filter terms and start constructing the search filter using the different interfaces. Unfortunately, the other databases did not have an 'application programming interface' (a set of routines, protocols, and tools for building software applications) that allowed communication with the software programs that were used for the development of these search filters. Instead the filters were directly translated into the syntax of the other databases, without optimization for that specific database.

We noticed that, in many cases, the title and abstract did not disclose sufficient information to determine whether (or not) an article was relevant for family medicine. In many cases the setting and/or relevance to family medicine could only be determined by scrutinizing the full text; this omission will influence both the

sensitivity and specificity of search filters. We emphasize that mentioning the setting in the title or abstract will help to find all relevant literature available for family medicine.

Conclusions

Two useful filters were created for a search on articles related to family medicine. The sensitive filter has a sensitivity of 96.8% with an adequate specificity of 74.9%. The specific filter has a specificity of 97.4% with an adequate sensitivity of 90.3%.

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Chapter 4

Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: a systematic review

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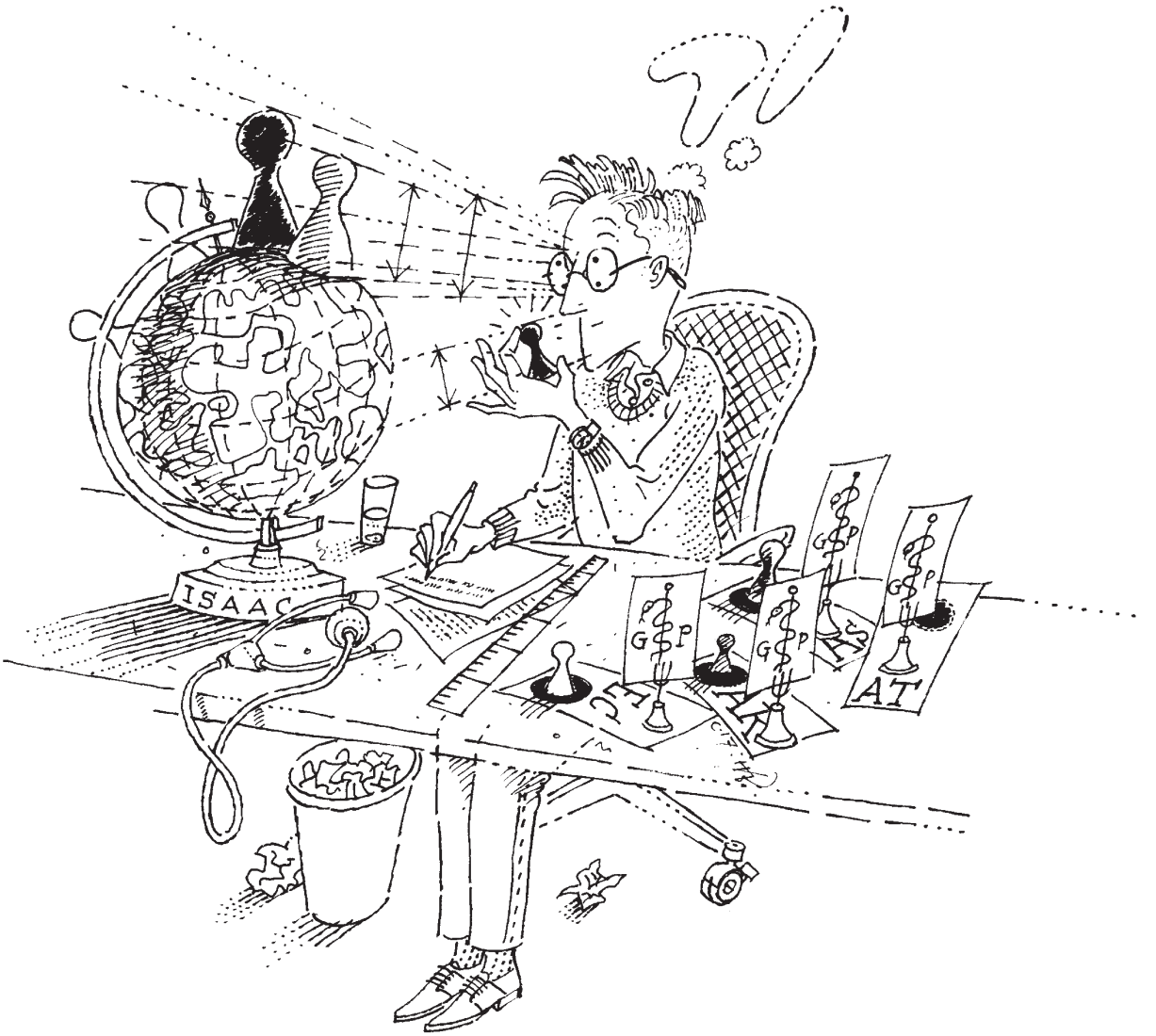


Abstract

Purpose: To examine whether significant differences exist between the self-reported prevalence of atopic disorders in the open population compared with physician diagnosed prevalence of atopic disorders in general practice.
Method: Medline (OvidSP), PubMed Publisher, EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register databases were systematically reviewed for articles providing data on the prevalence of atopic eczema, asthma and allergic rhinitis in a GP setting. Studies were only included when they had a cross-sectional or cohort design and included more than 100 children (aged 0-18 years) in a general practice setting. All ISAAC studies (i.e. the open population) that geographically matched a study selected from the first search, were also included. A quality assessment was conducted. The primary outcome measures were prevalence of atopic eczema, asthma and allergic rhinitis in children aged 0-18 years.
Results: The overall quality of the included studies was good. The annual and lifetime prevalences of the atopic disorders varied greatly in both general practice and the open population. On average, the prevalence of atopic disorders was higher in the open population.
Conclusions: There are significant differences between the self-reported prevalence of atopic disorders in the open population compared with physician diagnosed prevalence of atopic disorders in general practice. Data obtained in the open population cannot simply be extrapolated to the general practice setting. This should be taken into account when considering a research topic or requirements for policy development. GPs should be aware of the possible misclassification of allergic disorders in their practice.

Background

The atopic syndrome is a predisposition toward an exaggerated IgE-mediated immune response in reaction to an allergen. A patient with atopy typically presents with one or more of the following disorders: atopic eczema (atopic dermatitis), asthma or allergic rhinitis. In this article atopic disorders refer to allergic manifestations for which atopy is a prerequisite. Epidemiological data on atopic disorders in children can be obtained from various sources, each having its own advantages and limitations. This review examines data obtained from general practice and survey data obtained in the open population. Depending on the research topic or the requirements for policy development, reliable data from either the open population or general practice (or both) might be needed.

The International Study of Asthma and Allergies in Childhood (ISAAC) has yielded many publications related to the open population (1). Albeit such survey data provide useful information on the prevalence of self-reported symptoms of allergic disorders and the derived diagnosis (2), they also imply a risk of overestimation of the prevalence of atopic disorders. For example, a runny nose can be caused by allergic rhinitis or by a viral upper airway infection; distinguishing between these two causes may be difficult for a patient when completing a questionnaire. Although the prevalence based on a clinician-diagnosed disease might solve this problem, it will imply a risk of underestimation of the burden of disease. For example, patients might have a 'threshold' with regard to visiting a physician or might consider their complaints not serious enough to visit one. Because, epidemiological data on atopic conditions in children in a general practice are scarce, we performed a systematic review.

We expected to find a significant difference between the self-reported prevalence in the open population (ISAAC studies) and the clinician-diagnosed prevalence of a disorder in general practice. More insight into these differences may help policy-makers to optimize their policies and help general practitioners (GPs) become more aware about the possible underdiagnosis of allergic conditions in children.

Method

Search strategy

Two separate search strategies were used to collect data on the two sources (i.e. general practice and open population). First, a comprehensive search for relevant studies in general practice was performed in Medline (OvidSP), PubMed Publisher,

EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register databases. The search strategy (Appendix 1) combined the following items: 'Child' AND 'Epidemiology' AND 'Eczema' AND 'Asthma' AND 'Allergic rhinitis'. All articles in these five databases were considered and reviewed; no language restriction was imposed and the search was completed in January 2015. All references of the included studies were examined in order to be as comprehensive as possible.
A second search, performed in the ISAAC database, was also conducted in January 2015. ISAAC provides its users with a database that holds citations on all publications which are part of the ISAAC collaboration (1), representing the open population. However, because of known regional differences (3), we looked for studies that geographically matched (i.e. the same country) the studies finally selected in the first search strategy.

Study selection

Based on title and abstract, two reviewers (DP and EvA) independently selected articles retrieved in the first search strategy. All studies that provided data on the prevalence of asthma, allergic rhinitis and atopic eczema were considered, so long as they had a cross-sectional or cohort design and included more than 100 children (0-18 years) in a general practice setting. If the abstract was not conclusive regarding these items, the article was included for full-text assessment. Any disagreement was resolved in a consensus meeting. Finally, the full-text of the selected abstracts was independently reviewed by two reviewers (DP and JW). Studies were not included if they did not meet the above-mentioned inclusion criteria or if selection bias was present (e.g. data were retrieved from a specific cohort within a general practice setting).
The second search strategy focused on the ISAAC database (1). Two reviewers (DP and JW) independently checked this database for relevant articles. All studies were included that geographically matched (i.e. the same country) a study selected from the first search.

Quality assessment

The quality of the included studies was independently assessed by two reviewers (DP and AB). Any disagreement was resolved in a consensus meeting. Assessment of the quality of the finally included studies conducted in general practice, was done by scoring the following items: population size, description of participants (age and percentage males), study year, data sources (paper or digital patient files, structured interviews, etc.), selection bias (e.g. not using all patient files but a selection thereof) and whether or not the methods used are reproducible.

With regard to reproducibility, the emphasis was on the definitions used for atopic eczema, asthma and allergic rhinitis. ISAAC used a standardized method. Ellwood et al. showed that the ISAAC methodology could be replicated to a high standard by the majority of participating centers (4). This indicates that the ISAAC protocol is robust and working in accordance with this protocol implies high quality. Any important violations of this protocol were obtained for the quality assessment of the finally included studies.

Data extraction

All data extraction was independently performed by two reviewers (DP and AB). Data were collected on the number of children studied, study period, study design, and country. The outcome measures are the prevalences of atopic eczema, asthma, and allergic rhinitis in children aged 0-18 years.

Results

Selection and description of the literature

The search strategy regarding general practice yielded 4,274 unique articles. Most of these (n=4,242) did not meet the inclusion criteria, mainly because only 2.2% of these studies (n=95) were conducted in a general practice setting. Of the 34 articles retrieved for full-text evaluation, 28 were excluded because they did not meet the inclusion criteria.

Finally, six studies were included in the present review for further analysis with regard to general practice; one study was performed in the Netherlands (5) and five in the UK (6-10). These six studies were published between 1974 and 2009.

In table 1 the results of the quality assessment are presented. There was no evidence of selection bias. Four of the six studies had an adequate description of the methodology, whereas two studies failed to describe the exact definitions used for the disorders examined. Two studies presented data on annual prevalence and four U.K. studies presented data on lifetime prevalence.

The ISAAC database contained 604 articles. Of these, seven eligible studies (11-17) were selected that could be geographically matched to the selected general practice studies. Of these, six were performed in the UK (11-16) and one in the Netherlands (17). All four UK studies were conducted between 1995 and 2002 (11-14). The study on Dutch adolescents was conducted in 2003 (17). Table 2 presents the results of the quality assessment of these studies.

Table 1. Study characteristics and quality items general practice studies

First author/year	Country	No. analyzed	Age (years)	% Males	Study year	Data sources	Bias*	Reproducible
Blair 1974 (6)	UK	1,907	0-10	53.2%	1970-1973	Paper files + interview	No	No
Mortimer 1993 (9)	UK	1,077	3-11	50.5%	<1993	Interviews + survey	No	No
Punekar 2009 (8)	UK	24,112	0-18	51.1%	1990-2008	Digital files	No	Yes
Simpson 2002 (7)	UK	252,538[†]	0-14	53.6%	1999	Digital files	No	Yes
Simpson 2008 (10)	UK	492,411/486,804	0-14	49.6%/49.8%	2001/2005	Digital files	No	Yes
Wijga 2011 (5, 35)	NL	79,272	0-17	51.3%	2001	Digital files + interviews	No	Yes

* not using the entire patient files, but some selection thereof.

[†] Total study population, including adults

Table 2. Study characteristics and quality items of the open population (ISAAC) studies

First author/year	Country	No. analyzed	Age (years)	% Males	Response rate	Study year	English questionnaires	Violations protocol*
Austin 1999 (12)	UK	27,507	12-14	49.2%	85.9%	1995	Yes	3, 6
Jeffs 2000 (16)	UK	3,772	12-14	–	90.7%	1995-1996	Yes	3
Priftanji 2001 (13)	UK	1,050	13-14	–	79%	1998-2001	Yes	5, 6, 7
Anderson 2004 (11)	UK	15,083/15,755	12-14	–	87%	1995/2002	Yes	3, 6
Austin 2005 (15)	UK	4,298	12-15	49.1%	89%	2002	Yes	3, 6
Shamssain 2007 (14)	UK UK	6,000 4,038	6-7 / 13-14 6-7 / 13-14	48.5/50.3% 49.8/45.6%	80-90% 90-92%	1995-1996 2001-2002	Yes Yes	6 7
Ven 2006 (17)	NL	9,713	12-14	48.8%	91.2%	2003	No	None

* 1) Recruitment at schools; 2) All schools, or randomly selected; 3) Age groups 6-7 / 13-14 years; 4) Use of validated questionnaires; 5) questionnaires completed by parents (< 12 year olds) or by adolescents themselves (≥ 12 year olds); 6) Participation >90%; 7) N ≥3000

Atopic eczema

The annual and lifetime prevalences of the atopic disorders varied widely between the studies and the populations involved. The annual prevalence (Table 3) of atopic eczema ranged from 1.8%-9.5% in general practice and from 11.4%-24.2% in the open population, whereas the lifetime prevalences (Table 4) ranged from 7.2%-36.5% in general practice and from 16.5%-27.1% in the open population.

Asthma

In general practice, the annual prevalence (Table 3) of asthma ranged from 3.0%-6.5%, whereas in the open population it was as high as 12.3%-34.2%. The lifetime prevalence (Table 4) of asthma in general practice was 4.2%-22.9% compared with 19.1%-35.6% in the open population.

Allergic rhinitis

In general practice the annual prevalence (Table 3) of allergic rhinitis ranged from 0.4%-4.1% compared with 15.1%-37.8% in the open population; the lifetime

Table 3. Studies presenting annual prevalence

Study	Source	Country	No. included	Time period	Age group (years)	Eczema	Asthma	Allergic rhinitis
Wijga et al. 2011	General Practice	NL	79,272	2001	0-9	5.5%	5.3%	0.4%
					10-17	1.8%	3.0%	0.4%
Ven et al. 2006	Open Population	NL	9,713	2003	12-14	13.5%	12.3%	28.3%
Simpson et al. 2002	General Practice	UK	252,538*	1999	0-4 5-9 10-14	9.5%† 4.5%† 3.4%†	4.3%† 6.5%† 6.2%†	0.7%† 2.3%† 4.1%†
Austin et al. 1999	Open Population	UK	27,507	1995	12-14	16.4%	33.3%	18.2%
Jeffs 2000	Open Population	UK	3,772	1995-1996	12-14	22.7%	34.2%	37.8%
Anderson et al. 2004	Open Population	UK	15,083	1995	12-14	16.2%	33.9%	18.4%
Anderson et al. 2004	Open Population	UK	15,755	2002	12-14	11.4%	27.5%	15.1%
Austin 2005	Open Population	UK	4,298	2002	12-15	12.0%	27.8%	15.3%
Shamssain et al. 2007	Open Population	UK	3,000 3,000	1995-1996	6-7 13-14	15.8% 17.0%	18.1% 19.9%	20.6% 29.6%
Shamssain et al. 2007	Open Population	UK	1,843 2,195	2001-2002	6-7 13-14	24.2% 19.0%	25.4% 22.2%	15.8% 32.2%

* Total study population

† Prevalences calculated based on the assumption of male/female ratio = 1.04:1.00

Table 4. U.K. studies, lifetime prevalence

Study	Source	No. included	Time period	Age group (years)	Eczema	Asthma	Allergic rhinitis
Blair 1974	General Practice	1,907	1970-1973	0-10	7.2%	6.3%	4.8%
Mortimer 1993	General Practice	1,077	< 1993	3-11	20.2%	19.6%	7.6%
Simpson 2008	General Practice	126,348 366,063	2001	0-4 5-14	13.0%* 13.0%*	6.3% 15.7%	1.0%* 4.5%*
Simpson 2008	General Practice	125,020 361,784	2005	0-4 5-14	18.0%* 19.0%*	4.2% 15.7%	1.4%* 6.7%*
Punekar 2009	General Practice	24,112	2008	0-18	36.5%	22.9%	11.4%
Austin 1999	Open Population	27,507	1995	12-14	22.5%	20.9%	34.9%
Jeffs 2000	Open Population	3,772	1995-1996	12-14	25.6%	19.1%	47.7%
Priftanji 2001	Open Population	1,050	1998-2001	13-14	27.1%	20.2%	19.5%
Anderson 2004	Open Population	15,083	1995	12-14	21.1%	20.6%	34.8%
Anderson 2004	Open Population	15,755	2002	12-14	24.3%	25.9%	37.4%
Austin 2005	Open Population	4,298	2002	12-15	25.0%	24.5%	34.1%
Shamssain 2007	Open Population	3,000 3,000	1995-1996	6-7 13-14	18.3% 17.2%	29.3% 31.6%	22.6% 33.7%
Shamssain 2007	Open Population	1,843 2,195	2001-2002	6-7 13-14	21.8% 16.5%	35.6% 30.5%	18.3% 25.6%

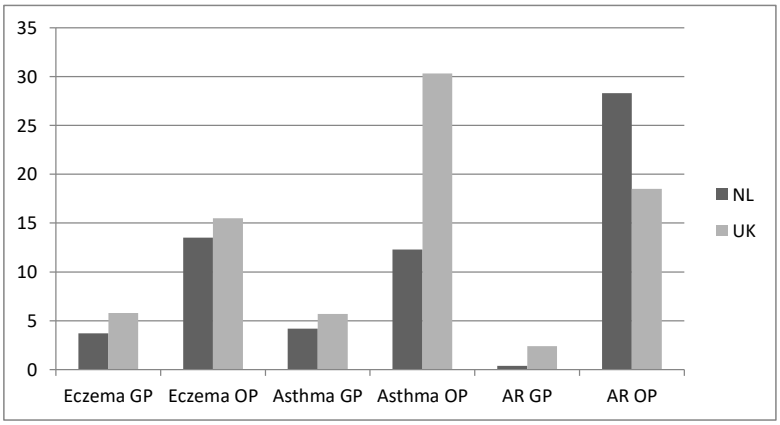
* Estimation based on graph

prevalence (Table 4) ranged from 1.0%-11.4% in general practice and from 18.3%-47.7% in the open population.

Differences between the Netherlands and the UK

In both the Netherlands and the UK, similar differences exist between the prevalences of the atopic disorders in the open population and the general practice population (Fig. 1). In general practice the annual prevalence of atopic eczema and asthma are very similar. There is a large difference in the prevalence of diagnosed allergic rhinitis: in the UK this diagnosis is registered more frequently (0.4% vs 2.4%). On the other hand, in the open population there is a higher prevalence of allergic rhinitis in the Netherlands (28.3%) compared to that of the UK (19.3%). Finally, a substantial difference exists between the two countries in the annual prevalence of asthma in the open population (12.3% vs 30.3%). Unfortunately, the data were not sufficient to allow comparisons at the regional level.

Figure 1. Annual prevalence in % (weighted mean): General Practice (GP) vs Open Population (OP) in UK (United Kingdom) and NL (The Netherlands). (AR = allergic rhinitis)



Discussion

On average, the prevalence of all three atopic disorders was substantially higher in the open population compared to general practice. For example, the annual prevalence of asthma ranged from 3.0%-6.5% in general practice compared to 12.3%-34.2% in the open population. At least a twofold difference. In both the Netherlands and the UK similar differences were found between the open population and the general practice population. Allergic rhinitis was an exception and was diagnosed more frequently in the UK by GPs (0.4% vs 2.4%) whereas a higher prevalence was found in the Netherlands in the open population (28,3% vs 19.3%). Our results implicate that data obtained in the open population cannot simply be extrapolated to the general practice setting. This should be taken into account when considering a research topic or requirements for policy development. General practitioners should be aware of possible underdiagnosis of allergic disorders in their practice. However, overestimation can also occur due to misclassification of the disorder by a GP (18, 19).

No articles were excluded in this review based on language restrictions. All articles were independently examined by two reviewers, all references of the included studies were also checked and all data extraction was done by two independent researchers.

The search strategy for the open population focused exclusively on the ISAAC database, with three related limitations. First, although the ISAAC study has yielded

many international publications, restricting our review to official ISAAC studies carries the risk of missing other relevant studies using different, but also validated, methodologies. A recently published meta-analysis based on both official and non-official ISAAC questionnaires showed annual prevalences for atopic eczema, asthma and allergic rhinitis of 7.9%, 12.0% and 12.7%, respectively (2). These prevalences are lower than the average annual prevalences that were observed in this review. It suggests the possibility of an higher estimation of the prevalence of atopic disorders when only ISAAC studies are included. However, using one methodology allowed us to make safer comparisons, especially because ISAAC's methodology is known to be solid. The second limitation is the ISAAC database itself, which we discovered is not 100% comprehensive. The third limitation is the cross-sectional design of ISAAC and of the studies in general practice. Okkes et al. studied the differences between general practice registration projects and a health survey (20). They considered an observation period of one year to be a source of problems; using data collected over a longer period of time showed more accuracy (20).

Since the definition of atopic disorders has changed over time, one could argue that the conclusions reached in this article do not take these changes into consideration. However, this argument does not hold for ISAAC, since ISAAC uses the same definition to define atopic disorders since its beginning in 1991. For studies conducted in general practice, this might be different, but cannot explain the remarkable difference between the two settings.

Finally, we included only two countries. We focused on general practice and not every country has a GP in its healthcare system. The use of other sources of primary care data is subject to more selection bias and was therefore avoided.

Existing literature provides various explanations for the wide variability found between the two settings. First, the worldwide prevalence of the three disorders have changed over time (3). The studies in this review were conducted between 1970 and 2008 and the reported prevalence might in part, reflect this worldwide time trend. Another explanation for changing prevalences over time are a change in definitions of atopic disorders over time. Van Wonderen et al. found 60 different operational definitions used in the literature on asthma (21). Applied in a single cohort, there was a substantial variation in estimated prevalences depending on the operational definition used. To deal with the remarkable amount of different definitions in atopic disorders worldwide, expert teams were given the task of finding consensus. For example, in 2006 a consensus regarding the diagnosis and treatment of atopic dermatitis was developed for this reason (22). Furthermore, for the lifetime prevalence, the age groups differed between the studies, resulting in different prevalences. Finally, not all GPs may be fully aware of what their patients actually experience regarding allergic symptoms (23) which might lead to misclassification

of allergic and therefor atopic diagnoses. Especially allergic rhinitis might be underestimated, since anti-allergic medication (antihistamines) is freely available over-the-counter thereby limiting the necessity for patients to visit their GP for related symptoms.

Data from both sources have both advantages and disadvantages as proven by existing literature. Data obtained from general practice databases can be considered specific, but not very sensitive. This lack of sensitivity might be the result of underdiagnosis or misclassification (19). This risk is particularly true for asthma. Spirometry under the age of six years is not considered reliable, resulting in a probability or clinical diagnosis. In other cases, spirometry is often underused or the technique is poor (19). Misclassification can also be the result of the differences of 'conceptual vocabulary' between parents and clinicians (24). On the other hand, a prevalence based on self-administered questionnaires will result in more sensitive data, but will be less specific. Questionnaires are often used in population studies mainly for epidemiological purposes. Although ISAAC put considerable effort into the validation of their questionnaires (25-28), external influences cannot be totally ruled out. The accuracy of data obtained from a questionnaire always depends on various influences, including the accuracy and knowledge of the responders and the definitions used. ISAAC uses dichotomous (Yes/No) definitions. There is evidence that suggests that using continuous (graded) definitions would result in better statistical power and will provide relevant additional information (29). Also the terminology used in a questionnaire influences the results. Wheeze for example is the cornerstone of asthma diagnosis. However, conceptual understandings of 'wheeze' differs between physicians, researchers and parents of children with reported wheeze. This difference will influence reported prevalences in the open population (using questionnaires) and clinical practice (using a physician interpretation of wheeze) (24). Dotterud et al. (30) considered questionnaires on atopic conditions a useful epidemiological tool for obtaining rough estimates of the prevalence of atopic disorders. They conclude that atopic eczema was generally underestimated and allergic rhinitis overestimated when using questionnaires in the open population (30); the present study seems to confirm their findings.

Furthermore, different prediction scores have been developed based on data from the open population and from general practice. For example, the PIAMA Risk Score, based on the open population, helps to predict which child with suggestive symptoms for asthma could develop asthma at school age (31), whereas the CAPS prediction score was developed in a primary care setting (32). Both models differ substantially with regard to the factors they take into account; this difference might be explained by the different reported prevalences. When using prediction scores, it is important to be aware of the setting in which they were developed and validated.

The prevalences of the three atopic disorders were on average higher in the open population compared with general practice. However, the degree of difference varied depending on the specific disorder. Policymakers should be aware that survey based data, obtained in the open population, cannot simply be extrapolated to the general practice setting.

GPs should consider to critically reevaluate the already diagnosed atopic disorders in a patient's medical record to reduce the risk of misclassification. The present data may also serve to prompt GPs to be more aware of possibly underdiagnosed atopic conditions in children. For example, a relatively large percentage of children in the open population reported symptoms of allergic rhinitis; confirming the results of Dotterud et al. based on survey data (30). The low prevalences found in general practice do not reflect this. Knowing that poorly regulated allergic rhinitis can have an influence on asthma regulation (33), our data emphasizes the importance of actively asking about allergic rhinitis symptoms in children with asthma. GPs should consider different atopic disorders when a child is already diagnosed with one, since the atopic disorders are closely related (2).

Future research could benefit from longitudinal research with standardizing diagnostic definitions and by standardized reporting (e.g. reporting lifetime prevalence's at standardized ages). Diagnosing an atopic disorder in general practice can be difficult, even if a clear definition is used. GPs often work with probability diagnosis and have to label their consultations with a standardized code like the International Classification of Primary Care (ICPC). ICPC is accepted by the WHO for labeling primary care encounters (34). Using ICPC codes in epidemiological studies implies a risk of dealing with misclassification, since some of the diagnosis should be regarded as 'probability diagnosis' and not as 'true diagnosis'. When analyzing electronic medical records from a GP with the use of ICPC codes; duration of follow-up, number of consultations and number of relevant prescriptions for that specific ICPC code should be taken into account. In this way, ICPC codes could be corrected, reducing the risk of misclassification. Regarding allergic rhinitis there is also another problem. GP registrations could show an underestimation of the number of children with allergic rhinitis due to the availability of 'over the counter' (OTC) drugs for this disorder. This may explain the higher observed prevalences for allergic rhinitis in the open population.

Conclusions

In conclusion, significant differences exist between the self-reported prevalence of atopic disorders in the open population compared with physician diagnosed prevalence of atopic disorders in general practice. Data obtained in the open

population cannot simply be extrapolated to general practice setting. GPs should be aware of possible misclassification of allergic disorders in their practice. Some suggestions how to limit this risk of misclassification in epidemiological research are given.

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Appendix 1

Search strategy:

For Embase

(asthma/exp OR wheezing/de OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) AND (eczema/de OR 'atopic dermatitis'/de OR (eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) AND (rhinitis/exp OR conjunctivitis/exp OR (rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti) AND (Epidemiology/exp OR 'epidemiological data'/exp OR epidemiology:lnk OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

For Medline via OvidSP

(exp asthma/ OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper ADJ (responsiv* OR sensitiv*))).ab,ti.) AND (exp Dermatitis, Atopic/ OR exp Eczema/ OR Eczem*.ab,ti. OR (atopic ADJ3 dermatit*).ab,ti.) AND (exp Rhinitis/ OR exp Conjunctivitis/ OR (rhinit* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen ADJ3 Allerg*) OR Pollinos* OR hayfever* OR hay fever*).ab,ti.) AND (exp Epidemiologic Studies/ OR exp Epidemiologic Factors/ OR epidemiology.xs. OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case ADJ3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR odds ratio* OR etiol* OR aetiol* OR natural histor* OR predict* OR prognos* OR outcome* OR course*).ab,ti.) AND (exp child/ OR exp infant/ OR (infan* OR newborn* OR new born* OR baby OR babies OR neonat* OR perinat* OR postnat* OR child* OR kid? OR toddler* OR teen* OR boy? OR girl? OR minor? OR underag* OR (under ADJ2 ag?) OR juvenil* OR youth? OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatric* OR

peadiatric* OR school* OR preschool* OR highschool* OR suckling*).ab,ti. OR ((adoles*.ab,ti. OR adolescent/) NOT exp adult/))

For Cochrane

((asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) AND ((eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) AND ((rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti) AND ((prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

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(asthma[mh] OR (asthma*[tiab] OR wheez*[tiab] OR hyperresponsiv*[tiab] OR hypersensit*[tiab] OR hyper responsiv*[tiab] OR hyper sensitiv*[tiab])) AND (Dermatitis, Atopic[mh] OR Eczema[mh] OR Eczem*[tiab] OR (atopic AND dermatit*[tiab])) AND (Rhinitis[mh] OR Conjunctivitis[mh] OR (rhinit*[tiab] OR rhinoconjunctivit*[tiab] OR conjunctivit*[tiab] OR (Pollen AND Allerg*[tiab]) OR Pollinos*[tiab] OR hayfever*[tiab] OR hay fever*[tiab])) AND (Epidemiologic Studies[mh] OR Epidemiologic Factors[mh] OR epidemiology[sh] OR (prevalenc*[tiab] OR inciden*[tiab] OR trend*[tiab] OR associat*[tiab] OR comorbid*[tiab] OR relat*[tiab] OR correlat*[tiab] OR (case AND (control*[tiab] OR comparison OR referent)) OR epidemiolog*[tiab] OR cohort*[tiab] OR risk*[tiab] OR caus*[tiab] OR odds ratio*[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR natural histor*[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome*[tiab] OR course*[tiab])) AND (child[mh] OR infant[mh] OR (infan*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby OR babies OR neonat*[tiab] OR perinat*[tiab] OR postnat*[tiab] OR child*[tiab] OR kid* OR toddler*[tiab] OR teen*[tiab] OR boy* OR girl* OR minor* OR underag*[tiab] OR under ag* OR juvenil*[tiab] OR youth* OR kindergar*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepuberty*[tiab] OR pediatric*[tiab] OR peadiatric*[tiab] OR school*[tiab] OR preschool*[tiab] OR highschool*[tiab] OR suckling*[tiab]) OR ((adoles*[tiab] OR adolescent[mh]) NOT adult[mh])) AND publisher[sb]

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Chapter 5

Reliably estimating prevalences of atopic children: an epidemiological study in an extensive and representative primary care database

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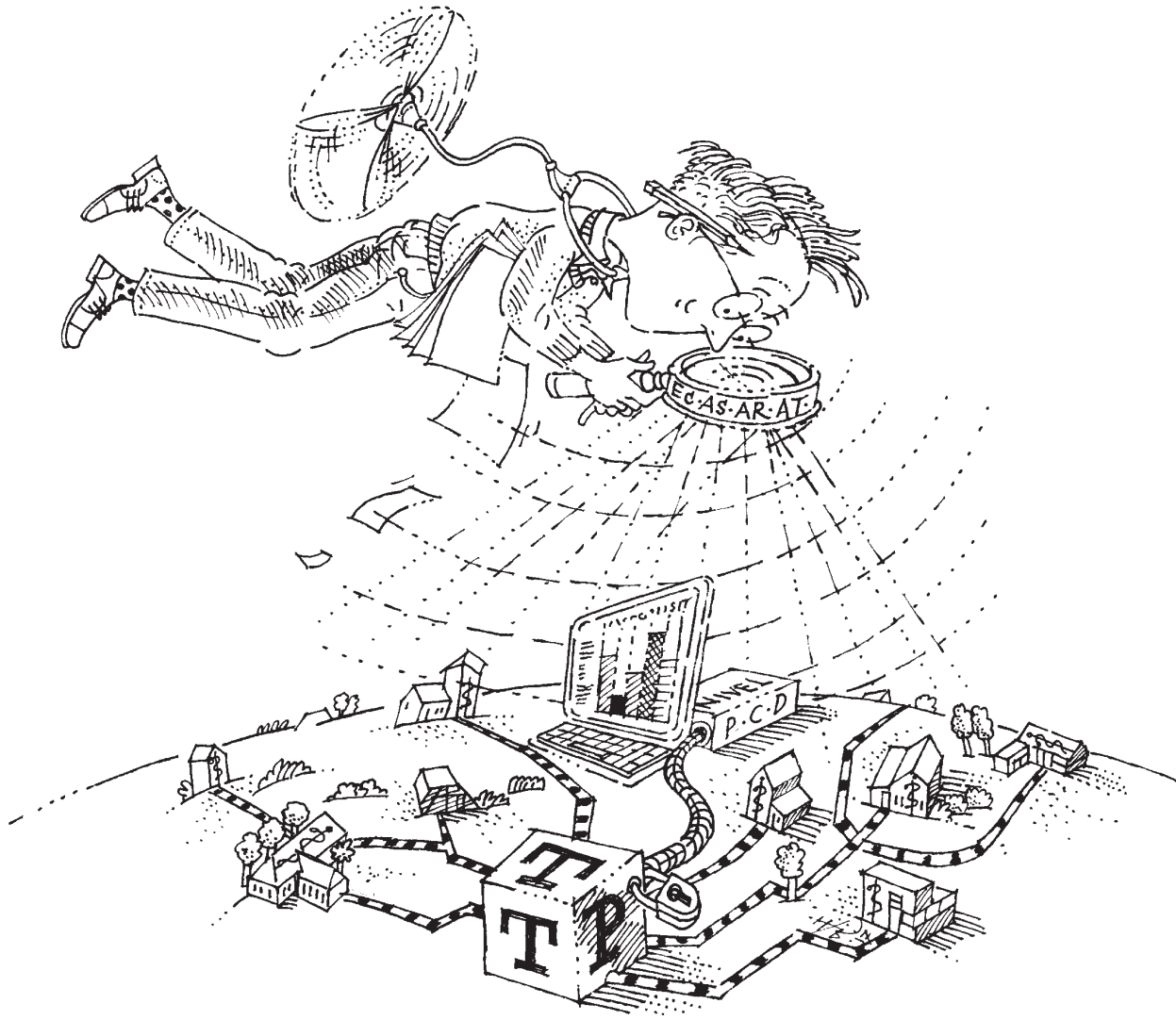


Abstract

Purpose: Electronic health records (EHRs) stored in primary care databases might be a valuable source to study the epidemiology of atopic disorders and their impact on healthcare systems and costs. However, the prevalence of atopic disorders in such databases varies considerably and needs to be addressed.

Method: For this study, all children aged 0-18 years listed in a representative Primary Care Database in the period 2002-2014, with sufficient data quality, were selected. The effects of four different strategies on the prevalences of atopic disorders were examined: 1) the first strategy examined the diagnosis as recorded in the EHRs, whereas the 2) second used additional requirements (i.e. the patient had at least two relevant consultations and at least two relevant prescriptions). Strategies 3) and 4) assumed the atopic disorders to be chronic based on strategy 1 and 2 respectively.

Results: When interested in cases with a higher probability of a clinically relevant disorder, strategy 2 yields a realistic estimation of the prevalence of atopic disorders derived from primary care data. Using this strategy, of the 478,076 included children, 28,946 (6.1%) had atopic eczema, 29,182 (6.1%) had asthma, and 28,064 (5.9%) had allergic rhinitis; only 1,251 (0.3%) children had all three atopic disorders.

Conclusions: Prevalence rates are highly dependent on the clinical atopic definitions used. The strategy using cases with a higher probability of clinically relevant cases, yields realistic prevalences to establish the impact of atopic disorders on health-care systems. However, studies are needed to solve the problem of identifying atopic disorders that are missed or misclassified.

Background

The rising prevalence of atopic disorders in children are an important global health problem (1, 2). Atopy is a (genetic) predisposition toward developing allergic hypersensitivity. The clinical manifestation of atopy is allergy. However, not all allergies are atopic. In this study the word 'atopic' refers to this genetically mediated predisposition, resulting in the clinical diagnosis by a GP of atopic eczema, asthma and allergic rhinitis. In many countries, primary care professionals, e.g., family doctors/general practitioners (GPs), diagnose and treat these atopic children. In the Netherlands, GPs, are in the frontline of the health care system, are freely accessible, and use uniform coding systems for recording diagnosis and prescriptions. In principle, all non-institutionalized residents in the Netherlands are registered in a general practice, even if they do not visit the GP. Therefore, the electronic health records (EHR) stored in primary care databases contain valid information about the epidemiological denominator, making it a potentially important source of epidemiological data.

A meta-analysis based on questionnaires in the 'open population', including children of all ages (0-18 years), showed average one-year worldwide prevalences for atopic eczema, asthma and rhinoconjunctivitis of 7.9%, 12.0% and 12.7%, respectively (3). However, the accuracy of data obtained from a questionnaire depends on various items, including the accuracy and knowledge of the responders, and the definitions used by the researcher (4). When comparing 'open population' data with data obtained from the EHRs of general practices, lower annual prevalences for atopic eczema, asthma and rhinoconjunctivitis were found, ranging (on average) from 1.8-9.5%, 3.0-6.5% and 0.4-4.1%, respectively (5). Since these diagnoses are based on the assessment of a physician, these data could potentially form a more specific epidemiological source. Unfortunately, the annual prevalences of atopic disorders in general practice databases vary considerably (5); moreover, since these differences cannot be fully explained by country or year of study, this variation needs further consideration. Part of this variation might be explained by the fact that GPs often work with a 'probability diagnosis' which inevitably creates a risk of misclassification, which could result in either over- or underestimation. Other possible explanations could be a variation in clinical knowledge and skills of the GP. Furthermore, there might also be some coding difficulties, when coding diseases in electronic health records.

Some studies using primary care data have presented life-time cumulative prevalences (6-9); the prevalences found for atopic eczema, asthma and rhinoconjunctivitis ranged (on average) from 7.2-36.5%, 4.2-22.9% and from 1.0-11.4%, respectively. However, the question arises as to what extent these *life-time*

cumulative prevalences provide relevant information compared with *annual* point prevalences, knowing that these disorders are not always chronic.
To establish the impact of atopic disorders on healthcare systems and their related costs, a more accurate estimation is required of the prevalence of atopic disorders derived from general practice databases. This study investigates the risk of misclassification which could either result in overestimation or underestimation of atopic disorders. The results for annual point prevalence versus life-time cumulative prevalence were compared using four different strategies using an extensive and representative primary care database.

Method

Study population

The Netherlands Institute for Health Services Research-Primary Care Database (NIVEL-PCD) is based on routinely recorded data in EHRs of all listed patients in the participating practices. In 2014, about 500 general practices participated, including data of about 1,700,000 patients (www.nivel.nl/en/dossier/nivel-primary-care-database). EHR data include a variety of information regarding type of consultation, morbidity, and prescriptions. Data were available from 2002–2014 and are representative for the Dutch population (10). Primary care physicians recorded morbidity using the International Classification of Primary Care (ICPC-1). The ICPC is a classification method for primary care encounters and is accepted by the WHO (11). Dutch GPs cluster relevant consultations, prescriptions and referrals in ICPC classified episodes of care.
For the present study, we only used morbidity data from the EHRs of general practices with sufficient data quality, fulfilling the following criteria: at least 500 listed patients (standard practice: 2,350 patients), complete morbidity registration (defined as ≥ 46 weeks/year), and sufficient ICPC coding of diagnostic information (defined as ≥ 70% of the recorded disease episodes labeled with an ICPC code).

Selection of atopic children

From the general practices in NIVEL-PCD, all listed children (aged 0-18 years) with sufficient data (in the period 2002-2014) were selected. For each child, a minimum follow-up of 3 years was required to reduce the risk of registration bias. According to NIVEL, Dutch GPs see about 77% of their patients at least once a year (12); therefore, a 3-year follow-up allows the GP sufficient time to diagnose a child with atopic disorders. Follow-up ends when a child would change to a GP that is not

working in a NIVEL-PCD clinic, or when the child would have died. For these children the following descriptive data were routinely collected: period in which the individual child was registered in the clinic, unique code of the GP practice, sex, and year and quarter of birth. For all these children ICPC-coded episodes regarding atopic eczema (S87), asthma (R96) and allergic rhinitis (R97) were extracted when applicable with their starting and closing dates.

Episode (re)construction

At each new encounter in general practice, a Dutch GP starts a new episode of care. If the patient returns to the GP for the same disorder, or when the patient orders (repeat) medication relevant to that disorder, it should be recorded as a follow-up contact within that specific episode of care.
In the present study, four different strategies were examined with the aim to obtain a better understanding of prevalence estimates based on primary care data: two strategies are related to the beginning of an episode of care and the other two are related to the ending of an episode of care. Table 1 presents a summary of the strategies.
Concerning the start of an episode, either the episodes of care were used as recorded in the database and one accepts the risk of *overestimation* due to working with 'probability diagnoses', or these episodes of care were corrected by applying selection criteria, focusing on cases with higher probability of a clinical relevant disorder (see below). With respect to the ending of an episode of care, two identical strategies were applied. Either the episodes of care were used as recorded or these episodes of care were corrected by extending the closing date, assuming that atopic disorders were chronic.

Table 1. Summary of the four strategies examined.

Strategy 1	Presents the prevalence based on the recorded episodes of care.
Strategy 2	Presents the prevalence based on corrected episodes of care (by applying selection criteria: at least two relevant consultations and at least two relevant prescriptions)
Strategy 3	Presents the prevalence based on the recorded episodes of care, but the disorders are considered to be chronic.
Strategy 4	Presents the prevalence based on corrected episodes of care (by applying selection criteria from strategy 2), but the disorders are considered to be chronic.

Start of an episode of care

Strategy 1 uses the episode of care as recorded in the EHRs of the GP and accepts a risk of overestimation. In the second strategy (strategy 2), correcting for a possible

overestimation, different selection criteria were taken into consideration based on our previous review (5). Using these criteria, ICPC codes and their related episodes of care can be corrected, reducing the risk of misclassification and selecting cases with a higher probability of a clinical relevant disorder. For example, if a GP suspects that a child has asthma and labels the encounter accordingly with R96, this can later be corrected as not having asthma if this child never visits the GP again for this problem or never receives the appropriate medication. In practice this implies the following requirements: at least two episode-related contacts (either consultations, home visits, telephone calls, or prescriptions) and a minimum of two relevant prescriptions had to be prescribed. The Anatomical Therapeutic Chemical (ATC) Classification System was used to identify relevant prescriptions. For atopic eczema the ATC code D07 (dermatological corticosteroids) was used, for asthma the ATC code R03 (drugs for obstructive airway diseases) was used, and for allergic rhinitis the ATC codes R01AC (nasal preparation of antiallergic agents, excl. corticosteroids), R01AD (nasal preparation of corticosteroids) and R06 (antihistamines for systemic use) were used. These medication proxies have been tested by Mulder et al. (13). Since some EHRs do not routinely link relevant prescriptions in the correct episodes, all recorded prescriptions in the EHRs were studied. When a patient could not meet the criteria of having at least two contacts and two relevant prescriptions, the patient is considered to be a child in the 'population at risk'.

Closure of an episode of care

In the present study, two strategies (3 and 4) considered the atopic disorders to be chronic for research purposes. Since data is available for all patients in our database regarding the first date on which a diagnosis was made (each child could be incident only once in its life), it is possible to determine the number of children diagnosed at each year and for each age. When adding these annual numbers for the consecutive years of interest, one in fact calculates a cumulative incidence. Since no data is missing regarding the first date of the disorder, this cumulative incidence will approximate a cumulative life-time prevalence. Strategy 3 shows the cumulative incidences based on strategy 1, and in strategy 4 it is based on strategy 2.

Atopic triad

Finally, 'atopic triad' episodes were created for research purposes, based on a suggestion reported in a meta-analysis (3). Such an episode was only created when a child was diagnosed with all three atopic disorders. The first date when a child was diagnosed with at least one of the disorder, is considered the starting date of the 'atopic triad' episode. The closing date of the episode is equal to the last contact date recorded for one of the atopic disorders.

Statistical analyses

Annual point prevalence rates were calculated as percentages on the first of January for each age (0-18 years). The denominators for the calculations were also determined on this date. Cumulative life-time prevalences, based on the assumption that the disorder is chronic, are based on the cumulative incidences (strategy 3 and 4). This cumulative incidence equals a life time prevalence, since the complete medical history of a patient is available in the EHRs. To calculate the interrelationships between the atopic disorders, for every child's EHR with sufficient data quality and at least 3 years of follow-up, it was determined whether he/she had one or more atopic disorders or not, in the period from 2002-2014. All calculations were conducted in Stata 13 and Excel 2010.

Ethical approval

Dutch law allows the use of anonymous EHR data for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458). Therefore, no waiver of ethical approval was obtained from an Institutional Review Board (IRB) or ethics committee. The authors did not have access to identifying information at any moment during the analysis of the data.

Results

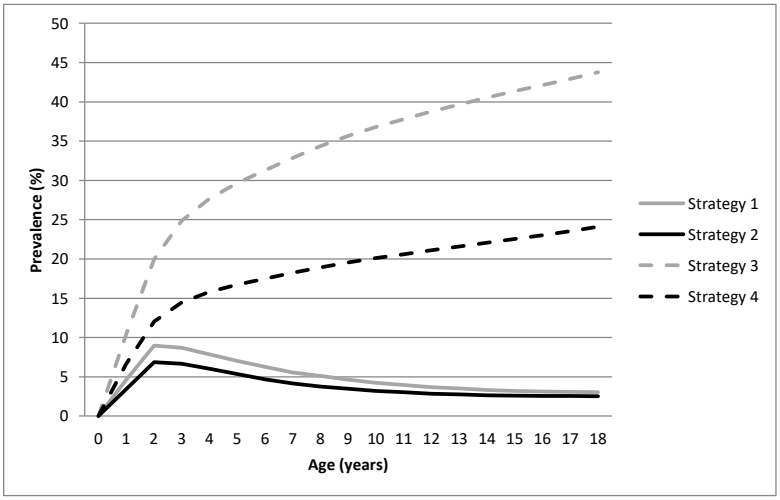
Patient selection

A total of 660,512 eligible children (aged 0-18 years) were derived from the NIVEL-PCD (period 2002-2014). Of these, 24,477 (3.7%) children did not pass the data quality checks (Appendix 1) and 157,959 (23.9%) children were excluded because they had less than 3 years of follow-up. The final study group included 478,076 children, of whom 51.1% were male. Mean age of the children when entering the NIVEL-PCD was 7.2 (SD 6.0) years: mean follow-up time was 6.6 (SD 4.7) years.

Prevalence of atopic eczema (Fig. 1)

According to strategy 1 and 2, the point prevalence rises to a maximum at age 2 years of 9.0% and 6.9%, respectively. At age 18 years this prevalence drops to 3.0% and 2.5%, respectively. However, if the disorder is considered to be chronic for research purposes, based on strategy 3 and 4 the lifetime cumulative incidences at age 18 years ranges from 24.0-43.8%.

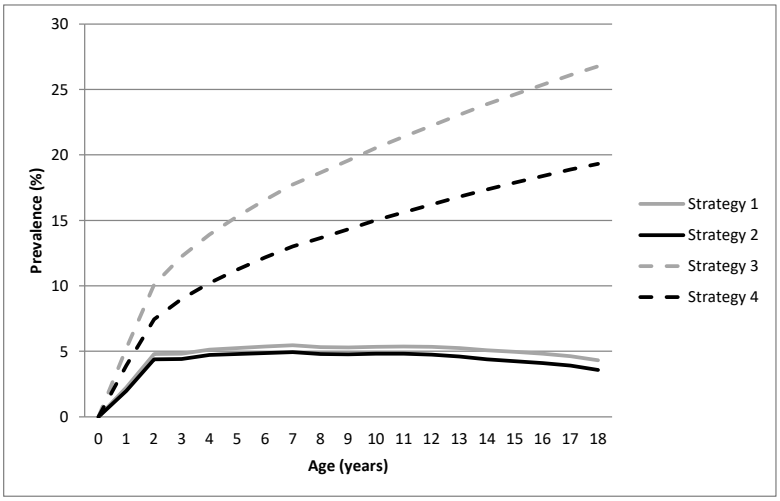
Figure 1. Prevalence by age for atopic eczema



Prevalence of asthma (Fig. 2)

The point prevalence of asthma shows a steep rise in the first two years of life with a maximum prevalence at age 7 years according to strategy 1 (5.5%) and strategy 2 (4.9%), and drops slightly at age 18 years to 4.3% and 3.6%, respectively. The (for research purposes) calculated lifetime cumulative incidences at age 18 year is 19.3-26.8%.

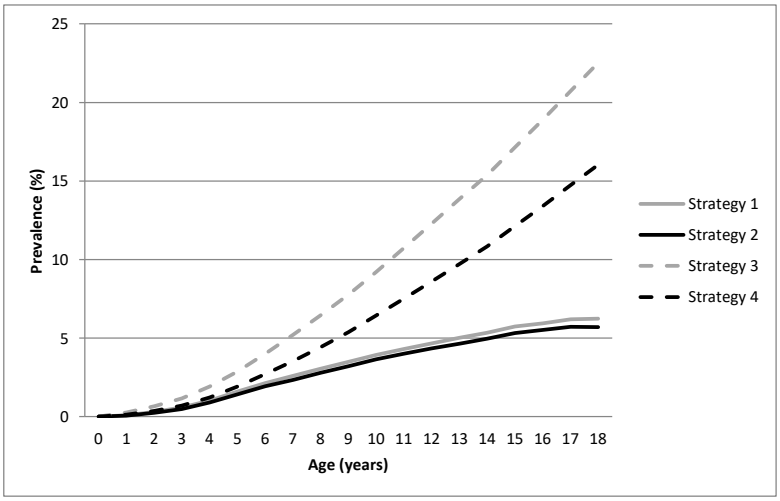
Figure 2. Prevalence by age for atopic asthma



Prevalence of allergic rhinitis (Fig. 3)

In contrast to atopic eczema and asthma, allergic rhinitis shows a relatively consistent rise in prevalence over the years. For strategy 1 and 2 the maximum prevalence at age 18 years is 6.2% and 5.7%, respectively. Assuming allergic rhinitis to be a chronic disorder for research purposes, the lifetime cumulative incidence also reaches its maximum at age 18 years, but is substantially higher, i.e. 16.0-22.5%.

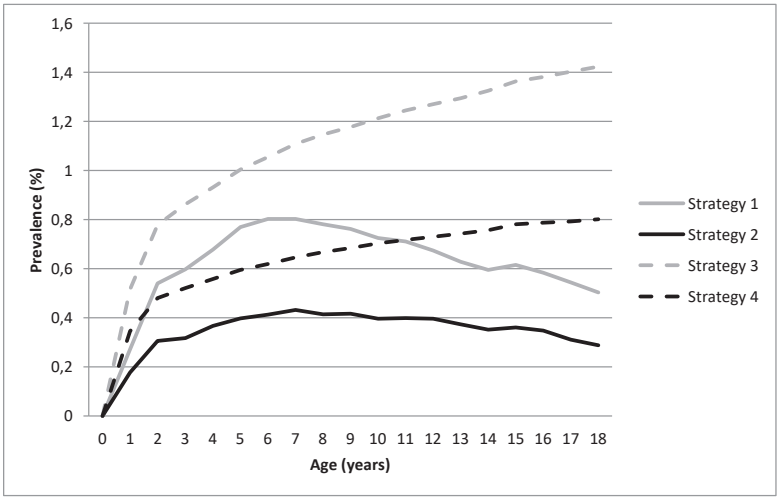
Figure 3. Prevalence by age for allergic rhinitis



Prevalence of atopic triad (Fig. 4)

The atopic triad is estimated for research purposes. Depending on the strategy used, the maximum prevalence for strategy 1 (0.8%) is reached at age 6 years and that for strategy 2 (0.4%) at 7 years. Both scenarios show a decrease resulting in a point prevalence at age 18 years of 0.5% and 0.3%, respectively. For all four strategies, a maximum prevalence of 1.4% is observed.

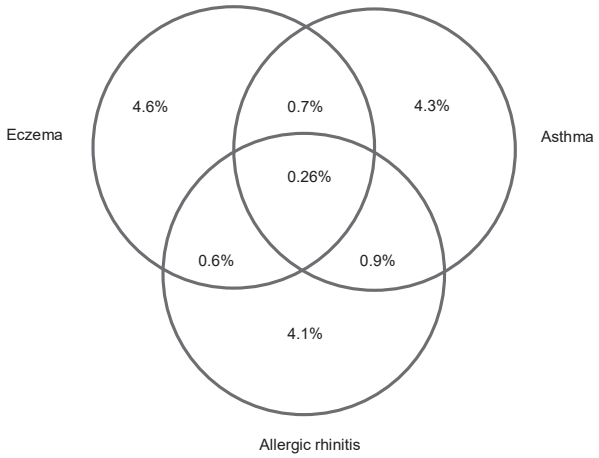
Figure 4. Prevalence by age for atopic triad



Interrelationship between the atopic disorders (Fig. 5)

Interrelationships between atopic disorders are well known. Of the 478,076 children, based on strategy 2 28,946 children (6.1%) had atopic eczema, 29,182 (6.1%) had asthma, and 28,064 (5.9%) had allergic rhinitis. Only 1,251 (0.26%) children had all three atopic disorders. This is a 12-fold higher prevalence than could be expected by chance (0.022%) based on the three prevalences of the individual atopic disorders.

Figure 5. Venn diagram of the overall prevalence (total population: 478,076 children)



In total 21,862 children had atopic eczema only, 20,382 children had asthma only, and 19,835 children had allergic rhinitis only and no other atopic comorbidity. Of all children with asthma, 19.2% also had allergic rhinitis.

Discussion

To retrieve more relevant data from primary care databases, four different strategies were explored. Based on the results of this study, strategy 2, which at least selects cases with potentially more clinically relevant disorders and does not assume that a child will have the disorder for life, seems preferable when interested in the current burden of atopic disorders. Of the 478,076 children finally included, after applying strategy 2, 6.1% had atopic eczema, 6.1% had asthma and 5.9% had allergic rhinitis; these annual point prevalences are in accordance with those found in a recent systematic review (5). Only 0.26% children had all three atopic disorders; this is a 12-fold higher prevalence than could be expected by chance based on the three individual prevalences of the atopic disorders (0.022%). This phenomenon was recently described in a meta-analysis (3) and supports the hypothesis that there could be a fourth distinct group of atopic children that have all three disorders, i.e. they may have their own unique characteristics.

Showing the data simply as recorded in the GP's database (strategy 1) will result in a risk of overestimation. A possible solution was offered in the literature by applying two selection criteria, i.e. at least two relevant consultations and at least two relevant prescriptions. When applying these criteria, the annual point prevalences only dropped slightly (as expected), but potentially show more clinically relevant cases. The results now more closely approach the annual point prevalences reported in the literature (5). However, ideally a gold standard is needed to identify atopic children. Such a gold standard could probably be the evidence of sensitisation by specific IgE (14). Checking specific IgE is now a requirement of assessment of the patient with asthma. When studying the observed differences between annual point prevalence and cumulative life-time prevalence, a greater understanding of the natural course of these atopic disorders is required. In Germany, Illy et al. studied the natural course of atopic dermatitis in a cohort of 1,314 children from the general population, until age 7 years (15). The prevalence increased to 21.5% at 2 years of age, but 43.2% were in complete remission by age 3 years. Regarding asthma, Jenkins et al. screened 7-year-olds for this condition (16). The study was repeated 25 years later in a random sample (n=750); a quarter of those who had asthma as a child, reported asthma in adulthood. According to Sears, about half to two-thirds of the children with asthma recover (17). An explanation for this observed recovery

could be that viral infections are the main cause of wheeze before the age of six rather than allergic asthma. This is supported by data from a different Dutch primary care study, which showed that for those children diagnosed with asthma between the age of 0-4 years, ≥ 60% were no longer known as such by the GP after two years, and after 10 years 80% no longer carried this diagnosis (18). When the same children were screened for asthma at a later age (10-23 years), 45% still had asthma (19). Finally, regarding allergic rhinitis, a prospective study on the course of hay fever in 738 individuals (with an average follow-up of 23 years) showed that in a majority of the adult patients the symptoms of hay fever reduce over the years (20). Another prospective study (n=257, mean follow-up to 8 years) on various forms of allergic rhinitis (confirmed by the presence of specific IgE to pollen, pets or dust mites), looked at the percentage of patients with complete remission of symptoms (21). This study found complete remission of symptoms in 12% of patients with pollen allergy, in 19% of patients with an allergy to pets, and in 38% of patients with house dust allergy. The third and fourth strategy assumed that a child would have the atopic disorder for life, resulting in cumulative life-time prevalences that are substantially higher than those reported in the literature (5). Based on all the available evidence, it seems incorrect to conclude that atopic disorders are by definition chronic and, therefore, we consider strategies 3 and 4 to be less reliable and are not recommended. Even though the underlying assumptions made for strategies 3 and 4 are not realistic, the differences found between strategy 2 and 4 nevertheless provide an estimation of the number of children that show complete reduction of symptoms. This results in remission rates of 84%, 68% and 43% at age 10 years and 90%, 81% and 64% at age 18 years for atopic eczema, asthma and allergic rhinitis, respectively.

For the present investigation we used an extensive and representative primary care database; the number of included cases gives this study substantial power. The potential for using primary care databases of routinely collected clinical data for epidemiology and health policy is therefore enormous. However, to use this potential, sound methodologies are needed to turn the huge amount of raw data into meaningful information. An easy to apply strategy is presented in this study to select potentially more clinical relevant cases.

Unfortunately, there is an important limitation. The present study is based on the assumption that the relevant ICPC codes are not missed. For example, a child that has ICPC code R03 (wheezing) and regularly uses inhalation corticosteroids probably has asthma. However, when the child is not coded correctly as having R96 (asthma), or is not coded at all, it will not be possible to identify this child as having asthma. To include this child as an asthmatic patient, a new or adjusted episode R96 needs to be created by the researcher. Although this is a complex problem, there are different

ways to deal with it. The most sensitive method is to study the complete EMR of the individual patient; unfortunately, this is very time consuming and raises privacy issues. Another option is to use computer software that analyses free text; however, the accuracy of this method is determined by the quality of the script used. A faster and probably more consistent way of identifying a child, is to use 'templates' that are based on a combination of routinely and standardized coded data from EHRs such as standardized measurements, ICPC-coded comorbidity, and ATC-coded prescriptions. According to a recent study (13) based on general practice data, children diagnosed with asthma can be reliably identified with a range of medication proxies (sensitivity 54% and PPV 84%). However, the use of prescription data for the identification of children diagnosed with atopic eczema and allergic rhinitis is more problematic; one reason for this is that (some) reliever medication is freely available over the counter. Comorbidity data could also be used as a source to identify misclassified children. However, although many studies have shown a relationship between different comorbidities and atopic disorders, to our knowledge no study has used comorbidity to identify atopic disorders.

Food allergies are also closely associated with atopic disorders. Unfortunately, in this study it was not possible to reliably analyze food allergies, since the ICPC-1 coding system does not have specific codes for food allergies.

The results of this study emphasize the importance of better coding. Further research is needed to create proxies based on standardized coded variables to identify atopic disorders in order to address the risk of underestimation. Some attempts have been made, such as AsthmaCritic (a decision-support system for asthma and chronic obstructive pulmonary disease) (22), which aims to generate patient-specific feedback based on routinely recorded data in EMRs. In order to address the risk of overestimation, future clinical guidelines should also include criteria that help physicians to identify atopic diagnoses which are no longer clinically relevant.

In the future, research using extensive databases will become more popular due to their increased availability. Epidemiological studies on atopic disorders are reaching the limit of what can be achieved through conventional hypothesis-driven research (23). This new era of 'big data' allows smarter and more powerful statistical analysis, especially when analyzing metadata. Future collaborative analysis could also facilitate interdisciplinary dialogue between clinicians and scientists.

Conclusions

In conclusion, research using extensive databases will become more popular due to their increased availability; we are now in the era of 'big data'. Future collaborative

(meta)analysis on the valid use of routinely recorded clinical data from big databases is needed in order to be able to develop valid search strategies to identify atopic children. This study contributes to a better understanding of the use of primary care data. Based on the results of this study, strategy 2, which at least corrects for the risk of overestimation due to misclassification and does not assume that a child will have the disorder for life, seems preferable and can easily be applied. The limitations of primary care data that result in underestimation are more challenging, since some patients are also able to self-manage their disorder. Studies are required to create proxies based on routinely recorded and standardized clinical coded data that can help identify atopic disorders that are missed or misclassified.

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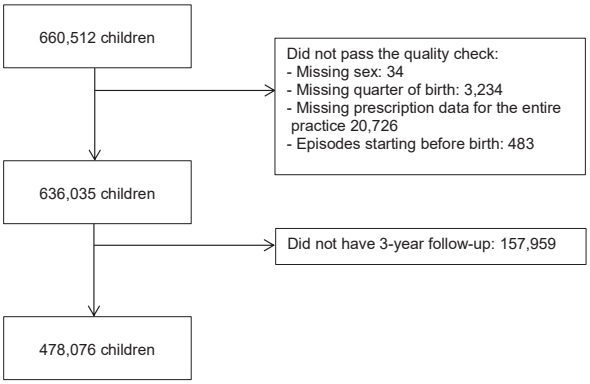
Appendix 1.

Flowchart showing inclusion of the study population



Chapter 6

Risks for comorbidity in atopic children: an epidemiological study in general practice

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Abstract

Purpose: This study aimed to investigate both atopic and non-atopic comorbid symptoms and diseases in children with physician-diagnosed atopic disorders (atopic eczema, asthma and allergic rhinitis).

Method: All children aged 0-18 years listed in a nationwide primary care database (NIVEL-PCD) with routinely collected health care data in 2014 were selected. Atopic children were matched on age and gender with non-atopic controls within the same general practice. A total of 404 ICPC codes were examined. Logistic regression analyses were performed to examine the associations between the presence of atopic disorders and (non-)atopic symptoms and diseases by calculating odds ratios (OR).

Results: Having one of the atopic disorder significantly increased the risk of having other atopic-related symptoms, even if the child was not registered as having the related atopic disorder. Regarding non-atopic comorbidity, children with atopic eczema (n=15,530) were at significantly increased risk for (infectious) skin diseases (OR: 1.2-3.4). Airway symptoms or (infectious) diseases (OR: 2.1-10.3) were observed significantly more frequently in children with asthma (n=7,887). Children with allergic rhinitis (n=6,835) had a significantly distinctive risk of ear-nose-throat related symptoms and diseases (OR: 1.5-3.9). Neither age nor gender explained these increased risks.

Conclusions: General practitioners are not always fully aware of relevant atopic and non-atopic comorbidity. In children known to have at least one atopic disorder, specific attention is required to avoid possible insufficient treatment and unnecessary loss of quality of life.

Background

Atopic disorders represent an important health problem in general practice. Acute upper airway infections, middle ear infections, warts, asthma, and atopic eczema represent the five most prevalent pediatric diseases diagnosed in general practice (1); allergic rhinitis is on the 12th place in this list. However, limited data are available on the co-morbidities of atopic children in primary care. In the present study we refer to atopy as one or more of the following established diagnosis: atopic eczema, asthma and/or allergic rhinitis.

Associations have been shown between atopic disorders and other diseases in children, but in different clinical settings (e.g. birth cohorts, hospitals, or pediatric clinics). Demonstrated interrelations exist with (among others) diabetes (2-4), ADHD (5-7), autism (8-10), and obesity (11-13). According to other studies, the presence of some comorbidities may even influence the course of atopic disorders. For example, acute upper airway infections, especially in early childhood, are related to atopic disorders later in life (14, 15). Acute viral 'non-respiratory syncytial virus' bronchiolitis in infants aged <6 months is linked with an increased risk of developing asthma (16). The developing immune system of a child might be affected by frequent or severe infections of the middle ear, resulting in increased risk for asthma and atopic eczema (17). On the other hand, otitis media with effusion is associated with allergic rhinitis (18-20). The quality of life of an atopic child can be significantly improved by providing sufficient treatment.

To our knowledge no study has investigated the complete range of potential comorbidities in atopic children in a general practice setting. A relevant question could be: Are atopic children at increased risk for non-atopic symptoms or diseases? Awareness by GPs of these risks may reduce the probability that relevant comorbidity is not diagnosed. To study possible associations between atopic disorders and 404 different symptoms and diseases, an extensive and representative nationwide general practice database is explored using a cross-sectional design. The design of this study allows new hypotheses to be generated, providing valuable input for future research.

Method

Study population

All non-institutionalized residents in the Netherlands are registered in a general practice, even if they do not visit the GP on a regular basis. The Netherlands Institute for Health Services Research-Primary Care Database (NIVEL-PCD) is based

on routinely recorded data in electronic health records (EHRs) of all listed patients in the participating practices. In 2014, about 500 general practices participated, including data of about 1,700,000 patients (www.nivel.nl/en/dossier/nivel-primary-care-database), which is over 10% of the total Dutch population. EHR data include a variety of information regarding type of consultation, morbidity, and prescriptions. Data available for 2014 are representative for the Dutch population (21). Primary care physicians (gatekeepers for the Dutch healthcare system) recorded morbidity using the International Classification of Primary Care (ICPC), a classification method for primary care that is accepted by the WHO (22). Dutch GPs cluster relevant consultations, prescriptions and referrals, in ICPC classified 'episodes of care'. An episode of care is a health problem or disease from its first presentation to the GP to the last presentation for the same problem. Atopic disorders are labeled with ICPC codes: S87 (atopic eczema), R96 (asthma) and R97 (allergic rhinitis). ICPC-codes specific for food-allergies are not available.
For the present study, only morbidity data from EHRs of general practices with sufficient data quality were used that fulfilled the following criteria: i) at least 500 listed patients (standard practice: 2,350 patients), ii) complete morbidity registration (defined as ≥ 46 weeks/year), and iii) sufficient ICPC coding of diagnostic information (defined as ≥ 70% of the recorded disease episodes labeled with an ICPC code; average ICPC coding in a Dutch general practice is >95%). The following descriptive data were routinely collected: period in which the individual child was registered in the general practice, the unique code of the GP practice, the child's gender, and year and quarter of birth.

Atopic children

For each child (0-18 years), a minimum follow-up of 3 years was required (e.g. data had to be available for 2012-2014) for the present study to reduce the risk of registration bias. For this reason, only data for children aged ≥ 2 years are presented here. In the Netherlands, GPs see about 72% of their patient population at least once a year (23). We considered a 3-year follow-up period to be sufficient time for a GP to diagnose a child with (atopic) disorders. Furthermore, in order not to miss any relevant atopic diagnosis, when available, the EHRs from 2002-2014 were examined. Since GPs inevitably work with probability diagnoses, there is a risk of misclassification. To select cases with a higher probability of a clinically relevant disorder, ICPC codes and their related episodes of care can be corrected. In practice, an atopic episode of care was maintained if (between 2002-2014) the child had at least contacted the GP twice in that episode of care and had received at least two relevant prescriptions. If the child did not meet these criteria, the child was

considered not to have that atopic disorder (24) and was excluded from the study (this child could not be used as a control patient, to make sure that controls did not have any atopic disorder). If a child was diagnosed with an atopic disorder for the first time during 2014, the child was considered to have the atopic disorder that whole year. In the present study, the atopic diagnosis was based on the physician's assessment and was considered to be a chronic problem.

Atopic triad

A recent meta-analysis supported the hypothesis that there might be a fourth distinct group of children with all three atopic disorders, in contrast to the traditional classification of children with asthma *or* allergic rhinitis *or* atopic eczema (25). To learn more about this potentially unique group of children, 'atopic triad' episodes were developed for research purposes. These episodes were only created when a child was diagnosed with all three atopic disorders, based on available data from EHRs in the period 2002-2014.

Symptoms and diseases studied

After establishing which child had an atopic disorder (see above), a child was considered prevalent for a specific symptom or disease if the child had at least one active episode of care for that symptom or disorder between January and December of 2014. All ICPC codes that describe a symptom or a disease were examined, with the exception of trauma-related ICPC codes, ICPC codes not relevant for children (e.g. presbyacusis), pregnancy, childbearing, family planning, sexual transmitted diseases and social problems, leaving 404 different ICPC codes. Furthermore, since different classifications are used for eczema, there is a risk of misclassification. The ICPC system distinguishes the codes S86 (seborrheic dermatitis), S87 (atopic eczema), S88 (contact dermatitis / eczema another) and S89 (diaper rash). Since clinical differentiation can be very difficult, especially between S87 and S88, S88 was excluded from our analyses, to get more reliable results for 'true' atopic eczema (S87).

Design

A nested case-control study design was used. For each atopic child, one matched control patient was selected (not diagnosed with an atopic disorder) within the same general practice, based on age and gender in 2014. Controls were only matched if a 100% match on age, gender and general practice with an atopic child was determined. Odds ratios (ORs) were calculated for children that solely had atopic eczema, asthma, or allergic rhinitis and therefore no other atopic comorbidity. Appendix 1 presents a list of all the ICPC codes that were examined. A 1:1 ratio

was chosen to be able to include as many pairs of cases and controls as possible, allowing the results to carry more weight and making the conclusions more generalizable to future populations. In the present study, a 1:2 ratio would have resulted in dropping over 40% of the cases.

Statistical analyses

Logistic regression analysis was performed to study associations between the presence of atopic disorders and (non-)atopic comorbid symptoms and diseases in children. Similarly, associations between atopic triad and the above-mentioned comorbid symptoms and diseases were examined. Due to multiple testing, only associations with $p \leq 0.001$ were considered statistically significant. All associations were tested for the modifying effects of age and gender. In case of a significant effect ($p \leq 0.01$), associations were also presented for subgroups for age (2-6 vs. 7-12 vs. 13-18 years) and gender (boy vs. girl). Finally, due to the hierarchical structure of the data (patients registered in general practices), a multi-level logistic regression analysis was performed to test whether clustering effects influenced our findings. All analyses were conducted in Stata 13 and Excel 2010. Prevalence rates are presented in percentages.

Ethical approval

Dutch law allows the use of EHRs for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458). Therefore, no waiver of ethical approval was obtained from an Institutional Review Board (IRB) or ethics committee. The authors had no access to any identifying information at any moment during the analysis of the data.

Results

General characteristics (Table 1)

409,312 children were identified in the NIVEL-PCD in 2014, initially including 70,494 atopic children with at least one atopic disorder. However, for an atopic child to be included in this study, one matched control patient had to be available (i.e. a child without an atopic disorder). There were 21,285 children with atopic eczema identified, of which 15,530 children had atopic eczema without another atopic disorder. For asthmatic children, 13,196 children were identified, of which

Table 1. General characteristics of the total study population

	n	Age in years (SD)	Male
Only atopic eczema	15,530	8.7 (4.5)	48.2%
Only asthma	7,887	10.7 (4.5)	59.0%
Only allergic rhinitis	6,835	13.5 (3.5)	57.8%
Atopic triad	559	11.6 (4.0)	61.4%

NB. Children in the first three groups had **only one** of the three atopic disorders: i.e. they had the disorder mentioned, but none of the **other** disorders, whereas children in the atopic triad group had **all three** disorders.

7,887 had asthma only and no other atopic disorders. In children with AR, 11,483 were identified of which 6,835 had AR without another atopic disorder. Finally, 559 children had all three atopic disorders. All the children in these groups were selected from 316 different general practices participating in NIVEL-PCD. Clustering effects did not influence our findings.

Atopic eczema (Table 2)

A substantial part of the significantly related comorbidity for children with atopic eczema concerns skin diseases such as (among others): warts (OR: 1.2), localized

Table 2. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only atopic eczema (Ec) and at least three year follow-up versus controls (non-atopic children) (n=31,060).

ICPC	OR	95% CI	Prevalence		OR per sex group		OR within age			Description ICPC codes
			Ec	No Ec	boy	girl	2-6	7-12	13-18	
Skin-related diseases and symptoms										
S03	1.15	1.06 – 1.26	7.85	6.88						Warts
S06	1.51	1.25 – 1.82	1.76	1.18	1.11	2.02	1.29	1.54	2.30	Rash localized *,†
S99	1.57	1.24 – 2.00	1.12	0.71						Skin disease, other
S02	1.71	1.31 – 2.23	0.97	0.57						Pruritus
S84	1.71	1.54 – 1.90	6.23	3.75			1.54	1.78	2.72	Impetigo†
S04	1.76	1.30 – 2.39	0.73	0.42						Lump/swelling localized
S74	1.76	1.54 – 2.00	4.20	2.44						Dermatophytosis
S98	1.77	1.50 – 2.09	2.49	1.42						Urticaria
S21	1.89	1.49 – 2.40	1.26	0.67						Skin texture symptom/complaint
S95	1.92	1.69 – 2.19	4.44	2.38						Molluscum contagiosum

Table 2 (*continued*)

ICPC	OR	95% CI	Prevalence		OR per sex group		OR within age			Description ICPC codes
			Ec	No Ec	boy	girl	2-6	7-12	13-18	
S86	2.31	1.87 – 2.84	1.89	0.83						Dermatitis seborrhoeic
S91	3.36	2.23 – 5.06	0.64	0.19						Psoriasis
Airway-related diseases and symptoms										
R05	1.29	1.17 – 1.43	5.94	4.67						Cough
R74	1.33	1.23 – 1.43	10.42	8.13						Upper respiratory infection acute
R78	1.49	1.22 – 1.80	1.66	1.13						Acute bronchitis/bronchiolitis
R04	***1.55***	***0.97 – 2.48***	***0.29***	***0.19***	0.91	3.58				Breathing problem, other *
R03	1.95	1.30 – 2.92	0.45	0.23						Wheezing
Ear-nose-throat-related diseases and symptoms										
H71	1.20	1.09 – 1.31	7.46	6.35						Acute otitis media/myringitis
H72	1.40	1.21 – 1.62	2.92	2.11						Serous otitis media
H01	1.43	1.24 – 1.65	3.01	2.13						Ear pain/earache
H04	1.47	1.17 – 1.86	1.13	0.77						Ear discharge
R21	1.50	1.27 – 1.78	2.13	1.43						Throat symptom/complaint
H70	1.56	1.27 – 1.90	1.58	1.02						Otitis externa
R07	1.95	1.32 – 2.89	0.48	0.24						Sneezing/nasal congestion
Gastro-intestinal-related diseases and symptoms										
D01	1.27	1.12 – 1.45	3.61	2.85						Abdominal pain/cramps general
D12	1.32	1.19 – 1.47	5.29	4.07						Constipation
D87	***1.48***	***0.87 – 2.51***	***0.22***	***0.15***	0.69	3.29				Stomach function disorder *
D99	2.28	1.51 – 3.44	0.48	0.21						Disease digestive system. other
Musculoskeletal										
L17	1.30	1.15 – 1.48	3.50	2.71						Foot/toe symptom/complaint
L98	1.39	1.20 – 1.60	2.90	2.11						Acquired deformity of limb
Miscellaneous										
A04	1.25	1.09 – 1.44	3.07	2.47						Weakness/tiredness general
S12	1.41	1.19 – 1.66	2.24	1.60						Insect bite / sting
F72	1.53	1.22 – 1.93	1.20	0.79			0.96	2.79	1.76	Blepharitis/stye/chalazion†
F70	1.53	1.29 – 1.81	2.18	1.44						Conjunctivitis infectious
Y81	1.83	1.47 – 2.72	1.49	0.83						Phimosis/redundant prepuce
F71	1.99	1.59 – 2.49	1.45	0.73						Conjunctivitis allergic
A12	3.11	2.62 – 3.69	3.42	1.13						Allergy

* significant ($p \leq 0.01$) influence of gender; † significant ($p \leq 0.01$) influence of age; ***Italics**: Overall model not significant*

rash (OR: 1.5), pruritus (OR: 1.7), impetigo (OR: 1.7), dermatophytosis (OR: 1.8), urticaria (OR: 1.8), molluscum contagiosum (OR: 1.9) and psoriasis (OR: 3.4). Otitis externa (OR: 1.6) and blepharitis (OR: 1.5) were also significantly associated with atopic eczema. The symptom diagnosis of wheezing (OR: 2.0), that could be attributed to asthma, is noteworthy since these children were not diagnosed or coded in the EHRs with asthma. The same applies to symptoms associated with allergic rhinoconjunctivitis, such as sneezing/nasal congestion (OR: 2.0) and allergic conjunctivitis (OR: 2.0). Older children with atopic eczema were at increased risk to develop a localized rash (OR: 1.3->2.3) and impetigo (OR: 1.5->2.7). Compared to boys, girls had an increased risk, to develop a localized rash (OR: 2.0 vs. 1.1), breathing problems (OR: 3.6 vs. 0.9) and stomach function disorder (OR: 3.3 vs. 0.7).

Asthma (Table 3)

Noteworthy are asthma-related symptoms that were diagnosed separately, such as shortness of breath/dyspnea (OR: 7.7) and wheezing (OR: 10.3). Furthermore, asthmatic children consulted their GP more frequently for airway-related infections such as: acute laryngitis/tracheitis (OR: 2.3), acute upper respiratory infection (OR: 2.4), pneumonia (OR: 4.0) and acute bronchitis (OR: 4.8). In children with asthma, there seems to be a higher risk for the development of gastrointestinal symptoms, e.g.: general abdominal pain/cramps (OR: 1.4), localized abdominal pain (OR: 1.4),

Table 3. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only asthma (As) and at least three year follow-up versus controls (non-atopic children) (n=15,774)

ICPC	OR	95% CI	Prevalence		OR per sex group		OR within age			Description ICPC codes
			As	No As	boy	girl	2-6	7-12	13-18	
Skin-related diseases and symptoms										
S98	2.10	1.61 – 2.73	2.21	1.07						Urtiacaria
Airway-related diseases and symptoms										
R05	2.14	1.86 – 2.46	7.99	3.93						Cough
R77	2.34	1.54 – 3.56	0.94	0.41						Laryngitis/tracheitis acute
R74	2.35	2.09 – 2.64	12.34	5.78						Upper respiratory infection
R81	4.04	3.03 – 5.37	2.97	0.76						Pneumonia
R78	4.80	3.78 – 6.11	4.79	1.05			3.74	5.63	8.09	Acute bronchitis/bronchiolitis[†]
R91	5.66	3.14–10.23	0.93	0.16						Chronic bronchitis
R02	7.74	5.05–11.87	2.31	0.30						Shortness of breath/dyspnoea
R03	10.30	4.73–22.42	0.90	0.09						Wheezing

Table 3 (*continued*)

ICPC	OR	95% CI	Prevalence		OR per sex group		OR within age			Description ICPC codes
			As	No As	boy	girl	2-6	7-12	13-18	
Ear-nose-throat-related diseases and symptoms										
H76	***0.86***	***0.40 – 1.85***	***0.15***	***0.18***	2.51	0.20				Foreign body in ear *
H01	1.45	1.16 – 1.81	2.46	1.71						Ear pain/earache
H71	1.52	1.32 – 1.76	6.44	4.4						Acute otitis media/myringitis
H70	1.60	1.22 – 2.08	1.79	1.13						Otitis externa
R75	1.90	1.32 – 2.75	1.05	0.56						Sinusitis acute/chronic
Gastro-intestinal-related diseases and symptoms										
D89	***0.76***	***0.37 – 1.57***	***0.16***	***0.22***	0.27	4.52				Inguinal hernia *
D01	1.40	1.16 – 1.69	3.32	2.40						Abdominal pain/cramps general
D06	1.43	1.15 – 1.77	2.59	1.83						Abdominal pain localized other
D12	1.44	1.22 – 1.70	4.43	3.12						Constipation
D73	1.60	1.25 – 2.05	2.10	1.33						Gastroenteritis, infection
D10	2.02	1.37 – 2.97	0.99	0.49						Vomiting
D99	2.70	1.52 – 4.79	0.55	0.20						Disease digestive system, other
Musculoskeletal										
L15	***1.11***	***0.90 – 1.37***	***2.42***	***2.18***			1.34	1.49	0.97	Knee symptom/complaint†
L12	***1.37***	***1.09 – 1.71***	***2.27***	***1.67***	1.00	2.13				Hand symptom/complaint*
L98	1.40	1.16 – 1.68	3.54	2.56						Acquired deformity of limb
L99	1.52	1.22 – 1.89	2.66	1.78						Musculoskeletal disease, other
L11	1.98	1.48 – 2.65	1.71	0.87						Wrist symptom/complaint
Miscellaneous										
P21	1.34	1.13 – 1.58	4.18	3.17						ADHD
A04	1.39	1.17 – 1.65	4.04	2.97						Weakness/tiredness general
N01	1.51	1.21 – 1.89	2.49	1.66						Headache
F70	1.72	1.31 – 2.27	1.78	1.04						Conjunctivitis infectious
T10	1.82	1.35 – 2.44	1.60	0.89						Growth delay
T83	2.09	1.41 – 3.10	0.98	0.47						Overweight
T82	2.47	1.50 – 4.05	0.68	0.28						Obesity
F71	2.55	1.85 – 3.49	1.72	0.68						Conjunctivitis allergic
A12	3.40	2.74 – 4.23	4.55	1.38						Allergy

* significant (p ≤0.01) influence of gender; †significant (p ≤0.01) influence of age; ***Italics**: Overall model not significant*

constipation (OR: 1.4) and vomiting (OR: 2.0). Acute bronchitis (OR: 3.7->8.1) was diagnosed more often in older children. Inguinal hernias were seen more frequently in girls than in boys (OR: 4.5 vs. 0.3).

Allergic rhinitis (Table 4)

Children with allergic rhinitis visit their GPs more frequently for ear-nose-throat related symptoms and diseases. Among others, the following were diagnosed more often: throat symptom/complaint (OR: 1.5), ear pain/earache (OR: 1.9), hypertrophy tonsils/adenoids (OR: 1.9), acute/chronic sinusitis (OR: 2.0), nose symptom (OR: 2.6) and sneezing/nasal congestion (OR: 3.9). Furthermore, symptoms associated with atopic eczema (pruritus; OR: 2.2) and asthma [shortness of breath/dyspnea (OR: 2.7) and wheezing (OR: 4.3)] were seen more frequently. Also, when a child was diagnosed with allergic rhinitis, there was a substantial risk for the development of gastrointestinal symptoms [constipation (OR: 1.5) and localized abdominal pain (OR: 1.8)]. Hypertrophy of the tonsils was diagnosed less frequently when children got older

Table 4. Significantly (p ≤0.001) associated comorbidity in children diagnosed with only allergic rhinitis (AR) and at least three year follow-up versus controls (non-atopic children) (n=13,670)

ICPC	OR	95% CI	Prevalence		OR per sex group		OR within age			Description ICPC codes
			AR	No AR	boy	girl	2-6	7-12	13-18	
Skin-related diseases and symptoms										
A76	***0.86***	***0.47 – 1.60***	***0.28***	***0.32***			0.32	0.64	4.51	Viral exanthem other†
S03	1.26	1.10 – 1.43	7.65	6.20						Warts
S74	1.39	1.15 – 1.68	3.85	2.79						Dermatophytosis
S82	1.39	1.15 – 1.67	3.99	2.91						Naevus/mole
S84	1.71	1.35 – 2.15	2.87	1.71						Impetigo
S98	1.71	1.31 – 2.23	2.15	1.27						Urticaria
S86	1.86	1.38 – 2.53	1.76	0.95						Dermatitis seborrheic
S02	2.21	1.44 – 3.38	0.99	0.45						Pruritus
Airway-related diseases and symptoms										
R05	1.89	1.58 – 2.25	5.24	2.85						Cough
R74	1.92	1.66 – 2.23	8.00	4.35						Upper respiratory infection acute
R78	2.32	1.60 – 3.37	1.35	0.59						Acute bronchitis/bronchiolitis
R02	2.67	1.74 – 4.11	1.13	0.42						Shortness of breath/dyspnoe
R80	3.89	1.79 – 8.47	0.45	0.12						Influenza
R03	4.30	1.89 – 9.80	0.44	0.10						Wheezing

Table 4 (*continued*)

ICPC	OR	95% CI	Prevalence		OR per sex group		OR within age			Description ICPC codes
			AR	No AR	boy	girl	2-6	7-12	13-18	
Ear-nose-throat-related diseases and symptoms										
R21	1.48	1.20 – 1.84	3.13	2.14						Throat symptom/complaint
H01	1.87	1.36 – 2.56	1.62	0.88						Ear pain/earache
R90	1.92	1.34 – 2.74	1.30	0.69			3.22	2.80	1.04	Hypertrophy tonsils/adenoids†
R75	1.95	1.45 – 2.63	1.89	0.98						Sinusitis acute/chronic
R08	2.62	1.72 – 4.00	1.14	0.44						Nose symptom/complaint other
R07	3.93	2.57 – 6.01	1.54	0.40						Sneezing/nasal congestion
Gastro-intestinal-related diseases and symptoms										
D12	1.50	1.23 – 1.82	3.79	2.57						Constipation
D06	1.76	1.39 – 2.22	2.90	1.67						Abdominal pain localized other
D73	1.96	1.42 – 2.71	1.59	0.82	1.29	3.39				Gastroenteritis presumed infection *
Musculoskeletal										
L98	1.36	1.15 – 1.62	4.54	3.37						Acquired deformity of limb
L17	1.42	1.19 – 1.70	4.40	3.15						Foot/toe symptom/complaint
L13	2.80	1.66 – 4.74	0.78	0.28						Hip symptom/complaint
Miscellaneous										
N19	***1.18***	***0.85 – 1.65***	***1.17***	***0.99***	0.89	2.43				Speech disorder *
N01	1.45	1.18 – 1.78	3.29	2.30						Headache
P24	1.45	1.18 – 1.78	3.37	2.37						Specific learning problem
A04	1.58	1.35 – 1.85	6.10	3.96						Weakness/tiredness general
F70	1.73	1.28 – 2.32	1.76	1.02						Conjunctivitis infectious
S12	1.92	1.40 – 2.63	1.67	0.88						Insect bite/sting
F72	1.95	1.36 – 2.79	1.27	0.66	1.21	3.29				Blepharitis/stye/chalazion *
A12	4.02	3.15 – 5.13	4.70	1.21						Allergy
F71	5.44	4.08 – 7.25	4.29	0.82						Conjunctivitis allergic

* significant (p ≤0.01) influence of gender; †significant (p ≤0.01) influence of age; ***Italics**: Overall model not significant*

(OR: 3.2->1.0). On the other hand, children were more frequently diagnosed with a viral exanthema when they became older (OR: 0.3->4.5). A presumed gastro-intestinal infection (OR: 3.4 vs. 1.3), speech disorder (OR: 2.4 vs. 0.9) and blepharitis/style/chalazion (OR: 3.3 vs. 1.2) were diagnosed more frequently in girls with allergic rhinitis.

Atopic triad (Table 5)

Having all three atopic disorders is relatively rare, with only a few symptoms and diseases being significantly related. The risk for developing an 'allergy', that the GP considers relevant to register in the EHR can be considered high (OR: 17.8). Allergic conjunctivitis (OR: 6.8) is also frequently seen in children with all three atopic disorders.

Table 5. Significantly (p≤0.001) associated comorbidity in children diagnosed with Atopic Triad (AT) and at least three year follow-up versus controls (non-atopic children) (n=1,118)

ICPC	OR	95% CI	Prevalence		Description ICPC codes
			AT	No AT	
R05	2.42	1.43 – 4.10	8.59	3.76	Cough
L17	3.25	1.63 – 6.50	6.08	1.97	Foot/toe symptom/complaint
R74	3.75	2.33 – 6.04	14.13	4.29	Upper respiratory infection acute
F71	6.79	2.35 – 19.60	4.65	0.72	Conjunctivitis allergic
A12	17.83	7.15 – 44.43	13.77	0.89	Allergy

Discussion

Main findings

The present study used an extensive and representative general practice database (21). The large number of children gives the study substantial power and generalizability. This could also allow evaluation of possible links between atopic disorders and rare childhood diseases. This study showed that atopic children have an increased risk for the development of both atopic and non-atopic diseases and symptoms. Children diagnosed with one atopic disorder were frequently diagnosed by their GP with symptoms associated with one of the other atopic disorders. This suggests that GPs are not always fully aware of relevant atopic comorbidity, or at least do not label it correctly. Two examples support this hypothesis. First of all, a child diagnosed with atopic eczema is also diagnosed with pruritus, suggesting possible misclassification. Secondly, a child with atopic eczema that presents with 'wheeze' or 'dyspnea' is at a higher risk for the development of asthma compared to a child without atopic eczema. A GP should be aware of this increased risk, since it could result in insufficient treatment of a child. However, a GP could also use symptom-related ICPC-codes deliberately when the purpose is to record a provisional

diagnosis (e.g. wheeze as the provisional diagnosis of asthma). Regarding non-atopic co-morbidity, strong associations were found between the atopic disorder and diseases and symptoms related to the same organ system. For example, children with atopic eczema are at increased risk for the development of other skin diseases, asthmatic children are at risk of other airway diseases, and children with allergic rhinitis are at risk of ear-nose-throat-related symptoms and diseases. Gastro-intestinal and musculoskeletal diseases and symptoms were also seen more frequently in atopic children. When exploring possible interactions of age and gender in children with one atopic disorders, no clear patterns arose.

Interpretation of findings in relation to previously published work

Children with atopic eczema had an increased risk of developing infectious skin diseases such as warts, impetigo, dermatophytosis and molluscum contagiosum. The common etiology could be the barrier dysfunction of the skin in children with atopic eczema. This barrier dysfunction is also seen in psoriasis, a disease that, according to the present study, is associated with atopic eczema (OR: 3.4). They share some common pathological backgrounds such as barrier dysfunction and enhanced IL-22 expression (26). Although the clinical pictures of these two diseases can be very different, the observed association could also suggest misclassification among these two chronic skin diseases that are often confused for one another. Otitis externa and blepharitis both had significant ORs. These disorders could in fact be an expression of atopic eczema.

Children with asthma seem to have consulted their GP more frequently for airway-related infections such as acute laryngitis/tracheitis, acute upper respiratory infection, pneumonia and bronchitis. An explanation for this could be that airway infections increase asthma symptoms or vice versa, that asthma resulted in increased susceptibility for infection, which increased their motivation to visit the GP. Furthermore, the awareness of parents is likely to be increased when a child suffers from asthma, since such an infection could predispose for an asthma exacerbation.

Children with allergic rhinitis consulted their GPs more frequently for ear-nose-throat-related symptoms and diseases. However, even more striking are the asthma-related symptoms. Both shortness of breath (OR: 2.7) and wheeze (OR: 4.3) were frequently seen in children with allergic rhinitis. There is strong evidence that allergic rhinitis has an adverse impact on asthma severity (27). Because allergic rhinitis can provoke asthma symptoms, allergic rhinitis symptoms should be taken more seriously by GPs to reduce insufficient treatment.

Gastrointestinal-related symptoms are also frequently diagnosed by GPs in atopic children. This is in accordance with a study in adults in a primary care setting

(28). These symptoms could be related to IgE-mediated food allergies or in rare cases even to eosinophilic esophagitis that are associated with atopic disorders (29); however, in children, abdominal pains can also be a general expression of not feeling well. Unfortunately, the ICPC classification system does not cover the above-mentioned gastrointestinal diseases with unique code and, therefore, gastrointestinal-related symptoms might have been used by the GP to label these diseases.

Some associations described in the literature were not confirmed in the present study, e.g. serous otitis media in patients with allergic rhinitis (18, 20), and inflammatory bowel disease (30, 31), leukemia (32, 33) and diabetes (34, 35) in atopic patients. The prevalence rates of some of these disorders are low and a cross-sectional design (as used in the present study), might not have enough power to prove these relationships.

Strengths and limitations of this study

Using general practice databases (by means of a cross-sectional design) also has its limitations. First of all, a limitation for the present study is the GP's choice for ICPC coding of an episode of care. For example, a child with a wheeze could either be labeled as 'asthma' (R96) or labeled as 'wheeze' (R03). This could result in both overestimation or underestimation of asthma. To decrease this risk of overestimation regarding atopic disorders, some episodes were corrected in order to increase the clinical relevance of the atopic disorder of interest. However, the risk of underestimation was not tackled, since too many assumptions need to be made. The second limitation regarding this type of explorative study is the unavoidable multiple testing. Although conservative p-values were used, type 1 errors cannot be avoided. In this study, some suggested associations might in fact reflect these type 1 errors. Thirdly, because data on socioeconomic status, tobacco smoke exposure and other lifestyle-related risk factors are not recorded in NIVEL-PCD, we cannot rule out the effect of these risk factors on the observed relations. However, since the children with atopic disorders were matched with controls within the same general practice, all children are most likely living in the same neighborhoods and therefore the effect of most of the earlier mentioned risk factors is expected to be small. Fourthly, atopic children might visit the GP more frequently than non-atopic children. And although this may be more representative of parental fears, rather than an indication of morbidity, it can result in more detected morbidity in atopic children and could partly explain some of the associations found. In future research, the number of consultations might need to be taken into account in the analyses. Fifth of all, in the present study the diagnosis are based on a physician's assessment and

not on confirmed sensitization pattern for allergens. According to the Dutch medical guideline for eczema (36), GPs are not advised to determine these sensitization patterns, since this doesn't have any clinical consequences. Although atopy is clearly associated with atopic eczema, the role of IgE sensitization in atopic eczema still needs further study (37). Also in children with AR, sensitization patterns don't have added value if the medical history clearly suggests e.g. a pollen allergy (38). Only when the cause of the rhinitis is uncertain, the determination of sensitization patterns adds value. The medical guidelines for asthma in children advises to determine sensitization patterns (39), since it can help diagnose allergic asthma (40) and because it could have clinical consequences. Finally, it is important to acknowledge the uncertainty of general practitioners to make a diagnosis of asthma or AR in young children (e.g. under the age of six).

Implications for future research and practice

First of all, could comorbidity data be used to create proxies that could support GPs in identifying atopic children that are not labeled as such? For example, could comorbidity data be incorporated in 'clinical decision support systems' to improve early diagnosis of both atopic and non-atopic disorders. Second of all, how is the quality of life of these atopic children affected by the associated comorbidity? GPs should be aware of the described associations when treating an atopic child, since the quality of life of an atopic child could be improved by paying more attention to diagnosis and treatment of these related disorders. Furthermore, one must be aware that atopic disorders and associated symptoms and diseases may well persist into adulthood.

Conclusions

The present study shows that atopic children have an increased risk of clinically relevant comorbidity, both atopic and non-atopic. General practitioners may not always be fully aware of relevant atopic and non-atopic comorbidity. In children known to have at least one atopic disorder, specific attention is required to avoid possible insufficient treatment and unnecessary loss of quality of life.

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Appendix 1

ICPC codes	Description
A03	Fever
A04	Weakness/tiredness general
A12	Allergic reaction
A15	Excessive crying infant
A16	Irritable infant
A70	Tuberculosis
A71	Measles
A72	Chickenpox
A73	Malaria
A74	Rubella
A75	Infectious mononucleosis
A76	Viral exanthem other
A77	Viral disease other/NOS
A78	Infectious disease other/NOS
A79	Malignancy NOS
A84	Poisoning by medical agent
A85	Adverse effect medical agent
A86	Toxic effect non-medicinal substance
A87	Complication of medical treatment
A88	Adverse effect physical factor
A90	Congenital anomaly OS/multiple
A92	Allergy/allergic reaction NOS
A93	Premature newborn
A94	Perinatal morbidity other
A95	Perinatal mortality
A96	Death
B02	Lymph gland(s) enlarged/painful
B70	Lymphadenitis acute
B71	Lymphadenitis non-specific
B72	Hodgkin's disease/lymphoma
B73	Leukaemia
B74	Malignant neoplasm blood other
B75	Benign/unspecified neoplasm blood
B78	Hereditary haemolytic anaemia

ICPC codes	Description
B79	Congen.anom. blood/lymph other
B80	Iron deficiency anaemia
B81	Anaemia, Vitamin B12/folate def.
B82	Anaemia other/unspecified
B83	Purpura/coagulation defect
B84	Unexplained abnormal white cells
B87	Splenomegaly
B90	HIV-infection/aids
D01	Abdominal pain/cramps general
D02	Abdominal pain epigastric
D03	Heartburn
D04	Rectal/anal pain
D05	Perianal itching
D06	Abdominal pain localized other
D07	Dyspepsia/indigestion
D08	Flatulence/gas/belching
D09	Nausea
D10	Vomiting
D11	Diarrhoea
D12	Constipation
D13	Jaundice
D22	Parasites
D70	Gastrointestinal infection
D71	Mumps
D72	Viral hepatitis
D73	Gastroenteritis presumed infection
D74	Malignant neoplasm stomach
D75	Malignant neoplasm colon/rectum
D76	Malignant neoplasm pancreas
D77	Malig. neoplasm digest other/NOS
D78	Neoplasm digest benign/uncertain
D79	Foreign body digestive system
D81	Congen. anomaly digestive system
D83	Mouth/tongue/lip disease

ICPC codes	Description
D84	Oesophagus disease
D85	Duodenal ulcer
D86	Peptic ulcer other
D87	Stomach function disorder
D88	Appendicitis
D89	Inguinal hernia
D90	Hiatus hernia
D91	Abdominal hernia other
D92	Diverticular disease
D93	Irritable bowel syndrome
D94	Chronic enteritis/ulcerative colitis
D95	Anal fissure/perianal abscess
D96	Worms/other parasites
D97	Liver disease NOS
D98	Cholecystitis/cholelithiasis
D99	Disease digestive system, other
F01	Eye pain
F02	Red eye
F03	Eye discharge
F04	Visual floaters/spots
F05	Visual disturbance other
F70	Conjunctivitis infectious
F71	Conjunctivitis allergic
F72	Blepharitis/stye/chalazion
F73	Eye infection/inflammation other
F74	Neoplasm of eye/adnexa
F75	Contusion/haemorrhage eye
F76	Foreign body in eye
F80	Blocked lacrimal duct of infant
F81	Congenital anomaly eye other
F82	Detached retina
F83	Retinopathy
F84	Macular degeneration
F85	Corneal ulcer
F86	Trachoma
F91	Refractive error

ICPC codes	Description
F92	Cataract
F93	Glaucoma
F94	Blindness
F95	Strabismus
F99	Eye/adnexa disease, other
H01	Ear pain/earache
H02	Hearing complaint
H03	Tinnitus, ringing/buzzing ear
H04	Ear discharge
H05	Bleeding ear
H70	Otitis externa
H71	Acute otitis media/myringitis
H72	Serous otitis media
H73	Eustachian salpingitis
H74	Chronic otitis media
H75	Neoplasm of ear
H76	Foreign body in ear
H77	Perforation ear drum
H80	Congenital anomaly of ear
H81	Excessive ear wax
H82	Vertiginous syndrome
H83	Otosclerosis
H86	Deafness
K01	Heart pain
K02	Pressure/tightness of heart
K04	Palpitations/awareness of heart
K05	Irregular heartbeat other
K07	Swollen ankles/oedema
K29	Cardiovascular sympt./complt. other
K70	Infection of circulatory system
K71	Rheumatic fever/heart disease
K72	Neoplasm cardiovascular
K73	Congenital anomaly cardiovascular
K74	Ischaemic heart disease w. angina
K75	Acute myocardial infarction
K76	Ischaemic heart disease w/o angina

ICPC codes	Description
K77	Heart failure
K78	Atrial fibrillation/flutter
K79	Paroxysmal tachycardia
K80	Cardiac arrhythmia NOS
K81	Heart/arterial murmur NOS
K82	Pulmonary heart disease
K83	Heart valve disease NOS
K84	Heart disease other
K85	Elevated blood pressure
K86	Hypertension uncomplicated
K87	Hypertension complicated
K88	Postural hypotension
K89	Transient cerebral ischaemia
K90	Stroke/cerebrovascular accident
K91	Cerebrovascular disease
K92	Atherosclerosis/PVD
K93	Pulmonary embolism
K94	Phlebitis/thrombophlebitis
K95	Varicose veins of leg
K96	Haemorrhoids
K99	Cardiovascular disease other
L01	Neck symptom/complain
L02	Back symptom/complaint
L03	Low back symptom/complaint
L04	Chest symptom/complaint
L05	Flank symptom/complaint
L06	Axilla symptom/complaint
L07	Jaw symptom/complaint
L08	Shoulder symptom/complaint
L09	Arm symptom/complaint
L10	Elbow symptom/complaint
L11	Wrist symptom/complaint
L12	Hand/finger symptom/complaint
L13	Hip symptom/complaint
L14	Leg/thigh symptom/complaint
L15	Knee symptom/complaint

ICPC codes	Description
L16	Ankle symptom/complaint
L17	Foot/toe symptom/complaint
L18	Muscle pain
L19	Muscle symptom/complaint NOS
L20	Joint symptom/complaint NOS
L70	Infections musculoskeletal system
L71	Malignant neoplasm musculoskeletal
L82	Congenital anomaly musculoskeletal
L83	Neck syndrome
L84	Back syndrome w/o radiating pain
L85	Acquired deformity of spine
L86	Back syndrome with radiating pain
L87	Bursitis/tendinitis/synovitis NOS
L88	Rheumatoid/seropositive arthritis
L92	Shoulder syndrome
L93	Tennis elbow
L94	Osteochondrosis
L95	Osteoporosis
L97	Neoplasm benign/unspec musculo.
L98	Acquired deformity of limb
L99	Musculoskeletal disease, other
N01	Headache
N02	Tension headache
N03	Pain face
N04	Restless legs
N05	Tingling fingers/feet/toes
N06	Sensation disturbance other
N07	Convulsion/seizure
N16	Disturbance of smell/taste
N17	Vertigo/dizziness
N18	Paralysis/weakness
N19	Speech disorder
N70	Poliomyelitis
N71	Meningitis/encephalitis
N72	Tetanus
N73	Neurological infection other

ICPC codes	Description
N74	Malignant neoplasm nervous system
N75	Benign neoplasm nervous system
N76	Neoplasm nervous system unspec.
N85	Congenital anomaly neurological
N86	Multiple sclerosis
N87	Parkinsonism
N88	Epilepsy
N89	Migraine
N90	Cluster headache
N91	Facial paralysis/bell's palsy
N92	Trigeminal neuralgia
N93	Carpal tunnel syndrome
N94	Peripheral neuritis/neuropathy
N99	Neurological disease, other
P01	Feeling anxious/nervous/tense
P02	Acute stress reaction
P03	Feeling depressed
P04	Feeling/behaving irritable/angry
P06	Sleep disturbance
P10	Stammering/stuttering/tic
P11	Eating problem in child
P12	Bedwetting/enuresis
P13	Encopresis/bowel training problem
P20	Memory disturbance
P21	ADHD
P22	Child behaviour symptom/complaint
P23	Adolescent behav. Symptom/complt.
P24	Specific learning problem
P71	Organic psychosis other
P72	Schizophrenia
P73	Affective psychosis
P74	Anxiety disorder/anxiety state
P75	Somatization disorder
P76	Depressive disorder
P78	Neuraesthenia/surmenage
P79	Phobia/compulsive disorder

ICPC codes	Description
P85	Mental retardation
P98	Psychosis NOS/other
P99	Psychological disorders, other
R01	Pain respiratory system
R02	Shortness of breath/dyspnoea
R03	Wheezing
R04	Breathing problem, other
R05	Cough
R06	Nose bleed/epistaxis
R07	Sneezing/nasal congestion
R08	Nose symptom/complaint other
R09	Sinus symptom/complaint
R21	Throat symptom/complaint
R22	Tonsils symptom/complaint
R23	Voice symptom/complaint
R24	Haemoptysis
R25	Sputum/phlegm abnormal
R29	Respiratory symptom/complaint oth.
R70	Tuberculosis airways
R71	Whooping cough
R72	Strep throat
R73	Boil/abscess nose
R74	Upper respiratory infection acute
R75	Sinusitis acute/chronic
R76	Tonsillitis acute
R77	Laryngitis/tracheitis acute
R78	Acute bronchitis/bronchiolitis
R80	Influenza
R81	Pneumonia
R82	Pleurisy/pleural effusion
R83	Respiratory infection other
R84	Malignant neoplasm bronchus/lung
R85	Malinant neoplasm respiratory, other
R86	Benign neoplasm respiratory
R87	Foreign body nose/larynx/bronch
R89	Congenital anomaly respiratory

ICPC codes	Description
R90	Hypertrophy tonsils/adenoids
R91	Chronic bronchitis
R93	Pleural effusion
R95	Chronic obstructive pulmonary dis
R96	Asthma
R97	Allergic rhinitis
R98	Hyperventilation syndrome
R99	Respiratory disease other
S01	Pain/tenderness of skin
S02	Pruritus
S03	Warts
S04	Lump/swelling localized
S05	Lumps/swellings generalized
S06	Rash localized
S07	Rash generalized
S08	Skin colour change
S09	Infected finger/toe
S10	Boil/carbuncle
S11	Skin infection post-traumatic
S12	Insect bite/sting
S13	Animal/human bite
S14	Burn/scald
S15	Foreign body in skin
S20	Corn/callosity
S21	Skin texture symptom/complaint
S22	Nail symptom/complaint
S23	Hair loss/baldness
S24	Hair/scalp symptom/complaint
S70	Herpes zoster
S71	Herpes simplex
S72	Scabies/other acariasis
S73	Pediculosis/skin infestation other
S74	Dermatophytosis
S75	Moniliasis/candidiasis skin
S76	Skin infection other
S77	Malignant neoplasm of skin

ICPC codes	Description
S78	Lipoma
S79	Neoplasm skin benign/unspecified
S80	Solar keratosis/sunburn
S81	Haemangioma/lymphangioma
S82	Naevus/mole
S83	Congenital skin anomaly other
S84	Impetigo
S85	Pilonidal cyst/fistula
S86	Dermatitis seborrhoeic
S87	Dermatitis/atopic eczema
S89	Diaper rash
S90	Pityriasis rosea
S91	Psoriasis
S92	Sweat gland disease
S93	Sebaceous cyst
S94	Ingrowing nail
S95	Molluscum contagiosum
S96	Acne
S97	Chronic ulcer skin
S98	Urticaria
S99	Skin disease, other
T01	Excessive thirst
T02	Excessive appetite
T03	Loss of appetite
T04	Feeding problem of infant/child
T05	Feeding problem of adult
T06	Anorexia nervosa
T07	Weight gain
T08	Weight loss
T10	Growth delay
T11	Dehydration
T15	Tumor thyroid
T70	Endocrine infection
T71	Malignant neoplasm thyroid
T72	Benign neoplasm thyroid
T73	Neoplasm endocrine oth/unspecified

ICPC codes	Description
T78	Thyroglossal duct/cys
T80	Congenital anom endocrine/metab
T81	Goitre
T82	Obesity
T83	Overweight
T85	Hyperthyroidism/thyrotoxicosis
T86	Hypothyroidism/myxoedema
T87	Hypoglycaemia
T88	Renal glycosuria
T89	Diabetes insulin dependent
T90	Diabetes non-insulin dependent
T91	Vitamin/nutritional deficiency
T92	Gout
T93	Lipid disorder
T99	Endocrine/metab/nutrit. dis. other
U01	Dysuria/painful urination
U02	Urinary frequency/urgency
U04	Incontinence urine
U05	Urination problems other
U06	Haematuria
U07	Urine symptom/complaint other
U13	Bladder symptom/complaint other
U14	Kidney symptom/complaint
U70	Pyelonephritis/pyelitis

ICPC codes	Description
U71	Cystitis/urinary infection other
U72	Urethritis
U75	Malignant neoplasm of kidney
U76	Malignant neoplasm of bladder
U77	Malignant neoplasm urinary other
U78	Benign neoplasm urinary tract
U79	Neoplasm urinary tract NOS
U85	Congenital anomaly urinary tract
U88	Glomerulonephritis/nephrosis
U90	Orthostatic albumin/proteinuria
U95	Urinary calculus
U98	Abnormal urine test NOS
U99	Urinary disease, other
X83	Congenital anomaly genital female
X84	Vaginitis/vulvitis NOS
X85	Cervical disease NOS
X99	Genital disease female, other
Y74	Orchitis/epididymitis
Y75	Balanitis
Y81	Phimosis/redundant prepuce
Y82	Hypospadias
Y83	Undescended testicle
Y84	Congenital genl anomaly (m) other
Y99	Genital disease male, other

Chapter 7

Atopic children and use of prescribed medication: a comprehensive study in general practice

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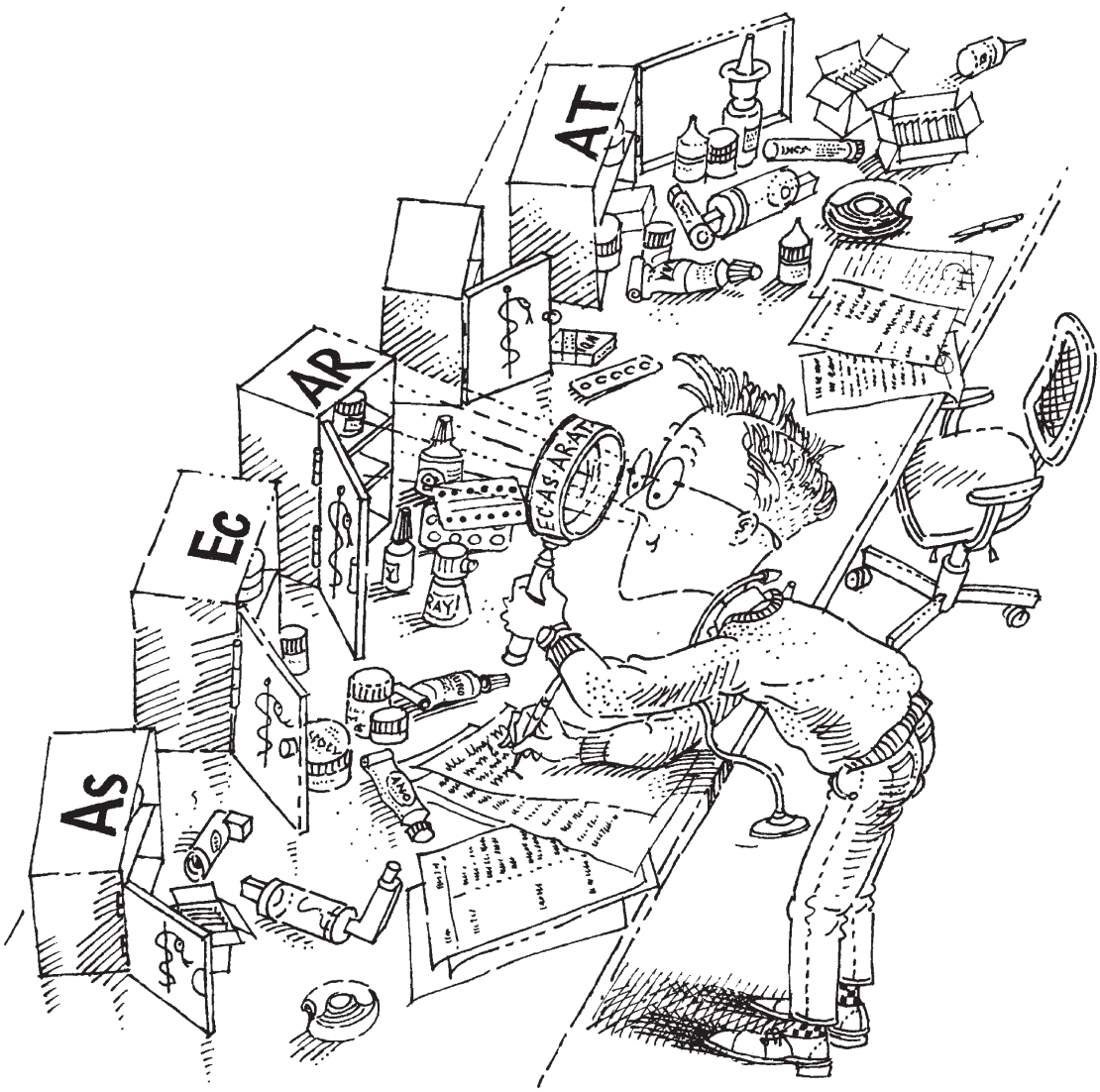

Abstract

Purpose: A comprehensive and representative nationwide general practice database was explored to study associations between physician diagnosed atopic disorders and prescribed medication in children.
Method: All children aged 0-18 years listed in the NIVEL Primary Care Database in 2014 were selected. Atopic children with atopic eczema, asthma and allergic rhinitis (AR) were matched with controls (not diagnosed with any of these disorders) within the same general practice on age and gender. Logistic regression analyses were performed to study the differences in prescribed medication between both groups by calculating odds ratios (OR); 93 different medication groups were studied.
Results: A total of 45,964 children with at least one atopic disorder were identified and matched with controls. Disorder-specific prescriptions seem to reflect evidence-based medicine guidelines for atopic eczema, asthma and AR. However, these disorder-specific prescriptions were also prescribed for children who were not registered as having that specific disorder. For eczema-related medication, about 3.7-8.4% of the children with non-eczematous atopic morbidity received these prescriptions, compared to 1.4-3.5% of the non-atopic children. The same pattern was observed for anti-asthmatics (having non-asthmatic atopic morbidity: 0.8-6.2% vs. controls: 0.3-2.1%) and AR-related medication (having non-AR atopic morbidity: 4.7-12.5% vs. controls: 2.8-3.1%). Also, non-atopic related medication, such as laxatives and antibiotics were more frequently prescribed for atopic children.
Conclusions: The present study shows that atopic children received more prescriptions, compared to non-atopic children. Non-atopic controls frequently received specific prescriptions for atopic disorders. This indicates that children with atopic disorders need better monitoring by their GP.

Background

Many children are diagnosed with atopic disorders (1, 2) and are likely to consult their general practitioners (GP) for atopic-related symptoms. In the present study, we refer to atopy as one or more of the following established diagnoses: atopic eczema, asthma and/or allergic rhinitis (AR).

Evidence-based medicine guidelines support Dutch GPs in the decision-making process when prescribing medication (3-5). According to these guidelines, the cornerstone for the treatment of atopic eczema in children are emollients and corticosteroid crèmes, prescribed in a stepwise approach (3). When anti-asthmatic inhalation medication is needed, a GP will start with a short-acting beta agonist, followed by inhaled corticosteroids when indicated (4). For AR, treatment will depend on the severity of symptoms. Intermittent symptoms are often treated with local or oral antihistamines on demand, while moderate to severe symptoms will be treated with corticosteroid nasal sprays (5). How often these atopic-related prescriptions are also given to children that are not labeled/diagnosed with a specific atopic disorder is not yet known and could reflect underdiagnosis or insufficient coding.

Atopic disorders are associated with comorbidity (6), and this can result in non-atopic related prescriptions for these atopic children as well. However, to what extent these atopic children have a higher risk to receive more (non-)atopic related prescriptions has not yet been examined in general practice. Knowing more about these differences can help a GP to provide better care for his atopic patients. Therefore, in this study, an extensive and representative nationwide general practice database was used to investigate associations between atopic disorders and prescribed medications. Two research questions were formulated: i) Which medications are prescribed by GPs for atopic disorders? ii) What kind of other medications do atopic children receive?

Method

Study population

All non-institutionalized Dutch inhabitants are compulsorily listed with a general practice, including patients who do not visit their GP on a regular basis. The Netherlands Institute for Health Services Research-Primary Care Database (NIVEL-PCD) uses the electronical health records (EHRs) of all listed patients in participating practices for research purposes. The data are representative for the Dutch population (7) and based on routinely recorded data (type of consultation, morbidity, and

prescriptions). In 2014, about 500 general practices participated, including data of about 1,700,000 patients (www.nivel.nl/en/dossier/nivel-primary-care-database), i.e. over 10% of the total Dutch population. Morbidity is recorded by GPs (frontline for the Dutch healthcare system) using the International Classification of Primary Care-1 (ICPC-1). This is a classification method for primary care and accepted by the WHO (8). Relevant consultations, prescriptions and referrals are clustered in ICPC classified episodes of care. Atopic episodes of care are labeled with ICPC codes: S87 (atopic eczema), R96 (asthma) and R97 (allergic rhinitis). ICPC codes specific for food allergies are not available.
Only data from EHRs of general practices with sufficient data quality were used. They had to fulfill the following criteria: at least 500 listed patients (standard practice size: 2350 patients), complete morbidity registration (defined as ≥ 46 weeks per year) and sufficient ICPC coding (defined as ≥ 70% of the recorded disease episodes labeled with an ICPC code). The following descriptive data were routinely collected: gender, year and quarter of birth, period in which the individual child was registered in the general practice, and the unique code of the general practice.

Identification of atopic children

To reduce the risk of registration bias for physician based atopic disorders, a minimum follow-up of 3 successive years (e.g. data had to be available for 2012-2014) was required for each child (age range 0-18 years). We considered a 3-year follow-up sufficient time for a GP to diagnose a child with atopic disorders, since a Dutch GP sees about 72% of pediatric patients at least once a year (9). Furthermore, when available, the EHRs from 2002-2014 were examined in order not to miss any relevant atopic diagnosis. Because there is a risk of misclassification (GPs work with probability diagnoses), ICPC codes and their related episodes of care were corrected in order to select cases with a higher probability of a clinically relevant disorder (2). In practice, an atopic episode of care was maintained if (based on available data from EHRs in the period 2002-2014) the child had at least two contact moments in that episode of care and had received at least two relevant prescriptions. If the child did not meet these criteria, the child was considered not to have that atopic disorder (2). It was not a requirement that the patient had visited the GP in 2014 for that specific atopic disorder.

Atopic triad

A forth distinct group of children, with all three atopic disorders, might exist according to a meta-analysis (1). This is in contrast to the traditional classification of children with atopic eczema or asthma or AR. ‘Atopic triad’ episodes were developed

for research purposes in order to learn more about this potentially unique group of children and were only created when a child was diagnosed with all three atopic disorders(based on available data from EHRs in the period 2002-2014).

Studied medication

GPs recorded prescriptions using the Anatomical Therapeutic Chemical (ATC) Classification System. This system is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC), and was first published in 1976. All ATC codes were examined at the second level, indicating the therapeutic main group and consisting of two digits. In some cases, a subgroup analysis was done at the ATC 3 level, indicating the therapeutic/pharmacological subgroup and consisting of one letter. All 93 ATC codes at the ATC 2 level were studied (Appendix 1). Prescription data from 2014 were examined.

Design

In a nested case-control study design, for each atopic child one matched control patient was selected (not diagnosed with an atopic disorder) within the same general practice, based on age and gender (in 2014). In order to include as many pairs of cases and controls as possible, a 1:1 ratio was chosen. This allows the results to carry more weight and make the conclusions better generalizable to future populations. When using a 1:2 ratio, over 40% of the cases had to be dropped.

Statistical analyses

To study associations between the presence of physician based atopic disorders and prescriptions in children, logistic regression analyses were performed for children that solely had atopic eczema, asthma, or AR and therefore no other atopic comorbidity. The same analyses were performed for the atopic triad. As a result of multiple testing, the level of significance was set on $p \leq 0.001$. Modifying effects of age and gender were tested for all associations. When the effect was significant ($p \leq 0.01$), associations were also presented for subgroups for age (2-6 vs. 7-12 vs. 13-18 years) and gender (boy vs. girl). All analyses were conducted in Stata 13 and Excel 2010. Prevalences are presented in percentages.

Ethical approval

Dutch law allows the use of EHRs for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational

study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458). No waiver of ethical approval was therefore obtained by an Institutional Review Board or ethics committee. The authors did not have access to identifying information at any moment during the analysis of the data.

Results

General characteristics (Table 1)

409,312 children were identified in the NIVEL-PCD, initially including 70,494 atopic children with at least **one** atopic disorder in 2014. However, for an atopic child to be included in this study, one matched control patient had to be available (i.e. a child *without* an atopic disorder). A total of 45,964 children with at least one atopic disorder could be identified and matched with controls. After selecting children with an atopic disorder **and** with a higher probability of a clinically relevant disorder **and** with at least three years follow-up, 21,285 children with atopic eczema were identified, of which 15,530 children had atopic eczema only and no other atopic disorders. For asthmatic children, 13,196 children were identified, of which 7,887 had asthma only and no other atopic disorders. In children with AR, 11,483 were identified of which 6,835 had AR only and no other atopic disorders. Finally, 559 children had all three atopic disorders. All the children in these groups were selected from 316 different general practices participating in NIVEL-PCD.

Table 1 Overall characteristics of the total study population

	n	**Age in years (SD)**	**Male**
Only atopic eczema	15,530	8.7 (4.5)	48.2%
Only asthma	7,887	10.7 (4.5)	59.0%
Only allergic rhinitis	6,835	13.5 (3.5)	57.8%
Atopic triad	559	11.6 (4.0)	61.4%

NB. Children in the first three groups had **only one** of the three atopic disorders: i.e. they had the disorder mentioned, but none of the **other** disorders, whereas children in the Atopic triad group had **all three** disorders.

Children registered with only atopic eczema (Table 3)

A child with atopic eczema received on average 1.5 different prescriptions in 2014, compared to 0.7 different prescriptions for the controls; this difference was significant (Table 2). In total, 61% of all children with atopic eczema did not receive

Table 2 Number of different prescriptions received in 2014

Disorder	Index patients	Control patients
Only atopic eczema*	1.5	0.7
Only asthma*	1.8	0.7
Only allergic rhinitis*	2.2	0.8

* the child did not have any of the other atopic disorder

Table 3 Significantly (p≤0.001) associated medication in children registered with **only atopic eczema** (Ec) versus controls (non-atopic children) (n=31,060)

ICPC	OR	95%-CI	Prevalence (%)		OR per sex group		OR within age			Description ICPC codes
			Ec	No Ec	boy	girl	2-6	7-12	13-18	
Atopic eczema related medication										
D02	13.09	11.58 – 14.80	19.85	1.87			11.68	12.63	20.00	Emollients and protectives†
D07	12.52	11.45 – 13.68	32.91	3.78			11.18	11.87	16.80	Corticosteroids, dermatological preparations†
Asthma related medication										
R03	1.97	1.72 – 2.26	3.98	2.07						Anti-asthmatics
Allergic rhinitis related medication										
R01	1.54	1.37 – 1.73	4.72	3.12						Nasal preparations
R06	2.90	2.59 – 3.24	7.72	2.81						Antihistamines for systemic use
Medication related to atopic disorders										
A06	1.35	1.21 – 1.50	5.48	4.13						Laxatives
J01	1.35	1.26 – 1.44	15.30	11.86						Antibacterial for systemic use
N05	1.43	1.17 – 1.75	1.48	1.04						Psycholeptics
S02	1.48	1.30 – 1.68	3.83	2.63						Otologicals
S01	1.64	1.46 – 1.84	5.14	3.21						Ophthalmologicals
D01	1.68	1.50 – 1.87	5.85	3.57						Antifungals for dermatological use
D06	1.87	1.71 – 2.05	9.29	5.21						Antibiotics and chemotherapeutics for dermatological use
D04	1.89	1.34 – 2.65	0.62	0.33						Antipruritic, including antihistamines, anaesthetics, etc.
L04	***2.37***	***1.17 – 4.80***	***0.17***	***0.07***			0.50	1.00	6.36	Immunosuppressive agents†
D08	2.64	1.69 – 4.11	0.46	0.17						Antiseptics and disinfectants
D11	2.79	2.24 – 3.47	1.94	0.71						Other dermatological preparations
D05	4.11	2.06 – 8.21	0.26	0.06						Antipsoriatics
C01	6.44	3.73 – 11.10	0.62	0.10						Cardiac therapy (e.g. epinephrine auto-injectors)

† significant (p≤0.01) influence of age; ***Italic**: overall model not significant*

relevant medication for atopic eczema in 2014. The highest ORs (12.5-13.1) were observed for atopic eczema related medication: emollients (D02) and dermatological corticosteroids (D07).
Other dermatological preparations were also frequently prescribed, e.g. antifungals (OR: 1.7), antipruritics (OR: 1.9), antibiotics (OR: 1.9), antiseptics (OR: 2.6), antipsoriatics (OR: 4.1) and other dermatological preparations (OR: 2.8), e.g. agents for dermatitis, excluding corticosteroids. Although less frequently prescribed, a high OR of 6.4 was observed for ATC code C01 (88% concerned epinephrine auto-injectors).
Children with atopic eczema received significantly more emollients (OR: 11.7->20.0) and dermatological corticosteroids (OR: 11.2->16.8) at older age. This also applied for immunosuppressive agents (OR: 0.5->6.4). Sex did not influence prescriptions in children with atopic eczema.
Eczema-related medication was also prescribed for children that were not registered as having atopic eczema. For eczema-related medication, about 3.7-8.4% of the children with atopic comorbidity received these prescriptions compared to 1.4-3.5% of the non-atopic children. Anti-asthmatics were used by 4% of the children with atopic eczema (OR: 2.0) even though the GP did not register them as having asthma. This same pattern is seen for medication related to AR (OR: 1.5-2.9).

Children registered with only asthma (Table 4)

A child with asthma received on average 1.8 different prescriptions in 2014 compared to 0.7 different prescriptions for the controls; this difference was significant (Table 2). Of the asthmatic children, 47% did not receive any asthma-related prescription at all in 2014. A high OR of 56.2 was observed for anti-asthmatics (R03). Examining R03 at the ATC 3 level, adrenergic inhalants (e.g. selective beta-2 adrenoreceptor agonists) were given to 46.1% of the children diagnosed with asthma during our 1-year observation period. Of the asthmatic children, 28.9% received (also) different inhalants (e.g. inhaled corticosteroids) for obstructive airway diseases. Only 2.0% of the children received other systemic drugs for airway diseases (e.g. leukotriene receptor antagonists). More than 3% received at least one short course of steroid tablets during the 1-year observation period (OR: 12.0).
According to our analysis (Table 4), asthmatic children use more hormonal contraceptives (G03A) (5.9% vs. 4.6%), received more viral vaccines (4.2% vs. 0.8%) and used more ADHD-related medication (OR 1.4). These asthmatic children also received more analgesics prescribed by the GP (M01 and N02) compared to children without asthma. This will most likely concern the prescription of paracetamol and NSAIDs.

Table 4 Significantly (p≤0.001) associated medication in children registered with **only asthma** (As) versus controls (non-atopic children) (n=15,774)

ICPC	OR	95%-CI	Prevalence (%)		OR per sex group		OR within age			Description ICPC codes
			As	No As	boy	girl	2-6	7-12	13-18	
Atopic eczema related medication										
D02	2.54	2.04 – 3.14	3.73	1.51						Emollients and protectives
D07	2.32	2.00 - 2.68	7.67	3.46						Corticosteroids, dermatological preparations
Asthma related medication										
H02	11.96	7.65 – 18.70	3.09	0.27						Corticosteroids for systemic use
R03	56.17	47.58 – 66.32	52.63	1.94			26.85	62.93	116.91	Anti-asthmatics†
Allergic rhinitis related medication										
R01	4.61	3.99 – 5.34	12.49	3.00			2.65	5.41	5.47	Nasal preparations†
R06	4.45	3.85 – 5.14	12.24	3.04			2.55	5.77	4.88	Antihistamines for systemic use†
Medication related to atopic disorders										
P02	***1.36***	***0.81 – 2.29***	***0.43***	***0.32***	3.44	0.55				Anthelmintic *
D06	1.36	1.17 – 1.57	5.64	4.23						Antibiotics and chemotherapeutics for dermatological use
N06	1.41	1.21 – 1.65	5.07	3.66						Psychoanaleptic
M01	1.48	1.23 – 1.78	3.70	2.55						Anti-inflammatory and anti-rheumatic products
G03	1.49	1.25 – 1.77	6.25	5.01						Sex hormones and modulators of the genital system
A06	1.52	1.29 – 1.77	5.08	3.42						Laxatives
S02	1.59	1.32 – 1.90	3.84	2.46						Otologicals
S01	1.68	1.43 – 1.98	4.97	3.02						Ophthalmologicals
J01	1.81	1.65 – 1.98	18.21	11.03						Antibacterial for systemic use
N02	2.00	1.52 – 2.62	2.00	1.01						Analgesics
A02	2.03	1.49 – 2.76	1.55	0.77						Drugs for acid-related disorders
A03	2.28	1.61 – 3.23	1.32	0.58						Drugs for functional gastrointestinal disorders
R05	2.37	1.86 – 3.03	2.75	1.18						Cough and cold preparations
J07	5.69	4.32 – 7.49	4.23	0.77						Vaccines
C01	13.01	6.02 – 28.08	1.14	0.09						Cardiac therapy (e.g. epinephrine auto-injectors)

* significant (p≤0.01) influence of gender; † significant (p≤0.01) influence of age; ***Italic**: overall model not significant*

In asthmatic patients, anti-asthmatics (OR: 26.9->116.9) were more often prescribed at older age.
Asthma-related medication was also prescribed for children that were not registered as having asthma. For anti-asthmatics about 0.8-6.2% of the children with atopic comorbidity received these prescriptions, compared to 0.3-2.1% of the non-atopic children. Medications related to atopic eczema (OR: 2.3-2.5) and AR (OR: 4.5-4.6) were more frequently prescribed for children with asthma.

Children registered with only allergic rhinitis (Table 5)

A child with AR received on average 2.2 different prescriptions in 2014, compared to 0.8 different prescriptions for the controls; this difference was significant (Table 2). Only 30% of these children did not receive any relevant AR prescription. High ORs are seen for medication prescribed by GPs to relieve AR symptoms (OR: 21.4-40.8). Looking at the prescribed nasal preparations, these refer to R01A (OR: 21.4; decongestants and other nasal preparations for topical use) and represent the prescription of anti-allergic agents and corticosteroids.
Ophthalmological medications prescribed for these children refer to the prescription of anti-infectives (2.6% vs. 1.6%) and of anti-allergics (17.8% vs. 0.7%). Also, these children used more analgesics (M01 and N02) and systemic antibiotics (13.3% vs. 9.9%) compared to children without AR.

Table 5 Significantly (p≤0.001) associated medication in children registered with **only Allergic Rhinitis** (AR) versus controls (non-atopic children) (n=13,670)

ICPC	OR	95%-CI	Prevalence (%)		OR per sex group		OR within age			Description ICPC codes
			AR	No AR	boy	girl	2-6	7-12	13-18	
Atopic eczema related medication										
D02	3.36	2.66 – 4.25	4.46	1.38						Emollients and protectives
D07	2.74	2.34 – 3.22	8.38	3.23						Corticosteroids, dermatological preparations
Asthma related medication										
H02	3.26	1.89 – 5.62	0.80	0.25						Corticosteroids for systemic use
R03	4.42	3.55 – 5.51	6.20	1.48						Anti-asthmatics
Allergic rhinitis related medication										
R01	21.36	18.55 – 24.60	42.09	3.29						Nasal preparations
R06	40.77	35.02 – 47.46	53.59	2.78						Antihistamines for systemic use

Table 5 (*continued*)

ICPC	OR	95%-CI	Prevalence (%)		OR per sex group		OR within age			Description ICPC codes
			AR	No AR	boy	girl	2-6	7-12	13-18	
Medication related to atopic disorders										
N03	***0.82***	***0.47 – 1.43***	***0.34***	***0.41***			0.50	0.20	1.25	Antiepileptic†
D11	***1.27***	***0.91 – 1.76***	***1.19***	***0.94***			2.01	2.40	0.96	Other dermatological preparations†
D06	1.38	1.16 – 1.65	4.49	3.29						Antibiotics and chemotherapeutics for dermatological use
J01	1.41	1.27 – 1.57	13.30	9.85						Antibacterial for systemic use
M01	1.43	1.22 – 1.67	5.98	4.30						Anti-inflammatory and anti-rheumatic products
D01	1.46	1.23 – 1.75	4.54	3.15						Antifungals for dermatological use
N02	1.51	1.18 – 1.92	2.44	1.64						Analgesics
A06	1.51	1.27 – 1.81	4.62	3.12						Laxatives
A02	1.68	1.28 – 2.19	2.11	1.27						Drugs for acid-related disorders
R05	1.80	1.40 – 2.31	2.55	1.43						Cough and cold preparations
S01	8.89	7.61 – 10.37	20.51	2.82						Ophthalmologicals
C01	10.31	3.69 – 28.80	0.60	0.06						Cardiac therapy (e.g. epinephrine auto-injectors)
V01	#	# – #	1,43	0,00						Allergens (e.g. immunotherapy)

† significant (p≤0.01) influence of age; # OR could not be calculated; ***Italic****: overall model not significant*

Sex or age did not influence the prescription of AR-related medication in children clearly with AR.

AR-related medication was also prescribed for children that were not registered as having AR. For AR-related medication about 4.7-12.5% of the children with atopic comorbidity received these prescriptions, compared to 2.8-3.1% of the non-atopic children. Medication related to atopic eczema (OR: 2.7-3.4) and asthma (OR: 3.3-4.4) were prescribed more frequently in children with AR.

Atopic triad (Table 6)

In total 559 children, who had all three atopic disorders, received more atopic-related prescriptions compared to non-atopic children (94% vs. 10%). Dermatological corticosteroids were prescribed more often for these children compared to non-atopic children (56.4% vs. 3.2%; OR 39.3). Also, the prescription of anti-asthmatics is much higher in these children compared to non-atopic

Table 6 Significantly (p≤0.001) associated medication in children diagnosed with **Atopic Triad** (AT) (p≤0.001) (n=1,118)

ATC	OR	95% CI	Prevalence (%)		Description ATC codes
			AT	No AT	
Atopic eczema related medication					
D02	21.73	12.42 – 38.01	35.42	2.50	Emollients and protectives
D07	39.29	23.84 – 64.75	56.35	3.22	Corticosteroids, dermatological preparations
Asthma related medication					
H02	28.56	3.86 – 211.08	4.83	0.18	Corticosteroids for systemic use
R03	176.13	81.65 – 379.94	68.34	1.25	Anti-asthmatics
Allergic rhinitis related medication					
R01	36.84	20.74 – 65.45	46.69	2.33	Nasal preparations
R06	82.50	45.16 – 150.70	62.79	2.15	Antihistamines for systemic use
Medication related to atopic disorders					
J01	2.10	1.47 – 2.99	18.25	9.66	Antibacterials for systemic use
D06	2.93	1.71 – 5.02	9.30	3.40	Antibiotics and chemotherapeutics for dermatological use
S01	6.17	3.94 – 9.66	22.36	4.47	Ophthalmologicals
D11	6.28	2.16 – 18.24	4.29	0.72	Other dermatological preparations
J07	17.21	4.10 – 72.30	5.72	0.36	Vaccines
C01	#	# – #	5.90	0.00	Cardiac therapy (e.g. epinephrine auto-injectors)

OR could not be calculated

children (68.3% vs. 1.3%; OR: 176.1). This pattern is also seen for antihistamines (62.8% vs. 2.2%; OR: 82.5). Antibiotics, especially penicillin and macrolides, were prescribed more frequently in children with all three atopic disorders.

Discussion

The present study shows that atopic children received both more atopic and non-atopic prescriptions, compared to non-atopic children. Age and gender did not clearly explain these differences. The prescriptions provided by a GP to relieve atopic symptoms seem to reflect preferred medication in relevant evidence-based medicine guidelines.

For atopic eczema the combination of emollients (cornerstone of the treatment) and corticosteroid crèmes are advised (3). However, a corticosteroid crème was prescribed more frequently than an emollient. An explanation could be the freely

available emollients at pharmacies or drugstores, which were not systematically registered in our database.

Anti-asthmatics are prescribed in accordance with the guidelines (4). This clear reflection of the guideline could be the result of the policy that anti-asthmatics are not freely available. However, since inhaled corticosteroids are the cornerstone of asthma treatment, the relatively low use (29%) of inhaled corticosteroids (ICS) is remarkable. There are three possible explanations for this observation. Primarily, GPs will treat more children with mild intermittent asthma and don't see more severe cases that justify (continuous) ICS use. Unfortunately, results from e.g. the 'Asthma Control Questionnaire' were not available to check this assumption. Secondly, there could be an overestimation of asthma diagnoses in the EHRs, since a proportion of the children will outgrow asthma. Finally, it could also reflect insufficient treatment, which could be supported by the observation that 3.1% received a short course of steroid tablets. All three explanations raise the question as to whether GPs adequately monitor the asthmatic children registered in their practice

Although oral antihistamines for AR are freely available, >70% of the patients still consult their GP for advice regarding AR-relevant medication. A systematic review (1) reported that the prevalence of AR in the open population, compared to the prevalence of AR in a primary care clinic, is much higher; therefore, we assume that only more severe cases visited the GP. This could explain the high number of prescriptions. Possibly because the free available antihistamines were not sufficient in the treatment of AR symptoms. Although the prescribed medication for AR also reflects the guideline (5), more information on the severity and type of symptoms of patients is needed to make a clearer judgement.

Finally, the existence of a fourth distinct group of atopic children is supported by the observation that children with all three atopic disorders receive more atopic-related prescriptions (94%) (with a distinct pharmacological profile) from their GP compared to non-atopic children or children with only one atopic disorder. This suggests that children with all three atopic disorders have a different phenotype. The GP seems to be aware of this, considering the high rate of prescriptions given to these children. However, since there is evidence for insufficient labeling of atopic disorders, this group might be even larger than observed in the present study.

This study shows that specific ATC codes are often prescribed for specific atopic disorders. Nevertheless, GPs did prescribe atopic-related medication to atopic children, even when they were not registered with that specific atopic disorder. Taking into account that the three atopic disorders are closely related, we postulate that when a child is already diagnosed with at least one atopic disorder and that child uses atopic-related medication for the other atopic disorders, it is plausible that the child will in fact have these other atopic disorders. For example, a child

is diagnosed with eczema and receives anti-asthmatics, it is likely that this child will also have asthma. Non-atopic children also receive prescriptions for specific atopic-related medication. Both of these observations might reflect underdiagnosis, or at least insufficient registration. A different study design is needed to prove this hypothesis. According to Mulder et al. (10), children diagnosed with asthma can be reliably identified with a range of medication proxies. However, the use of prescription data for the identification of children diagnosed with atopic dermatitis and AR remains questionable.

This study also shows that atopic children received more non-atopic related medication. For example, the prescription of dermatologicals is particularly increased in children with atopic eczema. The main indication seems to be the treatment of skin infections (antifungals, antibiotics, antiseptics). In children with atopic eczema the skin barrier function is negatively affected, causing an increased risk of secondary skin infections. All atopic children received more oral antibiotic prescriptions. GPs either consider these children to be at increased risk for a complicated course of an infection, or these children indeed have more bacterial superinfections that justify the oral antibiotics. Antibiotics are particularly interesting to study, since their use is associated with an increased risk for the development of atopic disorders, in particular asthma (11, 12). Or the relation between atopic disorders and antibiotics is a result of the confounding effect of early respiratory infections (13). Future research should focus on the reason why these atopic children receive more antibiotics and whether this is indeed necessary. When examining the data in more detail, one specific pattern stands out. Although in absolute terms not frequently prescribed, there appears to be a stronger indication for the prescription of epinephrine auto-injectors (C01) in children with atopic disorders. The only indication for such medication is the treatment of anaphylaxis. Apparently, these children are at higher risk for the development of severe allergic reactions (possibly due to a food allergy or insect bites), a well-known comorbidity for atopic children. These IgE-mediated food allergies could also explain gastro-intestinal symptoms that are frequently observed in atopic children (14, 15), which might explain prescriptions related to the gastro-intestinal system (e.g. laxatives). The possibility that gastrointestinal symptoms might be a manifestation of adverse reactions to drugs prescribed for e.g. asthma and AR, was considered. However, Powel et al. (14) found this unlikely, as the prevalence of gastrointestinal symptoms in patients with asthma treated with inhaled adrenergics, inhaled corticosteroids or neither of these drugs, showed no significant differences. Unfortunately, the ICPC-1 coding system does not allow the registration of food allergies, so this could not be explored. Overall, atopic children receive more (different) prescriptions compared to non-atopic children, indicating that children with atopic disorders should be better monitored by their GP.

For the present study we used an extensive and representative general practice database (7). The large number of children gives the study substantial power and generalizability. This allowed evaluation of links between atopic disorders and rare prescriptions, such as 'epinephrine auto-injectors' and immunotherapy, both of which were associated with atopic disorders in this study. Using only data from general practices with sufficient data quality increases the reliability of this study. Furthermore, ATC codes were automatically attached when a GP prescribed medication using the electronical medical record system.
A limitation of the present study is related to which ICPC code the GPs uses for the episodes of the atopic disorders. For example, a child with a wheeze could be labeled either as 'asthma' (R96) or labeled as 'wheeze' (R03). This could result in both overestimation or underestimation of asthma. To decrease this risk of overestimation of atopic disorders, some episodes were corrected to select more severe cases. Furthermore, due to the hierarchical structure of the data (patients registered in general practices), a multi-level logistic regression analysis was performed to test whether clustering effects influenced our findings. Since this was not the case, only the results of the logistic regression analyses were presented. Another limitation regarding this type of explorative study is the unavoidable multiple testing. Therefore, a low p-value was used. Furthermore, the aim of this study was only to explore associations and interactions in atopic children and not to test specific hypotheses. Therefore, type 1 errors cannot be avoided; some associations emerging from this study might in fact reflect these type 1 errors such as antiepileptic and anthelmintic prescriptions. Finally, atopic children might visit the GP more frequently than non-atopic children. This can result in more prescriptions for atopic children and might partly explain some of the associations found. In future research, the number of prescriptions might need to be taken into account in the analyses.

Conclusions

The prescriptions provided by a GP to relieve atopic symptoms seem to reflect preferred medication in relevant evidence-based medicine guidelines. The present study shows that specific atopic-related prescriptions are prescribed for atopic as well as for non-atopic children that are not registered as having that specific atopic disorder. This observation might reflect underdiagnosis or at least insufficient registration and the GP needs to be aware of this. Overall, atopic children receive more (different) prescriptions compared to non-atopic children. This indicates that children with atopic disorders need better monitoring by their GP.

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Appendix 1

ATC Codes	Description
Alimentary tract and metabolism	
A01	Stomatological preparations
A02	Drugs for acid related disorders
A03	Drugs for functional gastrointestinal disorders
A04	Antiemetic and antinauseants
A05	Bile and liver therapy
A06	Laxatives
A07	Antidiarrheal, intestinal anti-inflammatory/anti-infective agents
A08	Antiobesity preparations, excluding diet products
A09	Digestives, including enzymes
A10	Drugs used in diabetes
A11	Vitamins
A12	Mineral supplements
A13	Tonics
A14	Anabolic agents for systemic use
A15	Appetite stimulants
A16	Other alimentary tract and metabolism products
Blood and blood forming organs	
B01	Antithrombotic agents
B02	Antihemorrhagics
B03	Antianemic preparations
B05	Plasma substitutes and perfusion solutions
B06	Other haematological agents
Cardiovascular system	
C01	Cardiac therapy
C02	Antihypertensives
C03	Diuretics
C04	Peripheral vasodilators
C05	Vasoprotectives
C07	Beta blocking agents
C08	Calcium channel blockers
C09	Agents acting on the renin-angiotensin system
C10	Lipid modifying agents
Dermatologicals	
D01	Antifungals for dermatological use

ATC Codes	Description
D02	Emollients and protectives
D03	Preparations for treatment of wounds & ulcers
D04	Antipruritics, incl antihistamines, anaesthetics, etc.
D05	Antipsoriatics
D06	Antibiotics and chemotherapeutics for dermatological use
D07	Corticosteroids, dermatological preparations
D08	Antiseptics and disinfectants
D09	Medicated dressings
D10	Anti-acne preparations
D11	Other dermatological preparations
Genito-urinary system and sex hormones	
G01	Gynaecological anti-infectives and antiseptics
G02	Other gynaecologicals
G03	Sex hormones and modulators of the genital system
G04	Urologicals
Systemic hormonal preparations, excluding sex hormones and insulins	
H01	Pituitary and hypothalamic hormones
H02	Corticosteroids for systemic use
H03	Thyroid therapy
H04	Pancreatic hormones
H05	Calcium homeostasis
Anti-infective for systemic use	
J01	Antibacterials for systemic use
J02	Antimycotics for systemic use
J04	Antimycobacterials
J05	Antivirals for systemic use
J06	Immune sera and immunoglobulins
J07	Vaccines
Antineoplastic and immunomodulating agents	
L01	Cytostatics
L02	Endocrine therapy
L03	Immunomodulating agents
L04	Immunosuppressive agents
Musculo-skeletal system	
M01	Anti-inflammatory and anti-rheumatic products
M02	Topical products for joint and muscular pain
M03	Muscle relaxants

ATC Codes	Description
M04	Antigout preparations
M05	Drugs for treatment of bone diseases
M09	Other drugs for disorders of the musculo-skeletal system
Nervous system	
N01	Anaesthetics
N02	Analgesics
N03	Antiepileptics
N04	Anti-Parkinson drugs
N05	Psycholeptics
N06	Psychoanaleptics
N07	Other nervous system drugs
Antiparasitic products, insecticides and repellents	
P01	Antiprotozoals
P02	Antihelmintics
P03	Extoparasiticides, incl. scabicides, insecticides and repellents
Respiratory system	
R01	Nasal preparations
R02	Throat preparations
R03	Anti-asthmatics
R05	Cough and cold preparations
R06	Antihistamines for systemic use
R07	Other respiratory system products
Sensory organs	
S01	Ophthalmologicals
S02	Otologicals
S03	Ophthalmologicals and otologicals preparations
Various	
V01	Allergens
V03	All other therapeutic products
V04	Diagnostic agents
V06	General nutrients
V07	All other non-therapeutic products
V08	Contrast media
V09	Diagnostic radiopharmaceuticals
V10	Therapeutic radiopharmaceuticals

Chapter 8

Increased healthcare utilisation among atopic children compared to non-atopic children in general practice

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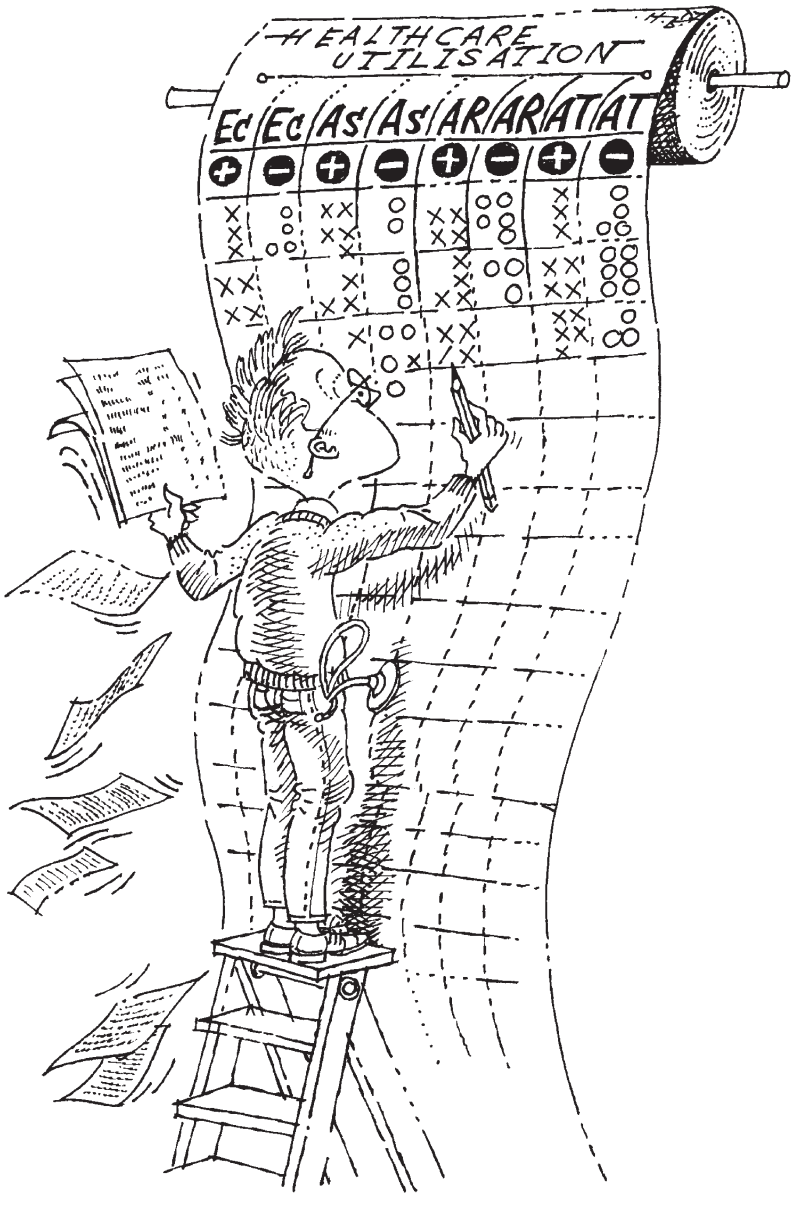
Submitted



Abstract

Purpose: To investigate the use of general practice resources (i.e. consultation visits, telephone contacts and home visits) in children with physician-diagnosed atopic disorders compared with non-atopic children.

Method: All children (aged 0-18 years) listed in a representative general practice database were selected in 2014. Children diagnosed with atopic eczema, asthma, allergic rhinitis or 'having all three atopic disorders' were matched on age and gender with non-atopic controls within the same practice. For all these different groups, the number and frequency of children contacting the general practitioner (GP) were calculated.

Results: Of the children with atopic eczema (n=15,202), 80% consulted the GP compared with 67% of their matched controls. Also, of the asthmatic children (n=7,754) 80% consulted the GP compared with 65% of their matched controls, and for children with allergic rhinitis (n=6,710) this was 82% (controls: 66%). Children with all three atopic disorders consulted the GP most often in 2014 (91%), compared with 68% of their matched controls. On average a child with atopic eczema contacted the GP 2.8 times a year (controls: 1.9), for asthmatic children the contact frequency was 3.0 (controls: 1.9), and for allergic rhinitis 3.2 (controls: 1.9). For having all three atopic disorders the contact frequency was 4.3 (controls: 2.0). Consultations related to the atopic disorders investigated only explain a smaller part of the increased healthcare utilisation in atopic children.

Conclusions: Atopic children use more general practice resources compared to non-atopic children, although this is not explained by regular follow-up visits of the atopic children.

Background

Atopic eczema, asthma and allergic rhinitis (AR) are among the most common chronic disorders in children (1, 2). As they are all associated with atopy (i.e. the tendency to develop an IgE-mediated immune response to allergens) they are often referred to as 'atopic disorders'. Although these atopic disorders in children represent a burden on general practice resources, the extent to which is largely unknown. A recent study examined healthcare utilisation in atopic children in a general practice setting. This study, based on health surveys, showed that children with atopic eczema, asthma, and AR used more healthcare resources than children without these disorders (3). However, questionnaire-based diagnoses cannot be simply inter-changed with physician-based diagnoses (1). When studying healthcare utilisation in a general practice setting, a diagnosis based on a physician's assessment, e.g. general practitioner (GP), provides more realistic results and should therefore be preferred. Previous studies examining healthcare utilisation of atopic children were often conducted in different clinical settings (e.g. birth cohorts). Also, whereas most of the studies on healthcare utilisation have focused on asthma (3-9), only a few focused on atopic eczema (3, 10) and allergic rhinitis (3). All these studies demonstrated that the healthcare utilisation of atopic children is significantly higher compared with non-atopic children. However, to our knowledge no study has examined to what extent this increased use of healthcare resources reflects extra consultations regarding the atopic disorders (e.g. consultations for follow-up), or reflects consultations regarding (non-)atopic comorbidity (e.g. consultations for common symptoms occurring in childhood).

Additional knowledge on healthcare utilisation in general practice is important for the planning of healthcare services and the workforce required. Therefore, the present study aimed to quantify the current health burden posed by atopic eczema, asthma, AR and children having all three atopic disorders, on general practice resources, as based on electronic health records. Furthermore, a differentiation is made between atopic-related consultations and non-atopic related consultations.

Methods

NIVEL Primary Care Database

Generally, all non-institutionalized residents in the Netherlands are registered in a general practice, even if they do not contact the GP. Since 2001, NIVEL-Primary Care Database (NIVEL-PCD) includes routinely extracted data from electronic

health records (EHRs) from a representative sample of Dutch general practices (11), including information about declared encounters, prescribed medication, and diagnoses. Diagnoses were recorded and classified according to the International Classification of Primary Care 1 (ICPC-1) (12). In 2014, we used data from all NIVEL-PCD practices (at least 500 listed patients; standard practice size: 2,350 patients) with sufficient data quality, fulfilling the following criteria: complete medical and financial registration of encounters (defined as ≥ 46 weeks per year), and sufficient ICPC coding of diagnostic information (defined as ≥ 70% of the recorded encounters with an ICPC code). An additional requirement was a minimum follow-up of three years for an individual child (e.g. data had to be available for 2012-2014), to reduce the risk of registration bias; for this reason, only data for children aged ≥ 2 years are presented here.
Dutch law allows the use of extracts of EHRs for research purposes under certain conditions. According to Dutch legislation, for the present type of observational study, neither informed consent nor approval from a medical ethics committee was required (Dutch Civil Law, Article 7:458).

Atopic children

When available, the EHRs from 2002-2014 were examined to avoid missing any relevant atopic diagnosis made in the past. Since GPs inevitably work with probability diagnoses, there is a risk of misclassification. Therefore, ICPC codes (e.g. S87: atopic dermatitis; R96: asthma; R97: AR) and their related episodes of care were corrected to select cases with a higher probability of the clinically relevant disorder. This method is described in detail elsewhere (2). In practice, an atopic episode of care was maintained if (based on available data from EHRs in the period 2002-2014) the child had at least two contact moments in that episode of care (e.g. S87; R96; R97) and had received at least two relevant prescriptions. In the Dutch setting, prescriptions are linked with a code based on the Anatomical Therapeutic Chemical (ATC) Classification System, making the identification of these relevant prescriptions possible. For atopic eczema the ATC code D07 (dermatological corticosteroids) was used, for asthma the ATC code R03 (drugs for obstructive airway diseases) was used, and for allergic rhinitis the ATC codes R01AC (nasal preparation of antiallergic agents, excluding corticosteroids), R01AD (nasal preparation of corticosteroids) and R06 (antihistamines for systemic use) were used. These medication proxies have been tested by Mulder et al. using registered diagnoses as a gold standard (13). If the child did not meet these criteria, the child was considered not to have that atopic disorder. It was not a requirement that the patient had contacted the GP in 2014 for that specific atopic disorder.

Atopic triad

In contrast to the traditional classification of children with atopic eczema or asthma or AR, according to a meta-analysis a fourth distinct group of children, with all three atopic disorders, might exist (1). Therefore, 'atopic triad' episodes were developed for research purposes to learn more about this potentially unique group of children. An atopic triad was only defined when a child was diagnosed with all three atopic disorders (corrected to select cases with a higher probability of the clinically relevant disorder), based on available data from EHRs in the period 2002-2014.

Design

In a nested case-control study design, for each atopic child one matched control patient was selected (not diagnosed with an atopic disorder) within the same general practice, based on age and gender (in 2014). When studying children with atopic eczema, asthma or AR for this study, only those children that had one atopic disorder were selected.

Statistical analyses

In the Netherlands, a financial declaration is automatically created in the EHRs at the end of every consultation (i.e. consultation visits, telephone contacts and home visits; the ordering of repeat medication was excluded). Financial declaration recordings from the year 2014 where therefore used to determine healthcare utilisation in general practice. Diagnoses were linked with declared encounters on the same day. If a child consulted the GP for both an atopic-related problem as well as for a non-atopic-related problem, the declared encounter was considered atopic related. All patients aged between 0 and 18 years were selected. Two different epidemiological markers were calculated: i) the percentage of patients consulting the GP in one year, including the percentage of patients consulting the GP for the specific atopic disorder of interest, and ii) contact frequency, defined as the number of declared encounters overall, including the number of declared encounters for a specific atopic disorder in one year.

For the year 2014, health care utilisation and contact frequency rates were calculated for atopic eczema, asthma, AR and the atopic triad in males and females for the age groups 2-6 years, 7-12 years, 13-18 years and 2-18 years. For the analyses of children with either atopic eczema or asthma or AR, the child was not diagnosed with any of the other atopic disorders. Statistical differences between the groups were tested using chi-square tests (the percentage of patients consulting) and t-tests (contact frequency). Due to multiple testing, differences were considered statistically significant with a p-value < 0.001. All analyses were performed with Stata 14.1.

Results

General characteristics

In 2014, 409,312 children were identified from the NIVEL-PCD. From this group children were identified fulfilling the selection criteria with: i) only eczema (n=15,202), ii) only asthma (n=7,754), iii) only AR (n=6,710) and iv) all three atopic disorders (n=555). For all these atopic children, one control patient (not diagnosed with an atopic disorder) was matched. For this study, 307 different general practices were involved. Of the included children with only atopic eczema, only asthma, only AR and with all three atopic disorders, 48.2%, 58.9%, 57.9% and 61.6%, respectively, were male.
In both the atopic and non-atopic group, girls visited the GP more often compared with boys. When examining age in more detail, boys showed an overall decrease in consultation rates as they became older, whereas girls showed a dip in the consultation rate just before adolescence (7-12 years). Both these trends were the same in atopic as well as non-atopic children (Tables 1 and 2).

Children with only atopic eczema

In 2014, 80% of the children diagnosed with only atopic eczema consulted their GP, compared with 67% in the control group ($p<0.001$). Of the children with atopic eczema, only 24% consulted their GP because of their atopic eczema. When examining the contact frequency, children with atopic eczema consulted their GP on average 2.8 times/year, compared with 1.9 consultations a year in the control group (difference 0.9 times/year; $p<0.001$). The average contact frequency for atopic eczema-related consultations was only 0.4 times/year; therefore, 0.5 of the additional consultations a year were due to non-atopic related reasons for consultation. The differences in contact frequencies (presented here and also below) are not explained by the few children who consulted their GP very often.

Children with only asthma

In 2014, 80% of the asthmatic children consulted their GP (not having another atopic diagnosis), compared with 65% in the control group ($p<0.001$). Only 28% of the asthmatic children had asthma related consultations with their GP. Asthmatic children consulted their GP on average 3.0 times/year, compared to 1.9 consultations a year in the control group (difference 1.1 times/year; $p<0.001$). Since an asthmatic child consulted their GP for asthma-related problems only 0.5 times/year, this implies that an atopic child consults the GP 0.6 times/year extra for other morbidity.

Table 1 Healthcare utilisation in 2014 for children with only atopic eczema, only asthma, only allergic rhinitis (AD: atopic disorder).

	Total no. of children	Children consulting a GP (%) *		Children consulting a GP for disorder (%)	Contact frequency (contact/ year) *		Contact frequency for disorder (contact/ year)
	n	No AD	AD	AD	No AD	AD	AD
Atopic eczema							
Male	**14,662**	**66**	**78**	**22**	**1.8**	**2.6**	**0.3**
Male 2-6 years	6,264	72	84	24	2.1	3.0	0.4
Male 7-12 years	5,322	63	75	21	1.6	2.3	0.3
Male 13-18 years	3,076	60	73	23	1.5	2.2	0.3
Female	**15,742**	**68**	**81**	**26**	**2.1**	**3.0**	**0.4**
Female 2-6 years	5,728	71	82	27	2.1	3.0	0.4
Female 7-12 years	6,126	62	77	23	1.7	2.5	0.3
Female 13-18 years	3,888	72	85	31	2.5	3.6	0.5
Total group	**30,404**	**67**	**80**	**24**	**1.9**	**2.8**	**0.4**
Asthma							
Male	**9,132**	**62**	**78**	**27**	**1.6**	**2.7**	**0.5**
Male 2-6 years	2,174	72	86	32	2.1	3.4	0.6
Male 7-12 years	3,698	60	78	28	1.4	2.5	0.5
Male 13-18 years	3,260	59	73	23	1.5	2.3	0.4
Female	**6,376**	**69**	**83**	**30**	**2.2**	**3.5**	**0.6**
Female 2-6 years	1,440	73	86	35	2.3	3.5	0.7
Female 7-12 years	2,292	63	79	24	1.7	2.7	0.4
Female 13-18 years	2,644	73	85	32	2.5	4.2	0.7
Total group	**15,508**	**65**	**80**	**28**	**1.9**	**3.0**	**0.5**
Allergic rhinitis							
Male	**7,766**	**62**	**79**	**35**	**1.6**	**2.7**	**0.5**
Male 2-6 years	326	75	94	52	2.3	4.4	1.0
Male 7-12 years	2,682	64	82	42	1.6	2.8	0.7
Male 13-18 years	4,758	59	77	30	1.5	2.4	0.4
Female	**5,654**	**71**	**87**	**39**	**2.4**	**3.8**	**0.6**
Female 2-6 years	218	77	95	48	2.2	5.0	0.9
Female 7-12 years	1,608	63	82	41	1.7	3.0	0.7
Female 13-18 years	3,828	74	88	38	2.7	4.1	0.6
Total group	**13,420**	**66**	**82**	**37**	**1.9**	**3.2**	**0.6**

* All differences are significant ($p < 0.001$)

Table 2 Healthcare utilisation in 2014 for children with atopic triad (AT) (AR: allergic rhinitis).

	Total no. of children	Children consulting a GP (%) *		Children consulting a GP for eczema (%)	Children consulting a GP for asthma (%)	Children consulting a GP for AR (%)	Contact frequency (contact/year) *		Contact frequency for eczema (contact/year)	Contact frequency for asthma (contact/year)	Contact frequency for AR (contact/year)
	n	No AT	AT	AT	AT	AT	No AT	AT	AT	AT	AT
Male	**684**	**65**	**89**	**29**	**35**	**35**	**1.7**	**3.9**	**0.5**	**0.7**	**0.5**
Male 2-6 years	98	67	98	35	49	53	1.9	5.8	0.5	0.9	1.1
Male 7-12 years	352	66	89	27	35	32	1.6	3.6	0.5	0.6	0.5
Male 13-18 years	234	63	85	28	31	32	1.6	3.4	0.4	0.6	0.4
Female	**426**	**72**	**93**	**38**	**39**	**40**	**2.4**	**5.0**	**0.6**	**0.9**	**0.6**
Female 2-6 years	36	72	94	67	50	44	2.8	5.0	1.2	1.3	0.8
Female 7-12 years	166	70	94	31	37	39	1.7	4.3	0.5	0.7	0.6
Female 13-18 years	224	74	93	38	39	40	3.0	5.5	0.7	0.9	0.6
Total group	**1,110**	**68**	**91**	**32**	**37**	**37**	**2.0**	**4.3**	**0.5**	**0.7**	**0.6**

* All differences are significant ($p < 0.001$)

Children with only allergic rhinitis

In 2014, 82% of the children diagnosed with only AR consulted their GP (controls 66%; p<0.001). Of the children with only AR, 37% consulted their GP because of this condition. Contact frequency of children with AR was on average 3.2 times/year, compared with 1.9 consultations a year in the control group (difference 1.3 times/year; p<0.001). Therefore, 0.6 times/year, such a consultation can be attributed to AR, whereas 0.7 times/year this is due to other health related reasons.

Children with all three atopic disorders

In 2014, only a small group of children were identified as being diagnosed with all three atopic disorders, of which 91% consulted their GP (controls: 68%; p<0.001). Examining how often these children consulted their GP in 2014 for atopic eczema, asthma and AR, revealed percentages of 32%, 37% and 37%, respectively. The contact frequency of children with all three atopic disorders was on average 4.3 times/year, compared with 2.0 consultations a year in the control group (p<0.001). The contact frequency for atopic eczema-related consultations was 0.5 times/year. For asthma-related consultations this contact frequency was 0.7 and for AR it was 0.6. Therefore, of the excess consultation rate of 2.3 times/year in this group, 1.8 is caused by the three atopic disorders and 0.5 is due to non-atopic related reasons for consultation.

Discussion

Main findings

This study is the first to examine healthcare utilisation of all three atopic disorders in a general practice setting, using physician based diagnoses. This study contributes new and detailed data on the increased healthcare utilisation associated with atopic eczema, asthma, and AR in a representative sample of Dutch children, selected from a representative general practice database. Children with atopic disorders use more general practice resources compared with children without atopic disorders. Remarkably, the excess consultation rates in children with only atopic eczema, only asthma and only AR, are mainly due to (non-)atopic symptoms and diagnoses (i.e. not labeled as any of the studied atopic disorders). In children with all three atopic disorders, a comparable excess rate (0.5 times/year) is caused by this (non-)atopic morbidity, suggesting that excess morbidity occurred in all four groups at an equal frequency. Nevertheless, children with all three atopic disorders consulted the GP

most frequently, indicating that this might be a unique group. Atopic disorders did not explain the trends regarding age and gender, that were observed in the present study.

Interpretation of findings in relation to previously published work

Our findings are in agreement with other studies (3-10) that also concluded that atopic children utilised more healthcare; however, we extended their findings by examining whether the extra consultations are a result of a child's specific atopic disorder or are due to other symptoms or diseases. Based on the present study, ≤ 50% of the extra consultations can be explained by atopic eczema, asthma and AR-related consultations. Therefore, the remainder of the consultations can be attributed to other symptoms or diseases. Although part of these consultations could still be related to atopy (i.e. food allergy or symptoms of undiagnosed atopic disorders), also non-atopic-related morbidity will most likely explain an important part of it. Future research might further unravel the precise reasons for the increased healthcare utilisation.

In 2015, a Dutch child (aged 5-17 years) consulted the GP (on average) twice a year (14), which is in accordance with the contact frequency of the control groups in the present study and endorses the conclusions that atopic children utilise more healthcare due to their atopic constitution. In contrast, senior elderly (>85 years) had 13 consultations a year (14). Unfortunately, it is not possible to compare the healthcare utilisation of atopic children with other chronic conditions in paediatric patients. Diseases like diabetes, auto-immune disorders and other serious chronic diseases in children are treated by experienced physicians (e.g. paediatricians), since the prevalence rates of these diseases are too low for GPs to gain the necessary experience. Therefore, problems associated with these chronic conditions in children will most likely be handled in secondary healthcare. Healthcare utilisation of children with these chronic conditions in general practice can therefore not be compared with atopic disorders (that are mostly treated by GPs). However, when comparing healthcare utilisation of atopic disorders with adult patients with chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM), an interesting difference emerges. Of the atopic children, at least 24-37% consulted their GP once a year for their specific atopic disorder. This is substantially lower compared to the 54% of COPD patients consulting their GP for COPD-related problems at least once a year (15) or even the 85% of diabetic patients that consults the GP at least once a year for this disease (16). The most likely explanations for this observation is that, in the Netherlands, adult patients with COPD and DM receive routine follow-up consultations as a result of 'integrated multidisciplinary care'. Unfortunately, such a follow-up system is not implemented for paediatric patients in general practice.

However, identifying asthmatic patients with insufficient follow-up and improving their medication management in accordance with asthma clinical guidelines is likely to result in lower healthcare utilisation (5) and may improve the quality of life of these children. The Dutch asthma guideline for children recommended at least one evaluation a year (17). As shown by others (18, 19), unawareness and undertreatment of asthma and AR is common and needs to be addressed. The problem of undertreatment becomes even more relevant when considering that when, for example, AR is undertreated, this can have a negative impact on asthma control (20, 21). Therefore, we suggest that atopic children will probably benefit from better follow-up (e.g. as part of 'integrated multidisciplinary care') and thereby provide them with the care they deserve.

Children with all three atopic disorders seem to have a different phenotype compared with children having one atopic disorder (22); the present study is in agreement with the conclusions of previous reports. Children with all three atopic disorders consult their GP more often than children with only one disorder. Only a minority of the extra consultations can be attributed to the specific atopic disorders of these children, suggesting that also most of these children consult the GP for associated morbidity. Therefore, children with all three atopic disorders should be considered by GPs as a separate group requiring additional attention.

Study strengths and limitations

The present study used an extensive and representative primary care database; the number of included children gives this study substantial power. Data from databases are generally considered reliable and there is no risk of recall bias. Furthermore, the present study included only practices with complete data regarding declared consultations. Using physician-based diagnosis of atopic disorders and selecting cases with a higher probability of a clinically relevant disorder (at least 2 consultations and 2 relevant prescriptions) made this study highly relevant for studying healthcare utilisation in the general practice setting.

Some limitations also need to be discussed. The present study is based on the assumption that the relevant ICPC codes are not missed; however, this risk cannot be excluded, neither can it be quantified. This study also lacks an objective measure of atopic disorders, such as lung function or allergy tests and the results of simple questionnaires to measure the severity of the disorder. For both index patients and controls, the lack of these details could mean that we did not correct for an important confounder. The study might also have included some children not currently affected, possibly due to insufficient follow-up by the GP. Finally, although our findings support the hypothesis that childhood atopic disorders increase

healthcare utilisation, we did not examine the effect on health service costs or, the precise comorbidity causing the increased healthcare utilisation.

Conclusion

Atopic children use significantly more primary healthcare resources compared with non-atopic children. Remarkably, consultations related to atopic disorders only explained a smaller part of the increased healthcare utilisation in atopic children. The majority of the excess consultations were therefore related to (non-)atopic comorbidity. Moreover, the present study provides evidence of insufficient follow-up of atopic children. Since this could result in insufficient treatment (and unnecessary loss of quality of life), we urge GPs to be more aware of their atopic children and take appropriate action so that atopic children can also benefit from 'integrated multidisciplinary care'.

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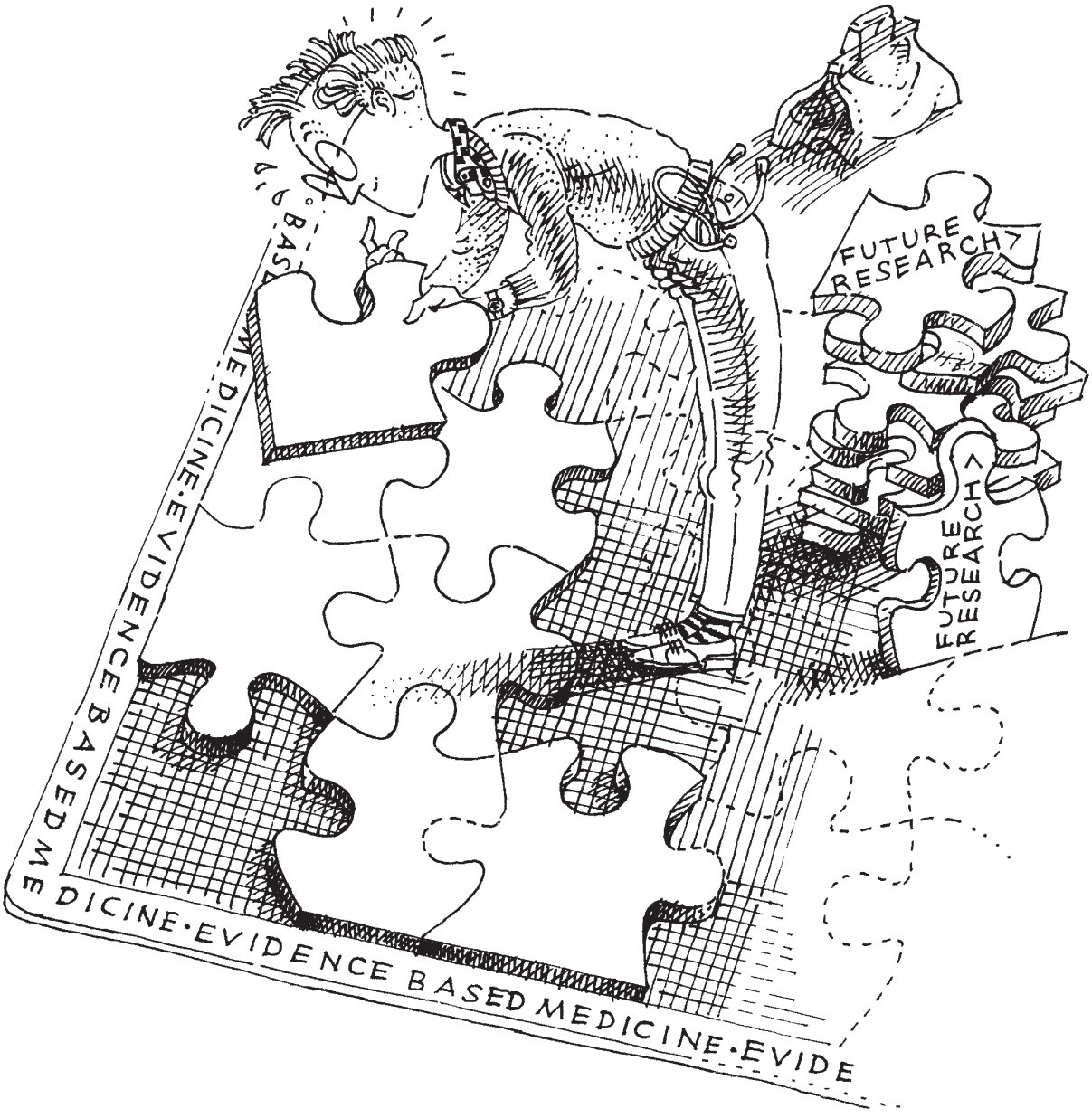
Chapter 9

General discussion



Epidemiological data are widely used to support general practitioners (GPs) in their daily practice, e.g. as a guide to the management of patients in whom disease has already developed and/or to develop strategies to prevent illness. Epidemiological data are also used by researchers to develop and prioritise research questions, and by policymakers to plan healthcare services and the workforce required. Although atopic disorders (atopic eczema, asthma, and allergic rhinitis) in children are an important health problem, epidemiological data for this group in a general practice setting are still scarce (Chapter 4). Therefore, the first part of this thesis provides an overview of the epidemiological data currently available (Chapters 2 and 4); then, the knowledge obtained from these reviews is used to acquire more reliable prevalence rates from the extensive and representative NIVEL Primary Care Database (Chapter 5). In the second part of this thesis, various characteristics of atopic children in general practice are explored, focusing on comorbidity, medication use and healthcare utilisation.
This final chapter is divided into two parts. The first part provides a brief overview of the main results emerging from this thesis. In the second part, the wider implications of the combined results are discussed and interpreted in the light of existing literature. Methodological issues are addressed, implications for the GP are discussed, and recommendations are made for future research. To guide the discussion, the second part focuses on the following research questions: i) How useful are general practice search filters in daily practice? ii) Are atopic children adequately identified by their GPs? and iii) Is there a unique fourth group of atopic children that requires special attention?

Main results

This thesis is divided into two parts. The first part (Chapters 2-5) discusses prevalence rates based on an overview of the literature and on the analyses of the NIVEL-Primary Care Database. In the second part of this thesis (Chapters 6-8), different characteristics of atopic children in general practice are explored, focusing on comorbidity, medication use, and healthcare utilisation.
In **Chapter 2**, a meta-analysis based on ISAAC questionnaires showed that the worldwide annual prevalence rates in the open population for atopic eczema, asthma and allergic rhinitis are: 7.88% (95% CI: 7.88-7.89), 12.00% (95% CI: 11.99-12.00) and 12.66% (95% CI: 12.65-12.67), respectively. The observed prevalence [1.17% (95% CI: 1.17-1.17)] of having all three disorders was almost 10 times higher than could be expected by chance. **Chapter 3** presents the development of two well-validated search filters that reliably identified studies that were conducted

in, or apply or refer to family medicine/general practice. The specific filter had a specificity of 97.4% with an adequate sensitivity of 90.3%. The sensitive filter had a sensitivity of 96.8% with an adequate specificity of 74.9%. As a result of applying the sensitive search filter, in Chapter 4 only 37% of the initially identified articles needed to be reviewed. The systematic review presented in **Chapter 4** demonstrates a substantial difference between annual prevalence rates of atopic disorders retrieved in the open population setting *versus* the general practice setting. The annual prevalence rate of atopic eczema in a general practice setting ranged from 1.8%-9.5%, that of asthma from 3.0%-6.5%, and that of allergic rhinitis ranged from 0.4%-4.1%. The prevalence rates in the open population were, on average, substantially higher; thus, data obtained in the open population cannot simply be extrapolated to the general practice setting. Therefore, new and up-to-date epidemiological data in a general practice setting would be of additional value. **Chapter 5** contributes to a better understanding of the use of general practice databases. Based on the results of Chapter 5, the strategy identifying cases with a higher probability of clinically relevant cases yields realistic prevalence rates and is also easy to apply. This strategy corrects for the risk of overestimation due to misclassification and does not assume that a child will have the disorder for life (i.e. the patient had at least two relevant consultations and at least two relevant prescriptions). Of all the included children, 6.1% had eczema, 6.1% had asthma, and 5.9% had allergic rhinitis; only 0.3% of these children had all three atopic disorders. **Chapter 6** shows that having one of the atopic disorders significantly increased the risk of also having other atopic-related symptoms, even if the child was not recorded (in the health records) as having the other related atopic disorder(s). Regarding non-atopic comorbidity, children with atopic eczema had an increased risk for (infectious) skin diseases (OR: 1.2-3.4). Airway symptoms or (infectious) airway diseases (OR: 2.1-10.3) were observed significantly more frequently in children with asthma. Children with allergic rhinitis had a significantly distinctive risk of ear-nose-throat related symptoms and diseases (OR: 1.5-3.9). According to **Chapter 7**, disorder-specific prescriptions seem to reflect evidence-based medicine guidelines for atopic eczema, asthma and allergic rhinitis. However, these disorder-specific prescriptions were also prescribed for children who were not recorded as having that specific disorder, which might be a sign of underdiagnosis. In addition, non-atopic related medication, such as laxatives and antibiotics, were more frequently prescribed for atopic children. Finally, healthcare utilisation is studied in **Chapter 8**. In 2014, of the children with atopic eczema, 80% visited the GP (controls: 67%), for asthmatic children this was also 80% (controls: 65%), for children with allergic rhinitis this was 82% (controls: 66%) and for the children with all three disorders, 91% visited the GP (controls: 68%). With regard to contact frequency: on average a child with

eczema visits the GP 2.8 times a year (controls: 1.9), for asthmatic children this is 3.0 (controls: 1.9), for allergic rhinitis this is 3.2 (controls: 1.9), and for having all three atopic disorders the contact frequency is 4.3 (controls: 2.0). Atopic children use significantly more general practice resources compared to non-atopic children. Remarkably, in atopic children, non-atopic comorbidity is the most important reason for the increased healthcare utilisation. In addition, the follow-up of atopic disorders does not seem to be sufficient. Moreover, the results in Chapters 6-8 provide more evidence that children having all three atopic disorders should be considered as a unique group.

Wider implications of the combined results

I. How useful are general practice search filters in daily practice?

Although many physicians use online medical databases to obtain biomedical information for clinical practice (1-3), the enormous volume and diversity of the available literature makes this a challenging process. Lack of time and skills, as well as a clear preference for asking an expert colleague or consulting a print source, are considered as barriers to the use of online literature databases (4, 5). Nevertheless, an effective retrieval of literature is essential to conduct health research, and develop teaching materials and health policy, as well as to support healthcare decision-making by a physician at the point of care (6).

Electronic search filters are frequently used to identify relevant studies in online medical literature databases and thereby support physicians, teachers, policymakers and researchers. A specific search filter might enhance the retrieval of appropriate articles at the point of care by the physician. On the other hand, researchers in the field of family medicine/general practice who are conducting a systematic review will need a 'sensitive' search tool to avoid missing relevant articles. Until now, all the electronic search filters that were developed for general practice have lacked adequate sensitivity (7-10). The same applies to search strategies in the Cochrane Reviews used for general practice (11-15). In both cases, these filters are likely to miss relevant publications due to low sensitivity. There is a need for a validated 'general practice' search filter to support, among others, GPs and researchers. Our specific filter was developed to help GPs find answers to clinical questions at the point of care when time is limited; however, this filter has a small risk of missing relevant articles. If an answer to the question is not found using the *specific* filter, use of the *sensitive* filter could be the next step. For example, our sensitive filter offers researchers conducting a systematic review two advantages. In the first

place, the sensitive filter provides considerable efficiency, as demonstrated in the systematic review presented in Chapter 4. As a result of applying the sensitive search filter, only 37% of the initially identified articles needed to be reviewed and, more importantly, no relevant articles would have been missed. Secondly, when conducting a review, if a researcher uses search filters that lack sufficient sensitivity, it can be assumed that relevant references will be missed. However, when applying our sensitive search filter, the risk of missing relevant references is very small. Chapter 3 presents a carefully developed method and validation process, both of which were unique and resulted in an optimally sensitive and optimally specific filter with better performance compared to the existing search filters. However, we noticed that, in many cases, the title and abstract did not disclose sufficient information to determine whether (or not) an article was relevant for general practice. In many cases the setting and/or relevance to general practice could only be determined by scrutinising the full text; this omission will influence both the sensitivity and specificity of a search filter. Therefore, we emphasise that mentioning the research setting in the title or abstract will help to find all relevant literature available for family medicine/general practice. Nevertheless, since relevant articles can still be missed if researchers fail to mention the research setting of their study in the title or abstract, checking the reference lists of the included studies is still recommended.

II. Are atopic children adequately identified by their GPs?

Atopic disorders are among the most frequent chronic conditions in children. It is known that atopic eczema, asthma and allergic rhinitis have a significant impact on the quality of life of children (and their parents) (16-18). The quality of life of an atopic child can be significantly improved by adequate treatment of the symptoms caused by these disorders, avoiding both insufficient treatment as well as overtreatment. However, when comparing prevalence rates obtained from biomedical literature (Chapters 2 and 4), these rates were substantially higher in the open population compared to the general practice setting (see Main Results). This raises the question: are atopic children adequately identified by their GPs?
Various explanations are proposed for the differences found between the two research settings. In the first place, the studies examined in this thesis were conducted between 1970 and 2014 and the reported prevalence rates might, in part, reflect a worldwide time trend (19). Therefore, when comparing the prevalence rates of the two research settings (i.e. open population vs. general practice setting), it should be established whether the time of 'data inclusion' was about the same in both settings, otherwise differences found between the prevalence rates could partly reflect this worldwide time trend. Secondly, differences also exist in the operational

definitions used between the different clinical settings and over time. For example, Van Wonderen et al. found that 60 different operational definitions were used in the literature on asthma (20); applied in a single cohort, there was a substantial variation in the estimated prevalences, depending on the operational definition used. There are also setting-dependent explanations for the differences found in prevalence rates between the two research settings. The incorrect classification of atopic symptoms in the open population, as a result of using health surveys, is also likely to explain some of the differences. This incorrect classification can be due to differences in the 'conceptual vocabulary' used by parents as compared to clinicians (21). For example, a 'runny nose' can be caused by allergic rhinitis or by a viral upper-airway infection; distinguishing between these two different causes may be difficult for a patient when completing a questionnaire. Although ISAAC put considerable effort into the validation of their questionnaires (22-25), other external influences cannot be totally ruled out. The accuracy of data obtained from a questionnaire depends on the accuracy and knowledge of the responders, and the definitions used by researchers. Dotterud et al. (26) considered questionnaires on atopic conditions to be a useful epidemiological tool to obtain rough estimates of the prevalence of atopic disorders. They concluded that, when using questionnaires in the open population, eczema was generally underestimated and allergic rhinitis overestimated.

General practice databases are a valuable source of longitudinal primary care records and are increasingly used for epidemiological research. When assessed against a gold standard (validation using GP questionnaire, primary care medical records, or hospital correspondence), most of the diagnoses were accurately recorded in the patient's electronic health record (EHR) (27, 28). However, misclassification of atopic disorders (or their related symptoms) by GPs could still occur and might also explain part of the differences found; these misclassifications might be a result of unawareness. Although the more severe cases are not likely to be missed by the GP (with the reservation that the patient visits the GP for this problem), less severe cases are likely to be missed for two reasons. First, the necessity for patients to visit their GP for atopic-related symptoms is sometimes limited. For example, allergic rhinitis might be underestimated by a GP since anti-allergic medication (e.g. antihistamines) is freely available over-the-counter, adequately dealing with the symptoms. The same applies to atopic eczema, for which emollients are freely available. Second, the GP might misinterpret the symptoms of less severe cases as being non-atopic related: for example, a child with a recurrent running and itchy nose for over 3 months, may be diagnosed as having a common cold.

Taking the above into consideration, data obtained in the open population, although widely available, cannot be simply extrapolated into the general practice setting.

Therefore, new epidemiological data, supplementing the limited epidemiological data available from previous general practice research, are needed.
Since there is evidence of insufficient recording of the ICPC codes of atopic disorders in general practice databases, a better understanding of a general practice database is needed. To achieve this, in this thesis, data from the extensive and representative NIVEL-Primary Care Database were analyzed; the number of included children (n=478,076) gave the studies in this thesis substantial statistical power. However, to properly apply the potential of such a representative database, sound methodologies are needed to convert the huge amount of raw data into meaningful and valid information. This means that, in the EHR of a patient, potential misclassification of an atopic disorder by a GP needs to be addressed. Such misclassification could result in either overestimation (29-31) or underestimation of prevalence rates (Chapter 4). Overestimation can be the result of not adequately dropping a diagnosis in an older child when he/she has outgrown the specific atopic disorder, or not dropping a probability diagnosis when the child did not eventually meet the diagnostic criteria of that specific atopic disorder. A recent study in a general practice setting demonstrated that in over 50% of the children with an ICPC code for asthma, the signs and symptoms reported in the EHR made asthma unlikely and, thus, this diagnosis was most likely overdiagnosed (31). The analyses in Chapter 5 provided an estimation of the number of children that show complete reduction of symptoms. This resulted in remission rates of 84%, 68% and 43% at age 10 years, and of 90%, 81% and 64% at age 18 years, for atopic eczema, asthma and allergic rhinitis, respectively. Overdiagnosis can lead to unnecessary treatment, disease burden, and impact on quality of life. In Chapter 5, an easy-to-apply strategy is presented to deal with part of this risk of overestimation and, thereby, to select potentially more clinically relevant cases. In this strategy, an atopic diagnosis is only maintained if the child consulted the GP at least twice and received at least two relevant prescriptions, dealing with part of the problem of working with a 'probability diagnosis'. Applying this strategy resulted in annual point prevalences for the Dutch GP setting, i.e. 6.1% had eczema, 6.1% had asthma and 5.9% had allergic rhinitis. As a result of this strategy, at the most, the prevalence rates dropped by 23% compared to the original data. Although this selection might still be too conservative in relation to what published reports suggest (31), it is a safe step in the right direction.
The 'true prevalence rates' of atopic disorders in a general practice setting are likely to be slightly higher than the ones we presented in Chapter 5 (as a result of underdiagnosis) and will almost certainly be lower than the prevalence rates found in the open population (Chapter 2). Since the ratio of overdiagnosis to underdiagnosis is unknown, it is not possible to give more reliable estimations. More data are required on the risk of both overdiagnosis and underdiagnosis.

Addressing the risk of underdiagnosis proves to be even more challenging than addressing the risk of overdiagnosis. Since some ICPC codes are missing in the EHRs, we need a way to fill in these missing codes. The most sensitive method to address underdiagnosis would be to examine the entire EHR of the individual patient to reveal clues that might suggest an atopic diagnosis; unfortunately, this is very time consuming and privacy issues are involved if this meticulous work is carried out by a third party. Another option is to use computer software that analyses free texts; however, the accuracy of this method will be determined by the quality of the script used. A study in primary care on heart failure in adult patients examined the EHRs of over 50,000 primary care patients. Heart failure signs and symptoms were frequently identified through automated text and data mining of the EHRs. This frequent identification of signs and symptoms demonstrates the rich data available within the EHRs (32). Although this technique requires further development it has the potential to help develop predictive models, also for atopic disorders in children. With the increased availability of extensive and representative general practice databases, a faster and probably more consistent way of identifying an atopic child is to use a combination of routinely and standardized coded data from EHRs such as standardised measurements, ICPC-coded comorbidity, and ATC-coded prescriptions. Analysing routinely recorded data in EHRs to identify undiagnosed asthmatic patients has been demonstrated (33), but no proxies are available for atopic eczema or allergic rhinitis. Although, 'computer-based decision-support systems' may support GPs in their daily practice to adequately identify atopic disorders, successful implementation depends on several factors: i) The right combinations of routinely recorded data need to be identified in (future) research. ii) A decision-support system needs to be integrated with EHRs. If such an integration is absent, GPs have to record data already available in the EHRs a second time, which significantly reduces the chance of successful implementation. iii) A decision-support system has to fit the daily practice: i.e. the GP should be able to control the system to match his/her available time and needs at any moment. Unfortunately, until now, the introduction of a decision-support system has been generally disappointing. To increase the chance of successful introduction of such a decision-support system, a better understanding of how these routinely recorded data can be used to identify underdiagnosed children is an essential first step.

Possibilities using routinely recorded data in general practice databases

Chapter 2 demonstrates that prevalence rates in the open population setting depend on age. Therefore, in Chapter 5, the influence of age on the prevalence rates of atopic disorders in the general practice setting was studied in more detail. The results of this study suggest that age can help in the prediction of having an atopic

disorder. For example, with increasing age the risk of a child having allergic rhinitis increases, whereas the opposite applies for atopic eczema.
In Chapter 6 it was demonstrated that children diagnosed with one atopic disorder were frequently diagnosed by their GP with symptoms associated with one of the other atopic disorders. For example, a child with atopic eczema that presents with 'wheeze' must be at a higher risk (OR: 2.0) for also having asthma, compared to a child with the same symptoms but without atopic eczema. The results emerging from this study suggest that comorbidity can help to predict atopic disorders.
In Chapter 7 we examined the use of medication in children. This chapter shows that specific drugs are often prescribed for specific atopic disorders. Nevertheless, GPs did prescribe atopic-related medication to atopic children, even when they were not recorded with that specific atopic disorder. Taking into account that the three atopic disorders are closely related (Chapter 2), we postulate that when a child is already diagnosed with at least one atopic disorder and that child uses atopic-related medication for the other atopic disorders, it is plausible that the child will in fact have these other atopic disorders. For example, a child is diagnosed with eczema and receives anti-asthmatic prescriptions, it is likely that this child will also have asthma (but is not coded as such). The results of this chapter suggest that prescriptions can help in the prediction of having an atopic disorder.
In Chapter 8 we described healthcare utilisation among atopic children. Although these data are more complicated to use for the identification of unlabelled atopic disorders, they can still support an 'automated decision-support system'. As shown in Chapter 8, atopic children consult their GP more often than non-atopic children. Therefore, above average healthcare utilisation should trigger a decision-support system to consider the possibility that a child might have an atopic disorder. Since frequent consultation can also be a sign of other chronic disorders (34) or even parental fears (rather than an indication of comorbidity), more supporting evidence of an atopic disorder should also be present.
In conclusion, there is evidence to support the hypothesis that GPs do not fully recognise atopic-related symptoms in children already diagnosed with an atopic disorder. However, more importantly, the routinely and standardised coded data from EHRs, such as ICPC-coded comorbidity and ATC-coded prescriptions, can be an important source to identify undiagnosed atopic disorders using a (yet to be developed) automated decision-support system. Therefore, the effort to examine the potential of such a system seems well justified.

Limitations using general practice databases

Limitations are encountered when using and exploring existing general practice databases. The studies presented in Chapters 5-8 are based on the assumption

that all relevant ICPC codes are recorded in the EHRs. However, as discussed above, it is reasonable to assume that there is a relevant risk of misclassification; both physicians and researchers should be aware of this limitation. Also, the completeness of registration of (for example,) other routinely recorded data might be questionable, since GPs do not always register everything. Other limitations relevant for the epidemiological exploration of general practice databases are: i) the unavoidable multiple testing involved in the studies presented in this thesis, i.e. over 9,000 different analyses were performed for the studies in Chapters 6 and 7 alone. Although conservative p-values were used in this thesis, type 1 errors cannot be avoided and some of the suggested associations might in fact reflect these type 1 errors. On the other hand, the explorative nature of these studies did not aim to test hypotheses, but rather to suggest new hypotheses that may warrant further investigation. Moreover, when focusing on clinically relevant differences, the risk of incorrect conclusions is limited. ii) No data were available on socioeconomic status, family history, tobacco smoke exposure and other lifestyle-related risk factors, whereas these risk factors (among others) can influence atopic disorders (35-40). Unfortunately, we could not correct for these risk factors, and their potential impact on the observed relations and healthcare utilisation cannot be ruled out. On the other hand, since all children with atopic disorders were matched with controls from the same general practice, all these children probably live in the same neighborhood and the effect of most of the mentioned risk factors is expected to be small. iii) Atopic children might visit the GP more frequently than non-atopic children (Chapter 8). This can result in more diagnoses and/or prescriptions in atopic children and might partly explain some of the associations found. For example, if an asthmatic child has an upper airway infection, the parents might visit the GP much sooner due to fear of an asthma exacerbation. iv) Finally, the extent to which successful data extraction can be accomplished will depend on the type of electronic health record used.

Implications for general practice

The results of the studies presented in this thesis emphasize the importance of better coding by GPs. Furthermore, the results should serve to prompt GPs to be more aware of the possible underdiagnosis of atopic conditions in children and, more specifically, in children already known with one atopic disorder. Our results also indicate that children with atopic disorders need more effective monitoring by their GP, since the results of the study in Chapter 8 indicate that these children might have insufficient follow-up.

Therefore, based on the results of this thesis, we suggest that a few easy-to-implement recommendations might help GPs in their daily practice (possibly supported, in the future, by a decision-support system):

- When a child is diagnosed with one atopic disorder, GPs should always be aware of the possibility of other atopic disorders.
- Provide routine follow-up consultations as a part of 'integrated multidisciplinary care' at least once a year, as already suggested for asthma (41).
  - critically re-evaluate the present atopic diagnosis (e.g. can the atopic diagnosis be dropped or inactivated?)
  - evaluate the presence of atopic-related symptoms (including recorded symptom diagnoses in the previous year that could reflect an atopic disorder) to identify signs of undertreatment of the present atopic disorder, or to identify unclassified atopic comorbidity
  - evaluate medication use (including freely available over-the-counter drugs) to identify unclassified atopic comorbidities, and to evaluate whether the atopic-related medications are still needed or can be stopped.

We believe that atopic children should be entitled to the same healthcare standards that adults receive through structured 'integrated multidisciplinary care' for chronic diseases like asthma, COPD, diabetes and cardiovascular diseases. Despite that GPs are very busy (42), we nevertheless encourage them to start an active follow-up policy for their atopic children. Based on relevant medical guidelines, an evaluation at least once a year seems to be preferred (41, 43-45). Since Dutch GPs already deliver 'integrated multidisciplinary care' for chronic diseases in adults, for which yearly follow-up contacts are a requirement, the logistical tools required are already in place. Furthermore, in absolute terms, this will not concern a large number of children. The current practice of 'case finding' is by no means an acceptable alternative, since the study in Chapter 8 showed that (in 2014) a substantial percentage of the children was not adequately monitored. Fortunately, nowadays, identifying children with recorded atopic disorders in a general practice is not complicated. EHRs allow GPs to easily obtain lists of patients diagnosed with specific ICPC codes, which can be used to invite these children for a follow-up consultation. We offer three practical solutions that might assist the GP in achieving an active follow-up of their atopic children. 1) Although future research should develop and validate a questionnaire in which symptom scores are obtained for all three atopic disorders, a few questionnaires are already available. These questionnaires could be used to monitor and control atopic symptoms (22-25, 46, 47), even though not all of them are validated for this purpose. These questionnaires might also help GPs to prioritise which children need to be evaluated first and to efficiently spread the flow of these consultations over a longer period; this initial inventory of symptoms (by

mail, or by telephone) can be performed by the doctor's assistant. 2) A physician-assistant could evaluate atopic disorders within the context of clearly-defined protocols that have to be developed for this purpose and which should be based on the existing medical guidelines (43-45). 3) Use the tools provided for structured 'integrated multidisciplinary care' for chronic diseases in adults, and for asthma in children, to more effectively manage these children.

Implications for future research

To support the GP in identifying undiagnosed atopic disorders, further research is needed to create proxies based on standardised and routinely recorded data in the EHRs. This will enable a decision-support system to be developed which can support GPs to better recognise atopic disorders. Although some attempts have been made for asthma (33, 48), to our knowledge no useful proxies have been created for atopic eczema and allergic rhinitis.

Since epidemiological studies on atopic disorders are reaching the limit of what can be achieved through conventional research (49), collaborative research is likely to be the future trend. The interdisciplinary exchange of ideas between general practitioners, statisticians and computer scientists can be stimulated when different research groups combine their data in data repositories. This new era of 'big data' will allow smarter and more powerful statistical analyses, especially when analysing metadata. Although several initiatives are underway to explore the possibility of merging databases, it is even more important to use unified datasets to be able to merge all these databases in the future. Therefore, epidemiological research in the general practice setting will benefit from standardising diagnostic definitions and standardised recordings of routinely registered data. Labelling consultations with a standardised code, like the International Classification of Primary Care (ICPC) (50), will allow a better exchange of data between research groups. For prescriptions, the Anatomical Therapeutic Chemical Classification System (ATC code) could be used (51). Data related to healthcare utilisation might be more complicated, since every country uses its own system; however, a 'conversion table' might be a solution to this problem. Regarding standardised measurements (e.g. weight and height), it is advised to use the recommended system of 'units of measurement'.

Albeit the ISAAC study has become the largest worldwide collaborative research project ever undertaken in the open population, we would support the development of an international collaborative research project based on general practice databases. The power of such a collaborative project would allow to analyse various research questions and aims, such as:

- Describe the differences between prevalence rates of atopic eczema, asthma and allergic rhinitis between countries.

- Estimate to what extent the observed variation in prevalence rates of atopic disorders can be explained by differences in known or suspected risk factors, or by differences in disease management.
- Explore new aetiological hypotheses regarding the development of atopic disorders in children.
- Examine time trends in the prevalence of atopic disorders in general practice.
- Determine the natural course of atopic disorders in general practice.
- Determine how atopic-related medication is used in daily practice.
- Determine whether GPs need to pay more attention to (atopic) comorbidity.

III. Is there a unique fourth group of atopic children that requires special attention?

In Chapter 2, the observed prevalence of having all three atopic disorders is 1.17% (95% CI: 1.17-1.17). This co-occurrence is substantially higher than could be expected by chance, based on the individual prevalence of each disorder (0.12%); the same observation emerged from Chapter 5. This supports the hypothesis that there could be a fourth distinct group of children with all three disorders.
In both Chapter 2 and 4, a wide variation was observed in the prevalence rates of atopic disorders. This variation has received considerable attention from other researchers (52-55). Possible causes of such variations include (amongst others): genetics (56, 57), use of paracetamol (58, 59), use of antibiotics (60, 61), diet (62), body mass index (63, 64), living in a rural area (36, 65), and air pollution (66, 67). However, none of these proposed factors fully explained this wide variation. Remarkably, when looking at the prevalence rates of having all three disorders, this wide variation does not occur to the same extent. Furthermore, the limited degree of overlap (found in Chapter 2) between the three conditions (1.17%) was very similar to that reported by others (53, 68). Asher et al. (69) even demonstrated that this overlap has been relatively consistent over a period of seven years; for 6-7 year olds this overlap increased from 0.8% to 1.0%, and for the 13-14 year olds the overlap increased from 1.1% to 1.3%. This consistency in prevalence also suggests that a fourth group of children with atopic disorders might exist.
Finally, the existence of a fourth distinct group of atopic children is also supported by different observations emerging from the studies in this thesis. In Chapter 6, some symptoms and diseases were significantly related to children having all three atopic disorders. For example, the risk for developing an 'allergy' that the GP considers relevant to register in the EHR can be considered high (OR: 17.8). Chapter 7 describes that children with all three atopic disorders receive more atopic-related prescriptions (94%) from their GP compared to non-atopic children (10%), and

compared to children with only one atopic disorder (39-70%). Chapter 8 is also in agreement with these conclusions. Children having all three atopic disorders consult their GP significantly more often than children with only one atopic disorder (contact frequency: 4.3 consultations/year vs. 2.8-3.2 consultations/year).
All this evidence suggests that children with all three atopic disorders might have a different phenotype. However, since there is evidence for insufficient labelling of atopic disorders, this group might be even larger than observed in the present thesis. In addition to the three regularly described groups of children with eczema, asthma, or allergic rhinitis, there seems to be a fourth distinct group of children who have all three disorders. This group may show distinct characteristics regarding severity, causes, treatment and/or prognosis.

Implications for general practice

GPs should be aware that atopic children with all three atopic disorders might present a more severe phenotype (e.g. needing more medication, and requiring more frequent follow-up consultations); however, additional research is needed to determine the actual clinical relevance and its related impact.

Implications for future research

We suggest that future (epidemiological) research should focus on this (potentially) distinct fourth group of children with all three manifestations. Research could address the following items. Is this group distinctive due to the severity of the symptoms? Does this group have a different genotype? Does this group have a different aetiology? Does this group need a different pharmacological approach? Does this group have a different prognosis? Is this group influenced by various (environmental) factors? These questions need to be addressed to further unravel the complexities related to identifying and treating these children with all atopic disorders in a general practice setting.

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Chapter 10

Summary

In this thesis the word 'atopic' refers to a predisposition toward developing a certain allergic hypersensitivity, which can result in the clinical diagnosis of atopic eczema (also called atopic dermatitis), asthma, or allergic rhinitis (also called allergic rhinoconjunctivitis, including hay fever). Food allergies are beyond the scope of this thesis.

Chapter 1 provides a short background of the research presented in this thesis. The atopic disorders examined in this thesis represent an important health problem in paediatric patients and create a serious burden on general practice resources as a result of frequent visits to the general practitioner (GP). Remarkably, epidemiological data from the general practice setting are scarce. Therefore, the first aim of this thesis was to obtain valid prevalence rates of atopic children in general practice. For this, two systematic literature searches were conducted to examine two epidemiological sources in more detail: one examining epidemiological data obtained from the open population using health surveys, and the other (albeit with limited availability) examining epidemiological data obtained from general practice databases. The knowledge obtained from these reviews is then used to acquire more reliable prevalence rates from the extensive and representative NIVEL-Primary Care Databases.

The second aim of this thesis was to examine different characteristics of atopic children in the same database, focussing on comorbidity, medication use, and healthcare utilisation. To our knowledge, no study has investigated the complete range of potential comorbidities in atopic children in a general practice setting, nor the complete range of potentially prescribed medication. Healthcare utilisation was also examined using the same database.

The first part of this thesis focused on obtaining valid prevalence rates of atopic children in general practice. **Chapter 2** presents the results of a systematic review (including a meta regression analysis) determining worldwide prevalence rates for children with atopic eczema, asthma, allergic rhinitis, and of having all three disorders. Data obtained from ISAAC questionnaires (including the non-official ISAAC studies) were used and the interrelationship between these disorders was examined. Therefore, the Medline, Pubmed Publisher, EMBASE, Google Scholar and the Cochrane Central Register of Controlled Trials databases were systematically reviewed. To study the interrelationships, a new approach was applied. Risk ratios were calculated, describing the risk of having two different atopic disorders when the child is known with one disorder. Finally, 31 studies were included, covering a large number of surveyed children (n=1,430,329) in 102 countries. The calculated worldwide prevalence for atopic eczema, asthma and allergic rhinitis is 7.88% (95% CI: 7.88-7.89), 12.00% (95% CI: 11.99-12.00) and 12.66% (95% CI: 12.65-12.67), respectively. The observed prevalence [1.17% (95% CI: 1.17-1.17)]

of having all three diseases is almost 10 times higher than could be expected by chance. For children with atopic eczema the calculated risk ratio of having the other two disorders is 4.24 (95% CI: 3.75-4.79), for children with asthma this is 5.41 (95% CI: 4.76-6.16), and for children with allergic rhinitis this is 6.20 (95% CI: 5.30-7.27).

The aim of the study presented in **Chapter 3** was to develop and validate objective search filters, applicable in frequently-used online medical literature databases (i.e. PubMed, Ovid (MEDLINE/ Embase), Embase.com, Cochrane), to identify studies that are conducted in, or apply to, or refer to family medicine and general practice settings. To develop a search filter for general practice, a precise definition was obtained which allows to classify articles as 'relevant' or 'irrelevant' to general practice and allowed us to create a reference standard set of articles. Using specialised software, filter candidate terms and phrases were derived from this reference standard. Using these candidate terms and phrases, an optimal sensitive filter and an optimal specific filter were created and then validated on two external validation sets. The sensitive filter has a sensitivity of 96.8% with an adequate specificity of 74.9%. The specific filter has a specificity of 97.4% with an adequate sensitivity of 90.3%. Both filters can be applied in daily practice by GPs and researchers. The quality of these filters is good when compared with other search filters applied in different scientific fields. As a result of applying the sensitive search filter, in Chapter 4 only 37% of the initially identified articles needed to be reviewed.

The review in **Chapter 4** compares self-reported prevalence rates in the open population (i.e. ISAAC studies) with clinician-diagnosed prevalence rates of the three atopic disorders in a general practice setting. The same online medical literature databases as used in Chapter 2 were systematically reviewed for articles providing data on the prevalence rates of atopic eczema, asthma and allergic rhinitis in a general practice setting. Also included were all ISAAC studies (i.e. the open population) that geographically matched a study selected from the 'GP search'.

A considerable difference was found between annual prevalence rates of atopic disorders retrieved in the open population setting versus the scarce available data in the general practice setting (e.g. in the Netherlands and the United Kingdom). The annual prevalence rate of atopic eczema in a general practice setting ranged from 1.8%-9.5%, that of asthma ranged from 3.0%-6.5%, and that of allergic rhinitis ranged from 0.4%-4.1%. On average, the prevalence rates in the open population are considerably higher compared to those in general practice.

In **Chapter 5**, the knowledge obtained from these reviews was used to acquire more reliable prevalence rates from the extensive and representative NIVEL Primary Care Database. The effects of four different strategies on the prevalences of atopic disorders were examined: 1) the first strategy examined the diagnosis as recorded

in the electronic health records, whereas 2) the second strategy used additional requirements (i.e. the patient had at least two relevant consultations and at least two relevant prescriptions). Strategies 3) and 4) assumed the atopic disorders to be chronic based on strategy 1 and 2, respectively. For this study, all children aged 0-18 years listed in this database in the period 2002-2014 (with sufficient data quality) were selected. Based on the results of Chapter 5, strategy 2, which at least corrects for the risk of overestimation due to misclassification and does not assume that a child will have the disorder for life, seems preferable and can be easily applied. This strategy will provide cases with a higher probability of a clinically relevant disorder and, therefore, yields a realistic estimation of the prevalence of atopic disorders derived from primary care data. Using this strategy, of the 478,076 included children, 28,946 (6.1%) had atopic eczema, 29,182 (6.1%) had asthma, and 28,064 (5.9%) children had allergic rhinitis. Only 0.26% children had all three atopic disorders; this is a 12-fold higher prevalence than could be expected by chance based on the three individual prevalences of the atopic disorders.

In conclusion: the first part of this thesis provides evidence to support the hypothesis that there could be a fourth distinct group of atopic children that have all three disorders. Furthermore, the significant differences between the *self-reported prevalence rates of atopic disorders in the open population* compared with *physician-diagnosed prevalence rates of atopic disorders in general practice* demonstrate that data obtained in the open population cannot simply be extrapolated to the general practice setting. This should be taken into account when considering a research topic or requirements for policy development. In turn, GPs should be aware of possible misclassification of allergic disorders in their practice, which could result in either overestimation or underestimation of prevalence rates. To retrieve valid prevalence rates, this potential misclassification of atopic disorders by a GP in the electronic health records of a patient, needs to be addressed. The strategy selecting cases with a higher probability of clinically relevant cases (Chapter 5), partly deals with the risk of overestimation by selecting cases that are, potentially, more clinically relevant. However, additional research is needed to solve the problem of identifying atopic disorders that are missed or misclassified.

In the second part of this thesis, different characteristics of atopic children in general practice are explored to gain a better understanding of general practice databases and of atopic children. This knowledge could support the development of effective methodologies that are needed to transform the huge amount of raw data obtained from databases into meaningful and valid information. Furthermore, this knowledge could help to identify atopic disorders that are missed or misclassified. We focused on comorbidity, medication use, and healthcare utilisation. For the analyses in Chapters 6-8, we used the recommended strategy from Chapter 5 to select atopic

cases with a higher probability of clinically relevant disorders. All children (aged 0-18 years) listed in the NIVEL Primary Care Database with routinely collected healthcare data in 2014 were selected. An additional requirement was a minimum follow-up of three years for an individual child, to reduce the risk of registration bias. Atopic children were matched on age and gender with non-atopic controls within the same general practice.

In **Chapter 6** a total of 404 different symptoms and diseases, and their possible association with atopic disorders, are examined. Logistic regression analyses were performed to examine the associations between the presence of atopic disorders and (non-)atopic symptoms and diseases by calculating odds ratios (OR). Having one of the atopic disorders significantly increased the risk of having other atopic-related symptoms, even if the child was not registered as having the related atopic disorder. Regarding non-atopic comorbidity, children with atopic eczema were at significantly increased risk for (infectious) skin diseases (OR: 1.2-3.4). Airway symptoms or (infectious) diseases (OR: 2.1-10.3) were observed significantly more frequently in children with asthma. Children with allergic rhinitis had a significantly distinctive risk of ear-nose-throat related symptoms and diseases (OR: 1.5-3.9). Neither age nor gender explained these increased risks.

In **Chapter 7** a total of 93 different medication groups were investigated for their possible association with atopic disorders. Logistic regression analyses were also performed to study the differences in prescribed medication between both groups by calculating ORs. Disorder-specific prescriptions seem to reflect evidence-based medicine guidelines for atopic eczema, asthma and allergic rhinitis. However, these disorder-specific prescriptions were also prescribed for children who were not registered as having that specific disorder. For eczema-related medication, about 3.7-8.4% of the children with non-eczematous atopic morbidity received these prescriptions compared to 1.4-3.5% of the non-atopic children. The same pattern was observed for anti-asthmatics (having non-asthmatic atopic morbidity: 0.8-6.2% vs. controls: 0.3-2.1%) and allergic rhinitis-related medication (having non-allergic rhinitis atopic morbidity: 4.7-12.5% vs. controls: 2.8-3.1%). Also, non-atopic related medication, such as laxatives and antibiotics, were more frequently prescribed for atopic children.

In **Chapter 8** a study is presented that aimed to investigate healthcare utilisation in children with

atopic eczema, asthma, allergic rhinitis and having all three atopic disorders in general practice. Of the children with eczema (n=15,202), 80% visited the GP in 2014 compared to 67% of controls. Also 80% of asthmatic children (n=7,754) visited the GP compared to 65% in controls and for children with allergic rhinitis (n=6,710) this was 82% and 66%, respectively. Of the children with all three

disorders 91% visited the GP (controls: 68%). On average a child with eczema visits the GP 2.8 times a year (controls: 1.9), for asthmatic children the contact frequency is 3.0 (controls: 1.9) and for allergic rhinitis 3.2 times a year (controls: 1.9). For having all three atopic disorders the contact frequency is 4.3 times a year (controls: 2.0). Remarkably, non-atopic comorbidity is the most important reason for the increased healthcare utilisation in atopic children.

In conclusion: the second part of this thesis provides additional evidence to support the hypothesis that there could be a fourth distinct group of atopic children that have all three disorders. Furthermore, there is ample evidence to support a second hypothesis: *GPs do not fully recognise other atopic disorders in children, irrespective of whether they are already diagnosed with one atopic disorder*. This indicates that children with atopic disorders need better monitoring by their GP. The routinely used and standardised coded data from electronic health records (such as ICPC-coded comorbidity, and ATC-coded prescriptions) seems to be an important source to support identification of these undiagnosed atopic disorders.

In **Chapter 9** the main results are discussed in a broader perspective, focusing on three main research questions, namely: i) How useful are general practice search filters in daily practice? ii) Are atopic children adequately identified by their GPs? and iii) Is there a unique fourth group of atopic children that requires special attention? Having discussed these topics, implications for clinical practice are addressed and recommendations are made for future research.

Chapter 11

Nederlandse samenvatting

In dit proefschrift verwijst het woord 'atopie' naar de aanleg om immunoglobulinen (antistoffen) van het type IgE aan te maken die specifiek gericht zijn tegen stoffen die in de omgeving kunnen voorkomen, zoals huisstofmijt en gras- of boompollen. Als 'atopie' klinisch manifest wordt, kan dit uiteindelijk resulteren in constitutioneel eczeem (ook wel atopische dermatitis genoemd), astma of allergische rhinitis (ook wel allergische rhinoconjunctivitis genoemd, inclusief hooikoorts). Voedselallergieën vallen buiten het bestek van dit proefschrift.

Hoofdstuk 1 beschrijft de achtergrond en de opbouw van dit proefschrift. Kort samengevat richt het onderzoek, zoals beschreven in dit proefschrift, zich op drie verschillende atopische aandoeningen bij kinderen, namelijk: constitutioneel eczeem, astma en allergische rhinitis. Deze atopische aandoeningen vormen onder kinderen een groot gezondheidsprobleem. Het is daarom des te opvallender dat er over deze aandoeningen slechts zeer beperkte cijfers beschikbaar zijn uit de huisartsenpraktijk. Het eerste doel van het onderzoek was dan ook het verkrijgen van valide prevalentiecijfers (hoe vaak komt een bepaalde ziekte voor) van deze drie atopische aandoeningen onder kinderen vanuit de huisartsenpraktijk. Als eerste werd daartoe de bestaande literatuur kritisch doorzocht middels twee *systematic reviews*, waarin twee 'epidemiologische' bronnen gedetailleerd werden bestudeerd. In de eerste *review* werd gekeken naar prevalentiecijfers die waren verkregen middels het afnemen van vragenlijsten op scholen (de zogenoemde prevalentie uit de 'open populatie'). In de tweede *review* werd er gekeken naar prevalentiecijfers die zijn gebaseerd op huisartsendatabases (de zogenoemde prevalentie uit de 'huisartsenpraktijk'). De kennis verkregen uit deze reviews kon vervolgens worden gebruikt om betrouwbaardere prevalentiecijfers te verkrijgen uit de 'NIVEL Zorgregistraties eerste lijn' (NIVEL-database). Deze database maakt gebruik van gegevens die routinematig in de zorg worden verzameld bij het leveren van zorg aan patiënten door zorgprofessionals. Hierbij kan gedacht worden aan gecodeerde diagnoses, gecodeerde recepten en gecodeerde financiële declaraties. In totaal doen 316 Nederlandse huisartsenpraktijken mee aan de onderzoeken die in dit proefschrift zijn beschreven. Deze database bevatte anonieme gegevens van 478,076 verschillende kinderen.

Het tweede doel van het onderzoek was om verschillende karakteristieken van atopische kinderen binnen de Nederlandse huisartsenpraktijk te bestuderen, waarbij de nadruk is gelegd op gediagnostiseerde comorbiditeit, voorgeschreven medicatie en het gerelateerde zorggebruik. Zover onze kennis rijkt, heeft geen enkel ander onderzoek de complete reeks van ziektes en symptomen bestudeerd bij atopische kinderen binnen de huisartsenpraktijk, noch de complete reeks van voorgeschreven medicatie. Ook het zorggebruik kon meer gedetailleerd worden bestudeerd vanuit de 'NIVEL Zorgregistraties eerste lijn'.

In het eerste deel van dit proefschrift ligt de focus dus op het verkrijgen van valide prevalentiecijfers van atopische aandoeningen bij kinderen binnen de huisartsenpraktijk. **Hoofdstuk 2** laat de resultaten zien van een *systematic review* (inclusief een meta-regressieanalyse) waarin de wereldwijde prevalentiecijfers werden berekend van kinderen met constitutioneel eczeem, astma, allergische rhinitis en het hebben van al deze atopische aandoeningen in de 'open populatie'. Om deze prevalentiecijfers te berekenen, maar ook om de onderlinge relaties tussen de drie atopische aandoeningen gedetailleerder te kunnen bestuderen, werd er gebruik gemaakt van data die waren verkregen van kinderen op school middels vragenlijsten. Deze vragenlijsten waren ontwikkeld in het kader van een grote internationale studie: 'International Study of Asthma and Allergies in Childhood' (ISAAC). Gepubliceerde data van zowel officiële als niet-officiële ISAAC-onderzoeksgroepen konden worden gebruikt voor deze review. Om geen relevante wetenschappelijke publicaties te missen werden meerdere online databases systematisch doorzocht, te weten Medline, Pubmed Publisher, EMBASE, Google Scholar en Cochrane Central Register of Controlled Trials. Om de onderlinge relaties tussen de aangegeven aandoeningen te bestuderen, is er gebruik gemaakt van een nieuwe aanpak. Hierbij werd de *risk ratio* (RR) berekend. De RR geeft het risico aan op het hebben van de andere twee atopische aandoeningen, als het kind bekend is met één atopische aandoening. Bijvoorbeeld: als de RR voor astma vijf is, betekent dit dat een kind met astma een vijf keer zo hoog risico heeft op het hebben van constitutioneel eczeem en allergische rhinitis vergeleken met een kind zonder astma. Uiteindelijk werden 31 onderzoeken geïncludeerd in deze review, waarmee in totaal 1.430.329 kinderen uit 102 verschillende landen konden worden geïncludeerd. De berekende wereldwijde prevalentie voor constitutioneel eczeem is 7,88% (95% CI: 7,88-7,89), die voor astma is 12,00% (95% CI: 11,99-12,00) en die voor allergische rhinitis 12,66% (95% CI: 12,65-12,67). De waargenomen prevalentie [1,17% (95% CI: 1,17-1,17)] van het hebben van alle drie de atopische aandoeningen was bijna 10 keer hoger dan wat verwacht had kunnen worden op basis van louter toeval. Voor kinderen met constitutioneel eczeem was de berekende *risk ratio* voor het hebben van de andere twee atopische aandoeningen 4,24 (95% CI: 3,75-4,79), voor kinderen met astma was dat 5,41 (95% CI: 4,76-6,16) en voor kinderen met allergische rhinitis 6,20 (95% CI: 5,30-7,27). Deze resultaten tonen aan dat de ziektes nauw met elkaar zijn verbonden.

In **Hoofdstuk 3** is de ontwikkeling en validatie van een objectieve zoekfilter beschreven die gebruikt kan worden voor het verkrijgen van gegevens uit veel gebruikte online databases zoals PubMed, Ovid (MEDLINE/Embase), Embase.com en Cochrane. Deze zoekfilter moet wetenschappelijke publicaties gaan identificeren die zijn uitgevoerd in, betrekking hebben op of verwijzen naar

'huisartsgeneeskunde'. Om een dergelijk filter te ontwikkelen, moest er eerst een precieze definitie geformuleerd worden van 'huisartsgeneeskunde'. Gebruikmakend van deze definitie konden vervolgens wetenschappelijke publicaties handmatig worden geclassificeerd als zijnde huisartsgeneeskundig relevant of niet. Hierdoor kon een 'referentiestandaard' worden gevormd. Uit deze referentiestandaard werden vervolgens middels specialistische software onderscheidende 'woorden' en 'zinnen' verkregen. Deze mogelijk onderscheidende 'woorden' en 'zinnen' vormden vervolgens de basis voor de ontwikkeling van een zo'n optimaal mogelijke sensitieve en specifieke filter. De ontwikkelde filters werden vervolgens gevalideerd op twee externe validatiestandaarden. De sensitieve filter had uiteindelijk een sensitiviteit van 96,8% met een adequate specificiteit van 74,9%. De specifieke filter had een specificiteit van 97,4% met een adequate sensitiviteit van 90,3%. Beide filters kunnen zowel door huisartsen als wetenschappers worden gebruikt. De kwaliteit van de filters blijkt goed te zijn, vergeleken met andere zoekfilters die ontwikkeld zijn voor andere vakgebieden. Het toepassen van de sensitieve filter voor de systematische review in Hoofdstuk 4 levert een grote mate van efficiëntie op, slechts 37% van de oorspronkelijk (zonder filter) gevonden wetenschappelijke publicaties hoeft nog maar bestudeerd te worden.

De review, zoals beschreven in **Hoofdstuk 4**, vergelijkt zelfgerapporteerde prevalentiecijfers van atopische aandoeningen uit de 'open populatie' (gebaseerd op ISAAC-studies) met de prevalentiecijfers die zijn gebaseerd op huisartsendatabases (diagnoses gesteld door huisartsen). Hiervoor zijn dezelfde online databases gebruikt als in Hoofdstuk 2 om relevante wetenschappelijke publicaties te vinden die prevalentiecijfers geven over constitutioneel eczeem, astma en allergische rhinitis in de huisartsgeneeskundige setting. Vervolgens werden ook alle relevante ISAAC-studies geïncludeerd voor zover deze geografisch gezien overeenkwamen met de geïncludeerde artikelen van de huisartsenzoekopdracht. Een aanzienlijk verschil werd gevonden tussen de jaarprevalenties van atopische aandoeningen bij kinderen in de 'open populatie' versus de 'huisartsenpraktijk'. De jaarprevalentiecijfers in de huisartsenpraktijk en open populatie varieerde van 1,8-9,5% respectievelijk 11,4-24,2% voor constitutioneel eczeem, 3,0-6,5% respectievelijk 12,3-34,2% voor astma en 0,4-4,1% respectievelijk 15,1-37,8% voor allergische rhinitis. Gemiddeld genomen zijn de prevalentiecijfers uit de 'open populatie' dus aanzienlijk hoger dan de prevalentiecijfers die worden gevonden in de 'huisartsenpraktijk'.

De kennis die is verkregen middels de reviews is vervolgens toegepast in **Hoofdstuk 5**. Het doel daarbij was om valide prevalentiecijfers te verkrijgen uit de omvangrijke en representatieve NIVEL-database. De effecten van vier strategieën op prevalentiecijfers van atopische aandoeningen werden daarom bestudeerd: 1) de eerste strategie bestudeert de diagnoses zoals deze daadwerkelijk zijn geregistreerd

in de database van NIVEL, terwijl 2) de tweede strategie extra voorwaarden stelt (een patiëntje moest minstens twee keer de huisarts hebben bezocht en minstens twee keer een relevant recept hebben ontvangen). Strategieën 3) en 4) veronderstellen dat atopische aandoeningen 'chronisch' zouden zijn, gebaseerd op respectievelijk strategie 1 en 2. Voor dit onderzoek werden alle kinderen van 0 tot 18 jaar die geregistreerd stonden in de NIVEL-database in de periode 2002-2014 (met voldoende datakwaliteit) geselecteerd. Gebaseerd op de resultaten van Hoofdstuk 5, geniet strategie 2 de voorkeur. Deze strategie corrigeert voor een deel het risico van overschatting, die het gevolg kan zijn van misclassificatie. Tevens gaat deze strategie er niet van uit dat deze atopische ziektes chronisch zijn. Deze strategie is eenvoudig toe te passen en zal kinderen selecteren met een hogere kans op een klinisch relevante ziekte. Op basis van deze strategie hadden, van de 478.076 geïncludeerde kinderen uit de NIVEL-database, 28.946 (6,1%) atopisch eczeem, 29.182 (6,1%) astma en 28.064 (5,9%) allergische rhinitis. Slechts 0,26% van de kinderen had alle drie de atopische aandoeningen. Dit is echter een twaalf keer hogere prevalentie dan kon worden verwacht op basis van het toeval.

Samenvattend: het eerste deel van dit proefschrift ondersteunt een nieuwe hypothese dat er een vierde onderscheidende groep atopische kinderen is die alle drie de aandoeningen heeft. Verder tonen de verschillen tussen de twee eerder genoemde epidemiologische bronnen aan dat cijfers verkregen uit de 'open populatie' niet zonder meer kunnen worden geëxtrapoleerd naar de 'huisartsenpraktijk'. Hiermee moet rekening worden gehouden bij het doen van wetenschappelijk onderzoek of het maken van beleid. Ook huisartsen zullen zich meer bewust moeten zijn van mogelijke misclassificatie van atopische aandoeningen in de dagelijkse praktijk. Deze misclassificatie kan zowel resulteren in een overschatting als in een onderschatting van de prevalentiecijfers betreffende atopische aandoeningen bij kinderen. Om toch valide prevalentiecijfers te verkrijgen uit de huisartsenpraktijk, moet deze potentiele misclassificatie van atopische aandoeningen door huisartsen in hun 'huisartseninformatiesysteem' (HIS) worden aangepakt. De strategie die atopische kinderen selecteert met een hogere kans op klinisch relevante aandoeningen (Hoofdstuk 5), pakt in ieder geval ten dele het risico aan op overschatting. Verder onderzoek zal nodig zijn om atopische aandoeningen te identificeren die zijn gemist of fout zijn geregistreerd in de huisartseninformatiesystemen.

In het tweede deel van dit proefschrift zijn verschillende karakteristieken van atopische kinderen in de huisartsenpraktijk bestudeerd om zo een beter begrip te krijgen van zowel atopische kinderen als van huisartsendatabases. Deze verworven kennis kan vervolgens gebruikt worden om in de toekomst methodes te helpen ontwikkelen die noodzakelijk zijn om de grote hoeveelheid ruwe data

uit huisartsendatabases om te zetten in betekenisvolle en valide data. Voorts kan deze verworven kennis mogelijk helpen bij het identificeren van atopische aandoeningen die zijn gemist of gemisclassificeerd. We zullen ons daarbij richten op door huisartsen gediagnosticeerde comorbiditeit, door huisartsen voorgeschreven medicatie en het gerelateerde zorggebruik. Voor de analyses in Hoofdstuk 6-8 wordt de voorgestelde strategie uit Hoofdstuk 5 toegepast om zo atopische kinderen te selecteren die een grotere kans hebben op een klinisch relevante aandoening. Alle kinderen (0-18 jaar) die in de NIVEL-database staan geregistreerd en van wie routinematig geregistreerde data beschikbaar zijn over het jaar 2014, zijn geselecteerd. Een aanvullende eis was echter een minimale follow-up van 3 jaar (2012-2014) om zo het risico op registratiebias te verkleinen. Uiteindelijk zijn de atopische kinderen gematcht met niet-atopische kinderen binnen dezelfde huisartsenpraktijk, op basis van geslacht en leeftijd.

In **Hoofdstuk 6** zijn de associaties bestudeerd tussen in totaal 404 verschillende symptoom- of ziektediagnoses (ICPC-codes) en de drie atopische aandoeningen. Logistische regressieanalyses werden uitgevoerd waarmee de *odds ratio* (OR) werd berekend. Deze odds ratio is een wetenschappelijke maat die aangeeft hoe sterk de relatie is tussen, in dit geval, een atopische aandoening en een (niet-)atopisch symptoom of een (niet-)atopische ziekte. Als een kind was gediagnostiseerd met één atopische aandoening dan bleek het risico op symptomen, die passen bij een andere atopische aandoening, significant te stijgen terwijl het betreffende kind niet met die andere atopische diagnose geregistreerd staat in het huisartsendossier. Bij niet-atopische comorbiditeit blijken kinderen met constitutioneel eczeem een vergrote kans te hebben op (infectieuze) huidziektes (OR: 1,2-3,4). Luchtwegsymptomen en (infectieuze) luchtwegziektes komen juist significant vaker voor bij kinderen met astma (OR: 2,1-10,3). Kinderen met allergische rhinitis liepen een uitgesproken risico op KNO-gerelateerde symptomen en ziektes (OR: 1,5-3,9). Zowel geslacht als leeftijd verklaarde de verhoogde risico's in deze studie niet.

In **Hoofdstuk 7** zijn in totaal 93 verschillende medicatiegroepen (ATC2-codes) bestudeerd voor hun mogelijke associatie met atopische aandoeningen. Logistische regressieanalyses werden ook hier uitgevoerd om de relaties tussen medicijnen en atopische aandoeningen te bestuderen. Ziektespecifieke prescripties (bijvoorbeeld inhalatoren voor astma) lijken in overeenstemming te zijn met de betreffende NHG-standaarden voor eczeem (M37), astma bij kinderen (M24) en rhinitis (M48). Het bleek echter dat deze ziektespecifieke prescripties ook voorgeschreven worden aan kinderen die niet waren gediagnostiseerd met die specifieke atopische aandoening. Voor eczeem gerelateerde medicatie gold dat 3,7-8,4% van de kinderen met astma of hooikoorts (maar zonder de diagnose eczeem), eczeem gerelateerde medicatie gebruikte tegenover 1,4-3,5% van de niet-atopische kinderen. Ditzelfde patroon is

gezien voor anti-astmamedicatie en hooikoorts gerelateerde medicatie. Kinderen met eczeem of allergische rhinitis (0,8-6,2%) kregen meer anti-astmamedicatie dan de controlegroep (0,3-2,1%). Voor hooikoorts gerelateerde medicatie gold dat 4,7-12,5% van de kinderen met eczeem of astma deze medicatie gebruikte tegenover 2,8-3,1% van de controlegroep. Ook niet-atopisch gerelateerde recepten, zoals laxantia en antibiotica, werden vaker aan atopische kinderen voorgeschreven. Zowel geslacht als leeftijd verklaarde de verhoogde risico's in deze studie niet.

In **Hoofdstuk 8** is het zorggebruik bestudeerd van kinderen die zijn gediagnostiseerd met constitutioneel eczeem, astma, allergische rhinitis en het hebben van alle drie de atopische aandoeningen. Van de kinderen met eczeem bezocht 80% de huisarts in 2014, in tegenstelling tot 67% van de patiënten in de controlegroep (gematchte kinderen zonder één van de atopische diagnoses). Ook 80% van de astmatische kinderen bezocht de huisarts in 2014, in tegenstelling tot 65% van de controlegroep en voor kinderen met allergische rhinitis lag het bezoekpercentage op 82% (controlegroep: 66%). Als een kind alle drie de atopische aandoeningen had, dan lagen de percentages nog hoger (91% versus 68%). Gemiddeld genomen bezoekt een kind met eczeem de huisarts 2,8 keer per jaar (controlegroep: 1,9). Voor astmatische kinderen is dit 3,0 keer per jaar (controlegroep: 1,9) en voor allergische rhinitis ligt de contactfrequentie op 3,2 keer per jaar (controlegroep: 1,9). Als een kind alle drie de aandoeningen had, dan was de contactfrequentie in 2014 4,3 keer per jaar (controlegroep: 2,0). Opmerkelijk genoeg zijn niet-atopische diagnoses de voornaamste reden voor dit toegenomen bezoek aan de huisarts.

Samenvattend: het tweede deel van dit proefschrift onderschrijft ook de hypothese dat er een unieke vierde groep atopische kinderen is die alle drie de aandoeningen heeft. Voorts is er voldoende bewijs om te stellen dat *huisartsen niet al hun atopische kinderen goed in beeld hebben*. Dit geeft dus aan dat er een noodzaak is om kinderen met atopische aandoeningen beter te laten volgen door hun huisarts. Verder lijken routinematig geregistreerde data in huisartseninformatiesystemen, zoals diagnoses en recepten, een rol te kunnen spelen om ongediagnostiseerde atopische kinderen te identificeren. Hiervoor is toekomstig nader onderzoek wel noodzakelijk.

In **Hoofdstuk 9** worden de belangrijkste resultaten van dit proefschrift in een breder perspectief besproken, waarbij de nadruk ligt op de volgende drie onderzoeksvragen: i) Hoe nuttig zijn huisartsenfilters in de dagelijkse praktijk voor huisartsen en wetenschappers? ii) Zijn atopische kinderen adequaat in beeld bij de huisarts? en iii) Is er daadwerkelijk een unieke vierde groep van atopische kinderen die extra aandacht behoeft? In dit hoofdstuk worden tevens praktische handreikingen gedaan voor de dagelijkse praktijk van de huisarts en worden er voorstellen gedaan voor toekomstig wetenschappelijk onderzoek.

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This thesis

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Curriculum Vitae

David Pols werd op 16 oktober 1980 geboren te Tilburg. Hij volgde het voortgezet wetenschappelijk onderwijs aan De Lage Waard te Papendrecht, alwaar hij in 2000 zijn atheneumdiploma behaalde. In datzelfde jaar begon hij, om ervaring op te doen in basaal wetenschappelijk onderzoek, onder leiding van prof.dr. P.M. van Hagen aan een onderzoek met betrekking tot somatostatine analoga in de immunologie. Na het doorlopen van de decentrale selectie kon hij in 2001 starten met de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Zijn artsexamen heeft hij in 2007 cum laude behaald, waarna hij gedurende een jaar werkzaam was als arts-assistent bij de afdeling interne geneeskunde van het Ikazia Ziekenhuis te Rotterdam. In 2008 werd hij toegelaten tot de huisartsopleiding aan het Erasmus MC. De huisartsopleiding combineerde hij met het geven van onderwijs aan bachelor- en masterstudenten geneeskunde van het Erasmus MC. In 2011 rondde hij de huisartsopleiding af waarna hij startte als waarnemend huisarts in de regio Rotterdam en Hoekse Waard. Naast zijn werk als waarnemend huisarts heeft hij zijn onderwijstaken bij het Erasmus MC voortgezet als docent binnen het studentenonderwijs. Hij begon in 2012 onder leiding van prof.dr. P.J.E. Bindels, dr. A.M. Bohnen en dr. M.M.J. Nielen aan zijn promotieonderzoek. In datzelfde jaar startte hij samen met collega-huisarts drs. M. Uil-Boersma een duopraktijk in Rotterdam Charlois. Sinds 2016 is hij begonnen als coördinator voor het huisartsgeneeskundige deel van de bachelorfase van de geneeskundeopleiding bij de afdeling huisartsgeneeskunde van het Erasmus MC. In 2017 heeft hij zijn Basiskwalificatie Onderwijs (BKO) behaald.

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In de eerste plaats wil ik Patrick Bindels bedanken. Toen ik in 2011 nog aan je vroeg of het realistisch was om te promoveren en gelijktijdig een duo-praktijk te beginnen, zei je: "Dan zal je hard moeten werken, maar dan gaat het wel lukken." Nou, daar heb je geen woord te veel of te weinig mee gezegd… Toch kijk ik terug op een goede en bovenal hele leerzame tijd. Jouw bijdrage was daarbij onmisbaar. Gedurende het gehele promotietraject was jij altijd een zeer stabiele factor en heb je mij die sturing gegeven die ik nodig had. Vooral de snelheid waarmee jij mijn manuscripten van goed en opbouwend commentaar retour zond, heb ik altijd enorm gewaardeerd. Ik ben zeer dankbaar dat jij mij als promotor hebt willen begeleiden en dat je tot het allerlaatst kritisch bent gebleven.

Heleen Moed was één van mijn initiële copromotoren. Gedurende de eerste twee jaar van dit traject was je een collega om op terug te kunnen vallen. Je was laagdrempelig te benaderen en hebt mij, gedurende de tijd dat je nog in het Erasmus MC werkte, vaak met praktische raad bijgestaan. Sinds de verhuizing naar het NA-gebouw heb ik eigenlijk mijn eerste copromotor, Arthur Bohnen, pas echt leren kennen. Jouw enorme methodologische kennis, scherpe inzichten en waardevolle aanvullingen op mijn manuscripten hebben mij enorm geholpen. Hoewel onze overleggen vaak met een korte vraag begonnen, eindigden ze steevast in 'dokterspraat'. Als laatste in dit rijtje natuurlijk mijn tweede copromotor Mark Nielen. Ik heb heel wat dagen in Utrecht versleten waarbij ik bezig was de NIVEL-database in mijn vingers te krijgen. De ene dag ging dat succesvoller dan de andere. In die periode heb je mij die sturing gegeven die ik nodig had om *zelfstandig* verder te komen. Daar heb ik enorm veel van geleerd. Daarnaast was jouw bijdrage in de laatste fase van dit promotietraject ook van grote waarde.

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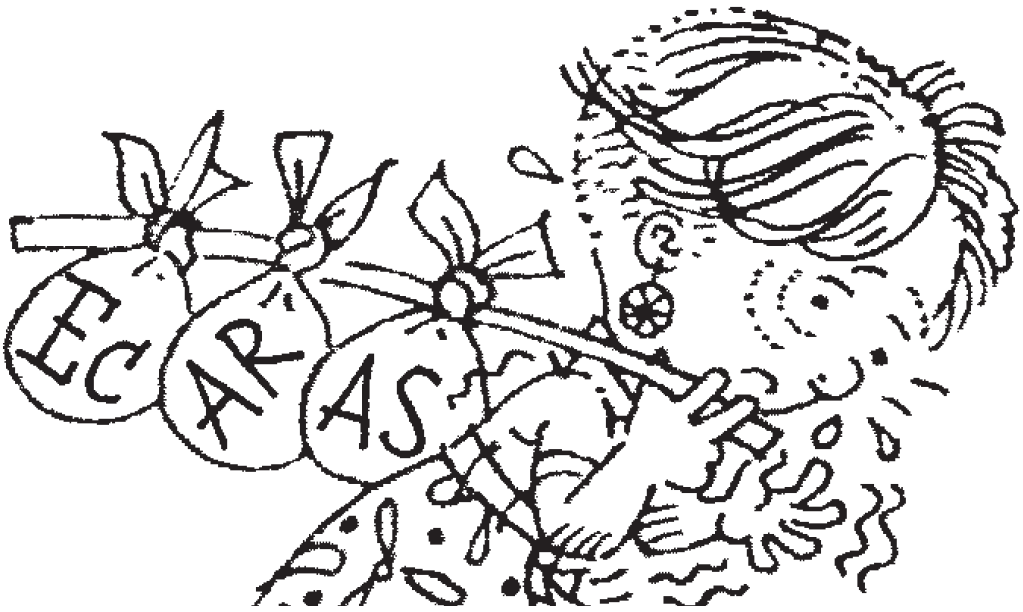
En tot slot lieve Chantal. Het valt niet in woorden uit te drukken wat jij voor mij betekent. Jouw doorzettingsvermogen: indrukwekkend. Jouw betrokkenheid: hartverwarmend. Jouw geduld (met mij): eindeloos. Jouw zorgzaamheid: onmisbaar. Jouw liefde: van levensbelang. Ik hoop van harte dat we net zo gelukkig blijven als we nu met elkaar zijn en ik kijk uit naar ieder moment dat ik samen met je mag zijn.

PhD portfolio



Erasmus MC Department:	General Practice
PhD period:	January 2012 – december 2017
Promotor:	Prof.dr. P.J.E. Bindels
Co-promotors:	Dr. A.M. Bohnen and dr. M.M.J. Nielen

VOCATIONAL TRAINING

GP training, Dept. of General Practice, Erasmus MC, Rotterdam	2008-2011

PhD TRAINING

Research skills	**Year**	**Workload (ECTS)**
Systematic literature search, Erasmus MC, Rotterdam	2012	0.3
Endnote, Erasmus MC, Rotterdam	2012	0.1
SPSS, VU, Amsterdam	2013	0.5
Biostatistics for clinicians, NIHES, Rotterdam	2013	1.0
Regression analysis for clinicians, NIHES, Rotterdam	2013	1.0
Scientific integrity, Erasmus MC, Rotterdam	2014	0.3
STATA, NIVEL, Utrecht	2015	0.5
CONFERENCES		
Oral presentations		
Dept. of General Practice, Rotterdam (1/yr.)	2012-2016	1.5
IPCRG 8th World Conference, Amsterdam	2016	1.0
CAHAG Conference, Utrecht	2017	1.0
Poster presentation		
CAHAG Conference, Utrecht	2013	1.0
NHG-wetenschapsdag, LUMC, Leiden	2013	1.0
CAHAG Conference, Utrecht	2015	1.0
CAHAG Conference, Utrecht	2017	1.0
TEACHING ACTIVITIES		
Teaching skills		
BKO-training (incl. courses and workshops)	2014-2017	7.0
Teaching		
Supervision of research projects by medical students (2x)	2013/2016	3.0
Clinical reasoning for bachelor and master students	2011-2017	11.0
Developing teaching materials and methods	2012-2017	7.0
Making exam questions	2012-2017	1.0
Supervision of medical interns	2011-2017	2.0
GP-training medical interns	2011-2012	4.0

Erasmus University Rotterdam