Towards asthma control in children in general practice: asthma insights and reality

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TOWARDS ASTHMA CONTROL
IN CHILDREN IN GENERAL PRACTICE
Asthma Insights and Reality
TOWARDS ASTHMA CONTROL
IN CHILDREN IN GENERAL PRACTICE
Asthma Insights and Reality

ACADEMISCHE PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Aula der Universiteit
op woensdag 12 december 2007, te 14.00 uur

door

Wanda Hagmolen of ten Have

geboren te Ermelo
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Introduction
Chapter 1

In this introduction an outline is given of the natural history of asthma and the present situation on asthma control with a special focus on children and adolescents. Also, background information is given on asthma pathophysiology and the treatment goals of asthma, and finally the benefit of guidelines and the need for implementation strategies of these guidelines in clinical practice is explored. At the end of the introduction, the aim, research questions and outline of the thesis are presented.

Definition of asthma, severity and control

Asthma is a chronic inflammatory disorder of the airway wall in which many cells and cellular elements play a role. Chronic inflammation of the airway wall is associated with airway hyperresponsiveness (AHR), an abnormal bronchoconstrictive reaction of the airways to certain triggers that does not occur in healthy individuals. AHR leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow limitation within the lung that is often reversible, either spontaneously or with treatment [1]. To participate in the study described in this thesis patients were eligible when asthma medications were prescribed more than once in the year before selection. An asthma diagnosis was verified at baseline of the study by means of asthma symptoms, AHR and medication usage.

Asthma severity can be classified in four distinct categories varying from mild intermittent to severe persistent asthma [1]. Besides asthma severity, the concept of asthma control is also widely used. Although closely related, asthma severity and level of control are two distinct concepts. Asthma severity is a relatively stable characteristic of the individual that may change slowly over time, whereas level of control reflects current functioning and may change markedly over relatively short periods of time. Control of asthma refers to reduction of the clinical manifestation of asthma achieved with treatment, and reflects adequacy of treatment [2]. In this thesis we refer to both: asthma severity and level of control, although they could not always be clearly distinguished with the methods used in this study. For example, participants with moderate to severe AHR and symptoms of asthma might have more severe asthma but also might have mild or moderate severe asthma that is not well controlled.

Pathophysiology of asthma

Chronic inflammation of the airway wall and excessive airway sensitivity to various triggers are features that asthma patients have in common. Genetic and environmental factors are generally accepted to play an important role in the development and presentation of asthma. The pathways of inflammation are complex, in which many inflammatory cells, including T-cells, basophils, eosinophils, mast cells, macrophages, epithelial cells, fibroblasts, and bronchial
smooth muscle cells are involved (Fig. 1). Eosinophils play an important role by release of pro-inflammatory and cytotoxic mediators, resulting in vascular leakage, hypersecretion of mucus, smooth muscle contraction, epithelial shedding and AHR [3]. Acute inflammation is often beneficial; it is a non-specific response of tissues to injury and generally leads to repair and restoration of normal structure and function. In contrast, asthma represents a chronic inflammatory process of the airway wall followed by healing resulting in an altered structure, referred to as a remodelling of the airways [4-6].

Airway hyperresponsiveness

In this thesis the degree of AHR is the primary study outcome. AHR is characterized by excessive airway narrowing in response to relatively low provocative levels of pharmacological (e.g. histamine and methacholine) or non-pharmacological stimuli (e.g. exercise and cold air) [7]. The mechanisms of AHR can be plural [4]. The ultimate mechanism by which these stimuli narrow the tracheobronchial tree is by inducing airway smooth muscle (ASM) contraction. First, excessive contraction of ASM may result from increased volume and/or contractility of ASM cells. Second, the airway wall of patients with asthma is usually characterized by an increased thickness involving an increase in smooth muscle mass and mucous glands, vascular congestion, fibrosis and thickening of the basement membrane. The thickened airway wall leads to a markedly and permanently reduced airways calibre that amplifies due to contraction of ASM for geometric reasons (Fig. 2) [3-5]. And third, sensory nerves may be sensitized by inflammation, leading to exaggerated bronchoconstriction in response to sensory stimuli. AHR is regarded as the resultant of these processes in the bronchi and may lead to excessive narrowing of the airways and a loss of the maximum plateau of contraction [8;9]. Non-asthmatic individuals and mild asthmatics appear to be

Figure 1. Mechanisms of acute and chronic inflammation in asthma and remodelling processes. Reproduced from Bousquet et al. [3].
Chapter 1

protected against the excessive airway narrowing that occurs in severe asthmatic patients; although their airways narrow in response to these stimuli, the degree of airway narrowing reaches a plateau in most healthy subjects and in subjects with mild asthma after modest amounts of narrowing (Fig. 3).

In the laboratory, AHR may be provoked by the inhalation of ‘direct’ or ‘indirect’ stimuli. Direct stimuli include agents that cause airway constriction by a direct stimulating effect on the airway smooth muscle, of which histamine and methacholine are most commonly used. In contrast, indirect stimuli (e.g. hypertonic saline and adenosine-5’-monophosphate (AMP)) have a primary effect on inflammatory cells. Airway constriction is a secondary event caused by inflammatory mediators and neuropeptides that are released by these intermediary cells.

In this thesis inhalation challenge was performed with methacholine, which has been used to a large extent in studies to characterize asthma in children [7,10]. The relationship between inflammation and AHR is supported by studies in asthma patients that have shown AHR to be associated with an increased number of eosinophils in the airways [11-13], and a decrease in the severity of AHR after anti-inflammatory treatment [14]. Other studies have shown that there is no clear correlation between the severity of AHR to histamine or methacholine, and inflammatory cells or mediators in the bronchi [15-19]. However, despite this controversy, AHR to methacholine is thought to reflect the severity of asthma [14].

AHR is commonly used as diagnostic aid, but it may be used as predictor as well. It predicts the progression of airflow limitation in adults [20,21]. Children with more severe AHR tend to have persistent wheeze, whereas symptoms resolve in less severe AHR [22-24]. In asymptomatic subjects, AHR has been shown to constitute

Figure 2. Airway narrowing in healthy individuals (left) and in asthmatic patients with a moderately (middle) and severely (right) thickened airway wall. Reproduced from Ph.H. Quanjer: www.spirxpert.com.
a risk factor for the development of asthma, and impaired lung function later in life [24-30].

The natural history of asthma

Only a few studies followed children with different patterns of wheezing and asthma from early childhood or from birth into adulthood [31-35]. Current guidelines are largely based on findings of these studies. The oldest follow-up study was set up in 1964 at the Royal Children’s hospital in Melbourne, Australia by the late Howard Williams [35;36]. Children were enrolled at age 7 years and were reviewed at ages 10, 14, 21, 28, 35, and 42. Over the years, the symptoms and FEV$_1$ in each of these groups continued to reflect the differences in the initial severity. Some of the children who never wheezed (10%) or had wheezing bronchitis (15-28%), and more of the children who had asthma (52-76%) at enrolment had frequent or persistent asthma by the age of 42 years (Table 1). Most children with ‘severe asthma’ at enrolment had continuing symptoms and a reduced lung function into adult life. In contrast, children who had ‘mild wheezy bronchitis’ generally had complete resolution of symptoms in adult life. It should be noted that the outcome for most participants was achieved despite the fact that anti-inflammatory treatment was not available for most of their childhood (Inhaled corticosteroids (ICS) are available since the early 1980s). At age 35, 85% of subjects in the ‘severe asthma’ group demonstrated increased AHR compared to only 21% of those in the two ‘wheezy bronchitis’ groups. However, the latter showed more AHR than the control subjects, even when there had been no asthma symptoms for more than 3 years [37]. The presence of hay fever, eczema, or positive skin test results increased the risk of more severe asthma in adult life.

A second follow-up study was initiated in 1966 in Groningen, the Netherlands. These hospital-based children were enrolled at the age of 5 to 14 and followed till
Chapter 1

Table 1. Distribution of asthma and lung function in participants aged 42 according to severity of asthma at age 7 or 10.

<table>
<thead>
<tr>
<th>Condition at enrolment</th>
<th>Condition at age 42</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No recent asthma</td>
<td>Infrequent asthma</td>
</tr>
<tr>
<td>Mild wheezy bronchitis</td>
<td>40 (66)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
<td>50 (57)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Asthma</td>
<td>28 (29)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Severe Asthma</td>
<td>8 (11)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Control</td>
<td>73 (85)</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

Data are presented as number of children with percentage of subgroup or as mean value with 95% Confidence Interval. FEV₁: Forced Expiratory Volume in one second as percentage of predicted. * P < 0.001 compared with controls.

Reproduced from Horak et al. [36].

Age 42. Severity of airflow limitation and less improvement over time predicted whether these individuals had more severe AHR at older age [38]. A higher lung function level in childhood and a higher subsequent increase in FEV₁ was associated with complete and clinical remission [39].

A first birth cohort study came from Dunedin, New Zealand, and consisted of children born in 1972 or 1973 [33]. They were seen every 2 years between 3 and 15 years and then at 18, 21 and 26 years. By the age of 26 years, 51% of 613 children had reported wheezing more than once. Eighty-nine children (14.5%) had wheezing that persisted from childhood to 26 years of age; 9.5% had intermittent wheezing episodes and 27% had “persistent” wheezing symptoms but were at some point during follow-up in remission. Almost half of these children (n = 76; 12.4% of total group) subsequently relapsed by the age of 26. Sensitization to house dust mites predicted the persistence of wheezing (OR 2.4) and ‘relapse’ (OR 2.2, as did AHR (defined as a PC₂₀ ≤ 8 mg/ml or a bronchodilator response > 10% at any assessment from 9-21 years; OR 3.0 for both). AHR was assessed by means of a methacholine challenge test [40]. Other factors predicting persistence or relapse were female gender, smoking, and early age at onset. Pulmonary function was consistently lower in those with persistent wheezing than in those without persistent wheezing (FEV₁ 97% of predicted versus 101 to 106% of predicted at age 26).

The second and important birth cohort is the Tucson Children’s Respiratory Study initiated in 1980 [32;34]. In this study 826 children were classified into four phenotypes at the age of 6 years: (1) ‘never wheeze’; (2) ‘transient early wheeze’; (3) ‘late-onset wheeze’ (first episode of wheezing or lower respiratory illness after
third year); and (4) ‘persistent wheeze’. Children were again seen at ages 8, 11, 13 and 16 years. The ‘transient early wheezers’ started life with lower lung function and continued to have lower lung function until at least the age of 16 years, but these children had no more wheezing episodes as they grew older than the ‘never wheeze’ control group [32]. The ‘late-onset wheezers’ and the ‘persistent wheezers’ had more episodes of wheezing in late childhood and adolescence compared to the other two groups. The frequency of wheezing increased until the age of 11 years and then declined. The Tucson, Groningen, Dunedin, and Melbourne study findings suggest that outcomes in adolescent and adult asthma are mainly determined in early childhood and, therefore, support the recommendation to start asthma treatment early in life.

**Prevalence of asthma symptoms in children**

Asthma has become the most common chronic disease during childhood. The prevalence of asthma has been increasing during the last decades of the previous century all over the world [41]. However, there are indications that this increase has come to an end [42]. The causes of the increase in asthma prevalence and the more recent flattening off are not clear, and are currently a major focus for asthma epidemiology research worldwide.

From the International Study of Asthma and Allergies in Childhood (ISAAC), a study on asthma prevalence in different places and involving more than 700,000 children, it is known that striking international differences in asthma symptom prevalence exist [43-45]. The global prevalence of recent wheeze (≤ 12 month) was 11.1% amongst children aged 6-7 years and 13.2% amongst children aged 13-14 years. In order to observe trends in time, prevalence has been re-assessed recently with an interval of 5-10 years [46]. Although there was little change in the overall global prevalence of current wheeze, international differences in asthma symptom prevalence have been reduced, particularly in the 13-14 year age group, with decreases in prevalence in English speaking countries and Western Europe and increases in prevalence in regions where prevalence was previously low. The Netherlands did not participate in ISAAC, but we know from a Dutch study that in Dutch 8-9 years old children the prevalence of recent wheeze decreased in the last decades steadily from 13.4% in 1981 to 9.1% in 2001 [47]. This decrease paralleled an increase in usage of inhaled corticosteroids (ICS), and therefore probably reflects improved asthma control.

**Global Initiative of Asthma**

The Global Initiative of Asthma (GINA) is a worldwide supported initiative [1;48] that has been introduced in 1993 to improve patient care and to provide optimal long-term control of the disease. The goal of the GINA guideline is to reach and maintain well-controlled asthma, which is defined as: no or nearly no asthma symptoms (e.g. coughing, shortness of breath, wheezing and chest tightness); no
or nearly no night-time waking due to asthma; no episodes of asthma that require a
doctor visit, urgent care or hospitalization; no absences from school due to asthma;
normal activities and normal, or near normal lung function. The GINA goals can be
achieved with the use of long-term controller medication; mainly ICS [49]. ICS are
considered the most effective and safe treatment for mild to severe persistent
asthma in children and adults [50-54]. Ideally, long-term use of ICS should
minimise the need for quick-relief bronchodilators (in this study mainly short acting
$\beta_2$-mimetics).

**Poor asthma control in children**

The Asthma Insight and Reality in Europe (AIRE) study showed for the first time
since the introduction of the GINA guidelines that the level of asthma control in
adults and children was poor and fell far short of the goals set out in the GINA
guidelines (Table 2) [55]. Only 5% of the children with asthma met all the GINA
criteria for asthma control. In the Netherlands, 21 of 117 identified children with
asthma were classified as having severe persistent asthma [56]. The parents of 13
of these children (62.1%) however, reported well or complete controlled asthma.
This striking underestimation of asthma severity was also seen in adult patients
and in other European countries [56;57]. Not only parents, but also physicians may
underestimate asthma severity and overestimate the degree of asthma control in
children as is described in several studies and in more detail in chapter 2 of this
thesis [58-60].

**Table 2. The Global Initiative for Asthma (GINA) recommendations and the Asthma Insights
and Reality in Europe (AIRE) results.**

<table>
<thead>
<tr>
<th>GINA recommendation</th>
<th>AIRE result</th>
<th>Perc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal chronic symptoms</td>
<td>Daytime symptoms once a week;</td>
<td>38.2</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances at least once a week;</td>
<td>28.0</td>
</tr>
<tr>
<td>Minimal episodes</td>
<td>Reported episodes of coughing, wheezing, chest</td>
<td>51.5</td>
</tr>
<tr>
<td></td>
<td>tightness or shortness of breath in the last month;</td>
<td></td>
</tr>
<tr>
<td>No emergency visits</td>
<td>Unscheduled urgent care visits, last year;</td>
<td>36.0</td>
</tr>
<tr>
<td></td>
<td>Emergency visits, last year;</td>
<td>18.0</td>
</tr>
<tr>
<td>Minimal need for $\beta_2$-agonists</td>
<td>Used as-required $\beta_2$-agonists, last month;</td>
<td>61.0</td>
</tr>
<tr>
<td>No limitations on activities</td>
<td>Limited with sports;</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>Normal physical activity;</td>
<td>19.1</td>
</tr>
<tr>
<td></td>
<td>Disturbed Sleep;</td>
<td>31.2</td>
</tr>
<tr>
<td></td>
<td>School absence;</td>
<td>42.7</td>
</tr>
<tr>
<td>Normal or near normal lung function</td>
<td>Never had a lung function test.</td>
<td>60.5</td>
</tr>
</tbody>
</table>

Data presented as percentage children with a positive answer (as given by a parent) on the
stated question. Reproduced from Rabe et al. [55].

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Chapter 1

The AIRE study reported in detail on the use of health care facilities in 1999 (one year before the start of the ‘Almere Asthma Project’). General Practitioners (GP’s) were primarily responsible for the treatment of the majority of the children (60.7%). The GP was also the primary source of advice about asthma. However, in contrast to recommendations in asthma guidelines, a large proportion of children had no follow-up visits except when they were experiencing limitations due to their asthma. Forty percent of the Dutch children with asthma needed unscheduled urgent care in the past year, eight (6.8%) had to visit an emergency room of the hospital and four (3.4%) had to be hospitalized because of their asthma [56].

The use of quick reliever bronchodilator therapy in the Netherlands and other European countries was inappropriately high compared to the use of ICS and the severity of asthma symptoms [56]. Adherence with ICS was poor. From literature it is known that, amongst others, this may be due to concerns about side effects, beliefs on the perceived need, and poor understanding of the role of therapy [61]. Poor patient adherence with medication is a major factor contributing to poor asthma control regardless of asthma severity [62].

Consensus about asthma therapies in the Netherlands

As mentioned above, the majority of children with asthma in the Netherlands, are treated by the GP. A smaller group is treated by a paediatrician or a paediatric pulmonologist. Paediatric pulmonologists working in the Netherlands came in 1991 with a documented consensus on the long-term treatment of children with asthma [63;64], that was updated in 1997 [65] and 2003 [66]. In the same period GP’s, organized in the ‘Dutch college of General Practitioners’, developed a national asthma guideline for children with asthma treated in general practice [67], a guideline that was updated in 2006 [68]. With the development of both documents representatives of both fields (GP’s and paediatric pulmonologists) were involved in order to create unity in asthma treatment approaches by GP’s, paediatricians and paediatric pulmonologists. In addition, the allocation of tasks and responsibilities between GP’s and paediatricians resulted in the ‘National transmural consensus: asthma in children’ [69]. However, nothing was arranged to implement these guidelines and consensus documents in clinical practice. Subsequently, there was a need for the implementation of current guidelines in clinical practice.

Implementation of guidelines

Implementation can be defined as ‘the structured and planned introduction of a developed guideline or a change in clinical practice with the aim to change professional behaviour within an organization or within the organization of health care’. The main hypothesis of this thesis is that the national asthma management guideline is not optimally implemented in general practice. It is likely that the
understanding demonstrated by the GP, and the beliefs and convictions with which the GP’s communicate the evidence for efficacy of treatment, has an important effect on patients’ adherence. As our hypothesis is true, optimal implementation of the guideline will improve asthma management.

However, the implementation of evidence based clinical guidelines into routine daily practice is a major challenge. One has to deal with barriers and problems that resist change. For example, the child or the child’s parents can show lack of insight or have different, even unusual believes about asthma and asthma therapy, and this can lead to poor adherence to asthma therapy recommendations or inadequate self-management. On the other hand, barriers and problems also occur with physicians. The guideline and implementation strategy has to deal with knowledge and beliefs of the physician with regard to the efficacy of treatment and guideline recommendations.

In this thesis we focused the implementation strategy on the GP. The three strategies used in our randomized controlled trial were cumulative. The first strategy: distribution of the national asthma guideline was applied to all GP’s. The second strategy offered in addition a single educational session. During the educational session we emphasized a structured approach of the treatment of children with asthma, including frequent monitoring of the child’s asthma (i.e. once per three months), and usage of asthma medication, and in addition providing the child and the child’s parents with a written treatment plan and information on asthma, medication usage and asthma triggers. The third strategy, a onetime individualized treatment advice based on symptoms and lung function including AHR, was provided to GP’s of one group only, in addition to the first two strategies. In this way, we provide the GP with a thorough assessment of the severity of the disease and feedback on current therapy linked to a treatment advice. The combination was offered in order to restrict the workload of the GP. The general hypothesis was that this third strategy was superior in improving asthma control in general practice compared to the distribution of the guideline and the educational session alone.
Aim and research questions

The current randomized controlled study was set up to implement a national asthma guideline for the management of asthma in children in general practices in Almere.

The following research questions were formulated and investigated:

1. To what degree can GP’s assess the severity of their patients’ asthma with current tools?
   a. What do GP’s think about the severity of their patients’ disease and their asthma management? And does it match with reality? Are there differences in their beliefs compared to paediatricians?
   b. Can GP’s predict the level of severity of AHR by means of clinical information, which is currently recommended in asthma guidelines to assess the severity of asthma in general practice?
   c. Is the current approach to monitor asthma adequate to select those children who are not well controlled?

2. Does implementation of a national asthma guideline improve asthma control of children treated for their asthma in general practice?
   a. Is a combination of strategies including an individual treatment advice based on the level of asthma control and AHR, more effective as compared to the single distribution of the guideline and an educational session alone?

Outline of the thesis

In chapter 2, paediatricians and GP’s, both working with asthma patients, were questioned whether they could estimate their patients’ symptoms, their limitation of physical and social activities, and the use of asthma medication. Answers were compared with the answers given by the patients themselves in the AIRE study.

In chapter 3 a method to assess AHR in children using a single concentration of methacholine was validated and compared with a standard dosimeter method to test airway responsiveness.

In chapter 4 we evaluated whether moderate to severe AHR could be suspected with the use of routinely available clinical and environmental information. Therefore, we examined cross-sectionally, the level of control of asthma in 526 asthmatics aged 7-17 years.

In chapter 5 we assessed the efficacy of three cumulative strategies to achieve and maintain asthma control by evaluating change in AHR in 362 children with asthma in general practice after one year.
Chapter 1

The monitoring of children with asthma in general practice is based on the occurrence and frequency of asthma symptoms. In chapter 6, we question whether the current approach is optimal enough to identify all children in whom a sufficient level of asthma control is not reached.

In chapter 7 the inhaler technique of all participating children is presented. Essential and non-essential inhalation manoeuvres were recorded against inhaler-specific checklists. Correct and incorrect performances were related to patient's characteristics and asthma severity.

In chapter 8 we investigated whether children with reported exposure to mould or dampness differed from children who were not exposed with respect to asthma symptoms and AHR.

In chapter 9 the findings of this thesis are discussed and implications for daily practice and further research are considered.

In chapter 10 a summary of the findings in each chapter is presented.
What general practitioners and paediatricians think about their patients’ asthma

Norbert J. van den Berg, Wanda Hagmolen of ten Have, Ad F. Nagelkerke, Patrick J.E. Bindels, Job van der Palen, Wim M.C. van Aalderen

Chapter 2

Abstract
The Asthma Insight and Reality in Europe (AIRE) study showed that the current management and treatment of asthma in Europe falls short of the goals set in the GINA guidelines. Patient care may be negatively influenced by the physicians’ underestimation of their patients’ disease state, and overestimation of their patients’ knowledge of asthma management.

We interviewed 118 paediatricians and 152 general practitioners (response rate 70 and 86%, respectively) in order to get an insight into the physicians view on his patients’ asthma management. A questionnaire containing similar items to those used in the AIRE study was used.

Dutch physicians believe that the asthma of the majority of their patients is well controlled and underestimate the prevalence of daytime symptoms. They believe that their patients are aware of the differences between reliever medication and maintenance medication and overestimate the number of patients in possession of a written action plan.

Dutch paediatricians and general practitioners underestimate the severity of their patients’ disease state and overestimate their patients’ knowledge of disease management.

Introduction
Asthma is one of the most common diseases of childhood and impacts greatly on both the children and their parents’ well being. Asthma reduces the quality of life and the ability to exercise; it may result in the loss of sleep and consequently may impair concentration at school. Moreover, asthma is responsible for more school absenteeism than any other chronic disease in childhood [70]. This is reason for considerable concern.

Asthma control has been defined in terms of eight goals of management, known as the GINA guidelines [48]. Several authors conclude that although asthma treatment guidelines are generally accepted by physicians, their adherence to them is poor. This may lead to a failure to achieve these treatment goals [71-73].

The Asthma Insights and Reality in Europe (AIRE) study was published in November 2000. This multinational survey assessed the level of asthma control among current asthmatics from the patients’ perspective [55]. Asthmatic patients in seven countries in Western Europe, including the Netherlands were studied. It showed that the current state of management and treatment in Europe falls short of the goals for long-term asthma management and treatment as set by the GINA guidelines. This is in accordance with the observations of guidelines adherence in the USA [74]. The health care providers’ sound knowledge of the severity, and of the prevalence of (specific) asthma-related problems among their patients may contribute to a better adherence to guidelines. Underestimating the prevalence and severity of asthma symptoms may negatively influence patients’ care. We hypothesise that Dutch general practitioners and general paediatricians
underestimate the prevalence and severity of asthma symptoms amongst their patients. We asked general paediatricians and general practitioners to complete a questionnaire with similar items to those used in the AIRE study to obtain an insight into asthma from the doctor's perspective.

**Method**

The survey was conducted from August to November 2000. All 176 general practitioners attending a postgraduate course on asthma were invited to participate in the survey. These general practitioners, all worked in two cities in the Netherlands, Almere and Haarlem. These two cities have a mixed population more or less representative of the Dutch population. Two thirds of all general practitioners in Almere, and about half of the general practitioners in Haarlem answered the questionnaire. All general practitioners in Almere, and 60% of the general practitioners in Haarlem work in group practices. On average, 70% of all Dutch general practitioners work in group practices.

The survey amongst the paediatricians was also conducted during a postgraduate course on asthma for general paediatricians. These paediatricians were all general paediatricians (50% of all paediatricians in the Netherlands, approximately 600, work in general hospitals, 50% work in university hospitals). The invitations to participate in this paediatric asthma postgraduate course were being send to all general paediatric practices. About 80% of this group of paediatricians visits this postgraduate course every 4-5 years.

Both postgraduate courses were credited with medical education points. Before the start of the course, the physicians were asked to complete a questionnaire containing questions derived from the AIRE study. The surveys were performed prior to the AIRE publication in November 2000. The purpose of the questionnaire was explained before the physicians answered the questions. They were all aware that this questionnaire was not intended to test their knowledge on asthma skills.

**Questionnaire**

The questions were selected from the questionnaire of the AIRE study. This questionnaire was based on the American Thoracic Society (ATS) questionnaire with additional questions on healthcare use and limitation of activity [75]. We changed the questions such that the answers represented the physician’s own opinion about his patients’ perception of disease. For example: “Have you suffered from cough, wheezing, or shortness of breath during the day during the previous 4 weeks” was changed to “What percentage of your asthma patients suffer from...” (Table 1).

The data was analysed using Excel (Microsoft office 2000).
Chapter 2

Table 1. Questionnaire

<table>
<thead>
<tr>
<th>The following questions were asked</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Can you estimate the percentage of your asthma patients, having their asthma completely controlled?</td>
</tr>
<tr>
<td>2 Can you estimate the percentage of your asthma patients having no symptoms during the previous 4 weeks?</td>
</tr>
<tr>
<td>3 Can you estimate the percentage of your asthma patients who suffered from cough, wheezing, or shortness of breath during the day during the previous 4 weeks?</td>
</tr>
<tr>
<td>4 Can you estimate the percentage of your asthma patients who suffered from awakening by cough, wheezing or shortness of breath during the night, during the previous 4 weeks?</td>
</tr>
<tr>
<td>5 Can you estimate the percentage of your asthma patients who are aware of the difference between preventive medication use and medication for quick relief from asthma symptoms?</td>
</tr>
<tr>
<td>6 Can you estimate the percentage of your asthma patients having a peak flow meter in their possession?</td>
</tr>
<tr>
<td>7 Can you estimate the percentage of your asthma patients in possession of a peak flow meter, who use this device regularly?</td>
</tr>
<tr>
<td>8 Can you estimate the percentage of your asthma patients who are in the possession of a written action plan for asthma treatment?</td>
</tr>
<tr>
<td>9 Can you estimate the percentage of your asthma patients who missed school during the previous 12 months, because of asthma?</td>
</tr>
<tr>
<td>10 Can you estimate the percentage of your asthma patients who missed work during the previous 12 months, because of asthma?</td>
</tr>
</tbody>
</table>

Results

Eighty-three of the 118 paediatricians answered the questionnaire (response rate 70%). One-hundred-and-fifty-two of the 176 general practitioners completed the questionnaire (response rate 86%).

The results of questions related to severity and prevalence of symptoms, impact of symptoms on daily functioning, and management issues of asthma are presented in Table 2. The results from the Dutch patients, included in this table, participating in the AIRE study were derived from the Executive Summary publication of GlaxoWellcome published in September 1999 [76].

Although only 25% of the Dutch patients consider their asthma completely controlled, all health care providers believe this percentage to be at least twice as high (with a maximum of 58% among general practitioners). Also 71% of the patients have daytime symptoms once a week, while the estimated percentage by paediatricians and general practitioners is considerably lower (24 and 22%, respectively).
Regarding medication use, the following was found: 77 and 66% of the paediatricians and general practitioners, respectively, think that patients know the difference between medication used for symptom relief and medication used for treatment of the underlying condition. Although 68% of the Dutch patients are aware that asthma is an inflammatory process, only 19% think that this condition can be treated and 24% of the Dutch patients report current use of inhaled corticosteroids.

Paediatricians and general practitioners, believe respectively that 47 and 20% of their patients are in the possession of a PEF meter and that 38 and 21% of these patients are using this PEF meter regularly. The AIRE survey showed that 50% of the Dutch asthma patients are in the possession of a PEF meter, but only 19% are actually using it on a regular basis. A 41% of Dutch patients report a limitation of physical activity, while paediatricians and general practitioners estimate that 33 and 34% of their patients, respectively, suffer from limitation of physical activity. Almost 51% of the patients report school absence, while the physicians estimate that only about 25% of their children are absent from school.

### Table 2. The Global Initiative for Asthma (GINA) recommendations, the Dutch participants in the AIRE survey compared to the answers of the Health Care Providers [76].

<table>
<thead>
<tr>
<th>GINA recommendation</th>
<th>AIRE result</th>
<th>Symptoms % Dutch patients</th>
<th>P</th>
<th>GP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/prevalence</td>
<td>Asthma completely controlled</td>
<td>25</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>No asthma symptoms during the week</td>
<td>24</td>
<td>56</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Daytime symptoms once a week</td>
<td>71</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances at least once a week</td>
<td>33</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Knowledge about medication</td>
<td>Difference preventive and reliever medication</td>
<td>24/61*</td>
<td>77</td>
<td>66</td>
</tr>
<tr>
<td>Management</td>
<td>Possession of a PEF meter</td>
<td>50</td>
<td>47</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Regular use of PEF meter</td>
<td>19</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>In possession of written action plan</td>
<td>17</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Impact on daily functioning</td>
<td>Limitation on physical activity</td>
<td>41</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>School/work absence</td>
<td>49/28b</td>
<td>26</td>
<td>23c</td>
</tr>
</tbody>
</table>

P: paediatricians; GP: general practitioners.
* 24% of patients used ICS as anti-inflammatory medication, 61% of patients used high levels of as required bronchodilator medication [55].
b Work absence adults.
c Work and school absence (GP).
Chapter 2

Discussion

In this descriptive study we have looked at physician’s perspective on the severity and impact of their patients’ asthma. We have shown that there is a substantial difference between the health care providers perspective compared to that of the patient regarding asthma in the Netherlands [76]. We found that physicians underestimate their patients’ symptoms, limitations of physical activity, school or work absence, and that they overestimate their patients’ knowledge of PEFR management and medication use. Paediatricians overestimate their provision of a written action plan, while general practitioners accurately estimate the percentage of patients that possesses such a plan.

Health care providers are consistent in underestimating their patients school and/or work absenteeism. Literature shows that 38-60% of paediatric asthma patients are frequently absent from school, assuming an average loss of schooldays due to asthma of 7-10 days per year per patient [77]. These figures are consistent with the AIRE survey [55]. Absence of school is mainly due to asthma symptoms overnight. The AIRE survey showed that approximately 50% of the asthmatic patients woke up at least once a week and 7% of the patients woke up every night due to their asthma. These percentages concur with the observations of Meijer et al. in children with asthma who were frequently controlled in an outpatient clinic [78].

We found that physicians overestimate their patients’ knowledge of PEF management and the use of medication. In our survey we found that paediatricians overestimate the number of patients that posses a PEF meter, while general practitioners quite accurately assess the percentage of patients that received a PEF meter. However while the general practitioners seem to assume that if patients have a PEF meter they use it, and thereby accurately asses the percentage using the device, paediatricians are aware that this may not be the case [79].

A 73% of the Dutch asthma patients are aware that inflammation of the airways is the underlying cause of asthma [55]. Only a minority knew that they used inhaled corticosteroids as anti-inflammatory medication. In addition they used disturbingly high levels of bronchodilator medication. Our data shows that physicians have great confidence in the patients’ knowledge of the use of different types of medication. In fact the majority of patients use inhaled corticosteroids for asthma exacerbations [55]. Physicians overestimate their patients’ knowledge of when and how to use their inhaled corticosteroids and bronchodilators.

Another disturbing observation is that only a few patients possess a written action plan. This latter observation is in accordance with the low percentage owning a written action plan in an Australian population [80]. Since even mild asthma may severely deteriorate, and the efficacy of such plans has clearly been demonstrated, all patients should be in the possession of such a plan [81].

A limitation of our study might be that the patients whose views/experiences are reported were not drawn from the patient population of paediatricians and general practitioners who completed the questionnaire. However, our observations are in
accordance with the observations of Price et al. who found similar results in the United Kingdom in a larger group of physicians who consistently underestimated the level of symptoms experienced by their patients [82].

A bias could be that physicians attending these asthma postgraduate courses may be more interested in asthma management than their colleagues that did not attend these courses. In this case the differences between the physicians views/experiences and those of the patient will have been underestimated.

Conclusion

In this descriptive study we have shown that paediatricians working in general hospitals and general practitioners underestimate their patients’ symptoms, limitation of physical activity, school or work absence. Paediatricians overestimate their patients’ knowledge about PEFR management, while general practitioners accurately estimate the use of PEF meters. Both groups of physicians overestimate their patients’ insight into the use of asthma medication. Paediatricians overestimate the number of times that they provide a written action plan, while general practitioners accurately estimate the percentage of patients that possess such a plan.

Practice Implications

One explanation may be that since the introduction of inhaled corticosteroids severe asthma exacerbations are less prevalent, leading physicians to believe that their patients’ asthma is better controlled. Our results suggest that doctors are not communicating adequately with their patients, as ongoing management difficulties are not being identified [83]. Lack of attention to the patients’ asthma management goals could be crucial in this discussion [84]. Our observations plus the tendency of patients to underestimate the severity of their condition are alarming. Physicians must be aware that overestimation of control by patients and doctors is a risk factor that may contribute to poor asthma management and merits further exploration.

Acknowledgement

The authors thank Mrs. S.A.B. Jurgens-Clur for her help with translating the manuscript.
Validation of a Single Concentration Methacholine Inhalation Provocation Test (SCIPT) in Children

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Chapter 3

Abstract

A new method to assess bronchial hyperresponsiveness (BHR) using a single concentration methacholine has already been validated in adults with asthma. Because the geometrical dimensions of the airways in children are different, the results from studies in adults cannot be extrapolated to children. In this study, we validated the single concentration methacholine inhalation provocation test (SCIPT) in children. Twenty-two children performed three methacholine inhalation challenge tests in random order. Two challenges were performed according to the SCIPT: doubling doses (0.03-1.8 mg; maximal cumulated dose 3.6 mg) were administered with an Aerosol Provocation System (Masterscope, Jaeger). The third challenge was performed according to a standard dosimeter method (SDM): doubling doses (0.002-1.8 mg; maximal cumulative dose 3.5 mg) were administered with a DeVillbiss 646 nebulizer. The degree of BHR is expressed as a PD$_{20}$. A difference of < 1.5 dose step was assumed to be due to intraindividual variation. We found an intraclass correlation of 0.91 between both tests according to the SCIPT and of 0.80 between the SCIPT and SDM. We found, according to the method of Bland and Altman, good agreement when comparing these two challenge tests. The single concentration inhalation provocation test is reproducible and shows good agreement with a standard dosimeter method to test bronchial responsiveness in children.

Introduction

Inhalation provocation testing can be used as a means of detecting and quantifying bronchial hyperresponsiveness (BHR) [7;85-91]. BHR is one of the characteristics of asthma. Assessment of BHR is a routine investigation in asthmatic adults and during the last decades also a more common investigation in school-aged children and adolescents [91-93]. Thanks to standardization and validation of provocation methods, assessment of BHR became comparable in different institutions and thus more relevant for diagnostics, therapeutic evaluation, and research [7;86-90;94]. There are two gold standard methods. The first is the tidal breathing method, introduced by Cockroft et al. [95]. The second one is the dosimeter method standardized by Chai et al. [96]. The dosimeter method is based on inhalation of doubling concentrations during inspiration by using a breath-actuated nebulizer. The dosimeter method is a highly reproducible, widely used method for measuring bronchial responsiveness. Nevertheless, these challenge tests are laborious and time-consuming for both the physician and the patient. Because concentration and cooperation of the child is crucial for the technical performance and the interpretation of the results of the challenge procedure, we were interested in a compacter version of the dosimeter method with a single concentration methacholine. The single concentration methacholine inhalation provocation test (SCIPT) has already been validated in adults with asthma [97]. The proposed
technique provides the advantage of a simpler challenge procedure than the established protocols.

In previous studies, the outcome of inhalation challenge methods in children were comparable with adults [92;93]. However, results of validation studies in adults cannot simply be extrapolated to children, because the functional development of the respiratory system changes from gestation to adulthood [98-100]. Moreover, inhaled aerosol deposition in the respiratory tract is not comparable between children and adults.

Therefore, the aim of this study was to validate the inhalation provocation test (SCIPT) in children. We investigated in a randomized manner the reproducibility of the SCIPT method and investigated whether the SCIPT method was in agreement with a SDM method for measuring bronchial provocation.

Materials and Methods

Three healthy volunteers were recruited among offspring of personnel working at the Flevohospital, and all other children were consecutively recruited from the paediatric outpatient department. In these children, BHR was tested either for diagnostic purposes or to evaluate their asthma. Children with a recent history of respiratory tract infection, clinical nonstable asthma, and/or a baseline FEV\(_1\) below 80\% of predicted before provocation were excluded.

Study Design

All 22 participating children performed twice an inhalation challenge test according to the single concentration inhalation provocation test (SCIPT) and once according to the standard dosimeter (SDM) method on 3 separate days at the same time (± 1 hour) of the day with intervals of 1 week. The challenge tests were performed in random order. All parents and children gave informed consent. The study was approved by the ethics committee of the Flevohospital and the CCMO (the central Dutch organization to approve and control research projects in children).

Measurement of Lung Function

Spirometric tests were performed according to the Spirometry Flow/Volume program (version 4.34; Jaeger, Würzburg, Germany). At baseline and after each provocation step, spirometry was repeated to assess FEV\(_1\). The best result of three FEV\(_1\) attempts was used for analysis. Provocation with methacholine was preceded by inhalation of phosphate-buffered saline (PBS) as a safety step.
Aerosol Generation and Inhalation: Single Concentration Inhalation Provocation Test

The aerosol was generated from an Aerosol Provocation System (Jaeger Masterscope + APS version 5.4; Würzburg, Germany), a medic aid side stream nebulizer primed with 2.5 mL solution and a nebulizer-power of 250 µL/min [97]. The aerosol was delivered into the mouth through a mouthpiece while the child was wearing a nose clip. The children breathed slowly from FRC to TLC several times until the aerosol was triggered with inspiration. The manoeuvre was without breath holding at TLC. Only a single concentration methacholine bromide 3.92% (784 mg = 20mL) was used. The SCIPT starts the challenge at a higher dose of methacholine than the SDM, respectively 33 and 1.7 µg. The doses of methacholine were doubled at each consecutive step by increasing the number of inhalations up to maximal 20 consecutive breaths and inhalation time (see Table 1). The intervals between the steps were fixed at 2 minutes. In general, starting at a larger dose can be easily done unless severity of asthma is taken into account. In children with (suspected) severe bronchial hyperresponsiveness, it is advised to start the challenge at a smaller dose.

Standard Dosimeter Method

The aerosol was generated from a DeVillbiss 646 nebulizer (Sunrise Medical HHG, Inc., Malsch, Germany) with its vent closed and primed with 3 mL solution [101]. The nebulizer was attached to a Rosenthal dosimeter (PDS Instrumentation, Inc., Louisville, KY) with a manual trigger and driven by air at 20 psi. The aerosol was delivered into the mouth through a mouthpiece while the child was wearing a nose clip. The child inspired as slowly as possible from FRC to TLC with a nebulization time of 0.6 seconds. A total of 20 µL of aerosolized solution was delivered to the mouth in four consecutive breaths. Methacholine bromide was given in doubling concentrations (see Table 2). The intervals between the provocation steps were fixed at 3 minutes. The degree of bronchial responsiveness was expressed as a PD20, a provocation dose that induces a 20% fall in FEV₁ from baseline.

<table>
<thead>
<tr>
<th>Table 1. Dose regimen for SCIPT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose number</td>
</tr>
<tr>
<td>Methacholine concentration (mg/mL)</td>
</tr>
<tr>
<td>Number of puffs</td>
</tr>
<tr>
<td>Nebulizer-time (seconds)</td>
</tr>
<tr>
<td>Nebulizer-power (µL/min)</td>
</tr>
<tr>
<td>Dose methacholine (µmol)</td>
</tr>
<tr>
<td>Dose methacholine (µg)</td>
</tr>
<tr>
<td>Cumulative dose methacholine (µg)</td>
</tr>
</tbody>
</table>
Statistical Analysis

Statistical analyses were performed with SPSS. First, the intraclass correlation coefficient (ICC) between the first and second SCIPT was calculated to assess reproducibility and between the first SCIPT and the SDM to estimate agreement. \( PD_{20_{\text{scipt}}} \) and \( PD_{20_{\text{SDM}}} \) were compared after log transformation. Second, the measurements were plotted in “Bland and Altman plots” to assess agreement between both assessments [102]. Power calculations were performed prior to the study. A difference of more than 1.5 dose steps is, in this study, regarded as a clinical relevant difference, and a difference of less than 1.5 dose steps is assumed to be due to intraindividual variation based on observations in within-subject repeatability studies [86;88;94]. With a power of 80% of achieving a significant result at the 0.05 level, the calculated sample size was 22 patients.

Results

All 22 children, 7-14 years old (mean 10.8, SD 2.43; 12F, 10M) completed the study. In Table 3, characteristics of the children are presented. Eighteen children had asthma according to ATS criteria. Two asthmatic children discontinued their medication 1 month before the study because they had been symptom-free for a long period. Fourteen stable children used fluticasone twice daily, nine children in combination with salmeterol, two additionally used montelukast. One child (no. 8) recruited from the pediatric outpatient clinic had a normal bronchial response. SCIPT was performed to evaluate dyspnea and fatigue. One of the healthy volunteers (no. 16) had BHR according to both tests, but no asthma symptoms. None of the children smoked.

Baseline FEV1 between the three assessments correlated very well with an ICC of 0.94 or higher \((P < 0.01)\). Mean (SD; 95% CI) values of \( PD_{20_{\text{scipt}}} \) 1st/2nd (after log transformation) were significantly higher than \( PD_{20_{\text{SDM}}} \): 2.90 (0.67; 2.60-3.20) vs. 2.66 (0.95; 2.24-3.08) \((P < 0.05)\).

Table 2. Dose regimen for Standard Dosimeter (SDM) method.

<table>
<thead>
<tr>
<th>Dose number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacholine conc. (mg/mL)</td>
<td>0.076</td>
<td>0.15</td>
<td>0.3</td>
<td>0.6</td>
<td>1.2</td>
<td>2.5</td>
<td>4.9</td>
<td>9.8</td>
<td>19.6</td>
<td>39.3</td>
<td>78.6</td>
</tr>
<tr>
<td>No. of puffs (5.6 mL/puff)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Dose methacholine (µmol)</td>
<td>0.007</td>
<td>0.014</td>
<td>0.028</td>
<td>0.06</td>
<td>0.11</td>
<td>0.23</td>
<td>0.46</td>
<td>0.92</td>
<td>1.84</td>
<td>3.68</td>
<td>7.36</td>
</tr>
<tr>
<td>Dose methacholine (µg)</td>
<td>1.7</td>
<td>3.4</td>
<td>6.8</td>
<td>14</td>
<td>27</td>
<td>54</td>
<td>110</td>
<td>220</td>
<td>440</td>
<td>880</td>
<td>1760</td>
</tr>
<tr>
<td>Cumulative dose (µg)</td>
<td>1.7</td>
<td>5.1</td>
<td>12</td>
<td>26</td>
<td>53</td>
<td>110</td>
<td>220</td>
<td>440</td>
<td>880</td>
<td>1760</td>
<td>3520</td>
</tr>
</tbody>
</table>
The ICC between both tests according to the SCIPT was 0.91 (Fig. 1). We found an ICC between the SCIPT and SDM of 0.80 (Fig. 2). Both comparisons showed good agreement according to Bland and Altman (Fig. 3 and 4) [102].

Table 3. Details of children studied.

<table>
<thead>
<tr>
<th>Child</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>FEV1a (mean)</th>
<th>Asthma</th>
<th>Therapyb</th>
<th>PD20SCIPT 1st (µg)</th>
<th>PD20SCIPT 2nd (µg)</th>
<th>PD20SDM (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>12</td>
<td>157</td>
<td>2.27</td>
<td>Y</td>
<td>Nilc</td>
<td>105</td>
<td>116</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>8</td>
<td>129</td>
<td>1.91</td>
<td>N</td>
<td>Nil</td>
<td>&gt; 3630d</td>
<td>&gt; 3630d</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>11</td>
<td>157</td>
<td>2.58</td>
<td>Y</td>
<td>F+S</td>
<td>1534</td>
<td>1056</td>
<td>331</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>13</td>
<td>158</td>
<td>2.78</td>
<td>Y</td>
<td>F</td>
<td>&gt; 3630d</td>
<td>&gt; 3630d</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>7</td>
<td>120</td>
<td>1.61</td>
<td>Y</td>
<td>Nilc</td>
<td>&gt; 3630d</td>
<td>&gt; 3630d</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>9</td>
<td>136</td>
<td>1.54</td>
<td>Y</td>
<td>F</td>
<td>621</td>
<td>1151</td>
<td>216</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>8</td>
<td>134</td>
<td>1.74</td>
<td>Y</td>
<td>F</td>
<td>1489</td>
<td>1341</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>13</td>
<td>169</td>
<td>3.32</td>
<td>N</td>
<td>Nil</td>
<td>&gt; 3630d</td>
<td>&gt; 3630d</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>8</td>
<td>127</td>
<td>1.83</td>
<td>Y</td>
<td>F</td>
<td>1506</td>
<td>2137</td>
<td>432</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>14</td>
<td>156</td>
<td>2.62</td>
<td>Y</td>
<td>F+M</td>
<td>&gt; 3630d</td>
<td>&gt; 3630d</td>
<td>2608</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>13</td>
<td>158</td>
<td>2.01</td>
<td>Y</td>
<td>F+S</td>
<td>52</td>
<td>20d</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>13</td>
<td>161</td>
<td>2.37</td>
<td>Y</td>
<td>F+S</td>
<td>25g</td>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>13</td>
<td>164</td>
<td>3.17</td>
<td>Y</td>
<td>F+S</td>
<td>1409</td>
<td>1635</td>
<td>160</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>8</td>
<td>130</td>
<td>1.53</td>
<td>Y</td>
<td>F+S+M</td>
<td>1785</td>
<td>&gt; 3630d</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>8</td>
<td>129</td>
<td>1.68</td>
<td>Y</td>
<td>F+S</td>
<td>2956</td>
<td>&gt; 3630d</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>10</td>
<td>143</td>
<td>1.97</td>
<td>N</td>
<td>Nil</td>
<td>210</td>
<td>986</td>
<td>496</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>12</td>
<td>154</td>
<td>2.51</td>
<td>N</td>
<td>Nil</td>
<td>2390</td>
<td>2167</td>
<td>2018</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>14</td>
<td>154</td>
<td>3.16</td>
<td>Y</td>
<td>F+S</td>
<td>2900</td>
<td>1729</td>
<td>&gt; 3520d</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>11</td>
<td>150</td>
<td>1.92</td>
<td>Y</td>
<td>F+S</td>
<td>147</td>
<td>131</td>
<td>186</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>10</td>
<td>147</td>
<td>2.13</td>
<td>Y</td>
<td>F+S</td>
<td>150</td>
<td>413</td>
<td>143</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>8</td>
<td>135</td>
<td>1.72</td>
<td>Y</td>
<td>F</td>
<td>368</td>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>14</td>
<td>173</td>
<td>3.11</td>
<td>Y</td>
<td>F</td>
<td>303</td>
<td>54</td>
<td>191</td>
</tr>
</tbody>
</table>

a The mean of three baseline FEV1 was calculated.
b F = Fluticasone, S = salmeterol, and M = montelukast; medication was used daily.
c In two children, asthma was in remission for a long period. Therefore, ICS was stopped 2 months before the study.
d Normal bronchial response, PD20 could not be calculated.
e Assessment of BHR for diagnostic purposes.
f FEV1 dropped from 2.08 to 1.47, which is a 29.3% fall in FEV1 after the 1st provocation step.
g FEV1 dropped from 2.32 to 1.69, which is a 27.2% fall in FEV1 after the 1st provocation step.
Discussion

This study shows that the SCIPT is an accurate method to measure bronchial responsiveness in school-aged children and confirms earlier observations in adult patients with asthma. Although ranges of 95% confidence intervals are wide because of the small number of children, the method is reproducible and shows good agreement with a commonly used standard procedure. We chose to compare the SCIPT method with the Standard Dosimeter (SDM) method described by Birnie et al. [101] because this method is studied in children of various ages. Furthermore, it has been shown in this latter study as well as in other studies that results obtained with the SDM method are comparable with the standard tidal breathing method that uses continuous generation of inhaled aerosol [94;103]. The main aim of our study was to compare test outcomes instead of convenience of the methods used, because the advantageous convenience of this method has already been demonstrated in adults with asthma [97], and there are no good reasons to think that these advantages in adults will be different in children.

Next to good agreement between the two methods, we found a statistically significant difference in PD_{20} between SCIPT and SDM, in which the PD_{20} for SDM was mostly smaller than SCIPT. This difference is, most likely, due to differences in aerosol generation and deposition. The differences in PD_{20} between both methods were in most cases smaller than one and a half dose step, and if so, the clinical importance of this finding was negligible. Short-term within-subject repeatability studies (1-8 wk) with subjects in a stable clinical state show that the 95% confidence interval for repeat determinations of methacholine PD_{20} lie within ± 1.5 doubling doses [86;88;94]. We excluded all children with nonstable asthma prior to inclusion in the study. Nevertheless, once included, nonstable children were not excluded. The mean intraindividual variation in baseline FEV\textsubscript{1} values in our study was 8.3% (SD 5.65), which is in accordance with the 8% found by Eiser et al. [104]. During the study three children (nos. 11, 12 and 21) had an exacerbation of asthma symptoms. One child without asthma symptoms (no. 22) had more than 15% variability in baseline FEV\textsubscript{1} between tests, suggestive of reversible airway obstruction.

The results of the validation study of the SCIPT in 18 asthmatic adults by Sterk and colleagues in 1999 were similar to ours [97]. Furthermore, they found that the method was easy to perform and that the mean (SD) duration of the SCIPT procedure was almost twice as short as the SDM method [94]. First, this gain in time was due to the omission of the first two steps of the SDM method and due to the preparation of a large number of methacholine solutions necessary in the SDM method, which need to be switched after each provocation step. In general, the length of the test depends on the method used, the patients’ skills, and per patient the number of challenge steps to be performed. However, gain in time was not the aim of our study because this advantage was earlier shown in adults with asthma.
Figure 1. Reproducibility SCIPT. Both axes show PD$_{20}$ on a logarithmic scale.

Figure 2. Agreement between SCIPT and SDM. Both axes show PD$_{20}$ on a logarithmic scale.
The SCIPT cannot be performed without the use of the Jaeger Masterscope technique. This dependence on a rather expensive and sophisticated medical device and software is a disadvantage of our method. However, the Jaeger Masterscope is available in an increasing number of lung function laboratories. For these laboratories, this study is of significant relevance. An advantage of the technique is that no air supply from the wall is needed, which makes it less dependent of the place where the test is performed.

In addition, since the validation of the SCIPT, more than 1000 children performed the SCIPT in our hospital; 600 children were recruited from general practice to participate in the Asthma in Almere Project, and hundreds of other tests were performed to diagnose or monitor children with asthma in the outpatient clinic. In the first population were a large number of children without asthma therapy. Even in these children we didn’t face complications because of the higher starting dose of methacholine. However, a child can always react very severely on bronchial provocation, not only after the first provocation dose, and therefore it is prohibited to leave the child alone during the test.

In general, assessment of BHR provides the physician with information about the disease state and gives a tool to investigate the efficacy of asthma treatment. Moreover, the information can be used for explanation and education of parents and children to improve understanding of the disease and compliance to therapy. The SCIPT method in adults with asthma was faster and less demanding for the patients. Our study in children with asthma showed that the SCIPT inhalation challenge test was reproducible and had good agreement with a standard dosimeter method to test bronchial responsiveness in children.

Acknowledgements

We thank all patients and their parents for taking part in this study; Wim Hop, GlaxoSmithKline, for his statistical assistance, and Niesje E.Verhey and Saedea J.A.Latif-Lone of the Lung Function Department of the Academic Medical Center, Amsterdam, for their critical remarks on the methods used. We also thank the “Stichting Astma Bestrijding” for financial support of the study.
Figure 3. Ratio \( \frac{PD_{20,SCIPT, 2^{nd}}}{PD_{20,SCIPT, 1^{st}}} \) against mean of two measurements according to the Single Concentration Inhalation Provocation Test method (Bland and Altman plot).

Figure 4. Ratio \( \frac{PD_{20,SDM}}{PD_{20,SCIPT}} \) against mean PD_{20} for the Standard DosiMeter method vs. the Single Concentration Inhalation Provocation Test method (Bland and Altman plot).
Severe airway hyperresponsiveness was not predictable with the use of current tools in asthmatic children in general practice

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Abstract

Objective: To evaluate whether moderate to severe airway hyperresponsiveness (AHR) could be suspected with the use of routinely available clinical and environmental information.

Study Design and Setting: Cross-sectional study of asthma in 526 asthmatics aged 7-17 years and treated in general practice.

Results: Moderate to severe AHR was present in 48% (n = 253) of the participants. The presence of inhalation allergy, nocturnal symptoms, and usage of β₂-mimetics were significantly associated with moderate to severe AHR. If all three factors were present, the probability of the presence of moderate to severe and severe AHR was 76% and 36%, respectively. If all three were absent, the probability decreased to 11% and 5%, respectively. In 319 subjects (64%) AHR could not be adequately predicted with routinely available information.

Conclusion: Moderate and severe AHR could not be suspected with the use of routinely available clinical and environmental information in the majority of children. Except for a subgroup of children, our models were not helpful in deciding in which child an inhaled corticosteroid should be started or whether the dose should be increased or decreased. We recommend measuring the severity of AHR in these children by means of an inhalation challenge test.

Introduction

Asthma, irrespective of the severity, is a chronic inflammatory disease of the airways associated with airway hyperresponsiveness (AHR), airflow limitation, and recurrent and often variable symptoms of wheezing, breathlessness, and cough, particularly at night [3]. The treatment of asthma is, in general, internationally agreed upon, and many national and international guidelines have been developed for the management of asthma [48;67]. In 1995 the Global Initiative for Asthma (GINA) guidelines specified eight goals for the long-term management of asthma with the overall goal to minimize the burden of the disease in patients with asthma [48]. However, since the publication of the GINA guidelines, many studies continue to show that a substantial proportion of the asthmatic children are inadequately treated [55;105;106].

General physicians (GPs) are the first in line to deal with asthma and asthma-related symptoms. Among the many children presenting with persistent respiratory symptoms, it is their task to select children with moderate to severe asthma. GPs are limited with respect to available tools to diagnose and monitor asthma. Compared to pediatricians who have a range of objective tools to evaluate the severity of asthma such as lung function, exhaled NO, and inhalation challenge tests, GPs use mainly presented asthma symptoms, response to asthma medication, and peak flow monitoring. It is unknown how successful GPs, with their limited tools, are in the identification of children with more severe disease. Among others, being unsuccessful may be one reason for GPs prescribing an insufficient
dose of inhaled corticosteroids (ICSs), resulting in progressive worsening of the child’s lung function [20;107-109].

AHR is a surrogate marker of inflammation, reflecting the severity and level of control of the disease [14]. Children with moderate to severe AHR can be defined as a target group for treatment modification. However, testing for AHR is not a routine monitoring tool in general practice and a testing facility is often not easily accessible. Therefore, we studied whether the presence of AHR can be suspected by the GP with the use of routinely available clinical information in a group of children treated for asthma in general practice.

Methods

Subjects

Children were participants of an intervention study to improve childhood asthma management in general practice. They were eligible for the study if at least two prescriptions of β₂-mimetics and/or an ICS were prescribed in the year before invitation. Totally 1,554 children, aged 7-17 years, were identified. Children treated by a pediatrician (n = 261) were excluded from participation. Informed consent was obtained from 539 children (response rate 42%). The medical ethics committee of the Flevohospital in Almere approved the study.

Nonparticipants

To assess potential selection bias, we questioned randomly selected nonparticipants on asthma symptoms and medication usage at home 1 year after the first invitation. Forced expiratory volume in 1 second (FEV₁) was assessed by means of a handheld spirometer. Children were randomly selected by inviting every fifth child from a complete list of nonparticipants. If the child refused participation, the next child on the list was invited.

Study design

Participants were invited for two visits with a 2-week interval. During the first visit, demographic details, asthma-related symptoms, medication use, allergic symptoms, smoking, and pet-keeping data were collected. Allergic symptoms were asked for but were not confirmed by means of allergy tests. Smokers were defined as those who smoked at least one cigarette per day for a period of 6 months and who were still smoking within 1 month prior to examination. During the second visit, children performed a methacholine challenge test. Between these visits, children kept a diary in which they recorded daily asthma symptoms, short-acting β₂-agonist usage, and peak expiratory flow (PEF) measurements twice daily. With the use of multiple logistic regression techniques, we constructed two models for the prediction of the presence of moderately severe to severe (first model) or severe (second model) AHR. According to the classification of severity of AHR of Sont et al. [14], the cutoff value for moderately severe to severe AHR was defined at
### Chapter 4

**Table 1.** General and clinical characteristics of all participants classified into three groups according to their severity of AHR.

<table>
<thead>
<tr>
<th></th>
<th>Severe AHR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Moderately severe AHR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mild AHR to normal airway response&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>111</td>
<td>142</td>
<td>273</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>54 (49)/57(51)</td>
<td>83 (58)/59(42)</td>
<td>149(55)/124(45)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>11.1 (3.4)</td>
<td>10.6 (2.5)</td>
<td>11.1 (2.6)</td>
</tr>
<tr>
<td>Age at asthma diagnosis (y)</td>
<td>4.4 (3.3)</td>
<td>4.0 (3.4)</td>
<td>4.8 (3.9)</td>
</tr>
<tr>
<td>Duration of asthma (y)</td>
<td>6.7 (3.6)</td>
<td>6.6 (3.4)</td>
<td>6.4 (3.6)</td>
</tr>
<tr>
<td>Presence of asthma in parents and siblings</td>
<td>66 (60)</td>
<td>88 (62)</td>
<td>166 (61)</td>
</tr>
<tr>
<td>ICS prescribed (puffs/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>·4 mo before study</td>
<td>0.15 (0.28)</td>
<td>0.11 (0.21)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.20 (0.30)</td>
</tr>
<tr>
<td>·12 mo before study</td>
<td>0.60 (0.70)</td>
<td>0.43 (0.46)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.60 (0.60)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>·Number of courses during lifetime</td>
<td>18</td>
<td>26</td>
<td>44</td>
</tr>
<tr>
<td>·Number of children</td>
<td>13 (12)</td>
<td>15 (11)</td>
<td>21 (8)</td>
</tr>
<tr>
<td>β&lt;sub&gt;2&lt;/sub&gt;-mimetic (puffs/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>·Prescribed in 1 y before study</td>
<td>0.9 (1.1)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.7 (0.9)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.5 (0.6)</td>
</tr>
<tr>
<td>·As scored in diary</td>
<td>0.9 (1.1)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.5 (0.8)</td>
<td>0.4 (0.8)</td>
</tr>
<tr>
<td>Asthma symptoms&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>·Total symptom score</td>
<td>2.1 (2.2)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1.5 (1.8)</td>
<td>1.3 (1.7)</td>
</tr>
<tr>
<td>·Overall night symptom score</td>
<td>0.9 (1.1)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.5 (0.8)</td>
<td>0.5 (0.8)</td>
</tr>
<tr>
<td>·Nocturnal wheezing and SOB</td>
<td>0.5 (0.7)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.3 (0.5)</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td>·Number of symptom-free days</td>
<td>6.1 (5.0)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>7.2 (4.9)</td>
<td>7.8 (5.3)</td>
</tr>
<tr>
<td>Presence of atopic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>·Inhalation allergy</td>
<td>90 (81)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>106 (75)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>160 (59)</td>
</tr>
<tr>
<td>·Chronic rhinitis, (non) allergic</td>
<td>58 (52)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>64 (45)</td>
<td>110 (40)</td>
</tr>
<tr>
<td>·Eczema</td>
<td>52 (47)&lt;sup&gt;§&lt;/sup&gt;</td>
<td>52 (37)</td>
<td>101 (37)</td>
</tr>
<tr>
<td>·Symptoms of conjunctivitis</td>
<td>60 (54)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>64 (45)</td>
<td>97 (36)</td>
</tr>
<tr>
<td>Lung function characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>·FEV&lt;sub&gt;1&lt;/sub&gt;, % of predicted&lt;sup&gt;e&lt;/sup&gt;</td>
<td>91.1 (11.2)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>96.6 (10.8)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>100.0 (10.7)</td>
</tr>
<tr>
<td>·PEF variability</td>
<td>11.8 (6.6)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>8.8 (4.7)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>7.2 (3.9)</td>
</tr>
<tr>
<td>Pets in the household, current</td>
<td>63 (57)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>74 (52)</td>
<td>141 (52)</td>
</tr>
<tr>
<td>Number of (ex-) smokers</td>
<td>4 (3.6)</td>
<td>5 (3.5)</td>
<td>10 (3.7)</td>
</tr>
</tbody>
</table>

300 µg methacholine and for severe AHR at 75 µg methacholine. Children were challenged to a maximum of 3,600 µg methacholine. Above 1,000 µg children were considered to have a borderline to normal bronchial response to methacholine.
Diary cards and medication use

The frequencies of asthma-related symptoms, cough, wheeze, and shortness of breath were scored ("0" [no complaints], "1" [once a day], "2" [more than once a day], "3" [whole day]). Total day as well as total night score could range from 0 to 9. Moreover, we calculated (1) a total symptom score; (2a) an overall night symptom score, defined as the average of the sum of the daily morning scores; (2b) a more asthma-specific night score, including only wheezing and dyspnea; symptom-free days score is defined as the total number of symptom-free days (range 0-14). The numbers of prescribed inhalers for ICS and β₂-adrenergic drugs were obtained from electronic medication lists of the GPs.

Peak expiratory flow and airway challenge test

The best of three PEF measurements was used. PEF variability was calculated as follows: evening PEF value minus the morning PEF value divided by their mean value. Lung function was assessed by means of spirometric tests using the Spirometry Flow/Volume program (Jaeger, Germany). A methacholine challenge test was performed when FEV₁% predicted was ≥75%. The method used is validated in children and described elsewhere [110]. The degree of airway responsiveness was expressed as the PD₂₀, a provocation dose that induces a 20% fall in FEV₁ from baseline.

Data analysis

Data analysis, including the Jackknife procedure [111], was performed with the statistical package SPSS/PC for Windows (version 12.2) (SPSS, Chigago, IL, USA). Univariable analyses were performed to analyze which variables were related to (moderate and/or) severe AHR. All variables analyzed are listed in Table 1. Variables with a univariate $P$-value <0.15 were incorporated in the multivariable models.
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First, best predictive models for (moderate to) severe AHR were constructed. Second, simplified predictive models were constructed, in which continuous variables were dichotomized. Variables included in the model were present (=1) or absent (=0). PEF variability and FEV$_1$ (% predicted) were primarily excluded from the simplified models because these items were not frequently used and/or not easy accessible for all GPs [79]. Finally, FEV$_1$ (cutoff 95% of predicted) was re-included in the best-simplified model to assess the additional value of spirometry in the prediction of AHR. For two models (model 1a and 2a) the probability of having (moderate to) severe AHR was estimated according to the Jackknife procedure. In each model the probabilities of having (moderate to) severe AHR were calculated for each child using the formula $Pr = 1/(1+e^{-\text{[logistic regression equation]}})$. Children with severe airflow limitation ($n = 21$; FEV$_1$ < 75% predicted) were considered to have severe AHR without additional challenging. Logistic regression analyses were repeated without these children, and the areas under the curve were compared.

Results

General characteristics (Table 1)

In all, 518 of 539 children (286 boys [54%]; mean age: 10.5 years) were challenged; 21 children were not challenged because of airflow limitation (FEV$_1$ <75% of predicted) prior to the challenge. In total, 111 (21%) children were classified as having severe AHR: 90 showed severe AHR (PD$_{20}$ <75µg) and 21 children were defined as having severe AHR because of airflow limitation. In addition, 142 (27%) showed moderately severe AHR. Thirteen children were challenged, but the result was unreliable because of a poor performance and they were excluded. The remaining 273 children (52%) had mild to borderline AHR or did not respond within the challenge range (PD$_{20}$ > 300µg).

There were no significant differences between the groups with regard to sex, age, age at diagnosis of asthma, and duration of asthma, nor could we find relevant differences in the prevalence of asthma in parents and siblings. Children with severe AHR scored significant worse on all symptom scores, atopic parameters, and lung function parameters presented compared to children with mild to borderline AHR or a normal response. Children with moderately severe AHR were only significantly different from children with mild to borderline AHR or a normal response with respect to inhalation allergy and lung function parameters. However, we show a trend of increasing symptoms with increasing severity of AHR. Mean FEV$_1$ decreased and mean PEF variability increased gradually with increasing severity of AHR. In general, based on prescriptions, less than 5% of children ($n = 28$) probably used ICS on a daily basis in the 12 months preceding the study. Another 16% probably used their prophylactic medication daily during a period of at least 6 months in a year. Children with moderately severe AHR seemed to use less ICS. Children with moderate to severe AHR were prescribed more β$_2$-mimetics.
Table 2. Logistic regression models to predict moderate to severe and severe AHR in children with asthma.

<table>
<thead>
<tr>
<th></th>
<th>Moderate to severe AHR, n = 236</th>
<th>Severe AHR, n = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1a: exclusive of FEV1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 1b: inclusive of FEV1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nocturnal symptoms of wheezing and dyspnea</td>
<td>2.3 ** (1.6-3.4)</td>
<td>2.2 ** (1.5-3.3)</td>
</tr>
<tr>
<td>β&lt;sub&gt;2&lt;/sub&gt;-mimetics</td>
<td>2.1 * (1.3-3.1)</td>
<td>2.0 * (1.3-3.1)</td>
</tr>
<tr>
<td>Inhalation allergy</td>
<td>2.7 ** (1.8-4.0)</td>
<td>2.9 ** (1.9-4.5)</td>
</tr>
<tr>
<td>ICS</td>
<td>0.5 ** (0.3-0.7)</td>
<td>0.5 * (0.3-0.7)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (&lt;95% of predicted)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intercept</td>
<td>-1.394</td>
<td>-1.762</td>
</tr>
</tbody>
</table>

Variables included in the model were present (=1) or absent (=0). For all scores, the corresponding probabilities of having (moderate to) severe AHR can be calculated from Pr = \(1/(1+e^{-\text{score}+\text{intercept}})\).

Score model 1a = 0.827*(nocturnal symptoms) + 0.718*(β<sub>2</sub>-mimetics) + 0.982*(inhalation allergy) - 0.725*(ICS).

Score model 1b = 0.805 *(nocturnal symptoms) + 0.702 *(β<sub>2</sub>-mimetics) + 1.056 *(inhalation allergy) - 0.719 *(ICS) + 0.560 *(FEV<sub>1</sub>).

Score model 2a = 0.780 *(nocturnal symptoms) + 0.837 *(β<sub>2</sub>-mimetics) + 0.829 *(inhalation allergy).

Score model 2b = 0.828 *(nocturnal symptoms) + 0.892 *(β<sub>2</sub>-mimetics) + 1.141 *(inhalation allergy) + 1.207 *(FEV<sub>1</sub>).

Intercepts are given in the table.

Notes: Data are expressed as odds ratios with 95% confidence interval of all simplified models to predict moderate and severe AHR.
* P < 0.05, ** P < 0.001.
<sup>a</sup> 496 participants.
<sup>b</sup> 474 participants.

Nonparticipants

Sixty-one randomly selected children who refused participation in our study were willing to participate in a limited evaluation at home. Baseline characteristics (mean age 12 years [SD 2.6]) and prevalence of atopic symptoms were comparable to those of the participants. Lack of asthma symptoms or having only mild disease was the most important reason for nonparticipation. However, in the week before
evaluation, 39 (64%) children reported asthma symptoms of whom 6 reported symptoms during the night and 19 on wakening; 15 children (25%) reported the use of rescue medication at least once that week. Mean FEV₁ was 88.7% of predicted (SD 12.6; range 64-126%). In 18 children (30%) FEV₁ was below 80% of predicted; all except one improved on salbutamol. In total, 12 children (20%) had a positive response on bronchodilation (≥12% improvement). Nine children with lung function abnormalities were asymptomatic. Sixty-one percent of the children had not used ICS in the previous 6 months and 28% had used the controller medication irregularly.

Multivariable model for moderate to severe AHR

With multivariate analysis the presence of moderate to severe AHR could be best predicted with the nocturnal score for wheezing and dyspnea, presence of inhalation allergy, prescribed rescue medication (puffs/day), prescribed ICS (puffs/day), PEF variability and FEV₁. Subsequently, variables were dichotomized to create a simplified model with routinely available clinical information for use during consultation in general practice. The simplified prediction model revealed the presence of nocturnal wheezing and dyspnea, presence of inhalation allergy, prescribed rescue medication and ICS use as independent variables (Table 2, model 1a). The summed scores ranged from −0.725 to 2.473, with corresponding predictive values ranging from 10.7% to 75.6% (Table 3). ROC curves of the best predictive model and the simplified model (model 1a) are shown in Fig. 1. Inclusion of FEV₁ in the simplified constructed model (Table 2, model 1b) did not significantly improve model 1a (P = 0.2; ROC curve not shown).

Multivariable model for severe AHR

The presence of severe AHR could be best predicted with the nocturnal score for wheezing and dyspnea, presence of inhalation allergy, gender, prescribed rescue medication (puffs/day), PEF variability and FEV₁ as independent predictors. The simplified prediction model included the presence of nocturnal wheezing and dyspnea, presence of inhalation allergy and prescribed rescue medication (Table 2, model 2a). The summed scores ranged from 0 to 2.446, with corresponding predictive values ranging from 4.7% to 36.4% (Table 4). Addition of FEV₁ to model 2a improved the predictive model (P = 0.02). The summed scores ranged from 0 to 4 with corresponding predictive values ranging from 1.6% to 47%. The ROC curves of the best predictive model and models 2a and 2b are shown in Fig. 2. Repeating all logistic regression analyses without 21 children classified as severe AHR (but who were not challenged) did not significantly influence the predictive power in any of the models.
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Discussion

The question addressed by the present study was whether the presence of moderate to severe AHR can be suspected by the GP with the use of routinely available clinical information in a group of children treated for asthma in general practice. Our results show that the presence of moderate to severe AHR can be suspected to a certain extent, primarily in children using rescue medication with symptoms of nocturnal asthma and inhalant allergy. About one third of the children with moderate to severe AHR would be selected for treatment modification because they have these three features of asthma. In children who do not have all three features of asthma mentioned above, clinical information obtained by the GP does hardly decrease or increase the already extremely high a priori probability of 48% of having moderate to severe AHR. Therefore, our data support the hypothesis that a GP cannot suspect moderate to severe AHR with the help of current tools in a large proportion of asthmatic children.

Table 3. Probabilities of having moderately to severe AHR in children with asthma (model 1a).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Presence of inhalation allergy</th>
<th>Nocturnal wheezing and dyspnea</th>
<th>Prescribed β2-mimetics in 1 y</th>
<th>Prescribed ICS in 1 y</th>
<th>Estimated probabilities (Jackknife)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>13</td>
<td>10.7 (6.9-16.3)</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>29</td>
<td>19.9 (14.0-27.4)</td>
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<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>13</td>
<td>19.8 (11.8-31.1)</td>
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<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>18</td>
<td>21.6 (14.1-31.5)</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>7</td>
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<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>39</td>
<td>33.7 (23.3-46.0)</td>
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<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>33</td>
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<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>48</td>
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<tr>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>10</td>
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<tr>
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<td>Yes</td>
<td>No</td>
<td>10</td>
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<td>No</td>
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<td>No</td>
<td>No</td>
<td>27</td>
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<td>Yes</td>
<td>Yes</td>
<td>67</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>68</td>
<td>75.6 (68.3-81.8)</td>
</tr>
</tbody>
</table>

Notes: Estimated probabilities of having moderate to severe AHR in 496 asthmatic children with 95% confidence interval between brackets. A priori probability = 48% (39-57%).

* Number of children who fulfill the described characteristics in our study population.
In individual cases, we could decrease or increase the post priori probability of having moderate to severe AHR with the help of our model to 11% or 76%, respectively. To illustrate, when a GP is confronted with an asthmatic child who was not prescribed rescue medication in the previous year, and has no symptoms of nocturnal asthma or inhalation allergy, an expectative policy can be justified because the probability of having moderate to severe AHR decreases from 48% to 20% or 11% depending on the use of ICS. However, in general, these children do not visit a GP. To illustrate the opposite, when a GP deals with a child with an inhalant allergy and nocturnal symptoms that sometimes or frequently needs rescue medication, ICS can be started or the dose modified, initially without objectification of AHR by means of challenging. However, in more than half of the children, only one or two of three features of asthma mentioned above are present. In these children, who all visited general practice more than once because of asthma (-like) symptoms, referral to a lung function laboratory to objectify the severity of AHR seems important and strongly advisable because of a probability of having moderate to severe AHR between 20% and 60%.

The predictive features of asthma for increased AHR found in our study were strongest for nocturnal asthma symptoms, inhalant allergy, asthma medication, PEF variability, and FEV₁. Moreover, nocturnal symptoms occur frequently in children with asthma and are caused by a nocturnal fall in lung function [78;112]. These symptoms cause patients to wake up, with consequences for family life, and are responsible for school absenteeism. Our observation that nocturnal symptoms and an increased PEF variation predicted increased hyperresponsiveness is in line with the observation that nocturnal symptoms indicate a more severe disease state of asthma [113]. PEF variability reflects the nocturnal fall in lung function values. However, the association between PEF variability and AHR is controversial.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nocturnal wheezing and dyspnea</th>
<th>Prescribed β₂-mimetics in 1 y</th>
<th>Estimated probabilities (Jackknife)</th>
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</thead>
<tbody>
<tr>
<td>Presence of inhalation allergy</td>
<td>No</td>
<td>No</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>52</td>
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<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>17</td>
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<td></td>
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<td>108</td>
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<td></td>
<td>Yes</td>
<td>No</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>135</td>
</tr>
</tbody>
</table>

Notes: Estimated probabilities of having severe AHR in 496 asthmatic children with 95% confidence interval between brackets. A priori probability = 21% (16-27%).

a Number of children who fulfill the described characteristics in our study population.
Several cross-sectional studies suggested a moderate-to-strong relationship between the two [114;115]. Others have shown that the association appears to be weak and depend upon the way of expressing the PEF variability [116;117]. With this in mind, plus the limited feasibility of calculations from PEF diaries in general practice, and the limited reliability of PEF diaries [79], we excluded PEF variability of the definite prediction model.

Another predictive feature of asthma in this study was inhalation allergy. Literature contains abundant evidence of a strong association between AHR and atopy assessed by means of a positive skin test or radioallergosorbant test results in asthmatic children [118-123]. However, in this study, allergic symptoms were simply questioned. We could not find any other study describing the association between allergic symptoms and AHR.

Yet another well-known predictive factor for increased AHR in our study was the presence of severe airflow limitation (FEV$_1$ <80%). In multivariate analysis, a FEV$_1$ below 80% of predicted did improve the prediction of severe AHR. Moderately severe AHR could not be predicted more accurately when FEV$_1$ was added to the model. The dependence of the FEV$_1$ on the degree of AHR is described in many

![Figure 1. ROC curves of two models to predict moderate to severe AHR. Optimal, best predictive model (continuous line): variables were inhalation allergy, nocturnal symptoms, spirometry (FEV$_1$), PEF variability, and asthma medication (rescue and ICS). All variables, except inhalation allergy, were continuous. Area under the curve (AUC) = 0.765; 95% confidence interval (CI) = 0.724-0.806. Simplified model (dotted line) or model 1a: variables were nocturnal symptoms, inhalation allergy, and asthma medication (rescue and ICS). All variables were dichotomized. AUC = 0.703; 95% CI = 0.657-0.748.](image)
other studies [108;124-128]. Besides airway wall remodeling, acute bronchoconstriction and reversible swelling of the airway wall can cause airway limitation [1]. In this study, the mechanisms causing airway limitation were not further evaluated.

The final predictive variables of more severe AHR found in this study were the use of ICS and rescue medication. Despite the general knowledge that asthma is a chronic inflammatory disease that causes symptoms of dyspnea and airway wall remodeling [3], and should be treated with anti-inflammatory medication [129], many children received a prescription with an insufficient dose of an ICS (less than twice daily fluticasone 100 µg [powder inhaler] or the equivalent of budesonide or beclomethasone [200 µg]). The children in our study were selected based on prescribed asthma medication in the year preceding the study. This indicated that all participating children had at least one episode with asthma symptoms for which they sought medical attention. The large group of children with moderate to severe AHR and the lack of sufficient prescription of preventive medication both suggest undertreatment or under-use of prescribed treatment in the children with asthma.

Figure 2. ROC curves of three models to predict severe AHR. Optimal, best predictive model (continuous line): variables were sex, inhalation allergy, nocturnal symptoms, FEV₁, PEF variability, and asthma medication (rescue and ICS). All variables, except sex and inhalation allergy, were continuous. Area under the curve (AUC) = 0.85; 95% confidence interval (CI) 0.80-0.89. Simplified model 1 (dotted line) or model 2a: variables were nocturnal symptoms, inhalation allergy, and rescue medication. All variables were dichotomized. AUC = 0.678; 95% CI 0.622-0.735. Simplified model 2 (dotted line) or model 2b: the same variables as in simplified model 1 plus FEV₁. AUC = 0.757; 95% CI: 0.705-0.810.
They also indicate a failure of the implementation of (the Dutch) asthma treatment guideline. Unfortunately, our observations are in accordance with many other studies [55;67;105]. Beliefs among physicians and patients, such as fear of overtreatment and side effects of ICS, may be of major concern. Whether in the future asthma therapy in children and adolescents should be guided based on AHR, as recommended by Sont et al. [14], should be further investigated.

We studied in depth the possibility of selection bias. We considered selection bias likely because the response rate was rather low. We hypothesized that we selected children with more severe disease. This hypothesis was supported by the fact that we found a high a priori probability of having moderate to severe AHR. We evaluated a group of randomly selected nonparticipants on asthma symptoms and medication usage and performed limited lung function. In this group, the prevalence of asthma symptoms and lung function abnormalities were comparable with our study population. We concluded that there was not convincing evidence for the possibility that we had selected children with more severe disease. Moreover, this study of selection bias showed also undertreatment of asthma in these children.

In conclusion, based on findings in this unique general practice-based population, we created several models for individual children to estimate the probability of having moderate to severe AHR with cheap and simple to obtain asthma parameters. Asthmatic children with a combination of inhalation allergy, nocturnal symptoms, and usage of $\beta_2$-mimetics had a high probability of moderate to severe (76%) and severe (36%) AHR. Children with the opposite profile (no inhalation allergy or nocturnal symptoms and no usage of $\beta_2$-mimetics) had a very low probability of moderate to severe (11%) and severe (5%) AHR. However, in all children with a profile different from the two profiles described, none of the models was helpful in deciding in which child an ICS should be started or whether the dose should be increased or decreased. We recommend measuring the severity of AHR in these children by means of an inhalation challenge test.

Acknowledgements

We would like to express our gratitude to the Health Care Organization “Zorggroep Almere” for their participation in the study. We would like to thank Paul Mulder, for his statistical assistance, as well as all participating patients and their parents. This study was sponsored by GlaxoSmithKline.
Airway hyperresponsiveness as a guide to treat childhood asthma in general practice

Wanda Hagmolen of ten Have, Norbert J van den Berg, Job van der Palen, Wim MC van Aalderen, Patrick JE Bindels

submitted
Chapter 5

**Abstract**

*Aims:* To assess the efficacy of different strategies to improve childhood asthma management.

*Methods:* Comparison of three interventions directed to three groups of general practitioners: group A: dissemination of a guideline; group B: plus an educational session; group C: plus an individualized treatment advice based on airway hyperresponsiveness (AHR) and symptoms. Efficacy of the strategies was assessed by evaluating change in AHR in 362 children after one year.

*Results:* AHR decreased significantly only in group C ($P < 0.0001$) and was correlated with an increased use of inhaled corticosteroids. Consistently, asthma symptoms, use of rescue medication, and peakflow variability improved. The overall between-group effect, however, was not significant. An improvement in asthma symptoms in group A was not supported by an increase in prescribed corticosteroids.

*Conclusion:* Our data show that the combined implementation strategy has positive effects on the severity of AHR and corticosteroids prescription behaviour of the general practitioner.

**Introduction**

In 2006, the revised Global Initiative for Asthma (GINA) guidelines were published specifying the overall goal to achieve and maintain clinical control in patients with asthma [1]. Recent studies showed that a substantial proportion of asthmatic children are still inadequately treated [55;105].

General practitioners (GP’s) are the first in line to deal with asthma. Among all children presenting with persistent respiratory symptoms, it is their task to select those with moderate to severe asthma, and, according to asthma guidelines, start treatment with an inhaled corticosteroid (ICS). Diagnosis and monitoring of asthma in general practice are primarily based on symptom severity and, less frequently, the level of airflow limitation. However, assessment of asthma severity or level of control is difficult if not impossible, based on symptoms only [130]. Airway hyperresponsiveness (AHR) reflects the severity of asthma [14], is a tool to monitor asthma treatment [131], and predicts it’s outcome [132]. In general practice, therapeutic decisions are not based on the degree of severity of AHR because assessment of AHR is not readily available.

This study investigates whether a combination of guideline distribution, a single educational session and a written treatment advice to the GP, based on symptoms, medication use, lung function, and the severity of AHR, resulted in an improvement of the child’s asthma after one year.
Figure 1. Design of the study and flow diagram of participants. HCC: health care centre. In italic the study strategies aimed at the general practitioners.
Chapter 5

Methods

Setting
In Almere, the Netherlands, a centralized health care organization with 18 health care centres (HCC) and approximately 100 GP’s was approached. All agreed to participate in the study. The medical ethics committee of the Flevohospital in Almere approved the study.

Patient selection
Children from the HCC’s, 7 to 17 years old, were eligible for this study if at least two prescriptions of $\beta_2$-mimetics or ICS were prescribed in the year before invitation. All GP’s and pharmacies gave officially permission to search in a joint data registration system for the selection of patients. Names and addresses of 1549 eligible children were thus obtained. Children and their parents were invited by their GP to participate in the study. Only after written consent we obtained the medication lists to calculate medication usage of the participants. Children who were also treated by a paediatrician or pulmonologist were excluded as were children with a disability, other relevant diseases, conductive disorders, or disturbing psychological problems. Informed consent was obtained from 539 children (Fig. 1). Randomisation of the intervention was on HCC level. The main argument to randomise HCC’s ($n = 18$) instead of GP’s ($n = \pm 100$) was the possibility of contamination bias due to collaboration between GP’s within a HCC. Because many GP’s work part-time, patients were very likely to visit other GP’s within a HCC. Randomisation took place before children were invited. The studied strategies could not be blinded. The primary study outcome was the change in AHR in children after one year. Secondary outcomes were changes in asthma symptom scores, peak expiratory flow (PEF) variability, FEV$_1$, and usage of asthma medication.

Sample size
The sample size was calculated such that a difference in the degree of AHR equal to one doubling dose could be detected assuming a standard deviation in PD$_{20}$ of 2.5 doubling doses with a power of 80% and a significance level of 0.05. We assumed that the intra-cluster correlation coefficient (ICC) was very low (0.01), mainly because patients often see different GP’s in the same HCC. With 18 clusters (HCC’s) we needed 20 children in each cluster, making a total number of 360 children. We planned to recruit a total of 600 children.

Study design
The study evaluated the efficacy of three strategies to improve childhood asthma care in general practice. The study design is shown in Fig. 1. Three groups of asthmatic children, if they responded positive on the inhalation challenge test, were
followed during one year (A, B and C). All interventions, however, were focused on
GP’s. GP’s (and their asthma patients) were randomised by HCC to one of three
study strategies. An extracts of the latest updated version of the Dutch College of
GP’s clinical practice guideline (CPG) concerning the treatment of childhood
asthma was sent to all GP’s of group A, B and C, see appendices. An invitation for
a 2-hour educational session on asthma and inhalation technique was sent to GP’s
of groups B and C. In addition to the CPG and the educational session, GP’s of
group C received a written individualized treatment advice based on symptoms, the
use of medication, lung function and the severity of AHR. The advice was
standardized and based on the treatment algorithm used in the study of Sont et al.
[14]. If the child had moderate to severe AHR (PD20 ≤ 300 µg) independent of
asthma symptoms, GP’s of group C were advised to intensify the current treatment
strategy. There were three options: start with an ICS twice daily, increase the dose,
or add a long acting β2-mimetic. GP’s of children with mild AHR and frequent
symptoms (> 3 days/ 2 weeks) also received the advice to intensify therapy. In the
remaining cases GP’s were advised to maintain current treatment policy or to
decrease medication if possible. All children and their parents were informed about
the result of the inhalation challenge test, but they were not given a treatment
advice. We encouraged parents to consult their GP in order to give the GP the
opportunity to optimize asthma treatment according to the current guidelines. The
primary and secondary outcomes were re-assessed one year after the primary
evaluation in those children who responded positive on an inhalation challenge test
at baseline.

Primary and secondary outcome parameters
The frequency of asthma related symptoms, cough, wheeze, and shortness of
breath were scored twice daily (’0’ (no complaints), ‘1’ (once a day), ‘2’ (more than
once a day), ‘3’ (whole day)) in a two-week diary. The symptoms were scored by
the child, sometimes with the help of a parent. We calculated: total symptom score
(range 0-18), night symptom score (range 0-9), and number of symptom-free days
(range 0-14). Children were provided with a ‘Personal Best’ PEF-meter and
instructed to perform three measurements of PEF in the morning and in the
evening, prior to the use of salbutamol. PEF variability was calculated as the best
evening PEF-value minus the best morning PEF-value divided by their mean value.
Spirometric tests were performed according to the Spirometry Flow/Volume
program (version 4.34, Jaeger, Würzburg, Germany). The best result of three FEV1
attempts was used for analysis. A single concentration methacholine challenge test
was performed when FEV1, % predicted was ≥ 75%. Methods, validity and reliability
of the test are described elsewhere [110]. The degree of AHR was expressed as a
PD20, a provocation dose that induces a 20% fall in FEV1 from baseline. Moderate
to severe AHR was defined as a PD20 ≤ 300 µg conform to a study of Sont et al.
[7;14]. The number of prescribed inhalers for ICS and β2-mimetics was obtained
from electronic medication lists.
Chapter 5

Table 1. Baseline characteristics of 362 children with asthma treated in general practice.

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>98</td>
<td>133</td>
<td>131</td>
</tr>
<tr>
<td>Age, years</td>
<td>10.8 (2.5)</td>
<td>10.6 (2.5)</td>
<td>11.0 (2.5)</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>1.4</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Duration of asthma, years</td>
<td>6.5 (3.4)</td>
<td>6.4 (3.3)</td>
<td>6.4 (3.6)</td>
</tr>
<tr>
<td>Age at onset asthma, years</td>
<td>4.3 (3.4)</td>
<td>4.2 (3.3)</td>
<td>4.6 (3.8)</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHR, log transformed PD\textsubscript{20}</td>
<td>8.0 (5-12)</td>
<td>7.8 (5-12)</td>
<td>7.7 (5-12)</td>
</tr>
<tr>
<td>Severe AHR</td>
<td>24 (24)</td>
<td>28 (21)</td>
<td>31 (24)</td>
</tr>
<tr>
<td>Moderately severe AHR</td>
<td>33 (34)</td>
<td>52 (39)</td>
<td>44 (34)</td>
</tr>
<tr>
<td>Mild AHR</td>
<td>21 (21)</td>
<td>26 (20)</td>
<td>26 (20)</td>
</tr>
<tr>
<td>Borderline response</td>
<td>20 (20)</td>
<td>27 (20)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, % of predicted</td>
<td>96.2 (10)</td>
<td>96.5 (11)</td>
<td>96.6 (12)</td>
</tr>
<tr>
<td>PEF variability, %</td>
<td>8.8 (5.0)</td>
<td>9.4 (5.4)</td>
<td>8.5 (5.2)</td>
</tr>
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<td>Asthma symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom score, day + night</td>
<td>0.8 (0-9)</td>
<td>1.0 (0-8)</td>
<td>0.8 (0-10)</td>
</tr>
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<td>Nocturnal symptom score</td>
<td>0.2 (0-5)</td>
<td>0.3 (0-3)</td>
<td>0.2 (0-5)</td>
</tr>
<tr>
<td>Symptom free days, no.</td>
<td>8.4 (0-14)</td>
<td>6.0 (0-14)</td>
<td>8.0 (0-14)</td>
</tr>
<tr>
<td>Asthma medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS from medication list, puffs/day</td>
<td>0.3 (0-3)</td>
<td>0.3 (0-2)</td>
<td>0.4 (0-2)*</td>
</tr>
<tr>
<td>β\textsubscript{2} -mimetics from medication list, puffs/day</td>
<td>0.3 (0-3)</td>
<td>0.5 (0-6)</td>
<td>0.5 (0-5)</td>
</tr>
<tr>
<td>β\textsubscript{2} -mimetics score in diary, puffs/day</td>
<td>0.07 (0-4)</td>
<td>0.04 (0-4)</td>
<td>0.08 (0-5)</td>
</tr>
<tr>
<td>Atopic symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema (%)</td>
<td>42</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Allergy (%)</td>
<td>70</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>Rhinitis (%)</td>
<td>52</td>
<td>52</td>
<td>57</td>
</tr>
<tr>
<td>Asthma in 1\textsuperscript{st} degree relatives (%)</td>
<td>65</td>
<td>66</td>
<td>60</td>
</tr>
</tbody>
</table>

Data are presented as numbers of children with percentages of subgroup, as median values with range, or as means with ± SD. * P < 0.05.

Statistical Analysis

Results were analysed on an intention-to-treat basis. Mixed model ANOVA analyses were performed in SAS (Table 2 and 3). The analyses accounted for the effects of clustering. Except for the mixed model analyses, all other statistics were performed in SPSS version 10.5 (Table 1).

If FEV\textsubscript{1} was < 75% of predicted before the challenge test, PD\textsubscript{20} was set at 14 µg. If the FEV\textsubscript{1} fell ≥ 20% within the first provocation step, PD\textsubscript{20} was set to 27 µg, the sensitivity of the Masterscope. If PD\textsubscript{20} was not reached within the provocative range, it was set at the maximal provocative dose of 1920 µg. For the ANOVA mixed model analyses PD\textsubscript{20} was log transformed.
Chapter 5

Results

Implementation strategies

One hundred-five GP’s received an update of the CPG. Of the 68 GP’s invited, 21 GP’s of group B (62%) and 19 of group C (56%) attended the educational session. The 38 GP’s of group C received 197 individualized treatment advices for their patients: the median number of treatment advices per GP was 5 (range: 1-13).

General characteristics.

Of 539 children 404 with a positive inhalation challenge test were included in the study. The study was completed by 362 children (90%; 202 boys (56%); median age 10 years). There were no significant differences in baseline characteristics between the three study groups, except for the number of prescribed puffs of inhaled corticosteroids (ICS) that was higher in patients in group C (Table 1). Only 13% of the children (n = 53) were prescribed one or more puffs ICS per day. At the end of the study this was only slightly higher at 17.5% (n = 64). Within the three groups, the number of children who were prescribed regular ICS treatment (≥1 puff per day) decreased in group A from 11 to 9%, increased in group B from 11 to 13%, and in group C from 16 to 25%.

Results of the three intervention strategies are presented in Table 2. PEF variability and all symptom scores improved significantly in group A. AHR did not change, while the improvement in log PD20 from 7.9 to 8.3 reached borderline significance (P = 0.06). In group B significant changes occurred in PEF variability and the number of symptom free days. AHR did not change. In group C significant improvements were seen in AHR, PEF variability, all symptom scores, and medication usage. Group C is the only group in which AHR improved significantly, coinciding with an increased mean use of ICS from 0.55 to 0.63 puffs per day (P = 0.04). A non-significant decrease in prescribed β2 -mimetics was seen during the year of follow-up but according to their two-week diary, children of group C used significantly less puffs at the end of the study. The overall effect between the groups did not reach significance for the primary outcome measure AHR (P = 0.09). The overall asthma symptom score was also not significantly different (P = 0.08). A significant difference between groups was found in nocturnal symptoms (P = 0.02) and the use of ICS (P = 0.03). The largest improvement occurred in group A for nocturnal symptoms and for the use of ICS in group C.
In a second analysis (Table 3), we aggregated groups A and B because we failed to reach the calculated sample size in group A. There were no statistical differences at baseline between these two groups. Another reason was that in this way the additional effect of an individual treatment advice could be studied. In this analysis the between-group difference reached significance for the primary outcome ($P = 0.03$). The between-group difference remained significant for the use of ICS ($P = 0.02$). Other secondary outcomes were not different.

**Table 2.** Results of the implementation of the guideline.

<table>
<thead>
<tr>
<th></th>
<th>End of study, baseline adjusted</th>
<th>Overall treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Log PD$_{20}$</td>
<td>8.3 (0.2)</td>
<td>8.2 (0.2)</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>FEV$_1$, % of predicted</td>
<td>96.7 (1.0)</td>
<td>95.6 (0.9)</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>-1.0</td>
</tr>
<tr>
<td>PEF variability %</td>
<td>7.5 (0.5)</td>
<td>7.2 (0.4)</td>
</tr>
<tr>
<td></td>
<td>-1.3 *</td>
<td>-1.7 **</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>0.9 (0.2)</td>
<td>1.2 (0.2)</td>
</tr>
<tr>
<td></td>
<td>-0.6 ′</td>
<td>-0.3</td>
</tr>
<tr>
<td>Nocturnal symptom score</td>
<td>0.3 (0.1)</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td></td>
<td>-0.24 ′</td>
<td>-0.07</td>
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<td>Symptom free days, no.</td>
<td>8.6 (0.5)</td>
<td>8.5 (0.5)</td>
</tr>
<tr>
<td></td>
<td>1.5 ′</td>
<td>1.3</td>
</tr>
<tr>
<td>ICS, ppd (GP, 1 yr)</td>
<td>0.4 (0.05)</td>
<td>0.5 (0.05)</td>
</tr>
<tr>
<td></td>
<td>-0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>$\beta_2$-mimetics, ppd (GP, 1 yr)</td>
<td>2.6 (0.3)</td>
<td>2.3 (0.3)</td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>-0.2</td>
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<tr>
<td>$\beta_2$-mimetics, ppd (diary)</td>
<td>0.45 (0.1)</td>
<td>0.43 (0.08)</td>
</tr>
<tr>
<td></td>
<td>-0.07</td>
<td>-0.09</td>
</tr>
</tbody>
</table>

Data are presented as means (adjusted for baseline) with the standard error between brackets and the difference between means (end of study minus baseline) presented in the row below. Significant changes within the cohort are indicated: ′ $P < 0.05$; ″ $P < 0.001$. Significant effects between the cohorts are presented in the last column. Log PD$_{20}$ is the logarithm of the provocation doses methacholine provoking a 20% fall in FEV$_1$. ‘Total symptom score’ is the mean score per day for cough, wheezing and dyspnoea as scored in the diary. The ‘nocturnal symptom score’ is the mean score during the night. Inhalation corticosteroids (ICS) and $\beta_2$-mimetics are presented in number of puffs per day (ppd). For $\beta_2$-mimetics two different assessments are included: the first obtained from data files of the health care centre (prescriptions during one year prior the start of the study and one year during study); the second is the mean number of puffs per day used during the diary period.
Table 3. Results of the implementation of the guideline (second analysis).

<table>
<thead>
<tr>
<th>End of study</th>
<th>Overall treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>(baseline adjusted)</td>
<td>A &amp; B</td>
</tr>
<tr>
<td>Log PD$_{20}$</td>
<td>8.3 (0.2)</td>
</tr>
<tr>
<td>FEV$_1$, % of predicted</td>
<td>96.0 (0.7)</td>
</tr>
<tr>
<td>PEF variability %</td>
<td>7.3 (0.3)</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>Nocturnal symptom score</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td>Symptom free days, no.</td>
<td>8.6 (0.4)</td>
</tr>
<tr>
<td>ICS, ppd (prescribed in 1 year)</td>
<td>0.4 (0.03)</td>
</tr>
<tr>
<td>$\beta_2$-mimetics, ppd (GP, 1 yr)</td>
<td>2.5 (0.2)</td>
</tr>
<tr>
<td>$\beta_2$-mimetics, ppd (diary)</td>
<td>0.44 (0.06)</td>
</tr>
</tbody>
</table>

Data are presented as means (adjusted for baseline) with the standard error, and the difference between means (end of study minus baseline) presented in the row below. Significant changes within the cohort are indicated: *P < 0.05; **P < 0.001. Significant effects between the cohorts are presented in the last column.

Log PD$_{20}$ is the logarithm of the provocation doses methacholine provoking a 20% fall in FEV$_1$. ‘Total symptom score’ is the mean score per day for cough, wheezing and dyspnoea as scored in the diary. The ‘nocturnal symptom score’ is the mean score during the night. Inhalation corticosteroids (ICS) and $\beta_2$-mimetics were presented in number of puffs per day (ppd). For $\beta_2$-mimetics two different assessments were included: the first obtained from data files of the health care centre (prescriptions during one year prior the start of the study and one year during study); the second is the mean number of puffs per day used during the diary period.

Discussion

An individualised treatment advice based on symptoms, medication use, lung function, and AHR, had positive effects on ICS usage and the severity of AHR. This was superior to sending the current CPG and an educational session alone. Within the ‘combined strategy’ group (C), the decrease in AHR was highly significant, and was not matched by the other groups. However, the between-group differences in the primary outcome parameter (AHR) did not reach significance. It is likely that the
decrease in AHR in group C was due to increased usage of ICS. Other clinical factors, such as PEF variability, use of rescue medication, and asthma symptoms improved consistently with this observation.

Recent studies in adults and in children showed that treatment based on symptoms only is inferior to treatment based on an additional “inflammatory” marker. Sont et al. and Green et al. demonstrated that treatment based on AHR, and sputum eosinophils, respectively, resulted in a decrease of asthma exacerbations compared to treatment based on symptoms alone [14;133]. Smith et al. in adults, and Pijnenburg et al. in children showed beneficial effects when information about exhaled nitric oxide was used in addition to treatment based on symptoms only [134;135]. However, the feasibility of these new strategies as guidance for asthma treatment is not studied (yet) in asthmatic children in general practice.

In an earlier study we showed that it is not possible for a GP to estimate whether a patient has moderate or severe asthma, based on easy to obtain parameters, such as asthma symptoms, spirometry and medication usage [130]. In the present study we showed that additional information about AHR and a treatment advice based on a simple algorithm results in moderate improvement of the asthma status of the patients.

Earlier studies showed that guideline implementation strategies, such as the simple dissemination of a protocol and a single educational program have been consistently ineffective [136]. Change, if it occurred, was of short duration, and care usually reverted back to that which occurred prior to the intervention [137]. A combination of strategies and real-time feedback, has already proven to be more successful in changing care [138].

We found no significant difference between the three groups in our primary outcome variable. However, our data suggests that there is a difference between the efficacy of the strategies. The probability of a ‘Type II error’ cannot be ruled out. The causes for the moderate difference between the intervention and the control groups may be multiple: the primary experimental unit was the GP, and the outcome was assessed in the child. The intervention directed to GP’s was only implemented once. Also a general improvement of asthma control occurred in groups A and B. This may be due to a number of factors, but may also be a result of regression to the mean.

A limitation of this study is the small (because clustered) randomisation number. Because Almere has a centralized primary care structure, we had to randomise by HCC. Another limitation is that the studied strategies could not be blinded. Children and parents could not be blinded to the outcome of the challenge test. And we did not reach the desired sample size in group A. However, we dealt with this issue by combining groups A and B in a secondary analysis shown in Table 3. Finally, the choice of AHR as primary outcome for level of control of asthma can be discussed.
The advantage of AHR is that it reflects the severity of airway disease [14]. A limitation of this choice may be that AHR is only one of the hallmarks of asthma.

This study showed in general practice that a combination of strategies including evaluation of AHR together with an individualized treatment advice has limited, but positive effects on ICS prescription behaviour of the GP and subsequently the severity of AHR of the asthmatic child. Therefore, we recommend to incorporate an inhalation challenge test (performed in a lung function laboratory) in the asthma guidelines for children as an additional tool in general practice for a variety of reasons: at first to confirm the diagnosis of asthma and assess the severity of AHR in order to optimise asthma therapy, and second to educate parents and children and, as a consequence, to improve adherence of physicians, parents and children with controller therapy.

**Key messages and recommendations for the future:**

- Despite the lack of significance, this randomized controlled study shows the benefits of a combination of strategies as compared to single strategies focused on GP’s to achieve control of asthma in children.
- The major methodological problems encountered in this study were cluster randomisation and the fact that the primary experimental unit was the GP, and not the patient. The study, however, was set up such that it approaches ‘real’ clinical practice.
- There is a need for better objective tools to assess asthma severity in children. The severity of AHR can fulfill in such an additional tool but is new in general practice care and should be further studied.
- New randomized and controlled studies are desired in order to further improve clinical control in asthmatic children by means of similar or new strategies.

**Acknowledgements**

We would like to express our gratitude to all patients and their parents and to the Health Care Organization ‘Zorggroep Almere’ for their participation in the study. We would like to thank Paul Mulder separately, for his statistical assistance.
Appendix A: Management of recurrent childhood asthma.

**treatment steps**

1. **Intermittent asthma symptoms:**
   - Salbutamol < 3-5x/week
   - PEF variability < 20%

2. **Persistent asthma symptoms:**
   - Salbutamol > 3-5x/week
   - PEF variability 20-30%
   - Exacerbations of asthma* 4x/month or more.

3. **Persistent asthma symptoms:**
   - Salbutamol > 3-5x/week despite controller medication
   - PEF variability > 30%
   - Exacerbations of asthma* 4x/month or more (also at night).

   **Assess:**
   - Family history of asthma and atopy (inclusive blood test (RAST)),
   - Check asthma medication and its usage,
   - Give inhalation advice and advice about allergen avoidance measures,
   - Make a new appointment to evaluate therapy.

   **Referral to paediatrician**
   - for evaluation asthma and additional lung function tests.

   **Salbutamol**
   - max. 6dd 200 mcg with DPI or pMDI and spacer.
   - In case of an exacerbation pMDI and spacer.

   **Start inhaled corticosteroids:**
   - Budesonide 2dd 400 mcg
   - or fluticasone 2dd 250 mcg.
   - Once stable for 3 months try to reduce the dose.

   **Add long-acting β-agonist:**
   - Salmeterol 2dd 50 mcg
   - or formoterol 2dd 12 mcg
   - or start combination fluticasone/salmeterol 2dd 250/50 mcg.
   - Once stable for 3 months try to reduce the dose.

*asthma exacerbation is defined as any increase in asthma symptoms

**Flowchart 1.** Presentation of clinical pathway for general practitioners for the management of recurrent childhood asthma as recommended in the distributed asthma clinical practice guideline (CPG). For more detailed information see guideline [67]. PEF variability is defined as percentage of change in PEF before and after salbutamol.
Appendix B: Acute asthma guideline for children.

Any increase in asthma symptoms

salbutamol 200 - 400 mcg with pMDI via spacer
repeat after 15 minutes
reassess severity of asthma after 30 minutes

improvement

in case of relapse
within 3-4 hours
after salbutamol:
start oral course of prednisolon
2 dd 1 mg/kg
during 5 days,
maximum 2 dd 25 mg.

no improvement

referral to ER

Flowchart 2. Presentation of clinical pathway for general practitioners in children with an exacerbation of asthma as recommended in the distributed asthma clinical practice guideline (CPG). For more detailed information see guideline [67].
Questioning asthma in general practice:  
a dilemma illustrated

Wanda Hagmolen of ten Have, Norbert J van den Berg, Job van der Palen,  
Wim MC van Aalderen, Patrick JE Bindels

submitted
Abstract

Background: The monitoring of children with asthma in general practice is based on the occurrence and frequency of asthma symptoms. We questioned whether the current approach is adequate to identify all children in whom a sufficient level of asthma control is not achieved.

The aim of this study is to illustrate that in some children asthma was incorrectly considered controlled, because the children failed to report current symptoms of asthma.

Patients and methods: 119 children were identified with recent wheezing plus moderate or severe airway hyperresponsiveness. We analyzed whether these children reported current symptoms of asthma (as normally questioned during a routine visit).

Results: In twenty children (18%) current asthma symptoms were absent despite moderate or severe airway hyperresponsiveness and wheezing in the last year. In addition, the usage of controller medication was very poor.

Conclusion: We conclude that the general practitioner has insufficient tools to adequately assess asthma control in all children. The assessment of airway hyperresponsiveness as an additional guide to manage asthma in children in general practice is recommended. In this way, better asthma control can be achieved.

Introduction

In asthma, disease control refers to control of the clinical manifestations (1). Therefore, it is current practice to use a symptom-based approach for the monitoring of patients with asthma in primary care settings. However, recent studies have shown that treatment based on symptoms alone is inferior to treatment also based on an additional (inflammatory) marker. Two studies demonstrated that treatment based on airway hyperresponsiveness (AHR) and sputum eosinophils, respectively, resulted in a decrease of asthma exacerbations compared to treatment based on symptoms alone [14;133]. Two other studies, one in adults and one in children, showed beneficial effects when information about the patients exhaled nitric oxide was used in addition to treatment based on symptoms only [134;135]. AHR is one of the hallmarks of asthma. It is an objective parameter of asthma reflecting the severity of airway disease [14]. In our opinion, children with moderate or severe AHR should be treated with controller medication if AHR is part of the clinical manifestation of asthma. In an earlier paper we reported on a large group of children treated for their asthma in general practice. We showed that in most children the severity of AHR in these children could not be suspected by their general practitioner (GP), based on symptoms alone [130]. In the present study, children with borderline to severe AHR were followed for one year to study prospectively the relationship between symptoms and AHR. In addition to the re-assessment of asthma symptoms (by means of a two-week diary) and AHR, we
questioned parents whether children had symptoms of wheezing during the study year. We hypothesized that in a substantial number of asthmatic children presenting with less pronounced, atypical or trivialized symptoms of asthma, the severity of their disease could be easily underestimated.

**Methods**

*Patients*

All children described in this paper participated in an intervention study that compared different methods to improve disease control in childhood asthma in general practice. GP’s were subject to one to three cumulative strategies to improve control in childhood asthma: 1) distribution of an asthma guideline, 2) a single educational session and 3), a onetime individualized treatment advice based on symptoms and lung function including the degree of AHR. Children were eligible to participate in the original study if at least two prescriptions of $\beta_2$-mimetics and/or an inhaled corticosteroid (ICS) were prescribed in the year before invitation. The patient selection is described in more detail elsewhere [130].

*Study design and patient selection*

At the end of the original one-year study, 362 asthmatic children were re-evaluated on asthma symptoms, peak expiratory flow (PEF) variability, degree of AHR, and medication usage. Parents were asked to fill in a standard questionnaire on asthma symptoms of their child in the past year. AHR was assessed by means of a methacholine inhalation challenge test when the FEV$_1$ was $\geq 75\%$ of predicted. The method used is validated in children and described elsewhere [110]. The degree of AHR was expressed as a PD$_{20}$, a provocation dose that induces a 20% fall in FEV$_1$ from baseline. Severe AHR was defined as a PD$_{20}$ below 75$\mu$g methacholine, moderately severe AHR as a PD$_{20}$ below 300$\mu$g according to the classification used by Sont and colleagues [14]. Children were challenged to a maximal cumulative dose of 3600$\mu$g methacholine. Children with a baseline FEV$_1$ value below 75$\%$ of predicted were not challenged. These children were classified as having severe AHR.

We analyzed whether children scored current symptoms of asthma in their diary. The diary was filled in during two weeks prior to the inhalation challenge test. In the diary the frequency of asthma related symptoms, cough, wheeze and shortness of breath were scored (‘0’ (no complaints), ‘1’ (once a day), ‘2’ (more than once a day), and ‘3’ (whole day)). Total day as well as total night scores could range from 0-9. Moreover, we calculated: 1) a total symptom score and 2) a symptom-free days score, defined as the total number of symptom-free days (range 0-14).

PEF variability was also assessed in the two-week diary. Children were provided with a ‘Personal Best’ PEF meter. The best of 3 PEF measurements was used and the percentage of predicted was calculated [139;140]. PEF variability was
calculated as: evening PEF value minus the morning PEF value divided by their mean value.
The number of prescribed inhalers for ICS and $\beta_2$-adrenergic drugs were obtained from electronic medication lists of the GP’s.

Statistical analysis
Data-analysis was performed with the statistical package SPSS (version 12.2) (SPSS, Inc., Chicago, IL). To compare groups with regard to continuous normally distributed data, independent-samples t-tests were performed.

Results
Of 404 children who were included on the basis of AHR at the start of the study, 328 participants (81%) completed follow-up for one year. At re-evaluation, 167 children (51%) had moderate or severe AHR (Table 1). Parents of 119 of these children (71%) reported wheezing in the last twelve months (‘recent wheezing’). Figure 1 shows the percentages of children with recent wheezing in subgroups of children with different degrees of AHR. In contrast to the report of ‘recent wheezing’, 20 children (17%) with moderate to severe AHR did not report wheezing, cough or shortness of breath in the last two weeks, despite the fact that nine of these children showed severe AHR ($PD_{20} < 75\mu g$). The PEF variability of these 20 children was significantly lower as compared to the children who reported symptoms in their diary (4.6% versus 7.8%, $P < 0.01$). Consistently with their lack of symptoms, these 20 children were prescribed fewer $\beta_2$ agonists (Table 1). The mean usage of inhaled corticosteroids was poor in both groups.

Children with moderate or severe AHR without ‘recent wheezing’ report less symptoms of asthma in their diary than those with wheezing (median 0.1 versus 1.1; $P = 0.005$). Subsequently, they were prescribed less short acting reliever medication (median 16 versus 55 $\mu g$ per day; $P = 0.04$). Except for these differences in symptoms and usage of reliever medication, no significant differences with respect to lung function were found.

Children with mild AHR or a normal response reported significantly less asthma symptoms, had more symptom free days, had better lung function (PEF variability and FEV$_1$) and were prescribed less short acting reliever medication compared to children with moderate or severe AHR (Table 1). There was no difference in mean prescribed controller medication (ICS).

Discussion
In this study we showed that almost one-sixth of asthmatic children with recent wheezing and moderate or severe AHR, were not identified as ‘at risk’ when questioning current asthma symptoms only. These children could be easily missed as ‘not well controlled’ by the GP at a routine visit. Eight of these children were not
prescribed any controller medication in the previous year; the majority of the others (except four), probably did not use their medication regularly. These findings support our earlier conclusion that it is difficult if not impossible to assess the severity of asthma in a number of “at risk” children by means of only questioning asthma symptoms. Also lung function (PEF variability and FEV\textsubscript{1}) is often not very helpful because of relative minor abnormalities.

All children in this study were treated for their asthma in general practice. A priori, participants of our study were likely to have (a diagnosis of) asthma because they were selected on the basis of prescribed asthma medication, which they were prescribed in the year prior to the start of the original study. Furthermore, all children were included for follow-up because of the presence of AHR. AHR could be mild or even borderline normal, but in most children (57\%), AHR was moderate or severe at inclusion in the study.

The severity of AHR reflects the severity of asthma \cite{14}, it is a tool to monitor asthma treatment \cite{131} and it predicts the outcome of asthma \cite{132}. Furthermore, it

<table>
<thead>
<tr>
<th>Number</th>
<th>92</th>
<th>20</th>
<th>7</th>
<th>48</th>
<th>161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12.0 (2.6)</td>
<td>12.6 (2.5)</td>
<td>11.6 (1.3)</td>
<td>10.8 (2.4)</td>
<td>10.6 (2.5)</td>
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<tr>
<td>Gender, male</td>
<td>47 (51)</td>
<td>8 (40)</td>
<td>5 (71)</td>
<td>29 (60)</td>
<td>103 (58)</td>
</tr>
<tr>
<td>Symptom free days (no.)</td>
<td>5.0 (0-13)</td>
<td>14**</td>
<td>-</td>
<td>13* (0-14)</td>
<td>12** (0-14)</td>
</tr>
<tr>
<td>Symptom score</td>
<td>1.4 (0-9)</td>
<td>0**</td>
<td>-</td>
<td>0.1* (0-5)</td>
<td>0.2* (0-8)</td>
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<tr>
<td>FEV\textsubscript{1} (% pred)</td>
<td>93 (56-125)</td>
<td>93 (76-114)</td>
<td>91.0 (71-103)</td>
<td>96 (76-118)</td>
<td>100** (78-168)</td>
</tr>
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<td>PEF variability</td>
<td>7.8 (2-27)</td>
<td>4.6** (2-11)</td>
<td>-</td>
<td>6.8 (1.3-20.1)</td>
<td>5.3** (0.9-24.7)</td>
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<td>Severe AHR</td>
<td>44 (48)</td>
<td>9 (45)</td>
<td>2 (29)</td>
<td>16 (33)</td>
<td>-</td>
</tr>
<tr>
<td>ICS (µg/day)</td>
<td>30 (0-410)</td>
<td>20 (0-140)</td>
<td>30 (0-150)</td>
<td>20 (0-200)</td>
<td>30 (0-300)</td>
</tr>
<tr>
<td>(\beta_2)-mimetics (µg/day)</td>
<td>70 (0-660)</td>
<td>50* (0-230)</td>
<td>30 (0-60)</td>
<td>20* (0-590)</td>
<td>20** (0-400)</td>
</tr>
</tbody>
</table>

Data are presented as mean with ± SD, as number of children with percentage of sub-group, or as median with range. *\(P<0.05\), **\(P<0.01\); \(^1\) statistical comparison versus children with moderate or severe AHR and wheezing and present symptoms, \(^2\) versus children with moderate or severe AHR and wheezing, \(^3\) versus children with moderate or severe AHR.
is an objective characteristic of asthma. AHR is considered to be one of the major consequences of airway inflammation and remodelling. The degree of AHR has been shown to correlate both with an increase in airway inflammatory cells and with altered structural components in the airway wall, such as a deposition of subepithelial collagen or proteoglycans [141;142]. The frequently observed lack of association between AHR and airway inflammation supports the assertion that other factors such as remodelling may be involved [18]. In our opinion, children with moderate or severe AHR should be treated with controller medication. In general practice, however, the degree of AHR is almost never assessed. Furthermore, our data suggest that it is relevant to question wheezing during the last year. Of all children with severe AHR, 80% were identified on the basis of the prevalence of recent wheezing. However, questioning wheezing is not very specific to assess the severity of asthma.

There are several possible explanations for the apparent absence of symptoms in children. It may be that children trivialize their asthma, or that children and parents do not recognize asthma symptoms as relevant enough to report. Because the perception of symptoms associated with airway obstruction follows a normal unimodal distribution in patients with asthma, patients with marked reductions in expiratory flow can sometimes be asymptomatic or have minimal symptoms [143]. Perceptual accuracy may be affected by physiological, psychological, cognitive and parent-child factors [144]. The absence of symptoms may be due to insufficient triggers, such as lack of exercise or absence of exposure to relevant allergens or respiratory irritants. Or it simply may be the natural course of the disease, which is known for its intermittent character. This is demonstrated in two studies who found large variations in morning PEF, asthma symptoms, and use of rescue medication, with the result that individual patients moved frequently across different severity categories over time [145;146].

In conclusion, a group of children with asthma in general practice is difficult to manage because reporting of current asthma related symptoms is absent. The children described in this study were found to have moderate or severe AHR. The assessment of AHR in these children is considered to be an additional and necessary tool to estimate the severity and control of the disease. Based on current guidelines these children would be incorrectly considered well controlled. At present, no consensus exists on how to monitor these children. We recommend monitoring of AHR or other validated inflammatory markers in children who have had airway symptoms in the past year but do not report current asthma related complaints. They might be poorly controlled and in need of controller medication.
Chapter 6

Acknowledgements
We would like to express our gratitude to all patients and their parents and to the Health Care Organization ‘Zorggroep Almere’ for their participation in the study.

Figure 1. The percentage of children who had wheezing in the last 12 months (as reported by the parents) is shown per subgroup. Children were stratified according to the degree of airway hyperresponsiveness (AHR).
Assessment of asthma control starts with checking inhalation technique

W. Hagmolen of ten Have, N.J. van den Berg, P.J.E. Bindels, W.M.C. van Aalderen, J. van der Palen

accepted in revised form
Journal of Asthma
Abstract

Background: Many outpatient children with asthma use their inhaler device incorrectly, even after inhalation instructions in the past.

Aim of the study: To evaluate inhalation technique in children inhaling asthma medication in general practice.

Methods & setting: Inhalation technique was evaluated in 530 asthmatic children aged 7-17 years, selected from general practice. Inhalers investigated were either dry-powder inhalers (DPI) Diskus®, Diskhaler®, Turbuhaler®, Cyclohaler® and pressurized metered-dose inhalers (pMDI) with and without a spacer device. Essential and non-essential inhalation manoeuvres were recorded against inhaler-specific checklists. Correct and incorrect performances were related to patient’s characteristics and asthma severity. After one year 362 children were reassessed.

Results: Overall 76% of the children inhaled correctly. However, important differences among inhalers were found. Children with the Diskus® performed best with 95% making no errors on essential inhalation manoeuvres, while children with a pMDI without a spacer device performed worst with only 21% of children inhaling without essential errors. One year after the first assessment 114 new devices were demonstrated. Performance with these new devices was significantly more often incorrect versus the unchanged devices (21.1% and 10.8%, respectively; \( P = 0.01 \)).

Conclusions: Many asthmatic children in general practice use their inhaler incorrectly. Children of 7 years and older should use a DPI or, if they are not able to inhale with sufficient force, a pMDI with spacer device. The use of a pMDI without a spacer device should be strongly discouraged. Providing children with a new device should be carefully controlled over time because these children are error prone.

Introduction

Many outpatients with asthma use their inhaler device incorrectly [147;148], even after having received inhalation instructions in the past [149]. Therefore, a thorough check of inhaler device technique and, subsequently, of adequate usage of prescribed asthma medication should be the first step in unstable asthma. The Global Initiative for Asthma (GINA) guidelines specified in 1993, and again in 2006, goals for the long-term management of asthma [1;48]. The overall goal is to reach and maintain clinical control of asthma in adults and children. However, to fulfil the GINA objectives turns out to be a difficult task. Since the publication of the guidelines many studies continue to show that a substantial proportion of asthmatic adults and children is inadequately treated [55;105;106]. In order to evaluate the extent of the problem, we checked inhalation technique in 530 children who were prescribed asthma medication and participated in a general practice based study on the management of childhood asthma. This paper describes differences in the performances of patients inhaling asthma medication with different types of inhalers. We related these performances (correct or incorrect) to patient
characteristics, medication usage, severity of airway hyperresponsiveness (AHR),
and previous inhalation instruction. We followed patients during one year to
observe changes in inhaler types and performances over time.

Methods
Subjects
Children were participants in a general practice based cohort study on childhood
asthma. Children were eligible for this study if at least two prescriptions of $\beta_2$-
mimetics and/or an inhaled corticosteroid (ICS) were prescribed in the year before
invitation. The original study was performed to compare different methods to
improve disease control in childhood asthma in a general practice population. This
study is discussed in more detail elsewhere [130]. Informed consent was obtained
from all participating children or their parents. The medical ethics committee of the
Flevohospital in Almere approved the study.

Study design
Inhalation technique was evaluated twice by using standardized checklists (Table
1): first, at enrolment in the study ($n = 530$) and second, after one year of follow-up
($n = 362$). If children used more than one device, children demonstrated the use of
all inhalers. No inhalation instructions were given. Severity and level of control of
asthma was assessed by means of a two-week symptom diary, lung function
measurement and an inhalation challenge test.

Inhalation technique
Three major categories of inhaler types can be distinguished: pressurized metered-
dose inhalers without and with a spacer device (pMDI and pMDI/s respectively)
and dry powder inhalers (DPI). For each inhaler type certain key actions are
essential for optimal delivery of the active drug into the lungs. All inhaler specific
actions are listed in Table 1. The checklists were based on those, issued by the
Dutch Asthma Foundation. When errors are made regarding these key actions, it is
likely that no, or only an insignificant amount of medicine will be inhaled. The
following key actions were identified for the different devices. The pMDI must be
shaken before use in order to mix the drug with the propellant (item 1). Without a
spacer device, the child should start to inhale slowly (less than 30 l/min),
immediately followed by activating the canister (item 6); he/she should continue to
inhale slowly throughout discharge (item 7). With a spacer device, the pMDI should
be actuated into the spacer (item 5). To maximize drug delivery, single actuations
should be used for inhalation [150]. The child should inhale and exhale slowly at
least three times (item 6). It is important that the spacer valve is seen to be moving
during breathing.
Table 1. Inhaler-specific checklists with quantification of actions that were correctly performed.

<table>
<thead>
<tr>
<th>Dry Powder Inhaler (DPI) -checklist (n = 296)</th>
<th>No. (%) of children performing item correctly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Hold DPI in correct position (^a,b)</td>
<td>269 (91)</td>
</tr>
<tr>
<td>2: Correctly load device for inhalation (^a,c)</td>
<td>291 (98)</td>
</tr>
<tr>
<td>3: Sit upright or stand</td>
<td>291 (98)</td>
</tr>
<tr>
<td>4: Exhale to residual volume away from mouthpiece</td>
<td>138 (47)</td>
</tr>
<tr>
<td>5: Keep head slightly tilted</td>
<td>102 (34)</td>
</tr>
<tr>
<td>6: Mouthpiece between teeth and lips</td>
<td>290 (98)</td>
</tr>
<tr>
<td>7: Inhale forcefully and deeply (^a)</td>
<td>274 (92)</td>
</tr>
<tr>
<td>8: Hold breath for five seconds</td>
<td>174 (59)</td>
</tr>
<tr>
<td>9: Exhale away from mouthpiece</td>
<td>289 (98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metered-dose Inhaler (MDI) plus spacer-checklist (n = 230)</th>
<th>No. (%) of children performing item correctly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Shake canister (^a)</td>
<td>166 (72)</td>
</tr>
<tr>
<td>2: Place canister in spacer device</td>
<td>229 (99)</td>
</tr>
<tr>
<td>3: Sit upright or stand</td>
<td>220 (96)</td>
</tr>
<tr>
<td>4: Place mouthpiece between teeth and lips</td>
<td>228 (99)</td>
</tr>
<tr>
<td>5: Press canister one time (no more) (^a)</td>
<td>183 (80)</td>
</tr>
<tr>
<td>6: Inhale slowly at least three times in and out (^a)</td>
<td>198 (86)</td>
</tr>
<tr>
<td>(Check that spacer valve is moving during breathing)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MDI checklist (n = 65)</th>
<th>No. (%) of children performing item correctly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Shake canister (^a)</td>
<td>36 (55)</td>
</tr>
<tr>
<td>2: Remove cap (^a)</td>
<td>65 (100)</td>
</tr>
<tr>
<td>3: Hold inhaler upright</td>
<td>63 (97)</td>
</tr>
<tr>
<td>4: Sit upright or stand</td>
<td>63 (97)</td>
</tr>
<tr>
<td>5: Exhale to residual volume</td>
<td>20 (31)</td>
</tr>
<tr>
<td>6: Keep head slightly tilted</td>
<td>18 (28)</td>
</tr>
<tr>
<td>7: Place mouthpiece between teeth and lips</td>
<td>63 (97)</td>
</tr>
<tr>
<td>8: Start a slow inhalation and press canister (^a)</td>
<td>33 (51)</td>
</tr>
<tr>
<td>9: Continue slow and deep inhalation (^a)</td>
<td>43 (66)</td>
</tr>
<tr>
<td>10: Hold breath for five seconds</td>
<td>36 (55)</td>
</tr>
<tr>
<td>11: Exhale away from mouthpiece</td>
<td>57 (88)</td>
</tr>
</tbody>
</table>
The DPIs evaluated in this study were the Diskus® (DK), the Diskhaler® (DH), the Turbuhaler® (TH), and the Cyclohaler® (CH). The blister of the DK should be opened completely (item 2). To achieve this, the lever should be slid away as far as it will go. To open the blister of the DH (item 2), the lid should be raised as far as it goes and closed. TH: grip should be twisted counter-clockwise and back until a ‘click’ is heard; CH: Pressing one-time the blue buttons to perforate the capsule; RH: Rotate the base. For all DPI’s applies that before activating, the medication should be in place.

Airway hyperresponsiveness

Airway hyperresponsiveness (AHR) is one of the characteristics of asthma, reflecting the severity and level of control of the disease. Lung function was assessed by means of spirometric tests using the Spirometry Flow/Volume program (Jaeger, Germany). A methacholine challenge test was performed when FEV₁ was ≥ 75% of predicted. The method used is validated in children and described elsewhere [110]. The degree of AHR was expressed as a PD₂₀, a provocation dose that induces a 20% fall in FEV₁ from baseline. Severity of AHR is classified according to Sont et al [14]. Severe AHR is defined as a PD₂₀ < 75µg. Moderate to severe AHR is defined as a PD₂₀ < 300µg. Above 300µg methacholine, AHR improves from mild via borderline to a normal bronchial response. Children were challenged to maximal cumulative doses of 3600µg methacholine.

Diary cards and medication use

The frequency of asthma related symptoms, cough, wheeze and shortness of breath were scored (‘0’ (no complaints), ‘1’ (once a day), ‘2’ (more than once a day), and ‘3’ (whole day)). Total day as well as total night score could range from 0-9. Moreover, we calculated: 1) a total symptom score and 2) a symptom-free days score, defined as the total number of symptom-free days (range 0-14). The number of prescribed inhalers for ICS and β₂-mimetics were obtained from electronic medication lists of the GPs.
Chapter 7

Statistical analysis

Inhalation technique was classified according to the checklists: if all key actions were performed adequately, the performance was classified as ‘correct’ (children who performed all actions correctly are mentioned separately in the results section as ‘perfect’ performances); if one or more of the key actions were missed, the performance was classified as ‘incorrect’. Children with a baseline FEV$_1$ value below 75% of predicted were not challenged. These children were classified as having severe AHR and excluded from follow-up in the study.

In univariate and multivariate analyses we related inhalation technique (correct/incorrect) to age, sex, duration of asthma, asthma in first-degree relatives, medication usage (number of puffs per day), asthma symptoms, peak expiratory flow (PEF) variability, FEV$_1$, and severity of AHR. To compare groups on categorical variables, chi-squared tests were performed. Data-analysis was performed with the statistical package SPSS/PC for Windows (version 12.2) (SPSS, Inc., Chicago, IL).

Results

Inhalation technique

At baseline 591 devices in 530 children were observed and performance was assessed based on the checklists (Table 1). 52 Children had two different devices and 5 children had three different devices. The most observed inhalers were DPI’s: DK ($n = 60$), DH ($n = 157$), TH ($n = 59$), and CH ($n = 17$).

In 261 DPI’s (89%) all essential actions were performed accurately. A perfect performance on all checklist-items was shown for 55 DPI’s (19%). In 32 devices (11%) essential actions were performed incorrectly. One of the non-essential actions often forgotten was to exhale to residual volume before inhaling the asthma medication. Others omitted holding the breath for five seconds or found it very difficult. A few counted up to twenty within 2 or 3 seconds. Furthermore, 9 children inhaled and exhaled slowly at least three times instead of holding their breath. Some of them shook their device after they perforated the blister.

Of the 295 pMDI’s that were demonstrated, only 229 children (78%) used it with a spacer device. Seventeen children had a spacer device with a mouth mask. Of these 229 children 177 (77%) performed all key actions as described and of these, 112 (49%) showed a perfect performance. The remaining 52 children (23%) failed on one or more of the essential actions. For example, shaking the canister before usage was often forgotten (28%). Approximately one-fifth of the children who were instructed to use more than one dosage pressed the canister more than once into the spacer device instead of repeating the manoeuvre after inhaling the first dosage. A variety of interpretations of the last action (number 6) were shown, from
Table 2. Characteristics of device users per device type and performance.

<table>
<thead>
<tr>
<th></th>
<th>Inhaler performance</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correct</td>
<td>Incorrect</td>
<td>Correct</td>
<td>Incorrect</td>
<td>Correct</td>
<td>Incorrect</td>
<td>Correct</td>
</tr>
<tr>
<td>Number of devices</td>
<td>455</td>
<td>137</td>
<td>456</td>
<td>137</td>
<td>456</td>
<td>137</td>
<td>530</td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.0 (2.6)</td>
<td>11.2 (2.5)</td>
<td>11.0 (2.6)</td>
<td>11.2 (2.5)</td>
<td>11.0 (2.6)</td>
<td>11.2 (2.5)</td>
<td>11.0 (2.6)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>248 (55)</td>
<td>73 (53)</td>
<td>248 (55)</td>
<td>73 (53)</td>
<td>248 (55)</td>
<td>73 (53)</td>
<td>248 (55)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>4.6 (3.7)</td>
<td>4.1 (3.7)</td>
<td>4.6 (3.7)</td>
<td>4.1 (3.7)</td>
<td>4.6 (3.7)</td>
<td>4.1 (3.7)</td>
<td>4.6 (3.7)</td>
</tr>
<tr>
<td>Duration of asthma</td>
<td>6.4 (3.5)</td>
<td>7.0 (3.4)</td>
<td>6.4 (3.5)</td>
<td>7.0 (3.4)</td>
<td>6.4 (3.5)</td>
<td>7.0 (3.4)</td>
<td>6.4 (3.5)</td>
</tr>
<tr>
<td>Years since start ICS</td>
<td>5.2 (3.2)</td>
<td>5.7 (3.3)</td>
<td>5.2 (3.2)</td>
<td>5.7 (3.3)</td>
<td>5.2 (3.2)</td>
<td>5.7 (3.3)</td>
<td>5.2 (3.2)</td>
</tr>
<tr>
<td>Lung function:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (% of predicted)</td>
<td>96.6 (12.4)</td>
<td>94.8 (14.9)</td>
<td>96.6 (12.4)</td>
<td>94.8 (14.9)</td>
<td>96.6 (12.4)</td>
<td>94.8 (14.9)</td>
<td>96.6 (12.4)</td>
</tr>
<tr>
<td>PD_{20}, logarithm</td>
<td>8.8 (2.8)</td>
<td>8.4 (2.8)</td>
<td>8.8 (2.8)</td>
<td>8.4 (2.8)</td>
<td>8.8 (2.8)</td>
<td>8.4 (2.8)</td>
<td>8.8 (2.8)</td>
</tr>
<tr>
<td>PEF variability (%)</td>
<td>8.5 (5.0)</td>
<td>8.8 (5.4)</td>
<td>8.5 (5.0)</td>
<td>8.8 (5.4)</td>
<td>8.5 (5.0)</td>
<td>8.8 (5.4)</td>
<td>8.5 (5.0)</td>
</tr>
<tr>
<td>Moderately or Severe AHR (%)</td>
<td>209 (46)</td>
<td>71 (52)</td>
<td>209 (46)</td>
<td>71 (52)</td>
<td>209 (46)</td>
<td>71 (52)</td>
<td>209 (46)</td>
</tr>
<tr>
<td>Inhaled Corticosteroids:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero prescriptions in past 4 months (%)</td>
<td>254 (56)</td>
<td>80 (58)</td>
<td>254 (56)</td>
<td>80 (58)</td>
<td>254 (56)</td>
<td>80 (58)</td>
<td>254 (56)</td>
</tr>
<tr>
<td>Prescribed dose in 1 year (ppd)</td>
<td>0.6 (0.6)</td>
<td>0.5 (0.5)</td>
<td>0.6 (0.6)</td>
<td>0.5 (0.5)</td>
<td>0.6 (0.6)</td>
<td>0.5 (0.5)</td>
<td>0.6 (0.6)</td>
</tr>
<tr>
<td>β_{2}-agonists prescribed in 1 year (ppd)</td>
<td>0.7 (0.9)</td>
<td>0.8 (1.0)</td>
<td>0.7 (0.9)</td>
<td>0.8 (1.0)</td>
<td>0.7 (0.9)</td>
<td>0.8 (1.0)</td>
<td>0.7 (0.9)</td>
</tr>
<tr>
<td>Asthma symptoms (two week diary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily score</td>
<td>1.6 (2.0)</td>
<td>1.4 (1.8)</td>
<td>1.6 (2.0)</td>
<td>1.4 (1.8)</td>
<td>1.6 (2.0)</td>
<td>1.4 (1.8)</td>
<td>1.6 (2.0)</td>
</tr>
<tr>
<td>Number of symptom free days</td>
<td>7.2 (5.2)</td>
<td>7.5 (5.1)</td>
<td>7.2 (5.2)</td>
<td>7.5 (5.1)</td>
<td>7.2 (5.2)</td>
<td>7.5 (5.1)</td>
<td>7.2 (5.2)</td>
</tr>
<tr>
<td>Instruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By health care worker(^a)</td>
<td>375 (82)</td>
<td>83 (61)(^c)</td>
<td>375 (82)</td>
<td>83 (61)(^c)</td>
<td>375 (82)</td>
<td>83 (61)(^c)</td>
<td>375 (82)</td>
</tr>
<tr>
<td>DPI</td>
<td>220 (92)</td>
<td>25 (81)</td>
<td>220 (92)</td>
<td>25 (81)</td>
<td>220 (92)</td>
<td>25 (81)</td>
<td>220 (92)</td>
</tr>
<tr>
<td>MDI/s</td>
<td>147 (94)</td>
<td>35 (78)</td>
<td>147 (94)</td>
<td>35 (78)</td>
<td>147 (94)</td>
<td>35 (78)</td>
<td>147 (94)</td>
</tr>
<tr>
<td>MDI</td>
<td>8 (96)</td>
<td>23 (49)</td>
<td>8 (96)</td>
<td>23 (49)</td>
<td>8 (96)</td>
<td>23 (49)</td>
<td>8 (96)</td>
</tr>
<tr>
<td>Not by health care worker or not at all(^b)</td>
<td>35 (8)</td>
<td>40 (29)(^c)</td>
<td>35 (8)</td>
<td>40 (29)(^c)</td>
<td>35 (8)</td>
<td>40 (29)(^c)</td>
<td>35 (8)</td>
</tr>
<tr>
<td>DPI</td>
<td>20 (8)</td>
<td>6 (19)</td>
<td>20 (8)</td>
<td>6 (19)</td>
<td>20 (8)</td>
<td>6 (19)</td>
<td>20 (8)</td>
</tr>
<tr>
<td>MDI/s</td>
<td>10 (6)</td>
<td>10 (22)</td>
<td>10 (6)</td>
<td>10 (22)</td>
<td>10 (6)</td>
<td>10 (22)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>MDI</td>
<td>5 (4)</td>
<td>24 (51)</td>
<td>5 (4)</td>
<td>24 (51)</td>
<td>5 (4)</td>
<td>24 (51)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>45 (10)</td>
<td>14 (10)</td>
<td>45 (10)</td>
<td>14 (10)</td>
<td>45 (10)</td>
<td>14 (10)</td>
<td>45 (10)</td>
</tr>
</tbody>
</table>

Data are presented as numbers of children with percentages of the sub-group or as means ±SD. In total 530 children participated. Of those, 57 children used more than one device. Ppd: prescribed number of puffs (of 100 µg) per day; AHR: airway hyperresponsiveness.

\(^a\) Inhalation instruction in pharmacy, by physician (GP, pulmonologist or paediatrician), by nurse practitioner, by video or combination of these.

\(^b\) inhalation instruction by family member or acquaintance or never had instruction.

\(^c\) Correct versus incorrect performance, \(P < 0.001\).

inhaling once very deeply to inhaling twenty times fast and superficial (in total 14% incorrect performance).
Sixty-five children (22\%) used a pMDI without a spacer device. Ten children (15\%) used the pMDI adequately, and only four (6\%) demonstrated a perfect inhalation. The remaining 51 children (79\%) failed on one or more essential action(s). For example, a difficult manoeuvre (requiring training) was to press the canister while inhaling slowly and deeply (50\% incorrect). The performance started in many children already with a poor exhalation to residual volume (70\% incorrect). Another example: at least six children breathed quietly in and out at least three times instead of holding their breath for five seconds. As seen in the other inhalers, for many children five seconds of breath holding appeared to be too long.

Figure 1. Percentage correct inhaler performances per inhaler type. All devices \((n = 588)\) are shown of 527 participating children at baseline. \(* P < 0.05, ** P \leq 0.001\). Above the bars the number of children with a correct performance is shown with the total number of observed children. MDI (/s) = Metered-Dose Inhaler without spacer device \((n = 65)\) and with a spacer device \((n = 230)\); DPI = Dry Powder Inhaler \((n = 293)\); DK = Diskus; DH = Diskhaler; CH = Cyclohaler; TH = Turbuhaler; RH = Rotahaler.
Within the DPI’s, the Diskus® was significantly more often correctly used compared to the Turbuhaler® ($P = 0.02$) (Fig. 1). DK and DH were significantly more often correctly used compared to MDI’s with a spacer device ($P < 0.001$), while all DPI’s were significantly more often correctly used compared to MDI’s without a spacer device ($P < 0.001$). Finally, a pMDI with a spacer was superior to an MDI without a spacer ($P < 0.001$).

Follow-up

Of 530 children, 362 were followed during one year (68%). Of these children, 313 children continued their asthma medication during the follow-up year. All children together used 391 devices at baseline and 355 devices at the end of the study (Fig. 2). The percentage of children using a pMDI without a spacer remained stable at 11%. More children who kept the same device demonstrated a correct technique (Fig. 3) compared to the year before. This was irrespective of the inhaler type, and only significant for children with a pMDI (without spacer). Despite this improvement after one year, children with a pMDI again performed significantly worse compared to all of the other inhaler types (Fig. 3). Moreover, DK and DH performed best compared to a pMDI with and without a spacer device.

New devices prescribed during the study are shown in Figure 4. The pMDI device without a spacer device was still significantly and strongly associated with incorrect technique. Of the children who were prescribed a new device, 21% (24/114) demonstrated an incorrect technique compared to 11% (26/241) of the children who kept the same device ($P = 0.01$) (Fig. 2). Furthermore, the figure shows that 41% (37/91) of incorrect performances appeared to be correct one year later. On the opposite, 4% (11/300) of the correct performances appeared to be incorrect at the end of the study.

Figure 2. Flow chart of the inhaler performances of 362 asthmatic children with 391 inhalers, shown at baseline and at the end of the study (one year later). All devices are shown. Above the dotted line all incorrect performances are shown.


Chapter 7

Discussion

In this study on inhalation technique in asthmatic children we found that many children failed in their inhalation performance, both on essential and non-essential actions. DK and DH were most often used correctly. Based on these findings a DPI is strongly preferred if the child is able to inhale with sufficient force. The use of a pMDI without a spacer device leads to faulty inhalation technique in the large majority of cases. During the follow-up year, about a third of the devices was changed into another inhaler type or newly prescribed. Children who continued to use the same inhaler performed significantly better compared to the children who received a new inhaler type. This can be an argument not to change a ‘winning’ combination (child and inhaler). Furthermore, it supports general consensus to invest in inhalation instruction and control after prescribing a new inhaler type.

Dutch and international guidelines [1;67] advocate that outpatient children aged six or seven years and older can be prescribed a DPI device or a pMDI/s. All guidelines advise physicians to prescribe a pMDI in combination with a spacer.

Figure 3. Inhaler performances after one-year follow-up. All children using same device(s) as year before (n = 241). * P < 0.05; ** P ≤ 0.001. MDI (/s) = Metered-Dose Inhaler without spacer device (n = 20) and with a spacer device (n = 100); DPI = Dry Powder Inhaler (n = 121).
Nevertheless, 22% of the children in this study used their pMDI without a spacer. The size of the spacers is socially not acceptable and may therefore be a disadvantage for many children. The small size makes the use of a DPI more attractive for children and adolescents compared to the pMDI with spacer.

One year after enrolment in our study, a lower proportion of devices was poorly used (23% and 14%). However, 68% of the inhaler usage remained unchanged (see Fig. 2). Changing from one device to another, led to an increase in errors. Children who kept their device during the follow-up year improved their performance. It was not evaluated in this study whether the observed improvement occurred spontaneously or because of (repeated) inhalation instruction by the GP or pharmacist. Children were not given any inhalation instructions as part of this original study.

Furthermore, for a small number of children, we saw that correct inhalation...
technique could deteriorate over time. This indicates that it remains important to check the children’s inhalation technique also if they use the same device for a long period of time.

Many studies evaluating inhalation technique agree on the occurrence of frequent errors in essential and non-essential actions in DPI’s and MDI’s [149;151-155]. In a recent study amongst 200 children visiting an asthma clinic in the northern part of the Netherlands, 21.5% performed one or more of the essential steps incorrectly [154]. Moreover, poor inhalation technique was more frequently observed in newly referred children if they used a DPI (74%) compared to children who used a pMDI/s (21%) device. However, these children were referred to a tertiary clinic for their asthma and may be not comparable to our population. Patients who had received repeated instruction sessions and patients who had previously been asked to demonstrate the use of their inhaler during an instruction session were more likely than other children to demonstrate a correct inhalation technique. In another study amongst 166 adult asthmatics, patients with a DH made the fewest errors as compared to pMDI, RH and TH [148].

Equal to in our study, Kamps and colleagues found no difference in characteristics or asthma severity between children who demonstrated correct or incorrect inhalation technique [154]. Giraud et al. found that amongst adult asthmatics using inhaled corticosteroids, misuse of pMDI was frequent and associated with poorer asthma control [156]. The studies mentioned above are all hospital-based and, therefore, may not in all aspects be comparable to our study.

We cannot conclude from our findings that the inhaler performance does not influence the level of control of the disease, despite that we did not find differences in asthma severity between correct and incorrect inhaling children. In both groups in our study about half of the children showed moderate or severe AHR and in both groups the use of inhaled corticosteroids in the months before evaluation was poor. This latter observation is probably more important for the control of disease of the children than inhalation technique alone.

In summary, in this study we found a poor inhalation technique in a large proportion of the investigated children in general practice. This study underlines the importance to prescribe pMDI’s in combination with a spacer device. Another superior alternative is a DPI device. The use of a pMDI without a spacer device should be strongly discouraged. Providing children with a new device should be carefully controlled over time because these children are prone to inhalation errors as well. Increasing the competence on inhalation technique is the first link in a chain of factors contributing to adequate asthma control.
Residential exposure to mould and dampness is associated with adverse respiratory health

W. Hagmolen of ten Have, N.J. van den Berg, J. van der Palen, W.M.C. van Aalderen, P.J.E. Bindels

accepted in revised form

Clinical and Experimental Allergy
Abstract

Background: Indoor exposure to mould and dampness is frequently associated with asthma symptoms with and without lung function changes. However, the mechanisms contributing to this threat to respiratory health are only partly understood.

Objective: To investigate the contribution of recent exposure to mould and dampness in the living room or bedroom to respiratory health in a general practice based cohort of 526 asthmatic children.

Methods: Parents were questioned about home characteristics, including moulds and dampness. The level of asthma control was evaluated in their participating children by means of asthma symptoms, PEF variability, severity of airway hyperresponsiveness (AHR) and medication usage.

Results: Children exposed to indoor moulds and dampness had more often severe AHR compared to non-exposed (42% versus 16%; \(P \leq 0.001\)). They also showed significant more PEF variability (11.3% versus 8.4%) and, however not significant, more frequent asthma symptoms. The use of controller medication was not significantly different between exposed and non-exposed children. The adjusted Odds Ratio for severe AHR in exposed children was 3.90 (95% CI: 1.81-8.41).

Conclusion: We found a consistent association between reported moulds and dampness in the living room or the child’s bedroom and an increased risk for severe AHR in a general practice based cohort of asthmatic children, even after adjusting for age, reported inhalant allergy, asthma medication usage and smoking.

Introduction

The prevalence of damp stains and moulds in Dutch homes is estimated at 18 and 17%, respectively [157]. Residential exposure to dampness and moulds is well known to influence respiratory health [158,159]. In literature, the association between living in a damp or mouldy home and an increased risk of wheezing and chronic cough is found to be consistent with an odds ratio between 1.4 and 3.5 [159]. Mould exposure is associated with asthma exacerbations, increased PEF variability, and persistent AHR [160,161]. Dampness at home was strongly associated with persistent AHR in a study amongst asthmatic children [162]. From these and other studies several possibilities are suggested which might explain the association of our respiratory health with damp conditions in home. Some evidence is available that supports the idea that exposure to house dust mite and moulds can stimulate allergic sensitization [163]. This can be true for house dust mites and moulds because both thrive in damp conditions. In addition to sensitization, exposure to mites- and moulds- allergens is thought to exacerbate pre-existent disease [164]. Finally, mycotoxins and the mould cell wall component (1→3)-\(\beta\)-D-glucan have been suggested to possess immuno-suppressant or irritant properties. Exposure to these agents may play a role in the aetiology of asthma [165,166].
The objective of this study was to investigate the association of reported exposure to mould and dampness and respiratory health in a general practice based population of asthmatic children. The main question was whether children exposed to mould or dampness in their bedroom or in the living room differed from children who were not exposed in these areas with respect to asthma symptoms and bronchial responsiveness.

**Methods**

**Setting & subjects**

Almere is a fast-growing city in the middle of the Netherlands and built on the sea floor in the past century. It is situated below sea level (2-5 metres) and surrounded by water and new land. The first inhabitants of Almere settled in November 1976. Since then, many families moved to this city. At the start of our study in 2001, Almere had about 140,000 inhabitants, most of whom lived in new, well-isolated houses. Children were participants in a general practice based cohort study on childhood asthma. Children were eligible for this study if at least two prescriptions of β₂-mimetics or an inhaled corticosteroid (ICS) were prescribed in the year before invitation. The original study was performed to compare different methods to improve disease control in childhood asthma in a general practice population. This study is discussed in more detail elsewhere [130]. Informed consent was obtained from 539 children or their parents. The medical ethics committee of the Flevohospital in Almere approved the study.

**Data collection**

The data used for the present study were collected at inclusion in the intervention study. Participants were invited for two visits within a two-week interval. During the first visit demographic details were registered and a questionnaire was completed by one of the parents. The questionnaire contained questions on housing conditions such as the presence of moulds and dampness in the house, identification of allergen reservoirs that facilitate mite growth, on pet-keeping, and on parental smoking (see Appendix).

One of the questions related to dampness and mould: (1) did you ever have damp stains or mould growth in your home in the past 2 years? If the question was answered positively, the next question specified the place where the problem occurred in the residence (bathroom, living, sleeping area of the child or somewhere else (free text)). Questions on smoking focused on each parent separately. For each child we examined whether he or she was exposed to a smoking parent or caregiver. Smokers were defined as those who smoked at least one cigarette per day for a period of 6 months and who were still smoking within 1 month prior to the examination. The researcher (WHoTH) questioned allergic symptoms. The presence of allergy was not confirmed by means of allergy testing.
During the second baseline visit children performed a methacholine challenge test [130]. Between these two visits children kept a diary in which they recorded asthma symptoms and peak expiratory flow (PEF) measurements twice daily.

**Asthma control parameters**

The level of asthma control was evaluated by the presence of asthma symptoms, the forced expiratory volume in one second expressed as percentage predicted (FEV₁), severity of airway hyperresponsiveness (AHR) and PEF variability. A single concentration methacholine challenge test [110] was performed in those children in

**Table 1. General and clinical characteristics of participants.**

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>526</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>240</td>
</tr>
<tr>
<td>Age (y)</td>
<td>11 ± 2.5</td>
</tr>
<tr>
<td>Smoker</td>
<td>19</td>
</tr>
<tr>
<td>Asthma in first degree relative</td>
<td>320</td>
</tr>
<tr>
<td>Mould and dampness In home during last 2 years</td>
<td>125</td>
</tr>
<tr>
<td>Mould and dampness In living- or child’s sleeping- room</td>
<td>33</td>
</tr>
<tr>
<td>Smoking in home None</td>
<td>275</td>
</tr>
<tr>
<td>Smoking in home 1 household member</td>
<td>156</td>
</tr>
<tr>
<td>Smoking in home ≥ 2 household members</td>
<td>95</td>
</tr>
<tr>
<td>Pet-keeping</td>
<td>270</td>
</tr>
<tr>
<td>Pet-keeping 7 household members</td>
<td>156</td>
</tr>
<tr>
<td>Pet-keeping ≥ 2 household members</td>
<td>95</td>
</tr>
<tr>
<td>Parental education low (≤ 11 years education)</td>
<td>70</td>
</tr>
<tr>
<td>Symptoms of inhalant allergy last year Hay fever, hairy pets, birch, grass pollen</td>
<td>356</td>
</tr>
<tr>
<td>Asthma symptoms Total symptom score</td>
<td>0.8</td>
</tr>
<tr>
<td>Asthma symptoms Symptom free days (no.)</td>
<td>7</td>
</tr>
<tr>
<td>Lung function PEF variability (%)</td>
<td>8.6 ± 5.1</td>
</tr>
<tr>
<td>Lung function FEV₁ % predicted</td>
<td>96.0 ± 12.9</td>
</tr>
<tr>
<td>Lung function FEV₁ &lt; 75 % predicted</td>
<td>21</td>
</tr>
<tr>
<td>Lung function Log transformed PD₂₀</td>
<td>8.7</td>
</tr>
<tr>
<td>Lung function PD₂₀ ≤ 75 µg (severe AHR)</td>
<td>90</td>
</tr>
<tr>
<td>Asthma medication (puffs per day) ICS prescribed</td>
<td>0.3</td>
</tr>
<tr>
<td>Asthma medication (puffs per day) β₂-mimetics prescribed</td>
<td>0.6</td>
</tr>
<tr>
<td>Asthma medication (puffs per day) β₂-mimetics score diary</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Data are presented as numbers of children with percentages of subgroup, as means ± SD or as median values with range.
whom the initial FEV$_1$ was $\geq 75\%$. The degree of AHR was expressed as a PD$_{20}$, a provocation dose that induces a 20\% fall in FEV$_1$ from baseline. Severity of AHR is classified according to Sont et al [14]. Severe AHR is defined as a PD$_{20} < 75\mu g$. Above 75\mu g methacholine, AHR improves from moderate via mild and borderline to a normal bronchial response. Children were challenged to maximal cumulative doses of 3600\mu g methacholine.

PEF measurements were registered twice daily in the diary and the best of three scores was used. PEF variability was calculated as best evening PEF value minus best morning PEF value divided by their mean value. The frequency of asthma related symptoms, cough, wheeze, and shortness of breath were scored twice daily (0' (no complaints), 1' (once a day), 2' (more than once a day), 3' (whole day)) in a two-week diary. Total symptom score could range from 0 (no symptoms) to 18 (maximum number of symptoms). In addition we calculated the number of symptomfree days (range 0-14). The number of prescribed inhalers for ICS and $\beta_2$-mimetics were obtained from electronic medication lists of the GP’s and presented as a mean daily dosage prescribed over one year.

Statistical analysis

Baseline characteristics are reported as mean values ± SD or as percentages for categorical or dichotomous variables for the whole group and stratified by exposure to mould and dampness. Values are reported as median with corresponding range if variables are not normally distributed. First, t-tests, in case of normally distributed variables, were performed to identify a subset of independent variables that were associated with exposure to mould and dampness. For non-normally distributed variables this was done by Mann-Whitney U test. Between groups comparisons of nominal or ordinal variables were performed by Chi-square tests. The a priori list of potential confounding variables included: age (y) as a continuous variable; gender, history of inhalant allergy, family history of asthma, the level of parental education ($\leq 11$ years of education), smoking status (current smoker yes or no), pet-ownership (yes or no) and the usage of ICS in the previous four months ($\geq 1$ prescription(s) = 1) as dichotomous variables and exposure to environmental smoking by parents or household members as a categorical variable (0, 1, or 2). We performed a multivariable logistic regression analysis in which we started with all candidate variables. Subsequently, we eliminated the variables with the highest $P$-value step by step, and verified at each step whether the $\beta$-coefficient of the risk factor mould and dampness had not changed by 10\% or more from its initial value.

Children with an initial airflow limitation (baseline FEV$_1 \leq 75\%$) were not challenged and were excluded from the univariable and multivariable analyses. Data-analysis was performed with the statistical package SPSS/PC for Windows (version 12.2) (SPSS, Inc., Chicago, IL).
Chapter 8

Results

Of 539 children, 526 (286 boys (54%); mean age 11 years) successfully completed all assessments. General and clinical characteristics of the children are described in Table 1. The median symptom score was 0.8 with a maximum of 9.9. The median number of symptomfree days during the two weeks that they kept their diary was 7. FEV₁ and PEF variability were normally distributed with mean values of 96% and 8.6%, respectively. Twenty-one children were excluded from further analyses because they were not challenged since their FEV₁ was below 75% of predicted. Ninety children were classified as having severe AHR (PD₂₀ < 75µg). Half of the children were prescribed equal or less than 0.3 puffs ICS per day during the year prior the study. β₂-agonists were prescribed more often.

During the last two years, mould and/or dampness were prevalent in 125 homes as reported by the parents of the participating children. In 33 cases, mould or dampness were located in the living room or bedroom of the child. Differences in clinical characteristics between exposed and non-exposed are described in Table 2. Exposed children scored higher on asthma symptoms and had less symptomfree days. Although the difference was not significant. PEF variability was significantly higher in exposed as compared to non-exposed. The same, even more pronounced, was seen for AHR: log transformed PD₂₀ decreased from 8.8 to 7.2 reflecting an increase in AHR severity; \( P = 0.009 \). The proportion of children with

<table>
<thead>
<tr>
<th>Table 2. Differences in clinical characteristics between children exposed and not exposed to mould and dampness in the living room or the child’s sleeping room.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposed</strong> to mould and dampness</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td><strong>Asthma symptoms</strong></td>
</tr>
<tr>
<td>Total score</td>
</tr>
<tr>
<td>Symptom free days (no.)</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
</tr>
<tr>
<td>PEF variability (%)</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
</tr>
<tr>
<td>Log transformed PD₂₀ (^{a})</td>
</tr>
<tr>
<td>PD₂₀ ≤ 75 µg (^{a})</td>
</tr>
<tr>
<td><strong>Asthma medication</strong></td>
</tr>
<tr>
<td>ICS prescribed</td>
</tr>
<tr>
<td>β₂-mimetics prescribed</td>
</tr>
<tr>
<td>β₂-mimetics score diary</td>
</tr>
</tbody>
</table>

Data are presented as mean values ± SD or as median values with range.

* \( P = 0.03 \); ** \( P = 0.009 \); *** \( P ≤ 0.001 \) as compared to non-exposed children.

\(^{a}\) Children with an initial airflow limitation (baseline FEV₁ ≤75%) were not challenged and were excluded from the descriptive PD₂₀ analyses.
severe AHR was significantly higher in exposed children (42%) as compared to non-exposed children (16%). Controller and rescue medication were not significantly more often prescribed in the exposed group. A trend towards increased usage of β₂-mimetics was seen in the exposed group: median score of 0.4 puffs per day versus 0.1 amongst non-exposed. We analysed whether the increased risk for severe AHR when exposed to mould or dampness in the bedroom or living area was consistent when potential confounding variables were taken into account. The results are shown in Table 3. In a separate analysis we also adjusted for health care center and season of assessment (data not shown). In this study the adjusted odds ratio (OR) for severe AHR is 3.90 (95% CI: 1.81-8.41) for children in whom mould and dampness were reported in the sleeping area of the child or in the living room. A history of inhalant allergy was another independent predictive factor for severe AHR. Removing all variables from the model did not change significantly the studied association nor did adjustment for HCC and season of assessment.

Discussion

We show in this study that respiratory health is at risk in children living in homes where mould and dampness are visible. The risk is highest when mould and dampness are visible in the living room or in the child’s bedroom. The prevalence of reported indoor dampness and mould growth in these areas in our study was 6.3%. We found that exposed children had an almost four-fold increased risk for severe AHR and suffered more often from symptoms of asthma. The prevalence of reported indoor dampness and mould growth in home (24%) found in our study is more or less comparable to the prevalences found in other European

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR Severe AHR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mould and dampness, living or child’s sleeping room</td>
<td>3.90</td>
<td>1.81-8.41</td>
</tr>
<tr>
<td>Male</td>
<td>1.44</td>
<td>0.88-2.36</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.90-1.12</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.16</td>
<td>0.32-4.20</td>
</tr>
<tr>
<td>Asthma in first degree relative</td>
<td>0.83</td>
<td>0.50-1.37</td>
</tr>
<tr>
<td>Parental education</td>
<td>1.37</td>
<td>0.71-2.65</td>
</tr>
<tr>
<td>History of inhalant allergy</td>
<td>3.67</td>
<td>1.87-7.20</td>
</tr>
<tr>
<td>ICS prescribed</td>
<td>0.68</td>
<td>0.40-1.13</td>
</tr>
<tr>
<td>Smoking in home by parents /household members</td>
<td>0.97</td>
<td>0.71-1.31</td>
</tr>
<tr>
<td>Pet-ownership</td>
<td>1.16</td>
<td>0.70-1.95</td>
</tr>
</tbody>
</table>

Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Data were complete for 498 children. Children with an initial airflow limitation (baseline FEV₁ ≤ 75%) were not challenged and were excluded from the multivariable analysis.

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Three studies performed in the Netherlands reported on the prevalence of damp stains and mould growth (independently) in the homes of Dutch schoolchildren; the prevalences varied from 14.8% to 31.5% and 9.1% to 23.4%, respectively [167;168]. Jacob et al. reported on dampness at home and not on mould growth; they found a prevalence of 25% amongst sensitized cases and 22% amongst controls aged 5-14 years [163]. In the European Community Respiratory Health Survey (ECRHS) adult asthmatics were questioned on water damage, water on the basement floor and prevalence of mould or mildew in home; the prevalences were 12%, 2% and 22%, respectively [158]. In these studies, dampness and mould growth were questioned and reported separately whereas in our study no differentiation was made between dampness and mould growth. None of the studies specified the exposure to the living room or bedroom. The occurrence of dampness and mould growth differ with climate conditions and housing characteristics. Therefore, the prevalence in Almere might differ from the described prevalences because of the (relative) new construction of houses that are better isolated compared to old houses or the typical location (see methods) and the sea climate.

The association with AHR that we found in our study has not been extensively studied. In asthmatic children, Nicolai et al. showed most convincingly an association between dampness at home and the persistence of AHR (OR 16.14; 95% CI: 3.53-73.73). The association was partly independent of the exposure to house dust mite antigen (OR 5.77; 1.17-28.44) [162]. In the ECRHS, a study to adult asthmatics, reported mould or mildew in the last year was associated with AHR (OR 1.14 (1.01-1.29) [158]. In this study, dampness was not questioned, and the severity of AHR was not taken into account. In another European study amongst children with chronic respiratory symptoms, AHR was not investigated but reported moulds (not dampness) in the home was associated with an increased PEF variability (OR 1.15; 1.03-1.28) [161].

In the Netherlands, the majority of the children with respiratory symptoms is treated in general practice [56]. Treatment algorithms in general practice are mainly driven by asthma symptoms. In this study we show that exposed children reported more symptoms, they used more often their reliever medication and probably also their controller medication. However, medication usage is poor in a number of the exposed and symptomatic children (data not shown). One explanation can be that the child or parent does not judge symptoms as severe. They even might not consult their GP. Also the GP could have underestimated the severity of the child’s disease because of a lack of tools to assess objectively the level of control of asthma. In an earlier study we showed that asthma symptoms do not predict the severity of AHR [130]. Therefore, children with severe AHR can be easily missed. However, the question whether children with asthma are bothered by mould or dampness in the living room or in the bedroom is an easy one. If the question is
answered positive we recommend assessment of AHR. Also atopy should be verified and allergen avoidance measures should be recommended to patients if appropriate. Based on the level of asthma control ICS should be prescribed.

The findings and conclusions in our study are limited because exposure to mould and dampness was not differentiated, the homes were not visited, atopy was not assessed and the data were obtained cross sectionally. Despite these limitations, we show that in asthmatic children reported exposure to mould and dampness in the living room and the child’s bedroom was consistently associated with severe AHR. Future studies are needed to unravel the pathophysiological mechanisms of the association between dampness, mould growth and asthma. Recently, Burr and colleagues published the results of a randomized controlled trial which was conducted to assess the efficacy of mould removal in asthmatic patients’ houses [169]. Although there was no evidence of benefit on PEF variability, symptoms and rhinitis improved and medication use declined following removal of indoor mould. Moreover, the authors state that the eradication of visible mould is a fairly simple procedure. New studies in children are needed to assess the efficacy of this method eventually in combination with other allergen avoidance measures. We recommend including severity of AHR to assess the efficacy of such interventions in future studies.

In summary, mould and dampness were reported in the living room and child’s bedroom in one of every fifteen asthmatic children in a general practice based population in Almere (the Netherlands). We show in this study that exposure was associated with severe AHR, and that children had more frequent symptoms. The association with AHR has been described previously, however, it has not extensively been studied. Airborne allergens and toxins are all suggested to play a role in the observed association; nevertheless, pathophysiological mechanisms are not completely unravelled yet. New evidence became recently available that mould removal had positive effects on asthma symptoms and medication usage in asthmatic patients. Therefore, it is time to increase emphasis on the role of the physician/GP in the identification of exposure to indoor mould and dampness that may contribute to the severity of asthma.

Acknowledgements

We would like to thank the Health Care Organization ‘Zorggroep Almere’ and all children and their parents for their participation in the study. GlaxoSmithKline sponsored this study with an unrestricted grant.
Overview of the major questions from the questionnaire used in this report.

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>(1) No</th>
<th>(2) Yes, in bathroom/living-room/sleeping area of the child/other</th>
<th>(3) Yes, in bathroom/living-room/sleeping area of the child/other</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Did you ever have dampness in your home in the past 2 years? (y/n)</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Did you ever have dampness or mould growth in previous home(s) during the child's lifetime? (y/n)</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Did you ever kept pets?</td>
<td>No, never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Which pets do you have (or did you have)?</td>
<td>cat (y/n), dog (y/n), bird (y/n), rodent (y/n), other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26a</td>
<td>Does the mother of the child smoke?</td>
<td>No, never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26a</td>
<td>How many does the mother, on the average, smoke per day inside the house?</td>
<td>number of smokes/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Did the (biological) mother of the child smoke during pregnancy? (y/n/don't know)</td>
<td>number of smokes/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27a</td>
<td>Does the caregiver of the child smoke? (if not the biological mother)</td>
<td>No, never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27a</td>
<td>How many does the caregiver, on the average, smoke per day inside the house?</td>
<td>number of smokes/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29a</td>
<td>Does the father of the child smoke?</td>
<td>No, never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29a</td>
<td>How many does the father, on the average, smoke per day inside the house?</td>
<td>number of smokes/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>How many other housemates smoke in the house?</td>
<td>number of smokes/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30b</td>
<td>How many does these housemates, on the average, smoke per day inside the house?</td>
<td>number of smokes/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
General discussion
Current treatment of childhood asthma in general practice and debate.

Asthma is one of the most common chronic diseases during childhood. As described in the introduction, its prevalence has increased during the last decades, although there is some evidence that this increase came to an end, at least in Western Europe. General practitioners (GP’s) treat the majority of asthmatic children [56] in whom mild asthma is more often present compared to moderate and severe asthma [170]. Asthmatic children will only be referred to a paediatrician if they fail to respond on the first treatment steps initiated by the GP (see chapter 5, appendix A). Reducing the morbidity (and mortality) of asthma is the major aim of asthma treatment. Except for intermittent asthma symptoms, asthma is most effectively treated with anti-inflammatory drugs [171-173]. Treatment with inhaled corticosteroids (ICS) for at least three months has demonstrated a reduction in airway inflammation/airway hyperresponsiveness (AHR) and a reduction in exacerbation rates [174]. A number of studies showed that even mild asthma can lead to severe exacerbations, with a frequency ranging from 0.13 to 0.77 exacerbation per patient-year [125;175;176]. Severe exacerbations in mild asthma represent 30-40% of asthma exacerbations requiring emergency consultation. There is, however, debate as to what extent we need to aim for asthma control. Is it realistic for physicians to aim for complete asthma control in all patients? What are the best strategies to approach asthma control and what is the best method to assess the effectiveness of these strategies [177]. A symptom-based treatment approach may have its limitations because children and their parents can be poor judges of disease symptoms and their severity. Subsequently, under-estimation may lead to inadequate treatment of airway inflammation and AHR.

Main findings of the baseline evaluation

Selection of the study population

The aim was to create a study group that was representative for asthmatic children treated in general practice and to whom the national asthma guideline was applicable. Therefore, we selected all children who were prescribed asthma medication in the year before they were invited to participate in the study. Children treated for their asthma by a paediatrician were excluded, as were children under the age of 7 because in these children the assessment of AHR by means of a challenge test is difficult if not impossible to perform. In chapter 5 patient selection is described in more detail, and a flow diagram of the participants is presented. We investigated the possibility of selection bias by three actions. First, the GP was questioned whether the child was eligible for the study and could be invited. Second, nonparticipants were asked about their reason for refusal at the moment of invitation or subsequently by phone. A variety of reasons for noninvitation by the GP or nonparticipation by the children/parents were given: 261 children (26%) were treated for their asthma by a paediatrician; 157 children (16%) reported that they were not willing to participate for reasons not related to their asthma; 87 children
(9%) had no asthma; 157 children (16%) were (almost) symptom free, and therefore not willing to participate; 51 children (5%) were bothered by other conditions (social problems; (mental) health reasons). Of 315 children (31%) the reason for nonparticipation remained unknown.

In addition, severity of asthma and medication usage in ‘nonparticipants’ was evaluated. The results are presented in chapter 4. Sixty-one children were evaluated at home. Half of the children were 7 to 12 years old, as compared to 78% in participants. Mild or absent asthma symptoms were the most important reason for nonparticipation. Nevertheless, we found that 64% of the children experienced asthma symptoms in the previous week as assessed by means of the 5 questions on symptoms of the Asthma Control Questionnaire (ACQ) [178]. Furthermore, we found lung function abnormalities, such as a FEV1 below 80% of predicted or reversibility of airway obstruction, in about 40% of these children (n = 25). Of these, nine children had no asthma symptoms (36%), eight had minimal (32%), and only eight had more severe asthma symptoms (ACQ symptom score ≥1; 32%). In conclusion, nonparticipants were older but they were not likely to have less severe asthma or less well-controlled asthma. Despite the limitations of this comparison (no AHR challenge was performed), the investigated group seems a representative group for the asthma population in the same age range in general practice.

Severity and control of asthma

In chapter 4 characteristics of all evaluated children (n = 526) are presented in detail, whereas in chapter 5 characteristics of children are presented who were included in the prospective part of the trial (positive response on inhalation challenge and complete follow-up (n = 362)). Of all evaluated children, 21 (4%) were not challenged because their pre-bronchodilator FEV1 was below 75% of predicted. Ninety children had severe (17%), and 142 moderate severe (27%) AHR. A striking finding of our study was the extremely high a priori probability in children in the age group 7 to 17 years of having moderate to severe AHR (44%).

Taking also into account the 4% of children with a low pre-bronchodilator FEV1, almost half of the children in this age range and treated with asthma inhalation medication was either having moderate to severe AHR or was having poor controlled asthma.

There were no significant differences in baseline characteristics between children with and without moderate to severe AHR. However, children with severe AHR had significantly more frequent asthma symptoms, also during the night, and they were prescribed more often β2-agonists suggestive for more severe or less well-controlled asthma. In addition, they had a lower pre-bronchodilator FEV1. No bronchial response on the inhalation challenge was seen in 101 children (19%). We assumed that these children had no persistent asthma or their asthma was well controlled. We did not classify children according to the currently available classification for the level of asthma-control [1] because the classification was not
available at the start of the study. The results of the studies presented in this thesis have shown that the estimation of asthma severity with currently available tools in general practice is difficult, if not impossible (chapter 4) and that GP’s and paediatricians often overestimate the level of control of the disease in their patients (chapter 2).

In chapter 6 we showed that it is useful to question recent wheezing, because 80% of the parents of children with severe AHR reported wheezing in the last year. When the child’s asthma seems well controlled because the child failed to report asthma symptoms during a control visit, but the parents do report wheezing in the past year, a discrepancy between control and severity might exist. In these children, we recommend to assess the severity of AHR, in order to get more insight in the severity of the child’s asthma. This recommendation indicates that GP’s should be able to have easy access to lung function facilities. All participants in our study underwent lungfunction testing in the regional hospital, demonstrating that such a cooperation and accessibility is feasible. In the near future, inflammatory markers such as exhaled NO are probably easier to measure and more readily available to the GP.

Assessment of Airway Hyperresponsiveness

For most participants and parents, assessment of AHR at inclusion in this study was the first objective assessment of the child’s asthma. Also a diagnosis of asthma was often not explicitly mentioned by the GP or the parents did not believe in an asthma diagnosis in their child before this provocation test. It is unclear whether this discrepancy was due to poor communication between GP and parents. In current guidelines for GP’s an asthma diagnosis is based on symptoms, and sometimes also based on reversibility of airflow limitation. In addition to the current guidelines, assessment of AHR could help to confirm the diagnosis and to assess asthma severity. A challenge test can mimic an exacerbation in a safe environment. After proper explanation, the test can also give parents and children more insight in the disease. Children have the right to optimal treatment of their asthma. GP’s certainly will endorse this statement. The findings of our study have shown that there still is considerable room for improvement. Therefore, an asthma diagnosis should be made explicit both to parents and the child. As shown in our study population, many parents were unaware or not properly informed on the asthma diagnosis in their children, which certainly will have consequences for the level of control in their children.

Asthma medication

As shown in chapter 4, controller medication was poorly prescribed. The guidelines recommend in children with mild persistent asthma a maintenance usage of 100 µg
fluticasone or an equivalent (budesonide or beclomethason; 200 µg) b.i.d. More than half of the children in our study were prescribed less than 0.5 puff ICS per day as calculated based on prescribed medication during one year. Only a minority of the children was prescribed sufficient medication for daily usage. This finding was independent of the degree of AHR and suggests underdiagnosis of current asthma symptoms and subsequent undertreatment.

Chapter 7 reported on inhaler devices and inhalation technique. Approximately half of the children used dry powder inhalers (DPI; Diskus®, Diskhaler®, Turbuhaler® and Cyclohaler®) and half used pressured metered-dose inhalers (pMDI). One fifth of children with a pMDI inhaled asthma medication without a spacer device. As reported by the children almost half of them never received instructions on the use of a pMDI without a spacer device. It is likely that children who were prescribed a spacer device with their pMDI stopped using the spacer device because of inconvenience (largely due to the size of the spacer) without informing their GP. Physicians should be more aware of this finding. In our study population the inhaler technique was best among children using a DPI. Best performances were seen with the Diskus and Diskhaler. We expected that children with more severe asthma, who are well-controlled are likely to use their asthma medication and use their inhaler device correctly. It is also expected that children with poorly controlled asthma or intermittent medication usage are likely to show more often incorrect inhaler techniques. In this cohort, no evidence was found for both considerations. We could not find any influence of a correct or incorrect inhaler technique performance on severity of AHR or asthma symptoms. However, inhaler technique performance was checked irrespective of medication group (ICS or reliever medication), and, as mentioned before, only few children were prescribed sufficient ICS for maintenance therapy. The impact of a poor inhalation technique on AHR and symptoms in children using only bronchodilators might be limited.

Mould and dampness

In chapter 8 we showed that children who are exposed to mould or dampness in the living room or bedroom have an almost fourfold increased risk of having severe AHR. It is known for a long time that a damp climate and mould exposure influence respiratory health negatively. However, the influence on AHR is not often described in children. In addition, it is the first time that the association is reported in a general-practice based cohort. The severity of AHR and the level of asthma control should be confirmed in exposed children with asthma, and we recommend close monitoring, or if needed, referral to a paediatrician. Additional information on how to remove mould and dampness from the home could be of benefit for the child.
Chapter 9

Methodological issues and considerations

There is no ‘gold standard’ for the definition and assessment of asthma in general practice. In the introduction of this thesis we described that asthma in our study population was assumed based on the prescription of asthma medication. However, a more objective and measurable parameter of asthma was needed to evaluate asthma in the participants and to assess the efficacy of implementation strategies with regard to improving asthma control. The following considerations were made: selected children may not all have a physician’s diagnosis of asthma, but were (at least temporarily) recently treated with asthma medication; registration of an asthma diagnosis was not available in the pharmacy database used; report of asthma symptoms by patients in order to define asthma is subjective as is the assessment of its severity by the physician; AHR is one of the hallmarks of asthma and in contrast to asthma symptoms, an objective assessment. Taking into account these considerations, AHR was chosen as the primary outcome parameter to assess the level of asthma control and the efficacy of guideline implementation. However, AHR is an entity that can also be present in children without asthma. Therefore, AHR cannot be considered as a synonym of asthma, and the presence of AHR has always to be interpreted in combination with other features of asthma of which the presence of airway symptoms is the most important one.

The severity of AHR was classified in four categories: borderline (> 1000 µg methacholine), mild severe (300-1000 µg), moderately severe (75-300 µg) and severe AHR (< 75 µg) in accordance to the ATS guidelines [179]. The ATS guidelines do not distinguish moderate and severe AHR as Sont and colleagues did in their study [14]. We had to translate the cut-off points used by the ATS from PC20 (provocative concentration) to PD20 (provocative dosage) because the ATS guideline used a tidal breathing method as compared to a dosimeter method used in this study. Different methods do never give exactly the same outcomes but are comparable. In addition, the cut-off points used to classify the severity of AHR are arbitrarily chosen and therefore should be interpreted with the other features of the child’s asthma.

Effect of implementation of a national asthma guideline

Main findings

The aim of the Asthma in Almere Project (AAP) was to evaluate whether the introduction of a national guideline for the treatment of asthma in children with three different implementation programs was effective with regard to the level of control of asthma in children. The general hypothesis was that a combined strategy including the distribution of the guideline, a single educational session, and an individualized treatment advice, was superior in improving asthma control in general practice compared to the distribution of the guideline and the educational session alone. Did we achieve our study aim? The statistics were conclusive: there
was no significant difference between the three strategies with respect to the primary outcome (AHR). There was a significant difference in two secondary outcomes, however, group A performed best with respect to the nocturnal symptoms score and group C with respect to the use of ICS. The outcome of the study is not satisfactory because we had to reject our hypothesis although the combination of strategies including evaluation of AHR together with an individualized treatment advice had positive and consistent effects towards improved asthma control in the participating children. This consistency was not seen in the other two groups.

Is it correct, based on our statistical findings, to conclude that the combination of strategies did not improve asthma control more effectively compared to the distribution of the guideline and the educational session alone? It is possible that we dealt with a type-2 error, which means that we rejected the hypothesis falsely due to sample sizes being too small. This is supported by a second analysis of our data in which we aggregated the data of group A and B (group AB) because we did not reach the calculated sample size in group A. In this analysis the improvement in AHR in group C differed significantly from group AB.

Methodological issues and considerations

The study is a randomized controlled trial, which is the best method by consensus to investigate a hypothesis as formulated in our study. Ideally the intervention is randomized over a large number of participants. In theory we could have chosen for patients (n = 560) or for individual GP’s (n ≥ 100). However, to prevent contamination bias that was likely to occur because GP’s in health centres work in close collaboration, we had to choose for randomization by health care centre of which there were only 18 in the study area. This restricted the statistical power of the analysis. This limitation was one of the causes that the difference between the three study groups reached no significance. The intervention in group C in our study was controlled but could not be blinded, which is a disadvantage of the study. In addition, the result of the challenge test could not be blinded to the parents who were interested in the outcome. Both facts may have positively influenced the level of asthma control in groups A and B and subsequently reduced the contrast with group C.

In addition, improvement of asthma control is a highly conditional event. Participants had to visit their GP during the study year (which was strongly advised, but voluntarily); the GP had to adhere to the asthma guideline; or in group C: the GP had to agree with the given treatment advice; and the child (or parent) had to adhere to asthma therapy as initiated by the GP. The chain of steps, the number of involved individuals (participant, parent, GP) and subsequently, the accumulation of uncertainties decreased the probability to achieve improved control of asthma in the child. However, these conditions were applicable for all three study groups.
Each GP received, dependent on the number of participants a median number of five treatment advices during the study year (one per child). The learning effect of such a small number of treatment advices will be low and not enough to influence effectively and persistently the knowledge and skills of the GP. It is therefore likely that continuation of the implementation strategies, with repeated attention to treatment plans will be more effective in the long term.

Treatment strategy

The treatment advice given to GP's in group C was based on a treatment strategy introduced by Sont and colleagues that was aimed at reducing AHR [14]. They showed convincingly that their AHR-guided strategy lead to better control of asthma in adults by means of a more accurate, but increased dosage of ICS, resulting in a 1.8 fold decrease in exacerbation rate (p=0.03), an increased FEV1, and a reduction of the thickness of the subepithelial reticular layer as compared with a control group who were treated according an asthma guideline similar to the GINA guideline. In children, we expected that an AHR-driven treatment approach would also be superior to a symptom-driven treatment approach in reaching optimal asthma control in children because symptoms of asthma are often difficult to judge in children.

Implementation techniques

We introduced three cumulative strategies. The first two strategies were only aimed at transferring information, one by means of the dissemination of the guideline and the other by means of a single educational session. Information transfer is an essential component of any implementation strategy, but additional techniques are usually needed to achieve changes in clinical practice [138]. In group C we provided very specific, individualized information on the level of asthma control and the degree of AHR, and additionally we gave feedback on current asthma therapy (inhalation technique and current medication usage). Besides, the latter implementation strategy promoted communication between the GP and the paediatrician and subsequently, it increased the social influence occurring between the two fields. Furthermore, the implementation strategy is a dynamic method and therefore suitable for adaptation when new insights in asthma therapy on the bases of new studies become available.

In literature, randomized and controlled studies investigating the implementation of asthma guidelines are scarce. Not because they are not needed. Rather, methodological problems to set up such studies and subsequently, the difficulties to effectuate change seems the cause of the limited number of such studies. Mitchell and colleagues introduced a clinical pathway for children with asthma in general practice in a randomized and controlled study [180]. Twenty-two cells (comparable to the health centres except that not all GP's necessarily worked at
the same place) were randomized. The pathway (guideline) was introduced by means of the distribution of the guideline and a 2-hour educational session. The primary outcomes were hospital admission and attendance to the Children's Emergency Department. Both decreased during the study, however the decrease did not significantly differ from the control group.

Massie and colleagues developed and implemented an evidence-based guideline dealing with acute asthma in children in a teaching hospital in Australia [181]. The implementation strategy was controlled, but not randomized. Implementation of the guideline was associated with improved provision of asthma management plans, but there were no effects on re-attendance, readmission to the hospital, asthma morbidity, or quality of life. A third, interesting study is from Jans and colleagues. They set up a non-randomized, but controlled before-and-after implementation study to evaluate the implementation of a national guideline on the management of adult patients with asthma or chronic obstructive pulmonary disease (COPD) in general practice [182]. The comprehensive implementation program included the identification of barriers, feedback, multiple education sessions, and peer review. The implementation strategy had a positive effect on PEF variability after one year as compared to the reference group, especially amongst patients with asthma or allergy or a high educational level. Improvement of respiratory symptoms was only found in the intervention group.

With the assessment of AHR an objective confirmation of the diagnosis and an indication of the severity or level of control of the child’s asthma are provided to the GP. This additional tool can support GP’s to start and continue long-term daily controller therapy in those children who are indeed in need of this treatment. The current guidelines lack such a tool, which probably contributes to the overestimation of the level of asthma control in children. The assessment of AHR may also contribute positively to therapy adherence in children and their parents. Finally, with the implementation of the combined strategy (guideline, educational session and individual treatment advice), the knowledge and skills of the GP on asthma treatment will increase. In addition, we believe that it is of interest to all (GP’s, paediatricians and patients) that the final responsibility and monitoring of the therapy of children with mild and moderate or sufficiently controlled asthma is left with the GP.

Two main conditions are necessary for the implementation of the strategy in other areas: 1) a working network between paediatricians and GP’s and 2) availability of a lung function laboratory. Furthermore, we recommend, in order to be successful in improving care, to evaluate and to deal with local barriers and settings [138].

**Perspectives and recommendations for future research**

In general practice interest in the quality of care is widespread [183-185]. Quality of care can be defined as ‘the relationship between the actual care provided and the
expectations of the various parties involved’ (i.e. GP’s, patients (and parents) and policy makers). This definition implies that the concept of quality is based on a comparison between what should be achieved and what has been achieved. In the introduction of this thesis we stated that the goals of asthma treatment as set by the GINA guidelines are not met in current clinical practice. There is some debate whether the goals should be achieved completely or if they should be approached to a certain (undefined) level of asthma control. The study described in this thesis was set up to improve the level of asthma control in children in general practice by means of the implementation of a current asthma guideline. The implementation of the combined strategy had positive effects towards improved asthma control, but optimisation of the model is necessary. To improve the quality of care, specific activities are needed to systematically and continuously evaluate and enhance the quality of care [186]. Therefore, quality improvement can be seen as a cyclic process, basically consisting of five activities:

In this thesis we identified two quality problems: the lack of a tool for the GP to adequately assess the level of asthma control (chapter 2 and 6) and the severity of AHR (chapter 4) and, secondly, the poor use of ICS that is independent of the severity of AHR (chapter 4 and 5). Based on the identified problems and following the circle it will be necessary to adapt the current available guidelines in general practice for the treatment of childhood asthma. Also future changes in asthma guidelines, because of new or improved therapeutical options and new or improved tools to diagnose and monitor asthma, need attention for implementation. Therefore, an ongoing search for good implementation strategies is necessary. The proposed strategy of a one time measurement of AHR in this thesis has to be further studied for its potential to improve the level of asthma control on the long-term.
Summary

Chapter 1
In the introduction of this thesis, an overview was given of current knowledge on asthma with respect to the natural history of asthma, prevalence of asthma and current status of asthma control in children. Asthma is one of the most common chronic diseases during childhood with a prevalence of about 12-14%. The major management goal as advocated by the Global Initiative for Asthma (GINA) is to achieve and maintain optimal asthma control. Asthma control can be achieved with the help of long-term treatment with inhaled corticosteroids. Despite the availability of effective controller medication and clinical practice guidelines, it is clearly shown that the GINA goals fall far short and that asthma control is poor for a substantial proportion of children with asthma. The hypothesis of this thesis is that the implementation in general practice of the current national guideline on asthma in children can be improved and subsequently, asthma control will be improved.

Chapter 2
In chapter 2 we explored whether patient care may be negatively influenced by the physician's underestimation of their patient's level of asthma control. Dutch paediatricians and GP's completed a questionnaire with similar items used as in the AIRE study, to obtain insight into the physician's perspective of their patients' asthma. Although 71% of the Dutch patients reported daytime symptoms once a week, health care providers believed this percentage to be around 23%. Physician's also underestimated limitations in physical activity, in absence from school or work, and they overestimated their patients' knowledge of PEF management and medication use. One explanation may be that since the introduction of ICS severe, life-threatening, asthma exacerbations are less prevalent, leading physicians to believe that their patients' asthma is better controlled.

Chapter 3
In chapter 3 we validate the single concentration inhalation provocation test (SCIPT) in children, a method to assess the severity of AHR. AHR was used in this thesis as an objective parameter to assess the severity of asthma and to evaluate the efficacy of three implementation strategies. The SCIPT method was already validated in adults and had shown to be faster and less demanding for the patients. We investigated the reproducibility of the SCIPT method and studied whether the method was in agreement with a standard dosimeter (SDM) method for measuring bronchial responsiveness. The ICC between both tests according to the SCIPT was 0.91. The ICC between the SCIPT and SDM was 0.80. Both comparisons showed good agreement according to Bland and Altman. We concluded that
Summary

SCPT is reproducible, and shows good agreement with the SDM method to test airway responsiveness in children.

Chapter 4

AHR is one of the hallmarks of asthma, reflecting the severity and level of control of asthma. According to clinical guidelines, children with asthma and moderately severe and severe AHR require controller medication. However, testing for AHR is not a routine monitoring tool in general practice and a testing facility is often not easily accessible. Therefore, we investigated in chapter 4 whether the presence of AHR could be suspected by the GP with the use of routinely available clinical information, such as patient characteristics, asthma symptoms, history of allergy for airborne allergens, FEV1, PEF variability, and asthma medication. Of all evaluated children, 21 (4%) were not challenged because their pre-bronchodilator FEV1 was below 75% of predicted. Ninety children had severe (17%), and 142 moderately severe (27%) AHR. Nocturnal symptoms, PEF variability, FEV1-value, presence of inhalation allergy, prescribed rescue medication and ICS were predictors for the presence of moderate to severe AHR. With logistic regression analysis an easy to use model with dichotomized variables was developed to predict the presence of moderate and severe AHR in children with asthma. PEF variability was excluded because the calculation is complex and time consuming and the measurement of PEF is not always reliable. In the final model the presence of nocturnal symptoms in the last two weeks (1), the presence of inhalation allergy (2) and any prescribed rescue medication in the last 12 months (3) were predictive of the presence of moderately severe and severe AHR. Children in whom ICS were prescribed in the last 4 months (4) were having a lower odds for the presence of moderately severe and severe AHR. The predictive values (posterior probability) in this model ranged from 10.7 to 74.5% depending on the clinical profiles of the children with asthma. The posterior probability of having moderate to severe AHR or having a FEV1 below 75% of predicted did not increase substantially in children in whom not all four predictive features of asthma were present, considering the already extremely high a priori probability of 48%.

For the prediction of severe AHR, a separate model was constructed. In this model the same features of asthma were predictive except prescribed ICS, which was not predictive anymore. The a priori probability for the presence of severe AHR or airway limitation was 21%. The posterior probability in this model ranged from 4.7 to 36.4% depending on the presence of nocturnal symptoms (1), inhalant allergy (2) and any prescribed rescue medication (3). Adding the FEV1-value (<95% of predicted) in the model improved the model significantly. However, the corresponding predictive values only moderately improved and ranged from 1.6% to 47%.
Summary

We concluded that the presence of moderate and severe AHR in children with asthma could not be predicted with the use of routinely available clinical and environmental information in the majority of the children. However, the absence of the identified predictive symptoms and/or features in children with asthma made the presence of moderate and severe AHR less likely. Our models could however not assist the GP in deciding in which child controller medication should be started or intensified.

Chapter 5

GP’s are the first in line to deal with asthma. Diagnosis and monitoring of asthma in general practice are primarily based on symptom severity and, less frequently, the level of airflow limitation. However, assessment of asthma severity is difficult if not impossible, based on symptoms only as we have demonstrated in chapter 4. In chapter 5 the efficacy of three strategies to improve childhood asthma care in general practice by means of the implementation of a national asthma guideline was investigated. We hypothesized that the distribution of the guideline in combination with an educational session on asthma and a written treatment advice to the GP, based on symptoms, medication use, lung function, and the severity of AHR (group C), resulted in an improvement of the child’s asthma after one year as compared to the distribution of the guideline in combination with an educational session on asthma (group B), or only the distribution of the guideline (group A). Three groups of asthmatic children who responded positive on an inhalation challenge test at baseline, were followed during one year (Groups A, B and C). All interventions were focused on the GP’s. GP’s (and their asthma patients) were randomised by Health Care Center to one of three study strategies. The primary outcome of the study was severity of AHR. AHR, lung function, symptoms, and medication usage were re-assessed one year after the baseline evaluation. The study was completed by 362 children (90%). AHR decreased only in the group in whom a treatment advice was part of the intervention (Group C; \( P < 0.0001 \)) and it was correlated with an increased use of ICS. Consistently, asthma symptoms, use of rescue medication, and PEF variability improved. In group A significant improvement was seen for PEF variability (\( P = 0.01 \)) and all symptom scores (\( P = 0.002 \)). In group B significant changes occurred only in PEF variability (\( P = 0.0001 \)) and the number of symptom free days (\( P = 0.002 \)). Despite the improvement of AHR in group C, no statistical significant difference was found in AHR between groups (\( P = 0.09 \)). Only nocturnal symptoms (\( P = 0.02 \)) and the use of ICS (\( P = 0.03 \)) reached significance between the three groups.

In a second analysis, we aggregated groups A and B because both groups can be considered control groups for the combined method applied in group C. In this analysis a significant improvement of group C was found as compared to group A and B with respect to AHR (\( P = 0.03 \)). Also the difference in prescription behaviour remained significant in this analysis (\( P = 0.02 \)). However, no other significant differences were found. Despite the lack of significance in the original three group
Summary

analysis, the combined analysis showed a benefit for the combination of dissemination of the guideline together with a treatment advice in achieving improved severity of asthma in children. Therefore, the assessment of AHR can be used as an additional guide to manage asthma in children in general practice and should become part of routine management.

Chapter 6

The monitoring of children with asthma in general practice is based on the occurrence and frequency of asthma symptoms. However, recent evidence suggests that treatment based on symptoms alone is inferior to treatment that is also based on additional (inflammatory) markers. Therefore, we tested in chapter 6 our hypothesis that the current symptom based approach is not adequate to identify all children in whom a sufficient level of asthma control is not achieved. One hundred and nineteen participants of 328 children (36%) who completed the study were identified as not well controlled based on recent wheezing (< 12 months) as reported by the parents and on the presence of moderate or severe AHR. Twenty of these children (17%) failed to present any current asthma symptoms at the end of the study. The use of controller medication in these children was very poor suggesting that parents and/or GP were not aware of the modest or even poor level of control of the child’s asthma.

Chapter 7

In chapter 7 differences in the performances of children inhaling asthma medication with different types of inhalers are described. Inhalation technique was evaluated twice by using standardized checklists: first, at enrolment in the study (n = 530) and second, after one year of follow-up (n = 362). Three major categories of inhaler types were distinguished: pressurized metered-dose inhalers without and with a spacer device (pMDI and pMDI/s, respectively) and dry powder inhalers (DPI). For each inhaler type certain key actions are essential for optimal delivery of the active drug into the lungs. Overall 76% of the children inhaled correctly. However, important differences among inhalers were found. Children with the Diskus® performed best with 95% making no errors on these essential inhalation manoeuvres, while children with a pMDI without a spacer device performed worst with only 21% of children inhaling without essential errors. One year after the first assessment 114 new devices were demonstrated. Performance with these new devices was more often incorrect as compared to the unchanged devices (21.1% and 10.8% respectively; P = 0.01). We concluded that inhalation technique in asthmatic children in general practice can still be improved and that GP’s should have a special focus on those children who are prescribed a new device and those with a pMDI.
Chapter 8

The indoor environment is known to influence respiratory health. Therefore, we asked parents of all participants to complete a questionnaire on parental smoking habits, pet keeping, carpets, beddings, and mould and dampness in the home. In a preliminary analysis we found that the report of indoor mould and dampness was related to AHR whereas other associations between indoor risk factors and features of asthma could not be shown. In chapter 8 the association between the presence of mould and dampness in home and respiratory health of asthmatic children is investigated more in-depth. The prevalence of mould and dampness in Dutch homes is estimated at about 18%. In our study a prevalence of 24% was found (n = 125). Thirty-three children were (recently) exposed to mould and dampness in their bedroom or in the living room. These children had significant increased PEF variability (11.3 versus 8.4%; $P = 0.03$) and an increased severity of AHR (log transformed PD20 7.2 versus 8.8; $P = 0.009$). However not significant, children presented also more asthma symptoms (1.3 versus 0.8; $P = 0.12$) and were prescribed more ICS (0.4 versus 0.3 puffs ICS per day; $P = 0.06$). The adjusted odds ratio for severe AHR (PD20 ≤ 75 µg) in exposed children was 3.90 (95% CI: 1.81-8.41). We concluded that asthmatic children exposed to mould or dampness in the bedroom or living room, were at risk for more severe AHR and asthma.

In chapter 9 the main findings of this thesis with methodological issues and considerations are presented. In the end, perspectives and recommendations for future research are given.
Samenvatting

Hoofdstuk 1

Inleiding

Astma is één van de meest voorkomende chronische ziekten op de kinderleeftijd. Wereldwijd is de prevalentie van ‘wheezing’ (piepen) voor kinderen van 6-7 jaar tussen de 11 en 12% en voor kinderen van 13-14 jaar tussen de 13 en 14%. In Nederland was deze prevalentie bij kinderen van 8-9 jaar 13.4% in 1981 en 9.1% in 2001. De ‘Global INitiative for Asthma’ (‘GINA’), voor het eerst verwoord in 1993, heeft zich ten doel gesteld om de behandeling van astma wereldwijd te optimaliseren. Zij stellen dat met de middelen die tegenwoordig beschikbaar zijn, het mogelijk is om bij alle patiënten te streven naar ‘astma controle’. Goede astma controle bij patiënten met persisterend astma wordt bereikt met behulp van een onderhoudsbehandeling met inhalatiecorticosteroiden (ICS). Ondanks de beschikbaarheid van effectieve behandelmogelijkheden voor astma laten vele studies zien dat astma controle zoals gesteld door GINA, bij een belangrijk deel van de astma patiënten niet wordt gehaald.

Consensus over de behandeling van astma in Nederland


Implementatie van richtlijnen

Implementatie kan worden omschreven als ‘een procesmatige en planmatige invoering van afspraken of behandelrichtlijn met als doel dat deze afspraken een structurele plaats krijgen in het beroepmatig handelen van artsen en andere behandelaars (zoals de astma verpleegkundige en doktersassistent) in alle lagen van de gezondheidszorg’. Een belangrijke aannemer van dit proefschrift is dat de huidige astma behandeldertijde niet of niet optimaal in de praktijk is
Samenvatting

geïmplementeerd. Als de hypothese waar is, dan zou (optimale) implementatie van de richtlijn moeten leiden tot betere astma controle.

De implementatie van een behandelrichtlijn in de dagelijkse praktijk is een grote uitdaging. De implementatiestrategie moet rekening houden met logistieke problemen in de praktijk, en met persoonlijke overtuiging en kennisniveau van de arts. Anderzijds hebben sommige kinderen of hun ouders een matig ziektelijke inzicht, of zelfs ongebruikelijke ideeën over astma en de behandeling ervan, hetgeen kan leiden tot een weinig effectieve naleving van de voorgestelde behandeling. In dit proefschrift is de implementatie strategie gericht op de huisarts. De drie methoden die worden gebruikt zijn cumulatief. De eerste methode is het verspreiden van de behandelrichtlijn onder alle huisartsen in Almere. De tweede methode biedt daarnaast een éénmalige bijscholing aan. De derde strategie biedt bovendien een op hun eigen patiënten toegesneden 'behandeladvies' gebaseerd op astma symptomen, medicatie gebruik en longfunctie (inclusief een meting van de ernst van bronchiale hyperreactiviteit (BHR of AHR ('airway hyperreactivity'))). De hypothese was dat deze derde strategie, in combinatie met de eerste twee, het meest effectief zou leiden tot een verbetering van astmacontrole bij de deelnemende kinderen.

Hoofdstuk 2 Hoe huisartsen en kinderartsen denken over het astma van hun patiënten.

Naar aanleiding van de resultaten van de studie 'Asthma Insight and Reality in Europe' (AIRE) rees de vraag of de zorg voor kinderen met astma mogelijk negatief wordt beïnvloed doordat huisartsen en kinderartsen de mate van astma controle van hun patiënten onderschatten. Dezelfde vragen als in de AIRE-studie werden door ons in een iets gewijzigde vorm voorgelegd aan huisartsen en kinderartsen om te toetsen of artsen een goede inschatting kunnen maken van de mate van controle van astma in hun patiëntenpopulatie. In de AIRE studie rapporteerde 71% van de Nederlandse patiënten dat zij wekelijks last hadden van klachten overdag maar in onze studie schatten huisartsen en kinderartsen dit percentage op 23%. De artsen onderschatten ook het percentage patiënten dat beperkt wordt door hun astma tijdens fysieke inspanning, en het percentage patiënten dat verzuimt van school en werk als gevolg van astma, en zij overschatten de kennis en vaardigheden van patiënten met betrekking tot het gebruik van de piekstroom meter en astma medicatie. Een reden zou kunnen zijn dat sinds de opkomst van inhalatiecorticosteroïden (ICS) het aantal levensbedreigende exacerbaties van astma sterk is afgenomen. Hierdoor hebben artsen wellicht ten onrechte het idee dat hun patiënten hun astma goed onder controle hebben.
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Hoofdstuk 3 Validatie van een één-concentratie methacholine inhalatie provocatie test (SCIPT) in kinderen.

Voor het meten van de bronchiale reactiviteit in deelnemende kinderen aan het Almere Astma Project is een inhalatie provocatie test gebruikt waarbij gebruik gemaakt wordt van één enkele concentratie methacholine: 'a Single Concentration Inhalation Provocation Test' (SCIPT). In hoofdstuk 3 is de SCIPT methode beoordeeld op zijn reproduceerbaarheid én vergeleken met een standaard dosimeter methode (SDM) bij 22 kinderen. De SCIPT methode was eerder al gevalideerd bij volwassenen op een vergelijkbare manier, en bleek sneller en eenvoudiger uit te voeren dan de SDM methode. Wij vonden een intraklassencorrelatiecoefficient (ICC) van 0.91 tussen twee metingen die beide volgens de SCIPT methode waren uitgevoerd. De ICC tussen de SCIPT en SDM methode was 0.80. Beide vergelijkende studies kwamen voldoende overeen volgens de Bland en Altman methode. Het kan daarom geconcludeerd worden dat de SCIPT methode reproduceerbaar is en voldoende overeen komt met de SDM methode om op een betrouwbare manier bronchiale reactiviteit te kunnen meten bij kinderen.

Hoofdstuk 4 Ernstige bronchiale hyperreactiviteit was niet te voorspellen met behulp van de huidige beschikbare middelen voor kinderen met astma in de huisartsenpraktijk.

BHR is één van de belangrijke kenmerken van astma, en zegt iets over de ernst van het astma en de mate van astma controle. Kinderen met astma en matig ernstige tot ernstige BHR zouden moeten worden behandeld met inhalatie corticosteroiden (ICS). Het meten van BHR heeft echter geen plaats in de NHG-standaard ‘Asthma bij kinderen’. Daarom hebben wij gekeken of matig ernstige en ernstige BHR voorspeld zouden kunnen worden met behulp van eenvoudige middelen die wel ter beschikking staan van de huisarts, zoals patiënten kenmerken, aanwezigheid van astma symptomen of het hebben van een inhalatie allergie, astma medicatie, en eventueel longfunctie: piekstroom variabiliteit en FEV₁ (= geforceerde uitgeademde ademvolume in 1 seconde).

Van alle 526 deelnemende kinderen werden er 21 (4%) niet getest op BHR omdat de uitgangswaarde van de FEV₁ al lager uitviel dan 75% van de voorspelde waarde. Negentig kinderen hadden ernstige (17%), en 142 matig ernstige (27%) BHR. Voorspellende indicatoren voor de aanwezigheid van matig ernstige tot ernstige BHR waren de aanwezigheid van astma symptomen, een verhoogde piekstroom variabiliteit, een verlaagde FEV₁-waarde, een aanwijzing voor een inhalatie allergie en astma medicatie. Met behulp van een logistische regressie analyse is een eenvoudiger model gemaakt met dichotome variabelen (wel/niet aanwezig) dat matig ernstige of ernstige BHR kan voorspellen. Piekstroom
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variabiliteit is uiteindelijk uit het model weggelaten omdat de berekening complex en tijdrovend is, en de meting van piekstroom niet altijd betrouwbaar is.

In het vereenvoudigde model voorspellen de aanwezigheid van nachtelijke klachten, het hebben van een inhalatie allergie en het gebruik van luchtwegverwijders de aanwezigheid van matig ernstige tot ernstige BHR. Kinderen aan wie in de voorgaande 4 maanden ICS waren voorgeschreven hadden een kleinere kans op het hebben van matig ernstige tot ernstige BHR. Hierboven is al beschreven dat matig ernstige tot ernstige BHR gevonden is bij 48% van de kinderen. De a-priori (vooraf) kans op matig ernstige tot ernstige BHR was daarmee al erg hoog. De individuele a-posteriori (achteraf) -kans op matig ernstige tot ernstige BHR in dit model varieerde van 11 tot 75% afhankelijk van het klinische profiel van het kind.

Op dezelfde manier is een model geconstrueerd voor het voorspellen van alleen ernstige BHR. In dit model zitten dezelfde astma variabelen als in het voorgaande model met uitzondering van de inhalatie corticosteroïden. De a-priori-kans voor de aanwezigheid van ernstige BHR was 21%. De individuele a-posteriori-kans in dit model varieerde van 5 tot 36% afhankelijk van de aanwezigheid van nachtelijke klachten, inhalatie allergie en voorgeschreven luchtwegverwijders. Toevoegen van de FEV₁-waarde (<95% van voorspeld) in dit model verbeterde het model significant. De corresponderende a-posteriori-kans verbeterde met waarden variërend van 2 tot 47%.

Voor beide modellen laten we zien dat bij een groot deel van de kinderen de aanwezigheid van matig ernstige tot ernstige BHR moeilijk beter te voorspellen is aan de hand van patiënt- en ziektekenmerken die eenvoudig kunnen worden verkregen in de huisartsenpraktijk. De afwezigheid van bovengenoemde voorspellers maakt de kans op de aanwezigheid van matig ernstige tot ernstige BHR in kinderen wel minder waarschijnlijk. Het stellen van de diagnose en het monitoren van astma in de huisartsenpraktijk zijn nu voornamelijk gebaseerd op astmasymptomen. Op basis van de resultaten van de modellen ontwikkeld in deze studie kunnen we echter vraagtekens zetten bij de betrouwbaarheid van het inschatten van de ernst van astma gebaseerd op symptomen.

Hoofdstuk 5 Bronchiale hyperreactiviteit als leidraad voor de behandeling van astma op de kinderleeftijd in de huisartsenpraktijk.

In het Almere Astma Project worden drie implementatie strategieën, zoals beschreven in hoofdstuk 1, voor het implementeren van de NHG-standaard ‘Asthma bij kinderen’ vergeleken. De studie hypothese was dat na één jaar de astma controle bij de deelnemende kinderen verbeterd zou zijn, met name in de intensieve interventie groep. Astmatische kinderen die positief reageerden op de inhalatie provocatie test bij aanvang van de studie werden twee keer geëvalueerd: bij aanvang van de studie en na één jaar. De interventies waren gericht op de
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huisarts. Huisartsen (en hun patiënten) werden per gezondheidscentrum gerandomiseerd in één van de drie studie groepen. De belangrijkste studie uitkomstmaat was de ernst van bronchiale hyperreactiviteit (BHR) maar ook is gekeken naar longfunctie, astmasymptomen, en medicatie gebruik. BHR werd gemeten in een longfunctie laboratorium in het ziekenhuis; het behandeladvies was mede gebaseerd op de uitkomst van de ernst van BHR.

De studie werd afgemaakt door 362 kinderen (90%). BHR nam alleen af in groep C ($P < 0.0001$) en deze afname ging samen met een toename in het gebruik van ICS. Consistent met het voorgaande, verminderden in deze groep ook de astma symptomen, het gebruik van luchtwegverwijders en de piekstroom variabiliteit. In groep A werden significante verbeteringen gezien van de piekstroom variabiliteit ($P = 0.01$) en in alle symptoom scores ($P = 0.002$). In groep B werden alleen verbeteringen gezien in de piekstroom variabiliteit ($P = 0.0001$) en het aantal symptoomvrije dagen ($P = 0.002$). Ondanks de significante verbetering van BHR in groep C, was het verschil in verandering van BHR tussen de drie studie groepen niet significant ($P = 0.09$). Er waren wel significante verschillen tussen de groepen met betrekking tot de nachtelijke klachten ($P = 0.02$) en het voorgeschreven aantal pufjes ICS ($P = 0.03$) ten gunste van groep A en C, respectievelijk.

Omdat groep A en B allebei gezien kunnen worden als controle groep voor groep C, zijn beide groepen in een tweede analyse samengevoegd. In deze analyse is het verschil in BHR tussen groep AB en C wel significant ($P = 0.03$). Het voorgeschreven aantal pufjes ICS was wederom significant verschillend tussen de groepen ($P = 0.02$). De andere variabelen (astma symptomen, piekstroom variabiliteit en gebruik van luchtwegverwijders) waren niet significant verschillend.

Ondanks dat in de originele analyse, met drie groepen, de gecombineerde strategie in groep C niet significant effectiever is gebleken met betrekking tot de primaire uitkomstmaat BHR, laten wij zien dat er sterke aanwijzingen zijn dat kinderen in groep C meer profijt hebben van de gecombineerde aanpak. Het meten van de ernst van BHR kan worden gebruikt als een aanvullende methode om de behandeling van kinderen met astma in de huisartsenpraktijk te sturen.

Hoofdstuk 6 De beperkingen van de astma-anamnese in de huisartsenpraktijk: het probleem geïllustreerd.

De behandeling van astma in de huisartsenpraktijk wordt gestuurd op basis van astma symptomen. Uit diverse studies komt echter naar voren dat de behandeling van astma op geleide van symptomen alleen inferieur is aan behandelen op geleide van bronchiale hyperreactiviteit, stikstofoxide in de uitademingslucht (eNO), of eosinofielien in het sputum (alle drie markers voor het ontstekingsproces in de luchtwegwand bij astma) al dan niet in combinatie met astma symptomen. De vraag is of en in welke mate huisartsen mogelijk ten onrechte veronderstellen dat kinderen met astma voldoende gecontroleerd zijn omdat ze op het moment van
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beoordelen klachtenvrij zijn. Honderdnegentien van 328 kinderen (36%) die de studie afgerond hebben, werden geïdentificeerd als ‘onvoldoende’ gecontroleerd op basis van het feit dat ze 1) klachten hadden gehad van piepen in het afgelopen jaar, en 2) de aanwezigheid van matig ernstige tot ernstige BHR aan het einde van de studie. Twintig kinderen (17%) scocord nul astma symptomen in hun dagboek. De meerderheid van deze kinderen werd niet adequaat behandeld met inhalatie corticosteroïden, hetgeen suggereert dat ouders en de behandeld arts zich in deze kinderen niet bewust zijn van de matige of onvoldoende astma controle.

Hoofdstuk 7 Het beoordelen van de mate van astma controle begint met het controleren van de inhalatie techniek.

De uitvoering van het inhaleren van astma medicatie middels een inhaler werd twee keer geëvalueerd met behulp van standaard checklijsten: allereerst bij inclusie in de studie (n = 530) en vervolgens na één jaar follow-up (n = 362). Drie belangrijke categorieën inhalers kunnen worden onderscheiden: de dosis-aërosol met en zonder een voorzetkamer (pMDI and pMDI/s, respectievelijk) en de droogpoeder inhaler (DPI). Voor elke inhaler zijn een aantal stappen essentieel om te waarborgen dat de astma medicijnen in de longen terechtkomen. In totaal inhaaleerde 76% van de kinderen correct. Er waren wel verschillen tussen de verschillende inhalers. Kinderen met een Diskus® maakten relatief de minste fouten: 5% maakte fouten in essentiële stappen. Kinderen die een dosis-aërosol gebruikten zonder een voorzetkamer maakten relatief de meeste fouten: 79% van de kinderen maakten fouten in essentiële stappen. Aan het einde van de studie waren 114 nieuwe inhalers voorgeschreven. De uitvoering van het inhaleren ging met deze nieuwe inhalers vaker mis vergeleken met onveranderde inhalers (21.1% en 10.8% respectievelijk; P = 0.01).

Er kan geconcludeerd worden dat er regelmatig fouten gemaakt worden bij het inhaleren van astma medicijnen. Huisartsen moeten speciaal letten op kinderen die hun dosis-aërosol gebruiken zonder voorzetkamer en op die kinderen die een nieuwe inhaler krijgen voorgeschreven.

Hoofdstuk 8 Blootstelling aan schimmel en vochtigheid in huis is geassocieerd met luchtwegklachten.

In 2001 publiceerde TNO een rapport waarin staat dat ongeveer 18% van het Nederlandse huizenbestand kampt met vochtigheidsproblemen. De aanwezigheid van een te hoge relatieve vochtigheid en schimmelgroei in huis zijn door de tijd heen vaak geassocieerd met luchtwegklachten en astma. In de medische literatuur is evident aangetoond dat blootstelling aan een hoge relatieve luchtvochtigheid en schimmelgroei een verhoogd risico geeft op astmatische klachten als piepen en chronische hoest. Dat verhoogde risico ligt tussen de 1.4 en 3.5.
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Schimmels en huisstofmijt gedijen beide goed als in huis de relatieve vochtigheid hoog is. Er zijn daarom diverse hypothesen over de pathofysiologische grondslag voor de gevonden associatie. De blootstelling aan schimmel allergenen of huisstofmijt allergenen zou de oorzaak kunnen zijn voor het ontwikkelen van een allergie. Anderzijds is het waarschijnlijk dat blootstelling leidt tot expressie van allergie en astma in patiënten die al een allergie hebben. Los van allergie is verder aangetoond dat zowel door schimmels geproduceerde toxines als ook componenten van de schimmelcelwand eigenschappen hebben die het afweersysteem beïnvloeden, en via die weg mogelijk een rol spelen bij het ontstaan van astma.

In het Almere Astma Project is aan de ouders van alle deelnemende kinderen gevraagd naar de woonomstandigheden. Uit de uitgebreide analyse kwam slechts één associatie consistent naar voren, namelijk dat kinderen vaker ernstige bronchiale hyperreactiviteit (BHR) hadden wanneer de ouders hadden aangegeven dat zij in de afgelopen 2 jaar last hadden (gehad) van vochtplekken en schimmelgroei in huis. Er zijn geen associaties met andere risicofactoren in huis gevonden zoals roken, meeroken en dieren in huis. Ook hebben we geen associatie gevonden tussen deze risicofactoren en astma symptomen en FEV₁. Ouders van 125 (van de 526; 24%) kinderen rapporteerden dat zij ergens in huis last hadden van vochtplekken of schimmelgroei in de afgelopen 2 jaar. In 33 (6.3%) van deze kinderen bevonden deze plekken zich in de slaapkamer van het kind of in de woonkamer. Deze blootgestelde kinderen hadden vaker ernstige BHR (42% versus 16%; P < 0.001). Ook hadden zij een hogere piekstromvariabiliteit (11.3 versus 8.4%; P = 0.03). Hoewel niet significant, hadden blootgestelde kinderen ook meer klachten (1.3 versus 0.8; P = 0.12), hadden ze meer ICS voorgeschreven gekregen (0.4 versus 0.3 pufjes ICS per dag; P = 0.06) en gebruikten ze vaker luchtwegverwijders. Blootgestelde kinderen hadden een bijna 4 x verhoogd risico op ernstige BHR ten opzichte van kinderen die niet waren blootgesteld aan een zichtbare hoge relatieve vochtigheid en/of schimmelgroei in huis. Middels logistische regressie analyse is gekeken of de gevonden associatie beïnvloed werd door andere factoren. Rekening houdend met geslacht, het gebruik van inhalatie corticosteroïden en het hebben van een inhalatie allergie, was het verhoogde risico op BHR door blootstelling nagenoeg onveranderd (odds ratio 3.90, 95% betrouwbaarheidsinterval: 1.81-8.41).

Geconcludeerd kan worden dat kinderen die in huis, in hun slaapkamer of in de woonkamer blootgesteld worden aan een hoge relatieve vochtigheid en/of schimmelgroei een verhoogd risico hebben op ernstige BHR en astma.
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Hoofdstuk 9
Discussie

In dit proefschrift stellen we dat huisartsen de mate van astma controle in een deel van hun patiënten overschatten. We laten verder zien dat huisartsen onvoldoende middelen tot hun beschikking hebben om op een eenvoudige manier astma controle bij kinderen correct te kunnen inschatten. De huidige (internationale) richtlijnen voor astma streven bij de behandeling naar goede controle van het astma. In de NHG-standaard wordt de diagnose astma gesteld op basis van symptomen, eventueel in combinatie met beperkingen in de longfunctie. In dit proefschrift laten we zien dat dit in een groep kinderen onvoldoende duidelijkheid geeft over de ernst van het astma. Een provocatie test kan op een objectieve manier helderheid verschaffen, ook om de diagnose uit te sluiten. De diagnose moet in elk kind duidelijk zijn; daarvoor heeft de huisarts meer middelen nodig dan tot nu toe ter beschikking zijn. In deze studie is de mate van BHR gebruikt als extra ‘tool’ voor de huisarts om het astma te evalueren. In de literatuur is veel discussie over het standaard meten van BHR in de evaluatie van astma. Hoewel er een aantal andere kandidaten zijn om het astma te beoordelen (NO in de uitademingslucht en eosinofiel in sputum), is er tot nu toe nog onvoldoende kennis vergaard over welk van deze kandidaten dan de beste zou zijn in de huisartsenpraktijk.

Er bestaan in de literatuur slechts weinig andere studies die onderzoek hebben gedaan naar implementatie strategieën van astma richtlijnen. Deze studies staan in hoofdstuk 9 beschreven. De studies hebben met elkaar gemeen dat ze laten zien dat het bereiken van statistisch significante verbeteringen in zorg moeilijk is, een goed plan en veel inspanning vergt.

Aanbevelingen voor nieuw onderzoek

Verbetering van de kwaliteit van zorg vraagt om systematische stappen en een voortdurende evaluatie en aanpassing. In dit proefschrift zijn twee kwaliteitsproblemen geïdentificeerd. Ten eerste ontbreken in de huisartsenpraktijk zowel de middelen om de mate van astma controle adequaat te kunnen beoordelen (hoofdstuk 2 en 6), als ook om de ernst van BHR te kunnen bepalen (hoofdstuk 4). Ten tweede is de gevonden onderbehandeling van astma in onze studiepopulatie onafhankelijk van de ernst van de BHR (hoofdstuk 4 en 5). Implementatie van richtlijnen zal in de toekomst een punt van aandacht moeten zijn omdat nieuw verworven kennis omtrent de diagnostiek en behandeling van astma steeds opnieuw in de praktijk zal moeten worden gebracht. De rol die het meten van de ernst van BHR hierin kan spelen zal verder moeten worden uitgezocht.
Dankwoord

Promoveren deed ik niet alleen! Graag wil ik daarom iedereen bedanken die betrokken is geweest bij het Almere Astma Project (AAP). Het was een hele toer maar ik ben heel trots op het eindresultaat en dat is een bedankje aan alle betrokkenen meer dan waard.

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Dankwoord

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