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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