Asthma in children: origins and outcomes

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Asthma in children: origins and outcomes

Astma bij kinderen: oorzaken en effecten op het dagelijks leven
(met een samenvatting in het Nederlands)

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Chapter 1

General introduction

Childhood asthma

Childhood asthma is an inflammatory disease of the airways characterized by episodes of airflow obstruction, often in response to triggers like infections, allergens, exercise and emotions.[1,2] The prevalence of childhood asthma and asthma-like symptoms has dramatically increased during the end of the last century.[3]

Asthma was first described as a medical term in the Corpus Hippocrates, a collection of works associated with Hippocrates and his teachings (406 to 370 BC). It is unknown whether asthma was seen as a separate disease at that time, or only as a symptom.[4] According to current international guidelines, asthma is described as a disease characterized by cough, wheeze and dyspnoea, reversible airway obstruction and bronchial hyperresponsiveness. The clinical symptoms of asthma are well known: recurrent attacks of wheezing, shortness of breath or dyspnoea and coughing at night, in response to a number of triggers. However, the clinical presentation of asthma in children may be highly variable in both its clinical presentation and time course. Therefore a clear and generally accepted definition of asthma does not exist,[5] and many different 'asthma-like' syndromes are recognized. These asthma-like syndromes are sometimes described with terms like 'early wheeze', 'transient wheeze', 'virus induced wheeze', 'multiple trigger wheeze', 'atopic wheeze', 'persistent wheeze' and many others. Wheeze is the main characteristic of all these entities, but additional symptoms and lung function vary between and within patients. In epidemiologic studies 'asthma' is often defined as a parental report of doctors' diagnosed asthma, but also parental reports of asthma symptoms, especially wheezing, or the use of specific asthma medication are sometimes used as a proxy for asthma.[6] It is clear that comparing studies performed in asthmatic children is challenging, both due to the underlying different entities of the disease, and the different definitions used in the literature.

Irrespective of the difficulty of asthma diagnosis in childhood, the impact on children is high. Persistent symptoms, decreased quality of life and absence from school and sports may hamper the development of young children. Knowledge on the determinant of this burden of asthma may be helpful to target relevant aspects of disease management in these children. Furthermore, the association between viral infections and exacerbations of asthma has been well described. The role of viral infections on the development of asthma and asthma outcomes is less clear.

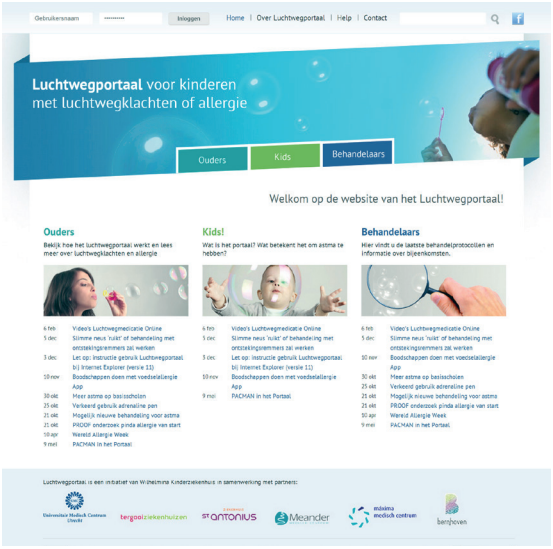
The first part of this thesis focuses on determinants of the burden of asthma in children. In different studies we study factors which influence asthma control and health related quality of life. The second part of this thesis describes the role of Respiratory Syncytial Virus (RSV)

on the development of asthma-symptoms and lung function in children.

Determinants of asthma control and health-related quality of life

The purpose of asthma treatment in children is to control symptoms, to prevent exacerbations and to enable the child to lead a normal active life, and to have normal lung function.[1] Although a large quantity of drugs is available, many studies still show only partial effectiveness of asthma care in daily life.[7,8] Despite advances in the management of asthma in children, it continues to be a condition that has significant impact on the life of both children and their families. To improve patient care in clinical practice there is an urgent need for knowledge on the determinants of the disease burden, as expressed in level of asthma control and health-related quality of life. We have set up a data-collection system that can help to fill this gap in clinical practice. A web-based application was developed, named 'Portal for children with respiratory and allergic symptoms' (Figure 1).

Figure 1. Portal for children with respiratory and allergic symptoms (Luchtwegportaal)

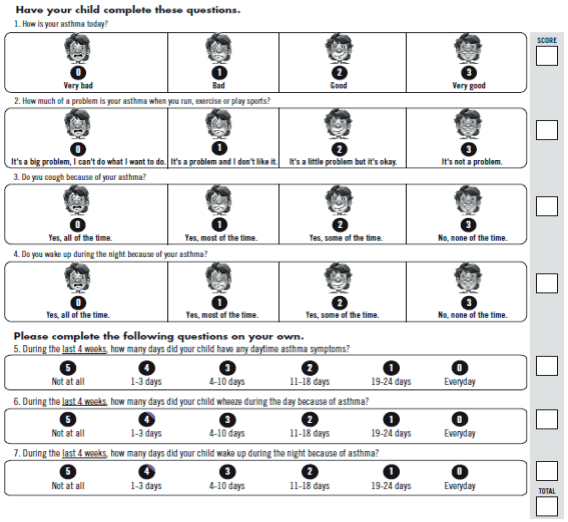


Asthma control

As disease prevention and cure still cannot be realized in asthma, the main goal in asthma treatment is to achieve control of the manifestations of disease and maintain control for prolonged periods.[1] Asthma control is considered the major goal of asthma management. Current guidelines recommend to measure asthma control at each doctor's visit. Asthma control is defined as the extent to which the various manifestations of asthma are reduced or removed by treatment[9] and can be measured in different ways. One validated tool, is the

Asthma Control Test (ACT), which in children exists in two forms: the ACT for children 12 years and older,[10] and the Childhood Asthma Control Test (C-ACT) for children 4 to 11 years old (figure 2).[11] Both questionnaires measure the presence of symptoms over the last 4 weeks, and a score below 20 indicates inadequately controlled asthma.

Figure 2. The Childhood Asthma Control Test



Health Related Quality of Life

Although objective measures, such as lung function and the Asthma Control Test score, provide useful information about the status of the disease, they may not fully assess how the patient functions in daily life. For instance, although lung function may improve as a result of treatment, patients may perceive the treatment itself as unpleasant and still not feel better in daily life.[12,13] Furthermore, Health Related Quality of Life (HRQOL)-questionnaires have shown low to moderate relationships with traditional effect parameters such as lung function.[9,14] There are several specific questionnaires to estimate HRQOL of children with asthma. One of the most frequently used is the Paediatric Asthma Quality of Life Questionnaire (PAQOL), which was developed to measure the functional problems (physical, emotional and social) that are most troublesome to children with asthma. The overall outcome is the mean score of all 23 questions, the individual domain scores are the means of the items within the three domains, with score 1 indicating that a patient was 'extremely bothered', to score 7 indicating 'not being bothered at all' in the previous week.

Several studies have shown that poor asthma control is an important determinant of lower HRQOL,[15,16] but little is known about further factors that influence HRQOL in children. Asthma often coexists with atopic conditions such as food allergy. Therefore we were

interested in the effects of food allergy on the outcomes in children with asthma, but we also studied the effects of having asthma on the outcomes of food challenge tests.

RSV and asthma

Respiratory Syncytial Virus (RSV) bronchiolitis is the most frequent cause for hospitalization in infancy.[31] It is unknown why RSV causes mild disease in some children, and severe disease, requiring hospitalization, in others. Several risk factors have been identified, however the largest number of RSV infections occur in otherwise healthy infants without known risk factors. Over the last 20 years, epidemiologic studies have suggested an association between RSV bronchiolitis and the subsequent development of wheeze and asthma up to school age.[19–23] Although the used outcome variables differ between studies, the relative risk of wheeze or asthma after RSV bronchiolitis is estimated to be between 2 and 6.6 times that without RSV bronchiolitis.[23,24] Lung function in children previously hospitalized for RSV was impaired in several studies,[22,25–27] while comparable to healthy controls in others.[21,28] A recent meta-analysis concluded that the quality of follow-up studies after RSV bronchiolitis was generally poor.[29] For that reason Stein and Martinez argued that the association between RSV hospitalization during infancy and asthma at school has still not been established.[30] Because decreased lung function and symptoms of wheeze might both precede RSV infections and be a consequence of RSV infections, the associations between these entities deserve long-term follow-up studies. In both premature infants, and infants of atopic mothers, lower levels of lung function shortly after birth have been shown to be associated with RSV lower respiratory tract illnesses. This association has never been studied in a healthy population.

No treatment during RSV bronchiolitis has been convincingly shown to decrease the risk of long-term airway morbidity. Steroids have been thought to modulate the immune system during the acute phase of infant wheeze, and thereby prevent asthma development. Assuming viral bronchiolitis contributes to asthma through an immunologic cascade, modulation of the immune system may prevent asthma. Early initiated high dose inhaled beclomethasone does not have a major effect on recurrent wheeze during a 1-year follow-up period.[32] Long term effects of high dose inhaled beclomethasone on asthma, lung function but also on linear growth have not been described.

Aims and outline of this thesis

The aim of this thesis was to investigate determinants of asthma related outcome measures, especially asthma control and HRQOL. The second aim was to study the effect of RSV infections on the development of asthma-related outcomes, especially symptom scores and lung function.

Outline of this thesis

The first part of this thesis focuses on determinants of asthma control, and health-related quality of life in children with asthma. **Chapter two** describes the rationale and design of the 'electronic portal for children with respiratory and allergic symptoms' (Luchtwegportaal). In **chapter three** the relation between respiratory tract infections and asthma control is studied and **chapter four** describes determinants of health related quality of life in children with asthma. Because foods and drinks in some children appear to trigger asthmatic symptoms, influencing asthma-related quality of life, in **chapter five** we study whether the presence of asthmatic symptoms in children with food related problems predicts a positive food challenge outcome.

The second part of this thesis describes the relationship between RSV infection and asthma development and lung function. In **chapter six** the association between premorbid neonatal lung function and severe RSV bronchiolitis, requiring hospitalization is described. Hereafter, the effect of high dose beclomethasone for RSV bronchiolitis on asthma development and lung function is described in **chapter seven**.

Chapter eight studies the risk of respiratory wheeze, asthma and lung function impairment at school age in infants previously hospitalized for RSV bronchiolitis as compared to a group of healthy children. The main findings are discussed in the last chapter (**chapter nine**) and is followed by a summary in Dutch in **chapter ten**.

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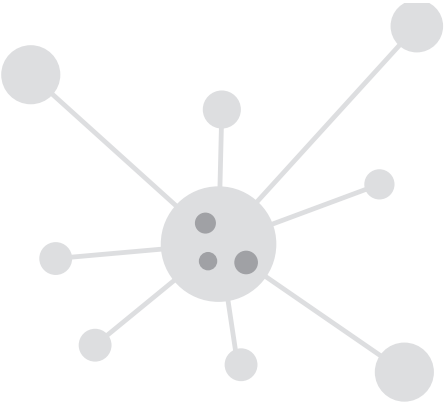

Part I

The burden of childhood asthma

Chapter 2

The Expert Network and Electronic Portal for children with respiratory and allergic symptoms: rationale and design

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Abstract

Data on baseline characteristics of children with asthma to predict individual treatment responses are lacking. We aimed to set up a data-collection system which can easily fill this gap in clinical practice.

A web-based application was developed, named 'Portal for children with respiratory and allergic symptoms', hereafter called Electronic Portal (EP). It contains health- and disease-related questionnaires on respiratory- and allergic diseases. All patients, 1-18 years of age, with respiratory- and/or allergic complaints are invited to enter the EP before their first visit. By using the EP large amounts of data, gathered during routine patient care can be used for research purposes. This may help to further investigate the different treatment related asthma phenotypes and will be helpful to monitor risk factors for other atopic diseases and respiratory infections.

Introduction

Asthma is the most prevalent chronic illness in childhood.[1] The prevalence of asthma is ranging from 4 to 12 percent of school age children.[2] A recent study in The Netherlands showed that in a population of 1614 school age children 5% had physician-diagnosed asthma, while an additional 8% had asthma symptoms without knowing to have asthma.[3] Despite advances in the management of asthma in children, it continues to be a condition that has significant impact on children and their families. In a Dutch study both children with diagnosed and undiagnosed asthma had impaired quality of life scores compared to healthy peers and had higher rates of absence from school.[4] The AIRE (Asthma Insight and Reality) study showed only partial effectiveness of asthma care in daily life.[5] In addition, Fuhlbrigge et al. showed that goals of therapy in asthma, based on the National Asthma Education and Prevention Program guidelines, have not been achieved for the majority of children, although more than 70% had mild intermittent disease.[6] The impact of asthma on daily activities is substantial; avoiding exertion (47%) and staying inside (37%) are common approaches to avoid asthma symptoms. These data indicate poor control of asthma in school-age children in affluent countries.

To improve patient care in clinical practise there is an urgent need for predictors of asthma treatment responses. Scarce data are available on predictors of treatment response. Several studies addressed the predictive capacity of family history, clinical symptoms, or lung function parameters for the effect of different treatment regimens. For example, a parental history of asthma or increased levels of exhaled Nitric Oxide (eNO) might predict a beneficial effect of ICS,[7-10] while in adults LTRAs might be especially beneficial in asthma patients who smoke.[11] In cases where group-wise differences between different therapies are lacking,[12,13] predictive baseline characteristics might be helpful to predict which therapy has the best risk-benefit ratio in the individual child.

The evaluation of the predictive capacity of comprehensive clinical and laboratory parameters for treatment responses requires analysis of a large and diverse patient population from different clinical settings and prospective follow-up. Recently, we started an extensive nationwide study in The Netherlands to compare different treatment strategies for children with respiratory and allergic symptoms and to evaluate predictors of treatment responses. In a strongly internet-supported network of academic and general pediatricians in The Netherlands (the 'Expert Network´) large numbers of patients are recruited and evaluated using an Electronic Portal. Here we aim to describe the design of both the Expert Network and the Electronic Portal.

Methods

Study design

The Electronic Portal (EP) is used by the members of the Expert Network (EN) as a clinical tool to prospectively collect data in children with respiratory and allergic symptoms. The EP is used firstly to thoroughly screen patients on the presence of certain symptoms and possible risk factors, before their first outpatient department-visit. Secondly, patients can be followed-up on a regular basis without intervention of their caregivers. At start uniform information about atopic diseases, respiratory infections, exposure to potential toxins, and demographic information is collected by the patients. Afterwards, data on treatment, disease control and treatment effects are monitored. In this way pre-treatment patient characteristics can be related to treatment and disease outcomes. Recruitment and follow up of children started in June 2011.

The Expert Network

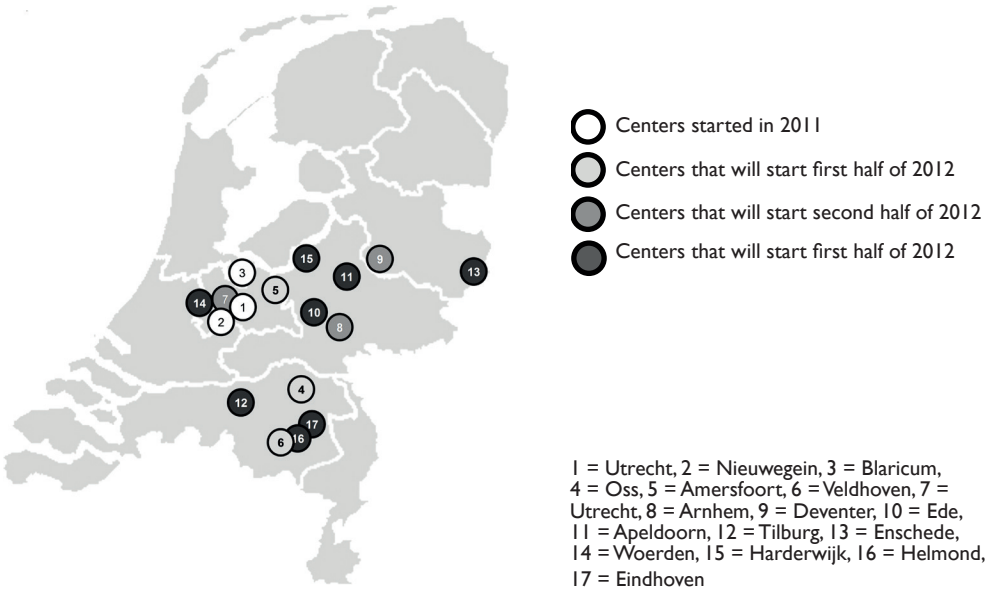
In a nationwide collaborative network of Dutch caregivers at least 3000 children presenting with asthma symptoms will be included from June 2011. The EN consists of caregivers in the primary-, second- and third line health care. The members of the EN are general practitioners, pediatricians and specialized pediatricians in pulmonology, allergology, dermatology, infectiology and otolaryngology. We aim to include at least 15 large pediatric clinics (for current status see figure 1). Members of the EN are personally instructed how to use the EP. The EN has three-monthly meetings in which data from the EP are analyzed and compared between centres. Information about meetings, diagnostic and treatment protocols, and scientific updates on atopic diseases can be found on a supporting website. Children between the ages of 0-18 years, referred to a member of the EN because of respiratory- or atopic complaints are eligible to participate and are asked to participate in the EP. Also known patients are eligible to participate in the EP. Each centre has its own account. With this, access is given to the data of their own patients, and records can be made and printed with results per patients. Informed consent for use of the questionnaires and clinical information is given by an electronic check mark. The medical ethics committee of the University Medical Centre Utrecht has approved the protocol.

The Electronic Portal

The Electronic Portal is a web-based application developed by the University Medical Centre Utrecht, in collaboration with Vital Health software. The EP can be approached via the url https://www.luchtwegportaal.com. The supporting website presents information on three levels: for the patient, the parents, and the members of the Expert Network, and contains disease information, information on the EP, and protocols for physicians. From this website

the EP can be entered with a unique personal code. The information in the EP consists of personal patient information, validated questionnaires, diagnostic test results, and an automatic follow up function. Individual data in the EP are accessible for both the patient and his caregiver and structured reports can be generated on screen and on paper. The content of the EP is summarized in Table 1. Three age-dependent questionnaire sets are available in the EP, and are automatically selected based on the age of the child; a set for children 0-1 years, one for children between 1-11 years and a set for children above 12, in which most of the questions are directed to the child itself. The structure of the EP, and the following order in which the EP is used is shown in figure 2.

Figure 1. The Dutch Expert Network



Baseline examination

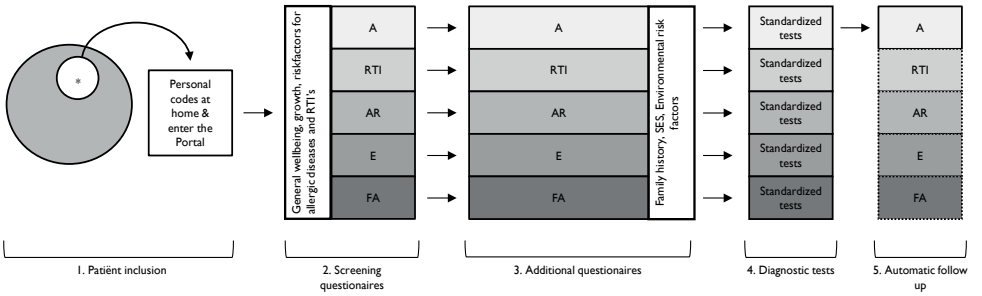
Screening questionnaires

After entering the EP, parents are asked to fill in screening questionnaires which aim to screen on the presence of atopic diseases. Core questions of the ISAAC questionnaire on asthma, allergic rhinoconjunctivitis and eczema are used for this purpose. In addition, questions about respiratory infections and food allergy are included.

Based on the answers in the screening part, additional specific questionnaires on each disease topic are selected or not, to be filled in subsequently. Information about growth parameters, breast feeding and vaccination status are obtained from personal health care files by the

parents. This health care file is a document that every child in the Netherlands owns and is used in the primary care setting during the first years of live. The general health status is determined based on the RAND questionnaire (table 2). The screening questionnaires also contain questions about known risk factors for infections (as use of a consoler, day care) and atopic diseases (as smoking, pets, and breastfeeding).

Figure 2. Structure and way of usage of the Electronic Portal



*	Patient consulting one of the EN members	E	Eczema
A	Asthma	FA	Food Allergy
RTI	Respiratory Tract Infections	----	To be developed
AR	Allergic Rhinoconjunctivitis		

Additional questionnaires

The aim of the additional questionnaires is to extensively explore the complaints of the patient, his medication use and habits, and measure the disease related quality of life. Details of the supplementary questionnaires in the EP, and the meaning of the corresponding scores are given in table 2. Questionnaires about asthma, respiratory tract infections, allergic rhinoconjunctivitis, eczema and food allergy are included. In addition to the questionnaires mentioned in table 2, additional questions about asthma and rhinoconjunctivitis are included.[14] Besides disease specific questionnaires, information on environmental factors, pet exposure, (parental) smoking and social economic status are obtained, partially adopted from the ISAAC questionnaire.[15]

Diagnostic tests

Caregivers from the EN can add results of diagnostic tests to the EP. Protocols are written to ascertain uniform performance of different tests.

Table 1. Content of the Electronic Portal for children with respiratory and allergic symptoms

	Subject	Includes
1. Screening Part		
Personal data		DOB, weight at birth, development, vaccination status
General Health Status		RAND questionnaire
General medical history questions		Known risk factors for atopic diseases
Screening questions on atopic and infectious diseases		ISAAC core questions and non-validated questions
2. Additional Part		
Asthma	Symptoms	ISAAC additional questions, ACT, medication use
	Treatment compliance	MARS
	Quality of life	PAQoL
Infections	Symptoms	Non-validated questionnaire
	Quality of life	OM-6
Allergic Rhinoconjunctivitis	Symptoms	ISAAC additional questions, ARIA, medication use
	Quality of life	RQLQ
Food allergy	Symptoms	Non-validated questionnaire
	Quality of life	FaQoL
Eczema	Symptoms	SA-EASI
	Quality of life	IDQL or CDLQI
3. Diagnostic test results		
Lung function tests		FEV1, NO, BDR or Methacholine challenge test
Laboratory results		Inhalation screening (sIgE)
Allergy test results (when applicable)		SPT, Food challenge results
4. Follow-up Part		
Treatment		Medication use
Symptom control		ACT
Treatment compliance		MARS scale

DOB = Date of Birth; FEV1 = Forced Expiratory Volume in 1 second; NO = Nitric Oxide; BDR = Bronchodilator response; SPT = Skin Prick Test; For abbreviations concerning questionnaires: see table 2

Questionnaire		Description	Score range
General	RAND GHRI[26,27]	7-item general health questionnaire. Developed for use in children 0,5-12 years of age	Range: 7-32 32 = good health
Asthma	C-ACT[28]	7-item questionnaire. Developed to measure asthma control in children 4-11 years of age. 4 questions are for the child, 3 for the parent	Range: 0-27 > 20 = well controlled
	ACT[29]	5-item questionnaire developed to measure asthma control in children 12+ years	Range: 5-25 > 20 = well controlled
	MARS[30]	9-item questionnaire, developed to measure medication adherence	Range 0-5 Mean score >4.5 = 'adherent'
	PAQLQ[31]	23-item questionnaire, in 3 domains. Developed to measure asthma-specific health-related QoL in children 6-18 years of age	Range 0-7 higher scores indicate better QoL
Infections	Brouilette score[32]	3-item questionnaire to assess presence of OSAS	> 3,5: OSAS present - 1 to 3.5: uncertain OSAS < -1: OSAS not present
	OM6[33]	6-item questionnaire in 6 domains. Developed to measure change in ear-related handicap in children with recurrent acute otitis media and otitis media with effusion	Range 0-7 (mean) 7 = severe
Allergic Rhinnoconjunctivitis	ARIA[34]	5-item questionnaire, developed to measure presence and severity of rhino-conjunctivitis	Classification into: intermittent or persistent rhinitis; and severity: mild or moderate/severe
	PRQLQ[35]	23-item questionnaire in 5 domains. Developed to measure the functional problems in rhino-conjunctivitis in children 6-12 years of age	Range: 0-6 (mean) 6 = maximal impairment in health related quality of life
	AdolRQLQ[36]	25-item questionnaire in 6 domains. Developed to measure the functional problems in rhino-conjunctivitis in children 12-17 years of age	Range: 0-6 (mean) 6 = maximal impairment in health related quality of life
Food Allergy	FAQLQ-CF[37]	24-item questionnaire, in 4 domains. Developed to measure food allergy related QoL in children 8-12 years of age	Range: 1-7 (mean score) 7 = maximal impairment in health related quality of life
	FAQLQ-TF[38]	23-item questionnaire, in 3 domains. Developed to measure food allergy related QoL in children 13-17 years of age	Range: 1-7 (mean score) 7 = maximal impairment in health related quality of life
Eczema	SA-EASI[39,40]	10-item questionnaire. Developed to measure the caregiver's self-assessment of the severity of his/her child's atopic dermatitis	Range: 0-72 (acute score) 72 = very severe
	IDQL[41]	10-item questionnaire. Developed to measure <4 years of age	Range: 0-30; higher score means larger impairment of QoL
	CDLQI[42]	10-item questionnaire. Developed to measure 4-16 years of age	Range: 0-30; higher score means larger impairment of QoL

Respiratory function

In all new patients suspected for asthma, lung function and allergy tests are performed according to the Dutch national guidelines.[16] Spirometric assessments, e.g. maximal flow-volume curves, are measured according to the ATS/ERS standards.[17] The highest values of three correctly performed manoeuvres are used for analysis. Recorded parameters are FEV_1 (forced expiratory volume in one second) and FVC (Forced Vital Capacity).

To measure the bronchodilator response 800 microgram of salbutamol is administered via a metered dose inhaler using a volumatic spacer (GSK, Uxbridge, UK). Airway reversibility is defined as an increase of FEV_1 of ≥12% of the predicted value 10 minutes after administration of salbutamol. Bronchial hyper responsiveness (BHR) is assessed by a challenge with nebulized methacholine according to the ERS/ATS guidelines.[18] All children will be asked to withhold from taking rescue medication for at least 12 hours, and long-acting beta-two agonists at least 24 hours beforehand. A child will be defined as having BHR when FEV_1 has dropped by ≥20% from baseline during the inhalation challenge. In children with a baseline FEV_1 ≤70% no challenge will be performed.
In all known patients with asthma spirometry assessment (a bronchodilator response (BDR) or on indication a challenge test) is annually performed, according to the national guideline.[16]

Other test results
Depending on the situation of the patient, more diagnostic tests may be performed when this is considered necessary for patient care by the physician. For instance, in a child presenting with recurrent infections initially a culture may be taken and lab tests to assess the immunologic status may be performed, before a lung function test will confirm the diagnosis of asthma. The EP does offer the opportunity to enter those test results in the system in a structured way. Cultures (nasopharyngeal, sputum, ear, nose) and lab results in case of suspicion of a immune deficiency can be registered when applicable. Atopic test results, such as an ImmunoCAP for food allergens or inhalation allergens, food challenge results or skin prick test results can be entered. Test results can be filled in on predefined schedules. Also the doctors-diagnosis will be entered in the EP, and other diagnoses can be entered over time.

Follow up and study endpoints
By activating the follow up function in the EP, patients are notified by email that a short questionnaire is ready to be filled in by parents and/or patient in the EP at predefined 3-month intervals, which is once every season. (content: see table 1 section follow-up). In order to obtain a validated measure of asthma control, the EP uses the validated C-ACT, or ACT, depending on the age of the child. Adherence to treatment is assessed by using the Medication Adherence Report Scale (MARS) comprising questions on medication use behaviour and adherence.[19] Medication use is registered by parents.

Privacy
The handling of personal data complies with the Dutch Personal Data Protection Act. All data are stored in a large database, which is maintained by Vital Health Software. Storage

and protection of the data is performed according to the NEN 7510 guideline. Privacy is protected by encrypted storage of personal information in the database.
Exchange of data is protected by a security protocol to prevent damage, loss, unauthorized access or abuse of data. The EP can only be accessed with personal access codes. The EP offers different user levels. Each level has its own function and privileges, such as a professional (to give access to the EP to patients, and to view their own recruited data), an application manager (to give access to the EP to professionals; access to all processes and modules, including the databases), and patient (access to their own data). Each participating centre has its own access codes, and data from other centres cannot be seen or modified.

Results

Recruitment

At the time of writing 1500 children have been invited to participate, of whom the baseline questionnaire has been completed in 740 (49%) patients. 478 patients were selected to be followed up based on a diagnosis of a recent asthma diagnosis or new symptoms that were assigned to asthma by the pediatrician. Recruitment has been underway for 1 year in 3 centres (figure 2), for 5 months in 2 centres and 2 months in one center. Two other centres have confirmed participation in the study, and will start at the end of 2012 with inclusion.

Discussion

In current clinical practice large amounts of data are gathered during routine patient care. Very little of these data are available for research purposes because data are not recorded in a structured way. Here we describe an EP which facilitates the EN to collect data in a structured way with minimal effort of the caregivers themselves. This EP offers several opportunities. Since the start of inclusion, in June 2011, 1500 patients were invited to participate. At present 740 patients (49%) have completed the baseline questionnaire. Most patients that have not completed the questionnaire are known asthmatic patients that visit their doctor once per year. These patients will fill in the questionnaire shortly before their next doctor visit. In 95% of the cases informed consent was given to use EP-data for research purposes. This shows the EN is able to gather a large number of patients within a relative short period. As a result a large database will be available within a relatively short time.
Large population based observational studies, mainly birth cohort studies, have been published and mainly studied determinants of asthma.[20-22] These data are not suitable to study treatment related asthma phenotypes of asthma in children (e.g. treatment response to inhaled steroids in asthmatic patients with eczema, compared to those without eczema;

or treatment response to long-acting beta-agonists in asthmatic patients with marked airway reversibility compared to those without (or with minor) reversibility); firstly because of the small number of patients with asthma in most of these studies. Although birth cohorts may be large, asthma may be present in about 5% of the children above the age of five. The number of patients using asthma medication on regular basis, which is only a sample of this 5%, does not allow comparing therapy response within the different treatment regimens. Especially in a heterogeneous disease such as asthma, large patient numbers are needed to explore those treatment defining phenotypes.

Strict inclusion criteria are used in randomized trials to study the efficacy of treatment trials. The outcomes of those studies are applicable to this selected group, but difficult to generalize in the heterogenic asthmatic population seen in daily practice. The EP enables collection of data gathered during daily practise of an unselected population with asthma (and other atopic diseases), for research purposes. By including large samples of patients, the outcomes will be usable in daily practice. Data from the EP will be used to study the effectiveness instead of the efficacy, which makes the outcomes more applicable in daily practise.

Currently, the automatic follow up function is enabled for asthmatic patients only. However, this function will be available at the end of this year for the other disease topics included in the EP: allergic rhinoconjunctivitis, eczema, food allergy and (upper and lower-) respiratory tract infections. Apart from the research relevance, the patients participating in the EP will be followed up in time, which means that their complaints will be monitored actively by the EP without extra effort from the doctor. In regular asthma care, the frequency of visits is often once per year in stable periods. During this visit it may be difficult for parents and patient to recall how the last 12 months have been. The EP makes it possible to have a whole year through-overview of asthma control, medical treatment response and medication use for the doctor, as well as for the patient. Transparency in hospital care is also increased by access to their test results in the electronic EP by each individual patient, which may increase the involvement of the patient in his treatment.[23]

The EP supports a more structured way of working within the collaborative network. This may support the use and implementation of national guidelines on atopic diseases. Each participating hospital creates its own patient database. With this database the performance of each centre can be monitored and compared to other centres. Furthermore, working strategies or other knowledge can be exchanged to improve daily practice within the centres. Due to the use of a web based application, there will be a selection in the population that is

included in the EP. Currently in the Netherlands, 1% of all persons between 11-45 years of age do not have access to internet at home.[24] The main reason for not having internet-access is 'no interest'. Because financial reasons seem to play a much smaller role, this will probably not lead to a selection in our patient group (in social economic state). However, also a good understanding of, and ability to read the Dutch language is an inclusion criterion. This will lead to a selection of patients, because the 1.5 million functional analphabetic persons in the Netherlands will mainly evolve within the lower social economic class. One third of those persons are foreigners.[25] How large this selection is will be analyzed.

We conclude that the use of current web-based services like the described EP can be helpful to support extensive data collection in Expert Networks.

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Chapter 3

Respiratory tract infections and asthma control in children

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Abstract

Introduction

Asthma control is considered the major goal of asthma management, while many determinants of control are difficult to modify. We studied the association between respiratory infection episodes (RTIs) of various types and asthma control.

Methods

Cross-sectional data were used from children aged 4-18 years with physician-diagnosed asthma who participated in a web-based electronic portal for children with asthma, allergies or infections. Asthma control was measured using the Childhood Asthma Control Test (C-ACT) or the Asthma Control Test (ACT). Linear regression was used to analyse the association between categories of numbers of various types of RTIs sustained in the preceding 12 months (categorized) and asthma control, adjusted for potential confounders.

Results

Asthma control was assessed in 654 children, and 68.5% were clinically well controlled (ACT≥20). Higher total numbers of RTIs in the last 12 months were strongly associated with a lower level of asthma control (p_{trend}<0.001). Similarly strong statistically significant associations were found for subtypes of RTI: ≥4 vs. 0 otitis episodes: coefficient -1.7 (95% CI -3.3 to -0.2); ≥5 vs. 0 colds: coefficient -2.3 (95% CI -3.0 to -1.6); ≥3 vs. 0 bronchitis episodes: coefficient -3.1 (95% CI -4.0 to -2.3), each with p_{trend} <0.05.

Conclusion

Higher numbers of reported respiratory tract infections are associated with lower level of asthma control. The different type of respiratory tract infections contribute equally to less controlled asthma.

Introduction

Asthma is the most prevalent chronic disease in childhood. International guidelines focus on asthma control as a therapeutic goal.[1] Various studies report that asthma control can be achieved for a majority of patients receiving appropriate asthma therapy,[2–4] yet poor asthma control remains a large problem in the developed world. During wheezing episodes, viruses are found in in approximately 80% of school-aged children.[5] Many studies have shown that upper respiratory tract infections (URTIs) can trigger asthma exacerbations,[6–8] but there is limited information about the association between the frequency of upper and lower respiratory tract infections and the impact on asthma control in children.
Several other factors have been associated with lower asthma control in children; e.g. older age,[9] the female sex,[10–12] medication adherence,[4,10,13] tobacco smoke exposure,[10,14,15] and increased body mass in boys.[16–19] Furthermore, allergic co-morbidity has been described as a determinant of poor asthma control,[20,21] with eczema being associated with uncontrolled asthma during autumn and winter, and allergic rhinitis during spring and summer.[22] In general, asthma control is best during summer, and lowest during autumn and spring.[22]

Poorly controlled asthma increases the risk for exacerbations.[23] In children, severe asthma exacerbations are often preceded by upper respiratory tract infections.[6–8,24,25] Despite the established relation between acute viral infections and exacerbations, solid evidence on the role of numbers of URTIs and lower respiratory tract infections (LRTIs) on longer term asthma control is lacking. We investigated if a higher number of RTI episodes in the last 12 months was related to impaired asthma control. We assessed the relative roles of URTIs (otitis, colds) and LRTIs (bronchitis) in asthma control.

Methods

Study population

Within a nationwide collaborative network of Dutch caregivers, children presenting with asthma symptoms at the outpatient department were included from June 2011 to June 2013.[26] In addition, children from the PACMAN cohort study, identified via a pharmacy network that received at least 3 prescriptions for asthma medication in the last 2 years were included.[27] From those, patients that were diagnosed with asthma, and completed the Asthma Control Test (ACT), were selected for further analyses. Asthma was defined as a doctors' diagnosed asthma, based on the ERS/ATS guidelines.[1] Parents gave informed consent for participation, and the medical ethics committee of the University Medical Center Utrecht approved the study.

Electronic Portal

Questionnaires were filled in by each patient or parents on a personal page within an Electronic Portal (EP). This web-based application contains health- and disease-related questions on respiratory- and allergic diseases, as well as questionnaires about exposures and demographic information. Information about current asthma symptoms was adopted from the ISAAC questionnaire. Detailed information about asthma control, treatment and adherence were obtained.[26] Medication adherence was measured by using the Medication Adherence Report Scale (MARS) comprising five questions on medication use behaviour.[28] Patients with a MARS score ≥20 were considered to be adherent.[29]

The number of LRTIs was defined as the answer to the question: 'how many bronchitis episodes (=coughing, dyspnoea and fever) did you child experience in the last 12 months?'. URTIs were divided into otitis episodes and colds; the number of otitis episodes was defined as the answer to the question 'how many otitis episodes (= earache, otorroea, fever) did your child experience in the last 12 months?' and for colds as: 'how many cold-episodes (=blocked nose, running nose and coughing), did your child experience in the last 12 months?'. As ages of all children ranged between 4 and 18 years, anthropometric measurements were transformed into z-scores.

Asthma control

Asthma control was measured using the Childhood Asthma Control Test (C-ACT) for children 4 to 11 years old[30] or the Asthma Control Test (ACT) for children 12 years and older.[31] For each patient, the total score was calculated ranging from 0-27 for the C-ACT and from 5-25 for the ACT, with a score below 20 indicates inadequately controlled asthma for both age categories. The ACT score as hereafter used in this article refers to the combination of ACT and C-ACT score.

Asthma treatment

Medication use was categorized into the treatment steps that are described in the Dutch guidelines.[32] Patients are stepped up in treatment when there is insufficient response to the current treatment step, despite sufficient adherence. Step 1 consists of Short-Acting Beta-Agonists (SABA); Step 2 adds inhalation corticosteroids (ICS) in start dosages (Beclomethasone twice daily 200 ug or equivalent). In Step 3, ICS dosage is doubled or Long-Acting Beta-Agonists (LABA) are added; Leukotriene Receptor Antagonists (LTRA) may be an alternative to LABA. Step 4/5 consists of double dosages of ICS (as compared to step 3) while LABA or LTRA are continued.

Atopic co-morbidity

Parent reported rhinitis was defined as yes to the question: 'In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?'; Parent reported eczema was defined as yes to the question 'Has your child had an itchy rash (which was coming and going) at any time in the last 12 months?', and parent reported food allergy was defined as yes to the question 'does your child have a food allergy, or do you suspect your child to have a food allergy?'. Atopic co-morbidity was defined as present if one of the three above questions were answered positive.

Statistical analysis

Descriptive analyses, including means and standard deviations (SD) or medians and interquartile ranges (IQR), and proportions were performed to describe the study population. As the C-ACT and ACT differ in range (0 to 25 and 0 to 27), the ACT score was standardized by calculating z-scores in order to analyse whether the association between determinants and ACT score differed from the association between determinants and the standardized ACT score. As we found no differences, further analyses were performed using the ACT score as outcome parameter. To avoid bias that might result from a complete case analysis, missing data were imputed by using multiple imputations. First, known determinants of asthma control were described by tertiles of numbers of RTIs, to assess potential confounding as input for main analyses. As gender and age, current smoke exposure and treatment are clearly related to both number of RTIs[14,33] and asthma control,[10,14,34] these were taken as a basic confounder set. We performed trend tests over categories of numbers of RTI by adding category indicators as continuous independent variables to the models.

Finally, as allergic sensitization increases risk for a severe RTI,[7,24,25] we explored whether allergic sensitization modified our associations of interest by testing for interaction. As asthma control varies by season,[22] and prevalence of RTIs shows seasonality,[24] we similarly tested for interaction by season of the year. Statistical analysis was performed using IBM SPSS statistics version 20.0 (Armonk, New York, USA).

Results

Physician-diagnosed asthma was present in 654 children (table 1). Sixty-two percent were male, and the mean age was 10.1 years (SD 3.5). Participants were predominantly of western origin (82.7%). The median ACT-score was 21 (IQR 18-24), and 68.5% of all asthmatic children were well controlled (ACT score ≥ 20). Most patients experienced 1 or more respiratory tract infections in the last 12 months (455 (69.6%)). The proportion of patients experiencing RTIs, categorized by otitis, cold and bronchitis episodes are shown in figure 1.

Figure 1. Proportion of patients with experiencing otitis episodes, colds or bronchitis episodes in the last 12 months (n=654)

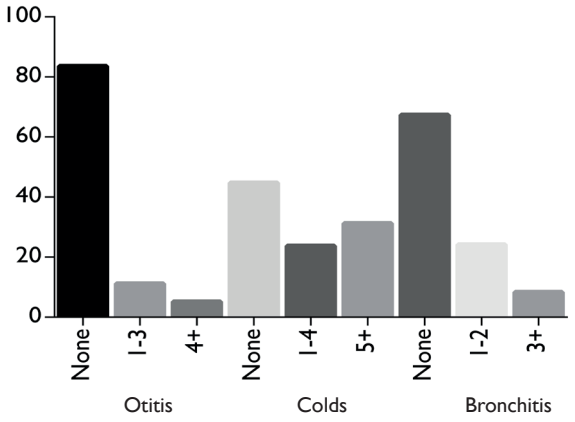
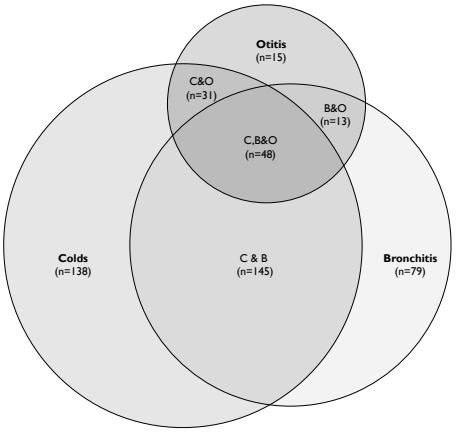


Figure 2 shows the proportional overlap in patients experiencing bronchitis, cold and/or otitis episodes. Determinants of asthma control by by tertiles of numbers of RTIs are shown in table 1. Younger age, western ethnicity, and presence of allergic rhinitis or atopic co-morbidity in general, were all significantly associated with a higher number of RTIs. Furthermore, a higher asthma treatment step was associated with a higher number of RTIs.

Figure 2. Proportion of patients with any otitis episode, colds or bronchitis episode, or a combination of those in the last 12 months (n=465)



When accounting for confounding in multivariable analyses, higher numbers of RTIs remained significantly associated with less asthma control (p-value for trend <0.001). Less asthma control was associated with more otitis episodes (p_{trend}= 0.015); more colds (p_{trend}= 0.001) and more bronchitis episodes (p_{trend}= 0.006) (table 2).

Table 1. Predictors of asthma control by increasing tertiles of numbers of Respiratory Tract Infections (n=654)

	N (%)	Lowest tertile (n=203)	Middle tertile (n=229)	Highest tertile (n=222)	p-value
Gender (male)	409 (62.5)	129 (63.5)	84 (36.7)	88 (39.6)	0.76
Age (years)	10.1 (3.5)	10.9 (3.0)	10.1 (3.4)	9.3 (3.9)	**<0.001**
Ethnicity (Western)‡	541 (82.7)	159 (78.7)	199 (86.9)	183 (82.4)	**0.007**
Mean height (z-score)	0.1 (4.0)	0.25 (-0.75 - 0.82)	0.11 (-0.88 - 0.97)	-0.18 (-0.99 - 0.81)	0.48
Mean weight (z-score)	-0.7 (7.6)	0.18 (-0.85 - 0.83)	0.07 (-0.85 - 0.81)	-0.11 (-0.77 - 0.70)	0.43
Maternal education (high)	291 (44.5)	98 (48.3)	104 (45.4)	89 (40.1)	0.24
Smoking by one of the parents (y)	52 (8.0)	18 (8.9)	21 (9.2)	13 (5.9)	0.33
Co-morbidity (last 12 months)					
Allergic rhinitis	498 (76.1)	138 (68.0)	176 (76.9)	184 (82.9)	**0.002**
Eczema skin rash (y)	282 (43.1)	76 (37.4)	101 (44.1)	105 (47.3)	0.13
Food allergy (suspected)	308 (47.1)	90 (44.3)	108 (47.2)	109 (49.1)	0.62
Atopic co-morbidity (any of the above)	563 (86.1)	164 (80.8)	199 (86.9)	200 (90.1)	**0.030**
Season					
Summer	168 (25.7)	49 (24.1)	66 (28.8)	54 (24.3)	0.57
Autumn	137 (20.9)	41 (20.2)	41 (17.9)	55 (24.8)	
Winter	140 (21.4)	43 (21.2)	48 (21.0)	50 (22.5)	
Spring	209 (32.0)	70 (19.7)	75 (32.8)	64 (28.8)	
Therapy step-up plan					
0. No medication use	58 (8.9)	25 (12.3)	16 (0.07)	18 (8.1)	**0.005**
1. SABA only	60 (9.2)	22 (10.8)	25 (10.9)	13 (5.9)	
2. ICS medium dose (+SABA)	237 (36.2)	66 (32.5)	95 (41.5)	76 (34.2)	
3. ICS high dose or LABA/LTRA medium dose (+ ICS any dose)	171 (26.1)	42 (20.7)	53 (23.1)	77 (34.7)	
4/5 LABA/LTRA (+ high dose ICS)	129 (19.7)	49 (24.1)	41 (17.9)	38 (17.1)	
Adherent to medication use (y)	471 (72.0)	70 (34.5)	101 (44.1)	119 (53.6)	0.33

Data are n (%), n/N (%),Mean (SD) or median (IQR). IQR = Interquartile range; ‡ Ethnicity: Western (North America, Australia and Europe, except Turkey) and Non-Western (South America, Caribbean, Africa, Asia) defined according to CBS-Definition on www.cbs.nl ; p-values from trend tests over tertiles.

Table 2. The association between Respiratory Tract Infections in the last 12 months and the Asthma Control Test score*

Number of:		Model 1		Model 2		
	Number (%)	Regression coefficient 95% CI	p-value	Regression coefficient 95% CI	p-value	p-trend
Total RTI episodes						
0	195 (29.8)	Ref	-	Ref	-	
1-7	257(39.3)	-0.89 (-1.65 to -0.14)	<0.001	-0.79 (-1.52 to -0.07)	0.032	**<0.001**
8+	202 (30.9)	-3.41 (-4.21 to -2.62)	<0.001	-3.20 (-3.99 to -2.41)	<0.001	
Otitis episodes						
0	547 (83.6)	Ref	-	Ref	-	
1-3	73 (11.2)	-0.95 (-2.00 to 0.10)	0.054	-0.70 (-1.72 to 0.33)	0.181	**0.015**
4+	34 (5.2)	-1.50 (-3.02 to 0.03)	0.077	-1.73 (-3.26 to -0.20)	0.027	
Colds						
0	293 (44.8)	Ref	-	Ref	-	
1-4	156 (23.8)	-0.62 (-1.14 to 0.18)	0.129	-0.51 (-1.27 to 0.25)	0.190	**0.001**
5+	205 (31.3)	-2.54 (-3.28 to -1.80)	<0.001	-2.27 (-2.98 to -1.55)	<0.001	
Bronchitis episodes						
0	441 (67.4)	Ref		Ref	-	
1-2	158 (24.2)	-1.46 (-2.21 to -0.70)	<0.001	-1.40 (-2.13 to -0.67)	<0.001	**0.006**
3+	55 (8.4)	-3.21 (-4.07 to -2.35)	<0.001	-3.14 (-4.01 to -2.26)	<0.001	

Model 1 = univariable association between each type of RTI and asthma control
Model 2 = model 1 + gender, age, ethnicity, smoke exposure and treatment regimen
*Higher scores indicates better asthma control

With standardized regression coefficients, associations with subtypes of RTI showed trends with similar strengths over categories; otitis -0.14 (95% CI -0.23 to -0.05); colds -0.13 (95% CI -0.20 to -0.05), bronchitis -0.11 (95% CI -0.19 to -0.03).

Discussion

This study shows that an increased number of upper respiratory tract infections in the last 12 months, namely ≥4 otitis episodes, ≥5 colds as well as any bronchitis episode are associated with less asthma control. It also shows that a rather large proportion of children have uncontrolled asthma (31.5%).

As asthma control is an important risk factor for an asthma exacerbation,[23] it is important to obtain and maintain asthma control. Previous studies have shown that respiratory tract

infections play a key role in asthma exacerbations.[6,8] However, to date no specific treatments are available to significantly alter the clinical outcome of viral infections in asthmatic children. Several therapeutic strategies have been considered; however, results are disappointing due to virus specificity,[5] side effects, and need for administration early in the course of the infection. Glucocorticosteroids are by far the most widely used drugs in asthma treatment, and have potent anti-inflammatory activity. The use of inhaled steroids, which was 82.1% in our study population, did not lead to the prevention of respiratory tract infections, which occurred in 69.6%. This may possibly be due to medication adherence, as low adherence may lead to lower asthma control. However, in contrast to many previous studies,[4,10,13] we found no association between medication adherence and the level of asthma control. This may be due to the method of measuring medication adherence, however, this parent-reported medication method has been shown to be a reliable tool to assess medication adherence.[35]

We did not find interaction between between the presence of atopic co-morbidity and number of RTI's. Previous studies have found that atopy (defined by the presence of sensitization) was associated with more severe illness and loss of control in asthmatic children.[7,24,25] Instead of atopy, we used the presence of atopic morbidity, defined as the presence of at least one of the following atopic diseases: food allergy, eczema or allergic rhinitis. This different definition may explain why the interaction was not found. However, this same study[24] did also show that there was no difference in the number of (viral) illnesses or infection rates in sensitized children as compared to non-sensitized children. As we have studied the number of RTI episodes and not the severity of the episodes, this may also explain differences. We did not find interaction between season and the number of RTIs. This may be due to the fact that we assessed the number of RTIs in the last 12 months, and did not have information about the number of infections per season.

The strength of this study is that it focuses on a heterogeneous group of asthmatic children, who were recruited from both general practitioners and hospital settings. All patients completed a broad questionnaire, which enabled us to study a large number of factors, besides RTIs, related to asthma control. However, some methodological considerations should be made.

First of all, the use of a cross-sectional study design to investigate interrelationships among variables limited our ability to study cause-and-effect relationships. It remains uncertain whether a higher number of RTIs causes the lower level of asthma control, or whether the higher number of RTIs are a result of lower level of asthma control. Longitudinal studies are needed to confirm causality. Secondly, selection bias may have played a role, due to non-random missing values of participants not willing to take the time to complete the

questionnaire. However, we have imputed missing values using multiple imputations, the currently accepted best way to avoid bias resulting from complete case analysis.[36] Thirdly, recall bias may have led to underreporting of mild infections in well controlled children. Fourthly, no viral samples were available of the RTI episodes in our patients, as patients were not seen by a physician during most of the episodes. However, it is known that in about 20% of wheezing episodes no virus is detected.[5]

Viral respiratory tract infections are inherent to the paediatric age; they occur frequently in early infancy where viral pathogens are detected in up to 90% of the symptomatic children. Furthermore, viral pathogens are also frequently found (in about 40%) in young children without respiratory symptoms.[37] School age children may easily be infected by their younger siblings. Therapeutic or preventive strategies have shown to be ineffective in influencing the course of a respiratory tract infection in children, or preventing asthma exacerbations.[5,38,39] As long as viral pathogens remain present in symptomatic and asymptomatic children, it is unlikely that complete asthma control will probably be achieved in all children.

In conclusion, our data suggest an association between a higher number of RTI episodes and lower level of long term asthma control in children. More otitis, cold or bronchitis episodes contribute equally to less asthma control.

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Chapter 4

Determinants of quality of life in children with asthma

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Abstract

Introduction

Health related quality of life (HRQOL) in children with asthma depends on multiple factors, among which poor asthma control is considered to be the most important determinant. Little is known about other independent determinants of HRQOL.

Methods

This study used cross-sectional data from a cohort of children with a doctors' diagnosis of asthma who participated in a web-based electronic portal for children with asthma, allergies or infections. Asthma specific HRQOL was measured using the Dutch version of the paediatric asthma quality of life (PAQOL), asthma control was measured using the Childhood Asthma Control Test (C-ACT) or Asthma Control Test (ACT).

Results

PAQOL questionnaires of 310 children with asthma were analysed. Asthma control was the most important determinant for HRQOL. Children who reported that symptoms of wheeze were triggered by foods and drinks or by emotions had significantly lower HRQOL ((B -0.33 (95% CI -0.57 to -0.08) and B -0.27 (95% CI -0.47 to -0.08), respectively), independent of the level of asthma control. HRQOL was lower during autumn (B -0.30 (95%CI -0.50 to -0.10).

Conclusion

Besides asthma control and the autumn season, children who perceive foods or drinks or emotions as triggers for wheeze, are at risk for lower HRQOL.

Introduction

Asthma is the most prevalent chronic disease in childhood. The major goal in asthma treatment is to achieve and maintain asthma control for prolonged periods.[1] Several studies have assessed the association between asthma control and HRQOL, and found that poor asthma control is associated with lower health-related quality of life (HRQOL) scores in both adults and children.[2–4] Because the focus in asthma treatment is not merely asthma control, but also quality of life, recent guidelines recommend periodic assessment of quality of life.[5] Many factors influencing asthma control have been identified.[6,7] However, little is known about factors that influence HRQOL in children, irrespective of their asthma control. Children with asthma are troubled not only by the asthmatic symptoms itself, but also by physical, social and emotional impairment due to their asthma. Though not routinely measured in daily practice, patient-reported outcomes, such as health-related quality of life (HRQOL) are useful indicators to understand the impact of asthma on functional status and well-being.

There are several specific questionnaires to estimate HRQOL of children with asthma. One of the most frequently used is the Paediatric Asthma Quality of Life Questionnaire (PAQOL).[8] HRQOL-questionnaires have shown to have variable strengths of association with traditional effect parameters such as lung function.[9] It has been hypothesized that other aspects like patient satisfaction and adverse effects from medication use are captured by HRQOL measurements, and not by measurements of asthma control. Because of the importance of improving HRQOL, we aimed to identify determinants of HRQOL in children, independent of asthma control.

Methods

Study population

Within a nationwide collaborative network of Dutch caregivers, consisting of general practitioners, paediatricians and specialized paediatricians in pulmonology, allergology, dermatology, infectiology and otolaryngology, children presenting with asthma symptoms at the outpatient department were included in an Electronic questionnaire Portal from June 2011 to June 2013.[10] In addition, the PACMAN cohort study, identified via a pharmacy network that received at least 3 prescriptions for asthma medication in the last 2 years were included.[11]including at least 1000 children with asthma medication (aged 4-12 years Asthma was defined as doctors' diagnosed asthma, based on the ERS/ATS guidelines.[12] Parents gave informed consent for participation, and the medical ethics committee of the University Medical Centre Utrecht approved the study.

Electronic Portal

Questionnaires were filled in by each patient on a personal page within an Electronic Portal (EP). This web-based application contains health- and disease-related questions on respiratory- and allergic diseases, as well as questionnaires about exposures and demographic information. Information about current asthma symptoms was adopted from the ISAAC questionnaire. Detailed information about asthma control, treatment and adherence, and health related quality of life (HRQOL) were obtained.[10] Factors that were self-reported to worsen wheeze were considered present when the question 'In the last 12 months, what has made your child's wheezing worse?' was answered by ticking one or more of the triggers. Medication adherence was measured by using the Medication Adherence Report Scale (MARS) comprising five questions on medication use behaviour.[13] Patients with a MARS score ≥20 were considered to be adherent.[14]

Health-related quality of life

Asthma-specific HRQOL was measured using the Dutch version of the PAQOL.[15] The PAQOL was developed to measure the functional problems (physical, emotional and social) that are most troublesome to children with asthma. It contains 23 questions and covers three domains: symptoms, emotional function and activity limitation.[8] The overall score is the mean score of all 23 questions, the individual domain scores are the means of the items within the three domains, with score 1 indicating that a patient was 'extremely bothered', to score 7 indicating 'not being bothered at all' in the previous week. The PAQOL is validated for children from age 7, and therefore only children between the ages of 7–18 years were included for analyses.

Asthma control

Asthma control was measured using the Childhood Asthma Control Test (C-ACT) for children 4 to 11 years old[16] or the Asthma Control Test (ACT) for children 12 years and older[17] depending on the age of the child. For each patient, the total score was calculated ranging from 0-27 for the C-ACT and from 5-25 for the ACT, with a score below 20 indicating inadequately controlled asthma for both age categories.

Statistical analysis

Descriptive analyses, including means and standard deviations (SD) or medians and interquartile ranges (IQR), and proportions were performed to describe the study population. Characteristics of the group of patients with a completed PAQOL questionnaire were compared to those who did not fill in the PAQOL to assess a possible selection of patients.

Univariable linear regression analysis was performed to assess the relation between each individual determinant and the overall PAQOL score, and the three domains scores subsequently. Determinants significantly associated with HRQOL ($p<0.05$) were selected to be included in the multivariable model. Bivariable linear regression analysis was used to assess whether associations between these determinants and HRQOL were independent of asthma control, which is the most important determinant of HRQOL.[2–4,18] We adjusted the analyses for the type of ACT questionnaire that was completed (C-ACT or ACT), as ranges of these scores differ. Gender differences in HRQOL have been described in literature.[23,24] Since the association between significant determinants and HRQOL might be modified by gender, interaction between these determinants and gender was tested by adding an interaction term to the model. Statistical analysis was performed using IBM SPSS statistics version 20.0 (Armonk, New York, USA).

Results

A completed PAQOL was available in 310 asthmatic patients. Sixty-one percent were male, and the mean age was 11.7 (range 7.0-17.8) years. Other baseline characteristics of the 310 children are presented in table 1.

HRQOL and determinants of HRQOL in asthmatic children

The median HRQOL in asthmatic children was high. The overall PAQOL score and scores of the three domains are presented in figure 1. In the univariable linear regression analysis (table 2), both male sex and better asthma control were associated with better QOL.

Several self-reported, perceived triggers for wheeze were also associated lower HRQOL: colds or 'flu, cigarette smoke, foods and drinks, emotions, the weather, dust and soap/sprays or detergents. Experiencing any lower respiratory tract infection (LRTI) or upper respiratory tract infection (URTI) in the last 12 months was associated with lower HRQOL. As compared to the summer, autumn was associated with lowest HRQOL. Neither the presence of any atopic disease in the last 12 months, nor the presence of any of the environmental exposures was associated with HRQOL. No differences were found between the activity limitation domain, emotional domain and symptoms domain of HRQOL (supplementary table 1).

Triggers for wheeze, independent of asthma control

Adjustment for sex and age did not alter the relation between the determinants in unadjusted models and HRQOL (data not shown). Therefore, sex and age were not added to the bivariable model.

Table 1. Characteristics of 310 asthmatic children aged 7-18 years.

	Mean (SD) n (%)
Patient characteristics	
Sex (male)	189 (61.0)
Age (years)	11.7 (2.79)
Western ethnicity (mother)	273 (97.8)
Educational level mother (high)	134 (47.2)
Season of filling in	
Summer	70 (22.6)
Autumn	62 (20.0)
Winter	69 (22.3)
Spring	109 (35.2)
Reported Triggers for wheeze	
Exercise	39 (12.7)
Colds or 'flu	164 (53.6)
Cigarette smoke	63 (20.6)
Foods or drinks	23 (7.5)
Emotions	44 (14.4)
Pets	90 (29.4)
Weather	161 (52.6)
Dust	118 (38.6)
Pollen	95 (31.0)
Wool clothing	18 (5.9)
Soaps, sprays or detergents	23 (7.5)
None	52 (17.0)

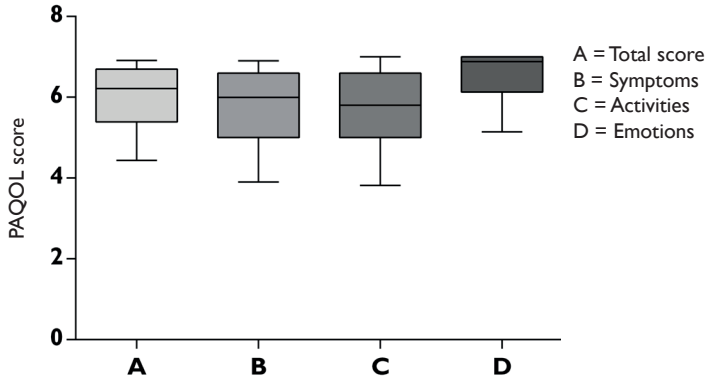
	Mean (SD) n (%)
Asthma control, treatment and compliance	
Median ACT	21.0 (18.0-24.0)
Uncontrolled (ACT<20) (y)	101 (33.7)
Asthma treatment:	
Inhaled steroids +/- SABA	129 (63.5)
Inhaled steroids + LABA	52 (25.6)
Medication adherence (MARS)	23.0 (20.0-24.0)
Atopic co-morbidity	
Hay fever (last 12 months)	239 (77.1)
Eczema (last 12 months)	127 (41.0)
Food allergy	135 (43.5)
Infections in last 12 months	
Any URTI	55 (17.7)
Number of URTI	0.0 (0.0-0.0)
Any LRTI	118 (48.0)
Number of LRTI	0.0 (0.0-1.0)
Environmental exposure	
Parental smoking (y)	13 (5.1)
Living area (urban)	134 (47.0)
Sibs (y)	257 (90.2)
Pets (y)	131 (46.0)

ACT = Asthma Control Test; SABA = Short Acting Betamimetics; LABA = Long Acting Betamimetics; MARS = Medication Adherence Score; URTI = Upper Respiratory Tract Infection; LRTI = Lower Respiratory Tract Infection; y = yes

After addition of asthma control, the negative association between perceived triggers for wheeze and HRQOL did weaken but remained statistically significant for both emotions (B -0.30 (95% CI -0.49 to -0.11)) and foods or drinks (B -0.33 (95% CI -0.57 to -0.08) (table 2). Ninety-one percent of the children that perceived wheeze to be triggered by foods or drinks, had been diagnosed with food allergy.

Besides perceived triggers for wheeze, the season of the year (autumn) remained significantly associated to lower HRQOL (B -0.30 (95% CI -0.50 to -0.10)). Adjustment for the type of ACT score (C-ACT or ACT) did also not affect the results.

Figure 1. Median PAQLQ scores (p10-p90), for the overall score and different domain scores in asthmatic patients (n=310)



We did also find no interaction between gender and the four determinants of HRQOL. Asthma control was the most important determinant of HRQOL based on the standardized regression coefficients (B 0.76 (95% CI 0.64 to 0.77)), followed by the autumn season (B -0.14 (95% CI -0.05 to -0.21)) and the perceived triggers for wheeze: foods or drinks (B -0.01 (95% CI -0.01 to -0.14)) and emotions (B -0.11 (95% CI -0.04 to -0.17)). Figure 2 shows the regression coefficients of the relationship between aforementioned determinants and HRQOL, adjusted for the level of asthma control.

Figure 2. Regression coefficients of the relationship between significantly associated determinants and HRQOL, adjusted for the level of asthma control.

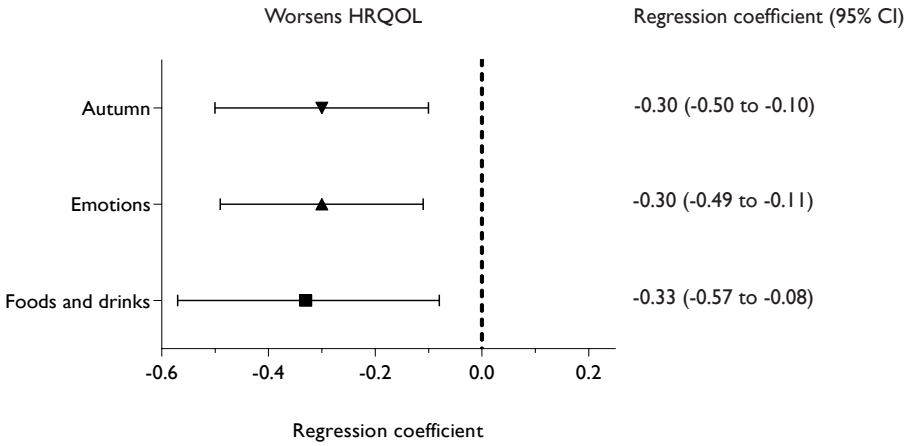


Table 2. The association between determinants and the Paediatric Asthma Quality of Life scores in 310 asthmatic children.

PAQOL overall score	Univariable analysis		Adjusted for level of asthma control	
	Regression coefficient (95% CI)[a]	p-value	Regression coefficient (95% CI)[b]	p-value
Patient characteristics				
Sex (male)	0.35 (0.14 to 0.57)	**0.001**	0.13 (-0.01 to 0.27)	0.068
Age (years)	0.01 (-0.02 to 0.05)	0.470	0.01 (-0.01 to 0.04)	0.292
BMI (kg/m^2)	-0.00 (-0.01 to 0.01)	0.755	0.00 (-0.00 to 0.01)	0.807
Western ethnicity (mother)	-0.04 (-0.81 to 0.74)	0.924	0.18 (-0.29 to 0.64)	0.447
Education mother (high)	0.10 (-0.12 to 0.32)	0.357	-0.10 (-0.24 to 0.03)	0.141
Asthma control				
Level of asthma control (ACT)	0.16 (0.15 to 0.18)	**<0.001**	-	-
Respiratory symptoms				
Trigger for wheeze				
Colds or 'flu	-0.44 (-0.64 to -0.23)	**<0.001**	-0.13 (-0.27 to 0.00)	0.057
Cigarette smoke	-0.40 (-0.65 to -0.14)	**0.003**	-0.05 (-0.12 to 0.22)	0.566
Foods and drinks	-0.47 (-0.87 to -0.07)	**0.020**	-0.33 (-0.57 to -0.08)	**0.009**
Emotions	-0.80 (-1.08 to -0.51)	**<0.001**	-0.30 (-0.49 to -0.11)	**0.002**
Weather	-0.43 (-0.64 to -0.23)	**<0.001**	-0.10 (-0.23 to 0.04)	0.172
Dust	-0.41 (-0.62 to -0.19)	**<0.001**	-0.12 (-0.26 to 0.02)	0.085
Soap, sprays or detergents	-0.62 (-1.01 to -0.22)	**0.002**	-0.11 (-0.36 to 0.15)	0.409
Exercise	-0.21 (-0.53 to 0.10)	0.185	-0.04 (-0.24 to 0.15)	0.660
Pollen	-0.14 (-0.37 to 0.08)	0.213	-0.05 (-0.19 to 0.09)	0.499
Wool clothing	-0.48 (-0.92 to -0.03)	**0.036**	-0.12 (-0.40 to 0.16)	0.408
Pets	-0.14 (-0.37 to 0.09)	0.237	-0.03 (-0.18 to 0.12)	0.688
Asthma medication use				
SABA only	Reference	-	Reference	-
Inhaled steroids +/- SABA	-0.08 (-0.36 to 0.52)	0.706	0.09 (-0.19 to 0.37)	0.534
Inhaled steroids + LABA	-0.20 (-0.67 to 0.28)	0.407	0.05 (-0.25 to 0.36)	0.730
Adherent for asthma medication (y)*	-0.02 (-0.04 to 0.01)	0.323	-0.03 (-0.18 to 0.11)	0.646
Allergic comorbidity				
Hay fever (last 12 months)	-0.20 (-0.45 to 0.05)	0.125	0.04 (-0.12 to 0.20)	0.626
Eczema (last 12 months)	-0.01 (-0.22 to 0.20)	0.894	0.12 (-0.01 to 0.26)	0.074
Food allergy	-0.04 (-0.25 to 0.17)	0.736	-0.10 (-0.23 to 0.03)	0.135

Table 2. Continued

PAQOL overall score	Univariable analysis		Adjusted for level of asthma control	
	Regression coefficient (95% CI)[a]	p-value	Regression coefficient (95% CI)[b]	p-value
Infections				
Any URTI (last 12 months)	-0.36 (-0.62 to -0.09)	**0.010**	-0.04 (-0.22 to 0.13)	0.641
Any LRTI (last 12 months)	-0.54 (-0.77 to -0.30)	**<0.001**	-0.08 (-0.23 to 0.08)	0.352
Environmental exposure				
Current smoking father or mother	-0.04 (-0.51 to 0.45)	0.884	-0.00 (-0.01 to 0.00)	0.134
Living area (urban)	0.01 (-0.21 to 0.23)	0.940	-0.01 (-0.15 to 0.12)	0.838
Sibs (y)	-0.14 (-0.51 to 0.23)	0.452	-0.20 (-0.42 to 0.03)	0.089
Pet (y)	-0.04 (-0.26 to 0.18)	0.731	-0.00 (-0.13 to 0.14)	0.958
Season questionnaire completed				
Summer	Reference	-	Reference	-
Autumn	-0.37 (-0.69 to -0.05)	**0.023**	-0.30 (-0.50 to -0.10)	**0.004**
Winter	-0.12 (-0.44 to 0.19)	0.433	-0.10 (-0.29 to 0.10)	0.334
Spring	-0.04 (-0.32 to 0.24)	0.829	0.03 (-0.15 to 0.21)	0.745

ACT = Asthma Control Test; SABA = Short Acting Betamimetics; LABA = Long Acting Betamimetics; URTI = Upper Respiratory Tract Infection; LRTI = Lower Respiratory Tract Infection; y = yes; *MARS score <20; [a]Univariable associations between determinant and HRQOL; [b]Bivariable association between a determinant and HRQOL, adjusted for level of asthma control (ACT score)

Discussion

This study confirms our knowledge that uncontrolled asthmatic patients experience lower HRQOL than well controlled patients. However, alongside asthma control, HRQOL was also lower in asthmatic patients who perceived emotions or foods or drinks as triggers for wheeze, and during autumn.

Our results confirm other studies, showing that asthma control is the most important factor influencing health related quality of life in asthmatic children.[3,4,18] Here we show that besides asthma control, perceived triggers for wheeze influence HRQOL in a broad sample of asthmatic patients.

Several determinants of HRQOL have been studied besides asthma control. One study assessed the effect of environmental factors in relation to the asthma severity and HRQOL, but showed no effect from the triggers (pets or carpet) on HRQOL in their multivariable

regression analysis.[18] Seasonal variations have also been associated with HRQOL in previous studies, with the worst season in terms of HRQOL measures being autumn.[19] This may be due to the higher prevalence of respiratory viral infections, influencing asthma control.

Two perceived triggers for wheeze, foods/drinks and emotions were associated with lower HRQOL, independent from asthma control. Emotions that are perceived as a trigger for wheeze do not necessarily have to be related to the asthma itself, but can also be influenced by factors that are not always known by the patient or the physician. In general, asthmatic children are at substantially higher risk of anxiety (an emotion) than their non-asthmatic peers.[20] A recent study showed that asthmatic children, who do not verbally share emotions, tend to have lower HRQOL.[21] Therefore, attention for emotions in asthmatic patients, and expressing these emotions by the patient may be effective in improving HRQOL. In children that are diagnosed with a food allergy, and in whom foods or drinks are perceived as a trigger for wheeze, underlying fear for a food related reaction may be present.[22] Effective illness management in this study by Avery et al. (through providing antihistamines or adrenalin injectors) led to better psychological adjustment. Therefore, workup to determine which factors influence emotions or fears might be indicated in children in order to improve HRQOL.

Chen et al, stated that girls have lower general health status, which is not reflected by asthma-specific HRQOL.[23] Gender differences in HRQOL are thought not to be due to differences in the disease itself, but most likely reflect different psychological responses to their disease.[24] Although girls had significantly lower HRQOL in our univariable analysis, adjustment for sex did not affect the associations between the determinants and HRQOL. We also found no interaction between gender and the four determinants of HRQOL (data not shown); this suggests that boys and girls do not respond differently to perceived triggers of wheeze or to the season of the year with respect to their HRQOL.
We also found no effect of the presence of any atopic comorbidity on asthma-specific HRQOL. The presence of allergic rhinoconjunctivitis, eczema or food allergy has also been shown to affect HRQOL by using a generic HRQOL instrument.[25] We used an asthma-specific HRQOL instrument, which may account for the fact that we found no differences in HRQOL between atopic and non-atopic children.

The strength of this study is the heterogeneous group of asthmatic children, which we recruited from both general practitioners, and hospital setting. All patients filled in a broad questionnaire, which enabled us to explore a large set of possible determinants of HRQOL. However, some methodological considerations should be made.

First, we used a cross-sectional study design to study the association between several determinants and HRQOL. This design limits our ability to interpret causality of these relationships, and longitudinal studies are needed to confirm causality. Second, from our database, it was not possible to obtain a valid classification for severity of asthma, based on the GINA guidelines. Instead, we used level of asthma treatment in our analyses, which was not associated with HRQOL. Published results of the association between asthma severity and HRQOL are conflicting, most likely due to different definitions that are used.[26] Our analyses may have been different when the GINA severity definition were used, however, a study by Chen et al, performed in adults, has shown that asthma control is the most important factor influencing HRQOL, and when asthma severity is taken into account this does not affect the association between asthma control and HRQOL.[23] Third, as the PAQOL is a validated questionnaire for children older than 6 years of age, no younger children were included in this study. This may limit the generalizability of the results to children younger than 7 years of age. However, due to higher age, all participants were diagnosed with asthma by their physician, which increases the validity or our results.

In conclusion, besides asthma control, children who perceive emotions, foods or drinks or the autumn season as a trigger for wheeze are at risk for lower HRQOL. Work-up to determine which factors influence emotions or anxiety might be indicated to improve HRQOL.

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Online supplement

Supplementary table 1. Univariable analysis of the association between determinants and the Paediatric Asthma Quality of Life scores in 310 asthmatic children

	Symptoms		Activity limitation		Emotional function	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
Patient characteristics						
Sex (male)	0.35 (0.10 to 0.60)	<0.01	0.50 (0.24 to 0.75)	<0.01	0.27 (0.08 to 0.46)	<0.01
Age (years)	-0.00 (-0.05 to 0.04)	0.85	0.01 (-0.04 to 0.05)	0.70	0.04 (0.01 to 0.07)	0.02
Western ethnicity (m)	-0.25 (-1.16 to 0.66)	0.59	-0.09 (-1.03 to 0.84)	0.85	0.26 (-0.42 to 0.94)	0.45
Educational level mother (high)	-0.15 (-0.11 to 0.41)	0.27	0.06 (-0.21 to 0.33)	0.65	0.07 (-0.12 to 0.27)	0.46
Season questionnaire completed						
Summer	Reference		Reference		Reference	
Fall	-0.44 (-0.82 to -0.06)	0.02	-0.37 (-0.76 to 0.02)	0.07	-0.29 (-0.57 to -0.00)	0.05
Winter	-0.20 (-0.57 to 0.16)	0.28	0.02 (-0.36 to 0.41)	0.91	-0.12 (-0.39 to 0.16)	0.41
Spring	-0.05 (-0.38 to 0.28)	0.79	0.05 (-0.29 to 0.40)	0.76	-0.07 (-0.31 to 0.18)	0.61
Respiratory symptoms						
Trigger for wheeze						
Exercise	-0.16 (-0.53 to 0.22)	0.41	-0.41 (-0.79 to -0.02)	0.04	-0.16 (-0.44 to 0.14)	0.25
Colds or 'flu	-0.56 (-0.80 to -0.32)	<0.01	-0.51 (-0.77 to -0.26)	<0.01	-0.24 (-0.42 to -0.06)	<0.01
Cigarette smoke	-0.56 (-0.86 to -0.26)	<0.01	-0.41 (-0.73 to -0.10)	0.01	-0.18 (-0.41 to 0.05)	0.11
Foods and drinks	-0.54 (-1.00 to -0.07)	0.03	-0.44 (-0.93 to 0.05)	0.08	-0.41 (-0.75 to -0.06)	0.02
Emotions	-0.79 (-1.13 to -0.44)	<0.01	-0.84 (-1.20 to -0.48)	<0.01	-0.78 (-1.03 to -0.53)	<0.05
Pets	-0.19 (-0.46 to 0.09)	0.18	-0.19 (-0.48 to 0.09)	0.18	-0.05 (-0.25 to 0.16)	0.66
Weather	-0.54 (-0.78 to -0.30)	<0.01	-0.52 (-0.77 to 0.27)	<0.01	-0.24 (-0.42 to -0.06)	<0.01
Dust	-0.58 (-0.83 to -0.33)	<0.01	-0.44 (-0.70 to -0.17)	<0.01	-0.17 (-0.36 to 0.02)	0.08
Pollen	-0.15 (-0.41 to 0.12)	0.29	-0.20 (-0.48 to 0.08)	0.16	-0.11 (-0.31 to 0.09)	0.29
Wool clothing	-0.67 (-1.19 to -0.15)	0.01	-0.40 (-0.95 to 0.15	0.15	-0.28 (-0.68 to 0.11)	0.16
Soap, sprays or detergents	-0.72 (-1.18 to -0.26)	<0.01	-0.81 (-1.29 to -0.32)	<0.01	-0.37 (-0.71 to -0.02)	0.04
Asthma control, treatment and compliance						
ACT score	0.19 (0.17 to 0.21)	<0.01	0.19 (0.17 to 0.21)	<0.01	0.11 (0.10 to 0.13)	<0.01
Uncontrolled asthma	-1.52 (-1.73 to -1.32)	<0.01	-1.49 (-1.71 to -1.27)	<0.01	-0.92 (-1.08 to -0.75)	<0.01

Supplementary table 1. Continued

	Symptoms		Activity limitation		Emotional function	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
SABA only	Reference		Reference		Reference	
Inhaled steroids +/- SABA	0.19 (-0.32 to 0.69)	0.47	0.08 (-0.45 to 0.61)	0.78	-0.04 (-0.44 to 0.37)	0.86
Inhaled steroids + LABA	-0.11 (-0.66 to 0.45)	0.70	-0.32 (-0.90 to 0.27)	0.28	-0.25 (-0.70 to 0.20)	0.27
Medication adherence	-0.02 (-0.05 to 0.02)	0.26	-0.03 (-0.06 to 0.01)	0.17	-0.00 (-0.03 to 0.02)	0.87

ACT = Asthma Control Test; SABA = Short Acting Betamimetics; LABA = Long Acting Betamimetics; URTI = Upper Respiratory Tract Infection; LRTI = Lower Respiratory Tract Infection; *MARS score <20

Chapter 5

Asthma does not predict a food challenge outcome

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Abstract

Introduction

In children with food related symptoms a food challenge is considered as the gold standard to diagnose allergy. If food allergy could be predicted by patient history and/or diagnostic tests, the number of time consuming and sometimes risky food challenges could be decreased. We aimed to determine whether questionnaire and test based characteristics, and specifically asthma co-morbidity, predict the food challenge outcome (FCO) in children referred to a tertiary centre for the evaluation of food related symptoms.

Methods

Pre-challenge standardized questionnaires, skin prick tests (SPT) and specific IgE-levels (sIgE) were obtained in patients that underwent a food challenge in our hospital in 2009. Characteristics of patients with positive and negative FCO's were compared and uni- and multivariable associations between predictors and the FCO were calculated. Based on the multivariate model a risk score was developed to predict the FCO.

Results

129 challenges were analyzed, 41.9% had a positive outcome. Median age of both groups was 4.9 years (range 2.8 to 8.3). Patients with a positive FCO reacted faster with symptoms after allergen ingestion, and had higher sIgE levels compared to children with a negative FCO. A clinical risk score was developed based on the index food, 'time between allergen ingestion and complaints' and sIgE-levels (range 0 to 10). The discriminative capacity of this model (AUC) was excellent (0.90). The very high- and low-risk groups (24.8% of patients) were both predicted excellently without misclassification.

Conclusion

The presence of asthma does not predict a FCO outcome, but a positive FCO can be predicted by the index food, time between allergen ingestion and development of symptoms, and the sIgE level.

Introduction

The term food allergy (FA) is used to describe an adverse effect on ingestion of a food caused by the immune system. Food allergy rates vary by age, local diet, and many other factors, but generally its prevalence is 2-6%.[1,2] The 2008 Centres for Disease Control and Prevention report indicated an 18% increase in childhood food allergy from 1997 to 2007.

The diagnosis of FA can be suspected on a combination of history and physical examination while diagnostic tests, like skin prick test (SPT) and serum food-specific IgE (sIgE), can be helpful to differentiate between IgE mediated and non-IgE mediated complaints.[3,4] In clinical practice a variety of adverse reactions that are not of allergic nature must be considered, and more than 20% of adults and children alter their diets for perceived food allergy.[5,6] To confirm the diagnosis of food allergy, the placebo controlled food challenge is usually considered as the golden standard.[7] However, this is time consuming, has cost expenses, the risk of anaphylaxis and requires a specialized setting and personnel. An easy way to differentiate between children with a high and low suspicion of a food allergy would facilitate patient care and might reduce the number of food challenge tests in clinical practice. Literature about the predictive value of diagnostic tests for food allergy is available.[8-10] However, data on the combined predictive capacity of both patient characteristics, as atopic co-morbidity, and diagnostic tests are scarce, and very little literature is available on clinically useful risk models.[11] In this study we aimed to investigate whether asthmatic co-morbidity predicts the outcome of food challenge tests (FCO's). Furthermore, we studied other predictors of the outcome of the Food Challenge (FC).

Methods

Study population

The UMC Utrecht is a tertiary hospital providing specialized allergologic care. Children, aged 0-18 years, consulting an allergologist for a suspected food allergy receive a standardized questionnaire prior to their first visit to the outpatient department, which is filled in at home by the parents. All patients undergoing a challenge (medication or food) are registered in a database. Patients who underwent a food challenge and completed the questionnaire in 2009 were included in our study. Patients with inconclusive FCO's were excluded from analysis. All patients gave informed consent to the collection and analyzation of their anonymized data gathered during regular hospital visits for medical purposes. Because this is an analysis of data gathered in routine clinical practice, formal approvement of the ethics committee was waived.

Measurements

From the questionnaire information regarding the history of allergic reactions, co-morbidity, exposure to allergens and pollution, the family history and general well being of the patient was obtained. Based on the availability in our questionnaire and known risk factors from the literature, 21 candidate predictor variables were selected. Candidate predictor variables were patient characteristics (2 variables), the potential allergen (1), family history (1), parental reported atopic co-morbidity (independent of intake of potential allergen) (5), factors associated with intake of potential allergen (9), exposure to pets (1), and outcome of diagnostic tests (2) (table 1). Sensitisation was established by measuring specific Immunoglobulin E-level (sIgE), or by performing a Skin Prick Test (SPT) against the suspected allergen. SIgE was measured in serum, using the CAP system FEIA (Pharmacia Diagnostic, Uppsala, Sweden). A positive test result was defined as a sIgE-level above 0.35 kU/l.[10,12] A skin prick test was performed according to the EAACI-guidelines,[13] using commercially available extracts (ALK, Abelló, Nieuwegein, The Netherlands), or fresh material (in case of a fruit allergy) and compared with a negative- (glycero-saline) and a positive control (histamine HCL). Antihistamine medication was withheld for at least 72 h prior. The test was performed on the back of the child, and the resulting wheal was measured after 15 min. A positive SPT was defined as a wheel ≥ 3 mm larger then the negative control.[9]

All peanut, hazelnut and cow's milk challenges were performed as Double-Blind Placebo Controlled Food Challenge (DBPCFC) according the EAACI guidelines and the local protocol.[14,15] Challenges with other foods were performed as open challenges. Indications to perform a food challenge are sensitization to the allergen confirmed by a SPT or sIgE, positive history of an allergic reaction to a specific allergen, or currently avoiding eating this potential allergen. A FCO was considered positive and terminated when at least one of the following occurred: (1) objective symptoms indicative of an allergic reaction (as urticaria, facial swelling, rhinoconjunctivitis, vomiting, diarrhea, dyspnea, bronchoconstriction, and hypotension) or (2) subjective complaints (abdominal pain, nausea) after at least three subsequent doses. The most severe symptoms were scored based on the Sampson-score by the specialist to measure severity.[16] A FCO was considered inconclusive when the criteria for a positive FCO could not be met, or when the test material was refused. Subsequently, patients were observed for 2 hours in case of a negative outcome, and 4 hours in case of a positive outcome. One day after the challenge a phone call was made to evaluate whether late symptoms developed. A positive FCO was considered as the gold standard for the diagnosis of food allergy in this study. Patients with a previous anaphylaxis, that were challenged to test the severity of the current reaction, were not included in this analysis (n=6).

Statistical analysis

The predictors 'amount of ingested allergen provoking complaints', 'time lag between

ingestion and development of symptoms', the challenge food, and the sIgE level were defined as a categorical variable. All remaining variables were dichotomized.
Univariable associations between candidate predictor variables and the outcome of a positive food challenge were investigated by univariable logistic regression. In the eligible study population the overall proportion of missing data on candidate predictor variables was 9.6%. In a standard complete case analysis, subjects with 1 or more missing values are excluded from analysis. To avoid bias that might result from a complete case analysis our missing data was imputed by using multiple imputations.[17] Predictors that were univariably associated with the outcome (with a p-value <0.15), and unrelated to clinical treatment, were included in stepwise backward fashion selection in a multivariable logistic regression model to evaluate their independent value (p-value <0.05) in the prediction of a positive outcome of a food challenge. Reliability (of goodness of fit) was estimated using the Hosmer-Lemeshow test. Subsequently, the discriminative capacity to differentiate between a patient with and without a positive FCO was estimated using the area under the receiver operating characteristics curve (AUC). An AUC of 0.9 and above is considered excellent for a prognostic model.[18] Internal validation of the final model was performed by using the bootstrap resampling technique. The calculated regression coefficients were equally modified to create a simple risk score for use in clinical practice. Multivariable regression analyses, imputation and model validation were performed with the statistical program PASW Statistics 18 (version 18.0.0, SPSS Inc., 2009, Chicago USA).

Results

In 2009 a total of 129 children underwent food challenge and had a valuable questionnaire (figure 1). Missing data (9.6%) in the questionnaires was imputed. Median age was 4.9 years and food challenges were more often performed in boys (83 versus 49 girls, NS). Of all 129 food challenges 54 challenges (41.9%) had a positive outcome. Most frequently performed food challenges were peanut (23.5%), cow's milk (25.0%), egg (19.7%) and hazelnut (12.9%). Table 1 shows the characteristics of all patients, and the characteristics of patients with a positive FCO.

Univariable analysis

None of the atopic diseases, including asthma, were significantly associated with the FCO. However, several other variables were. Two questionnaire variables were positively associated with a positive FCO: symptoms developing within 5 minutes after ingestion of the allergen (p=0.044), and complaints provoked by pets (p=0.025). The index foods cow's milk (p=0.05), egg and nuts (both p=0.004) were also strongly associated with a positive FCO. Sensitization

to an allergen as presented as a level of specific sIgE > 0.7 was strongly associated with a positive FCO (p values for different categories, see table 1). Based on the p-values and the incidence of positive FCO's in our population, 5 variables were included in the multivariate analysis (table 1).

Table 1. Characteristics of the population, and univariable relationship with a positive FCO

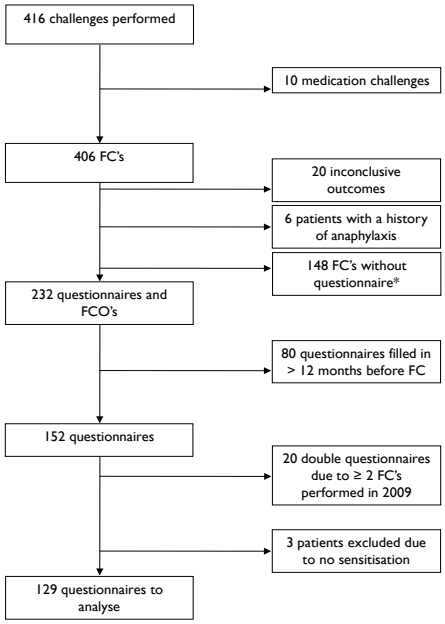
	All children (n=129) no.(%)	Positive FCO (n=54) no.(%)	OR for positive FCO	p-value
Patient characteristics				
Male sex	81 (63)	32 (60)	0.81	0.572
Age at time of the FCO (years)	4.9 (2.9-8.3)*	4.9 (3.0-7.3)*	0.956	0.325
Challenged food				
Peanut (DBPCFC)	30 (23)**	12 (22)	3.56	0.083‡
Hazelnut (DBPCFC)	16 (12)**	5 (9)	2.42	0.285
Cow's milk (DBPCFC)	27 (21)**	12 (22)	**4.27**	**0.050‡**
Egg (OFC)	26 (20)	16 (29)	**8.53**	**0.004‡**
Nuts (OFC)	9 (7)	7 (13)	**18.67**	**0.004‡**
Other (OFC)	21 (16)	3 (6)	Reference	-
Positive family history for atopic diseases	100 (78)	43 (80)	1,02	0,969
Parental reported complaints of child, independent of ingestion of potential allergen				
Eczema	108 (84)	47 (86)	1.13	0.800
Allergic rhinoconjunctivitis	45 (35)	20 (37)	1.07	0.866
Asthma	52 (40)	27 (50)	1.36	0.405
Urticaria	44 (34)	22 (41)	1.66	0.181
Allergic complaints provoked by pets	63 (49)	34 (63)	**2.31**	**0.025‡**
Parental observed complaints provoked by specific food intake				
Mouth: swelling lips/tongue, itchiness	59 (46)	31 (57)	2.18	0.143
Nose: sneezing. rhinorroea	27 (21)	11 (20)	0.87	0.835
Eye: tears. Itchiness	42 (33)	17 (31)	0.85	0.739
Skin: redness, urticaria, increase of eczema	93 (72)	39 (72)	0.94	0.917
GIT: stomach-ache, diarroea, vomiting	58 (45)	23 (42)	0.79	0.604
Pulmonary: coughing, dyspnoea	38 (29)	15 (28)	0.88	0.775
Cardiovascular: hypotension, fainting	6 (5)	18 (33)	0.59	0.525
Time within reaction is provoked by ingestion				
<5 min	67 (52)	32 (59)	**7.34**	**0.044‡**
5-60 min	49 (38)	21 (39)	6.29	0.089‡
>60 min	14 (11)	2 (4)	Reference	-
Smallest amount provoking a reaction				
Tip of knife	81 (63)	37 (69)	0.00	0.754
More than a tip of knife	47 (36)	17 (31)	0.00	0.867

Table 1. Continued

	All children (n=129) no.(%)	Positive FCO (n=54) no.(%)	OR for positive FCO	p-value
Pets ownership				
Cat	27 (21)	7 (13)	0.40	0.059
Dog	19 (15)	6 (11)	0.59	0.327
Horse	9 (7)	3 (6)	0.69	0.623
Rabbit	13 (10)	4 (7)	0.59	0.413
Diagnostic test results				
Positive SPT	88 (68)	43 (80)	2.49	0.064‡
Specific IgE-level <0.35	26 (20)	2 (4)	Reference	-
0.35-0.7	10 (8)	1 (2)	1.28	0.848
0.7-3.5	34 (26)	16 (30)	**10.24**	**0.004‡**
3.5-17.5	30 (23)	14 (26)	**10.42**	**0.005‡**
17.5-50	16 (12)	10 (19)	**17.13**	**0.002‡**
50-100	13 (10)	12 (22)	**141.64**	**0.000‡**

DBPCFC, double-blind placebo controlled food challenge; FC, food challenge; FCO, food challenge outcome; OFC, Oral Food Challenge; OR, odds ratio; GIT, Gastro Intestinal Tract; SPT, skin prick test. Bold data are significantly related to the outcome, p<0,05; *Data are presented as median ± interquartile range; ‡Included in the multivariable logistic regression model.

Figure 1. Selection of patients and questionnaires for analysis



*These patients are seen by general paediatricians or subspecalists other than allergologists and therefore not sent a questionnaire before their outpatient department visit.

Predictive model

After stepwise multivariable analysis of the selected variables independent predictors were (1) the index food, (2) sIgE level and (3) time lag between food ingestion and development of allergic response. To develop a predictive model, the regression coefficients were calculated, and points were assigned to each of those three variables. Subsequently, for every child a score, ranging from 0 to 10, was calculated based on the equation shown below table 2. The discriminative power of this model was 0.90, which is excellent for a prognostic model, defined as an AUC of 0.9 and above.

Table 2. Independent predictors of a positive food challenge outcome

Predictor variable	OR*	Beta	Points
Allergic reaction:			
Acute (within 5 minutes)	3.08	1.126	1
Subacute (5-60 minutes)	1.88	0.632	0.5
Late (>60 minutes)	Reference	0	0
Specific IgE-level (kU/l)			
<0.35	Reference	0	0
0.35-0.7	3.27	1.186	1
0.7-3.5	16.04	2.775	2.5
3.5-17.5	32.84	3.491	3
17.5-50	125.90	4.835	4.5
50-100	2146.09	7.671	7
Tested food			
Peanut	7.27	1.985	2
Hazelnut	0.87	-0.135	0
Cow's milk	20.1	3.001	2.5
Egg	33.6	3.515	3
Nuts	291.6	5.676	5
Other	Reference	0	0
ROC area (95% CI)	0.904 (0.85-0.96)		0.900 (0.85-0.95)
Hosmer-Lemeshow**	5.88 (p=0.634)		

OR = Odds Ratio; *adjusted for overoptimism by bootstrapping;**Chi-square and significance; ROC = Receiver operator characteristics.

Individual score = 0 × Complaints after 60 minutes (yes =1, no =0) + 0.5 × Subacute complaints (yes =1, no =0) + 1 × Acute complaints (yes =1, no =0) + 0 × sIgE-level below 0.35 (yes =1, no =0) + 1 × sIgE-level between 0.35-0.7 (yes =1, no =0) + 2.5 × sIgE-level between 0.7-3.5 (yes =1, no =0)+ 3 × sIgE-level between 3.5-17 (yes =1, no =0) + 4.5 × sIgE-level between 17.5-50 (yes =1, no =0) + 7 × sIgE-level between 50-100 (yes =1, no =0)+ 2 × SFA Peanut (yes =1, no =0) + 0 × SFA Hazelnut (yes =1, no =0) +2.5 × SFA Cow's milk (yes =1, no =0) + 3 × SFA Egg (yes =1, no =0) + 5 × SFA Nuts (yes =1, no =0).

The prediction scores and the corresponding numbers of positive and negative FC outcomes are shown in figure 2. Figure 3 shows the test characteristics at different cut off values. The very high- and low-risk groups, with scores ≥9 and ≤3 respectively (n=9 and n=23 respectively, see figure 2) are both predicted excellent without any misclassification.

Figure 2. The distribution of positive and negative FCO's by prediction score (imputed data)

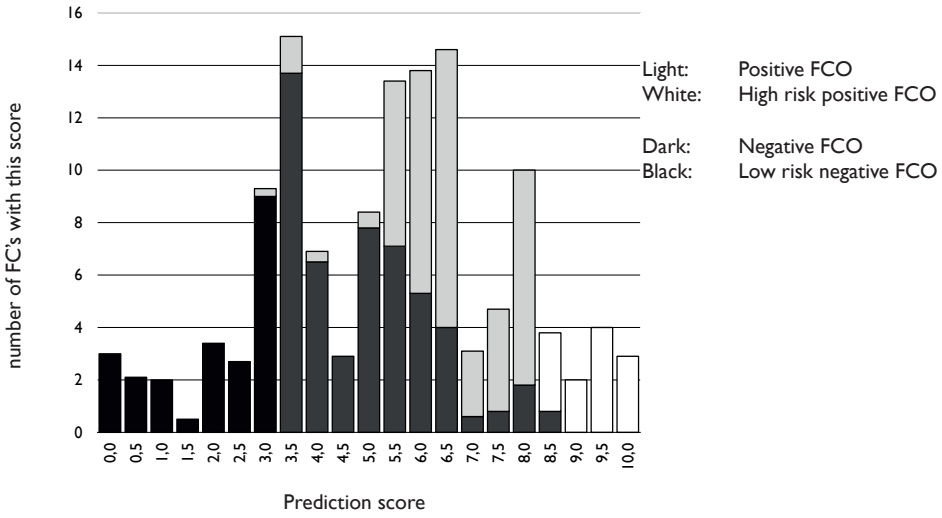
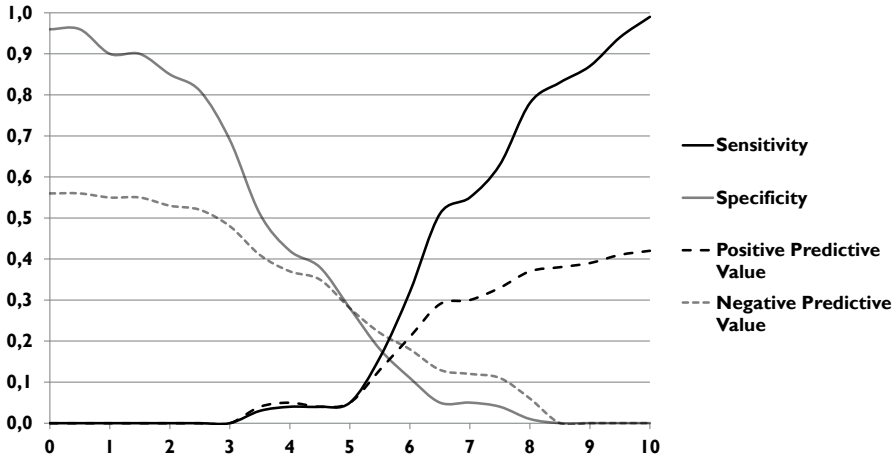


Figure 3. Test characteristics at various cutoff points



Therefore, extrapolating from the current sample, the total number of food challenges could be decreased with 24.8% when those two patient categories would not be challenged. If the scores between 3.5-5 (n=33) would be added to the low risk-group to predict the FCO,

96.9% (63 out of 65) of the patients within the high- and adjusted low-risk group would be predicted adequately. The total number of challenges could then be decreased with 50.4%, when accepting this misclassification of 3.1%. Prediction for the intermediate group remains difficult.

Discussion

In this study we showed that in a group of hospital patients the presence of asthma, or other atopic co-morbidity, did not predict the FCO. However, a short time lag between food ingestion and allergic response together with a positive sIgE-level and the index food can acceptably predict a positive FCO. In individual patients a sure prediction can be reached in 24.0%.

Our findings, that increasingly higher concentration of food-specific IgE antibodies is correlated with an increasing risk for a clinical reaction are consistent with literature.[6,19] There are a number of reports about predictive values of diagnostic tests for the outcome of food challenges in children.[20-22] Food-specific IgE antibody levels, with cut-off values with a PPV >95% have been defined for different foods.[7,23] However, those values may not be applicable in all settings because of methodological differences in challenge protocols between hospitals and differences in patient populations (age, nuances in diets).[24] We have also studied questionnaire based factors, and combined the independent risk factors with the outcome of the FC, resulting in a simple prediction rule for daily clinical use.

There are some limitations that should be considered when interpreting the results. Firstly the diagnosis food allergy was made based on the questionnaire, the level of sensitisation, and the food challenge. In our setting not all challenges are performed in a double-blind, placebo controlled (DBPC) manner. In the high-risk group 2 out of 9 FC's were not performed in a double-blind manner. Open challenges may have false positive results, as shown in cow's milk allergy studies ranging from 50-68% depending on the setting where the OFC's are performed.[4,25] This may have overestimated the total correct predicted percentage of patients to some degree. However, this effect might be neutralized in our study, because the size of the low-risk patient group may possibly have been larger if all FC's would have been performed in a DBPC manner.
Secondly, the retrospective design of our study has resulted in a number of missing values, which can lead to considerable loss of power in a multivariable analysis. We therefore imputed missing values, which we believe lead to unbiased complete results.[26]
Thirdly, in this study we did a proper internal validation of the model. However, as in every study with regard to prediction models, the model asks for additional external validation

and, of course, the use of the model should be limited to the tertiary clinical setting.

Our model consists of three factors, namely the index food, the time gap between ingestion and the development of symptoms, and the level of sIgE. Scarce literature is available about the exact time within symptoms develop after ingestion of food in patients with an IgE-mediated food allergy. Generally it is assumed that allergic reactions mediated by specific IgE antibodies are typically developed rapidly, usually within minutes.[27] However, they may also be delayed by up to an hour and rarely by up to a few hours.[28] Our study shows that rapid onset symptoms, developing within 5 minutes after ingestion, are associated with a higher risk on a positive FC outcome. This may be partially explained by the high prevalence (72.5%) of IgE-mediated cutaneous reactions in our population, but also other organ systems may respond with IgE mediated allergic symptoms within minutes. Late complaints are more likely to be caused by another cause than food allergy.[28] In our population a positive SPT was not an independent predictor for a positive FCO, and was therefore not included in the prediction model. There is literature that shows that in skin testing, wheal diameters greater than 7 or 8 mm are highly predictive of clinical allergy to peanut, cow's milk or egg allergy.[33,34] In our study the SPT result was dichotomized in positive or negative. This might have negatively influenced the predictive capacity of the SPT in our population. However, a recent study shows that also a dichotomized SPT results does significantly contribute to the accuracy in predicting a FCO.[11] Age, which was an independent predictor in that same study, was not an independent predictor in our model. This may be explained by the age-difference between the two cohorts (mean age difference 1-3 years). We have described several variables that were significantly related to a positive food challenge outcome. Those variables depend on the availability in our dataset, which was based on a questionnaire and diagnostic test results. This might have resulted in a difference in variables in our model, compared to previous literature. Also the accuracy of filling in a (not previously validated) questionnaire might have led to differences, as the history of symptoms, which were not related to the FCO in our cohort. Many children in our study had multiple sensitisations to food allergens, and had complaints to more than one food. Those symptoms, for different foods, were marked in one table. Symptoms were classified according to the Sampson criteria. However, filling in this large table might still have led to more inaccuracy then specifically asking parent or child for the symptoms provoked by ingestion of an allergen. A 100% correct prediction of a FCO was possible in 24.8%. We do realize that in clinical setting food challenges are also used to reject a diagnosis. Therefore, if non-specific symptoms do develop in the low-risk group after reintroduction at home, preferably a DBPCFC can be performed to prevent unnecessary restriction of the diet. In high-risk patients it is advisable to periodically check the level of sIgE, to assess if the risk of the patient to respond positive to a FC has decreased (based

on the risk-score and literature).[6] If this is the case, a FC may be useful to assess whether restriction of the diet is still necessary. If in clinical practice the prediction rule would be used with less strict criteria, cut-off values of ≤5 and ≥9 can be used. In patients with low scores the FC might be postponed or skipped, because the risk on an unexpected (positive) outcome is only 3.1%. Whether our prediction rule is a useful rule in clinical decision-making, internal and external validation has to show. Future research should be aimed to determine prediction rules that are useful in primary and secondary healthcare institutions.

Food challenges do often have negative outcomes, in our population in 58.1%. The presence of asthma does not predict a FCO outcome; however, a positive FCO outcome can be well predicted by using a rule, consisting of a risk score based on three variables: the index food, the time gap between ingestion and the development of symptoms, and the sIgE-level, with an AUC of 0.90. Using this rule as a clinical guideline may decrease the number of food challenges with 24.8% with a 100% certainty in a tertiary-centre setting. Or, when accepting a proportion of 3.1% wrongly classified, with 50.4%. However, in the majority of patients (54%) a food challenge remains the golden standard to confirm or reject the diagnosis of food allergy.

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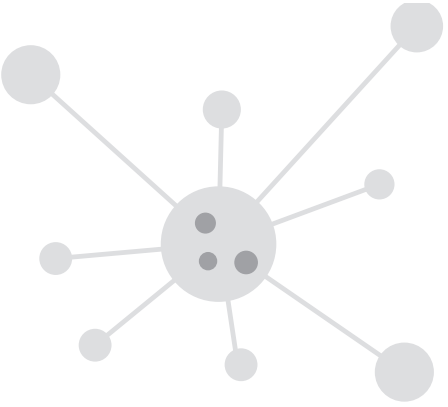

Part 2

The relation between RSV infection, lung function and asthma development

Chapter 6

Decreased lung function precedes severe RSV infection and post-RSV wheeze in term infants

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Abstract

Introduction

It is unknown why RSV causes mild disease in some children, and severe disease, requiring hospitalization, in others. We aimed to assess whether diminished pre-morbid lung function in healthy term infants predisposes to hospitalization during RSV bronchiolitis, and to post-RSV wheeze.

Methods

In a prospective birth cohort study of unselected term healthy children, neonatal lung function measurements were performed before the age of 2 months (n=2133). From birth through the first year of life, respiratory symptoms were kept in a diary, and general practitioner consultations and hospitalizations were documented. In a subgroup (n=417) repeated nose and throat swabs were collected for polymerase chain reaction to detect RSV infections.

Results

Median neonatal respiratory system compliance (Crs) was significantly lower (41.2 versus 47.4 ml/kPa, p=0.03) and resistance (Rrs) was higher (8.2 versus 6.3 kPa/l/s, p=0.10) in hospitalized RSV patients (n=18), compared to non-hospitalized RSV positive infants (n=84). Every 10 ml/kPa increase in Crs was associated with 55% less post-RSV wheeze (OR 0.56 (95% CI 0.35-0.90), and each kPa/l/s increase in Rrs was associated with 42% more post-RSV wheeze, only marginally explained by pre-RSV wheeze or severity of the RSV disease.

Conclusion

This unselected birth cohort study shows for the first time that decreased lung function at birth predisposes to severe RSV disease, and to post-RSV wheeze.

Introduction

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) in children in the first year of life,[1] and the most frequent cause for hospitalization in infancy.[2] By 2 years of age almost all children have been infected with RSV,[3] however, mechanisms underlying the variability of the severity of RSV infections are unclear. Several risk factors, including premature birth,[1,4] have been identified, however, the largest number of RSV infections occur in otherwise healthy infants without any known risk factors. Lower levels of lung function shortly after birth are associated with the occurrence of respiratory illness during the first year of life.[5–8] Stein et al. found that school age children who had suffered from RSV lower respiratory tract infection before the age of 3 years had lower levels of lung function than children without such history. Based on that finding they hypothesized that RSV lower respiratory tract illnesses might be associated with pre-existent lower lung function.[9] The latter association has been found in prematurely born infants,[10] and in a high risk population,[11] however, these results have never been studied in term infants. To our knowledge, no prospective study has assessed the association between neonatal lung function and subsequent RSV infection severity and post-RSV wheeze in term infants. We questioned whether diminished neonatal lung function is associated with subsequently increased severity of RSV infection. It was recently shown that palivizumab treatment for RSV prevention in otherwise healthy preterm infants did reduce recurrent wheeze in the first year of life.[12] This implies that RSV infection plays a causal role in post-infection recurrent wheeze. It does not preclude the possibility that other factors predispose children for both the severity of RSV infection and post-RSV wheeze. Therefore, our second question was whether neonatal lung function is associated with the presence of post-RSV wheeze. We conducted a community-based birth cohort study, investigating the role of neonatal lung function on the severity of RSV infection and on post-RSV wheeze in the first year of life.

Methods

Study population

All infants participated in the Wheezing Illnesses Study Leidsche Rijn (WHISTLER), an ongoing population-based, prospective birth cohort study on determinants of wheezing illnesses in children,[13] which started in December 2001. Exclusion criteria are gestational age <36 weeks, major congenital abnormalities and neonatal respiratory disease. Information about pre- and post natal risk factors and about the health status of the parents was obtained by questionnaires. The medical ethical committee of the University Medical Center Utrecht

approved the study (project approval number 01/176) and all parents gave written informed consent.

Lung function measurement and respiratory symptoms

From our cohort, we selected all children who had a successful lung function measurement shortly after birth. Lung function was performed in healthy neonates before the age of 2 months during natural sleep. Lung function was assessed from measurement of passive respiratory mechanics (resistance (Rrs) and compliance (Crs) of the total respiratory system) using the single occlusion technique (SOT), Lung function measurements were performed in the health center in the Leidsche Rijn district where all children lived, consistently using the same device on all participants. Further details about lung function measurement were previously reported.[14] In all children of the birth cohort respiratory symptoms in the first year of life were documented on a daily basis, using diaries completed by the parents.

RSV positivity

In two periods of the cohort study (2003-2005 and 2006-2007) we collected respiratory virus samples on a regular basis in children below the first year of age.

In the first period respiratory virus samples were collected on the second day of each episode with wheeze or cough (n=311), with the aim to assess whether neonatal lung function predisposes to wheezing during viral respiratory tract infections.[15] In the second period samples were collected at the start of every month regardless of respiratory symptoms (n=166), with the aim to assess whether neonatal lung function predisposes to wheezing during viral respiratory tract infections.[16] Viral samples were collected by the parents with a cotton-tipped swab from both the nose and posterior oropharynx. Both swabs were collected into a single vial containing GLY medium with 0.1 mg/ml pimaricine as viral transport medium and sent to our laboratory via regular mail. Samples were stored at -20°C until analysis.[17] RSV positivity was defined as having a RSV PCR-positive swab in the first year of life. From the 477 children that were sampled in both study periods, 417 had a successful lung function test. From these 417 children, 84 children were positive for RSV but did not require hospitalization (figure 1).

Outcome variable: RSV hospitalization

We selected all infants from the complete cohort with a successful lung function measurement (n=2133) that had been hospitalized for bronchiolitis at any moment during the first year of life. Twenty-six infants were hospitalized for a viral bronchiolitis. In 8 of those 26 patients, the immunofluorescence test or PCR was negative for RSV, while the remaining 18 patients had a positive test result. Other reasons for hospital admission in the remaining patients

were pneumonia (n=1), pertussis (n=1), bronchial hyperreactivity (n=3), and laryngomalacia/ bronchitis (n=3). Eighteen patients, with a proven RSV bronchiolitis were selected for further analyses (Figure 1).

Post RSV wheeze

Days with respiratory symptoms were obtained from the diaries, which were filled in during the first year of life. The total number of days with wheeze was calculated before and after the occurrence of the RSV infection up to age 1, with exclusion of the month in which the RSV infection occurred. Post RSV wheeze was expressed as the mean number of days with wheeze per month following the documented RSV infection.

Analysis

Missing values for birth length (9.1%), birth weight (0.2%) and weight and length at measurement (5.5% and 7.0%) were imputed by their mean values, as these values did not differ from multiple imputations. For our first research question, we selected the RSV positive infants, both hospitalized and non-hospitalized. Absolute (unadjusted) values of Crs and Rrs were compared using the Mann Whitney U test. We used logistic regression analysis in order to explore the relationship between neonatal lung function and the severity of RSV (defined as hospitalization, yes or no). Each factor was added separately to the model to investigate its influence on the association. We made a distinction between possible confounding factors, (sex, season of birth, siblings, breast feeding, daycare, maternal allergy, ethnicity, educational level and study year, as strains of RSV may differ in virulence over years[18–20]) and factors that may be in the causal chain, as birth weight and maternal smoking.[21] We studied the effect of those intermediates in order to understand whether they explain the association between neonatal lung function and RSV hospitalization for preventive purposes. Possible confounders, affecting the OR with 5% or more, were added to the multivariable model for both Crs and Rrs. Hereafter, for our second research question the association between lung function and the development of post-RSV wheeze was investigated. Again, each possible confounding factor was added separately to the model to investigate its influence on the association. In addition to the prior mentioned factors, we also added the intermediates pre-RSV wheeze and RSV bronchiolitis hospitalization to the model separately, to study whether lung function was associated with post-RSV wheeze, independent of the presence of pre-RSV wheeze and RSV bronchiolitis hospitalization. These factors may explain any association between neonatal lung function and post-RSV wheeze. Poisson regression was used to analyze the difference in number of days with wheeze between hospitalized patients and non-hospitalized RSV positive children). Results are presented as odds ratios (OR), 95% confidence intervals (CI) and p-values. Statistical analysis was performed using IBM SPSS statistics version 20.0 (Armonk, New York, USA).

Results

The complete cohort consisted of 2689 infants, in which in 2133 infants a successful lung function measurement was obtained (79.3%). Of the complete cohort with a successful lung function measurement, 18 infants (0.84%) were hospitalized for RSV bronchiolitis (figure 1). Of the infants with a successful lung function measurement 417 (19.5%) infants were sampled for viral infections during one of the 2 sampling periods. In 84 infants (20.1%) a positive RSV sample was detected; 52 (61.9%) of the infants were sampled during an episode with wheeze or cough, and 32 (38.1) were sampled randomly at the start of every month. Of those, 22 (68.8%) infants did have respiratory symptoms at the time of sampling. Baseline characteristics for the 3 groups are presented in table 1. The virus sampling group was representative for the complete study group (data not shown).

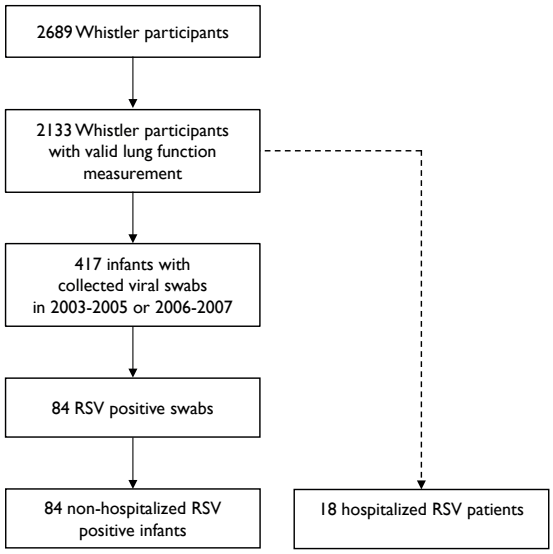
Infants with and without a successful lung function were compared. Except for a higher birth weight in the group without successful lung function, no significant differences between groups were found (supplementary table 1). Within the cohort with swabs we did not find differences between children with and without a successful lung function measurement (data not shown).

Table 1. General characteristics of the study population.

	Total cohort (n = 2133)	Hospitalized RSV patients (n=18)	Non hospitalized RSV positive infants (n=84)	p-value*
Sex (male)	1033 (48.4)	10 (55.6)	48 (57.1)	0.903
Birth weight (grams)	3519 (509)	3538 (620)	3596 (529)	0.688
Birth length (cm)	51 (49-52	51 (49-53)	51 (50-52)	0.263
Median gestational age (weeks, IQR)	39.9 (39.0-40.9)	40.2 (39.1-40.5)	40.0 (39.0-41.0)	0.696
Age at bronchiolitis (weeks, IQR)	NA	34 (22-68)	30 (21.8-39.0)	0.210
Siblings (y)	1133 (53.9)	10 (58.8)	43 (51.8)	0.602
Breastfed in first 3 months of life (y)	1395 (70.0)	13 (76.5)	63 (75.0)	0.899
Daycare in first 3 months of life (y)	895 (44.8)	11 (64.7)	44 (52.4)	0.357
Maternal allergy (y)	147 (8.2)	1 (5.9)	3 (3.8)	0.548
Maternal smoking during pregnancy	130 (6.1)	1 (5.6)	3 (3.6)	0.546
Western mother	1852 (79.7)	15 (88.2)	66 (82.5)	0.568
High educated mother (y)	1221 (68.5)	15 (88.2)	74 (92.5)	0.566

Data are n (%), or mean (SD) unless stated otherwise. *p-value for differences between the two RSV groups; y = yes.

Figure 1. Flow chart of the infants included in this study. In total, 102 infants with a positive RSV test and valid neonatal lung function were included in the analysis.



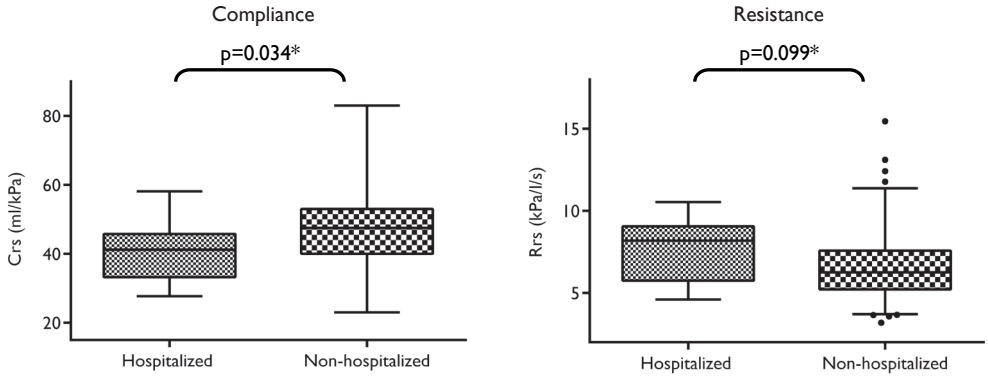
Neonatal lung function in RSV positive children

Children who were hospitalized for RSV bronchiolitis had significantly lower median compliance (41.2 (IQR 33.2-45.8) versus 47.4 ml/kPa (IQR 40.1-52.6), p=0.03) and higher resistance (8.2 (IQR 5.8-9.1) versus 6.3 kPa/l/s (IQR 5.2-7.6), p=0.10) of the respiratory system (figure 2). Table 2 shows the ORs for the association between lung function and RSV hospitalization. In the univariable model, each 10 ml/kPa increase in Crs was associated with 45% lower odds for hospitalization. After adjustment for potential confounders this association strengthened: each 10 ml/kPa increase in Crs was associated with 66% lower odds for hospitalization. Adding intermediate factors to the model slightly weakened the association between Crs and RSV hospitalization, but it remained statistically significant. Each kPa/l/s increase in Rrs was associated with 20% higher odds of RSV hospitalization. After adjustment for study year, this association attenuated (OR 1.30 (95% CI 1.02-1.66).

Neonatal lung function and post-RSV wheeze

Data about days with wheeze were available in twelve hospitalized infants and seventy-eight non-hospitalized infants. As diaries were filled in up to the age of twelve months, this information was not available for four infants that were hospitalized at or after the age of one, and five non-hospitalized infant with a RSV positive swab at the age of twelve months. In two hospitalized infants, and one non-hospitalized infants this information was missing. No differences were found between children who were and were not included in the analysis (data not shown).

Figure 2. Crude median compliance and resistance of the respiratory system for 18 hospitalized RSV patients and 84 non-hospitalized RSV positive infants.



*p-values based on logistic regression analysis

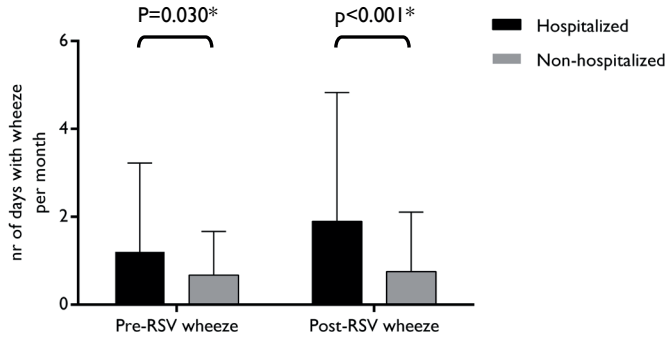
Table 2. Association between lung function and RSV hospitalization in RSV positive infants (n=102).

	Crs (10 ml/kPa)			Rrs (kPa/l/s)		
RSV hospitalization	OR	95% CI	p-value	OR	95% CI	p-value
Crude	0.55	0.31-0.96	0.03	1.20	0.97-1.49	0.10
Adjusted for potential confounders						
Sex (male)	0.55	0.31-0.96	0.04	1.20	0.97-1.49	0.10
Birth length (cm)	0.56	0.31-1.02	0.06	1.18	0.94-1.47	0.15
Gestational age (weeks)	0.54	0.30-0.96	0.04	1.20	0.96-1.49	0.11
Season of birth April to September	0.53	0.30-0.94	0.03	1.20	0.97-1.49	0.10
Siblings (y)	**0.60**	0.34-1.05	0.07	1.17	0.93-1.46	0.18
Breastfed in first 3 months of life (y)	**0.49**	0.27-0.89	0.02	1.18	0.95-1.47	0.14
Daycare in first 3 months of life (y)	**0.45**	0.24-0.84	0.01	1.22	0.97-1.53	0.09
Maternal allergy (y)	0.55	0.31-0.97	0.04	1.19	0.95-1.48	0.13
Western mother (y)	0.53	0.30-0.96	0.04	1.19	0.95-1.49	0.13
High educated mother (y)	0.55	0.31-0.98	0.04	1.18	0.95-1.47	0.14
Study year	**0.50**	0.27-0.92	0.03	**1.30**	1.02-1.66	0.03
Adjusted for intermediates						
Maternal smoking during pregnancy (y)	0.55	0.31-0.97	0.04	1.20	0.97-1.49	0.10
Birth weight (grams)	**0.50**	0.26-0.94	0.03	1.20	0.96-1.50	0.11
Adjusted multivariable model	0.34*	0.15-0.73	<0.01	1.30**	1.02-1.66	0.03

OR = Odds Ratio; CI = Confidence Interval; Crs = Compliance of respiratory system; Rrs = Resistance of the respiratory system; y = yes; *Adjusted for siblings, breastfeeding, daycare and study year; **Adjusted for study year; Bold numbers indicate OR's that are affected with 5% by adjustment.

A total of 34 out of 90 children experienced post-RSV wheeze during one or more days: 10/12 (83.3%) hospitalized RSV patients versus 24/78 (30.8%) RSV positive non-hospitalized infants, p<0.001). In the children where post-RSV was present (n=34), the number of days with post RSV wheeze was significantly higher in hospitalized RSV patients (n=10, median nr of days per month 1.9 (IQR 0.4 to 4.8) versus 0.8 (IQR 0.4 to 2.1), p<0.001) compared to non-hospitalized infants (n=24).
Also prior to the RSV infection, hospitalized infants did experience more days with wheeze per month compared to non-hospitalized infants (figure 3).

Figure 3. Median number of days with wheeze per month pre-RSV and post-RSV in 10 hospitalized RSV patients and 24 non-hospitalized RSV positive children.



Median number of days with wheeze per month (range); *p-values are based on Poisson regression analyses for the total number of days with wheeze pre- or post-RSV in relation to the severity of the RSV infection, adjusted for the number of months before and after the RSV infection.

Table 3 shows the association between lung function and the presence of any days with post-RSV wheeze. Each 10 ml/kPa increase in Crs was associated with 44% lower odds for post-RSV wheeze. After adjustment for potential confounders this association strengthened: each 10 ml/kPa increase in Crs was associated with 55% lower odds for post-RSV wheeze. Each kPa/l/s increase in Rrs was associated with 34% higher odds of post-RSV wheeze. After adjustment for study year, this association attenuated (OR 1.42 (95% CI 1.11-1.82). Adding pre-RSV wheeze to the model did slightly weaken the association between both Crs and Rrs and post-RSV wheeze. Similar results were seen after addition of RSV hospitalization to the model.

Table 3. Association between lung function and the presence of post RSV wheeze in RSV positive infants (n=90).

	Crs (10 ml/kPa)			Rrs (kPa/l/s)		
RSV hospitalization	OR	95% CI	p-value	OR	95% CI	p-value
Crude	0.56	0.35-0.90	0.02	1.34	1.07-1.68	0.01
Adjusted for potential confounders						
Sex (male)	0.55	0.34-0.89	0.02	1.35	1.07-1.69	0.01
Birth length (cm)	0.58	0.35-0.97	0.04	1.33	1.05-1.67	0.02
Gestational age (weeks)	0.57	0.35-0.93	0.02	1.33	1.05-1.67	0.02
Season of birth April to September	0.57	0.35-0.93	0.02	1.34	1.07-1.69	0.01
Siblings (y)	0.56	0.35-0.90	0.02	1.33	1.06-1.67	0.01
Breastfed in first 3 months of life (y)	0.54	0.33-0.88	0.01	1.36	1.07-1.71	0.01
Daycare in first 3 months of life (y)	0.57	0.36-0.91	0.02	1.33	1.06-1.67	0.01
Maternal allergy (y)	0.53	0.33-0.87	0.01	1.30	1.03-1.63	0.03
Western mother (y)	0.52	0.32-0.85	0.01	1.34	1.06-1.68	0.01
High educated mother (y)	0.54	0.33-0.88	0.02	1.32	1.05-1.66	0.02
Study year	**0.52**	0.31-0.85	0.01	**1.42**	1.11-1.82	0.01
Adjusted for intermediates						
Maternal smoking during pregnancy (y)	0.56	0.35-0.90	0.02	1.37	1.08-1.73	0.01
Birth weight (grams)	**0.59**	0.35-0.98	0.04	1.32	1.05-1.66	0.02
Pre-RSV wheeze (y)	**0.63**	0.38-1.04	0.07	1.31	1.03-1.66	0.03
RSV bronchiolitis hospitalization (y)	0.66	0.41-1.07	0.09	1.30	1.03-1.63	0.03
Adjusted multivariable model	0.45*	0.26-0.77	<0.01	1.42*	1.11-1.82	<0.01

OR = Odds Ratio; CI = Confidence Interval; Crs = Compliance of respiratory system; Rrs = Resistance of the respiratory system; y = yes. *Adjusted for study year; Bold numbers indicate OR's that are affected with 5% by adjustment.

Discussion

This study showed that in term infants impaired neonatal lung function precedes a severe course of RSV infection. There was no significant association between resistance of the respiratory system and hospitalization, except after correction for study year. However, increased resistance of the respiratory system and lower compliance of the respiratory system were both associated with post-RSV wheeze, independent of the severity of the disease and the presence of pre-RSV wheeze. Although the role of pre-morbid lung function on the severity of RSV disease was suggested in preterm and high risk infants, to our knowledge, this is the first study confirming this effect in an unselected birth cohort of

healthy term infants, which accounts for the majority of hospitalizations for RSV bronchiolitis. Several risk factors for a severe course of disease during RSV infection, including premature birth,[1, 4] have been identified. Two studies assessed the role of neonatal lung function in RSV bronchiolitis in prematurely born infants.[4, 10] Drysdale et al prospectively studied 159 premature born infants that were sampled at each episode with wheeze, cough or shortness of breath.[10] They found impaired neonatal lung function in patients that were hospitalized for a viral lower respiratory tract illness, including RSV, compared to non-hospitalized patients. Broughton et al, prospectively studied 39 premature infants and described significantly higher premorbid resistance of the respiratory system in symptomatic RSV patients compared to patients with no lower respiratory tract illness.[4] They concluded that in preterm infants abnormal airway function is associated with subsequent symptomatic RSV lower respiratory tract illness. Recently, Chawes et al., described airway hyperresponsiveness as a risk factor of acute severe bronchiolitis, including RSV bronchiolitis, in children of atopic mothers.[11]
The largest number of RSV infections occurs in otherwise healthy infants without any known risk factors. Several studies have described the association between a pre-existent decreased lung function and the development of wheezing illnesses during unspecified viral respiratory tract infections in term infants.[5, 7, 22] Until now, RSV specific data on unselected healthy children were lacking. Several prediction models for RSV hospitalization in infants have been published,[18, 23, 24] but none incorporated neonatal lung function measurements.

Both compliance and resistance of the respiratory system were associated with RSV hospitalization, for Rrs after adjustment for study year. Although the virulence of the RSV strain is not associated with neonatal lung function, we have previously shown that lung functions have improved over years in our cohort.[25] One important explanation for this phenomenom may the smoke-free legislation. Previous studies have found an association between a reduced airway caliber (reflected by V_{max}FRC or Rrs) and wheezing symptoms in the first years of life.[5,7,8,22] Our results, showing an independent association between Rrs and post-RSV wheeze are in line with these finding. Crs and Rrs possibly reflect distinct tissue properties which are differently associated with wheezing phenotypes later on in life; impaired Rrs is associated with wheezing early in childhood, and impaired Crs with phenotypes that do persist into later childhood.[26, 27] As hospitalized RSV patients have lower Crs, they are likely to be more prone to a severe course of RSV, as well as to persistent respiratory complaints up to school age. Although underlying mechanisms whereby reduced Crs leads to RSV hospitalization are unknown, it is possible that reduced Crs reflects differences in lung characteristics leading to both a severe RSV infection and childhood asthma.

Several prospective studies have described the association between RSV bronchiolitis and

the development of post-bronchiolitis wheeze.[28–30] Our data suggest that beside the severity of the RSV infection, premorbid increased resistance and decreased compliance also are independent determinants of post-RSV wheeze. Up to 40% of all children experience wheeze after an RSV infection.[31] Whether wheezing is also present in these children before the occurrence of the RSV infection is unknown. Lower neonatal lung function is associated with an increased risk of wheeze in the first years of life.[26] We have shown that the association between both Crs and Rrs and post-RSV wheeze is not dependent on the presence of pre-RSV wheeze, or the severity of the RSV infection, as the association between lung function and pre-RSV wheeze was only marginally affected by pre-bronchiolitis wheeze or by hospitalization for RSV itself. Our findings therefore provide evidence for the statement that lower lung function in school aged children that were previously hospitalized for RSV bronchiolitis, can not only be attributed to the RSV infection itself, but might at least be partially pre-existent. The Tucson birth cohort study followed the natural course of lung functions in children up until the age of 22 and showed that lower lung function is tracking over life.[32] Whether RSV adds to this lung function impairment is unknown. Future research, focusing on the prevention of RSV and long term follow up will provide more insight in this question.

The major strength of this study is the design and the techniques used. In an unselected birth cohort, lung function was performed before the second month of life, before the occurrence of any respiratory symptoms. Infants were prospectively followed up for respiratory symptoms, and swabs were collected on the second day of each episode with wheeze or cough. Due to the large size of our birth cohort, we were able to detect 18 confirmed RSV bronchiolitis patients within our cohort, and to compare these patients to non-hospitalized RSV positive infants. All RSV diagnoses were confirmed using molecular techniques.
However, some limitations need to be discussed. First, for this study we selected RSV positive infants with a successful lung function only, as lung function was the main focus of study. A successful lung function is dependent on natural sleep. The measurement was cancelled if the infant woke up before or during the measurement. Because this likely occurs randomly, it is unlikely that this resulted in bias. However, we did find a higher birth weight in the group without successful lung function; no other significant differences between groups were found (supplementary table 1). Second, for our control group, we used two different sampling cohorts within the Whistler cohort. These cohorts have been recruited in two different time periods, and were sampled in different ways (during an episode with lower respiratory symptoms, or regardless of symptoms at the beginning of the month). Correction for the study year did not effect the association between Crs and RSV hospitalization, but the association between Rrs and RSV hospitalization became stronger, and statistically significant.

We might have missed controls with upper respiratory tract infections only, or those that carried RSV along between two sample moments. Third, as the first symptoms of a RSV infection may start before detection of the virus, this may have influenced our definition of pre-RSV wheeze. We therefore have not included the days with wheeze during the month in which the RSV infection occurred in our analysis, which in our view excludes this explanation. Fourth, viral strains may have been less virulent outside the years that the controls were sampled, but in which some of the hospitalizations took place. Correction for study year did strengthen the association between both Crs and RSV hospitalization and Rrs and RSV hospitalization, and the association between Rrs and RSV hospitalization did also become statistically significant. Last, for this study we have assessed patients that were RSV positive only. We were not able to analyze single virus infections with RSV as this information was not present in the hospitalized patients. We therefore cannot exclude the possibility that other viral agents may have contributed to the severity of the infection leading to hospitalization, or leading to post-RSV wheezing.

We conclude that both decreased Crs and increased Rrs in otherwise healthy infants are risk factors to develop a severe course of RSV bronchiolitis, requiring hospitalization during RSV infection. Furthermore, decreased Crs and increased Rrs are both independent risk factors for post-RSV wheeze.

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Online supplement

Supplementary table 1. General characteristics of the total cohort, the population with and without a successful lung function measurement.

	Total cohort (n=2689)	Group with successful nLF measurement (n=2133)	Group without successful nLF measurement (n=634)	p-value*
Sex (male)	1326/2686 (50.6)	1033/2132 (48.5)	293/553 (53.0)	0.06
Birth weight (grams)	3530 (512)	3520 (510)	3565 (520)	0.05
Birth length (cm)	50.8 (2.5)	50.8 (2.5)	50.8 (2.5)	0.81
Median gestational age (weeks, IQR)	40.0 (39.0-40.9)	39.9 (39.0-40.9)	40.0 (39.0-40.9)	1.00
Median age at study date (days, IQR)	35 (28-42)	35 (28-42)	35 (28-43)	0.42
Daycare in first 3 months of life (y)	1066/2391 (44.6)	895/2000 (44.8)	171/391 (43.7)	0.71
Siblings (y)	1445/2651 (54.5)	1133/2103 (53.9)	312/548 (56.9)	0.20
Maternal asthma (y)	194/2291 (8.5)	147/1797 (8.2)	47/493 (9.5)	0.34
Maternal smoking during pregnancy (y)	163/2681(6.1)	130/2126 (6.1)	33/554 (6.0)	0.89
Breastfeeding (first 3 months of life) (y)	1676/2385 (70.3)	1395/1994 (69.9)	281/391 (71.9)	0.11
Western mother (y)	1872/2321 (79.8)	1482/1823 (81.3)	389/497 (78.3)	0.53

Data are n/N (%), or mean (SD) unless stated otherwise; IQR = Inter Quartile Range; y = yes; nLF = neonatal lung function, *for differences between the group with and without a successful lung function measurement.



Chapter 7

Lack of long-term effects of high-dose inhaled beclomethasone for Respiratory Syncytial Virus bronchiolitis: a randomized placebo-controlled trial.

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Abstract

Introduction

Previously, we showed that high-dose early initiated inhaled corticosteroids during respiratory syncytial virus bronchiolitis partially and transiently prevents subsequent recurrent wheeze. Here, we study treatment effect on respiratory outcome at age 6.

Methods

This is a 6-year follow-up report of a randomized placebo-controlled trial, in which 185 infants hospitalized for respiratory syncytial virus bronchiolitis were treated with early initiated, high-dose inhaled beclomethasone (n=86) or placebo (n = 99) for 3 months. The primary outcome was forced expiratory volume in 1 second as percentage predicted. Secondary outcomes were bronchial hyperresponsiveness, physician-diagnosed asthma, hay fever and eczema. Possible toxicity was assessed by linear growth measurements.

Results

At age 6, no significant differences were found in mean forced expiratory volume in 1 second percentage predicted between beclomethasone-treated and placebo-treated patients (91.4 vs. 93.4, mean difference 2.05 (95% confidence interval: -1.98 to 6.08). The proportion of bronchial hyperresponsiveness, physician-diagnosed asthma, parent reported hay fever and eczema was comparable between groups. There were no differences in linear growth.

Conclusion

Early initiated prolonged treatment with high-dose inhaled beclomethasone during hospitalization for respiratory syncytial virus infection during infancy did not improve the long-term respiratory outcome, but was safe.

Introduction

Respiratory syncytial virus (RSV) infection is the most common cause of severe bronchiolitis in infants. In the United States, bronchiolitis is the leading cause of hospitalization for lower respiratory tract infections in infants.[1] Recently, we showed that RSV bronchiolitis is causally related to recurrent wheeze in the first year of life in late preterm infants.[2] Additionally, several longitudinal studies have shown an association between viral bronchiolitis and the development of asthma during childhood and adolescence.[3–8]

Steroids have been thought to modulate the immune system during the acute phase of infant wheeze, and thereby prevent asthma development.[9] Assuming viral bronchiolitis contributes to asthma through an immunologic cascade, modulation of the immune system may prevent asthma. In the previous report of the current trial we have shown that early initiated high dose inhaled beclomethasone did not have a major effect on recurrent wheeze during a 1-year follow-up period.[10] The purpose of the current study was to investigate the effect of inhaled beclomethasone for RSV bronchiolitis on lung function, and risk of asthma at the age of 6 years. Daily use of inhaled steroids has been associated with reduced linear growth in childhood,[11,12] and until recently this effect was thought not to accumulate into adulthood.[13] However, a recent large study has shown that this reduction in height did persist into adulthood.[14] Effects of high dose steroids on linear growth in infancy are lacking. Therefore, we also aimed to evaluate the long term safety of high dose inhaled beclomethasone in infants on linear growth at the age of 6.

Methods

Participants

We did the study within the framework of a randomized, placebo controlled, double blind trial on the effectiveness of extra fine HFA beclomethasone dipropionate on the occurrence and severity of recurrent wheeze after respiratory syncytial virus related lower respiratory tract infections.[10] In the current study we investigated the long term effect of inhaled beclomethasone for RSV bronchiolitis on lung function, and risk of asthma. Between 2004 and 2006, 243 previously healthy infants aged less than 13 months were admitted to the hospital with a RSV infection, as described earlier in detail. Summarized, hospitalized patients with a proven RSV bronchiolitis by a positive immunofluorescence test for RSV in epithelial cells from nasopharyngeal aspirates were randomly assigned to receive either high dose extra fine HFA beclomethasone dipropionate, hereafter called inhaled beclomethasone, or placebo. The intervention, in a dosage of 200 mcg twice daily for a period of 3 months, is equivalent to 200% the highest advised therapeutic dose for children between 5-11 years

old.[15] This treatment was started within 24 hours of RSV being detected and was continued for three months. These infants were invited to participate in the follow-up study visit at 6 years of age (see below). From April 2010 to November 2011, 185 (76%) children attended this study visit. The medical ethics committee of the University Medical Centre Utrecht approved the study. Written informed parent consent was obtained from all parents.
The study was conducted according to the principles of the Declaration of Helsinki (version 2000) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). Good Clinical Practice (GCP) guidelines were followed.

Outcomes

Questionnaire

The questionnaire contained standardized questions about atopic diseases from the ISAAC questionnaire,[16] medication use (e.g. antihistamines, inhalation steroids and beta-mimetics) in the last 12 months and known risk factors for atopic diseases (i.e. positive family history). All questions were filled in by the parents of the RSV patients. A positive history of parental allergy was defined as questionnaire-reported allergy to pollen, house dust mite, pets or food. Smoke exposure was defined as smoking of one of the parents in the first 5 years of life, and data from the first year of life were used to obtain information about smoke exposure in the first year of life to prevent recall bias. A non-western origin was defined as 'country of birth in Asia (including Turkey), Africa, Latin America, excluding Indonesia and Japan'. In the Netherlands, children regularly visit child healthcare centers for standardized anthropometry. These measurements are recorded in a personal file, which every child owns. Parents were asked to use this file to report these anthropometric measures in the questionnaire.
From each child we obtained the recorded asthma diagnoses from the general practitioner after a primary care visit (R03 wheezing, R96 asthma), according to the International Classification of Primary Care (ICPC).[17] Physician diagnosed asthma was defined as a history of physician diagnosed asthma plus asthma symptoms or medication use in the last 12 months (beta-mimetics or inhaled corticosteroids).

Lung function

The primary outcome of this study was lung function at age 6. Spirometry was performed using a calibrated spirometer (Zan 100 pulmonary spirometer system (nSpire, USA). Maximal flow-volume curves were measured according to the ATS/ERS standards.[18] The largest forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF) were selected from three correctly performed manoeuvres. These measurements were performed in 139 (75%) of the RSV patients. Expiratory measurements of respiratory

system resistance (R_{int}) were obtained in the RSV group using MicroRint (Micro Medical Limited, Kent, UK). Median R_{int} was calculated from at least 5 acceptable interruptions. FeNO was measured in exhaled breath using the NioxMino (NIOX; Aerocrine AB, Solna, Sweden). In addition, in the RSV group a challenge with nebulized metacholine was performed to assess bronchial hyperresponsiveness (BHR) according to the ERS/ATS guidelines.[19] All children withheld their rescue medication for at least 12 hours beforehand. If the child had suffered from a respiratory tract infection in the last 2 weeks, the test was postponed. BHR was defined as a decrease in FEV_1 of ≥20% from baseline at a cumulative dose of ≤0.61 mg methacholinebromide during the challenge.

Allergic sensitization

Serum IgE antibodies to inhaled allergens (sIgE) were measured using a screening test with a combination of the most prevalent inhaled allergens (Pharmacia Diagnostic, Uppsala, Sweden). A positive test result was defined as a sIgE-level above 0.35 kU/l for one of the aero-allergens.

Adverse effects

To estimate whether groups differed in linear growth, we measured the height (in centimeters during the study visit). Height was converted into gender specific z-scores, which describes the number of standard deviations from the population mean. The population norms were derived from the database of the Netherlands organization for Applied Scientific Research.[20]

Statistical analysis

We analysed the effect of inhaled beclomethasone on lung function, the proportion atopic diseases and height. Mean differences and associated 95% confidence intervals (95% CI) of the predicted values for lung function between the inhaled beclomethasone and placebo group were calculated. In case of a non-parametric distribution, a median difference and associated 95% CI was calculated. Risk differences and associated 95% CI were calculated for the risk on a physician diagnosed asthma and atopic diseases between the inhaled beclomethasone and placebo group. In the first instance, we looked only at risk and mean difference and did not adjust for potential confounders, as we were reporting on the long term effects of a randomized placebo controlled trial. To be sure that confounding was not a problem in the post-randomization period we also studied the following potential confounders of lung function by using linear regression analysis: smoke exposure, allergic family history, ethnicity, height and sex. Height was converted into gender specific z-scores, adjusted for the exact age by using linear regression, and compared between groups using the independent-samples t tests. To prevent bias caused by missing data, missing data in the

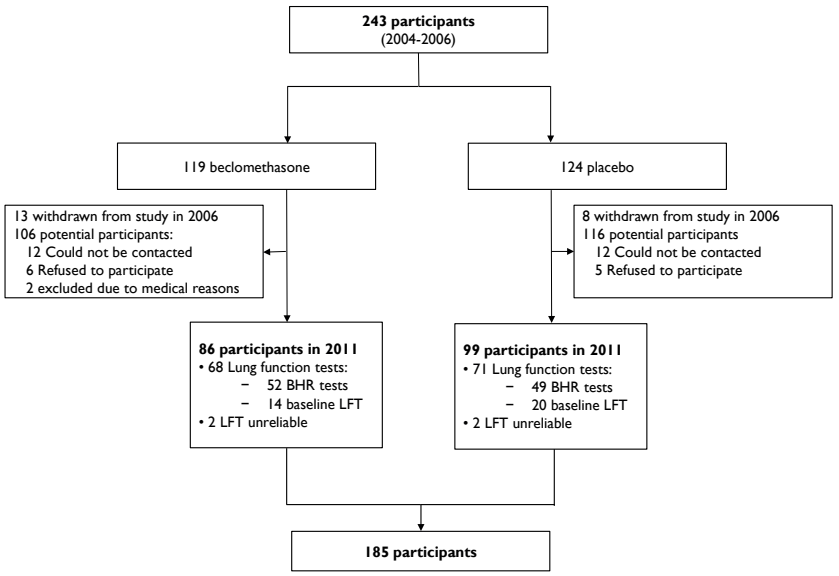
questionnaire were imputed by using multiple imputations. We did all analyses with SPSS 18.0 (version 18.0.0, SPSS Inc., 2009, Chicago USA) on an intention to treat basis.

Results

Lung function

Of the 243 children that underwent randomization, 185 participated in the follow-up study (figure 1). After the initial study, 21 caregivers refused participation in the follow-up study. For the current study we attempted to include the remaining 222 infants. Of these, follow-up data were available from 185 (83.3%) children.

Figure 1. Study flow chart



BHR = Bronchial Hyperresponsiveness; LFT = Lung Function Test

The median age of the RSV group was 5.9 years (IQR 5.8-6.3) and 50.3% were male. Baseline characteristics of the 185 participants did not differ between the beclomethasone and placebo group (table 1), nor between participants and non-participants (supplementary table 1). Table 2 shows the results of the spirometry performed at the age of 6 years. In 135 patients a successful baseline spirometry was performed. No differences in lung function, resistance (Rint) or FeNO were found between the beclomethasone and placebo group (table 2). Adjustment for potential confounders did not alter the relationship between treatment and lung function. Challenge tests were successfully performed in 101 children and again, results

were comparable between both groups (table 2). BHR was present in 25.0% of the beclomethasone group and in 34.7% of the placebo group (risk difference -9.7% (95% CI -27.4 to 8.1%)). BHR plus current wheezing, obtained from the ISAAC questionnaire, was present in 3.8% (2/52) of the beclomethasone group and in 6.1% (3/49) of the placebo group (risk difference -2.3% (95% CI -10.8 to 6.2).

Table 1. Baseline characteristics for 185 RSV patients hospitalised < 13 months of age, presented in relation to the randomly assigned treatment, measured at the age of 6 years. Data are numbers (percentages) unless stated otherwise

Characteristics	Beclomethasone (n = 86)	Placebo (n = 99)
Median age in yrs (IQR)	5.83 (5.7-6.2)	6.00 (5.8-6.3)
Sex (male)	42 (48.8)	51 (51.5)
Mother born in western country[a]	83 (96.5)	97 (98.0)
Father born in western country[a]	84 (97.7)	96 (98.0)
Atopic mother	35 (40.7)	39 (39.4)
Atopic father	44 (51.2)	42 (42.4)
Smoke exposure	26 (30.2)	25 (25.3)
Premature birth[b]	15 (17.4)	14 (14.1)
Mean height in cm (SD)	118.4 (5.3)	119.0 (6.4)
Mean weight in kg (SD)	21.9 (3.3)	22.6 (3.9)

Data are numbers (percentages) unless stated otherwise; [a]Defined as a gestational age < 37 weeks; [b]Non-western = Africa, Latin America and Asia (Japan and Indonesia excluded) or Turkey

Table 2. Lung functions of RSV patients at the age of 6 years. Values are expressed as absolute values and the % of the predicted values (mean +/- SD) unless stated otherwise.

	Beclomethasone (n =66)			Placebo (n = 69)			
	n	Absolute	% predicted	n	Absolute	% predicted	Mean difference[a] (95% CI)
FEV_1 (l)	66	1.21 (0.19)	91.4 (12.1)	69	1.26 (0.22)	93.4 (12.1)	0.04 (-0.03 to 0.02)
FVC (l)	66	1.33 (0.22)	96.8 (13.7)	69	1.37 (0.26)	97.9 (13.7)	0.04 (-0.04 to 0.04)
FEV_1/FVC (%)	66	91.6 (8.0)	96.7 (8.6)	69	92.4 (8.3)	97.5 (8.6)	0.87 (-1.90 to 3.64)
PEF (l/s)	55	2.72 (0.38)	94.3 (17.1)	61	2.91 (0.56)	98.2 (17.1)	0.19 (0.02 to 0.37)[b]
Rint (kPa L^{-1} s)	54	0.76 (0.23)	124.2 (37.2)	53	0.77 (0.247)	126.5 (36.2)	0.01 (-0.08 to 0.10)
FeNO (ppb), median (IQR)	44	8.5 (6.0-12.0)	-	45	10.0 (6.0-14.9)	-	1.30 (-0.40 to 3.80)[c]
BHR present (n, %)	51	13 (25.5)	-	49	17 (34.7)	-	-8.3 (-26.1 to 9.6%)[d]

[a]Between absolute values; [b]Two-tailed P<0.05; [c]Median difference (95% CI); [d]Risk difference (95% CI); IQR = Interquartile range

Asthma diagnosis and allergic diseases

In the RSV group, allergy tests were performed in 96 RSV patients (48 beclomethasone, 48 placebo). Seventeen children had detectable serum IgE against one of the aero-allergens, but proportions between groups were not significantly different (beclomethasone 16.6%, placebo group 18.8%, RD -2.1 (95% CI -17.4 to 13.2)). Physician diagnosed asthma was present in 24.4% of the beclomethasone group versus 21.2% of the placebo group, RD 3.2 (95% CI -8.9 to 15.3). Proportions of other atopic diseases were also comparable between both groups (table 3).

Table 3. The prevalence of atopic diseases for RSV patients at the age of 6 years (questionnaire based). Values are numbers (percentages)

	Beclomethasone (n = 86)	Placebo (n=99)	Risk difference (95% CI)
Asthma			
Physician diagnosed asthma	21 (24.4)	21 (21.2)	3.21 (-8.9 to 15.3)
Current asthma symptoms	36 (41.9)	41 (41.4)	0.45 (-13.8 to 14.7)
Current medication use			
Inhaled steroids	5 (5.8)	9 (9.1)	-3.28 (-10.8 to 4.2)
Bronchodilator	10 (11.6)	9 (9.1)	2.54 (-6.3 to 11.4)
Parent reported allergic diseases			
Asthma ever	8 (9.3)	14 (14.1)	-4.84 (-14.1 to 4.4)
Hayfever ever	7 (8.1)	6 (6.1)	2.08 (-5.4 to 9.5)
Eczema ever	26 (30.2)	33 (33.3)	1.94 (-15.5 to 11.6)

Linear growth

Patients treated with prolonged high dose of inhaled beclomethasone had similar linear growth as patients treated with placebo. Both groups did have a slightly lower height for age and sex (z-score -0.16 in the placebo group and -0.18 in the treatment group), compared with the normal population.[20]

Discussion

Early initiated high dose extra fine HFA beclomethasone administered to infants (<13 months) for three months after RSV related lower respiratory tract infection did not improve lung function at the age of 6. It did also not affect the development of BHR, physician diagnosed asthma or other atopic diseases. No adverse effect on linear growth at the age of 6 was found.

To our knowledge, we are the first to study long term effects of high dose inhaled beclomethasone in children with RSV bronchiolitis using a randomized placebo controlled trial. Our study was designed to study whether treatment of RSV bronchiolitis with early initiated, high dose beclomethasone prevents the development of recurrent wheezing in infancy.[10] In the original study, the total number of wheezing days in the year following the RSV bronchiolitis was not different between the beclomethasone and placebo group. In the current study we have also found no differences in lung function and BHR between both groups.

No treatment during RSV bronchiolitis has been convincingly shown to decrease the risk of long-term airway morbidity. Leukotriene receptor antagonists were suggested to be effective in reducing long-term wheeze, but this conclusion could not be confirmed in a large double-blind study.[21] Previous studies have shown that treatment of bronchiolitis in patients with inhaled steroids may decrease the risk of developing asthma.[22,23] Our early report showed that the number of wheezing days in the year following the RSV bronchiolitis did not differ between the beclomethasone and placebo group.[10,24] In line with our initial report, we have found no differences in the proportion patients with physician diagnosed asthma, the presence of BHR or differences in lung function between the beclomethasone and placebo group. Previous studies have shown that RSV bronchiolitis is associated with a lower lung function at schoolage.[7,25,26,27] Our results are in line with those results, as the %predicted values of the lung function measurements are all below the expected values for age and sex. These results give rise to the question which strategy is required to prevent RSV-related loss of lung function. The answer depends on the causal relationship between RSV bronchiolitis and loss of lung function.[28] If the lower lung function in RSV patients is preexisting, as shown in preterm infants[29] and high risk infants,[30] attempts to alter the natural course of disease during RSV bronchiolitis will prove to be futile. Alternatively, if RSV infection is a major factor in the pathogenesis of loss of lung function, attempts to prevent RSV infection or dampen the host response during early course of disease may beneficially impact on RSV-related development loss of lung function.

Long-term safety of high-dose inhaled glucocorticosteroids during infancy was an important outcome of our study. A recent study of Martinez et al. shows that daily use of normal dose inhalation steroids in asthmatic children negatively affects linear growth.[11] Intermittent administration in this study does not lead to a reduction of linear growth on short term. However, a recent large study has shown that the reduction in height did persist into adulthood.[14] We used a high dose of inhalation steroids, equivalent to 200% of the highest advised therapeutic dose in the Netherlands for children between 5-11 years old.[15] We did

not find an effect of a 3 months course of high-dose inhaled steroids on linear growth in children at the age of 6 years.

The strengths and limitations of this study deserve further discussion. First, we were able to retain 76% of patients in this 6-year follow up study. Because we have found no differences in baseline characteristics, we conclude there is no selection bias. Second, to prevent bias that might result from a complete case analysis our missing data in the questionnaires was imputed by using multiple imputations.[31]
Our study also has limitations. First, we were not able to measure BHR in all patients. International guidelines describe asthma as a disease characterized by a triad of specific symptoms (cough, wheeze and dyspnoea), reversible airway obstruction and bronchial hyperresponsiveness.[32] Consequently, we could only evaluate asthma based on lung function in a subset of the RSV group. Secondly, our study was powered to demonstrate a treatment effect on our primary outcome, i.e. wheezing days in the first year after end of therapy. Our study was underpowered to show smaller but potentially relevant treatment effects on asthma diagnosis or lung function. Third, the initial study was designed as a randomized, double blinded controlled trial, and was unblinded one year after the end of therapy. The current study was single blinded as the researchers measuring outcome, including spirometry, were blinded to the treatment. This minimizes the potential effect of information bias on the lung function measurements. Because parents were informed about treatment allocation, this may have influenced the presentation of the symptoms of their child.

In summary, our study demonstrated that treatment with inhaled beclomethasone was safe, but did not lower the risk on lung function decline, BHR or physician diagnosed asthma. Based on the current study we conclude that RSV bronchiolitis is associated with a substantial decrease in lung function compared to reference values,[33] but this is not prevented by use of early-initiated high-dose inhaled steroids during course of infection.

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Online supplement

Supplementary table 1. Baseline characteristics of participants and non-participants. Groups were statistically comparable for all variables. Values are mean (SD), or n (%).

	Study Group[a]	Questionnaire Group[b]	Lost to follow up	No consent
Nr of patients	135	50	24	34
Age (years)	6.78 (0.51)	6.76 (0.55)	6.76 (0.47)	6.57 (0.45)
Sex (male)	69 (49.6)	26 (54.2)	15 (62.5)	3 (37.5)
Mother born in western country	132 (95)	42 (87.5)	9 (37.5)	6 (75)
Birth weight (grams)	3136 (476)	3062 (555)	3161 (441)	3083 (491)
Educational level (mother)	25 (18.2)	11 (25.0)	7 (43.8)	2 (33.3)
Atopic mother	54 (38.8)	26 (54.2)	4 (25)	3 (50)

[a]patients that attended the study visit for lung function measurements and filled in the questionnaire; [b]patients that did not attend the study visit, but did fill in the questionnaire.




Chapter 8

Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection

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Abstract

Introduction

A relationship between hospitalization for respiratory syncytial virus (RSV) bronchiolitis and asthma development has been suggested in case-control studies. The aim of this study was to assess the risk of current wheeze, asthma, and lung function at school age in infants previously hospitalized for RSV bronchiolitis compared to non-hospitalized children.

Methods

For this study, data from a prospective birth cohort of unselected, term-born infants (n=553), of whom 4 (0.7%) were hospitalized for RSV bronchiolitis, and a prospective patient cohort of 155 term infants hospitalized for RSV bronchiolitis were used. Respiratory outcomes at age 6 in children hospitalized for RSV bronchiolitis were compared to non-hospitalized children.

Results

The risk of current wheeze was higher in hospitalized patients (n=159) compared to non-hospitalized children (n=549) (adjusted odds ratio (OR) 3.2 (95% CI 1.2-8.1). Similarly, the risk of current asthma, defined as a doctor's diagnosis of asthma plus current symptoms or medication use, was higher in hospitalized patients (adjusted OR 3.1 (95% CI 1.3-7.5). Compared to non-hospitalized children, RSV bronchiolitis hospitalization was associated with lower lung function (mean difference FEV_1% predicted -6.8l (95% CI -10.2 to -3.4).

Conclusion

This is the first study showing that hospitalization for RSV bronchiolitis during infancy is associated with increased risk of wheezing, current asthma, and impaired lung function as compared to an unselected birth cohort at age 6.

Introduction

Respiratory syncytial virus (RSV) infection is a common cause of severe bronchiolitis in infants. The annual global incidence of RSV infection in children younger than 5 years, has been estimated at 34 million per year, with at least 10% episodes representing severe infections that require hospitalization.[1] Over the last 20 years, epidemiologic studies have shown an association between RSV bronchiolitis and the subsequent development of wheeze and asthma up to school age.[2] Most studies had a case-control design,[3–7] which bears the challenge of control selection. In order to prevent selection bias, sampling of controls needs to be independent of the determinant studied.[8] The ALSPAC study retrospectively analyzed the relationship between a discharge code of hospitalization for RSV bronchiolitis and long-term airway disease up to age 7 years within in the study registry.[9] In that study there was an excess of subjects with missing data among RSV cases. A recent meta-analysis concluded that study quality of follow-up studies after RSV bronchiolitis was generally poor.[10] For that reason Stein and Martinez argued that the association between RSV hospitalization during infancy and asthma at school has still not been established.[11] To our knowledge, no study has prospectively compared wheezing and lung function at school age between term hospitalized RSV bronchiolitis patients and a large birth cohort of healthy term children. We performed a prospective cohort study of healthy infants, including a group of well characterized, hospitalized RSV infants with bronchiolitis.[12] Our aim was to determine whether the risk of wheeze and asthma at age 6 is related to RSV bronchiolitis hospitalization during infancy.

Methods

Participants

The WHISTLER project is an ongoing population based, prospective birth cohort on determinants of wheezing illnesses in children, which started in December 2001. Participants are healthy, term-born infants born in Leidsche Rijn, a residential area near the city of Utrecht. Infants are enrolled at the age of 2 weeks, and are prospectively followed with (1) a diary for respiratory symptoms in the first year of life, and with (2) study visits including lung function at age 5 and 8.[12] For each participant, data from the most recent study visit was used (either from the visit at age 5 or age 8), resulting in 553 children of similar age for analysis. Children that were hospitalized during infancy for a proven RSV bronchiolitis (positive immunofluorescence test or PCR) were identified. This birth cohort was compared to a cohort of children that had been hospitalized for RSV bronchiolitis. Summarized, between 2004 and 2006, 243 previously healthy infants aged less than 13 months were admitted to the hospital with an RSV infection, as described earlier in detail.[13] Patients

with a proven RSV bronchiolitis by a positive immunofluorescence test for RSV in epithelial cells from nasopharyngeal aspirates were randomly assigned to receive either high dose extra fine HFA beclomethasone dipropionate or placebo. At age 6, no differences in lung function or presence of respiratory symptoms were found between groups, and therefore we combined both groups for the current report. All children were invited to participate in the follow-up study visit at 6 years of age, including a questionnaire, and lung function assessment. From April 2010 to November 2011, 185 (76%) children attended this study visit (supplementary figure 1). Only term born infants (155/185) were included, and added to the 4 hospitalized RSV bronchiolitis patients in the Whistler cohort. Respiratory outcomes of hospitalized RSV bronchiolitis patients within the complete cohort (n=159, hereafter called hospitalized patients), were compared to non-hospitalized children (n=549). Parents gave written informed consent for study participation.

Ethics Statement

The medical ethics committee of the University Medical Centre Utrecht approved both studies. Written informed parent consent was obtained from all parents. The study was conducted according to the principles of the Declaration of Helsinki (version 2000) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). Good Clinical Practice (GCP) guidelines were followed.

Outcomes

Questionnaire and definitions

The questionnaire contained standardized questions about atopic diseases from the ISAAC questionnaire,[14] medication use (e.g. antihistamines, inhalation steroids and beta-mimetics) in the last 12 months and known risk factors for atopic diseases (i.e. positive family history). All questions were filled in by the parents of the hospitalized patients and non-hospitalized children. Parental allergy was defined as a questionnaire-reported allergy to pollen, house dust mite, pets or food. Smoke exposure was defined as smoking of one of the parents in the last 5 years of life, and data from the first year of life were used to obtain information about smoke exposure in the first year of life to prevent recall bias. A non-western origin was defined as a country of birth in Asia (including Turkey), Africa, Latin America, excluding Indonesia and Japan. In the Netherlands, children regularly visit child healthcare centers for standardized anthropometry. These measurements are recorded in a personal file for every child, kept by parents. Parents were asked to use this file to report these anthropometric measures in the questionnaire. Current wheeze, in both the hospitalized patients and non-hospitalized children, was defined as a positive response to the question "Has your child had wheezing or whistling in the chest in the last 12 months?" Current asthma was defined as a history of doctor's diagnosis of asthma plus asthma symptoms or medication (beta-mimetics

or inhaled corticosteroids) use in the last 12 months.
A doctor's diagnosis of asthma ever was defined as an ever recorded asthma diagnosis from the general practitioner after a primary care visit (R03 wheezing, R96 asthma), according to the International Classification of Primary Care (ICPC).[15]

Lung function
Spirometry was performed using a calibrated spirometer (Zan 100 pulmonary spirometer system (nSpire, USA). Maximal flow-volume curves were measured according to the ATS/ERS standards.[20] The largest forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF) were selected from three correctly performed manoeuvres. Results were related to Dutch normative values.[16] Expiratory measurements of respiratory system resistance (R_{int}) were obtained using MicroRint (Micro Medical Limited, Kent, UK). Mean R_{int} was calculated from at least 5 acceptable interruptions. FeNO was measured in exhaled breath using the NioxMino (NIOX; Aerocrine AB, Solna, Sweden). All children withheld their rescue medication for at least 12 hours beforehand. If the child had suffered from a respiratory tract infection in the last 2 weeks, the test was postponed.

Statistical analysis
Logistic regression was used to investigate the effect of RSV bronchiolitis hospitalization on current wheeze and asthma. Hereafter, multivariable analysis was used to adjust for possible confounders influencing both current wheeze or asthma (outcomes) as well as RSV bronchiolitis hospitalization (determinant). Results are presented as odds ratio (OR) with a 95% confidence interval (CI). Linear regression was used to investigate the effect of RSV bronchiolitis hospitalization on lung function. Again, multivariable analyses was used to adjust for possible confounders, and results are presented as crude and adjusted mean differences with a 95% CI. Data were analyzed using PASW Statistics 18 (version 18.0.0, SPSS Inc., 2009, Chicago USA).

Confounders
Baseline characteristics between the two cohorts were likely to be different with respect to risk factors for RSV bronchiolitis hospitalization. These risk factors were considered to be potential confounders of the association between RSV hospitalization and current wheeze or asthma. The following confounders were corrected for in our analysis: male gender, breastfeeding, siblings, day care attendance, smoke exposure, birth weight, being born between April and September, year of birth, and educational level of the mother.

Results

Of the 243 hospitalized RSV bronchiolitis patients that participated in the initial trial, 185 participated in the follow-up study. 155 Previously healthy, term infants were selected for further analyses, of whom 113 (72.9%) agreed to take part in the lung function test (supplementary figure 1). Non-participants were more often of non-Caucasian ethnicity compared to participants or the excluded premature born participants (supplementary table 1). Participants with a successful lung function measurement were significantly younger compared to participants with unsuccessful lung function measurement (5.8 versus 6.3 years, p<0.001, supplementary table 2). Children hospitalized for RSV bronchiolitis had lower birth weight, were more often born between September and March, more often exposed to maternal smoking in pregnancy, less often breastfed, did go to daycare less often, had more often siblings, had lower educated parents and more often Caucasian parents compared to non-hospitalized children (table 1).

Table 1. Group characteristics at age 6 for 159 hospitalized RSV bronchiolitis patients,[13] and non-hospitalized children.[12]

	Hospitalized RSV bronchiolitis patients (n=159)	Non-hospitalized children (n=549)	p-value
Sex (male)	87/159 (54.7)	265/549 (48.3)	0.153
Median age at follow-up in yrs (IQR)	5.88 (5.67-6.25)	5.33 (5.17-7.75)	0.923
Median age at hospitalisation (months)	2.0 (1.0-4.0)	-	-
Birth weight (grams)	3250 (3250-3750)	3557 (3260-3860)	<0.001
Gestational age (weeks)	40.0 (39.0-40.6)	40.0 (39.1-40.9)	0.081
Born September-March	99/159 (62.3)	270/549 (49.2)	0.002
Smoking during pregnancy	27/155 (17.0)	26/548 (4.7)	<0.001
Smoke exposure up to age 6	42/159 (26.4)	126/451 (27.9)	0.721
Breastfed in first 3 months	97/155 (62.6)	3768/515 (71.5)	0.036
Daycare in first 3 months	52/155 (33.5)	227/515 (44.1)	0.020
Pets in first year of life	79/154 (51.3)	274/475 (57.7)	0.166
Siblings	134/155 (86.5)	297/548 (54.2)	<0.001
Maternal atopy	66/154 (42.9)	224/466 (48.1)	0.262
Maternal ethnicity Caucasian*	149/154 (96.8)	386/469 (82.3)	<0.001
Maternal high educational level	53/153 (34.6)	301/470 (64.0)	<0.001
Median height at age 6 (cm, IQR)	117.2 (113.0-126.10	118.2 (114.3-121.8)	0.094
Median weight at age 6 (kg, IQR)	21.0 (19.0-25.0)	21.6 (19.7-24.0)	0.567

Data are numbers (percentages) unless stated otherwise; *Caucasian = Not born in Africa, Latin America and Asia (Japan and Indonesia excluded) or Turkey.

Current wheeze, asthma and allergic diseases

In the univariable logistic regression analysis hospitalized RSV bronchiolitis patients had a 3.0 fold increased odds for wheeze in the last 12 months (table 2). Hospitalized RSV patients more often were diagnosed with asthma at any point in life, and a higher proportion had current asthma defined as a history of doctor's diagnosis of asthma plus asthma symptoms or medication use in the last 12 months. Hospitalized patients more often used airway medication compared to non-hospitalized children, however this did not reach statistical significance. In multivariable analysis we initially adjusted the risk of current wheeze and asthma for sex and age only, but this did not change our results. We repeated our analysis by adjusting for sex, age, birth weight, season of birth, year of birth, smoke exposure during pregnancy and during life, breastfeeding, daycare, siblings, maternal atopy and maternal ethnicity. This slightly changed the odds for current wheeze and current asthma to 3.2 (95% CI 1.2 to 8.1) and 3.1 (95% CI 1.3 to 7.5) respectively.

Table 2. Respiratory morbidity of hospitalized RSV bronchiolitis patients and non-hospitalized children at the age of 6 years

	Hospitalized RSV bronchiolitis patients (n =159)	Non-hospitalized children (n-549)	Crude		Adjusted*		Adjusted**	
			OR	95% CI	OR	95% CI	OR	95% CI
Current wheeze	33/155 (21.3)	42/516 (8.1)	3.0	**1.9-5.0**†	3.0	**1.9-5.1**†	3.2	**1.2-8.1**‡
Current use of:								
ICS	11/159 (6.9)	25/549 (6.9)	1.6	0.7-3.2	1.5	0.7-3.2	3.4	1.0-11.3
Betamimetics	17/159 (10.7)	46/549 (8.4)	1.3	0.7-2.4	1.3	0.7-2.3	2.1	0.8-5.7
Doctor's diagnosis asthma	63/158 (39.9)	58/517 (11.2)	5.2	**3.5-8.0**†	5.3	**3.4-8.0**†	5.8	**2.8-11.8**‡
Current asthma	34/159 (21.4)	29/549 (5.3)	4.9	2.9-8.3	4.8	2.8-8.2	3.1	1.3-7.5‡

†=p<0.001; ‡=p<0.01; Data are numbers (percentages) unless stated otherwise; * Adjusted for sex and age; **Adjusted for sex, age, birth weight, birth season, smoke exposure during pregnancy and during life, breastfeeding, daycare, siblings, maternal atopy, ethnicity, year of birth, and maternal educational level; *** Defined as combination of a history of doctor's diagnosed asthma plus asthma symptoms or medication use in the last 12 months (beta-mimetics or inhaled corticosteroids); ICS = Inhaled Corticosteroids

Comparable adjusted odds ratios were found for current wheeze in atopic children (OR 3.7 (95% CI 0.8 to 15.6) and non-atopic children (2.9 (95%CI 0.8 to 10.5), as well as for current asthma in atopic (OR 3.3 (95% CI 0.8 to 13.6) and non-atopic children (2.6 (95%CI 0.8 to 8.8)). Proportions of parent-reported allergic diseases in their children were not significantly different between the hospitalized patients and non-hospitalized children (hay fever 5.7% versus 5.5%, and eczema 34.0% versus 27.5%).

Lung function

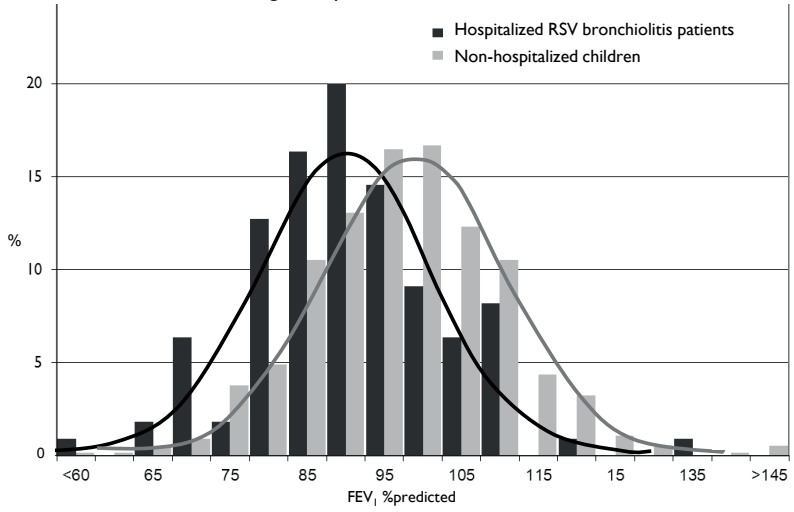
Compared to the non-hospitalized children, lung function was significantly impaired in the hospitalized RSV patients (table 3, figure 1). Hospitalized patients had lower FEV_1 (mean difference (MD) -6.8l. %predicted (95% CI -10.2 to -3.4), lower FVC (MD -6.5l. %predicted) (95% CI -10.4 to -2.7), a lower Tiffeneau index (MD -2.0% (95% CI -3.6 to -0.3), higher FeNO (MD 4.0 ppb (95% CI 1.9 to 6.2) and increased resistance of the respiratory system (MD 15.6 kPa/L/s (95% CI 6.5 to 24.6) compared to the non-hospitalized children.

Table 3. Lung functions of hospitalized RSV bronchiolitis patients and non-hospitalized children at the age of 6 years.

	Hospitalized RSV bronchiolitis patients (n=117)		Non-hospitalized (n=549)		Crude	Adjusted†
	Absolute	% predicted	Absolute	% predicted	Mean difference (95% CI)	Mean difference (95% CI)
FEV_1 (l)	1.24 (0.2)	93.3 (12.2)	1.43 (0.4)	100.3 (13.9)	-6.97 (-9.7 to -4.2)*	-6.82 (-10.2 to -3.4)*
FVC (l)	1.35 (0.2)	98.2 (13.8)	1.53 (0.4)	104.3 (15.6)	- 6.16 (-9.2 to -3.1)*	-6.54 (-10.4 to -2.7)*
FEV_1/FVC (%)	92.32 (8.7)	-	93.68 (6.0)	-	-1.36 (-2.8 to 0.0)	-1.97 (-3.6 to -0.3)***
PEF (l/s)	2.86 (0.5)	98.1 (15.2)	3.17 (0.9)	101.4 (21.5)	-3.28 (-7.7 to 1.2)	-2.93 (-8.6 to 2.7)
Rint (kPa $L^{-1}s$)	0.76 (0.2)	124.7 (35.7)	0.66 (0.2)	112.7 (31.9)	11.99 (4.5 to 19.4)**	15.59 (6.6 to 24.6)*
FeNO (ppb)	10.85 (9.0)	-	8.12 (5.5)	-	2.73 (1.2 to 4.3)**	4.02 (1.9 to 6.2)*

Values are expressed as % of the predicted values (mean (SD)); Presented mean differences are differences in mean %predicted values; *<0.001; ** <0.01; ***<0.05; †Adjusted for sex, age, birth weight, birth season, smoke exposure during pregnancy and during life, breastfeeding, daycare, siblings, maternal atopy, ethnicity, year of birth, and maternal educational level.

Figure 1. FEV_1 values presented as % predicted values for hospitalized RSV bronchiolitis patients and non-hospitalized children measured at the age of 6 years.



Discussion

In this prospective study we studied the risk of wheeze and asthma after RSV bronchiolitis hospitalization during infancy. We established a 3.2 fold increased risk of current wheeze and a 3.1 fold increased risk of current asthma in hospitalized RSV bronchiolitis patients compared to non-hospitalized children. In hospitalized RSV bronchiolitis patients the mean FEV_1 percentage predicted was 6.8% lower compared to non-hospitalized children.

To our knowledge, this is the first study comparing prospectively followed hospitalized infants with RSV bronchiolitis to a normal birth cohort, and obtaining valid risk estimates on respiratory morbidity in childhood. Late effects of RSV bronchiolitis requiring hospitalization have previously been studied by others.[3–5,9,17] A study by Sigurs et al.[3] reported a 2 fold increased risk of "any wheezing" in prospectively followed hospitalized RSV bronchiolitis patients without concomitant chronic disease, whereas Henderson et al. reported a 3.2-6.6 fold increased risk of wheeze in hospitalized RSV patients selected from a large cohort study.[9] Asthma prevalence in the control population was 3% in the Sigurs study, which is much lower than in the general Swedish population.[18] In our non-hospitalized group the prevalence of wheeze and asthma was 8.1% and 5.3% respectively. These numbers are comparable to the prevalence of wheeze and asthma in 6-7 year old children in western surrounding countries,[18] indicating that this group reflects the general population of the Netherlands with respect to wheeze and asthma.
Although symptoms may subside with age, lung function has been shown to track over life.[19] Lung functions in the hospitalized RSV patients were impaired compared to the non-hospitalized children, and differences between groups were larger than described in previous reports.[4,20,21] Lung function decline could be of vital importance because low lung function in adulthood is one of the strongest predictors of chronic airway obstructive pulmonary disease later on in life.[19]

The mechanism underlying long-term consequences of severe RSV bronchiolitis is intriguing. Here, we confirm the results from the Tucson study showing that atopy does not play a major role in the development of wheeze and loss of lung function following RSV infection. Numerous hypotheses explaining the association between RSV bronchiolitis and asthma development have been published, including innate immune mechanisms, adaptive immune mechanisms as well as neurogenic mechanisms.[22] RSV bronchiolitis is associated with a strong local neutrophil response. Production of proteases and radical oxygen species may cause major damage to the airways resulting in abnormal development of lung architecture and function. An alternative hypothesis is based on our previous observations that children

with severe RSV bronchiolitis have a stronger local IL-10 response, which may partially be genetically determined.[23–25] Increased local IL-10 production is associated with decreased production of type I and type 2 interferons, leaving patients susceptible to respiratory viral infections.

Previous studies as well as ours were not designed to determine whether RSV bronchiolitis causes airway morbidity at school age or reflects a common predisposition, probably abnormal lung function at birth.[26] It is clear that both hypotheses are not mutually exclusive. We have recently shown that RSV infection is causally related to recurrent wheeze in the first year of life in otherwise healthy preterm infants 33-35 weeks gestational age.[27] RSV immunoprophylaxis prevented 60% of all cause wheeze, even after end of therapy. Similarly, intervention studies are required to assess to what extent RSV hospitalization causes asthma at school age, which will prove instrumental in estimating the potential long-term benefit of new preventive and therapeutic interventions against RSV, of which many are currently under development.[28]

In this study we assessed the unbiased risk of wheeze and asthma in childhood after RSV bronchiolitis hospitalization. However, some limitations need to be discussed. First, although our study has some advantages over previous retrospective or case-control studies, the optimal study design was not met. In our cohort, we have actively enriched the group of children hospitalized for RSV bronchiolitis. This led to the limitation that we were not able to assess absolute respiratory risks of hospitalization for RSV, but we were able to validly estimate relative respiratory risks. Second, lung function measurement was not successful in 42 patients (27%) in the RSV hospitalization group. Surprisingly, children with a successful lung function were younger compared to those without a successful lung function. As the remaining baseline characteristics (demographics) in these children were similar to patients with successful lung function measurements, we think that the lung functions measured are representative of all RSV patients. Third, we were able to obtain follow up data from 76% of the hospitalized RSV cohort. Non-participants were more often non-Caucasian compared to participants, which may limit the generalizability of our results to the non-Caucasian group. Fourth, residual confounding may have influenced our conclusions, even though we aimed to correct for all known potential confounders. Fifth, cohort effects may have influenced our outcomes. Although asthma prevalence has increased over the last decades, the prevalence of wheeze and asthma in our study is most likely not affected by the slight variation in time periods between our cohorts. Finally, we did not assess post bronchodilator reversibility which is thought to have added value to make an asthma diagnosis in children.[29]
In summary, this is the first prospective study comparing previously healthy term infants

hospitalized for RSV bronchiolitis with an unselected healthy, term population. We established that hospitalization for RSV bronchiolitis was associated with a 3.2-fold increased risk of wheeze, a 3.1-fold increased risk of asthma and a 6.8% decrease in FEV_1% predicted at age 6 compared to non-hospitalized children. Intervention studies will have to determine to what extent RSV bronchiolitis is causally related to long-term airway disease.

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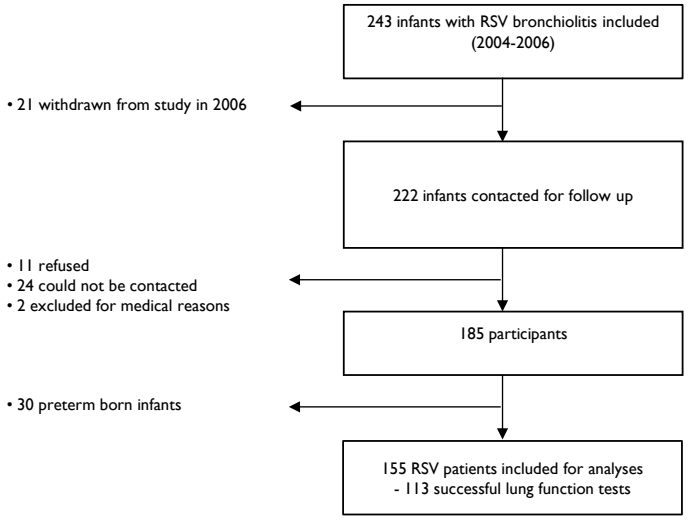
Online supplement

Supplementary figure 1. RSV study population at 6 years follow up



Supplementary table 1. Baseline characteristics of participants, non-participants and premature participants that were excluded from analyses. Values are mean (SD) unless stated otherwise

	Participants[a]	Non-participants[b]	Premature (non-participant)[c]	p-value
Nr of patients	155	58	30	
Sex (male)	83 (53.5)	33 (56.9)	10 (33.3)	0.089
Median age at follow-up in yrs (IQR)	5.9 (5.7-6.3)	-	5.9 (5.8-6.3)	0.497
Birth weight (grams)	3250 (3250-3500)	3250 (2750-3500)	2250 (1750-2750)	<0.001
Maternal atopy	68/155 (43.9)	18/37 (48.6)	10/30 (33.3)	0.435
Maternal ethnicity Caucasian*	144/155 (92.9)	28/58 (48.3)	29/30 (96.7)	<0.001
Maternal high educational level	50/150 (33.3)	9/36 (25.0)	10/29 (34.5)	0.303

a: patients that attended the study visit for lung function or filled in the questionnaire
b: patients that were lost to follow up, or refused to participate
c: Participants which were excluded from analyses as they were prematurely born
*Caucasian = Not born in Africa, Latin America and Asia (Japan and Indonesia excluded) or Turkey.

Supplementary table 2. General characteristics of the population with and without a successful lung function measurement.

	Group with successful LF measurement	Group without successful LF measurement	p-value
Nr of patients	113	42	
Sex (male)	60 (53.1)	23 (54.8)	0.853
Median age at follow-up in yrs (IQR)	5.83 (5.67-6.08)	6.25 (6.00-6.67)	<0.001
Gestational age (weeks)	40.1 (39.1-40.7)	39.4 (38.3-40.4)	0.292
Birth weight (grams)	3250 (3250-3750)	3250 (3250-3750)	0.759
Maternal atopy	46/112 (41.1)	18/39 (46.2)	0.579
Maternal ethnicity Caucasian*	110/112 (98.2)	36/39 (92.3)	0.109

Data are numbers (percentages) unless stated otherwise; *Caucasian = Not born in Africa, Latin America and Asia (Japan and Indonesia excluded) or Turkey.





Chapter 9

General discussion

The aim of this thesis was to investigate determinants of asthma-related outcome measures, especially asthma control and Health Related Quality of Life (HRQOL). The second aim was to study the effect of RSV infections on the development of asthma-related outcomes, especially symptoms and lung function.

The main findings of this thesis are:

- A lower level of asthma control is associated with an increased number of both upper (colds and otitis episodes) and lower respiratory tract infections (bronchitis episodes).
- Asthma control is the most important determinant of HRQOL in children with asthma.
- In the autumn season children perceive lower HRQOL, and children who perceive foods/drinks or emotions as triggers for wheeze, are at risk for lower HRQOL.
- The presence of asthma does not predict a food challenge outcome (FCO) in children suspected for having food allergy.
- Impaired lung function at birth predisposes to more severe RSV disease and to more frequent post-RSV wheeze in term, and previously healthy children.
- Hospitalization for RSV bronchiolitis during infancy is associated with increased risk of wheezing, asthma, and impaired lung function at age 6, as compared to an unselected birth cohort.
- Treatment with high dose inhaled beclomethasone during RSV bronchiolitis does not affect lung function, nor prevent the development the atopic diseases during long term follow-up.

The burden of asthma on children

The estimated prevalence of asthma in Dutch, school age children is between 4 and 7%.[1] Asthma is one of the most common chronic diseases in the world, and it is estimated that around 300 million people – adults and children together - in the world currently have asthma. The burden of asthma, reflected in the number of disability-adjusted life years (DALYs) lost due to asthma worldwide, is about 15 million per year, which is comparable to that of diabetes, cirrhosis of the liver or schizophrenia.[2] The benefits of good asthma control compared to poor asthma control have been well studied and include reduced loss of schooldays, higher probability of a normal quality of life, and reduced risk of exacerbations.[3] Improvement of asthma control and health related quality of life may lower the huge burden of this disease. This requires insight into the determinants of asthma control and asthma related quality of life.

Asthma control

Traditionally, in guidelines lung function was regarded as the primary endpoint, both in daily clinical practice and in trials. After the recognition of poor correlation between lung function, inflammation and symptoms, the focus has changed to the assessment of asthma control. Asthma control is defined as 'to which extent the manifestations of asthma have been reduced or removed by treatment'.[4] It does not only include daytime and nocturnal symptoms, and need for reliever medication, but is also an estimation of future risk of exacerbations. When asthma is controlled, there should be no more than occasional recurrence of symptoms and severe exacerbations should be rare. Uncontrolled asthma is one of the most important predictors of an asthma exacerbation.[3]
Poor asthma control among children leads to limited physical activity, missed school days and parental work absenteeism. Nocturnal symptoms may lead to sleep disturbance, with lower school performance as result. Among school-age children, the direct and indirect costs attributable to these exacerbation-related outcomes exceed two billion US dollars annually.[5]

In order to lower the burden for the patient, a lot of effort has been put into identification of risk factors for both determinants of asthma exacerbations and asthma control. Besides a recent viral respiratory tract infection,[6,7] older age,[8] the female sex,[6,9,10] medication adherence,[6,11] allergic comorbidity,[12,13] tobacco smoke exposure,[6,14] and an increased body mass[15–17] have been associated with uncontrolled asthma in children. Asthma control has been shown to be lower during autumn to spring as compared to the summer season, and asthma exacerbations have a clear seasonal pattern with most occurring shortly after the summer break from school. Viral upper respiratory tract infections have been shown to be causally related to this seasonal pattern.[18]

Although it seems to be attractive to control all the determinants of asthma control in order to achieve proper asthma management, in clinical practice we do not succeed.[7,8,19] In chapter three of this thesis, we showed that in children upper and lower respiratory tract infections are the most important determinants of asthma control. In view of the huge prevalence of viral infections in children,[20] it explains why complete asthma control will probably be never achievable in children. Viral infections are inherent to the paediatric age. Both upper and lower airway infections frequently occur in childhood and preventive measures are ineffective or are hard to implement. The most effective method to prevent the spread of viral respiratory tract infections is regular hand washing, however, even this intervention was not effective in the prevention of asthma exacerbations in children when applied in schools, although these results may have been confounded by the H1N1 pandemic.[21] A

recent Cochrane review did not find evidence to support effectiveness of hand sanitizer use over hand washing in general.[22]

Virus specificity is a drawback for vaccination programs. Rhinoviruses seem to be the most frequent trigger of wheezing attacks in children with asthma.[23] In our studies we were able to analyze the number of respiratory tract infections, but did not have the information about which virus caused the infection. Many studies have also shown that RSV can be an important trigger for wheeze at the young age.[24–26] A recent study by Blanken et al. has shown that prevention of RSV by palivizumab in late premature infants did reduce the number of days with wheeze in the first year of life.[27] However, until to date no treatment has been convincingly shown to decrease the risk of long-term airway morbidity. Leukotriene receptor antagonists were suggested to be effective in reducing long-term wheeze, but this conclusion could not be confirmed in a large double-blind study.[28] Preventing RSV may possibly lead to prevention of asthmatic symptoms, and lung function deterioration. Previous studies have shown that treatment of bronchiolitis in patients with inhaled steroids may decrease the risk of developing asthma.[29,30] This thesis shows that treatment with high doses of inhaled steroids during 3 months did not affect the course of post-bronchiolitis symptoms (chapter seven). These findings make it unlikely that inhaled steroids will be effective in the treatment of other virus-induced wheezing syndromes.

Another approach to prevent virus infections at the young age might be reduction of virus exposure at day-care facilities. Results of infection control procedures (training, hand washing, and aseptic nose wiping technique) have been shown to be effective in the reduction of colds in children in child care, up to 3 years.[32,33] However, whether those interventions do also positively affect asthma control in for instance asthmatic siblings, is unknown.

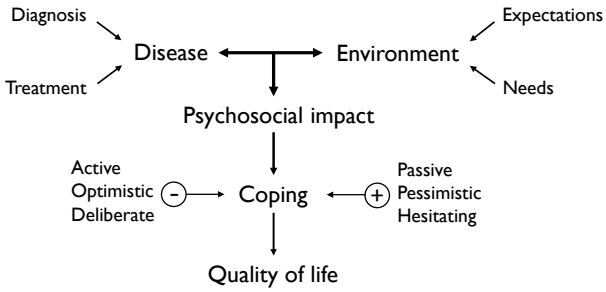
Quality of life

Besides the physical consequences of uncontrolled disease, asthma also has psychological impact on children and parents.[34] Children need to cope with taking their medication daily while some may have concerns about side effects. Symptoms may lead to avoidance of social activities, and children may feel different from peers due to their disease.[35] For caregivers, their caring role might result in absence from work or social activities, leading to a variety of consequences and stress.[34] Improvement of, for instance, lung function as a result of treatment, does not necessarily lead to improved HRQOL, as patients may be bothered by the treatment itself. HRQOL is a useful indicator to understand the impact of asthma on functional status and wellbeing. In 1948 the World Health Organization (WHO) defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[34]

Asthma control is the most important determinant of asthma related quality of life. However, besides asthma control, other factors may influence health related quality of life (HRQOL) in children with asthma. Asthma severity, gender, allergic rhinoconjunctivitis, eczema, food allergy, the season and parental factors have been described as determinants of HRQOL.[36–42] Many of these factors first affect asthma control, and thereby influence HRQOL.

Although recognized as an important outcome in asthma treatment, and recommended in the international paediatric guidelines to be assessed periodically,[43] clinicians still focus on symptoms and physical functioning but rarely on emotional or social problems.[44] We have shown in chapter four that self perceived emotions that trigger wheeze are associated to lower HRQOL. Furthermore, perceived foods and drinks that trigger wheeze were also associated to lower HRQOL, and 91% of the children that reported this were known with food allergic symptoms. It is not unlikely that underlying fear for food related respiratory symptoms may be present in this group of children. These feelings may influence the coping strategy of child and parents, leading to lower HRQOL (figure 1).

Figure 1. The level of quality of life greatly depends on individual expectations as well as individual specific factors, especially regarding coping strategies.[34]



The autumn was also associated with lower HRQOL in our study. Two hypotheses for this finding can be suggested; first, during autumn there is a higher prevalence of respiratory viral infections, influencing asthma control. However, our association between the autumn season and HRQOL was independent of asthma control. Second, the autumn season has been associated with depressive symptoms,[45] again influencing the patients' coping strategy. Reasons for not assessing HRQOL may be related to the fact that doctors may not see it as their task to identify problems that are not inside the traditional area of medical care. [44,46] It may also be due to the fact that there is currently insufficient evidence that implementation of pediatric HRQOL measures in clinical practice improves patient healthcare outcome. Implementation of HRQOL measures in daily practice on patient satisfaction, communication

and disease control might help to improve treatment outcome of the asthmatic paediatric population. Furthermore, to improve the treatment outcome, there remains a great need for individualized predictors for treatment response in asthma care. Therefore, a large cohort of asthmatic patients which is followed up in time is needed, in which demographic, lung function parameters, immunological and possibly genetic factors are measured and combined in a predictive model. These data are expected to become available from the Luchtwegportaal in the near future.

Respiratory Syncytial Virus and asthma

Because viral infections play an important role as trigger of asthma symptoms and are a major determinant of asthma control in children, in the second part of this thesis we focused on the association between RSV infection and asthma-like symptoms.

Literature suggests that an association between RSV bronchiolitis and the development of asthma in childhood exists. Some evidence on this association was put forward by Sigurs et al, who followed a cohort of hospitalized infants for RSV bronchiolitis.[47,48] Up to 18 years of age, an increased risk of asthma, recurrent wheeze, allergic rhinitis and allergic sensitization was found in the hospitalized group. However, asthma prevalence in the comparison group of children was only 3%. As this is much lower than in the general Swedish population, it suggests that selection has influenced these results. Other studies have confirmed the finding that RSV hospitalized infants have increased risks for asthma,[49–51] however, in general the quality of these studies was considered to be poor.[52] Some studies showed that at school age lung function was lower in children who had been hospitalized for RSV as compared to healthy children.[25,53,54] Although symptoms may subside with age, an impaired function might persist over time.[55]

An important question is whether respiratory infections (as RSV) can cause asthma and lung function impairment or whether these infections are only indicators of (pre-existing) asthma or low lung function. This association has been studied in prematurely born infants and in children of atopic mothers. In prematurely born infants, children hospitalized for a viral lower respiratory tract illness (including RSV) had an impaired neonatal lung function,[56] and had a higher premorbid resistance of the respiratory system[57] as compared to non-hospitalized patients. In children of atopic mothers, airway hyperresponsiveness was a risk factor of acute severe bronchiolitis.[58] However, the largest number of RSV infections occur in otherwise healthy infants without any known risk factors.
In chapter six we showed that decreased compliance of the respiratory system in otherwise

healthy infants is a risk factor to develop a severe course of RSV bronchiolitis, requiring hospitalization during RSV infection. Furthermore, decreased resistance was an independent risk factor for post-RSV wheeze. This suggests that lower lung function in school aged children that were previously hospitalized for RSV bronchiolitis, cannot be exclusively attributed to the RSV infection itself, but might at least be partially pre-existent. This finding also supports the hypothesis that RSV infection may be the earliest stimulus for wheezing in children who are predisposed to wheeze by genetic susceptibility or pre-existing abnormal lung function at birth.[59] Whether the RSV infection itself adds to this lung function impairment is unknown.

In chapter seven we studied the effect of early initiated high-dose extra fine beclomethasone in infants previously hospitalized for RSV bronchiolitis on lung function, and risk of asthma at the age of 6 years. In line with the initial study, in which we studied the effect of this intervention on recurrent wheeze, we did not find any long term effects of the intervention with respect to lung function, bronchial hyper responsiveness and risk of physician diagnosed asthma. These results are in contrast to previous studies, in which decreased risks of asthma were seen after treatment with inhaled steroids for shorter periods as our study.[29,30] In chapter seven, we also performed lung function measurements and we compared asthma prevalence and lung function in the children who had been hospitalized for RSV bronchiolitis to an unselected healthy birth cohort. We established a 3.2 fold increased risk of current wheeze and a 3.1 fold increased risk of current asthma in hospitalized RSV bronchiolitis patients compared to non-hospitalized children. As the prevalence of wheeze and asthma in our birth cohort is comparable to that in 6-7 year old children in western surrounding countries,[60] we feel that this group reflects the general population of the Netherlands with respect to wheeze and asthma. In line with previous studies,[25,51,61] we found that hospitalized RSV bronchiolitis patients had a mean FEV_1 percentage predicted that was 6.8% lower compared to non-hospitalized children.

As described in the Introduction section of this thesis, the term 'asthma' no longer reflects a single disease entity but rather describes a collection of different wheezing phenotypes. In a recent study from the PIAMA cohort, using longitudinal data from 6-8 years, different wheezing phenotypes were identified, and these were confirmed in the ALSPAC cohort (both large birth cohort studies).[62] The authors also speculated about the development of lung function in the different phenotypes. Table 1 shows the different phenotypes, with hypothesized neonatal lung functions at birth, and measured lung function and asthma development at age 6-8.[63]

Table 1. Wheezing phenotypes and lung function development[63]

	Lung function at birth	Lung function at age 6	Asthma development
Never-infrequent wheeze	ref.	ref.	No
Transient early wheeze	↓	↓/=	No
Intermediate onset wheeze	=	↓	Yes
Late onset wheeze	=	↓	Yes
Persistent wheeze	↓	↓↓	Yes

Transient early wheezers are thought to have a diminished neonatal lung function level, before a first infection occurs. They catch up in lung growth, leading to less diminished lung function levels compared to 'never wheezers' around school age than at birth. Persistent wheezers do have an even lower lung function level directly after birth as compared to transient early wheezers. The airway growth remains diminished compared to never wheeze during childhood, and leads to a lower lung function level at school age. Interestingly, these children are also at risk to develop allergic sensitisation before age 4.

The asthmatic children from our RSV-cohort (chapter seven) would best match the lung function characteristics belonging to the persistent wheezers, while the children that have no longer respiratory complaints at age 6, belong to the transient early wheezers. How these two groups differ pathophysiologically is currently unknown, but it is acknowledged that normal lung development during the fetal period (and especially the first 16 weeks) is crucial in the development of healthy lungs.[64] Factors affecting this development may have effects up to adulthood.[65,66] Risk factors for impaired neonatal lung function, as maternal smoking, and genetic constitution may be different between those phenotypes, accounting for at least part of the differences in neonatal lung function and lung function later on in life.

The question whether RSV is causally related to asthma, can only be answered by the follow up of effective RSV-prevention studies, such as the study by Blanken et al.[27] Another important question that remains unanswered is whether RSV adds to lung function impairment, or whether the lung function impairment is completely pre-existent and lung function measured at child age is due to tracking of lung function only. Therefore it is required to obtain lung function measurements before and at several time points after RSV bronchiolitis, in for instance a high risk birth cohort. Adequate adjustment for other potential confounders factors (as smoke exposure, other viral pathogens) is required to prove causality between RSV and lung function decline. Although this is a time consuming and expensive approach, it may be beneficial as low lung function in adulthood is one of the strongest predictors of chronic airway obstructive pulmonary disease later on in life,[55] and hypothesizing that

RSV adds to the lung function impairment, long term problems may be prevented. Finally, most studies are approached from either the cause or effect perspective. An approach that combines both these approaches might prove beneficial.

This thesis shows that a severe RSV RTI is associated with asthmatic symptoms in childhood, and respiratory tract infections are a major determinant of asthma control, which again affects health related quality of life. Due to the large number of circulating respiratory pathogens in young symptomatic and asymptomatic children, and the inability to prevent them from transmitting to others or to affect the clinical course of reparatory tract infections, it is unlikely that complete asthma control in asthmatic patients that respond to viruses with wheezing will be reached in the near future. It may even be possible that a proportion of children, currently considered as 'severe asthmatic patients' are simply more prone to viral infections, and therefore difficult to treat. As this category of asthmatic children has also been shown to be less steroid-responsive,[67] decisions about further step up of inhaled steroids, or addition of oral steroids should be taken cautiously.[68]

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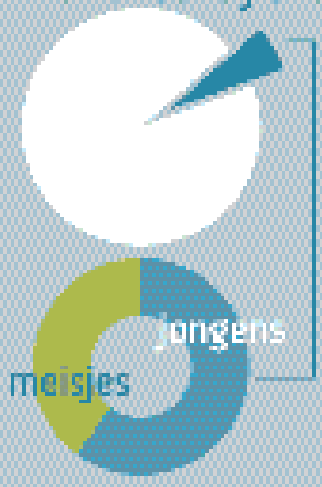
Chapter 10

Infographic
Nederlandse samenvatting
Contributing authors
List of publications
Curriculum Vitae
Dankwoord

Astma bij kinderen

Komt voor bij 6 %



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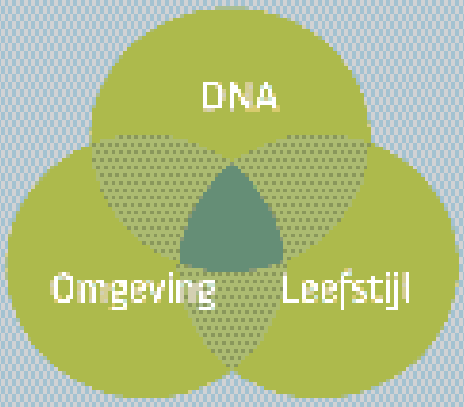


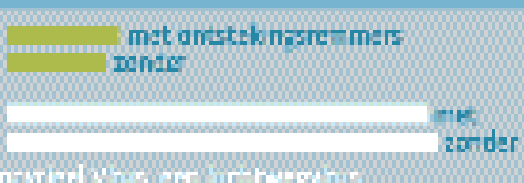
Na ernstige RSV* een grotere kans op astma

	Milde RSV	Ernstige RSV
Kans op astma	x1	x3
Longfunctie	100%	93%

Longfunctie baby voorafgaand aan RSV

Soepelheid luchtwegen	++	+/-
Weerstand luchtwegen	↓	↑

Ontstekingsremmers voorkomen astma na ernstige RSV niet



* RSV = Respiratoir Syncytieel Virus, een luchtwegvirus

Kinderen die meer last hebben van astma hebben vaker luchtweginfecties

Oor

≥3

Verkoudheid

≥4

Factoren die kwaliteit van leven beïnvloeden

Piepklachten uitgelokt door:

Voedsel Emoties

Herfst

Slechtere kwaliteit van leven

Astmatische luchtwegsymptomen

Rook

≥1

- Ernstige RSV is een vroege indicator voor astma op kinderleeftijd
- Hoe meer luchtweginfecties, hoe meer astma symptomen...
- en hoe slechter de kwaliteit van leven

Astma bij kinderen: oorzaken en effecten op het dagelijks leven

Astma is een veelvoorkomende aandoening bij kinderen: op basisschoolleeftijd heeft ongeveer 4-7% van de kinderen astmatische luchtwegklachten. De gevolgen van deze ziekte kunnen op verschillende manieren worden gemeten, bijvoorbeeld: de hoeveelheid klachten (dit noemen we 'astma controle'), de effecten op de luchtwegen (door het meten van longfunctie onderzoek), en de gevolgen van de ziekte op kinderen in hun dagelijks leven (kwaliteit van leven). In dit proefschrift beschrijven we enkele van deze gevolgen, evenals het effect van het RS-virus (RSV, een veelvoorkomende veroorzaker van luchtweginfecties) op de ontwikkeling van luchtwegsymptomen en longfunctie.

Hoofdstuk 1: Algemene inleiding

Over de definitie van astma bestaan nog veel onduidelijkheden. Internationale richtlijnen omschrijven astma als een ziekte die gekenmerkt wordt door hoesten, piepen en benauwdheid. Dit gaat vaak gepaard met een omkeerbare vernauwing van de luchtwegen en overgevoeligheid van de longen. Hoewel dit vrij eenduidig lijkt, worden tussen kinderen grote verschillen gevonden; zowel de klachten als de longfuncties verschillen sterk. Daarnaast is er variatie in de manier waarop de ziekte verloopt. Daarom is het wellicht beter om niet van astma te spreken, wat suggereert dat het slechts één enkele ziekte is, maar van astma-syndromen. Door het verkrijgen van kennis over zowel oorzaken van astma-syndromen, als factoren die de astma controle en kwaliteit van leven beïnvloeden, kan de zorg voor kinderen met astma worden verbeterd.

In dit proefschrift staat het effect van het RS-virus op de ontwikkeling van luchtwegsymptomen en longfunctie centraal. Het RS-virus is een luchtwegvirus waarmee nagenoeg ieder kind voor de leeftijd van 2 jaar minimaal éénmaal besmet raakt. Bij de meeste kinderen veroorzaakt het slechts een snotneus, maar sommige kinderen worden ernstig benauwd en moeten daarom opgenomen worden in het ziekenhuis. Zo'n ernstige virusinfectie, waarvoor ziekenhuisopname noodzakelijk is, wordt in verband gebracht met de ontwikkeling van astmatische luchtwegklachten op kinderleeftijd. Een klein deel van de kinderen heeft een grotere kans op deze ernstige vorm van RSV, doordat ze bijvoorbeeld te vroeg geboren zijn. Maar van het grootste deel van de kinderen die een ernstige RSV-infectie doormaakt, kunnen we dat niet voorspellen. Door deze virusinfectie te behandelen, bijvoorbeeld met hoog-gedoseerde ontstekingsremmers, zouden langetermijngevolgen, zoals astmatische luchtwegklachten misschien kunnen worden voorkomen.

Hoofdstuk 2: Het Luchtwegportaal

Om verschillen tussen de diverse astma-syndromen bij kinderen te onderzoeken is een online applicatie ontwikkeld: het Luchtwegportaal. Met de gegevens uit het Luchtwegportaal kunnen veel vragen met betrekking tot karakteristieken van kinderen met astma of andere allergische aandoeningen worden beantwoord. Het verzamelen van gegevens gebeurt met vragenlijsten over vijf groepen aandoeningen: astma, hooikoorts, luchtweginfecties, eczeem en voedselallergie. Naast een onderzoeksfunctie heeft het Luchtwegportaal ook een informatiefunctie. Zo kunnen ouders informatie vinden over de vijf aandoeningen.

Het Luchtwegportaal wordt gebruikt binnen een Expert Netwerk. Dit netwerk bestaat uit professionals die werken volgens vastgestelde richtlijnen, waardoor de behandelwijzen vergelijkbaar worden. Naast kinderlongartsen, zijn er ook kinderallergologen, -dermatologen, -infectiologen, -KNO artsen en huisartsen werkzaam binnen dit netwerk.

Hoofdstuk 3: Luchtweginfecties en astma controle

In dit hoofdstuk beschrijven we de relatie tussen het aantal luchtweginfecties en de hoeveelheid astmatische luchtwegklachten (astma controle). Verschillende studies tonen aan dat een luchtweginfectie een belangrijke uitlokkende factor is voor een aanval van astma bij kinderen. Het is onbekend of de hoeveelheid astmatische luchtwegklachten verschilt wanneer het kind bovenste luchtweginfecties (bv. oorontstekingen of verkoudheden) of juist lagere luchtweginfecties (bv. een bronchitis) doormaakt. Met data uit het Luchtwegportaal van 654 astmatische kinderen, hebben we onderzocht of kinderen die vaker een luchtweginfectie hadden doorgemaakt in het afgelopen jaar, een slechtere controle van hun astma hadden. We concludeerden dat kinderen die een groter aantal luchtweginfecties hadden doorgemaakt in het laatste jaar, meer astmatische luchtwegklachten hadden ten tijde van het invullen van de vragenlijst. Daarnaast onderzochten we of de mate van controle afhankelijk was van het type luchtweginfectie dat een kind doormaakte. Uit dit onderzoek bleek dat er geen verschillen zijn in de mate waarin oorontstekingen, verkoudheden of lagere luchtweginfecties de astma controle beïnvloeden.

Hoofdstuk 4: Factoren die de kwaliteit van leven beïnvloeden

Het is bekend dat astma controle een grote invloed heeft op de kwaliteit van leven van kinderen met astma. Kwaliteit van leven wordt echter niet alleen door de klachten zelf beïnvloed, maar ook door de fysieke, sociale en emotionele gevolgen van astma. In de huidige richtlijnen wordt geadviseerd om kwaliteit van leven bij kinderen met astma periodiek te meten.

In de literatuur zijn verschillende factoren beschreven die van invloed zijn op de kwaliteit van leven bij kinderen met astma. De hoeveelheid astmatische luchtwegklachten (astma controle) blijkt de belangrijkste factor; meer klachten leiden tot een slechtere kwaliteit van leven. Weinig is echter bekend over welke andere factoren de kwaliteit van leven beïnvloeden, zonder dat die worden verklaard door de hoeveelheid astmatische luchtwegklachten die een kind ervaart. Om meer inzicht in deze factoren te krijgen, gebruikten we data uit het Luchtwegportaal van 310 kinderen met astma. Drie factoren bleken de kwaliteit van leven te verslechteren, zonder dat dit kon worden toegeschreven aan de hoeveelheid astmatische luchtwegklachten die een kind had: een verergering van piepende luchtwegklachten door het eten van bepaalde voedingsmiddelen, emoties en het herfstseizoen. Hoewel kennis over deze factoren interessant is, realiseren we ons dat deze factoren moeilijk te beïnvloeden zijn. Het is wel aan te bevelen om angsten en emoties meer bespreekbaar te maken, om zo de kwaliteit van leven bij kinderen met astma positief te beïnvloeden.

Hoofdstuk 5: Astma en voedsel allergie

In veel gevallen heeft een kind last van meerdere allergische aandoeningen. Zo hebben kinderen met astma ook regelmatig voedselgerelateerde klachten. De meest betrouwbare test om te onderzoeken of voedselgerelateerde klachten worden veroorzaakt door een voedselallergie, is de voedselprovocatie. Dit is een test waarbij het voedingsmiddel dat klachten zou geven in steeds hogere doseringen wordt gegeven, onder strikte supervisie. We onderzochten in dit hoofdstuk of de aanwezigheid van allergische aandoeningen, en in het bijzonder astma, een voorspeller is voor de uitkomst van een voedselprovocatie. Daarnaast werd het effect van andere persoonsfactoren, vragenlijstfactoren en de aanwezigheid van eiwitten tegen het voedingsmiddel in het bloed (sIgE) onderzocht.

De aanwezigheid van astma bleek de uitkomst van de voedselprovocatie niet te voorspellen. Maar de uitslag van de voedselprovocatie kon heel nauwkeurig worden voorspeld met het type allergeen, de tijd waarbinnen klachten ontstaan na inname van het allergeen (op basis van de vragenlijst) en de hoogte van het sIgE. Met deze voorspelregel kan het aantal voedselprovocaties verminderd worden met minimaal 25%.

Hoofdstuk 6: Longfunctie op babyleeftijd en de ernst van de RSV infectie

In dit hoofdstuk beschrijven we de relatie tussen longfunctie op de babyleeftijd en de ernst van de RSV infectie. Eerdere studies hebben al een verband laten zien tussen lagere longfunctie na de geboorte en luchtwegklachten in het eerste levensjaar. In hoog-risico groepen (te vroeg geboren baby's of kinderen van ouders met allergische ziekten) is er ook een verband gevonden tussen een lagere longfunctie op babyleeftijd en een verhoogd risico

op een ernstige lagere luchtweginfectie door RSV. Het grootste deel van de kinderen dat een ernstige RSV-infectie doormaakt, heeft geen bekende risicofactoren. Daarom hebben we bij gezonde kinderen onderzocht of een lagere longfunctie een verhoogd risico geeft op een ernstige RSV infectie en of een lagere longfunctie een grotere kans geeft op piepklachten na een RSV infectie. Deze vragen hebben we beantwoord met data uit het WHeezing Illnesses STudy LEidsche Rijn (WHISTLER) onderzoek. Dit is een geboorte cohort waarbij bij alle baby's in Leidsche Rijn (Utrecht) longfuncties zijn gemeten - nog voordat zich luchtwegklachten konden ontwikkelen. Ouders hielden tijdens het gehele eerste levensjaar dagboekjes bij waarin ze de luchtwegklachten van hun kind noteerden. Bij een deel van de kinderen werd gedurende het eerste levensjaar af en toe een kweekje afgenomen (een wattenstokje met neus- en keelslijm) om te onderzoeken of er RSV aanwezig was in de luchtwegen. De kinderen die opgenomen waren geweest voor een ernstige RSV-infectie, werden vergeleken met de kinderen waarbij we in het eerste levensjaar wel RSV vonden in de kweekjes, maar die daar niet zo ziek door werden dat ze moesten worden opgenomen. Kinderen met minder soepele luchtwegen (lagere Crs) bleken een verhoogde kans te hebben op een ernstige RSV-infectie. Kinderen met nauwere luchtwegen (verhoogde Rrs) hadden een verhoogde kans op piepen na de RSV-infectie. Hieruit concluderen we dat RSV niet de veroorzaker is van lagere longfuncties bij kinderen na een RSV infectie, maar dat deze lagere longfuncties – in elk geval gedeeltelijk – al voor het doormaken van de RSV-infectie bestaan.

Hoofdstuk 7: Late effecten van ontstekingsremmers voor RSV

Na een RSV-infectie houden veel kinderen last van piepklachten. In een eerdere studie hebben we laten zien dat de behandeling van RSV met hoog-gedoseerde ontstekingsremmers tijdelijk voor vermindering van de piepklachten zorgde. Na een jaar was deze vermindering van piepklachten echter verdwenen. In dit hoofdstuk onderzochten we of deze behandeling op kinderleeftijd (6 jaar) effect had op het ontwikkelen van astma en longfunctie afwijkingen. Alle kinderen die tussen 2004 en 2006 opgenomen werden in het ziekenhuis vanwege een RSV-infectie, werden verdeeld in twee groepen die drie maanden lang een medicijn moesten gebruiken: één groep kreeg de ontstekingsremmer, de andere groep een placebo (nep-medicijn). Dit onderzoek laat zien dat de behandeling van een ernstige RSV-infectie met ontstekingsremmers ook op de lange termijn geen effect heeft op de ontwikkeling van astma-symptomen en longfunctie. We concluderen op basis van deze studie dat het behandelen van RSV met hoog-gedoseerde ontstekingsremmers geen positief effect heeft op luchtwegklachten op de lange termijn.

Hoofdstuk 8: RSV en astma ontwikkeling

Zoals eerder beschreven, is in meerdere onderzoeken het verband bestudeerd tussen RSV

en astma. Wanneer deze onderzoeken kritisch worden bekeken, kan worden gesteld dat de kwaliteit van deze onderzoeken matig is. Dit kan komen door de controlegroep, die eigenlijk geen goede controlegroep is, of doordat in de analyse niet voor 'vertekening' is gecorrigeerd waardoor het de vraag is of de associaties die gevonden zijn wel correct zijn. In dit hoofdstuk vergeleken we de in het ziekenhuis opgenomen kinderen met een RSV-infectie (uit de studie beschreven in hoofdstuk 7), met de groep gezond geboren baby's (die we beschreven hebben in hoofdstuk 6). We onderzochten of het risico op piepklachten en astma op 6-jarige leeftijd samenhangt met het doormaken van een ernstige RSV-infectie op babyleeftijd (<1 jaar).

Dit onderzoek laat zien dat kinderen die worden opgenomen in het ziekenhuis met een ernstige RSV-infectie een drie maal hogere kans hebben op piepen en astma op de leeftijd van 6 jaar, in vergelijking tot kinderen die niet opgenomen zijn geweest. Ook hebben kinderen die opgenomen zijn geweest in het ziekenhuis voor een ernstige RSV-infectie een lagere longfunctie dan kinderen die niet opgenomen zijn geweest. Dit onderzoek bevestigt dat kinderen die opgenomen zijn geweest voor een ernstige RSV infectie, een verhoogde kans hebben op astmatische klachten en longfunctie afwijkingen. Of dit een gevolg van de RSV-infectie zelf is, kan op basis van dit onderzoek niet worden geconcludeerd.

Hoofdstuk 9: Algemene discussie

Dit proefschrift wordt afgesloten met een algemene discussie van de resultaten van de verschillende onderzoeken. Daarnaast doen we aanbevelingen voor toekomstig onderzoek. Om beter te kunnen voorspellen wat de beste therapie is voor een kind, blijft het onderzoeken van voorspellers van een goede therapierespons bij astmatische kinderen belangrijk. Daarnaast is het belangrijk om te onderzoeken wat het effect van een ernstige RSV-infectie is op de ontwikkeling van longfunctie afwijkingen. Dit zou onderzocht kunnen worden door longfunctie te meten voor- en na een ernstige RSV infectie in bijvoorbeeld een hoogrisico cohort.

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Curriculum Vitae

Kim Zomer-Kooijker was born on June 2nd 1982 in Velp, the Netherlands. She graduated from secondary school in 2000 at the Greydanus College in Zwolle. At that same year she started as a nurse in training at the HAN University of Applied Sciences, and after a year she was able to start her medical training at the Radboud University in Nijmegen. During the study period, she participated in an investigation at the Department of Anaesthesiology of the Radboudumc in Nijmegen. The topic of the research was pain experience after surgery for breastcancer. She did several optional subjects, of which an internship tropical medicine in Tanzania.

After graduation in 2007 she worked as a resident at the department of Paediatrics at the Gelderse Vallei Hospital in Ede, the Netherlands (supervisor Dr. G. van Enk), followed by a short period at the department of Paediatrics in the Wilhelmina Children's Hospital in Utrecht.

In January 2010 she started working on the research described in this thesis under supervision of Prof. Dr. C.K. van der Ent and Dr. C.S.P.M. Uiterwaal. She obtained her Master of Science degree in Clinical Epidemiology at the Utrecht University in 2013.

Kim is married to Wilmar, and together they have a son, named Quinten.

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