

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, $\geq 60\%$ 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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