Pediatric asthma and allergy

An epidemiological approach

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Pediatric asthma and allergy

An epidemiological approach

Astma en allergie bij kinderen

Een epidemiologische aanpak

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op maandag 26 juni 2017 des middags te 12.45 uur

door

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geboren op *22 juni 1969*
te *Sary*, *Iran*

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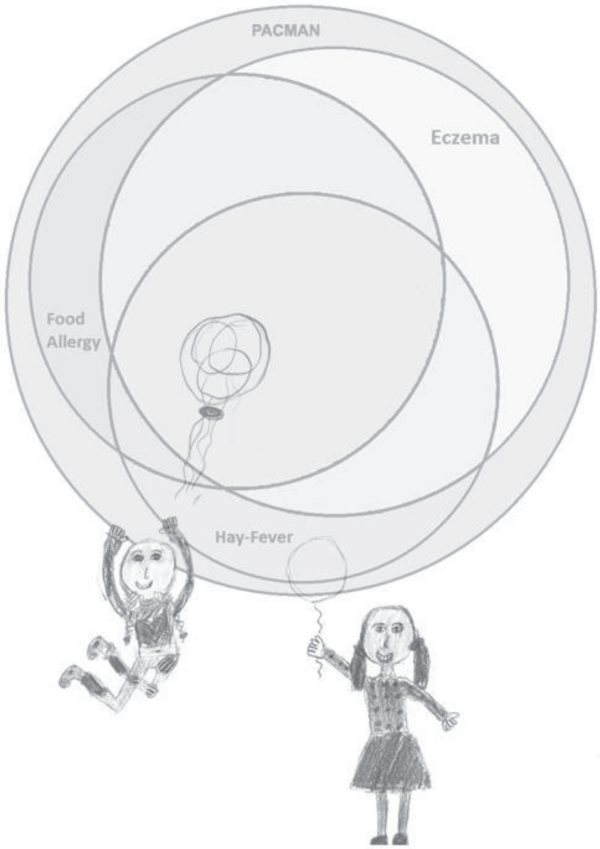
To my family

TABLE OF CONTENTS


PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 1 | General introduction

Although we are all continuously being exposed to a wide range of environmental allergens (substances capable of inducing an immune reaction), only a limited group of individuals will develop an immunological reaction to these allergens (allergic sensitization), and could subsequently experience allergic symptoms [1]. The most common allergens include: pollen, dust, food, insect stings, animal dander, mold, latex and medications.

Allergic phenomena are increasing in prevalence in the western world, they are common in early life and different allergic entities may co-exist [2]. Allergic diseases, such as allergic asthma, food allergy, atopic dermatitis and hay fever, are called atopic diseases and related by overlapping etiology. They are characterized by elevated immunoglobulin E antibody (IgE) levels and caused by a complex interaction between genetic and environmental factors. Initial allergic sensitization occurs on exposure to an allergen breaching the epithelial barrier, due to disruption or dysfunction, which may have genetic and/or environmental causes [3]. Atopy, a genetic susceptibility for increased IgE levels, is a common driver for allergic diseases. Epidemiologic studies of multigenerational families and twin studies have demonstrated a hereditary component to these diseases, distinct from common environmental exposures [4-6]. Several genes have been identified associated with atopic diseases [3], as well as genetic mechanisms involved in different ways like Th2 immunity, T-cell differentiation, TGFβ signaling, regulatory T-cell function and skin/mucosal function. For example loci encoded TLR1 (Toll-like receptor 1) and TLR6 (Toll-like receptor 6) variants, in the 4p14 region near rs2101521. Those genes encode for pattern-recognition receptors that play a role in recognizing external molecules and are involved in innate immunity and immune responses [7]. Even though certain genes are important risk factors for these diseases, environmental factors are also important requirements in atopic disease. Social class, early exposure to allergens, atmospheric pollution, month of birth, Caesarean section, non-breastfeeding, early and late introduction of solid foods and use of antibiotics were shown to be risk factors. However, the magnitude of the risk of many of these factors could not be reproduced in different settings [8]. Although genetic predisposition is clearly evident, gene-by-environment interaction probably explains much of the variations in prevalence rates for allergy and asthma [9].

The term "Atopic March" refers to the sequence in which atopic manifestations can emerge. The March is characterized by a typical sequence of IgE responses and clinical symptoms which may appear early in life, persist over years or decades and may in some patients diminish spontaneously with age [10,11]. Asthma, food allergies, eczema, and hay fever are common in children [2]. In order to improve the understanding of eczema and allergic asthma, it is important to increase our knowledge of the risk factors and co morbidities of allergic diseases [12,13].

Atopic dermatitis

Atopic dermatitis (AD) is one of the most common skin diseases worldwide, particularly in infants and children. There is an increasing prevalence of AD, particularly in developed countries. Atopic dermatitis is a chronic inflammation of the skin that starts in infancy or early childhood. Genetic mutations leading to cutaneous hypersensitivity to environmental stimuli (i.e. a defective skin

barrier) play a role. In general, AD peaks in the first years of life as an "entry point" for subsequent allergic disease and declines after that time Besides AD, symptoms of asthma and allergic rhinitis can emerge over time as sensitization develops. (figure 1) Diagnosis is based on chronicity of the clinical features, which have typical and age-related patterns, and is associated pruritus. Early age of onset, xerosis (dry skin) and atopy (IgE reactivity) support the diagnosis [14].

AD can have a major impact on Quality of Life (QOL)[15]. The classical treatments include moisturizing, topical corticosteroids (TCSs), antiseptics and antibiotics. Emollients hydrate the skin and can relieve the itching [16]. TCSs are the cornerstone of AD treatment. They have anti-inflammatory, immunosuppressive and vasoconstrictive effects. Four classes of TCSs strength are distinguished, from mild (A) to very potent (D) in pharmacy data [17]. In patients with more severe conditions, topical calcineurin inhibitors (TCIs), oral corticosteroids or immunosuppressive medications such as azathioprine or cyclosporine can be prescribed [18]. Moreover sublingual immunotherapy (SLIT) has been used in a group of children who suffer from concomitant allergy to house dust mites [19]. The current Dutch clinical guidelines for general practitioners (GPs) advise that general practitioners (GPs) should only prescribe treatment for mild disease (emollients and low potency TCSs) in children. Otherwise, if they need stronger treatment they should be referred to the second line [20]. It is unclear whether physicians actually follow these guidelines.

Allergic Asthma

Asthma is a heterogeneous chronic lung disease, usually characterized by airflow obstruction caused by inflammation of the airways. Symptoms like cough, wheezing, dyspnea, shortness of breath and chest tightness occur in paroxysms and are usually related to a specific triggering event [21]. Chronic airway inflammation is an important aspect of asthma pathophysiology [22].

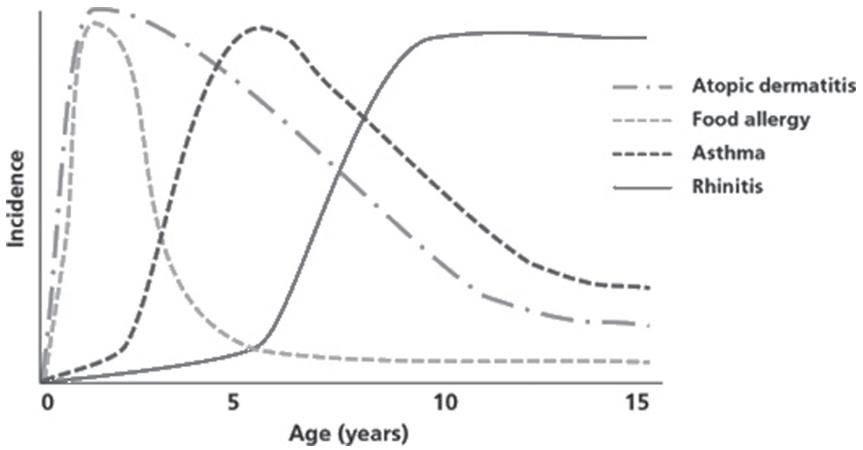


Figure 1. Development of atopic diseases over life-time [39].

Effector cells are eosinophils, neutrophils, CD4+ T-lymphocytes and mast cells that contribute to the pathophysiological changes [22,23]. Although allergic asthma is more common in early-onset asthma, there are still children with asthma that do not have this allergic component [24]. Asthma can present at any age, with the highest prevalence among 5-9 year old [25]. It is the most common chronic disease in childhood and the leading cause of childhood morbidity from a chronic disease, defined by absence from day care, emergency department visits and hospitalizations [22]. Prevalence of asthma has increased globally during the last decades, and is now 0.18% and 0.28% per year for 6-7 year age and 13-14 year age groups respectively [26]. Asthma medications like inhaled corticosteroids (ICS) or inhaled β-agonists are the most commonly chronically used drugs in children [27]. In the Netherlands and many other western countries, asthma is treated using a stepwise approach [28,29]. Guidelines advise to start treatment at the most appropriate step according to clinical severity. Step up of treatment is advised if a child does not reach asthma control in the current step, and step down is advised if a child is well controlled for a period of 3 months [28,30].(figure 2) Short-acting beta2-adrenergic agonists (SABA) as needed should be prescribed to relieve symptoms. If a patient remains symptomatic despite SABA use, long-term control therapy with inhaled corticosteroids (ICS) can be prescribed in a next step. When control on low ICS dose is inadequate, ICS dose should be increased or additional therapy with long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA) should be considered. When

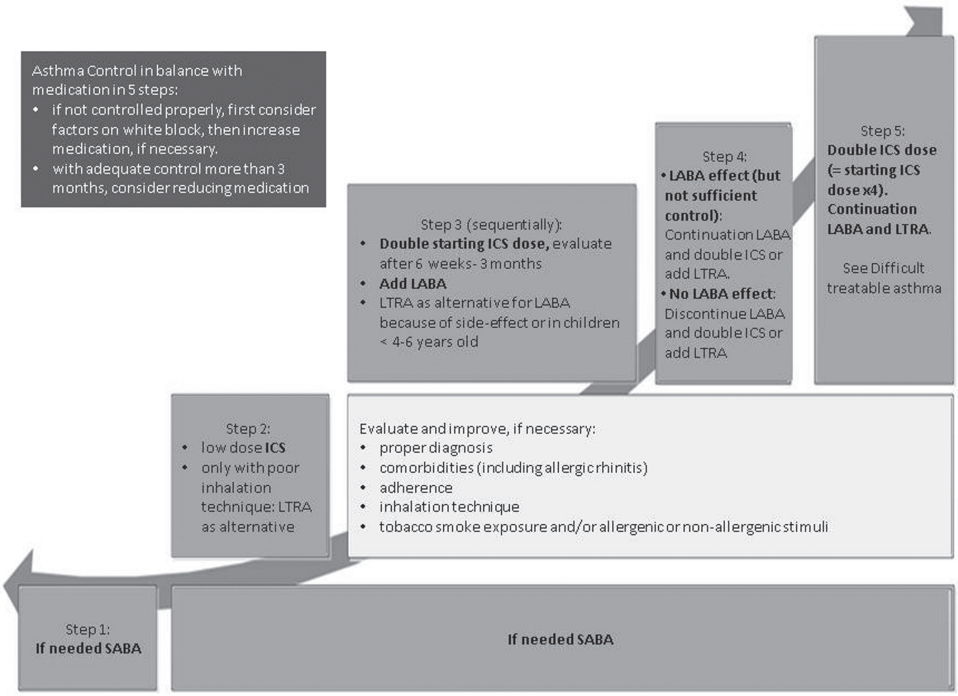


Figure 2. Stepwise asthma treatment in children in the Netherlands. Based on the clinical guideline Dutch Association pediatrics [28].

control is inadequate, before step up, reasons for poor control should be examined. Little is known about how well the stepwise approach in the guidelines is followed in clinical practice.

Asthmatic patients may suffer from acute episodes of acute worsening of asthma symptoms (exacerbations). The treatment for acute asthma exacerbations can include short acting β_2-adrenergic agonists (SABA) and oxygen. Furthermore, short courses of oral corticosteroids (OCS) are commonly prescribed for acute asthma exacerbations [27,30-33]. However, the use of OCS should be limited because of potential significant side effects. Most of these side effects only occur during long-term use; however hyperglycemia, gastro-intestinal side-effects and mood changes may occur even with short-term use [22]. For this reason, we were interested in examining the extent to which OCS were being prescribed to children in various age groups, as the optimization of asthma therapy in groups with a high burden of exacerbations might help to reduce the amount of OCS prescriptions.

Many studies have investigated the prevalence of OCS use for exacerbations in children with asthma and reported a wide range of variety (between 12% and 58%) , as well as the proportion of children with asthma that use OCS. However, these studies have not investigated the relationship with age on the prescribing of these OCS courses [34-38].

Scope of this thesis

The research presented in this thesis aims to gain better insight into allergic diseases in children using epidemiological approaches and different angles (severity, medication use and risk factors). The following research questions will be addressed:

- Do children with multiple atopic conditions suffer from more severe symptoms?
- Which factors influence prescribing medication in children with allergic diseases?
- Can genetic variations predict the risk of developing allergic diseases in childhood?

Thesis outline

This thesis contains three main chapters preceded by an introductory chapter (**chapter 1**) and concluded by a general discussion(**chapter 5**).

The studies described in **Chapter 2**, mainly focus on the severity of allergic symptoms in children with multiple allergic diseases. In **Chapter 2.1** the coexistence of reported allergies in children who use asthma medication is studied, as well as whether asthma severity is greater among children with multiple allergic diseases. In the following section **(Chapter 2.2)** clinical factors associated with AD related QoL and AD severity in children using asthma medication are studied. Furthermore, it is assessed whether pharmacy dispensing data can be used as a measure of AD severity and AD-related QoL.

In **Chapter 3**, three pharmaco-epidemiological studies on asthma and AD related prescriptions in children are described. In **Chapter 3.1**, the incidence of OCS prescriptions in Dutch children

with asthma are studied to identify high risk groups of children who are prone to develop asthma exacerbations. **Chapter 3.2** focusses on physician adherence to asthma treatment guidelines, with special interest in the step-up and step-down patterns. **Chapter 3.3** addresses AD medication patterns in Dutch asthmatic children using pharmacy dispensing data to assess whether Dutch physicians prescribe AD medication according to the clinical guidelines.

Chapter 4 addresses genetic risk factors for developing allergic diseases. This chapter describes a genetic study in which the predictive capacity of a genetic risk score based on genetic variants associated with, allergic disease in adults is tested for the onset of allergic disease in early life.

In conclusion, a general discussion, as well as an outlook for future work, is presented in **Chapter 5**.

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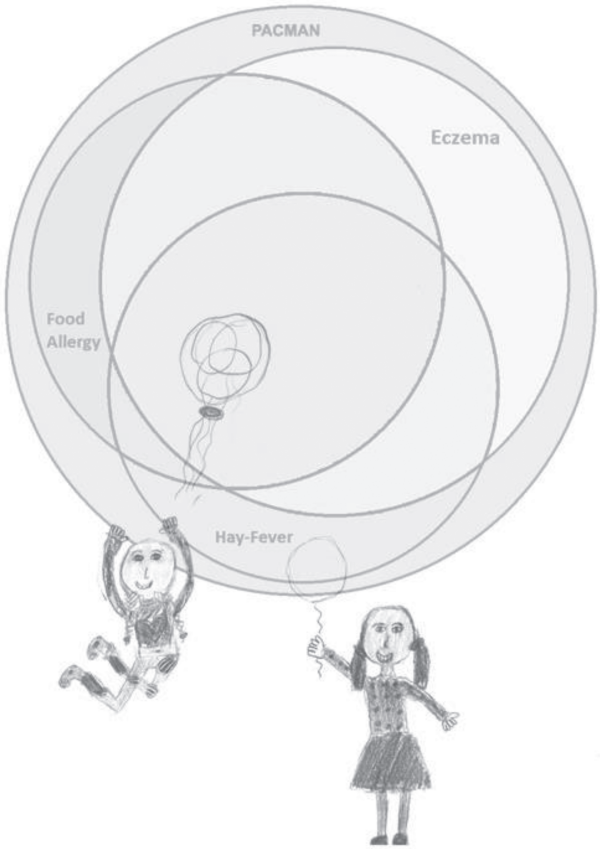
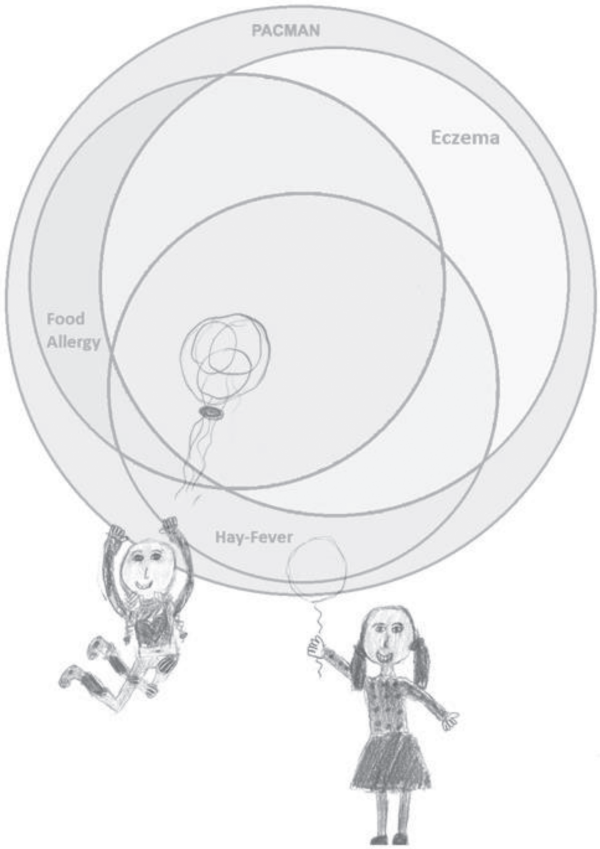

PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 2

Severity of allergic symptoms in children with multiple allergic diseases


PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 2.1

Characteristics and severity of asthma in children with and without atopic conditions: a cross-sectional study

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ABSTRACT

Background

Childhood allergic diseases have a major impact on a child's quality of life, as well as that of their parents. We studied the coexistence of reported allergies in children who use asthma medication. Additionally, we tested the hypothesis that asthma severity is greater among children with certain combinations of co-morbid allergic conditions..

Methods

For this cross-sectional study, 703 children (ages 4 to 12 years) from the PACMAN cohort study were selected. All of the children were regular users of asthma medication. The study population was divided into nine subgroups according to parental-reported allergies of the child (hay fever, eczema, food allergy or combinations of these). In order to assess whether these subgroups differed clinically, the groups were compared for child characteristics (age, gender, family history of asthma), asthma exacerbations in the past year (oral corticosteroids (OCS) use; asthma-related emergency department (ED) visits), asthma control, fractional exhaled nitric oxide level (FeNO), and antihistaminic usage.

Results

In our study, 79.0 % of the parents reported that their child suffered from at least one atopic condition (hay fever, food allergy and eczema), and one quarter of the parents (25.6 %) reported that their child suffered from all three atopic conditions. Having more than one atopic condition was associated with an increased risk of OCS use (OR = 3.3, 95 % CI = 1.6 – 6.6), ED visits (OR = 2.3, 95 % CI = 1.2 – 4.6) in the past year and inadequate short term asthma control (OR = 1.9, 95 % CI = 1.3 – 2.8).

Conclusions

Children who use asthma medication often also have other allergic conditions. Parental reported allergies were associated with a higher risk of more severe asthma (more asthma complaints and more asthma exacerbations).

INTRODUCTION

Childhood allergic diseases have a major impact on a child's quality of life, as well as that of their parents [1]. Therefore, it is important to have a better understanding of the risk factors associated with the development of asthma in children, as well as the factors associated with more severe asthma. The term "allergy" refers to a hypersensitivity reaction initiated by immunologic mechanisms, and although all people are continuously exposed to different allergens, only a limited group of individuals experience adverse immunologic mechanisms [2]. Persistent asthma is often treated with inhaled corticosteroids (ICS) in combination with short acting beta agonists (SABA) as needed, or sometimes in more severe cases, long acting beta agonists and/or leukotriene antagonists [3]. When asthma is controlled, there should only be occasional recurrence of symptoms, and severe asthma exacerbations should be rare [4]. One of the risk factors for asthma severity that has been identified is atopy [5,6]. Atopic individuals are prone to developing allergic symptoms. Asthma, food allergies, eczema, and hay fever are common childhood atopic conditions with an increasing prevalence in the western world [7].

In general, eczema peaks in the child's first years of life as an "entry point" for subsequent allergic disease, and consequently the prevalence of asthma and allergic rhinitis increases over time as sensitization develops [8].

Several studies have investigated the coexistence of food allergies and asthma, hay fever and asthma, or eczema and asthma [8-11]. However, most of these studies have only assessed the relationship between two conditions. They did not assess the effect of a combination of allergies, and they only focused on atopic patients. In his study, we examined the coexistence of allergies and the use of allergy related medication in a large cohort of children who use asthma medication and were recruited through community pharmacies. As a result of the inclusion of the participants from the community pharmacies, this cohort covered the whole spectrum of children with mild to severe asthma. Furthermore, we assessed the differences in the measurement of asthma severity among children with and without different allergies and combinations thereof.

METHODS

Study population

At the time of this analysis, 744 children (ages 4 to 12 years) were included in the ongoing PACMAN (Pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects) cohort study. Complete data on allergies was available for 703 children. The children were regular users (≥3 prescriptions in the last two years and ≥ 1 prescription in the last 6 months) of asthma medications (R03 on the ATC (Anatomical Therapeutic Chemical) coding system) and were recruited through community pharmacies in the Netherlands. The children and their parents were invited to their regular pharmacy for a study visit [12]. The design and rationale of the PACMAN study has been described elsewhere [12]. Data were collected with the help of pharmacists belonging to the Utrecht Pharmacy Practice Network for Education and Research (UPPER), and the work was conducted in compliance with the requirements of the UPPER institutional review board

of the Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. The PACMAN study has been approved by the Medical Ethics Committee of the University Medical Centre Utrecht. Written, informed consent for all participants in the study was obtained from either the participants themselves, or, where participants were minors, a parent or guardian [12].

Data collection

The parents completed a questionnaire during the pharmacy visit. The questionnaire contained questions regarding general health, asthma and respiratory symptoms, allergy symptoms, medication use, adherence to medication (Medication Adherence Rating Scale (MARS) questionnaire [13]), socio-demographic factors, and asthma symptoms. In addition, the child's fractional exhaled nitric oxide level (FeNO) was measured with a handheld analyzer (Niox Mino, Aerocrine, Solna, Sweden).

To measure co-morbid atopic conditions, parents were asked: Has your child ever had a food allergy (FA) (itching, rash/hives, vomiting, diarrhea, runny nose, sneezing, stuffiness and cough)? Has your child ever had eczema? Has your child ever had hay fever (HF)?

The use of oral corticosteroids (OCS) and the amount of emergency department (ED) visits were used to measure asthma severity. Furthermore, the Dutch version of the 6-item Asthma Control Questionnaire (ACQ) was applied to assess current asthma control. ACQ ≥ 1.5 was used as a cut-off value indicating poorly controlled asthma [14].

Statistical analyses

The study was a cross-sectional analysis in the baseline measurements of the PACMAN cohort study. The study population was stratified into nine subgroups according to the allergies that the parents had reported. The first three groups reported HF, FA, or eczema irrespective of whether or not they had also reported one or more of the other studied allergies. Then all possible combinations of allergies were defined (FA + eczema, eczema + HF, FA + HF, FA + eczema + HF) (see Fig. 1 and Table 1).

The characteristics and asthma severity measures of these groups (age, gender, family history of asthma, breast feeding, FeNO, use of allergy medications, OSC usage, ED visits and ACQ) were compared between the groups of children with and without specific combination of atopic conditions (colored area in the first column of Table 1 and the rest of PACMAN population).

We used the independent samples T-test and the Chi-Square test where appropriate. As the distribution of FeNO was not normal, according to the Kolomogorov-Smirnov and the Shapiro-Wilk test, the Mann–Whitney test was used to compare median FeNO between different groups. Logistic regression was applied for multivariate analyses. Age, gender and use of antihistamines were considered potential confounding factors. The potential confounding factors were included in the multivariate model. The Odds Ratios (OR) for OCS use, ED visits and ACQ were adjusted for age and gender and reported with 95% confidence intervals CI). Adjusting the OR for the use of antihistamines and adherence to therapy did not change the results (Table 4).

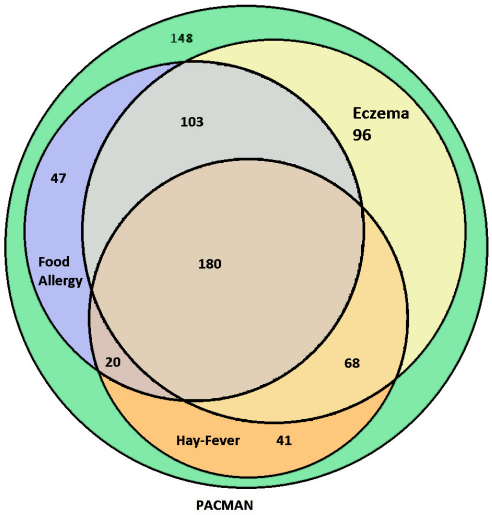

Figure 1. The co-existence of allergies in the study population.

Table 1. Characteristics and antihistamines usage

The population in the Venn diagram [a]		Number (Percentage)	Mean Age ± SD (P Value)	Median FeNO (P Value) [IQR]
	Study Population	703	8.4 ± 2.4	13.0 [7.0 – 27.0]
	Food allergy	350 (49.8%)	8.4 ± 2.5 (.695)	13.0 (.294) [8.0 – 27.0]
	Eczema	447 (63.6%)	8.5 ± 2.5 (.485)	13.0 (.222) [8.0 – 26.0]
	Hay fever	309 (44.0%)	8.9[d]± 2.3 (.000)	15.0[d] (.005) [8.0 – 29.8]
	Without history of allergies	148 (21.1%)	8.1 ± 2.4 (.104)	11.0 (.084) [6.0 – 27.0]
	Food allergy + Eczema	283 (40.3%)	8.5 ± 2.5 (.646)	14.0(.072) [8.3 – 27.8]
	Eczema + Hay fever	248 (35.3%)	8.8[d] ± 2.4 (.002)	15.0[d] (.036) [8.5 – 27.5]
	Food allergy + Hay fever	200 (28.5%)	8.7[d] ± 2.4 (.035)	15.0 (.153) [8.0 – 28.0]
	Food allergy + Eczema + Hay fever	180 (25.6%)	8.8[d] ± 2.4 (.035)	15.0 (.099) [9.0 – 27.0]
	At least two allergies	371 (52.8%)	8.6 ± 2.4 (.109)	14.0[d] (.029) [8.0 – 28.0]

[a] For a bigger diagram see figure 1
[b] With independent samples T-test
[c] With Mann–Whitney test
[d] P Value < 0.05

RESULTS

Co-existence of allergies

In the study population, 79.0% (555/703) of the parents reported that their children had suffered from at least one of the assessed allergies. Eczema was the most common condition (63.6 %). Almost half of the study population reported a history of food allergy (49.8 %), and hay fever was reported by 44.0 %. 25.6 % (180/703) of the participants reported symptoms of all three allergies (food allergy, eczema and hay fever), while 21.1 % did not report any of these symptoms. (See Fig. 1 and Table 1).

Baseline characteristics

Characteristics of the study population are shown in Table 2.

The trends of the main allergic groups' age distributions are shown in Fig. 2. For hay fever an ascending trend is visible (Fig. 2). The mean age of the study population was 8.4 years. However, the mean age of the subgroup of children that reported having hay fever (irrespective of whether they had other allergies) was significantly higher (8.9 years, $p < 0.001$) (Table 1). Also, the occurrence of hay fever increased from almost 20 % in the 4-year-olds to more than 50 % in the 12-year-olds (Fig. 2). The frequency of children with a positive asthma family history (father or mother) in the total studied PACMAN population was 48.0 %. In the subgroup of children who reported

Table 2. Characteristics of study population

Study population (n=703)	
General characteristics	
Male gender, %	62.0
Age, mean ± SD	8.4 ± 2.5
Clinical characteristics	
Parental-reported Food Allergy, %	49.8
Parental-reported Eczema, %	63.6
Parental-reported Hay fever, %	44.0
Asthma family history (One or more parents with history of asthma), %	48.0
Antihistamine usage, %	30.6
SABA usage	84.8
ICS usage	87.8
LABA usage	23.5
LTRA usage	8.8
Breast fed, %	74.9
Median FeNO (IQR)	13.0 (7.0 – 27.0)
OCS usage in the past year, %	7.0
Asthma-related ED visit in the past year, %	6.3

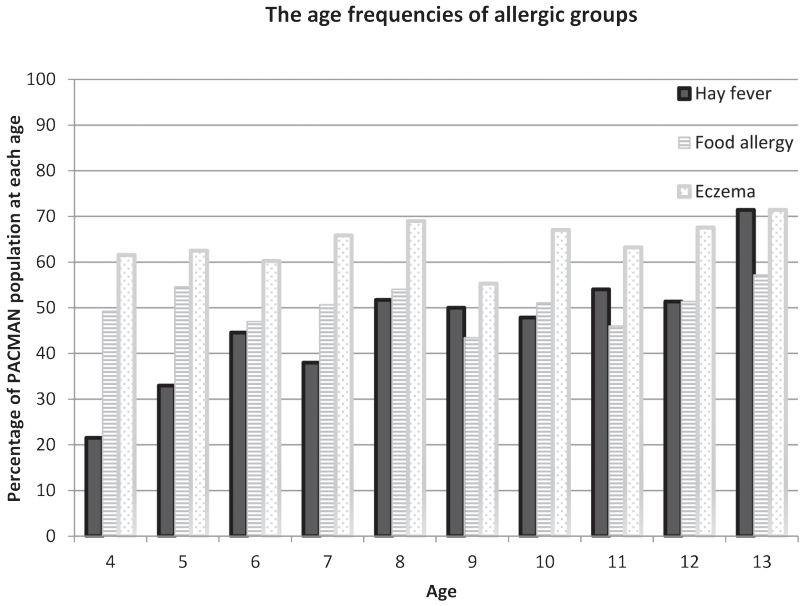

Figure 2. The age frequencies of allergic groups in the study population.

having had hay fever, there was an even higher risk of a family history of asthma (55 %) compared to the children who did not report having had hay fever (45.0 %) (OR = 1.7 95 % CI = 1.2 – 2.3). Furthermore, in the subgroup of children with a reported food allergy, there was a trend towards a higher risk of a family history of asthma (51.2 % to 48.8 %, OR = 1.3 95 % CI = 1.0 - 1.8) (Table 3). The median of FeNO in the study population was 13.0 (Interquartile Range (IQR) = 7.0 – 27.0). The children who reported having had hay fever had a significantly higher FeNO (median = 15.0, IQR = 8.0 – 29.8, $p < 0.01$) (Table 1). Gender or having been breastfed did not significantly differ between allergic subgroups.

Oral antihistaminic drug usage

Oral antihistaminic drugs were used by almost 30 % of the study population. The top three oral antihistaminic drugs (Loratadine, Cetirizine and Fenistil) were equally distributed among all the allergy subgroups.

Asthma outcomes

Severity of asthma was assessed by OCS usage, ED visits and ACQ using both univariate and multivariate analyses. 9.1 % of the children who reported eczema symptoms used OCS (Table 4). This was significantly higher when compared to the use of OCS in the non-eczema population (3.2 %) (OR = 3.0, 95 % CI = 1.4 – 6.6). The use of OCS for the subgroup that had symptoms of food allergy was 9.6 %; this was also statistically significantly different compared to 4.3 % of the non-food

Table 3. Differences in asthma family history in the allergic subgroups

	Asthma Family history % (P Value)	Odds Ratio (95% CI)	
Group	**Present**	**Not present**	
Study population	48.0		
Food allergy	51.2 (.096)	48.8	1.3 (1.0 - 1.8)
Eczema	48.5 (.741)	51.5	1.1 (0.8 – 1.4)
Hay fever	55.0[a] (.001)	45.0	1.7[a](1.2 – 2.3)
Without history of allergies	44.0 (.230)	56.0	0.8 (0.5 – 1.2)
Food allergy + Eczema	51.5 (.137)	48.5	1.3 (0.9 – 1.7)
Eczema + Hay fever	54.8[a] (.009)	45.2	1.5[a](1.1 – 2.1)
Food allergy + Hay fever	57.7[a] (.001)	42.3	1.7[a](1.2 – 2.4)
Food allergy + Eczema + Hay fever	57.5[a] (.004)	42.5	1.7[a](1.2 – 2.4)
At least two allergies	51.3 (.070)	48.7	1.3 (1.0 – 1.8)

[a] P Value < 0.05 with chi-square test

allergy population (OR = 2.3, 95 % CI = 1.2 – 4.4). There was a trend towards a higher risk for the use of OCS in all allergy subgroups. However, the group of children who did not report a history of allergic conditions did not have an increased risk for the use of OCS (Table 4).

Emergency department visits during the past year were significantly higher (8.1 %, OR = 2.7, 95 % CI = 1.2 – 6.0) in the population who had a history of eczema as compared to the rest of the population (3.2 %) (Table 4).

The Asthma Control Questionnaire (ACQ) was assessed in all the defined groups, and 18.2 % of the total study population suffered from poorly controlled asthma. The frequencies of poorly controlled asthmatics in all allergic subgroups were significantly higher ($p < 0.05$) as compared to the non-allergic population. They were 21.3 %, 20.4 % and 22.1 % in the populations with a history of eczema, food allergy or both, respectively. The frequencies of poorly controlled patients were even higher in all the subgroups that reported hay fever (22.7 % - 25.4 %) or more than one allergy (22.4 %) compared to the rest of study population (Table 4).

DISCUSSION

In this large pharmacy-based study of children with a reported use of asthma medication, we found that the prevalence of children that reported symptoms of one or more allergy syndromes was high, and patients that reported more atopic conditions had a greater odds of more severe asthma.

In general, children with asthma and co-morbid allergic conditions were more often poorly controlled compared to their non-allergic peers. Furthermore, usage of OCS and asthma-related

Table 4. Differences in outcomes of each subgroups in whole study population

	OCS usage % (P Value)	Univariate analysis OR (95% CI)	Multivariate analysis [b] OR (95% CI)	E.D visit in past year % (P Value)	Univariate analysis OR (95% CI)	Multivariate analysis [b] OR (95% CI)	Poorly controlled refer to ACQ-6 % (P Value)	Univariate analysis OR (95% CI)	Multivariate analysis [b] OR (95% CI)
Study population	7.0			6.3			18.2		
Food allergy	9.6[a] (.007)	2.3[a] (1.2 – 4.4)	2.3[a] (1.2 – 4.4)	8.0 (.068)	1.8 (1.0 – 3.4)	1.8 (0.9 – 3.4)	21.3[a] (.039)	1.5[a] (1.0-2.2)	1.5[a] (1.0 – 2.2)
Eczema	9.1[a] (.003)	3.0[a] (1.4 – 6.6)	3.0[a] (1.4 – 6.6)	8.1[a] (.010)	2.7[a] (1.2 – 5.9)	2.7[a] (1.2 – 6.0)	20.4 (.053)	1.5 (1.0-2.3)	1.5[a] (1.0 – 2.4)
Hay fever	8.0 (0.36)	1.3 (0.7 – 2.4)	1.4 (0.8 – 2.5)	6.0 (.765)	0.9 (0.5 – 1.7)	1.1 (0.6 – 2.1)	22.7[a] (.007)	1.7[a] (1.2-2.5)	1.8[a] (1.2 – 2.7)
Without history of allergies	4.1 (0.12)	0.5 (0.2 – 1.2)	0.5 (0.2 – 1.2)	4.1 (.215)	0.6 (0.2 – 1.4)	0.5 (0.2 – 1.3)	14.3 (.118)	0.7 (0.4-1.1)	0.7 (0.4 – 1.1)
Food allergy + Eczema	11.6[a] (.000)	3.2[a] (1.7 – 6.0)	3.3[a] (1.8 – 6.1)	9.6[a] (.005)	2.4[a] (1.3 – 4.6)	2.5[a] (1.3 – 4.7)	22.1[a] (.028)	1.5[a] (1.0-2.3)	1.6[a] (1.1 – 2.3)
Eczema + Hay fever	9.5 (.056)	1.8 (1.0 – 3.2)	1.8[a] (1.0 – 3.3)	7.1 (.557)	1.2 (0.6 – 2.3)	1.4 (0.7 – 2.7)	24.5[a] (.002)	1.9[a] (1.3-2.8)	1.9[a] (1.3 – 2.9)
Food allergy + Hay fever	9.2 (0.14)	1.6 (0.9 – 2.9)	1.6 (0.9 – 3.0)	6.7 (.776)	1.1 (0.6 – 2.2)	1.2 (0.6 – 2.5)	25.4[a] (.002)	1.9[a] (1.3-2.8)	1.9[a] (1.3 – 2.9)
Food allergy + Eczema + Hay fever	10.3[a] (.045)	1.9[a] (1.0 – 3.4)	1.9 (1.0 – 3.6)	7.5 (.467)	1.3 (0.7 – 2.5)	1.5 (0.7 – 2.9)	25.3[a] (.005)	1.8[a] (1.2-2.7)	1.9[a] (1.2 – 2.8)
At least two allergies	10.1[a] (.001)	3.2[a] (1.6 – 6.4)	3.3[a] (1.6 – 6.6)	8.4[a] (.020)	2.2[a] (1.1 – 4.3)	2.3[a] (1.2 – 4.6)	22.4[a] (.003)	1.9[a] (1.2-2.8)	1.9[a] (1.3 – 2.8)

The referent group for all these odds ratios is the entire study population
[a] P Value < 0.05 with logistic regression test
[b] Adjusted for age and gender

ED visits were more common in children who reported more than one atopic condition, which was approximately half of the study population. This indicates that the presence of a more complicated allergic phenotype significantly influences the severity of asthma [15].

To our knowledge, there is limited research that has studied the association of allergic comorbidities and asthma severity [16]. However several longitudinal studies have shown that approximately half of eczema patients will develop asthma, particularly patients with severe eczema [8]. study by Roberts *et al.* showed that children with food allergies are around 6 times more likely to suffer from severe asthma later in life than children who did not have food allergies. Similarly, Priftis *et al.* showed that approximately 40 % of children who were diagnosed with an egg and/or fish allergy in the first three years of their life reported current asthma symptoms at school age [17,18]. Moreover, hay fever has been described as a major risk factor for asthma [19,20]. In the current study, eczema was the most frequently reported allergy among the three allergies (food allergy, eczema and hay fever), reported by 63 % of the population (Table 2). A remarkably high percentage of the parents (25.6 %) reported that their children had experienced all three allergies (Fig. 1). The prevalence of food allergy in the current study was also very high (49.8 %). Earlier studies showed that the prevalence of food allergy varied between 3 % and 35 % [7]. Likewise a Dutch study reported a prevalence of (current) self-reported food allergy around 7.2 % among school children in the Netherlands [21]. The high prevalence in our study may have been influenced by the fact that we asked whether the child had ever experienced symptoms. Some children might have only experienced symptoms in early childhood, and this may have caused a larger prevalence than the prevalence of current food allergy symptoms. Nevertheless, we do realize that self-reporting might lead to an overestimation. Unfortunately, data regarding provocation testing to confirm an actual diagnosis of food allergy were not available. However, it has been shown that results from screening questionnaires, comparable to the one we used in this study, were in concordance with results from specific IgE measurements and information obtained from patient records[22,23].

When we assessed the effect of age on the development of allergic disease, we noticed that the occurrence of hay fever increased with age in our study population (Fig. 2). Moreover, the mean age of the hay fever group (8.9 ± 2.5) was significantly higher than the mean age in the overall study population (Table 2). The same trend was reported by Spergel et al. where the incidence of hay fever increased over time during childhood. This might be caused by sensitization developed through other allergic conditions [8]. Ghouri et al. showed an increase in the prevalence of hay fever during childhood in England as well [24]. On the other hand, age trends in the occurrence of the eczema were not observed. Spergel et al. reported age incidence of eczema peaks in the first years of life [8]. It might, therefore, be that our population was too old to observe this trend. The median FeNO level was significantly higher in the hay fever group. This is in alignment with other studies that confirm high FeNO levels in hay fever sufferers [25,26].

Our study was limited by the lack of physicians' diagnoses on allergic diseases or objective immunological test results. We used a questionnaire to obtain information about the history of

allergic conditions. Other studies (such as ISAAC [27]) have also used questionnaire data. We realize, however, that this questionnaire data might differ from objective tests, and the occurrence of allergic diseases might therefore have been overestimated due to the use of parental-reported data. However, the strength of our study is in the selection of a large set of asthmatic children through community pharmacies. Our population represents a cross-section of the everyday pediatric asthma population that varies in the severity of the disease, health care utilization and asthma control.

CONCLUSION

In conclusion, our study suggests that children with asthma and co-morbid atopic conditions are at risk for more exacerbations and less well-controlled asthma in comparison to children who did not report allergies. The children who were reported to have had more than one allergic co-morbidity were especially at risk of having less well controlled asthma and more severe exacerbations. This may have clinical implications, such as more unscheduled health care visits and hospitalizations, as these patients may experience more severe asthma. These children should be carefully monitored and might benefit from asthma/allergy specialist care at an earlier stage.

ABBREVIATIONS

oral corticosteroids (OCS), emergency department (ED), Inhaled Corticosteroids (ICS), short acting beta agonists (SABA), PACMAN (Pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects), ATC (Anatomical Therapeutic Chemical), Utrecht Pharmacy Practice Network for Education and Research (UPPER), Medication Adherence Rating Scale (MARS), fractional exhaled nitric oxide level (FeNO), food allergy (FA), hay fever (HF), Asthma Control Questionnaire (ACQ), Odds Ratios (OR) and (Interquartile Range (IQR).

COMPETING INTERESTS

Francine C. van Erp declares that she has no competing interests. Susanne J.H. Vijverberg had been paid by an unrestricted grant from GlaxoSmithKline (GSK). Jan A. M. Raaijmakers is a part-time professor at the Utrecht University and he was Vice-president External Scientific Collaborations for GSK in Europe, and holds stock in GSK. Anke-Hilse Maitland-van der Zee received an unrestricted grant from GSK. Cornelis K. van der Ent received unrestricted grants from GSK and Grunenthal. Furthermore, the Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, employing authors Ali Arabkhazaeli, Susanne J.H. Vijverberg, Jan A.M. Raaijmakers, and Anke-Hilse Maitland-van der Zee, has received unrestricted research funding from the Netherlands Organization for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (http://www.tipharma.nl website, includes

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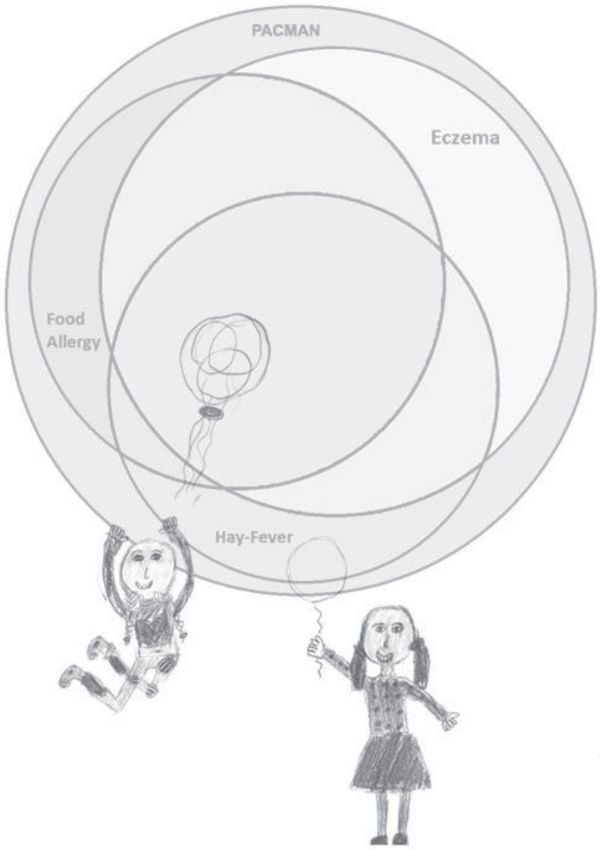
PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 2.2

Atopic dermatitis characteristics and medication-use patterns in school-age children with atopic dermatitis and asthma symptoms

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ABSTRACT

Background

Atopic Dermatitis (AD) and asthma often coexist. Both diseases can have a major impact on the life of pediatric patients and their caregivers. The aim of this study was to investigate the association of patient characteristics, comorbidities and the impact of AD on children who have both asthma and AD.

Methods

Children with AD (n=140) were selected from a larger cohort of children with a reported use of asthma medication. The Children's Dermatology Life Quality Index (CDLQI) was used to assess Quality of Life (QoL). The Self-Assessed Eczema Area and Severity Index (SA-EASI) was used to measure AD severity. Characteristics assessed included: age, gender, amount and type of atopic comorbidities. Medication use for AD was defined using the total amount of AD prescriptions, the amount of different topical AD prescriptions and the highest potency topical corticosteroid (TCS) used. Determinants of AD severity and QoL were evaluated using Spearman rank tests.

Results

The following factors were most strongly associated with a lower QoL: characteristics of AD lesions (Rs=0.61 to 0.69, $p< 0.01$), a higher SA-EASI score (Rs=0.54, $p<0.01$) and a higher amount of different topical AD prescriptions (Rs=0.38 $p<0.01$). The following factors were correlated with more severe AD: age (Rs=-0.36, $p<0.01$), more different TCS preparations used (Rs=0.27, $p<0.05$) and more TCS prescriptions (Rs=0.25, $p<0.05$).

Conclusions

In children with asthma and AD, the amount of TCSs children use are associated with a lower quality of life and an increased AD severity.

INTRODUCTION

Atopic Dermatitis (AD) is a chronic skin disease with a high prevalence (7-9% for children) that often co-exists with asthma [1]. Genetic predispositions seem to play a role [1,2]. Children with asthma and AD display more severe symptoms compared to children suffering from only one atopic disease, therefore, this is a subgroup that requires attention [1]. Asthma and AD are diseases that can have a major impact on Quality of Life (QOL) [3]. Few studies have investigated factors related to the QoL of children with AD. Most studies have focused on the prevalence of AD, but did not look at severity or at a population with asthma [4-6]. It has not conclusively been shown that AD severity influences the QoL [7,8]. It does, however, seem likely.

Topical treatment of AD usually consists of an emollient, a topical corticosteroid (TCS) or a combination. For therapy-resistant AD, or in the case of TCS-related adverse events, topical calcineurin inhibitors (TCIs) can be used. Guidelines recommend treating more severe AD with more potent TCSs [9,10]. The amount of topical AD therapies dispensed might also be associated with AD severity and QoL.

This study aimed to assess whether clinical factors are associated with AD related QoL and AD severity in children using asthma medication. Furthermore, we aimed to assess whether pharmacy dispensing data can be used as a measure of AD severity and AD related QoL.

METHODS

Setting

We used the data collected in the PACMAN (Pharmacogenetics of Asthma medication in Children, Medication with ANti-inflammatory effects) cohort study and the Portal for children with respiratory and allergic symptoms (the Electronic Portal (EP)) [11,12].

In the PACMAN study children (4-12 years old), who regularly use asthma medication, were selected from Dutch community pharmacies. Parents and children were asked to fill out a questionnaire about asthma symptoms, risk factors and atopic comorbidities [12]. All diagnoses were parental reported. Afterwards participants were asked to take part in a digital follow-up, the EP. The EP contains questionnaires regarding general wellbeing and the presence and severity of atopic diseases [11].

The children were selected based on a positive answer to the question: "Are you currently experiencing symptoms of eczema?".

Questionnaires

Severity of AD was assessed with the Self-Assessed Eczema Area and Severity Index (SA-EASI), ranging from 0 (very mild AD) to 72 (extremely severe AD) [11-13]. AD related QoL was assessed using the Children Dermatology Life Quality Index (CDLQI), ranging from 0 (no impact on QoL) to 30 (severe impact on QoL) [11,14,15]

Children were directed to the CDLQI questionnaire if they answered the following question with "yes": "Did you (your child) have an itchy rash in the past 12 months?" The SA-EASI was filled out if they answered "Do you currently have eczema complaints?" with "yes".

Pharmacy data

Pharmacy dispensing records were collected for all patients. In the Netherlands, individuals are usually registered at one pharmacy, which provides a full record of a patients' medication use[16]. Moreover TCSs cannot be bought over the counter (OTC) in the Netherlands and should be prescribed by a physician.

From the dispensing data all topical AD medication (Anatomical Therapeutic Chemical (ATC) codes; D07, D02AX, D11AH01 and D11AH02) dispensed in the 12 months prior to the EP was collected. The ATC system subdivides active substances into groups based on their therapeutic indication [17]. The therapies were subdivided into the following categories: emollients, TCS and TCI. The TCS preparations were further subdivided into potency classes (1 being the least potent and 4 the most potent) according to the European classification system [18,19]. The total amount of AD prescriptions, the amount of different topical AD prescriptions and the highest potency TCS used were evaluated. The dispensed amount of TCSs is generally 30 gm (72.1% of the prescriptions in our study). In the Netherlands, a pharmacist is only allowed to dispense for three months at a time, the rest of the prescription is kept at the pharmacy to be dispensed later on.

Statistical analysis

The correlation between age, gender and the amount of comorbidities in relation to the SA-EASI and CDLQI score was investigated using Spearman rank and Mann-Whitney U-tests. The appearance of AD lesions and their correlation with the CDLQI, the relation between the amount of medication and the SA-EASI and CDLQI scores and the correlation between the individual CDLQI questions compared to the end score of the CDLQ were analyzed using Spearman rank tests. To assess the influence of body areas affected the population was divided into two, the cut-off was 10% of body areas affected. The effect on the QoL was assessed using a Mann-Whitney U-test. Analyses were performed using IBM SPSS 20.0 for Windows.

RESULTS

Patient characteristics

In total, 140 children were included. One child filled out only the SA-EASI questionnaire, 22 only the CDLQI and 117 filled out both questionnaires. The majority (58.6%) of the children were boys (see Table 1). Half of the children (50%) reported to suffer or have suffered from hay fever and 37.4% from food allergies.

The majority (>77%) of children reported to have no more than 10% of the different body areas affected (Supplementary Table 1). One child reported that the hands and arms were covered with AD as more than 90% body surface area, another child reported that the neck only was affected

Table 1. Patients' characteristics

	Children included in study N=140	Children included for medication analyses N=94[a]	P-value
General characteristics			
Age (in years), mean (sd)	10.1 (2.4)	10.0 (2.5)	0.71
Male, %	58.6	59.6	0.73
Questionnaire data			
SA-EASI, Median (IQR)	0.8 (0.0 – 4.1) N=118	0.8(0 - 4.0) N=85	0.96
CDLQI, Median (IQR)	1.0(0 - 4.0) N=139	(0 - 4.0) N=93	0.92
Comorbidities, n (%) [b]			
Atopic dermatitis, %	89.2 (124/139)	93.6 (88/94)	0.02
Asthma , %	79.3 (111/140)	78.7 (74/94)	0.81
Hay fever, %	50.0 (70/140)	52.1 (49/94)	0.47
Food allergies, %	37.4 (52/139)	41.9 (39/93)	0.12
Medication use			
Emollients, %		24.5	
TCS class 1, %		9.6	
TCS class 2, %		16.0	
TCS class 3, %		7.4	
TCS class 4, %		1.1	
TCI, %		2.1	
Coal tar, %		1.1	
Any kind of therapy, %		29.8	
Potency of TCSs used, Median (IQR)		2.0 (1.0)	
Amount of different therapies, Median (IQR)		0.0 (1.0)	
Total amount of prescriptions, Median (IQR)		0.0 (1.0)	

SA-EASI: Self-Assessed Eczema Area and Severity Index, CDLQI: Children's Dermatology Life Quality Index.
a: All children with a fully up to date dispensing record available. b: comorbidities are self-reported for children age 12 or older and parental reported for children younger than 12, out of a total of 4 comorbidities

as more than 90%. None of the children reported that the genitalia/anus were affected more than 10% body surface area, for all other body parts they did.

For 94 children complete pharmacy dispensing data was available. Self-reported diagnosis of AD was the only factor that was different in the overall study population, compared with the study population with up to date medication data (see table 1). Almost 70% of the children did not receive a topical AD prescription. Most commonly used were emollients (used by 24.5%) and class 2 TCSs (16.0%), TCIs were used by 2.1%.

AD severity

The median AD severity (SA-EASI) score was 0.8 (IQR: 0.0-4.1). Age was negatively correlated with the SA-EASI (R_s=-0.36, p<0.01) (table 2). The SA-EASI score was not significantly different for boys compared to girls (p=0.66) nor for the amount of comorbidities (R_s=0.14, p=0.15). None of the other atopic comorbidities (hay fever or food allergies) was statistically significant related to the SA-EASI score. The amount of different AD therapies and the total amount of AD prescriptions were statistically significantly correlated with the SA-EASI score (R_s=0.27, p=0.013 and R_s=0.25, p=0.021 respectively). However, TCS potency was not (R_s=-0.10, p=0.67).

AD-related quality of life

The median CDLQI score in the population was 1.0 (IQR:0.0–4.0). Age (R_s=-0.01, p=0.92) and gender (p=0.13) were not correlated with the CDLQI. Being affected by additional atopic diseases (hay fever or food allergy) was statistically significantly correlated with the CDLQI score (R_s=0.26, p<0.01). Children with hay fever scored higher on the CDLQI (mean=3.4) than children without (1.8), children with hay fever were slightly older (10.36 versus 9.49, p=0.049) For food allergies these numbers were 3.4 and 1.4 respectively, with no statistically significant difference in age (table 3).

For all body areas there was a statistically significant difference in the CDLQI score between those children whose AD affected <10% body surface area vs >10% body surface area (supplementary table 1).

Potency of the TCSs was not correlated with the CDLQI (R_s=0.15, p=0.50). However, the amount of different therapies and total amount of AD prescriptions were moderately correlated (R_s=0.38 p<0.01 and R_s=0.36 p<0.01 respectively) (table 2).

Table 2. Correlations between different AD severity and quality of life measurements in children with AD and asthma

	SA-EASI R_s (p-value)	**CDLQI R_s (p-value)**
Maximum TCS potency	-0.095 (0.67) N=22	0.149 (0.50) N=23
Number of different therapies	0.267* (0.01) N=85	0.379** (<0.01) N=93
Total amount of prescriptions	0.251* (0.02) N=85	0.362** (<0.01) N=93
Age	-0.361** (p<0.01) N=118	-0.009 (p=0.92) N=139
Number of atopic comorbidities	0.135 (0.15) N=116	0.256** (<0.01) N=137

*is significant at p<0.05, **is significant at p<0.01. SA-EASI: Self-Assessed Eczema Area and Severity Index, CDLQI: Children's Dermatology Life Quality Index. Correlations were assessed with Spearman rank's test. Comorbidities being hay fever, food allergies, asthma and AD.

Table 3. Influence of atopic comorbidities on AD severity and AD related quality of life in children with AD and asthma symptoms

		CDLQI score, Median (IQR)	P-value	SA-EASI-score, Median (IQR)	P-value
Hay fever	Yes	1.5 (0.0 - 6.0)		0.8 (0.0 – 5.0)	
	No	0.0 (0.0 - 2.0)	<0.01	1.0 (0.0 - 3.8)	0.95
Food allergies	Yes	1.0 (0.0 - 5.0)		2.2 (0.0 – 8.2)	
	No	1.0 (0.0 - 3.0)	0.04	0.8 (0.0 - 3.5)	0.28

AD: Atopic Dermatitis, CDLQI: Children's Dermatology Life Quality Index, SA-EASI: Self-Assessed Eczema Area and Severity Index.

SA-EASI correlates with CDLQI

The distribution of the CDLQI and SA-EASI scores are shown in figure 1a. There was a statistically significant correlation between the value of the SA-EASI scores and the CDLQI scores (Rs=0.54, p<0.01) (figure 1b)." All lesion characteristics, were statistically significantly correlated with the CDLQI (R_s ranging from 0.61 to 0.69 (p< 0.01)) (supplementary table 2).

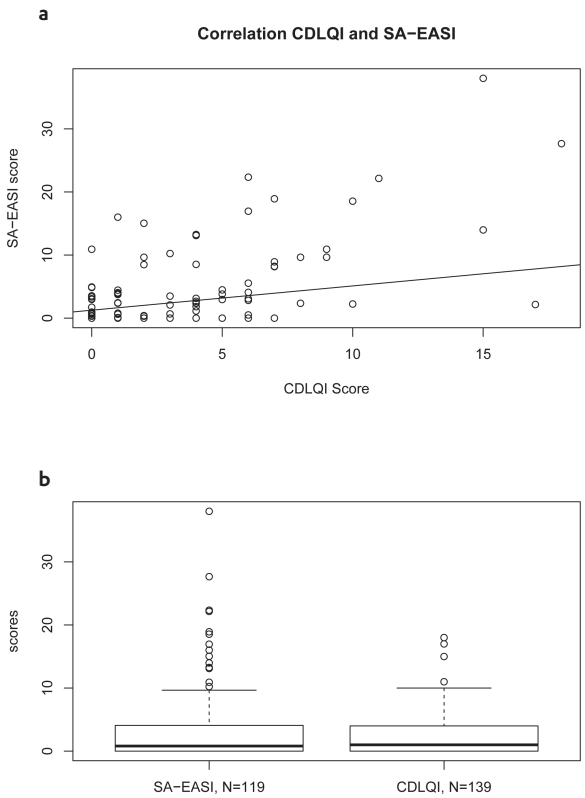

Figure 1. (**a**) Severity distribution of the SA-EASI and the CDLQI in our study population. The thick lines represent the average score and the boxes the inter quartile ranges. (**b**) Correlation between the SA-EASI and CDLQI scores in children with AD and asthma symptoms. Rs=0.54, p<0.01.

SA-EASI: Self-Assesses Eczema Area and Severity Index, CDLQI: Children's Dermatology Life Quality Index.
SA-EASI ranges from 0-72, CDLQI ranges from 0-30.

DISCUSSION

This study showed that QoL in children with AD and asthma is correlated with clinical characteristics of the lesions, AD severity and AD medication use. Furthermore, the amount of topical therapies used might be a marker for AD-related QoL and AD severity, the potency of TCS's is not.

We found that the amount of atopic comorbidities was correlated with the QoL but not with AD severity. Having more comorbidities might cause the child to experience AD symptoms as more impairing. Some of the symptoms might also be due to other comorbidities, e.g. an allergic rash.

It was noticed that children with hay fever or food allergies scored higher on the CDLQI but not on the SA-EASI. The children with hay fever were slightly older than the ones without. However, there was no link between the CDLQI and age which suggests that age was not a confounding factor. A strong relation between hay fever and AD severity and prevalence has been shown previously [20-22]. Silverberg *et al*. studied the link between AD and atopic comorbidities. They reported a relation between severe hay fever and AD and between food allergies and AD [20]. We were not able to replicate these results, which might be due to the mild AD population or to pre-selection of our population on the use of asthma medication. Asthma itself is linked to more severe AD and a higher prevalence of AD [20,21]. However, even though the children in this study were mostly asthmatic children it was still a population with relatively mild AD, which is the most likely explanation.

Even though guidelines recommend treatment with TCSs with higher potencies for more severe AD [9,10,23], we did not find a correlation between TCS potency and AD severity or QoL. A possible explanation might be that physicians are hesitant to treat children with a higher potency TCS, or are not following the guidelines, possibly due to steroid phobia. This might lead to under-treatment of these patients.

Both the amount of different topical AD therapies and the total amount of topical AD prescriptions were correlated with AD severity and, more strongly, with the QoL.

Eight out of 140 children received a total of 14 systemic corticosteroids prescriptions in the study period. None of the prescriptions were prescribed concurrently with AD medication. Ten were prescribed with asthma medication, making it very likely that these corticosteroid prescriptions were used for asthma and not for AD.

Medication used in the last 12 months might not necessarily reflect current medication use, due to the small sample size of this study it was not possible to focus on a shorter time frame. An explanation for the correlation between medication use and AD related QoL might be that the children find the application of the therapies difficult or bothersome. However we did not find a strong correlation between the CDLQI question about AD treatment and the QoL.

The amount of different AD therapies used seems to be the most suitable parameter to be used as a marker in epidemiological studies for AD severity and AD related QoL.

One of the major strengths of this study was the detailed data available on AD severity and AD related QoL in combination with complete pharmacy dispensing data. One of the limitations of

this study is the fact that analyses were performed with correlation tests and not with (linear) regression, which would have allowed for correction of confounders. The reason for this is the non-Gaussian distribution of the outcomes and the residuals, even after transformation. Another limitation was that the diagnoses might be confounded as they were parental-reported and not all were confirmed by physicians. However, a previous study reported that the agreement between the parental reported diagnoses and the GP-reported diagnoses in the PACMAN study was high [24].

CONCLUSION

This study provides valuable information about the correlation of atopic comorbidities, age and medication use with AD severity an AD related QoL. Potency of TCSs used was not correlated with AD severity or QoL, however the amount of different therapies and the total amount of prescriptions were. These last two parameters might serve as a measure for AD severity and AD related QoL. On top of that, it seems that children with multiple atopic disorders experience AD as more impairing. Interventions specifically targeted at this group might empower these children and improve QoL [25].

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Quality of life related to areas affected in children with AD and asthma

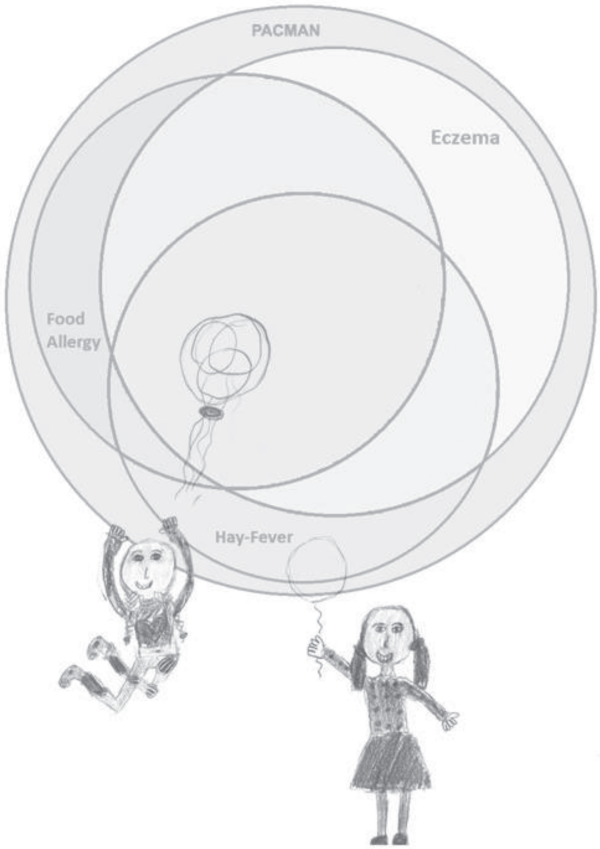
	<10% affected		≥10% affected		
	N	Median (range) CDLQI-Score	N	Median (range) CDLQI-Score	P-Value
Head	114	1.0 (0-17)	4	10.5 (2-18)	0.01
Face	108	1.0 (0-18)	10	7.0 (4-15)	<0.01
Neck	107	1.0 (0-17)	11	9.0 (2-18)	<0.01
Hands	106	1.0 (0-18)	12	6.5 (1-17)	<0.01
Arms	91	0.0 (0-17)	27	6.0 (0-18)	<0.01
Trunk	107	1.0 (0-17)	11	5.0 (0-18)	<0.01
Legs	91	0.0 (0-17)	27	5.0 (0-18)	<0.01
Feet	113	1.0 (0-17)	5	11.0 (4-18)	<0.01
Anus	118	1.0 (0-18)	0	NA	NA

CDLQI: Children's Dermatology Life Quality Index. Comparison was made with Mann-Whitney U-tests

Supplementary table 2. Atopic dermatitis characteristics and the correlation with quality of life

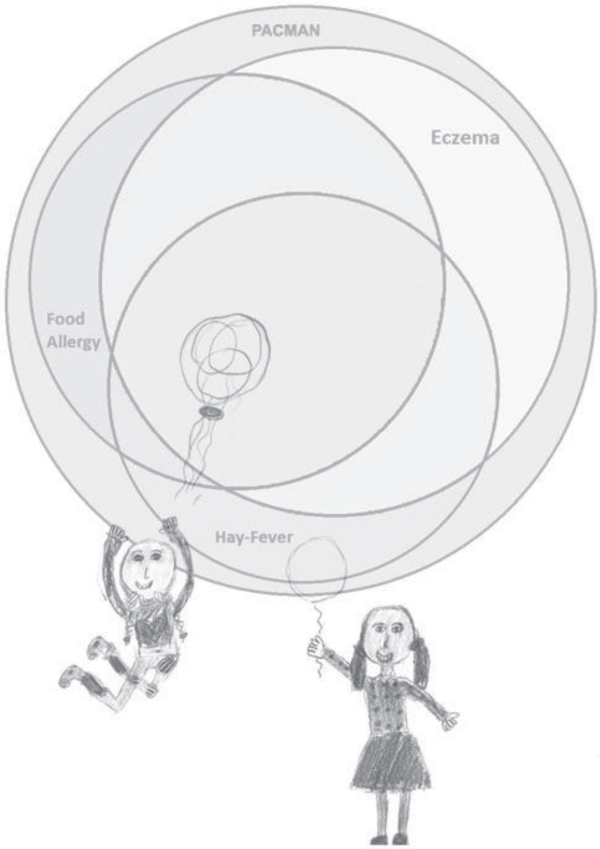
N=117	Median score (0-100)	CDLQI
Redness	24	0.611**
Thickness	1	0.623**
Dryness	25	0.635**
How many wounds by scratching	2	0.680**
Itchiness	25	0.691**

CDLQI: Children's Dermatology Life Quality Index.
**: p-value<0.01. Correlations were assessed with Spearman rank's test.


PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 3

Pharmacoepidemiological studies on asthma and atopic dermatitis


PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 3.1

High incidence of oral corticosteroids prescriptions in children with asthma in early childhood

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ABSTRACT

Background

Severe asthma exacerbations are often treated with short courses of oral corticosteroids (OCS). This study assessed the incidence of OCS being prescribed in asthmatic children of various age groups and calculated their chances of receiving subsequent OCS prescriptions.

Methods

Longitudinal Dutch community pharmacy data of 2272 children who were regular users of asthma medication was analyzed retrospectively. Incidence rates for first, second and third prescriptions of OCS were calculated, stratified by age and sex. Probabilities of receiving first, second or third OCS prescriptions were assessed with Kaplan–Meier analysis.

Results

Incidence rates for first OCS prescriptions were 4.5 for the 1st year of life per 100 person-years (100PY); 3.9 for the 2nd; 4.6 for the 3rd; 4.2 for the 4th, and 4.7 for the 5th year of life per 100PY. This was relatively high compared to incidence rates for children between the ages of 6 and 11 (ranging between 2.2 per 100PY (age 9) and 3.7(age 11)). Incidence rates for second and third OCS prescriptions were very high: 78.2(95%CI: 45.0–123.7) and 241.2(95%CI: 81.2–583.4) per 100PY for infants, respectively. The chances of receiving a first OCS prescription was higher in males (P value < 0.01).

Conclusions

In the Netherlands, the incidence of OCS being prescribed to children being treated with asthma medication in early childhood is relatively high for first OCS prescriptions and extremely high for second and third OCS prescriptions compared to other ages. Furthermore, there is a high probability of receiving a further OCS prescription shortly after an OCS prescription.

INTRODUCTION

Childhood asthma creates a substantial burden for the affected children and their families by restricting the child's activities and increasing the risk of school absences [1]. The diagnosis of asthma, however, is complicated in preschool children for various reasons; lung function tests, for example, are difficult to perform in this age group [2,3]. Nevertheless, it is well known that asthma-like symptoms frequently occur in this period of life. Cloutier et al. reported asthma-like symptoms in 34% of children aged <5 years in an urban community (Hartford, CT, USA) [4]. In general, there is a lot of controversy on how to diagnose asthma in young children (under the age of 5), and there is a paucity of data regarding the efficacy of available treatments in this age group, as well [5].

Longitudinal cohort studies have shown that asthma-like symptoms at a young age persist in only a minority of cases. The lack of strict criteria for the diagnosis of asthma results in an empirical therapeutic approach in children below the age of 4. In both children and adults with overt asthma, short-acting β2;-adrenergic agonists (SABA) can be used to relieve symptoms. If patients remain symptomatic despite SABA use, long-term control therapy with inhaled corticosteroids (ICS) can be prescribed, sometimes in combination with add-on, long-acting β2-adrenergic agonists. The treatment for acute asthma exacerbations can include short acting β2-adrenergic agonists (SABA) and oxygen. Furthermore, short courses of oral corticosteroids (OCS) are commonly prescribed for acute asthma exacerbations [3,6-10]. Although these treatment guidelines are supported by vast amounts of literature for patients with documented asthma, the efficacy of these drugs are less well documented in young children with asthma-like symptoms.

Furthermore, the use of OCS is limited by significant side effects. Most of these side effects only occur during long-term use; however hyperglycemia, gastro-intestinal side-effects and mood changes may occur even with short-term use [5]. Thus, we were interested in examining the extent to which OCS were being prescribed to children in various age groups, as the optimization of asthma therapy in groups with a high burden of exacerbations might help to reduce the amount of OCS prescriptions.

Many studies have investigated the prevalence of OCS use for exacerbations in children with asthma, as well as the proportion of children with asthma that use OCS; however, these studies have not investigated age-categorized incidence of use [4,11-14]. For that reason, this study examined the incidence of OCS prescriptions in Dutch children with asthma from different age groups to determine if there were differences in OCS prescription incidence rates in different age categories. We also assessed a child's chances of receiving a second or third OCS prescription in different age groups. In brief, we tried to identify high risk groups of children who were prone to developing asthma exacerbations (and therefore receiving OCS prescriptions), who should then be more carefully monitored.

METHODS

Study population and data collection

Longitudinal deidentified data on medication was available for 3575 children (age: 4–12 years) who were eligible for inclusion in the PACMAN (Pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects) cohort study (Figure 1). Children were selected from Dutch community pharmacy databases based on their regular use of asthma medication (ATC code R03) (3 prescriptions in the last two years and1 prescription in the last 6months) with the help of the Utrecht University's UPPER network. The design and rationale of the PACMAN study has been described elsewhere [15]. The PACMAN study has been approved by the Medical Ethics Committee of the University Medical Centre Utrecht [15].

For this study, we excluded children who had no medication data available starting with their first year of life, and one child whose gender was unknown. All OCS prescriptions for the rest of the population (2272 children) were identified until the end of follow-up (time of extraction medication data), or until the child's 13th birthday (Figure 1). If there were two prescriptions for the same OCS on the same day we calculated this as one prescription. If the difference between two OCS prescriptions was more than 10 days, they were considered as one exacerbation episode.

Incidence measurements

We assessed the incidence rates per person year (the product of the number of years times the number of members of a population who were at risk for an event) for the first prescriptions of OCS at every year of age. The frequencies of the first OCS prescriptions for every child in each age category (all prescriptions within 1-year-olds, 2-year-olds, etc.) were used as a numerator to calculate incidence.

For the denominator, the sum of the years or part of the years (Days/365.25) the patients were at risk for the prescription of OCS was calculated for each age category. For this calculation we excluded the time after the patient started taking OCS. After the first prescription of OCS, children were at risk for a second prescription. We calculated the years (days/365.25) after the first prescription as "time at risk for second prescription of OCS." We did this in a similar way for the risk of a third prescription. We also calculated the "days at risk" separately for both sexes. We compared the incidence rates of the various age groups using chi-square or Fisher tests when the sample sizes were too small (less than 5 observations per cell) using R statistics software.

Probability measurement

The probability of receiving a first, second or third OCS prescription during follow-up visits and the differences between sexes were assessed with Kaplan–Meier analysis. Statistical analyses were performed using R software/environment and SPSS v.20.0 (IBM Corp., Armonk, NY, USA).

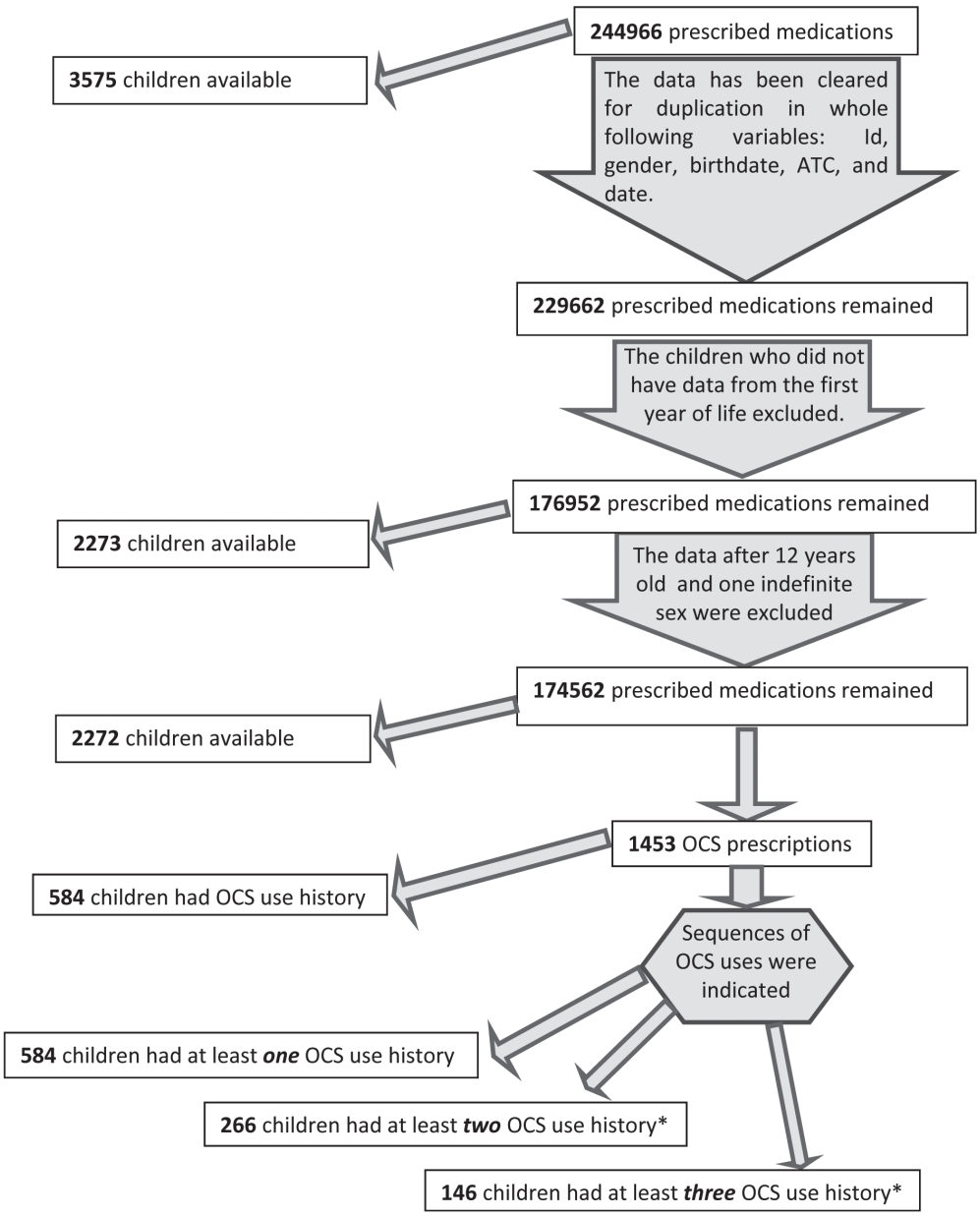

Figure 1. Flowchart of the prescribed medications and OCS for our study population. *If the difference between two OCS prescriptions were less than 10 days, it counted as continuing of the previous course of treatment.

RESULTS

Characteristics of the study population

Our population consisted of 2272 children; 65% of our study population were males, and the median age was 8.3 years (IQR =6.0–10.7) at the time of data extraction (Table 1). In our study population, the age distribution at the time of data extraction showed a relatively uniform pattern, meaning that the number of children in each year of age was almost equal. The total time at risk for 1st, 2nd and 3rd prescription was 15377, 1594 and 549 person-years, respectively. The mean time of medication follow-up was 8.3 years (see Figure 3).

Amount of prescribed medicines

Our population received 174562 drug prescriptions (all drug classes) in total. Most of the children in our study (98.0%) received prescriptions for inhaled beta agonists at least once, and ICS were prescribed for 93.9% of the children. Moreover, OCS was prescribed for 584 children (25.7%) at least once during their follow-up. Half of these children (n = 266, 11.7%) also received a second prescription for OCS, and 146 (6.4%) children received 3 or more prescriptions for OCS.

Incidence of OCS prescriptions

First OCS prescription

The incidence rates of OCS prescriptions are shown in Figure 2. The overall incidence rates for first OCS prescriptions for age groups were statistically significantly different (P value < 0.01). The incidence rates for a first OCS prescription in the first 5 years of life were as follows: first year of life = 4.5 (95% confidence interval [CI]: 3.6 to 5.7); second year of life = 3.9 (95% CI: 3.1 to 4.8); third year of life = 4.6 (95% CI: 3.7 to 5.6); fourth year of life = 4.2 (95% CI: 3.3 to 5.2); fifth year of

Table 1. Characteristics of the population

Study population (n = 2272)	
Male gender, %	65.3%
Median age at extraction dates (IQR)[1] [Mean]	8.3 (6.0 – 10.7) [8.3]
Prescribed beta-adrenoreceptor agonists, %	98.0%
Prescribed SABA[2] , %	97.4%
Prescribed LABA[3], %	28.9%
Prescribed ICS[4] , %	93.9%
Prescribed Leukotriene receptor antagonists , %	12.5%
Prescribed OCS[5] , %	25.7%

[1] interquartile range
[2] Short-acting beta2-agonists
[3] Long-acting beta-agonists
[4] Inhaled corticosteroids
[5] Oral corticosteroids

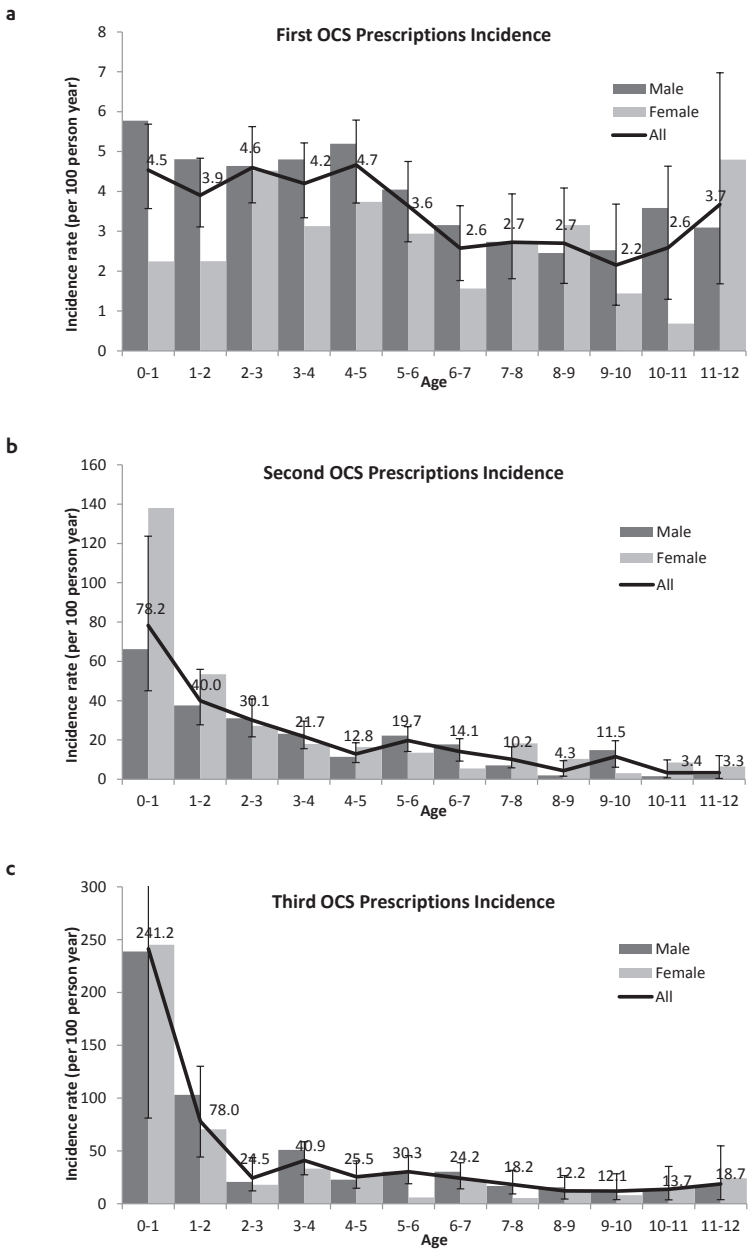

Figure 2. Incidence rates for (**a**) first, (**b**) second and (**c**) third OCS prescriptions.

life = 4.7 (95% CI: 3.7 to 5.7) per 100 person-years. These rates are relatively high in comparison with the incidence rates for children between the ages of 6 and 11, with the lowest incidence rate being 2.2 (95% CI: 1.1 to 3.7) at age 9 and the highest incidence rate 3.7 (95% CI: 1.8 to 7.0) OCS prescriptions per 100 person-years at age 11 [16].

Second and third OCS prescriptions

The incidence rates for second and third OCS prescriptions were very high for children under the age of one: 78.2 (95% CI: 45.0 to 123.7) and 241.2 (95% CI: 81.2 to 583.4) per 100 person-years, respectively. The incidence rate for a second OCS prescription was lowest at the age of 11: 3.3 (95% CI: 0.4 to 12.0) per 100 person-years. Children at the age of 9 had the lowest incidence rate of a third OCS prescription: 12.1 (95% CI: 4.0 to 28.5) per 100 person-years. The overall incidence rates for age groups were different for second OCS prescriptions (P value < 0.01) and third OCS prescriptions (P value < 0.01).

Probability of OCS prescriptions related to the time of previous OCS prescription

In Figure 3, a Kaplan–Meier plot illustrates the probability of a child receiving no OCS prescriptions at each age.

The slope of the Kaplan-Meier curve is relatively steep in early childhood, indicating that the probability of receiving an OCS prescription in early childhood is high for our study population. The chance of ever receiving a prescription for OCS was approximately 14.8% for a 4-year-old child with asthma; however, this chance increased to approximately 25.5% for an 8-year-old child with asthma. There was a statistically significant difference between males and females with regards to their chances of receiving a first OCS prescription. Males had a 1.5 (95% CI: 1.2–1.8) times higher chance of receiving OCS at all ages compared to females (P value < 0.01).

The probability of receiving a second OCS prescription during the 2 years following the first OCS prescription was 38.5%; similarly, the probability of receiving a third OCS prescription in the 2 years after the second OCS prescription was 47.5%. There seemed to be a difference in the risk of receiving a second or third OCS prescription between males and females; however these differences did not reach statistical significance.

DISCUSSION

This study assessed the incidence of OCS prescriptions in a population of children who had used asthma medication. Higher OCS prescriptions' incidence rates were found in early childhood (age: 0 to 4 years) compared to school age children (age: 6 to 10 years).

Our data showed that OCS were prescribed in high numbers in children with asthma. In our study population, 26% of the children had been prescribed OCS. Other studies that had previously investigated the incidence or prevalence of OCS prescriptions were conducted within shorter timeframes. For example, in France over the course of three months, Mahut et al. reported even higher numbers [17]. They reported 31% severe exacerbations in 359 children treated for asthma [17]. Mudd et al. assessed OCS use over a period of 6 months in asthmatic

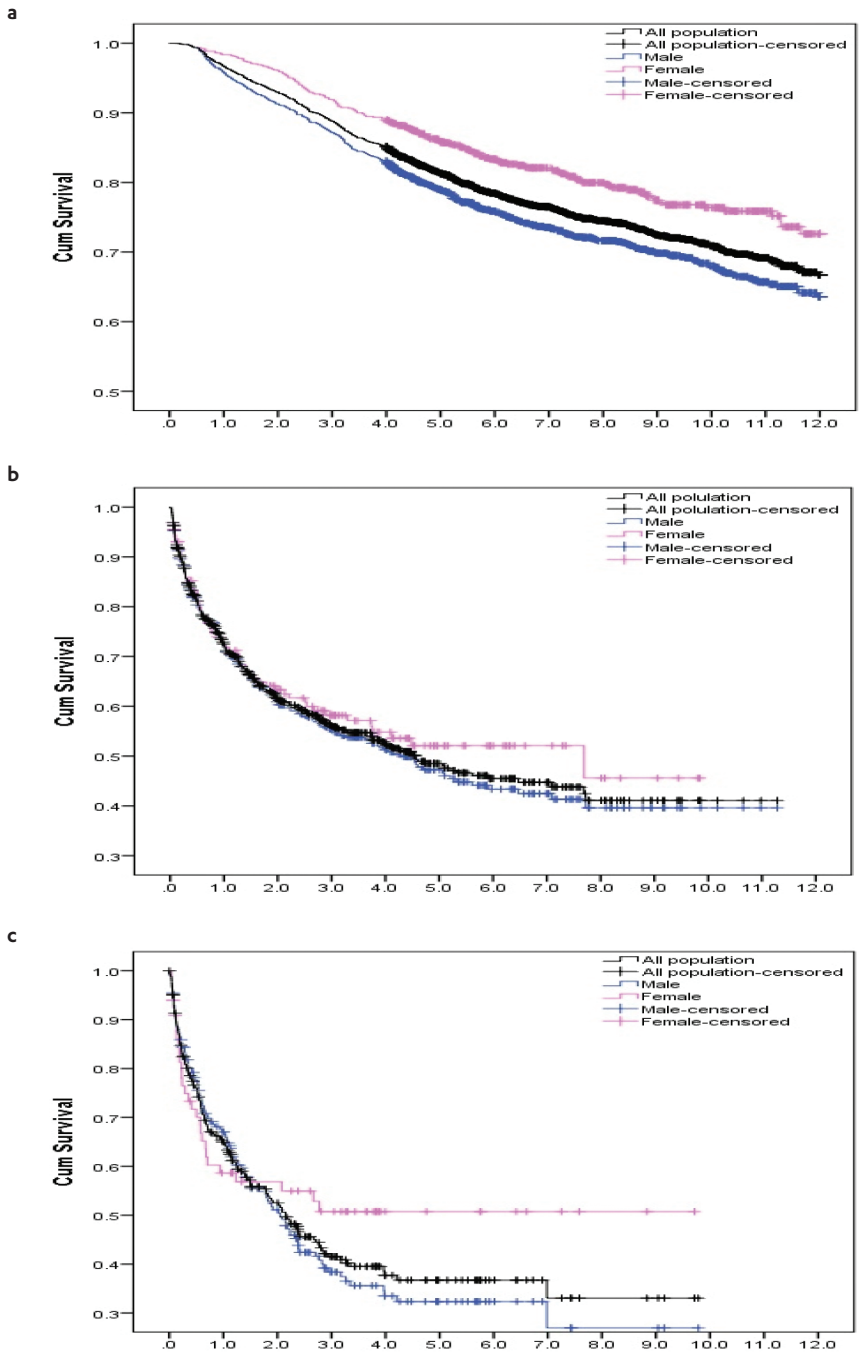

Figure 3. Probability of receiving OCS prescriptions (**a**) per age category in the total population and stratified per sex; (**b**) after first prescription. Follow-up time in years after first OCS prescription; (**c**) after 2nd prescription. Follow-up time in years after 2nd OCS prescription. "Time = 0" is the time of previous OCS prescription.

children (age: 2–9 years) who had used 3 asthma medication nebulizers in the past 30 days and who had had an Emergency Department visit in the last 12 months. They showed that 45% of the children had received one OCS prescription [11]. Although the inclusion criteria of these different studies are not fully comparable, these data stress the common use of OCS as a treatment modality, as well as the high impact of asthma in the young children.

Furthermore, in our study the probability of a child receiving another OCS prescription shortly after their first or second OCS prescription was high. When he or she received an OCS course for respiratory symptoms, there was an almost 50% chance that the child would receive another course of OCS within 2 years. Half of the children that had received a first OCS prescription in our study also received a second OCS prescription. These findings are in line with Miller et al., who included 2780 severe or difficult-to-treat, physician-diagnosed asthma patients (12 years of age) and assessed their records after 1.5 years. They compared the severity of asthma between a group of patients with non-recent, severe exacerbations and a group of patients with recent, severe exacerbations, and they concluded that recent exacerbations are a strong independent predictor of future exacerbations [18].

This high prevalence of repeated OCS prescriptions is also in line with the earlier mentioned study of Mudd et al., who showed that 14.8% of the children had received more than one OCS prescriptions in the 6-month study period [11]. These combined data strongly demonstrate the necessity of extra attention being paid to children who have recently experienced asthma exacerbations, as they are at the highest risk for repeated OCS prescriptions.

Our data also showed striking differences in OCS prescriptions between males and females; males had a higher chance of receiving their first OCS prescription during childhood (0 to 12 years).

The age-dependent approach in this study also highlights the high risk for OCS prescriptions in young children (<2 years of age). Second and third OCS prescriptions incidences were especially high in the first and second year of age. There are two possible explanations for this: firstly, since viral respiratory infections that frequently trigger wheezing and asthma-like symptoms are common in this young age group, OCS could have been prescribed as a result. Nevertheless, most studies that have evaluated the efficacy of OCS among preschool children with episodic wheezing have not demonstrated beneficial effects [19]. Therefore, even short-term OCS use may lead to side-effects, and need to be prescribed cautiously. A second reason may be that children in this age group are ineffectively treated with ICS, or cannot yet inhale the asthma medication adequately. In a drug utilization study like ours, it is impossible to disentangle the different reasons for the frequent use of OCS. However, optimization of drug treatment, especially in children who have already received a first prescription for OCS is important, and might help to prevent subsequent second and/or third prescriptions.

An important strength of this study was the use of a large dataset, in which the prescription data from 100 Dutch community pharmacies was combined. However, the sole use of prescription data obtained from community pharmacies might have led to an underestimation of the incidence

rates, as OCS prescriptions might have also been provided by hospital pharmacies. Furthermore, the number of children who received OCS and had follow-up data for second and third OCS prescription available was limited, therefore there was not enough power in our study to show a statistically significant difference between males and females.

CONCLUSIONS

In conclusion, in the Netherlands the incidence of OCS prescriptions in children treated with asthma medication is relatively high for first OCS prescriptions and extremely high for second and third OCS prescriptions in early childhood as compared to other age groups (>6 years). Further research is needed to assess the risks and benefits of OCS use in this young age group. Furthermore, the study also shows that there is a high probability of receiving another OCS prescription shortly after an OCS prescription. Therefore, children who have recently received an OCS prescription are prone to receiving another one, and should be carefully monitored.

DECLARATION OF INTEREST

Jan A. M. Raaijmakers is a part-time professor at the Utrecht University and he was Vice-president External Scientific Collaborations for GSK in Europe, and holds stock in GSK. Cornelis K. van der Ent received unrestricted grants from GSK and Grunenthal. Furthermore, the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, employing authors Ali Arabkhazaeli, Susanne J.H. Vijverberg, Jan A.M. Raaijmakers, and Anke-Hilse Maitland-van der Zee, has received unrestricted research funding from the Netherlands Organization for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (http://www.tipharma.nl website, includes co-funding from

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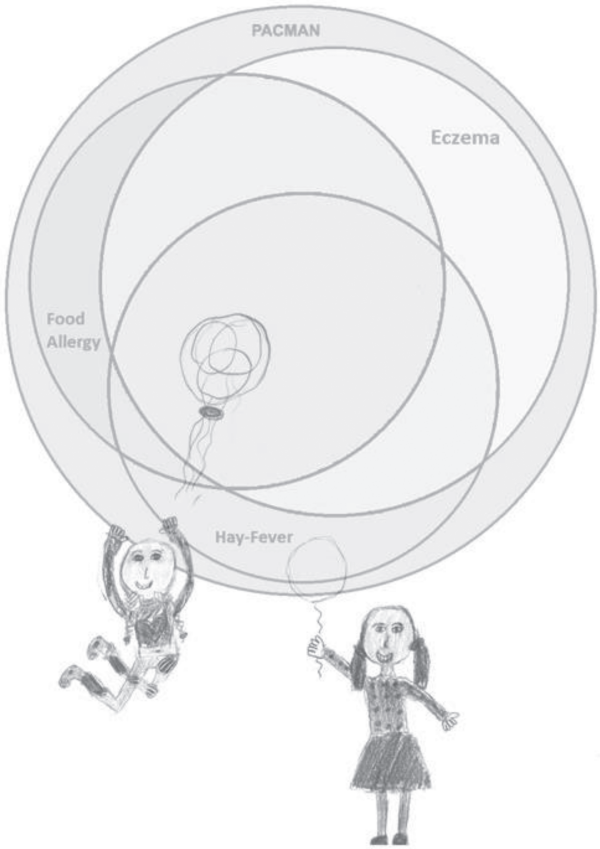
PACMAN
Eczema
Food
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Hay-Fever

chapter 3.2 | Asthma treatment patterns in Dutch children

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Submitted for publication

ABSTRACT

Background

Asthma is treated using a stepwise approach. Little is known about how this stepwise approach is applied in clinical practice. Therefore, we studied the step-up and step-down patterns of asthma medication prescriptions in a large group of Dutch children.

Methods

We analyzed all prescriptions dispensed for the treatment of asthma of 3,573 children who were regular users of asthma medication. Children were recruited through Dutch community pharmacies. Asthma medication prescriptions from birth to the date if extraction of the data (2010-2015) were extracted from the pharmacy dispensing systems. Step of treatment was determined for each combination of asthma medications with the same dispensing date according to the Dutch clinical asthma guidelines; step 1: short-acting beta-2 agonists (SABA), step 2: SABA and low dose inhaled corticosteroids (ICS) and etc. (steps 1 to 5). Short courses of oral corticosteroids (OCS) were considered to be a separate treatment step. No asthma medication prescriptions for >6 months was considered as no treatment ("step 0"). Subsequently, we assessed whether the intended treatment step of a new dispensing was different from the former dispensing. Logistic regression was used to assess the characteristics of prescriptions that followed the guidelines (1 step up or down) compared to prescriptions that did not (>1 steps up or down).

Results

The 3,573 children received in total 61,127 dispensings of asthma medications defined as asthma medications dispensed on the same date. The most frequent dispensing consisted of a combination of SABA and ICS (step 2; 37.1% of all prescriptions). In total 30,926 times a change in treatment step was observed (Table 1). Almost half of the changes (45.5%) consisted of > 1 treatment step, and 4.1% of the asthma prescriptions were followed by prescription of an OCS. Children who were in higher treatment steps (steps 3-5) were more likely to step up or down with >1 treatment step at a time (OR = 1.14 , p<0.01). Children ≥4 years had a higher risk on changes with >1 step at a time compared to younger children (OR = 1.42, p<0.01) and specialists more often adapted treatment >1 step at a time compared to GPs (OR = 1.27, p<0.01).

Conclusions

The changes of two steps or more were more likely prescribed by specialists (in comparison with GPs), in children that were already in higher treatment steps, and in older children. This might reflect the higher volatility of asthma in the children with more severe disease.

Asthma medication like inhaled corticosteroids (ICS) or inhaled β-agonists is the most commonly chronically used medication in children [1]. In the Netherlands, asthma is treated using a stepwise approach according guidelines derived from the British Thoracic Society (BTS) or others [2,3]. Guidelines advice to start treatment at the most appropriate step according to clinical severity. Step up of treatment is advised if a child does not reach asthma control in the current step, and step down is advised if a child is well controlled for a period of 3 months [2,4]. Little is known about how well the stepwise approach in the guidelines is followed in clinical practice. Therefore, we studied patterns of asthma medication prescriptions in a large group of Dutch children, with special interested in the step-up and step-down patterns [2].

We retrospectively analyzed all prescriptions dispensed for the treatment of asthma of 3,573 children who were regular users of asthma medication. Children were recruited in community pharmacies (PACMAN cohort study). Children were included in the study if they had used ≥ 3 prescriptions of asthma medication in last 2 years and ≥ 1 prescription in last 6 months, and were between 4-12 years of age. Records of dispensed asthma medication from birth were extracted from the pharmacy dispensing systems. In the Netherlands, individuals are usually registered at one pharmacy, which provides a full record of a patients' medication use [5,6]. Each dispensing of asthma medications (defined as asthma medications dispensed on the same date) was categorized according to the Dutch clinical asthma guidelines [4]; step 1: only short acting β-agonists (SABA) dispensed; Step 2: monotherapy with low-dose inhaled corticosteroid (≤ 400 µg budesonide diproprionate (BDP) equivalent) or leukotriene modifier, with SABA if needed. Step 3: monotherapy with medium-dose inhaled corticosteroid (400 – 800 µg BDP equivalent) or combination therapy of low-dose inhaled corticosteroid (≤ 400 µg BDP equivalent) with a long-acting β-agonist or a leukotriene modifier and SABA if needed; Step 4: monotherapy with high-dose inhaled corticosteroid (> 800 µg BDP equivalent) or combination therapy of medium-dose inhaled corticosteroid (400 – 800 µg BDP equivalent) with a long-acting β-agonist or leukotriene modifier and SABA if needed; Step 5: high-dose inhaled corticosteroid (> 800 µg BDP equivalent) plus long-acting β-agonist with or without omalizumab and SABA if needed. Generally, Dutch physicians prescribe chronic medications for 3-months periods and therefore, if no asthma prescriptions were recorded for ≥ 6 months we assumed the child did not use asthma medication at that time ("step 0"). Exacerbations are often treated with short course of oral corticosteroids (OCS). Therefore, a short course of OCS was considered to be a separate treatment step ("OCS"), outside the conventional treatment steps. We assessed whether the intended treatment step of a new dispensing was more than one step higher or lower than the former dispensing. Univariate logistic regression was used to assess which factors were associated with ≥1 step up or down (not following guidelines). The following factors were studied: former treatment step, prescriber ((GP versus related specialist [pediatricians, (pediatric) pulmonologist and (pediatric) internists]), age of the child at the time of dispensing (younger or older of 4 years), and gender of the child.

In total 61.127 asthma prescriptions were available of 3,573 children. The mean age at the dates of dispensing of asthma medications was 6.0 ± 3.1 years. The majority of the children in the study were boys (n=2240, 63.2%), and 65.9% of all prescriptions were for boys. The most frequent treatment

step was step 2 (37.1% of prescriptions). In total, 9.2% (n=5641) of the prescriptions did not fit in a treatment step according to the guidelines (for example: only LABA was dispensed, without ICS or only systemic SABA). These prescriptions were excluded from the analysis; with 55.486 prescriptions remaining of which 80.6% were prescribed by GPs. In 9,099 cases a time gap > 6 months between two following prescriptions was observed, which was classified as step 0 (period without asthma treatment). In total, 30,926 times a change in asthma treatment step was observed.

Table 1 summarizes the proportion of changes upon each treatment step. Overall approximately half of the changes (50.4 %) concerned 1 treatment step at a time; 45.5% of the changes concerned > 1 treatment step at a time, while 4.1% of the asthma prescriptions were followed by prescription of an OCS. Children in step 1 had the highest chance (76.3%) to step up or down with 1 treatment step. In contrast, patients who were in higher treatment steps (step 3-5) were more likely to step up or down with more than 1 treatment step at a time (63.3%– 79.4%). Older children (≥ 4 years) had a higher risk on changes with more than 1 step at a time compared to younger children (OR = 1.5, p value<0.01) and specialists more often adapted treatment more than 1 step at a time compared to GPs (OR = 1.4, P value<0.01). Gender of the child was not associated with changes > 1 treatment step at a time (OR = 1.0 , p value > 0.1).

This is the first study to describe the clinical practice of the stepwise approach as described in international guidelines for asthma treatment. More than half of the asthma prescriptions in children of Dutch physicians are in line with these guidelines, changing asthma medication one step at a time. However, changes of two steps or more, which is not in line with guidelines regardless to clinical features, were also frequently observed. These larger steps were more likely prescribed by specialists (in comparison with GPs), in children that were already in higher treatment steps (steps 3 to 5), and in children that were older. This might reflect the higher volatility of asthma in the children with more severe disease. Because we do not have detailed clinical data of the children

Table 1. Percentages of treatment changes per category of different initial treatment steps in 30926 changes in 3,573 children

	Initial step					
	Step 0	Step 1	Step 2	Step 3	Step 4	Step 5
Next step	n=8442	n=9056	n=8711	n=3473	n=1137	n=107
Step 0		32.9	43.6	30.0	20.1	9.3
Step 1	37.6		36.2	33.0	30.2	24.3
Step 2	43.9	43.4		24.7	22.3	31.8
Step 3	13.2	14.9	11.4		18.4	14.0
Step 4	3.0	4.0	3.4	7.4		15.0
Step 5	0.1	0.3	0.4	0.3	1.8	
OCS	2.2	4.4	5.0	4.5	7.1	5.6
Total	100.0	100.0	100.0	100.0	100.0	100.0

OCS: oral corticosteroids

in this pharmacy database study, we chose our outcomes irrespective of clinical features (>1 steps up or down as "not following guidelines"). In clinical practice physicians tend to make bigger steps in treatment changes in children at higher treatment levels, although the rationale for such a strategy is lacking in literature. Future studies might answer the question whether a more differential approach in treatment steps between children with mild and more severe asthma may lead to improved outcomes and less side effects.

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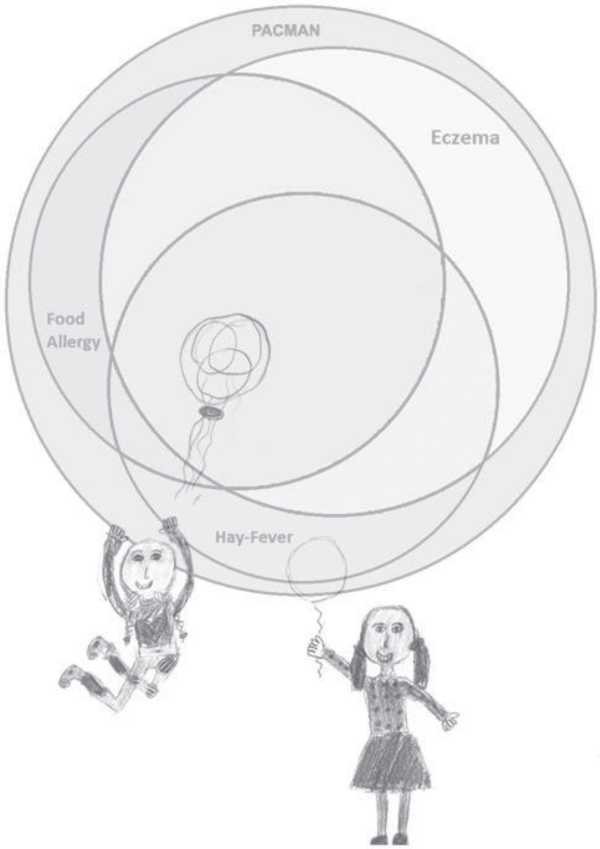
PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 3.3

Patterns of topical corticosteroids prescriptions in children who are regular users of asthma medication

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ABSTRACT

Background

To study topical Atopic Dermatitis (AD) medication use in Dutch asthmatic children using pharmacy dispensing data and to assess whether Dutch physicians prescribe TCSs in this population according to clinical guidelines.

Methods

Medication histories of children using asthma medication were extracted from the pharmacy dispensing system in 100 Dutch community pharmacies. The incidence rate and the potency of TCS prescriptions per age were assessed. The TCS incidence rates of the different age groups were compared using Pearson's chi-square test. Generalized linear models were applied to study the prescription behavior of general practitioners (GPs) and AD-related specialists regarding different classes of TCSs.

Results

Thirty percent of the infants received a TCS prescription, compared to 15-18% of the children ≥4 years. Similarly, the mean number of TCS prescriptions in infants is 2.2 prescriptions per year, compared to 1.6-1.9 prescriptions per year in children ≥4 years. In concordance with the clinical guidelines, we observed that first prescriptions of potent and very potent TCSs are more often prescribed by AD-related specialists compared to GPs (RR: 2.55, 95% CI: 1.79-3.63). Statistically significant differences (P value<0.01) were found between different prescribed TCSs' potencies.

Conclusion

This study has shown that younger children receive more TCS prescriptions compared with children ≥4 years old. Also, there is a statistically significant higher prescription rate of TCS for infants. Sometimes GPs do not follow guidelines and prescribe more potent TCSs without a prior prescription of the same potency by a specialist.

INTRODUCTION

Atopic Dermatitis (AD) (also known as atopic eczema) is a common inflammatory, relapsing skin disease. It is characterized by severe itching and eczematous skin lesions. Prevalence rates in Western Europe range between 4.5-30.4% [1]. The disease mainly affects infants and children and can have a severe impact on the health-related quality of life [2]. Approximately, 30 percent of children with atopic dermatitis will develop asthma later in life [3]. In a population of children that used asthma medication we even found a self-reported prevalence of 64%.[4]. It remains unclear which dominant mechanism drives this common coexistence [5]. Children with AD and asthma may have distinct interacting disease phenotypes compared to children with AD or asthma solely. This might also impact the effect of pharmacological interventions.

Standard medication for AD consists of emollients and topical corticosteroids (TCSs) use. Emollients hydrate the skin and can relieve the itching. They may reduce the need for TCSs [6]. TCSs are the cornerstone of AD treatment. They have anti-inflammatory, immunosuppressive and vasoconstrictive effects. Four classes of TCSs strength are recognized, from mild (A) to very potent (D) in the pharmacy data [7].

In patients with more severe disease, topical calcineurin inhibitors (TCIs) or systemic immunosuppressive therapies such as oral corticosteroids, azathioprine or cyclosporine can be prescribed [8]. TCIs have anti-inflammatory effect and can be prescribed as ointment or cream.

The current Dutch clinical guidelines for general practitioners (GPs) last revised in 2014 advise that general practitioners (GPs) should only prescribe treatment for mild disease (emollients and low potency TCSs) in children [9]. If the disease cannot be controlled by emollients and low potency TCSs, the patient should be referred to a dermatologist, pediatrician or otherwise related specialist [9]. However, it is unclear whether physicians actually follow these guidelines. The aim of this current descriptive pharmacoepidemiological study was to study AD medication patterns in Dutch asthmatic children using pharmacy dispensing data, and to assess whether Dutch physicians prescribe AD medication according the clinical guidelines.

METHODS

Study population and data collection

Medication histories of children between 4 and 12 years old using regular asthma medication were extracted from the pharmacy dispensing systems in 100 Dutch community pharmacies containing data from 1996 to 2013. The pharmacies were part of the UPPER Network of the Utrecht Institute for Pharmaceutical Sciences [10]. Regular asthma medication was defined as ≥ 3 prescriptions of asthma medication in the last 2 years and ≥1 prescription in the last 6 months before inclusion (2009-2013) [11]. Only children for whom the medication history was available starting in the first year of life were included in this study.

AD medication dispensing data

A TCS prescription was identified based on the Anatomical Therapeutic Chemical (ATC) code within the pharmacy dispensing system. All preparations starting with ATC code D07A (plain topical corticosteroids) were selected. To subdivide TCSs into potency classes the next letter in the code was used. 'A' represents a weak potency TCS, 'B' a moderate potency TCS, 'C' a potent TCS and 'D' represents a very potent TCSs.

If ≥2 AD related prescriptions were recorded on the same day (irrespective to the dosage) only the most potent TCS prescription was included in the all analyses. As combinations of TCSs and an antifungal (ATC code: D07B) or antibacterial agent (ATC code: D07C) are used for treatment of infections, they were not counted as TCS therapy for AD in this study.

The incidence rate and the potency of TCS prescriptions per age were assessed. We assessed the incidence rates per person year (the product of the number of years times the number of members of a population who were at risk for an event) at every category of age. For every child the age on which they received their first potent (class C) or very potent TCSs (class D) prescribed was extracted. The duration of TCS use was estimated by counting the mean number of TCS prescriptions in children that received at least one TCS prescription per age category.

Prescribers of AD medication

Prescribers of the distinct prescriptions were extracted from the pharmacy records. Prescribers were subdivided in three categories: 1. General Practitioners (GPs), 2. AD related specialists (dermatologists, pediatrics, allergists, pulmonologists and ophthalmologist) and 3. Non-AD related specialists (for example: urologists). The prescribed potency of TCSs were compared between two mutually exclusive groups of children 1) who were prescribed TCSs only by an AD related specialist and 2) the children who were prescribed TCSs only by a family doctor.

Statistics

The TCSs incidence rates of the different age groups were compared using Pearson's chi-square test [12]. Generalized linear models were applied to assess whether distinct categories of prescribers prescribe different classes of TCSs (SPSS v.20.0, IBM Corp., Armonk, NY, USA).

RESULTS

Study population

Medication histories were extracted of 3575 children. For 2220 children medication histories were available from the first year of life (Figure 1). The majority of these children were boys (65.3%) and the median age was 8.3 years (Interquartile range (IQR): 6.0-10.7) (Table 1). Overall, 62.8% of the children who regularly used asthma medication also received a TCS prescription at least once. Almost half of the children with a TCS prescription received a weak potent TCS (class A). The most

potent TCSs (class D) were only prescribed in 3.2% of the study population. Prescriptions of TCIs were relatively rare (1%) in our study population. For 936 children TCS were prescribed only by GPs and for 74 children TCS were only prescribed by specialists.

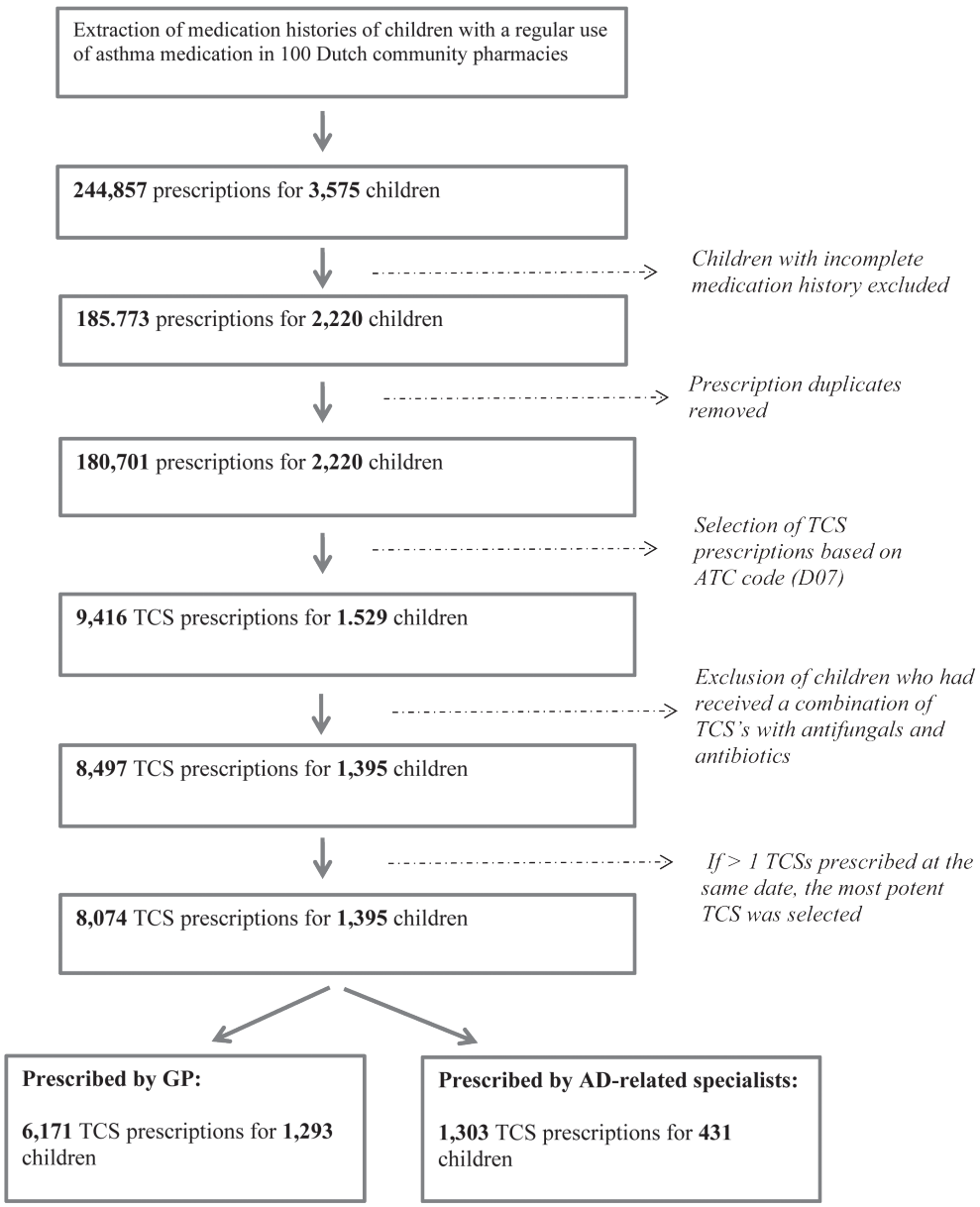


Figure 1. Flowchart of the data extraction.
AD: Atopic Dermatitis, GP General Practitioner, TCS Topical Corticosteroids

Table 1. Characteristics of the study population; children with a regular use of asthma medication and medication dispensing data available from the first year of life

	Study population (n = 2220)
Male gender, N (%)	1450 (65.3)
Median age in years [at time of data extraction date] (IQR)	8.3 (6.0 – 10.7)
Received a prescription of TCSs at least once, N (%)	1395 (62.8)
weak TCSs (class A), N (%)	1084 (48.8)
moderate potent TCSs (class B), N (%)	668 (30.1)
potent TCSs (class C), N (%)	466 (21.0)
very potent TCSs (class D), N (%)	56 (3.2)
Received a prescription of TCI at least once, N (%)	23 (1.0)

TCI: topical calcineurin inhibitors, TCS: topical corticosteroid

Age and TCS prescriptions

Older children received TCSs statistically significantly less frequently than younger children (Figure 2, Supplementary Table 1and Supplementary Figure 1). Thirty percent of the infants received a TCS prescription, compared to 15-18% of the children ≥ 4 years (Supplementary Figure 1). The mean number of TCS prescriptions in infants is 2.2 prescriptions per year, compared to 1.6-1.9 prescriptions per year in children ≥ 4 years (Table 2). Young children received a prescription for a weak TCS more often compared to older children. From age 5 years and older weak, moderate and potent TCSs were used in a similar degree (Supplementary Figure 1). There were no statistically significant differences in TCS prescriptions between boys and girls.

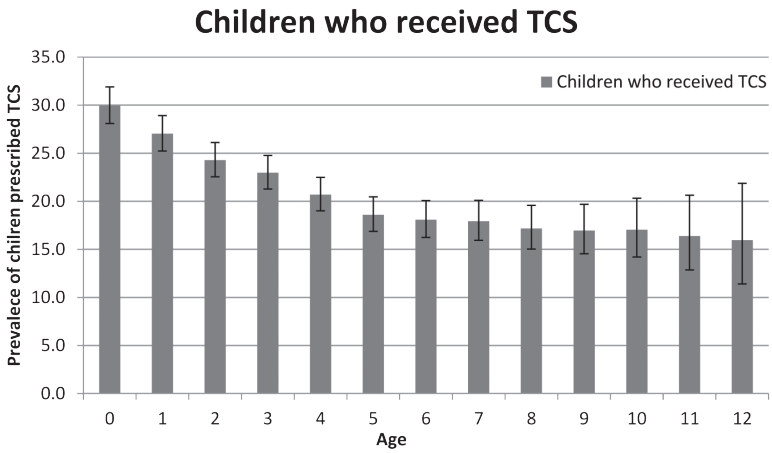


Figure 2. Prevalence of TCS prescriptions the children with a regular use of asthma medication. The prevalence of TCS prescriptions in asthmatic children decreases when children become older. There is no significant difference in the amount of TCS prescriptions between boys and girls.

Table 2. Mean number of TCS prescriptions stratified per age category

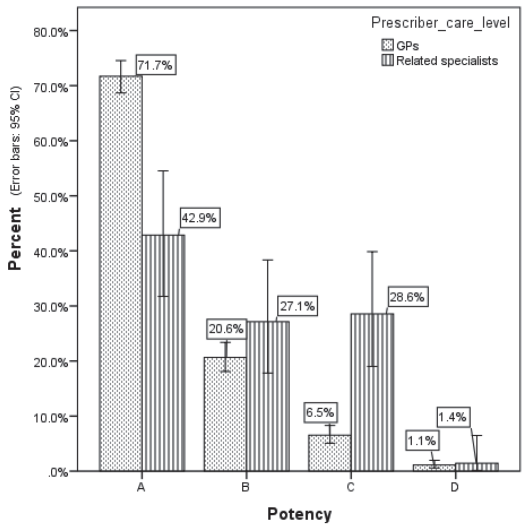
Age (years)	Weak TCSs (class A)	Moderate TCSs (class B)	Potent TCSs (class C)	Very potent TCSs (class D)	Total TCSs
0	1.76	1.64	1.73	1.20	2.20
1	1.60	1.97	1.95	1.80	2.19
2	1.46	1.91	2.04	1.25	2.13
3	1.42	1.79	2.16	1.07	1.96
4	1.37	1.66	2.03	1.33	1.88
5	1.35	1.52	2.07	1.36	1.86
6	1.29	1.55	2.04	1.00	1.82
7	1.33	1.59	2.30	1.11	1.88
8	1.29	1.52	2.02	1.25	1.77
9	1.22	1.69	2.04	1.38	1.86
10	1.42	1.68	1.95	1.60	2.00
11	1.13	1.65	1.56	1.00	1.67
12	1.25	1.70	1.22	0.00	1.59

AD medication prescribers

In concordance with the clinical guidelines, we observed that first prescriptions of potent and very potent TCSs are more often prescribed by AD-related specialists compared to GPs (RR: 2.55, 95% CI: 1.79-3.63). Nevertheless, GPs do still prescribe potent and very potent TCSs in some patients (Table 3 and Figure 3). For both groups of prescribers, AD-related specialists and GPs, weak TCSs were the most commonly prescribed starting of TCS (Figure 3). Combined potent and very potent TCSs cover < 10% of all (first) TCS prescriptions by the GPs. For AD-related specialists potent and very potent TCS cover almost 30% of all (first) TCS prescriptions (Figure 3). Statistically significant differences (P value<0.01) found between frequency of different potencies of prescribed TCSs using generalized linear models.

Table 3. TCS prescribed by only GPs, only AD-related specialists or mixed

	TCS Potency				
Prescriber	Weak (class A)	Moderate (class B)	Potent (class C)	Very potent (class D)	Total TCS prescriptions
Only AD-related specialist	102 (41.5)	51 (20.7)	84 (34.1)	9 (3.7)	246 (for 74 children)
Only GP	1805 (52.6)	1066 (31.1)	509 (14.8)	53 (1.5)	3433 (for 936 children)
GP and AD-related specialist	1047 (23.5)	1472 (33.5)	1810 (41.2)	66 (1.5)	4395 (for 385 children)



chapter 3.3

Figure 3. First TCS prescriptions stratified by TCS potency and prescriber. Prescribers have been classified into GPs and AD-related specialists (dermatologists, pediatricians, allergists, pulmonologists and ophthalmologists). When focusing on the first TCS prescription a patient receives, GPs more often prescribe weak potency TCSs (class A), while AD-related specialists more often prescribe more potent TCSs (class B-D).

When we divided the first potent or very potent prescriptions by different age groups, a statistically significant difference in prescription behavior between AD-related specialists and GPs was only found for children ≤ 2 years (RR : 2.86 (95% CI: 1.84, 4.45)) in which AD-related specialists prescribed the higher amount of potent or very potent TCSs for young children (Figure 4). The incidence rate for prescribing a potent or very potent TCSs for AD-related specialists was 12.6 prescriptions per 100 person years, compared to 4.4 prescriptions per 100 person years for GPs.

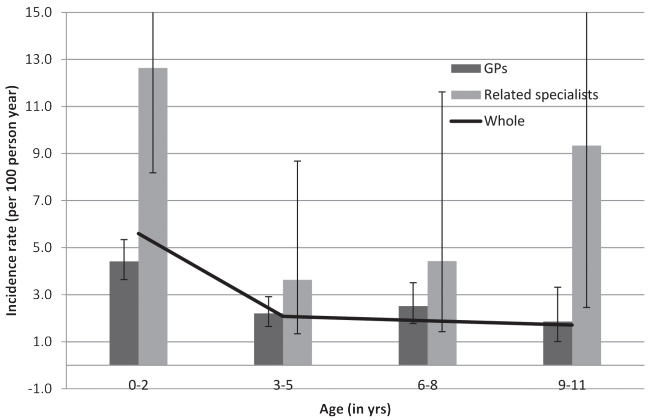


Figure 4. Incidence rate for first **potent or very potent** TCS prescriptions in children using asthma medication.

DISCUSSION

Atopic dermatitis and asthma often co-exist. Children with atopic dermatitis have a large risk to develop asthma later on, yet early asthma symptoms such as wheeze may also precede AD symptoms [13]. AD treatment with TCSs is often required for months or years. This large pharmacy-based study provides more insights in the amount of prescriptions for AD in children who have asthma symptoms and the TCS prescription behavior of GPs and AD-related specialists. In this study we focused on TCS prescriptions, since this is considered to be the cornerstone in topical treatment of moderate to severe AD. The amount of children who received TCSs (62.8%) was comparable to the amount of children with self-reported AD (63.6%). Prospective cohort studies have shown that the disease often resolves when children get older [13]. This trend is also reflected in our study, children were prescribed less TCSs when they got older. Previous studies have shown that AD is more prevalent amongst boys compared to girls [14], however, in our study the amount of TCS prescriptions did not significantly differ between boys and girls.

While younger children received a TCS prescription more often, older children were generally treated with a more potent TCS. In younger children fear about corticosteroid use might play a bigger role [15]. Anxiety concerning the adverse effects of TCS use is common among TCS users [15], and might even play a bigger role in parents of young children. Lack of knowledge of pharmacists or physicians regarding the safety and side effects of TCS use might also contribute to this anxiety and the hesitance to prescribe more potent TCSs [16]. Furthermore, older children often suffer from more persistent AD symptoms, which might also explain why older children are more often treated with more potent TCSs.

As expected, AD-related specialists prescribe potent TCSs more often compared to GP. However, we also observed that in some cases GPs still prescribe potent TCSs, even in children who, according to the pharmacy dispensing system, have not received a TCS prescription before. This is not in line with the Dutch GP guidelines [9]. The guidelines state that GPs should not prescribe very potent TCSs, if this treatment has not been previously prescribed by a specialist. However, we cannot exclude that patients have received a previous potent TCS prescription outside their community pharmacy, for example in the hospital pharmacy.

This study has shown that younger children are more prone to be prescribed TCS and the number of prescriptions is higher than in children ≥ 4 years old. Also, there is a statistically significant difference in TCS prescribing pattern for infants. Which is according to the guidelines[9]. However, sometimes GPs prefer to prescribe potent TCSs without a prior prescription of the same potency by a specialist. This is not advised in the guidelines.

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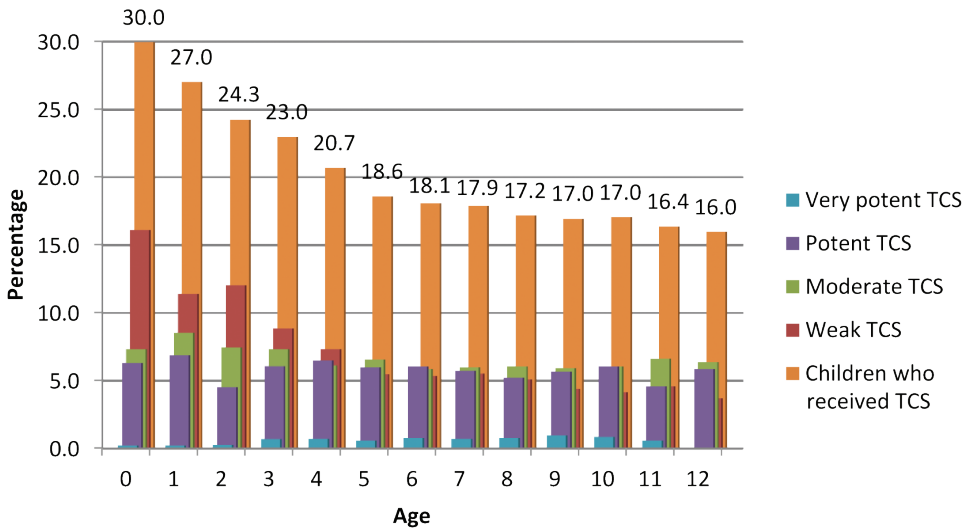
SUPPLEMENTARY MATERIALS

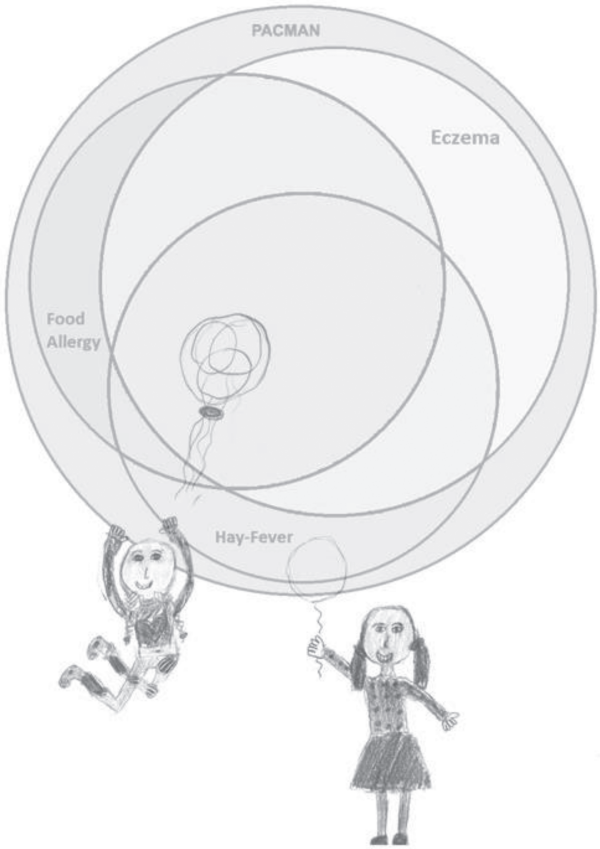
Supplementary Table 1. The number of children who received TCS prescriptions per age category

Age (years)	Weak TCSs	Moderate TCSs	Potent TCSs	Very potent TCSs	Children who received TCSs	Total
0	357	163	140	5	665	2220
1	253	189	153	5	600	2220
2	267	165	101	6	539	2220
3	197	163	135	15	510	2220
4	153	128	135	15	431	2083
5	99	119	108	10	336	1807
6	83	91	94	12	280	1549
7	72	78	75	9	234	1306
8	54	64	55	8	181	1054
9	36	48	46	8	138	814
10	24	35	35	5	99	581
11	16	23	16	2	57	348
12	7	12	11	0	30	188

The most potent TCSs during that age has been mentioned.

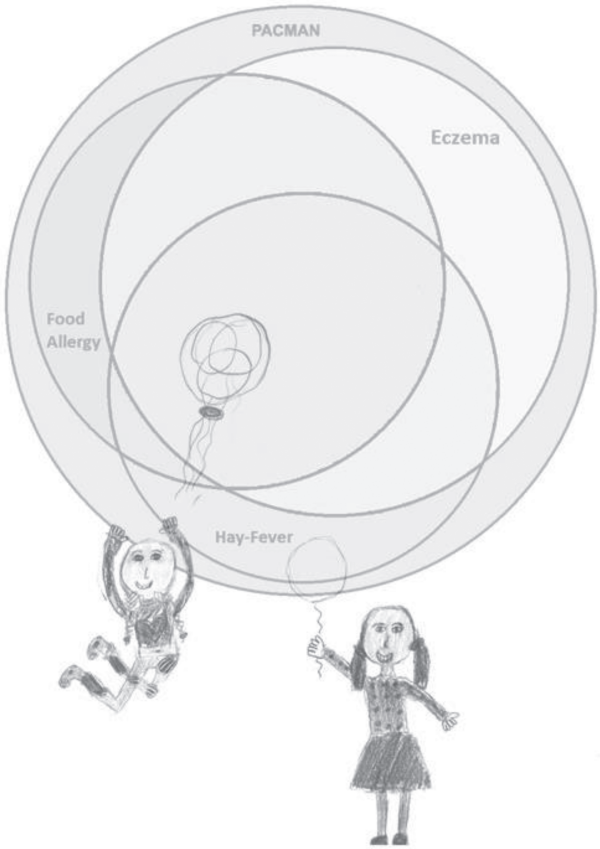


Supplementary Figure 1. The prevalence of TCS prescriptions in asthmatic children. The most potent TCSs during each life year has been selected.


PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 4

Genetic risk factors for developing allergic diseases


PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 4.1

Association of Allergy genetic risk score with allergies in children - Wheezing illnesses study Leidsche Rijn cohort

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Submitted for publication

ABSTRACT

Background

Several genes have been associated with the susceptibility to allergic disease in adults, but it remains unclear whether these genes are also associated with the onset of allergic disease early in life. The aim of this study was to develop a genetic risk score (GRS) for allergy based on findings in adults and study its predictive capacity for allergy in children.

Methods

A GRS was constructed based on 10 SNPs previously associated with allergies in adults. The GRS was tested in children who participated in a population-based newborn cohort (WHISTLER) and were followed from birth to school age. Logistic regression analysis was used to study the association between the GRS and the parental-reported allergies at age 5 (based on a reported allergy to ≥1 of the following allergens: pollen, house dust mites or pets). A Cox regression model was used to study the association between GRS and a physician-diagnosed allergy during follow-up (allergic conjunctivitis, allergic rhinitis and eczema/dermatitis). Cohen's kappa coefficient was calculated to study the agreement between physician-diagnosed allergy and parental-reported allergy at age 5.

Results

The GRS was significantly associated with parental-reported allergy (OR: 9.25, 95%CI: 1.02-83.85) at age 5, as well as with a physician-diagnosed allergy during follow-up (hazard ratio(HR):1.79 (95% CI: 1.06 -3.02)). The overall agreement between physician-diagnosed and parental-reported allergies was 70.5% (Kappa: 0.10, 95% CI: 0.03-0.18).

Conclusions

The allergy GRS based on SNPs related to allergies in adults predicted the risk on developing allergies in childhood.

INTRODUCTION

Allergic diseases are characterized by hypersensitivity to normally innocuous antigens. The prevalence of allergic disease has increased globally in the last few decades. More than a third of the world population is affected by allergies; this causes a significant economic burden [1]. The development of allergic disease is complex and not fully understood, however it has been proven that it is associated with both environmental and genetic components [2]. Several linkage analyses and candidate gene association studies have identified genes associated with allergic diseases, such as atopic dermatitis (e.g. *COL6A5* [3], *FLG* [4], *TLR9* [5], *IL13* [6], *SPINK5* [7], *CMA1* [8], *IL4RA* [9] and *RANTES* [10]) and allergic rhinitis (e.g. *FLG* [11], *S100A7* [12], *HDC* [13], *IL13* [14], *IL6* [15] and *TLR7* [16]) [1]. A meta-analysis of genome-wide association studies (GWAS) in 53,862 individuals has identified 16 genome-wide loci significantly associated with self-reported allergy to pollen, dust-mite and cat [17]. Of these loci, 8 had previously been associated with asthma. Additionally, loci encoded *TLR1* (Toll-like receptor 1) and *TLR6* (Toll-like receptor 6) variants, in the 4p14 region near rs2101521. Those genes encode pattern-recognition receptors that play a role in recognizing external molecules and are involved in innate immunity and immune responses. Previous candidate gene studies have also identified associations of the same *TLR* genes with sensitization to grass and rhinitis [18]. Other associations in the GWAS meta-analysis included loci in genes involving in the presentation of intracellular peptides to T cells, genes involved in the initiation of skin immune responses, Th2-differentiation (*BCL6, IL2/ADAD1*), cell-cell adhesion (*LPP*), and genes involved in the regulation of TH2-mediated inflammation and mucus production in allergic airway disease [17].

In order to summarize the combined effect of genetic variants on an outcome, such as the susceptibility of allergies, a genetic risk score (GRS) can be constructed. A GRS - sometimes called allele scores, gene scores or genotype scores - comprise of a quantitative score of previously associated SNPs [19].

Although most of the genetics studies for allergies were performed in adults, the collective dataset suggests an important genetic basis for allergic diseases. This raises the question whether genetic risk factors are predictive for development of allergic diseases in later life. In this current study, we aimed to develop a GRS for the onset of allergy in children based on findings in adults, in order to study whether genetic risk factors for allergy later in life are also predictive for allergy early in life.

METHODS

Study population

We analyzed data collected in the Wheezing illnesses study Leidsche Rijn (WHISTLER) cohort, a prospective population-based birth cohort study in the Netherlands, which studies determinants and prediction of wheezing illnesses. Study design and rationale of WHISTLER have been described in detail elsewhere [20]. Briefly, healthy neonates and infants born in a newly developed residential area in the Netherlands (i.e. Leidsche Rijn) were invited by telephone to participate in this study before the age of 2 months. Exclusion criteria were gestational age younger than

36 weeks, major congenital abnormalities and neonatal respiratory disease. Written informed consent was obtained from the parents. During an extended first consultation an "Individual Health Profile" (IHP) was compiled. At the age of 5 years, children were invited for a second visit, in which information about general health, allergic symptoms, asthma and respiratory symptoms, medication use, pre- and post-natal risk factors was obtained by questionnaires. Children were invited for a third visit at the age of 8 years. During the total follow-up, information on physician diagnoses, primary care consultations and medication prescriptions for respiratory symptoms was collected. Genomic DNA extracted from buccal cells of infants is available. The pediatric medical ethics committee of the University Medical Center Utrecht, Utrecht, the Netherlands, approved the WHISTLER cohort study.

Study Design

In this population-based birth cohort, we assessed the association between a genetic risk score for allergy susceptibility based on genetic variants associated with allergy in adults and parental-reported and doctor diagnosed allergies (parental and doctor-diagnosed) in children.

Genotyping & Quality control

Genomic DNA was extracted from buccal cells of infants using the QIAamp DNA blood mini kit (Qiagen) and concentration was determined using PicoGreen (Molecular Probes) [20]. Genotyping was performed using the Infinium HumanExome chip (Illumina, San Diego, CA), version 1.1, which contains 242,902 variants [21]. Genotypes obtained from GenomeStudio were used for quality control (QC), and PLINK v1.07 was used for the downstream process. Sample QC was performed on common SNPs (MAF ≥5%) of high quality (missingness<1%, Hardy-Weinberg equilibrium P >1e-4, and LD-pruned to leave no pairs with r2 >0.2). We removed samples based on heterozygosity, keeping samples within 4 standard deviations. European ancestry was verified using EIGENSTRAT [22], and non-European samples were excluded for further analysis. Identity-by-descent estimates from PLINK were used to identify siblings or otherwise related children (pi-hat >0.2), one of which was randomly excluded. As the calling algorithms in GenomeStudio are not designed for rare SNPs, genotypes from zCall [23] were used in subsequent analyses, where we excluded SNPs with a call rate less than 95% and a Hardy-Weinberg equilibrium p-value<1e-6.

Genetic risk score

A GRS was constructed based on SNPs previously associated with allergies in adults in a GWAS meta-analysis by Hinds *et al*. [17], since there was no GWAS available for children. In this meta-analysis 16 SNPs were found to be associated with at least one of three common self-reported allergy phenotypes (pollen allergy, dust-mite allergy and cat allergy) in two cohorts with a total of 53,862 individuals.

Out of the 16 identified shared susceptibility loci with association P < 5e-8, reported by Hinds *et al*, three were available on the exome-chip. Moreover, we found a suitable alternative on the chip

for seven more SNPs, for which our criterion was that they should have an r2 > 0.8. The r2 could be regarded as the correlation between the original and the alternative SNP, as a rough measure, with r2 = 0.8, in 80% of the cases, if you have genotyped the original SNP, you will also have information on the correlated SNP. Therefore, we could include 10 SNPs in our GRS. We weighted the SNPs in proportion to their effect size, as these varied considerably between the SNPs. The weighting was based on the natural logarithm of the reported odds ratios (ORs) for the allergy SNPs in the original GWAS [17]. The GRS was weighted in such a way that an increase in the GRS would be associated with an increase in allergies in the original GWAS. SNPs included in the risk score, as well as effect sizes, effect alleles, references to studies identifying them and detail on generating GRS can be found in the supplementary materials (Table S1).

Study outcomes

1. Parental-reported allergy to pollens, dust-mites and/or pets at age 5. This was based on ≥1 positive answer to one of the following questions in the questionnaire during the study visit at age 5 and age 8: "Is your child allergic to pollen?", "Is your child allergic to house dust mite?", "Is your child allergic to certain pets?"

2. Physician diagnosis of allergic symptoms, using the International Classification of Primary Care (ICPC) [24], allergic conjunctivitis (ICPC: F71), allergic rhinitis (ICPC: R97) or eczema/dermatitis (ICPC: S87, S88) during follow-up.

Statistical analysis

A univariate logistic regression analysis was applied to study the association between the GRS and the parental reported allergies at age 5 and age 8. A Cox regression model was used to study the association between GRS and physician-diagnosed allergies during follow-up. The agreement between parental-reported allergy (to specific allergens) and physician-diagnosed allergy (based on allergic symptoms) was assessed with Cohen's Kappa statistics and interpreted using the classification system developed by Landis and Koch [25]: $\kappa \leq 0$ indicates poor agreement, κ between 0 and 0.20 indicates slight agreement, 0.21-0.40 indicates fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement and κ values of 0.81 to 1.00 indicates almost perfect to perfect agreement.

For the analyses, we used several statistical packages: R (version 3.0.2), SPSS (version 23.0, IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and PLINK (version 1.07).

RESULTS

Study population

In total, 2112 children who participated in the WHISTLER study were genotyped, of which 692 were excluded in the genotyping quality control process, leaving 1420 children for our analyses. Physician diagnosis data during follow-up were available for 1330 children, and parental-reported

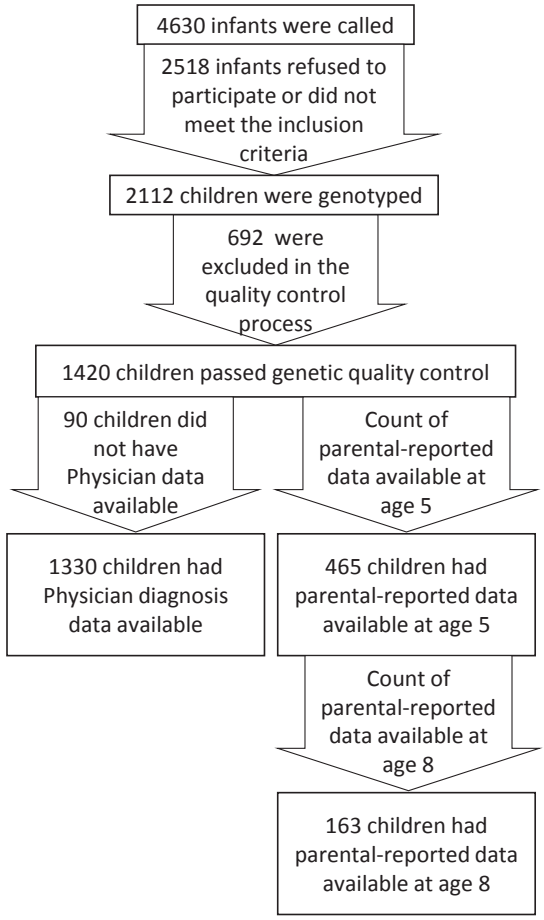

Figure 1. Overview of the recruitment and inclusion of children from the Wheezing Illnesses Study Leidsche Rijn (WHISTLER) project.

data at age 5 and 8 were available for 465 and 163 children, respectively(Figure 1). Characteristics of the study population are shown in Table 1. Median age for our study population was 7.0 years (Interquartile Range (IQR): 4.0 – 9.0). Half of the children were girls (50.8%). The mean genetic risk score was 0.65 ± 0.18.

GRS and self-reported allergies association

At age 5, parents of 28 of the 456 children (6.0 %) reported that their child suffered from an allergies. The GRS was statistically significantly associated with parental-reported allergy in this population (OR: 9.25, 95%CI: 1.02-83.85) (Table 2). At age 8, 16 out of 163 children (11.2 %) suffered from allergies based on parental-reported questionnaire. The GRS was not significantly associated in this population.

Table 1. Study characteristics

WHISTLER database	
Subjects, n	1330
Age, median (IQR)	7.0 (4.0 – 9.0)
Dutch ethnicity*, n (%)	471/569 (82.8)
Gender (female), n (%)	675/1330 (50.8)
Follow-up duration**, median (IQR)	3.8 (5.1)
Genetic allergies risk score, mean (SD)	0.7 (0.2)
Physician diagnosed asthma, n (%)	110/1330 (7.1)

Abbreviations: IQR, interquartile range; SD, standard deviation; *Both parents; **From birth to data extraction dates

Table 2. Association results for the allergy GRS and reported allergy to pollen, house-mites or pets at age 5

	Unadjusted	Adjusted for gender
Outcome	**OR (95% CI), P-value**	**OR (95% CI), P-value**
RA	9.47 (1.04 - 86.45), 0.046	9.25 (1.02 - 83.85), 0.048

Abbreviations: GRS: genetic risk score; OR; odd ratio; CI: confidence interval; RA: Parental-reported allergy to pollen, house-mites or pets

GRS and physician-diagnosed allergy

We retrospectively assessed the time to a physician-diagnosed allergy in the WHISTLER population. The median follow-up time was 3.6 years (IQR: 1.5 – 6.7 years) starting from birth to the occurrence of any allergies or extraction date. The allergy GRS was statistically significantly associated with a physician diagnosis of allergies (hazard ratio (HR):1.79, 95% CI: 1.06 -3.02). Children with higher allergy GRS had a higher chance to be diagnosed with allergic conjunctivitis, rhinitis or dermatitis during the follow-up. The effect of GRS on diagnosed allergic conjunctivitis or rhinitis was not statistically significant (HR= 1.90, 95% CI: 0.6 – 5.9) (Table 3).

Table 3. Reported or physician diagnosed allergic symptoms

Physician diagnosed allergic rhinitis or allergic conjunctivitis, n (%)	97/1330 (7.3)
Physician-diagnosed allergic rhinitis, n (%)	72/1330 (5.4)
Physician-diagnosed allergic conjunctivitis, n (%)	33/1330 (2.5)
Physician-diagnosed allergic dermatitis, n (%)	458/1330 (34.4)
Physician-diagnosed allergies, n (%)	497/1330 (37.4)
Parental-reported allergy to pollen, house-mites or pets at age 5 years, n (%)	28/465* (6.0)

*The children who reached to age 5 years and had parental-reported data available

The agreement between parental-reported and physician-diagnosed allergies

For 455 children data were available to assess the agreement between diagnosed allergies (allergic conjunctivitis, allergic rhinitis or dermatitis at age 5 years) and self-reported allergy to pollen, house-mites or pets at age 5. Overall agreement was 70.5% (Table 4); Kappa was 0.10 (95% CI: 0.03-0.18) which indicated 'slight agreement'. Equally, the agreement was the same (62.9 %) at age 8 (Table 5) with a kappa of 0.14 (95% CI: 0.02-0.26). When dermatitis would be left out of the physician-diagnosed allergy outcome the agreement were 94.9 % (Table S2) with kappa statistics of 0.49 at 5 years old and 89.1% (Table S3) with kappa of 0.47 at 8 years old, which indicate "moderate agreement".

We also tested the agreement between allergic dermatitis and self-reported allergy to food or medications, however these were not statistically significant at both age 5 and 8 (Tables S4 and S5).

Table 4. The agreement between parental-reported and physician-diagnosed allergies at age 5 years

			Physician-diagnosed allergic symptoms at age *5* years	
			No	**Yes**
Parental-reported allergy to pollen, house-mites or pets at age *5* years	No	Count	305	122
		% of Total	67.0%	26.8%
	Yes	Count	12	16
		% of Total	2.6%	3.5%

Kappa (95% CI) = 0.10 (0.03 – 0.18)

Table 5. The agreement between parental-reported and physician-diagnosed allergies at age 8 years

			Physician-diagnosed allergic symptoms at age *8* years	
			No	**Yes**
Parental-reported allergy to pollen, house-mites or pets at age *8* years	No	Count	79	48
		% of Total	55.2%	33.6%
	Yes	Count	5	11
		% of Total	3.5%	7.7%

Kappa (95% CI) = 0.14 (0.02 – 0.26)

DISCUSSION

This study showed that genetic variants previously associated with allergies in adults are also predictive of the onset of allergies in children. Development of allergic diseases is complex.

Both environmental factors such as diet, family size, education level in the household, specific infections, exposures to non-pathogenic microorganisms, living in urban settings and regions with low exposure to ultraviolet radiation and low humidity [26] and genetic factors have been shown to be involved [2]. A century ago it was already shown that there is a heritable component in the risk of developing allergies [27]. More recently, large GWAS have identified genetic variants associated with allergic sensitization and allergic symptoms [17,28]. Here, we showed that combining established genetic risk factors in a predictive risk score can be used to predict the onset of allergy in children.

That a GRS might be a useful tool to predict allergies has also been shown by Bønnelykke *et- al*.[28]. They constructed a GRS based on 10 genome-wide significant loci based on a different, somewhat smaller, reference GWAS [29] including 10 studies (birth cohorts and population-based cohorts). They tested the predictive capacity of the GRS for allergic sensitization and allergic rhinitis in a population-based study (n=9258 mostly adults) and showed that a higher GRS score indicated a higher prevalence of sensitization. In our study, we applied a similar approach but restricted the GRS to genetic variants associated with allergy in adults and tested the GRS in an independent birth cohort to assess the predictive value for allergies early in life. Nevertheless, there is a large overlap in the loci studied; of the ten loci Bønnelykke *et al*. studied, 5 loci were also included in our study. A complete report of similarity and differences of the two mentioned reference GWAS was published by Bønnelykke *et al*. [29].

The comparability of different studies is limited due to the application of different definitions of allergy [1]; some studies focus on allergic symptoms and use self-reported allergy, others focus on physician diagnosis of allergy or measures of allergic sensitization such elevated levels of allergen-specific IgE and/or a positive skin prick test. Although allergic sensitization can be measured more objectively, it does not provide proof that the sensitization will also cause allergic symptoms. In this study we assessed allergic symptoms, focusing on self/parental-reported, as well as physician-diagnosed allergies. Since both outcomes might measure different aspects of allergic diseases, we performed agreement analyses to see whether these outcomes identified different individuals. We found a slight statistically significant agreement between reported allergy to pollen, house-mites or pets and diagnosed allergies. We assume that one of the reasons for the lack of agreement is that not all children visit their physician with allergic complaints. Nevertheless, the GRS was associated with parental-reported allergy (at age 5), as well as physician-diagnosed allergy (during follow-up). In summary, an allergy GRS based on SNPs associated to allergies in adults predicted the risk on developing allergies in childhood. Since allergy has multiple risk factors including genetic components, we believe that this allergy GRS can be used to develop a prediction model for allergic symptoms.

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Table S1. SNPs included in allergies GRS and effect on allergies

Data from GWAS catalog[1]						Results analysis single SNPs in WHISTLER					
								DA		RA	
CHR	BP	SNP	Alleles	OR	P-value	ID on exome-chip	Effective Allele	HR	P-value	OR	P-value
4	38811551	rs2101521	A/G	1.15	5.3E-21	exm394605	T	1.1	0.51	1.1E9	1.00
5	110467499	rs1438673	T/C	1.12	2.3E-20	exm2265991	G	1.2	0.03	0.9	0.85
11	76299194	rs2155219	G/T	1.11	1.6E-19	exm-rs2155219	T	1.1	0.14	1.1	0.80
6	32626311	rs6906021	T/C	1.10	7.1E-15	exm-rs6906021	C	1.0	0.77	0.7	0.74
5	40486896	rs7720838	G/T	1.08	8.2E-11	exm-rs10440635	A	1.0	0.64	0.8	0.65
2	198914072	rs10497813	T/G	1.08	6.1E-10	exm-rs6738825	A	1.1	0.18	1.2	0.65
9	6172380	rs7032572	A/G	1.12	1.7E-09	exm-rs1342326	G	1.0	0.97	1.6	0.24
17	38074031	rs9303280	T/C	1.07	8.9E-09	exm-rs7216389	T	1.0	0.8	0.5	0.27
15	67450305	rs17228058	A/G	1.08	1.2E-08	exm-rs17293632	T	1.1	0.4	1.7	0.17
4	123329362	rs17388568	G/A	1.08	3.9E-08	exm-rs17388568	A	0.9	0.49	3.0	0.01

Abbreviation: SNPs: single nucleotide polymorphisms; GRS: genetic risk score; CHR: Chromosome, BP: chromosomal location based on hg19, OR: odds ratio; HR: hazard ratio, DA: Physician diagnosed allergies, RA: Reported allergy to pollen, mites and pets

Table S2. The agreement between parental-reported allergy and physician-diagnosed allergic conjunctivitis or rhinitis at age 5 years

			Physician-diagnosed allergic conjunctivitis or rhinitis at age *5* years	
			No	**Yes**
Parental-reported allergy to pollen, house-mites or pets at age *5* years	No	Count	420	7
		% of Total	92.3%	1.5%
	Yes	Count	16	12
		% of Total	3.5%	2.6%

Kappa (95% CI) = 0.49 (0.28 – 0.66)

Table S3. The agreement between parental-reported allergy and physician-diagnosed allergic conjunctivitis or rhinitis at age 8 years

			Physician-diagnosed allergic conjunctivitis or rhinitis at age *8* years	
			No	**Yes**
Parental-reported allergy to pollen, house-mites or pets at age *8* years	No	Count	121	8
		% of Total	82.9%	5.5%
	Yes	Count	8	9
		% of Total	5.5%	6.2%

Kappa (95% CI) = 0.47 (0.23 – 0.67)

Table S4. The agreement between parental-reported allergy to food or medications and physician-diagnosed allergic dermatitis at age 5 years

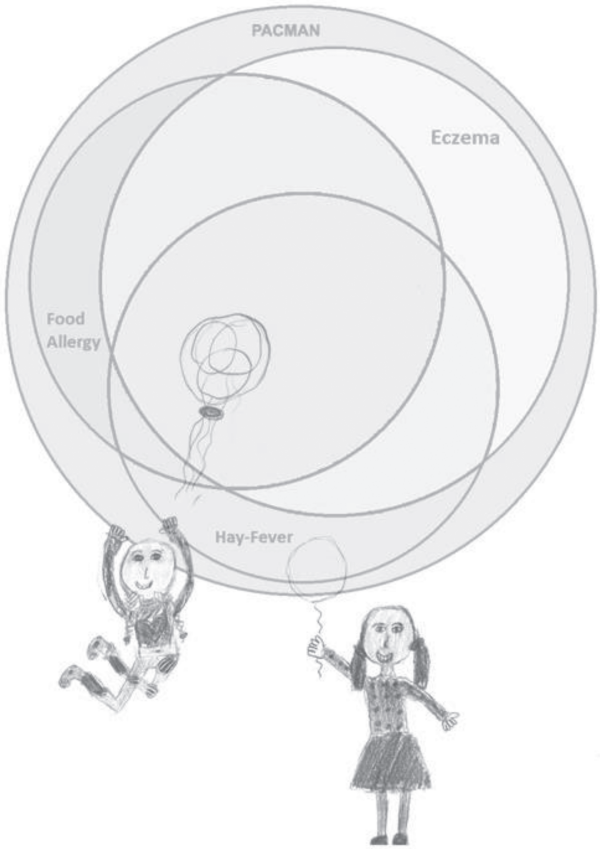
			Physician-diagnosed allergic dermatitis at age *5* years	
			No	**Yes**
Parental-reported allergy to food or medications at age *5* years	No	Count	307	125
		% of Total	67.3%	27.4%
	Yes	Count	13	11
		% of Total	2.9%	2.4%

Kappa (95% CI) = 0.05 (-0.02 – 0.12)

Table S5. The agreement between parental-reported allergy to food or medications and physician-diagnosed allergic dermatitis at age 8 years

			Physician-diagnosed allergic dermatitis at age *8* years	
			No	**Yes**
Parental-reported allergy to food or medications at age *8* years	No	Count	85	50
		% of Total	57.0%	33.6%
	Yes	Count	8	6
		% of Total	5.4%	4.0%

Kappa (95% CI) = 0.03 (-0.09 – 0.15)


PACMAN
Eczema
Food
Allergy
Hay-Fever

chapter 5 | General discussion

SCOPE OF THESIS

Allergic diseases, such as asthma, atopic dermatitis and rhinitis, are common in children [1]. These diseases share important epidemiological and pathological connections [2]. Atopic dermatitis often precedes the development of asthma and allergic rhinitis. Genetic susceptibility seems to drive the onset of allergic diseases [3-5].

Allergic diseases often co-exist, and this co-existence may influence the burden of disease and the prescription of medication. In this thesis, studies are described that assess the severity of allergic phenomena, drug prescription and genetic risk factors in Dutch children with allergic diseases. In this chapter we will, firstly, discuss our main findings and place them in a broader perspective. Secondly, we will discuss the methodological challenges we encountered. Finally, we will provide suggestions for clinical implications and future research.

MAIN FINDINGS

Severity of allergic symptoms in children with multiple allergic diseases

A course of allergic disease during childhood has been proposed as an atopic march, with a progression from eczema and food allergy in early childhood to asthma and allergic rhinitis at school age [3-5]. The co-existence of multiple allergic diseases might influence the severity of allergic symptoms and quality of life [6]. In **Chapter 2.1**, we studied the coexistence of allergic diseases (atopic dermatitis, food allergy and allergic rhinitis) in a large cohort of children with a recorded use of asthma medication (PACMAN cohort). Children who reported asthma and two other atopic condition such as rhinitis and eczema, had a higher risk of oral corticosteroids (OCS) use (odds ratio (OR) = 3.3, 95 % CI = 1.6 – 6.6) as well as, emergency department (ED) visits (OR = 2.3, 95 % CI = 1.2 – 4.6) in the past year compared to children who reported only one or no other atopic conditions. In addition, children with more atopic conditions, had a higher risk of poor asthma control during the study visit than children with less atopic conditions (OR = 1.9, 95 % CI = 1.3 – 2.8). Based on our results, we reported that the prevalence of children that reported symptoms of one or more atopic conditions was high, which is in agreement with what Gough *et al*. found [7]. They studied the prevalence of eczema, allergic rhinitis and asthma and allergic multi-morbidity in children up to the age of 20 years and reported that asthma occurred in both sexes more frequently in patients with coexisting allergies than in those without comorbidity. Additionally, we showed that patients with multiple atopic conditions had a higher risk of severe asthma.

Asthma and atopic dermatitis (AD) often co-exist. Asthma and AD are diseases that both can have a major impact on quality of life (QoL) [6]. Few studies have investigated factors related to the QoL of children that are suffering from both diseases [8,9]. Therefore, in **chapter 2.2** we investigated the association of patient characteristics, comorbidities and their impact on QoL in children within the PACMAN cohort who have both asthma and AD. We found a correlation between AD-related QoL scores and AD severity in this population (R_s=0.54, p<0.01).. Additionally, there were moderate correlations between AD severity and the amount of different TCS preparations used (R_s=0.27,

p<0.05) and the amount of total TCS prescriptions received (R_s=0.25, p<0.05). In conclusion, this study showed that the QoL is associated with AD severity in asthmatic children. It seems that children with multiple atopic disorders experience AD as more impairing.

Based on our studies in **chapter 2**, it can be concluded that children with both asthma and AD display more severe allergic symptoms compared to children suffering from only one allergic condition. This suggests that children with multiple allergy symptoms are a distinct subgroup that should be carefully monitored and might benefit from asthma/allergy specialist care at an earlier stage. These findings are consistent with those of Celakovská J *et al.* who evaluated the dependence between the severity of AD and the occurrence of asthma, and reported a significant relationship between the occurrence of asthma and the severity of AD [10].

Medication use in children with asthma and atopic dermatitis

The diagnosis and management of asthma in preschool-aged children differs from that of asthma in school-aged children and adolescents. The evaluation of asthma in this preschool-aged group is further complicated by the lack of objective lung function measurements and definitive biomarkers. Asthma management in preschool-aged children is also complex because of anatomic differences in young children. They have a smaller airway size and a lower inspiratory flow rate [1,11,12]. This may influence efficacy of inhaled treatment in young children [13]. In **chapter 3**, we performed three pharmacoepidemiological studies on drug use in children, taking age into account and focusing on different types of medication: asthma medication in general, oral corticosteroids and topical corticosteroids.

Medication use at different ages

We studied whether age is associated with different treatment patterns in asthma and atopic dermatitis. In **chapter 3.1**, the use of oral corticosteroids (OCS) was studied retrospectively in different age categories of children with asthma. Many studies investigated the use of OCS for exacerbations in children, but none of them investigated age-categorized incidence of OCS use[14-18].In **chapter 3.1**, we examined the incidence of OCS prescriptions in Dutch children with asthma from different age groups. Incidence rates for first OCS prescriptions were between 3.9 per 100 person-years (100PY) and 4.7 per 100PY for the first 5 years of life. This was relatively high compared to incidence rates for children between the ages of 6 and 11 (ranging between 2.2 (age 9) and 3.7 (age 11) per 100PY). Incidence rates for second and third OCS prescriptions were very high: 78.2(95%CI: 45.0–123.7) and 241.2(95%CI: 81.2–583.4) per 100PY for infants, respectively. In the Netherlands, the incidence of first OCS prescriptions in young children with asthma is relatively high compared with older children and extremely high for second and third OCS prescriptions compared to other ages. Furthermore, there is a high probability of receiving a next OCS prescription shortly after an OCS prescription. Therefore, children who have recently received an OCS prescription should be carefully monitored. These results are in line with previous studies. Chung *et al.* reviewed eight studies on risk factors for hospital admission in asthmatic children and reported higher readmission rate in younger children [19], suggesting that younger children

have a higher risk of a severe asthma exacerbation. Mahut *et al.* studied the influence of age on the occurrence of a severe exacerbation and stated that the risk of a severe exacerbation reduces each year of life by 15% from infancy to adolescence [20]. In **chapter 3.2**, we assessed the step-up and step-down patterns of asthma medication prescriptions. Prescriptions in older children were more likely to go up or down with >1 treatment step at a time. In **chapter 3.3** we studied the use of topical corticosteroids in children with atopic dermatitis and found that younger children had a higher risk of receiving a TCS prescription, than older children; 30% percent of the infants received a TCS prescription, compared to15-18% of the children ≥4 years (P<0.01). Similarly, younger children received more TCS prescriptions; the mean number of TCS prescriptions in infants was 2.2 prescriptions per year compared to 1.6-1.9 prescriptions per year in children ≥4 years (P≈0.1). Because of the high incidence of OCS and TCS prescriptions in early life, we believe children with allergic symptoms in early life should be more carefully monitored.

Medication use and treatment guidelines

In **chapter 3.2**, we studied whether factors such as age, prescriber category and previous treatment could explain different prescription patterns in allergic children. Children who were treated with higher treatment steps of asthma medication (steps 3-5) were more likely to step up or down with >1 treatment step at a time (OR = 1.14, p<0.01). These larger steps were more likely prescribed by specialists (in comparison with GPs) and in children that were older. This might reflect the higher unpredictability of asthma in the children with more severe disease. To our knowledge this is the first study to assess adherence to stepwise asthma treatment guidelines.

Childhood asthma and AD often co-exist. In **chapter 3.3** we assessed whether Dutch physicians prescribe TCSs for atopic dermatitis in children who also use asthma medication according to clinical guidelines. The current Dutch clinical guidelines for general practitioners (GPs) advise that general practitioners (GPs) should only prescribe treatment for mild disease (emollients and low potency TCSs) in children. Children with more severe disease should be referred to a specialist. In concordance with the clinical guidelines, we observed that first prescriptions of potent and very potent TCSs are more often prescribed by AD-related specialists compared to GPs (RR: 2.55, 95% CI: 1.79 - 3.63). To our knowledge this is the first study about adherence of GPs to TCS treatment guidelines.

Genetic risk factors for the susceptibility to allergic diseases in children

In addition to clinical factors and medication use in pediatric allergic diseases, this thesis also addressed the influence of genetic factors. It has been shown that allergies have a genetic basis[2,21,22]. A meta-analysis of genome-wide association studies (GWAS) on allergic diseases has identified 16 genome-wide significant loci in adults [23]. Based on these loci, we developed and tested an adult derived genetic risk score (GRS) for allergy susceptibility in a birth cohort (WHISTLER) in **chapter 4**. In a GRS various SNPs can be included to assess whether carrying more risk alleles provides a higher risk for the outcome of interest. In our study, we tested whether a GRS based on genetic risk variants identified in adults, also had predictive value for allergy in children.

The GRS was statistically significantly associated with an increased risk of parental-reported allergy to pollen, house-mites or pets at age 5 in this population (OR: 9.25, 95%CI: 1.02-83.85). The allergy GRS was statistically significantly associated with a physician diagnosis of allergies ever during follow-up. The hazard ratio (HR) was 1.79 (95% CI: 1.06 -3.02). Only one other study previously assessed the predictive value of a GRS for allergy. Bønnelykke *et al.* constructed a GRS based on 10 loci originating for a different GWAS meta-analysis in birth cohorts and population studies [24]. Five loci were also included in our GRS. Bønnelykke *et al.* tested the GRS in the population and showed that subjects with a higher genetic risk based on the allergy GRS had two times higher prevalence of allergic sensitization compared with subjects with a lower GRS [24]. However, they mostly studied adults. We concluded that the allergy GRS based on SNPs related to allergies in adults also predicted the risk on developing allergies in childhood.

STRENGTHS, LIMITATIONS AND METHODOLOGICAL CHALLENGES

Pharmacoepidemiological data sources

Two dataset were used in this thesis, a community-pharmacy based cohort of children with regular asthma medication use (PACMAN) and a Dutch birth cohort (WHISTLER). Most of the studies (**chapters 2 and 3**) were performed within the PACMAN cohort dataset. In this dataset children were included based on regular use of asthma medication. The strength of this cohort is that a large number of children has been included with relatively mild to severe asthma. It is expected that this cohort provides a good representation of the heterogeneous pediatric asthma population. However, because children were recruited through Dutch pharmacies there is a large amount of prescription data available, but a limited amount of clinical data [25]. Furthermore, we have to be aware that children were included based on regular asthma medication use and not based on a confirmed asthma diagnosis, and PACMAN might therefore include children with asthma-like symptoms without an official asthma diagnosis [26,27]. However, in **chapter 2.1** we showed that the incidence and prevalence-rates of medication use in our population were comparable to other pediatric asthma population from primary care with an asthma diagnosis [28]. This suggests that our data can be generalized to other studies. An important strength of using the PACMAN data, was the availability of a large number (n>229.662) and longitudinal asthma related prescriptions and a complete medication history of the children invited to participate in the PACMAN study. In the Netherlands, individuals are usually registered at one pharmacy. This made it possible, to extract complete pharmacy records of a large group of pediatric asthma medication users to generate a unique dataset for pharmacoepidemiological research. Van Boven *et al.* previously showed the potential for pharmacists to use pharmacy records to study medication in asthma patients [29].

In **chapter 4** the WHISTLER birth cohort dataset was used to assess the predictive capacity of an allergy GRS for allergic conditions in children. In contrast to the PACMAN cohort in which participant selection was based on asthma medication use, in WHISTLER healthy infants before the age of 2 months were enrolled in the study. During the total follow-up, information on physician

diagnoses, primary care consultations and medication prescriptions for respiratory symptoms was collected. Genomic DNA extracted from buccal cells of infants and parents is available.

In some of our studies such as **chapters 2 and 4**, the main variables of interest were parental (self)-reported based on retrospective events. The use of parental-reported data could lead to recall bias. In **chapter 4** we tested the agreement of parent-reported allergic diseases with physician reported measurements. There was only a moderate agreement. This could indicate recall bias, yet it also may show differences in how parents perceive allergic symptoms.

Use of large real life datasets such as the PACMAN and WHISTLER data, was an advantage of our study, since it is expected to reflect the general asthma or allergic population more accurately. However observational research is prone for selection bias and/or confounding. Therefore, our studies may be hampered by some degree of selection bias due to selective non-response. However, analysis of demographics such as age and gender and medication use did not reveal any differences between responders and non-responders in the PACMAN study [25]. Moreover, we used the complete pharmacy data (including non-responders) in the medication studies.

Longitudinal analyses

Timing of the assessment of exposure or outcomes is often different between cross-sectional studies, which make their results difficult to compare. Longitudinal data could provide insight in temporality of associations. A key strength of a longitudinal study is the ability to measure change in outcomes and/or exposure at the individual level [30]. Longitudinal studies provide the opportunity to observe individual patterns of change. We used longitudinal analyses in **chapter 3** using pharmacy data to calculate incidence or risk to receive our outcome medication where we indicated the importance of children's age in the right treatment for allergic diseases.

Generalizability of the results

Although, we used large datasets to have enough power to generalize them, we did not have enough power when comparing incidence of second and third OCS prescription between boys and girls in **chapter 3.1**. Because our main outcome of interest was the incidence of first OCS in various age group of children with asthma, we used data included children with wide variety of asthma. Therefore, children who received OCS were limited.

Asthma medication use in young children

An accurate diagnosis of asthma in young children (< 5 years) is often difficult [31], nevertheless, in the PACMAN cohort it was observed that young children also use asthma medication and even receive OCS prescriptions quite regularly. This could indicate that there is a need for a standard asthma diagnosis measurement for children under 5 years old. However, in the PACMAN study children with asthma were included based on their asthma medication use when they were 4 years or older. We used the medication data of these children to study their drug use at a younger age, and therefore we know that the children we studied were still using asthma medication when they

were older. This means that the young children within our study are a selection of the population, and that asthma medication use in children that are very young might be different in those children that do not get any asthma medication after their fourth birthday.

Subjective measures versus objective clinical measurements

In this thesis we studied various allergic outcomes, such as asthma, allergic rhinitis and eczema. The outcomes were often based on questionnaires. Self-reported allergy to allergens, serum IgE level and clinical diagnosis are some strategies to report allergy outcomes. Some studies have aimed to report their outcomes with more quantitative measures of allergic disease like specific IgE, which is a well-defined objective measurement for allergic sensitization, however it requires a venipuncture and might not be predictive of allergic symptoms. In parallel, some others use clinical diagnoses such as allergic conjunctivitis, allergic rhinitis, hay fever, or eczema/dermatitis as their outcomes, which are easy to translate to clinical practice [32].

IMPLICATIONS FOR CLINICAL PRACTICE

Based on the results presented in this thesis, the following recommendations for clinical practice can be made:

Asthma guidelines for young children should be reviewed and standardized

There are several guidelines that address the management of asthma in young children (GINA, EPR-3, PRACTALL and ERS). The reason for having different global guidelines is based on lack of agreement on the diagnosis of asthma in young children [31]. This complicates the treatment of young children. The studies in this thesis suggest that physicians do not always adhere to the guidelines. Adherence to treatment guidelines should carefully be reviewed, guidelines standardized and in case they do not reflect the needs of clinical practice, adapted.

More careful monitoring is needed for allergic diseases in early childhood

In addition, we found that the incidence of OCS is high in early childhood (**chapter 3**), suggesting that more attention is needed to optimize for treatment of asthma in infancy and early childhood to decrease the amount of exacerbations and short term OCS in early childhood.

More research into genetic predisposition of allergy

There have been recommendations for allergy prevention in cases of high-risk infants [33-35]; nevertheless, there have been no definite criteria to identify those at risk. More insights in the genetic basis of severe allergic disorders might eventually lead to interventions to prevent the development of these diseases by limiting exposure to specific allergens or modulating the immune system at an early age.

FUTURE DIRECTIONS

In addition, pediatric asthma management would benefit from close collaboration of healthcare providers within the primary care setting (primary care physicians and the pharmacist). Besides the general practitioner who should monitor asthma control regularly, there is an important role for the community pharmacist. First of all, Hammerlein *et al.* showed that a pharmacy intervention study to improve inhalation technique in patients with asthma was very successful. They reported all patients did benefit from the pharmacists' intervention regardless of their former training experiences [36]. Moreover, Gums *et al.* showed benefit of the pharmacist in the physician-pharmacist collaborative management of asthma in primary care [37]. Furthermore, in **chapter 3.2**, we found that changes of two steps or more in asthma treatment, which is not in line with guidelines regardless to clinical features, were frequently observed. Why physicians do not follow guidelines is not yet explained and requires further investigation. Pharmacists have a good overview of the medication use of allergic children. They might play an important role in providing advice to the primary care provider when changes in medication are considered that do not follow clinical guidelines. Then, they can confirm and record if the children's clinical status led to this treatment or the treatment should be followed in another way. In the case of the first assumption (clinical status led to not following the guidelines), it should be reported to mention in the guidelines for revision. The diversion from guidelines can be found by instruments which have been programed for this reason**.**

CONCLUSION

The studies presented in this thesis address atopic diseases in children from different angles; medication use, clinical characteristics and genetics. We have confirmed that comorbidity of allergies and asthma are common and that atopic comorbidities negatively influence severity of disease and quality of life. Moreover, we have shown that medication use in early childhood needs special attention. Community pharmacists have a good overview of the changes in medication use of allergic children and might play a valuable role in monitoring allergic medication use in young children with consultation with primary care providers.

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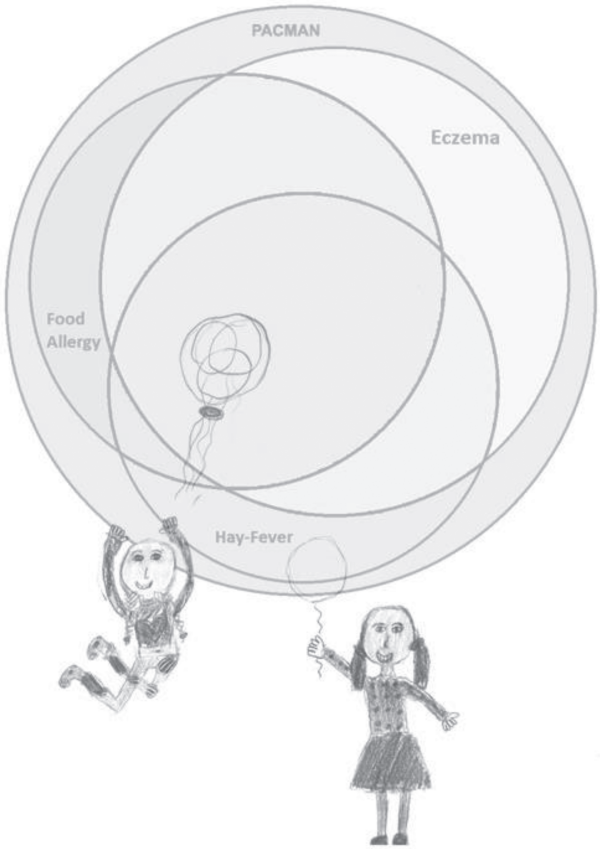
PACMAN
Eczema
Food
Allergy
Hay-Fever

Appendix

ENGLISH SUMMARY

The research presented in this thesis aims to gain better insight into allergic diseases in children using epidemiological approaches and different angles (severity, medication use and risk factors). The aim of this thesis was to answer the following questions: Do children with multiple atopic conditions suffer from more severe symptoms? Which factors influence prescribing medication in children with allergic diseases? And can genetic variations predict the risk of developing allergic diseases in childhood?.

Chapter 1 gives a general introduction on allergy and atopy.

In **chapter 2.1** we investigated the coexistence of allergic diseases (atopic dermatitis, food allergy and allergic rhinitis) in a large cohort of children with a recorded use of asthma medication. 703 children (ages 4 to 12 years) from the PACMAN (Pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects) cohort study were divided into nine subgroups according to parental-reported allergies. The characteristics (age, gender, family history of asthma, breast feeding and FeNO) and asthma severity measures (use of allergy medications, oral corticosteroids (OCS) usage, emergency department (ED) visits and asthma control questionnaire (ACQ)) were compared between the groups of children with and without specific combinations of atopic conditions. We showed that having more than one atopic condition was associated with an increased risk of OCS use and ED visits in the past year and inadequate short term asthma control in children with asthma. Finally, we concluded that children who had asthma and co-morbid atopic conditions were at risk for more asthma complaints, more asthma exacerbations and poor asthma control. In **chapter 2.2** we studied children who had both asthma and atopic dermatitis (AD) within the PACMAN cohort. The Children's Dermatology Life Quality Index (CDLQI) was used to assess QoL. The Self-Assessed Eczema Area and Severity Index (SA-EASI) was used to measure AD severity. The total prescribed amount of AD medications, the amount of different topical AD prescriptions and the highest potency topical corticosteroid (TCS) prescribed were assessed. Characteristics of AD lesions (redness, thickness, dryness, number of scratching and itchiness), a higher SA-EASI score and a higher amount of different topical AD prescriptions were associated with a lower QoL. Children with multiple atopic disorders experienced AD as more impairing. The amount of different therapies and the total amount of prescriptions might serve as a proxy for AD severity and AD related QoL in prescription database research.

In **chapter 3.1**, the incidence of OCS prescriptions in asthmatic children of various ages and their risk of receiving subsequent OCS prescriptions were assessed. Longitudinal Dutch community pharmacy data of 2272 children who were regular users of asthma medication and had medication data available starting in their first year of life was analyzed retrospectively. The incidence rates for first OCS prescriptions were relatively high for the first 5 years of life (ranging between 3.9 and 4.7 per 100PY) compared to incidence rates for children between the ages of 6 and 11 (ranging between 2.2 and 3.7 per 100PY). Incidence rates for second and third OCS prescriptions were very high for infants. Moreover, there was a high probability of receiving a next OCS prescription shortly after an OCS prescription. In **chapter 3.2**, we studied whether factors such as age, prescriber

category and previous treatment could explain different prescription patterns in children with asthma. All prescriptions dispensed for the treatment of asthma of 3,573 children who were regular users of asthma medication were analyzed. Step of treatment was determined for each combination of asthma medications with the same dispensing date according to the Dutch clinical asthma guidelines. Subsequently, we assessed whether the intended treatment step of a new dispensing was different from the former dispensing. Almost half of the changes (45.5%) consisted of > 1 treatment step. Children who were in higher treatment steps (steps 3-5), older children and children who were treated by specialists were more likely to step up or down with >1 treatment step at a time.

In **chapter 3.3**, we studied whether Dutch physicians prescribe TCSs for atopic dermatitis in children who also use asthma medication according to clinical guidelines. We observed that 30% percent of the infants received a TCS prescription, compared to 15-18% of the children ≥4 years. This was a statistically significant higher prescription rate of TCS for infants. Furthermore, first prescriptions of potent and very potent TCSs were more often prescribed by AD-related specialists compared to GPs. In **chapter 4**, we developed a genetic risk score (GRS) for allergy based on a meta-analysis of genome-wide association studies (GWAS) in adults and tested its predictive capacity for allergy in children. The GRS was constructed based on 10 SNPs previously associated with allergies in adults. The GRS was tested in children who participated in a population-based newborn cohort (WHISTLER) and were followed from birth to school age. The association between the GRS with both the parental-reported allergies at age 5 (based on a reported allergy to ≥1 of the following allergens: pollen, house dust mites or pets) and a physician-diagnosed allergy during follow-up (allergic conjunctivitis, allergic rhinitis and eczema/dermatitis) were studied. The GRS was significantly associated with both parental-reported allergy, and physician-diagnosed allergy during follow-up. We concluded that the risk of developing allergies in childhood can be predicted by allergy GRS based on SNPs related to allergies in adults.

In the general discussion in **Chapter 5** we argue that more careful monitoring is needed for allergic diseases in early childhood. In addition, pediatric asthma management would benefit from close collaboration of healthcare providers within the primary care setting (primary care physicians and pharmacists).

SAMENVATTING

Het onderzoek dat in dit proefschrift wordt gepresenteerd, is bedoeld om een beter inzicht te krijgen in allergische aandoeningen bij kinderen. Door middel van een epidemiologische benadering zijn de risicofactoren en de ernst van allergie en astma bij kinderen onderzocht. Daarnaast is het medicatiegebruik bij deze aandoeningen bij kinderen onderzocht. De volgende onderzoeksvragen komen aan bod in dit proefschrift: hebben kinderen met meerdere atopische aandoeningen vaker meer ernstige symptomen in vergelijking met kinderen die aan één atopische aandoening lijden? Welke factoren beïnvloeden de voorgeschreven medicatie bij kinderen met allergische aandoeningen? Kunnen genetische variaties het risico op het ontwikkelen van allergische ziekten in de kindertijd voorspellen?

Hoofdstuk 1 is een algemene inleiding op het gebied allergie en atopie bij kinderen.

In **hoofdstuk 2.1** onderzochten we hoe vaak allergische aandoeningen (atopische dermatitis, voedselallergie en allergische rhinitis) samen voorkomen in een grote groep kinderen die astmamedicatie gebruiken. We bestudeerden 703 kinderen (4 tot 12 jaar oud) uit de PACMAN cohortstudie. In deze studie werden via Nederlandse apotheken gegevens verzameld van kinderen die regelmatig astmamedicijnen gebruiken. We verdeelden deze kinderen in negen subgroepen op basis van (ouder)gerapporteerde allergieën. De kenmerken van de kinderen in de subgroepen (zoals leeftijd, geslacht, familiegeschiedenis van astma, borstvoeding als baby, en de mate van stikstofoxide in uitgeademde lucht) en de mate van ernst van de astmaklachten (o.a. gebruik van medicijnen, oraal corticosteroïden (OCS) gebruik, bezoeken aan de spoedeisende hulp (SEH) voor astma en de score op de astmacontrole vragenlijst) werden vergeleken. We hebben aangetoond dat het hebben van meer dan één atopische conditie in deze groep geassocieerd was met een verhoogd risico op OCS gebruik en SEH bezoeken en een slechte astmacontrole in vergelijking met kinderen die maar één atopische conditie rapporteerden. In **hoofdstuk 2.2** bestudeerden we de kwaliteit van leven en de ernst van atopische dermatitis (AD) van kinderen in het PACMAN cohort met zowel astmaklachten als AD-klachten die ook hadden deelgenomen aan het Luchtwegportaal van het Wilhelmina Kinderziekenhuis. De ouders en kinderen vulden digitaal een vragenlijst in (Children's Dermatology Life Quality Index; CDLQI)) om de kwaliteit van leven te meten die geassocieerd is met het hebben van atopische dermatitis. Ook vulden de ouders en kinderen een vragenlijst in (Self-Administered Eczema Area and Severity Index; SA-EASI) om de ernst van AD te meten. We bestudeerden hoe de kwaliteit van leven en de ernst van de atopisch dermatitis samenhingen met de totale hoeveelheid voorgeschreven AD-medicijnen, de hoeveelheid verschillende voorgeschreven AD-medicijnen en de voorgeschreven dosis van dermale corticosteroïden. Een lagere kwaliteit van leven was geassocieerd met de fysieke kenmerken van de AD klachten (zoals meer roodheid, dikte van de huid, droogheid, aantal krassen en jeuk van de plekken met AD), ernstigere AD klachten, en het gebruik van meer verschillende AD medicijnen Verder zagen we dat het aantal verschillende AD medicijnen en het totale aantal voorschriften correleert met ernst en kwaliteit van leven van AD. Medicijngebruik kan daarom wellicht als een proxy dienen voor de ernst of kwaliteit van leven in farmacoepidemiologisch database onderzoek.

In **hoofdstuk 3.1** bestudeerden we het gebruik van orale corticosteroïden (OCS) in kinderen astmamedicijnen gebruiken. We onderzochten hoe vaak OCS wordt voorgeschreven in deze groep. Tevens onderzochten we of jongere kinderen vaker of minder vaak een recept voor OCS kregen dan oudere kinderen. Voor deze analyses gebruikten we medicatiegegevens geëxtraheerd uit apotheekinformatiesystemen van 2272 kinderen. We analyseerden alleen de gegevens van kinderen van wie er retrospectief medicatiegegevens beschikbaar waren vanaf hun eerste levensjaar. De incidentiecijfers voor een eerste OCS-voorschrift waren relatief hoog in de eerste 5 levensjaren (tussen 3,9 - 4,7 per 100 persoons-jaren (PY)), ter vergelijking: de incidentiecijfers van kinderen tussen de 6 en 11 jaar varieerden tussen de 2,2-3,7 per 100PY. De incidentiecijfers voor een tweede of derde OCS-recept waren zeer hoog voor zuigelingen. Bovendien was er een hoge kans dat kinderen die als zuigeling een OCS recept hadden ontvangen, binnen korte tijd een nieuw OCS recept zouden ontvangen. In **hoofdstuk 3.2** hebben we bestudeerd of factoren zoals leeftijd van het kind, voorschrijver en eerdere astmabehandeling, van invloed zijn op de patronen in voorgeschreven astmamedicatie. Alle voorschriften die werden uitgeschreven voor de behandeling van astma van 3.573 kinderen (regelmatige gebruikers van astmamedicatie), werden geanalyseerd. Astmabehandeling verloopt in stappen, waarbij medicatie per stap kan worden toegevoegd of afgebouwd volgens astma behandelrichtlijnen. Op basis van de voorschriften uit het apotheekinformatiesysteem met dezelfde afgiftedatum werd de stap van de astmamedicatie bepaald. Vervolgens zijn we nagegaan of de beoogde behandelingsstap van een nieuw recept verschilde van behandelstap op basis van het voorgaande medicatierecept en indien er een wijziging plaatsvond of dit 1 of meerdere behandelstappen betrof. Bijna de helft van de veranderingen van behandelstap (45,5%) bestond uit de wijziging van >1 behandelingsstap. Kinderen die volgens een hogere behandelingsstappen werden behandeld (stap 3-5), oudere kinderen en kinderen die door specialisten werden behandeld (ipv de huisarts), hadden meer kans op een wijziging van meer dan 1 behandelingsstap.

Appendix

In **hoofdstuk 3.3**, zijn we nagegaan of Nederlandse artsen TCS's voor atopische dermatitis voorschrijven volgens de klinische richtlijnen bij kinderen die ook astmamedicatie gebruiken. Zuigelingen kregen statisch gezien vaker een TCS dan kinderen≥4 jaar. In onze onderzoekspopulatie, kregen 30% van de zuigelingen een TCS-voorschrift kreeg, in vergelijking met 15-18% van de kinderen ≥4 jaar. Daarnaast zagen we dat AD-gerelateerde specialisten vaker sterke en zeer sterke TCS's voorschreven bij kinderen die ook astmamedicatie gebruiken dan huisartsen.

In **hoofdstuk 4**, ontwikkelden we een genetische risicoscore (GRS) voor allergie op basis van genetische risico-varianten geassocieerd met allergie uit een meta-analyse van genoomwijde associatiestudies (GWAS) bij volwassenen. Vervolgens testten we de voorspellende waarde van deze GRS voor allergie bij kinderen. De GRS werd gebouwd op basis van 10 genetische varianten (single nucleotide polymorphismen). De GRS werd getest bij kinderen die deelnamen aan de WHISTLER studie, een geboortecohort van kinderen dat gevolgd is vanaf de geboorte tot aan de schoolleeftijd. De GRS was statistisch significant geassocieerd met zowel ouder-gerapporteerde allergie (op 5-jarige leeftijd) als met door de arts gediagnosticeerde allergie tijdens de follow-up (allergische conjunctivitis, allergische rhinitis of eczeem/dermatitis). We

concludeerden dat SNPs die verband houden met allergieën bij volwassenen ook geassocieerd zijn met allergieën op kinderleeftijd.

In de algemene discussie in **hoofdstuk 5** stellen we dat meer en zorgvuldige monitoring nodig is voor allergische aandoeningen in de vroege kindertijd. Daarnaast zou een nauwe samenwerking tussen zorgverleners in de eerste lijn (bijvoorbeeld huisarts en apothekers) tot een beter astmamanagement bij kinderen kunnen leiden.

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Appendix

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PUBLICATIONS RELATED TO THIS THESIS

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Ali Arabkhazaeli was born on 22nd of June 1969 in Sari, Iran. After completing secondary school in Sari in 1987, he passed national university entrance exam and started studying medicine at "Zanjan university of medical sciences and health services" in the same year. He obtained his M.D. degree from Zanjan University in 1994 and started to work as a manager and physician of the Kiasar rural health care unit. After two yours work in the rural area, he received permission to have his private clinic in his homeland city Sari. He worked in Mehr general hospital until he moved to Tehran in 2000. After passing some courses, he started to work as a match physician for "sport medicine federation of I.R of Iran" and from 2001 until 2006 he was team physician of the national wrestling team. In that time he worked as a physician of the emergency and screening Unit in Arad general hospital. From 2006, he joined "Blood Transfusion Organization of I.R of Iran" as physician of occupational safety and health unit beside working in hospital until 2010 when he moved to the Netherlands. Following a short research internship in 2010 at the biopharmacy division about virus like particles as a vehicle for vaccine, he started his PhD project, at the division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University and at the department of pediatric respiratory medicine of the WKZ Utrecht, entitled "Pediatric asthma and allergy, An epidemiological approach" under the supervision of prof. Jan Raaijmakers, prof. C. Kors van der Ent and Dr. Anke-Hilse Maitland-van der Zee from 2012. In the last year Dr. Susanne Vijverberg was added to the team and Dr. Anke-Hilse Maitland-van der Zee entitled professor in Amsterdam medical center.