

## 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.