Undiagnosed asthma in childhood

René van Gent

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Niet gediagnosticeerd astma op kinderleeftijd

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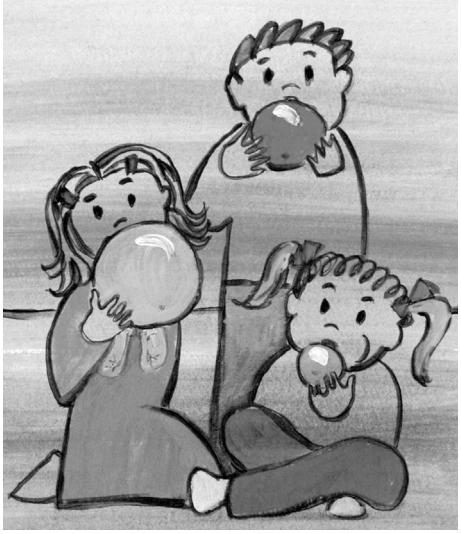

Chapter 1

General introduction

General introduction

Diagnosed asthma

In western European and in affluent countries asthma is the most common chronic disease, with a prevalence of asthma symptoms up to 32% in childhood.[1] In the Netherlands, in 2003 the prevalence of diagnosed asthma in childhood was 5%.[2] Maintenance treatment with inhaled corticosteroids is the principal strategy, in accordance with international guidelines (GINA 2006). Daily use of inhaled corticosteroids on the long term is reported to improve lung function and bronchial responsiveness, as well as participation in school, sports activities and social life and is, therefore, advised when asthma is classified as moderate to severe. For mild asthma, however, there is an ongoing discussion in the scientific community regarding the usefulness of inhaled corticosteroids on a daily or an intermittent basis.[3]

Although medication is available, the burden of diagnosed asthma in daily life remains high. The AIRE (Asthma Insight and Reality) study showed only partial effectiveness of asthma care in daily life and also reported that a large proportion of asthmatic children (38%) had daytime symptoms once a week.[4] Fuhlbrigge and colleagues showed that the goals of treatment, as described in the guidelines of the National Asthma Education and Prevention Program, were not met in the majority of children;[5] i.e. a large proportion of the children avoided exertion (47%) and stayed inside (34%) reflecting a common approach to improve control of asthma symptoms. The estimated total costs of childhood asthma in the European Union amounted to EUR 3000 million in 2004 and around half of the healthcare costs of asthma management is used by unscheduled events.[6,7]

Undiagnosed asthma

Since 1980 numerous studies have shown that asthma in children is underdiagnosed and subsequently undertreated.[8-13] Currently, mild asthma still tends to be overlooked by the medical profession and several reports have shown that underdiagnosed asthma is still a problem, with a prevalence up to 11.7%.[14-17]

Undertreated asthma raises concerns about airway remodeling, lung function deficits and impairment of quality of life. It has been suggested that treatment of asthma should be initiated in an early phase of the disease before any lung abnormalities have developed.[18-21] In addition, duration of asthma is associated with parameters of asthma

severity, suggesting that early diagnosis and intervention may be necessary to ameliorate these adverse effects of persistent asthma.[22] Furthermore, chronic childhood asthma is associated with irreversible lung function deficits, i.e. irreversible airway obstruction.[23]

Information about the burden of undiagnosed childhood asthma in daily life (i.e. quality of life, participation in physical/school activities) is difficult to obtain. Undiagnosed asthma might cause school absence, a higher risk for acute hospitalization, sleep disturbances and impairment of physical activity, whereas children with moderate to severe undiagnosed asthma have shown improvement in asthma control after medical intervention.[8,15,24-27] However, information about the actual prevalence and impact of undiagnosed childhood asthma in the Netherlands is unknown.

Therefore, for the work presented in this thesis the following questions were posed:

1) What is the prevalence of undiagnosed asthma in childhood?
2) What is the impact of undiagnosed asthma on daily life in these children?
3) What are possible explanations for undiagnosed asthma?
4) Should children with undiagnosed asthma be treated?

To address these questions we performed a large survey in children aged 7 - 10 years in the Veldhoven area (southern part of the Netherlands). This observational study investigated the influence of undiagnosed asthma on quality of life, school absence and level of physical activities, as compared with children with diagnosed asthma and with healthy controls. In addition, having advised the parents of all children with undiagnosed asthma in our study to consult the general practitioner, we followed-up on the results of our advice.

The following chapters present our work investigating the prevalence and impact of undiagnosed asthma in the Netherlands.

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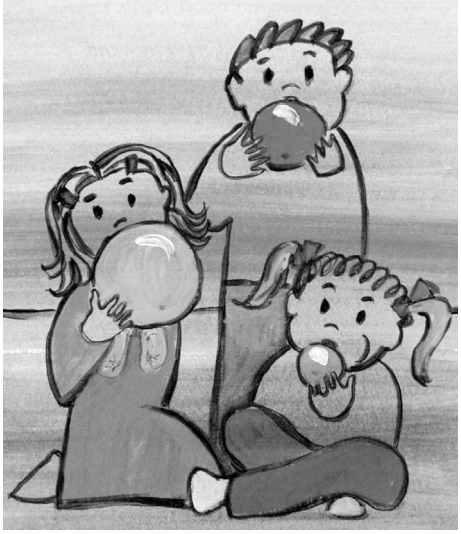

Chapter 2

Participation in daily life of children with asthma

van Gent R, van Essen-Zandvliet LEM, Klijn PHC, Brackel HJL, Kimpen JLL, van der Ent CK.

Submitted

Abstract

Asthma has a negative effect on psychological and social well-being in childhood. Sport participation, school attendance and quality of life are important issues for asthmatic children and their parents. However, a structural evaluation of these factors is not incorporated in the routine medical approach of children with asthma. Moreover, goals in asthma treatment, such as minimal symptoms and normal activity levels, are achieved in a minority of children. In this review we describe determinants that are important for the well-being of asthmatic children and their parents. Besides the control of symptoms, these factors are sport participation, socializing in peer groups, school attendance and quality of life. These issues are relevant when evaluating the management of children and adolescents with asthma. A multidisciplinary evaluation might contribute to an important decrease in the impact of asthma on daily life.

Abbreviations

FEV_1	Forced expiratory volume in 1 second
ICF	International classification of Functioning, Disability and Health
EIA	Excercise induced asthma

Introduction

Asthma is one of the most common chronic diseases in childhood with major public health consequences. According to the ISAAC study the prevalence of asthma ranges worldwide between 2% and 32% in childhood.[1] Although many highly effective asthma drugs are available for symptom control, current treatment strategies provide insufficient reduction of disease-related morbidity or mortality.[2]

Despite advances in the management of asthma in children, it continues to be a condition that has significant impact on children and their families. Guidelines for the management of asthma issued by the Global Initiative for Asthma (GINA)/National Institutes of Health (NIH) state that the therapeutic aim should be to achieve overall asthma control in order to minimize the impact of asthma on the individual patient; i.e. control of symptoms, prevention of asthma episodes or attacks, minimal need for $ß_2$-agonist therapy, no emergency visits to doctors or hospitals, normal activity levels including exercise, pulmonary lung function as close to normal as possible, and minimal (or no) adverse effects from drugs.[3,4] However, the AIRE (Astma Insight and Reality) study showed only partial effectiveness of asthma care in daily life.[5] In addition, Fuhlbrigge et al. showed in 2006 that goals of therapy in asthma, based on the National Asthma Education and Prevention Program guidelines, have not been achieved for the majority of children, although more than 70% had mild intermittent disease.[6] According to Fuhlbrigge et al. the impact of asthma on the daily activities is substantial; avoiding exertion (47%) and staying inside (34%) are common approaches to improve control of asthma symptoms.

Patients with mild persistent asthma form a significant proportion of people with asthma (up to 70%); these individuals could be called the silent majority because they rarely visit their general practioner with symptoms of the disease.[6,7] In these patients, lung function will generally be normal or close to normal. Furthermore, lung function (FEV_1), level of bronchial hyperresponsiveness (histamine/metacholine challenge) and markers of inflammation only partially reflect the patient's health condition.[8,9,10-12] In addition, patients perceive some asthma symptoms as more troublesome than others and may report benefits from asthma treatment which cannot be explained on the basis of clinical lung function.[11,13] Therefore, it has been suggested that in contrast to conventional end-points of clinical trials, such as forced expiratory volume in one second (FEV_1), the use of a composite measure incorporating a range of clinically relevant end-points provides a more complete view of the overall level of asthma control for the individual patient.[14] These measures should include symptom scores,

control questionnaires, or quality-of-life methods.[7]

Further improvement of asthma treatment probably asks for a broader view on the global health status of children with asthma. In addition to parameters of asthma treatment of body functions (e.g. lung function or hyperreactivity), other important determinants (e.g quality of life, physical activity) of health might be used. The International Classification of Functioning, Disability and Health (ICF), describes how people live with their health condition.[15] The ICF is a classification of health and health-related domains that describe body functions and structures, activities and participation (see Figure 1). Functioning encompasses all body functions, activities and participation. Disability describes impairments, activity limitations or participation restrictions. The ICF also includes both personal and environmental factors because an individual's life occurs in a context.

With this concept we can draw a model of functioning and disability in children with asthma. Figure 1 illustrates the impact of asthma on many factors in different domains. For instance, asthma influences participation of the child in sport and school activities.

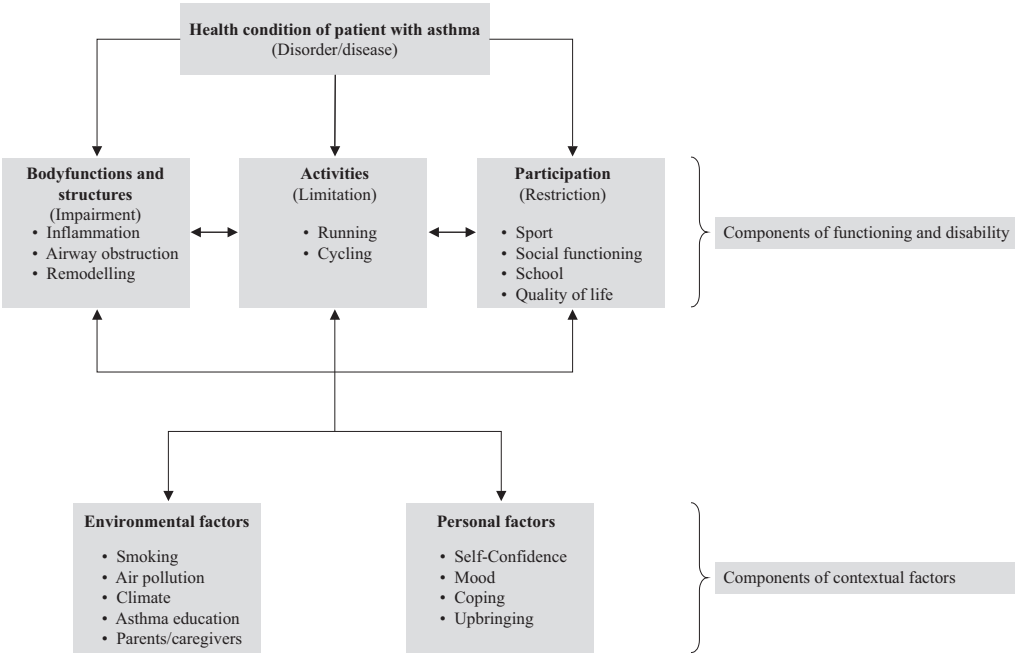

Figure 1: Health condition of patient with asthma according to the ICF model

The ICF provides a broader view on the health status of children with asthma and emphasizes functioning and disability in the daily life of asthmatic children. In this paper we concentrate on the factors concerning participation e.g. sport participation, social impact, school attendance and quality of life, and discuss these items in relation to primary schoolchildren and their parents.

Sport participation

Regular physical activity and participation in sports are considered important components in the overall management of asthma, and the American Academy of Pediatrics guidelines for sports medication states that "with proper medication and education, only athletes with the most severe asthma need to modify their participation".[16] In addition, asthmatic children report, when asked, that being able to participate in activities is very important to them. Furthermore, physical activity is an important part of both a healthy lifestyle and of a child's daily routine, and development of good health and fitness habits in childhood is associated with physical fitness as an adult.[17,18] Although in western society 85% of healthy children participate in sports, overall physical activity in children is declining, resulting in a higher prevalence of obesity and cardiovascular diseases.[19-21] Furthermore, excessive body weight is associated with an additional decrease in quality of life in children with asthma.[22]

Asthma plays an important role in the ability of children to participate in sports. Only 18% of children with asthma have a normal physical activity pattern.[19,23] Croft et al. conclude that in 41% of children, asthma seriously impairs sporting activities.[23] Others suggest that many children with asthma experience problems with social play and other outdoor activities such as camping, horse riding and walking in the country due to their asthmatic symptoms.[24,25] In second grade 78% of schoolchildren report that the worst thing about their asthma is their inability to participate in sport.[26] The AIRE study shows that 29.5% of children have limitations with sport and that only 19.7% have a normal physical activity pattern.[5] Another study shows that children with moderate or severe asthma are more likely to be active < 30 minutes/day, which is far below international recommendations.[27,28]

Exercise-induced symptoms often remain undiagnosed. First, perception of exercise-induced asthma (EIA) by children and their parents do not correlate with lung function abnormalities.[29] Furthermore, in an epidemiologic study Kattan et al show that 50% of children with asthma and a negative history of EIA have a bronchoconstrictor response to exercise challenge.[30] Second, school teachers have a poor understanding of triggers

for asthma. Stohlhofer et al. reported that only 34% of teachers know that playing games in cold wind may provoke an asthma exacerbation.[31] Another report shows that only 57% of school teachers know that wheezing after physical exertion is a strong indicator of asthma and only 33% know that exertion in cold weather increases the risk of an acute asthma exacerbation.[32] In an outpatient clinic it can be difficult to investigate whether the child has exercise-induced symptoms, or problems with participation in sports. Diaries for registration of physical activity or questionnaires could be helpful to evaluate whether children with asthma have enough possibilities to participate in physical activity. Objective measures of physical activity are currently too costly and too difficult to implement in routine asthma management.

Activities play a central role in the ICF model. Disease severity, but also parental beliefs contribute to a lower activity level of asthmatic children.[28] To improve sport participation asthmatic children, as well as their parents and other people involved in sporting activities, need to be educated about symptom perception and treatment modalities during physical activities. Physical training programs can improve cardiopulmonary fitness and coping behavior in children with asthma, although lung function remains unchanged.[33,34] Whether the improvement in fitness translates into a reduction of symptoms or an improvement in the quality of life is still subject of debate. An adequate warming-up procedure is the most practical and effective approach for scheduled activities such as gym or sport club activities, but not for spontaneous increases in activity that are part of daily life (e.g. running to catch up with your school friend while walking home). In younger children exercise is more random and warming up procedures are even more difficult to implement.[35,36] Inhaled corticosteroids improve exercise tolerance in children.[37,38] Addition of short or long-acting $ß_2$-agonists or leukotriene receptor antagonists might be necessary.[39-41] With all these measures normal physical activity is achievable for the majority of children with asthma and should be regarded as an important goal of optimal asthma control.[3,42]

Social functioning

One of the main goals of asthma treatment is to enable children to feel and function normally in their daily lives.[3,42] This includes normal psychosocial and motor development in childhood and equal socioeconomic chances in later life. However, management strategies for their asthma (for instance, trigger avoidance) can create restrictions in daily life activities of children. Although asthma patients claim to lead "normal lives", such perception of normality may be based on adjustments and restrictions that have already been incorporated into their lifestyles.[43]

The social impact of asthma on daily life can be divided into the impact on the individual and on his/her family. For the individual child asthma can have impact on usual activities, study activities, school participation, contacts with friends and relatives, and participation in social events. For the family asthma can restrict social activities, holidays, keeping pets, hours able to work and contacts with friends and relatives, and participation in social events.[44-46] Highly symptomatic children are more at risk to experience a behavior problem than moderately symptomatic children.[45,47] However, even mild asthma can lead to disability and social isolation with harmful effects on the child's self-confidence, motor development and restriction in everyday activities.[48,49] Up to 50% of children with asthma could not complete sport lessons, and school work productivity was reduced due to being sleepy in lessons and having attention deficit problems.[49] Many days missed at school can contribute to problems in maintaining peer relationships and extracurricular activities, which in turn can cause social isolation, low self-esteem, and depression.[50,51] Sport and exercise are ways to socialize with peers and obtain self-confidence, and a systematic review indicated that exercise can improve self-esteem.[52] In addition, the reluctance of children to participate fully in exercise programs results in lower levels of fitness and might lead to poor psychological adjustment. Furthermore, asthma considerable impaires the child's ability to enjoy and partake of such activities as playing a musical instrument and sporting activities.[49]

Classical methods to evaluate asthma from the body function domain (like lung function) do not correlate with the impact of asthma on social life.[11] Although social participation is important to parents and children, a structural evaluation of this item can be difficult. Perhaps the best method to evaluate the social impact of asthma on children is a structural evaluation of the child's behavior by the mother, as evaluated by Strunk et al.[53] However, even with a structural approach, the clinician is not able to make a reliable evaluation of the adjustment of the child to his/her disease. Recently, a short 10-item questionnaire was developed to help identify children at risk for problems adjusting to asthma.[54] Perrin et al. performed the only randomized controlled trail (RCT) published to date; they show a beneficial effect on psychological status and on children's daily lives of a combined educational and stress management program.[55] The ICF model clearly demonstrates that personal factors (like self-confidence and social participation) can make an important difference in the general condition of children with asthma.

School performance

Children with asthma may be at risk for decreased school performance for various reasons, including acute exacerbations of symptoms, night-time symptoms with disturbance of sleep, iatrogenic effects of asthma medication, teachers or parents perception that the child is too vulnerable to participate in certain school activities, absenteeism, and stress associated with chronic illness.[56] Even short absences from school can influence academic performance in later life.[57] Although teachers generally have accepting attitudes towards asthma, their knowledge about asthma is low and they are not adequately prepared to assist children with the management of asthma in the classroom.[58,59] Clearly, school attendance is important for parents and asthmatic children in daily life.[60,61]

Asthma is the most prevalent cause of childhood disability in the USA, leading to 14 million school absence days in 1996.[62] Data derived from the National Health Interview Survey in the USA show that disabling asthma resulted in an annual average of 10 days lost from school per child. This is almost twice the level of illness burden experienced by children with disabilities due to other chronic conditions.[63] In the group of children with asthma, 5.3% were unable to attend school, 6.4% had a special education program and 12.8% had a limited school attendance.[64] On average, children with disabilities caused by asthma were restricted in their daily activities slightly less than 3 weeks per year. Furthermore, undertreatment and underdiagnosis of asthma may result in a considerable number of days of absence from school.[65,66] In their study Stores et al. demonstrated a greater disruption of sleep, greater daytime sleepiness and lower cognitive function on a test of memory recall in asthmatic children.[67] More important: after optimizing treatment, the asthmatic children improve in sleep disruption, daytime sleepiness and cognitive function.[67]

The ICF model clearly shows that school participation is important for the health condition of children with asthma. Most physicians get information only from the children and their parents. Although teachers might be better able to appreciate the impact of asthma on school performance, many teachers are unable to recognize the negative effects asthma can have on school performance.[31,32] Night-time symptoms as a proxy for school performance have prognostic value for school performance, since nocturnal asthma in children affects school performance independently of asthma severity.[68]

According to the guidelines, children with asthma should be able to attend school like healthy children.[3,42] Because asthma is a common disease in childhood it is relevant for teachers to have more knowledge about asthma symptoms. An annual report by the teacher might be an effective method for all parties to get a better understanding of the impact of asthma on school attendance. Several recent studies have shown that normal school attendance can be reached. Proper medication reduces the school absenteeism in asthmatic children to a comparable degree of absence per term in comparison to healthy peers.[69] Furthermore, Silverstein et al. showed in a white population with few low income groups and high access to health care that good cognitive function can be reached.[70,71] These promising results in subgroups of patients illustrate that better management of asthma is achievable, resulting in a better school performance.

Quality of life issues

Quality-of-life instruments reflect patients' real experiences and perceptions of living with asthma. Available quality of life questionnaires incorporate symptom, physical activity and emotional domains. An advantage of specific questionnaires is that they can capture the symptoms and areas of functioning that are relevant for patients with a specific disease and are sensitive for specific problems associated with asthma.[72] However, these questionnaires do not cover all aspects of physical activity, social impact and school performance on asthma (as described earlier).

Assessment of health-related quality of life alongside conventional clinical monitoring is increasingly proposed as a means of aligning patient's expectations with the clinician's therapeutic goals. Quality of life comprises the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient.[73] This definition emphasizes the restrictions that patients themselves consider important. Many patients complain about the interference of asthma with daily activities and the emotional impact on their lives.[74,75] They also have concerns about social relationships, self image, medical and school support, and others.[76] Recent research clarifies that quality of life is a different component of health status in patients with asthma than clinical outcomes (e.g. lung function).[11] Furthermore, in adults, poor quality of life predicts greater use of health services and quality of life scores can distinguish between patients with total and well controlled asthma.[11,77,78]

The clinical interpretation of differences in quality of life is difficult because experience in their use is still limited. At the onset of a chronic disease, but also after a period of follow-up, quality of life might be misunderstood by healthcare professionals,

especially in the subjective attributes.[79] If we become more familiar with these standardized measurements of quality of life we can better understand the needs of our patients and target our therapy more precisely. Both generic and asthma-specific instruments have been developed to evaluate quality of life of children in recent years. These questionnaires quantify the effects of disease on the patient's daily life and well-being in a formal and standardized manner. Guyatt et al. showed that clinicians can rely on children as young as 7 years old to accurately report changes in symptoms for periods as long as 1 month. Although parents provide complementary information up to age 10 years, parental perception of their child's quality of life is inaccurate in older children.[80] Parent and child perceptions about quality of life thus merit separate attention, as the quality of life of the child with asthma may be different from what is important to their caregiver. For several questionnaires minimal important differences for specific domains are defined that would mandate a change in the patient's medication.[75,81,82] The most commonly used questionnaire in childhood is probably the Pediatric Asthma Quality of Life Questionnaire (PAQLQ).[83] This contains 23 items and takes approximately 10 minutes to complete. It also has the advantage in population monitoring of being designed for children with a wide age range (7 - 17 years)) and addresses the physical, psychological and social domains of health with scores for domains in symptoms, activity limitations and emotional function. The advantage of this questionnaire is that Juniper et al. proposed a difference of 0.5 or higher as being clinically relevant for the PAQLQ.[81] Juniper et al. also developed a questionnaire for caregivers; the Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).[84]

Traditional measurements of asthma severity and asthma control fail to achieve an optimal asthma control, as they explain only half of the variance of quality of life.[85,86] Furthermore, quality of life can not be assessed from symptoms or lung function.[11] However, assessment of quality of life is a useful tool to complement the clinical follow-up of the child with asthma, and in adults it can differentiate between patients with total and well controlled asthma.[78,87] Furthermore, children with undiagnosed asthma have a lower quality of life than healthy controls.[66] RCT's have shown that inhaled corticosteroids, long-acting $ß_2$-agonists, leukotriene receptor antagonists, a swimming program, basketball training, an education program for children with asthma in schools, and a peer-led program for asthma education improve the quality of life of both children and parents.[88-96]

Conclusion

To improve asthma control and minimize the impact of asthma on the health status of children we have to broaden the instruments of asthma control to non-traditional areas. These effects on health status are clearly demonstrated in the ICF model. Structural evaluation of sport participation, school attendance and quality of life seems appropriate. Although some short questionnaires have been developed, these questionnaires do not fully take into account the items described in this review.[97] Because powerful medications are available to treat asthma, the next challenge is to achieve optimal asthma control in everyday life for all children. A multidisciplinary evaluation might contribute to an important decrease in the impact of asthma on daily life.

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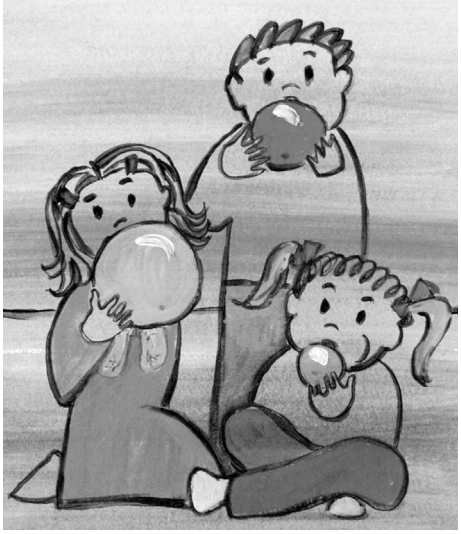

Chapter 3

Quality of life in children with undiagnosed and diagnosed asthma

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Abstract

This study describes the impact of undiagnosed and diagnosed asthma on quality of life in schoolchildren aged 7 - 10 years and their caregivers in a cross-sectional community-based study. Diagnosed asthma was defined as the parents' confirmation of a physician's diagnosis of asthma. Undiagnosed asthma was defined by asthma symptoms combined with airway reversibility or BHR. Quality of life was evaluated in all children with asthma and a sample of healthy controls by the Pediatric Asthma Quality of Life Questionnaire, and by the Paediatric Asthma Caregiver's Quality of Life Questionnaire. We studied the impact of breathing problems on school absence. Compared to healthy controls, quality of life scores among children and their caregivers were lower if the child had asthma ($p < 0.05$), with lowest scores in diagnosed asthma ($p < 0.05$ compared to undiagnosed asthma). Children with asthma reported more school absence ($p < 0.05$), with highest absence rate in those with diagnosed asthma. Conclusion: both undiagnosed and diagnosed asthma have a significant impact on the quality of life of both children and their caregivers.

Abbreviations

UDA	Undiagnosed asthma
DA	Diagnosed asthma
HC	Healthy controls
BHR	Bronchial hyperresponsiveness
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PACQLQ	Paediatric Asthma Caregiver's Quality of Life Questionnaire
FEV_1	Forced expiratory volume in 1 second

Introduction

In Western European and affluent countries, asthma is the most common chronic disease with prevalence rates up to 32%.[1] Since 1980 numerous studies have shown that asthma in children is underdiagnosed and subsequently undertreated.[3,6,9,17,21,23] Recent data show that underdiagnosis is still a problem.[8] Chew et al. reported that 49% of all children with asthma-like symptoms had not been diagnosed with asthma and Joseph et al. reported a prevalence of undiagnosed asthma of 11.7%.[5,10]

Information about the quality of life in children with mild to moderate asthma is scarce. The AIRE (Asthma Insight and Reality) study showed only partial effectiveness of asthma care in daily life.[20] Only 5.8 % of children met all criteria for asthma control and over one third of children had daytime symptoms at least once a week despite adequate treatment. For undiagnosed asthma, Yeatts et al. concluded that undiagnosed frequent wheezers report more sleep disturbances, school absence and activity limitations than diagnosed asthmatics; however, their study lacked objective measures to diagnose asthma.[24]

The present study describes the impact of having asthma on daily life in a community-based population of schoolchildren with and without a physician's diagnosis of asthma. For this we evaluated the quality of life both in children and their caregivers, as well as the occurrence of asthma symptoms and their effect on school absence.

Methods

Population and study protocol

The study was conducted in 41 out of 44 primary schools in four cities in the south of the Netherlands. We asked all children aged 7 - 10 years and their parents to participate in our study. All participating parents completed a questionnaire on respiratory symptoms, demographic and household characteristics. All participating children were invited for lung function testing with assessment of reversibility to salbutamol. Children with asthma symptoms in the past 12 months or reversible airway obstruction were invited for bronchial challenge with hypertonic saline. Based upon results from questionnaires, airway reversibility and bronchial hyperresponsiveness (BHR) children were identified as 'diagnosed asthma' (DA), 'undiagnosed asthma' (UDA), 'healthy controls' (HC), 'asymptomatic airway reversibility', or 'asthma symptoms only'.

Quality of life was assessed in all children with asthma (diagnosed and undiagnosed) and a sample of healthy controls that were randomly selected from the same classroom as children with asthma. Parents received a letter with the results of the symptom questionnaire and lungfunction two weeks after finishing the study protocol.

We obtained approval for the study from the central Committee on Research involving Human Subjects (CCMO) in the Hague, the Netherlands. Informed written consent was obtained from the parents of all children.

Questionnaire

Parents completed a questionnaire that included the ISAAC core questions on symptoms of asthma, rhinitis and eczema.[2] Additional data were collected on household characteristics. Asthma symptoms were defined as wheeze or a dry cough at night in the past 12 months.

Spirometry and reversibility

Maximal flow-volume curves were measured using a hand-held spirometer (Vitalograph Ltd, Buckingham, UK) according to the ERS guidelines.[18] A minimum of two technically acceptable baseline flow-volume curves were performed and the highest of two reproducible (within 5%) measurements of forced expiratory volume in one second (FEV_1) was recorded as baseline FEV_1. Subsequently 800 microgram of salbutamol was administered via a metered dose inhaler using a volumatic spacer (GSK, Uxbridge, UK). Airway reversibility was defined as an increase of FEV_1 of ≥ 10% of the predicted value 10 minutes after administration of salbutamol.

Hypertonic saline testing

Bronchial hyperresponsiveness was assessed by inhalation challenge with nebulized hypertonic (4.5%) saline using an ultrasound nebulizer (Klava 2000/4000, Klava Eltromed, Bielefeld, Germany) according to the ISAAC protocol. BHR was assessed on a different day than the spirometry.[22] All children were asked to withhold all asthma medications for at least 12 hours beforehand. Children with a baseline $FEV_1 \leq 75\%$ were excluded. The children inhaled the saline for periods of increasing duration: 0.5, 1, 2, 4, and 8 min. FEV_1 was measured 1 min after each inhalation period and the next inhalation period started after 3 min. Bronchial challenge was stopped if FEV_1 had fallen at least 15% from baseline or if the total inhalation period of 15.5 min had been

completed. A child was defined as having BHR if FEV_1 had dropped by ≥ 15% from baseline during the inhalation challenge.

Daily impact of asthma

Quality of life was measured with the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) for children, and with the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) for their caregivers.[11,12] For both questionnaires scores range from 1 to 7, with 7 indicative of maximal quality of life. The PAQLQ consists of three domains, i.e. the emotions domain, activity domain and symptom domain. The PACQLQ consists of two domains, i.e. the emotions domain and activity domain.

School absence because of respiratory disease was evaluated by the question: "How often was your child absent from school due to breathing problems in the last 12 months?" Additionally, children completed a 5-day diary addressing the following question: "Did you feel different or left out today because of shortness of breath, coughing or wheezing?"

Definitions

A child was considered having diagnosed asthma if the parents confirmed that their child had physician-diagnosed asthma in the last 12 months. A child was considered having undiagnosed asthma if the child had 1) no physician-diagnosed asthma in the last 12 months, 2) asthma symptoms (wheeze or dry cough) in the last 12 months, and 3) either had reversible airway obstruction or BHR. Healthy controls (HC) had no asthma diagnosis or symptoms in the last 12 months, and no reversible airway obstruction. The remainder children comprised those with asymptomatic airway reversibility (airway reversibility without asthma diagnosis or symptoms), and children with asthma symptoms only.

Data analysis

All data of the questionnaires were double-entered into the database using Microsoft Access software. Chi-square tests and ANOVA with a Bonferroni post-hoc test were used to analyse differences between the groups. Data were analysed using the statistical package SPSS version 11.0.

Results

Participants

Of 44 eligible schools 41 participated in the study. Reasons for non-participation were recent involvement in another study (n = 2) and school policy never to participate in medical studies (n = 1). We invited 2745 children and their parents to participate in the study in the period September 2002 to April 2005 of which 64% (n = 1758) gave informed consent to participate. We excluded 144 children from further analysis; reasons for excluding were missing questionnaire data (n = 60), refusal to participate in bronchial challenge testing (n = 31), not completing the bronchial challenge test due to nausea or coughing (n = 3) or inability to meet technical conditions (n = 50).

Diagnosis and demographics

The final study population comprised 1614 children of whom 81 (5.0%) had diagnosed asthma and 130 (8%) undiagnosed asthma according to our criteria. Asymptomatic airway reversibility occurred in 14% and 19% had asthma symptoms only. Of the remaining healthy controls, we randomly selected 202 children for assessment of quality of life. Table 1 presents the characteristics of the study population. Children with diagnosed asthma more frequently had a father with asthma compared to the children with undiagnosed asthma ($p < 0.05$) and healthy controls, whereas having a mother with asthma occurred more frequently in children with both diagnosed and undiagnosed asthma ($p < 0.001$).

Table 2 presents clinical characteristics of the patient groups. Wheeze in the last 12 months occurred most frequently in diagnosed asthma (86%) compared to undiagnosed asthma (56%) and healthy controls (0%) ($p < 0.001$ for all comparisons). In contrast, children with undiagnosed asthma had the lowest baseline FEV_1, which showed the greatest increase after inhalation of salbutamol (9%, 5%, 2% respectively; UDA vs. HC; $p < 0.001$, UDA vs DA; $p = 0.07$). Furthermore airway reversibility and BHR occurred more frequently in children with undiagnosed asthma than in children with diagnosed asthma and healthy controls (reversibility 52%, 24% and 0% for respectively UDA, DA and HC, $p < 0.001$; respectively 73%, 47%, and 11% for BHR, $p < 0.001$).

Table 1: Characteristics of the patient groups

	Undiagnosed asthma (n = 130)	Diagnosed asthma (n = 81)	Healthy controls (n = 202)
Sex, n (%)			
Male	73 (56)	47 (58)	100 (50)
Female	57 (44)	34 (42)	102 (50)
Mean age ± SD (years)	9.4 (0.7)	9.4 (0.8)	9.4 (0.7)
Mother asthma ever, n (%)	19 (17)	16 (23)	4 (2)
Father asthma ever, n (%)	7 (5)	11 (16)	12 (7)
Mother current smoker, n (%)	26 (20)	10 (14)	41 (22)
Father current smoker, n (%)	30 (26)	17 (24)	42 (22)
Mother's education			
Low, n (%)	17 (15)	14 (20)	33 (17)
Moderate, n (%)	56 (49)	34 (48)	95 (50)
High, n (%)	41 (36)	23 (32)	62 (33)
Father's education			
Low, n (%)	20 (20)	16 (24)	37 (20)
Moderate, n (%)	41 (40)	22 (32)	65 (35)
High, n (%)	40 (40)	30 (44)	82 (45)
Pet ownership			
Currently, n (%)	78 (70)	39 (54)	117 (61)
Ever, n (%)	89 (80)	55 (76)	142 (74)

Table 2: Clinical characteristics of the patient groups

	Undiagnosed asthma (n = 130)	Diagnosed asthma (n = 81)	Healthy controls (n = 202)	p-value
Symptoms in last 12 months				
Wheeze, n (%)	72 (56)	70 (86)	0 (0)	< 0.001 [a,b,c]
Dry cough at night, n (%)	90 (71)	54 (70)	0 (0)	< 0.001 [b,c]
Lung function parameters				
Mean baseline FEV_1 % predicted	94	98	100	< 0.001 [b]
Mean baseline FVC % predicted	89	95	95	< 0.05 [a,b]
Change in FEV_1 after BD (%)	+ 9	+ 5	+ 2	< 0.001 [b]
Reversibility ≥ 10%, n (%)	67 (52)	19 (24)	0 (0)	< 0.001 [a,b,c]
BHR, n (%)	93 (73)	38 (47)	21 (11)	< 0.001 [a,b,c]
Inhaled corticosteroids	12 (9%)	60 (74%)	0 (0)	

BD indicates bronchodilator; BHR indicates bronchial hyperresponsiveness
[a] *Significant difference between undiagnosed asthma and diagnosed asthma*
[b] *Significant difference between undiagnosed asthma and healthy controls*
[c] *Significant difference between diagnosed asthma and healthy controls*

Table 3: Quality of life mean score of children and caregivers with undiagnosed asthma, diagnosed asthma and healthy controls

	Undiagnosed asthma (n = 130)		Diagnosed asthma (n = 81)		Healthy controls (n = 202)		p-value
	n	Mean (95% C.I.)	n	Mean (95% C.I.)	n	Mean (95% C.I.)	
Quality of life score of children							
Emotions domain	103	6.6 (6.4-6.8)	67	6.4 (6.1-6.6)	153	7.0 (6.9-7)	< 0.05 [a,b,c]
Activity domain	90	5.6 (5.3-5.9)	54	5.1 (4.8-5.4)	93	6.9 (6.8-7)	< 0.05 [a,b,c]
Symptom domain	91	6.2 (6.0-6.4)	55	5.6 (5.3-5.9)	122	6.9 (6.9-7)	< 0.001 [a,b,c]
Combined domain	77	6.1 (5.8-6.3)	47	5.6 (5.4-5.9)	90	7.0 (6.9-7)	< 0.05 [a,b,c]
Quality of life score of caregivers							
Emotions domain	103	6.7 (6.6-6.8)	69	6.2 (5.9-6.4)	165	7.0 (6.9-7)	< 0.001 [a,b,c]
Activity domain	111	6.7 (6.6-6.8)	72	6.4 (6.2-6.6)	168	7.0 (6.9-7)	< 0.05 [a,b,c]
Combined domain	102	6.7 (6.6-6.8)	68	6.3 (6.1-6.5)	165	7.0 (6.9-7)	< 0.001 [a,b,c]

[a] *Significant difference between undiagnosed asthma and diagnosed asthma*
[b] *Significant difference between undiagnosed asthma and healthy controls*
[c] *Significant difference between diagnosed asthma and healthy controls*

Impact on daily life

Table 3 presents data on the quality of life of children and their caregivers. For all domains, children with diagnosed or undiagnosed asthma had lower quality of life scores than healthy controls ($p < 0.05$). Quality of life in children with diagnosed asthma was lower than in children with undiagnosed asthma for all domains ($p < 0.05$). Quality of life scores in caregivers showed a similar pattern. Irrespective whether diagnosed or not, asthmatic children showed a lower score on the activity domain than their caregivers did ($p < 0.05$).

We estimated the effect on daily function by a 5 days' symptom diary and evaluation of school absence in the last 12 months. Children with diagnosed asthma reported twice as many symptoms in the diary than children with undiagnosed asthma (11% and 5% respectively, $p < 0.05$). Children with diagnosed and undiagnosed asthma were more than one week absent from school in the last 12 months due to respiratory symptoms than healthy controls, i.e. 31%, 17%, and 0%, respectively ($p < 0.001$) (table 4).

Table 4: Annual absence from school due to respiratory symptoms

	Undiagnosed asthma n (%)	Diagnosed asthma n (%)	Healthy controls n (%)	
Never	56 (50)	28 (40)	179 (93)	*a*
< 1 week	37 (33)	20 (29)	13 (7)	*a*
1-2 weeks	12 (11)	21 (30)	0	*a*
3-4 weeks	5 (4)	1 (1)	0	*a*
> 4 weeks	2 (2)	0	0	*a*

[a] *indicates p-value < 0.001*

Because corticosteroid treatment may affect lung function and quality of life score, we repeated the analysis after excluding children with undiagnosed asthma that used inhaled corticosteroids. Results remained essentially the same.

Discussion

In the present study, we found a lower quality of life on all domains in children with diagnosed and undiagnosed asthma as compared with healthy children. We found the same results for their caregivers. Lowest scores were observed in children with diagnosed asthma. Similarly, symptoms during five consecutive days and school absence in the last 12 months occurred more frequently in asthmatic children, with the highest impact in children with diagnosed asthma.

The major strength of our study is that to our knowledge this is the first population-based study that evaluated quality of life with standardized disease specific questionnaires in children with undiagnosed asthma and diagnosed asthma and their caregivers and compared these children with healthy controls.

We found a higher frequency of BHR and a lower prevalence of wheeze in children with undiagnosed asthma than children with diagnosed asthma. There are several explanations for this finding. First, bronchial hyperresponsiveness was used in the definition of undiagnosed asthma, whereas bronchial hyperresponsiveness was not required in the definition of diagnosed asthma. Another explanation might be the dependence on recall of asthma symptoms. Recall by parents can be faulty. Furthermore, parents may not witness every asthma symptom a child experiences, which might explain that night time symptoms are equal in children with undiagnosed

asthma and diagnosed asthma. Nonetheless, patient report of asthma symptoms has long been a key factor in physician's decision making, and the survey mimics the questions they pose as part of assessment. Responses to the questionnaire are equally reliable as similar questions in the physician's office.

Our results on quality of life with the lowest score in diagnosed asthma suggest that children with undiagnosed asthma have a milder degree of asthma than children with diagnosed asthma. This is in agreement with quality of life scores reported by others. For example, our children with diagnosed asthma had quality of life scores similar to those in children with moderate asthma, and our scores for undiagnosed asthma were comparable with those in children with mild asthma as reported by Raat et al.[19] The relevance of mild asthma should not be underestimated. Fawcett et al. showed that life-threatening exacerbations regularly occur in mild asthma.[7] Moreover, mild asthma accounts for the majority of pediatric admissions.

The clinical interpretation of differences in quality of life is difficult because experience in their use is still limited. Juniper et al. proposed a difference of 0.5 or higher as being clinically relevant for the PAQLQ.[13] Knorr et al. studied the effect of treatment in 6 - 14 year old asthmatic children and observed a significant improvement of both FEV_1 and quality of life scores (with 0.4 for the emotional domain and 0.5 for the activity domain).[15] In the light of these studies, our results suggest a clinically relevant impairment of quality of life in asthmatic children, irrespective of whether diagnosed or not. Until now, no reports are available on the clinical relevance of the parental scores of quality of life.

Our observations of lowest quality of life and highest symptom impact in diagnosed asthma compared to undiagnosed asthma seem in contradiction with observations on markers of airway obstruction (FEV_1, reversibility, BHR), which was highest in undiagnosed asthma. Juniper et al. reported a similar discrepancy. It is probable that clinical measures of airway status (such as airway calibre and markers of inflammation) evaluate a different component of asthma health status than quality of life.[14] For instance lung function is a static indicator in a variable disease, whereas quality of life scores reflects the patient's perceptions of the condition over a longer period of time. In addition, the stigma of being labelled as having asthma can be an explanation for the lower quality of life scores in children with diagnosed asthma. Further studies are needed to evaluate the effect of being diagnosed and medical treatment on quality of life in a community sample of undiagnosed asthma.

The following points may have affected our study results. First, we did not collect information on the reasons for non-response or the extent to which this may have biased our results. Second, bias may have been introduced if parents interpreted symptom questions different than the questionnaire definition.[4,16,25] Additionally, recall bias can not be excluded since questions referred to a period of the past 12 months. For symptoms we attempted to minimize bias by using the validated ISAAC questionnaire. One might argue that asthma-specific quality of life questionnaires are inappropriate to be used in healthy controls or in subjects without a diagnosis of asthma. However, the PAQLQ and PACQLQ also include questions on the impact of respiratory symptoms without making reference to 'asthma'. Therefore, we have considered them appropriate to use in children with undiagnosed asthma and healthy controls. Our observations of the highest scores in healthy controls that approximated the maximum value may be considered a confirmation. Furthermore the disease specific quality of life was significantly impaired in subjects who could be expected to experience impairments: the children with undiagnosed asthma. In addition, the results of more school absence in children with undiagnosed asthma compared to healthy controls supports the results of lower quality of life scores in children with undiagnosed asthma. A last comment addresses the selection of our patient groups. In this study children with "asymptomatic airway reversibility" or "asthma symptoms only" were excluded, because we aimed at a highest discrimination between asthma and healthy controls. Therefore, we included objective parameters (airway reversibility and BHR) for the definition of undiagnosed asthma. Nevertheless misclassification may have occurred since airway reversibility is variable present in asthma.

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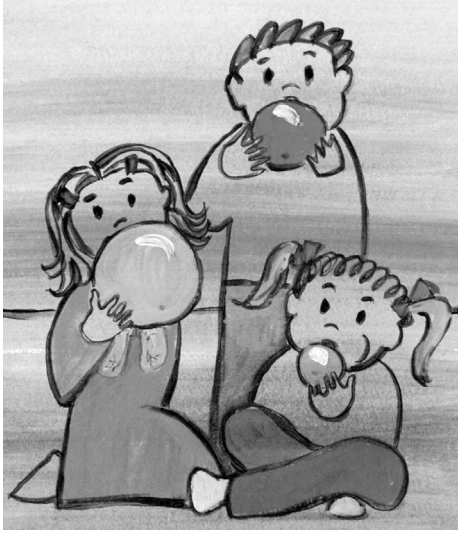

Chapter 4

Excessive body weight is associated with additional loss of quality of life in children with asthma

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Abstract

Background: Asthma and excessive body weight frequently coexist, whereas the exact relationship between the 2 diseases is unknown.

Objective: To study whether asthma combined with excessive body weight has a greater effect on quality of life in children than the separate effects of asthma or excessive body weight alone.

Methods: In a cross-sectional design, 1758 school children (age 7 - 10 years) participated: 4 study groups were composed of children with asthma and with/without excessive body weight, and healthy controls with/without excessive body weight. Diagnosis of asthma was defined by either a doctor's diagnosis or by core questions of the International Study of Asthma and Allergies in Childhood questionnaire in combination with either reversible airway obstruction or bronchial hyperresponsiveness. Excessive body weight was defined by using international cutoff points for body mass index. Quality of life was evaluated by the Pediatric Asthma Quality of Life Questionnaire.

Results: For all domains of quality of life, children with both asthma and excessive body weight had lower scores than children with either asthma alone or excessive body weight alone. Compared with healthy controls, the score was 25% lower in children with asthma and excessive body weight, 14% lower in children with asthma and normal weight, and only 1% lower in overweight controls.

Conclusion: Excessive body weight is associated with an additional decrease in quality of life in children with asthma.

Clinical implications: Clinicians should be aware of the interaction between asthma and excessive body weight and the effect on quality of life and should give extra attention to children with both conditions.

Abbreviations

BHR	Bronchial hyperresponsiveness
BMI	Body mass index
CI	Confidence interval
FEV_1	Forced expiratory volume in 1 second
PAQLQ	Pediatric Asthma Quality of Life Questionnaire

Introduction

Asthma and excessive body weight frequently coexist, but the underlying mechanism remains obscure. Recently, Hallstrand et al. reported shared genetic risks for asthma and obesity.[1] Other potential mechanisms include obesity-related changes in lung volumes and adipocyte-derived factors that might alter airway smooth muscle function.[2] Moreover, it was recently hypothesized that the elementary lesion of obesity might be inflammatory in origin, making a link with asthma as an inflammatory condition more plausible.[3] Furthermore, the decreased activity level associated with poorly controlled asthma may predispose a child to gain excessive body weight. Although a considerable number of studies using different designs indicate that excessive body weight might increase the risk of asthma development, the topic remains controversial due to potential methodological limitations including definitions of asthma, different anthropometric measures, directionality of causality, and residual confounding in many of these studies.[4]

In addition to clinical measures of airway status (such as airway caliber and markers of inflammation) quality of life provides valuable information about functional impairment (physical, emotional, and social) that is relevant to a patient's everyday life.[5] Children with excessive body weight are less fit and may have more symptoms of breathlessness on exertion than their healthy peers.

Because asthma and excessive body weight frequently coexist, we hypothesized that excessive body weight may be related to an additional decrease in quality of life in children with asthma. Therefore, in children with asthma we studied the combined effect of asthma and excessive body weight on quality of life compared with the effect of asthma with normal weight alone, and also compared with healthy controls with normal weight or excessive body weight.

Methods

Population and study protocol

From 2002 to 2005 we conducted a survey among primary school children aged 7 - 10 years in the southern region of the Netherlands. The study protocol was composed of a questionnaire for parents on respiratory symptoms, demographic and household characteristics, and the child's assessment of height and weight, lung function, and assessment of airway reversibility to salbutamol. First, the ISAAC

questionnaire and a consent form were distributed at participating schools to all eligible children. Lung function and assessment of airway reversibility were performed at school by experienced lung function technicians in all children that gave written consent. All eligible children with asthma symptoms (wheeze or dry cough in the past 12 months) or with proven airway reversibility to salbutamol were invited to Máxima Medical Center in Veldhoven for bronchial challenge with hypertonic saline.

For the present study, asthma was considered if one of the following criteria was fulfilled: 1) a parent's report of asthma diagnosis, with or without airway reversibility or bronchial hyperresponsiveness (BHR); or 2) asthma symptoms in the past 12 months combined with airway reversibility or bronchial hyperresponsiveness (BHR). For each child with asthma, a healthy control was selected randomly from the same classroom. Healthy controls had no asthma diagnosis, no asthma symptoms in the last 12 months, and no airway reversibility to salbutamol. Selected healthy controls were invited for bronchial challenge as well. Quality of life was assessed in children with asthma and healthy controls after completing the bronchial challenge with hypertonic saline. Questionnaires were returned by mail. Parents received a letter with the results of the symptom questionnaire and lungfunction tests 2 weeks after finishing the study protocol.

Approval was obtained from both the National Committee on Research involving Human Subjects (The Hague, the Netherlands), and the local Hospital Ethics Committee. Informed written consent was obtained from the parents of all participating children at the start of the study, when they returned the questionnaire. Apart from a small present for the children there was no compensation for the participants.

Body mass index

Before lung function testing, height and weight were assessed by trained research assistants. The child was stretched against the wall and height was measured to the nearest 0.1 cm, without wearing shoes. Children were weighed on a calibrated electronic step-scale, wearing no shoes and only light indoor clothing with empty pockets. Body mass index (BMI) was calculated from height and weight measurements (BMI = weight [kg]/(height [m])^2). Excessive body weight was defined using international cut-off points for children with overweight and obesity stratified by sex, which are defined to match with the adult cut-off point of a BMI of 25 kg/m^2 (overweight) and 30 (obesity) kg/m^2 at 18 years of age.[6]

Questionnaire

Parents completed a questionnaire that included the ISAAC core questions on symptoms of asthma, rhinitis and eczema.[7] Additional data were collected on household characteristics such as parental education, passive smoking, and pet ownership. Questions asked a response of Yes/No. Asthma symptoms were defined as wheeze or a dry cough at night in the past 12 months.

Lung function testing

Maximal flow-volume curves were measured using a hand-held spirometer (Vitalograph Ltd, Buckingham, UK) according to the European Respiratory Society guidelines.[8] Airway reversibility was defined as an increase of FEV_1 of ≥ 10% of the predicted value 10 minutes after administration of 800 mcg salbutamol using a volumatic spacer (GSK, Uxbridge, UK).[9]

Hypertonic saline testing

Bronchial hyperresponsiveness (BHR) was assessed by inhalation challenge with nebulized hypertonic (4.5%) saline by using an ultrasound nebulizer (Klava 2000/4000, Klava Eltromed, Bielefeld, Germany) according to the ISAAC protocol.[10] All children were asked to withhold all asthma medications for at least 12 hours beforehand. Children with a baseline FEV_1 ≤ 75% were excluded. The children inhaled the saline for periods of increasing duration: 0.5, 1, 2, 4, and 8 min. FEV_1 was measured 1 min after each inhalation period and the next inhalation period started after 3 min. Bronchial challenge was stopped if FEV_1 had fallen at least 15% from baseline or if the total inhalation period of 15.5 min had been completed. A child was defined as having BHR if FEV_1 had dropped by ≥ 15% from baseline during the inhalation challenge.

Quality of life

Quality of life was measured with the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) for children.[11] Children were asked to recall impairments they experienced the last week; for instance. “How much did wheezing bother you during the past week?” Scores range from 1 to 7, with 7 indicative of maximal quality of life. The PAQLQ consists of 3 domains, i.e. the emotions domain, activity domain and symptom domain. Individual items within the Pediatric Asthma Quality of Life Questionnaire were equally weighted. Results are expressed as the mean score per domain as well as

for overall quality of life. Raat et al showed good validation of the PAQLQ in a Dutch population.[12]

Statistical analysis

All data of the questionnaires were double-entered into the database using Microsoft Access software. Data were analyzed using the statistical package SPSS version 13.0. To analyze potential differences in clinical characteristics (i.e. asthma symptoms and lung function and quality of life) Chi-square tests and analysis of variance (with a Bonferroni post-hoc test) were used. To adjust for potential confounders (e.g. parental asthma, current parental smoking and the education level of parents) multivariate regression analyses were performed. In this model we tested the effect of all potential confounders one by one, i.e. the following model was tested: QoL = α + ß 1 x group + ß 2 x potential confounder. Because the estimates were not influenced by these possible confounders, crude effect estimates were presented. To evaluate the interaction between excessive overweight and asthma, we compared the combined effect of asthma and excessive body weight with the sum of separate effects as described by Pearce.[13]

Results

Participants

Of 44 eligible schools 41 participated in the study. Reasons for non-participation were recent involvement in another study (n = 2) and school policy (n = 1). Subsequently, all 2745 children and their parents were invited for the study, of whom 1758 (64%) agreed. We excluded 144 children from further analysis because of missing questionnaire data (n = 60) or refusal to participate in bronchial challenge testing (n = 31). Additionally, 53 children did not complete the bronchial challenge test because of nausea or coughing (n = 3) or were unable to meet technical conditions (n = 50). All children with a parent's report of asthma reported asthma symptoms (wheeze or dry cough at night) in the last 12 months. For each child with asthma, a healthy control was selected from the same classroom. There were no differences in FEV_1 and forced vital capacity (FVC) between the selected control group and the whole non-asthmatic population, i.e. 98% predicted for FEV_1 and 93% for FVC. The final study population was composed of 1614 children of whom 204 (13%) had asthma (171 [84%] with normal weight and 33 [16%] with excessive body weight), and 200 were defined as healthy controls (174 [87%] with normal weight and 26 [13%] with excessive body weight). Number of children with

overweight was 24 (73%) in the asthma group and 23 (89%) in the healthy controls. The number of obese children was 9 (27%) in the asthma group and 3 (12%) in the healthy controls.

Table 1 presents the characteristics of children with asthma and healthy controls. The occurrence of excessive body weight was similar for both groups. Asthmatic children with excessive body weight more frequently had a smoking father ($p < 0.05$) and more frequently used inhaled corticosteroids ($p < 0.05$).

Table 1: Characteristics of the four study groups

	Asthma		Healthy controls	
	Normal weight	Excessive body weight	Normal weight	Excessive body weight
n (%)	171 (84)	33 (16)	174 (87)	26 (13)
Sex, n (%)				
Male	97 (57)	17 (52)	86 (49)	12 (46)
Female	74 (43)	16 (48)	88 (51)	14 (54)
Mean age ± SD (years)	9.3 (0.8)	9.5 (0.8)	9.4 (0.7)	9.6 (0.6)
Mother asthma ever, n (%)	28 (19)	6 (19)	4 (3)	0 (0)
Father asthma ever, n (%)	16 (12)	2 (8)	7 (5)	5 (24)
Mother current smoker, n (%)	24 (16)	10 (32)	36 (22)	5 (22)
Father current smoker, n (%)	34 (23)	12 (40)	40 (24)	2 (8)
Mother's education level				
Low, n (%)	24 (16)	5 (16)	24 (15)	9 (37)
Moderate, n (%)	73 (49)	15 (48)	88 (53)	6 (26)
High, n (%)	53 (35)	11 (36)	53 (32)	9 (37)
Father's education level				
Low, n (%)	24 (17)	10 (38)	29 (18)	7 (32)
Moderate, n (%)	52 (38)	9 (35)	59 (37)	6 (27)
High, n (%)	62 (45)	7 (27)	73 (45)	9 (41)

n = absolute number for the weight or disease group
(%) = percent of total weight or disease group, however, because of to missing values, data can be lower or higher than calculated

Table 2 presents clinical characteristics of asthmatic children and healthy controls. Wheeze or dry cough at night was equally distributed in asthmatic children with normal weight or overweight. There were also no differences in symptoms based upon the ISAAC questionnaire. Lung function reversibility was most frequent in normal weight asthmatic children (43% of children). Bronchial hyperresponsiveness was most frequent in children with asthma combined with excessive body weight (73% of children). In healthy controls with excessive body weight bronchial

hyperresponsiveness was also more frequent than in healthy controls with normal weight (respectively, 19% and 9%; $p < 0.001$). Lung function reversibility was present in 24% of children with parent's report of asthma. Bronchial hyperresponsiveness was present in 47% of these children.

Table 2: Clinical characteristics of the four study groups

	Asthma		Healthy controls		
	Normal weight	Excessive body weight	Normal weight	Excessive body weight	p-value
n (%)	171 (84)	33 (16)	174 (87)	26 (13)	
BMI (mean)	16.0	21.9	15.8	20.9	
Wheeze, n (%)	115 (67)	21 (64)	0	0	
Dry cough at night, n (%)	53 (31)	11 (33)	0	0	
Lung function parameters					
Mean baseline FEV_1 % predicted	95	98	100	101	0.001[a]
Mean baseline FVC % predicted	91	95	94	94	NS
Change in FEV_1 after bronchodilation (%)	8.6	2.1	1.7	0.6	< 0.05[a,b,c]
Reversibility ≥ 10%, n (%)	73 (43)	12 (36)	0	0	< 0.00[a,c,d,e]
BHR, n (%)	102 (60)	24 (73)	16 (9)	5 (19)	< 0.001[a,c,d,e]
FEV_1 < 75%, n	1	0	0	0	
Medication					
Inhaled corticosteroids, n (%)	52 (30)	14 (46)	0 (0)	0 (0)	
Bronchodilator, n (%)	73 (43)	15 (45)	0 (0)	0 (0)	
Cromoglycate, n (%)	2 (1)	0 (0)	0 (0)	0 (0)	
Theophylline	0 (0)	0 (0)	0 (0)	0 (0)	
Oral steroids	0 (0)	0 (0)	0 (0)	0 (0)	

n = absolute number for the weight or disease group
(%) = percent of total weight or disease group, however due to missing values, data can be lower or higher than calculated
NS = not significant
a Significant difference between asthmatics with normal weight and healthy controls with normal weight
b Significant difference between asthmatics with normal weight and asthmatics with excessive body weight
c Significant difference between asthmatics with normal weight and healthy controls with excessive body weight
d Significant difference between asthmatics with excessive body weight and healthy controls with excessive body weight
e Significant difference between asthmatics with excessive body weight and healthy controls with normal weight

Quality of life

Figure 1A to D and table 3 present data on the separate and combined effects of asthma and excessive body weight for different domains of quality of life. Children with asthma combined with excessive body weight had the lowest quality of life compared to all other groups of children for all domains ($p < 0.01$). For the combined domain, scores were 5.2 (95% CI; 4.5 - 5.9) in children with asthma and excessive body

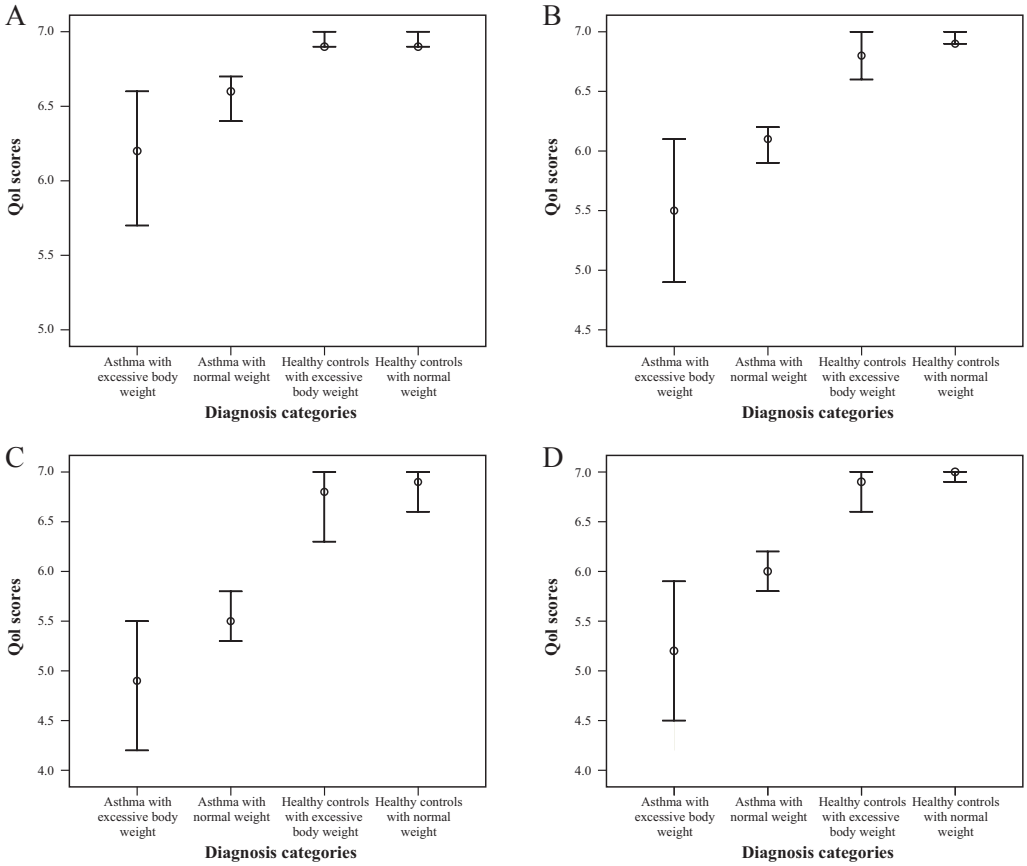

Figure 1. A. *Separate and joint effects of asthma and excessive body weight for the emotions domain. P < 0.05 for all comparisons except between healthy controls with normal weight and healthy controls with excessive body weight.* ***B.*** *Separate and joint effects of asthma and excessive body weight for the symptom domain. P < 0.05 for all comparisons except between healthy controls with normal weight and healthy controls with excessive body weight.* ***C.*** *Separate and joint effects of asthma and excessive body weight for the activity domain. P < 0.05 for all comparisons except between healthy controls with normal weight and healthy controls with excessive body weight.* ***D.*** *Separate and joint effects of asthma and excessive body weight for the combined domain. P < 0.05 for all comparisons except between healthy controls with normal weight and healthy controls with excessive body weight.*

Table 3: Data on quality of life scores of the study groups

	Asthma with excessive body weight		Asthma with normal weight		Healthy controls with excessive body weight		p-value
	Absolute difference mean (95% CI)	% diff.	Absolute difference mean (95% CI)	% diff.	Absolute difference mean (95% CI)	% diff.	
Symptom domain	1.5 (0.8-2.1)	21%	0.9 (0.7-1.1)	13%	0.2 (0.0-0.4)	3%	0.01[a]
Emotions domain	0.7 (0.3-1.3)	10%	0.3 (0.2-0.6)	4%	0 (0-0.1)	0%	< 0.05[a]
Activity domain	2.0 (1.1-2.8)	29%	1.4 (0.8-1.7)	20%	0.1 (0.0-0.7)	1%	0.01[a]
Combined domain	1.8 (1.0-2.5)	25%	1.0 (0.8-1.2)	14%	0.1 (0.0-0.4)	1%	0.001[a]

[a] *Significant difference in quality of life scores among all study groups except between healthy controls with excessive body weight and healthy controls with normal weight*

weight, 6.0 (95% CI; 5.8 - 6.2) in children with asthma with normal weight, 6.9 (95% CI; 6.9 - 7.0) in healthy controls with excessive body weight , and 7.0 (95% CI; 6.6 - 7.0) in healthy controls with normal weight (Figure 1, D; $p < 0.05$ for all comparisons, except between healthy controls with excessive body weight and with normal weight).

Table 3 presents percentage differences in the quality of life scores between three of the study groups compared with healthy controls with normal weight. Compared to healthy controls with normal weight, quality of life scores for the combined domain were respectively 14% lower in children with asthma and normal weight, and 1% lower in healthy controls with excessive body weight. On the basis of the separate effects for asthma and overweight we expected a 15% lower score; however the score for the combined effect in overweight asthmatic children proved to be 25% lower.

Discussion

In the current study quality of life in children with both excessive body weight and asthma was lower than expected based on the sum of the separate effects of asthma alone or excessive body weight alone. Children with asthma and excessive body weight had a lower quality of life compared with children with asthma and normal weight , and compared with healthy controls irrespective of their weight.

Our results are in agreement with results in adults that showed a significant association between BMI and quality of life in adults with asthma.[14,15] Data on the impact of asthma in children with excessive body weight in the population are scarce. Blandon et al. found a lower quality of life in children with asthma recruited from a population attending a specialized allergy and immunology clinic.[16] In a sample of inner-city children Belamarich et al. reported that obese asthmatic children had more unscheduled emergency department visits and received more medication than nonobese children.[17] The effect of overweight and obesity is higher with increasing BMI. For instance, among 3457 subjects in the Framingham Study, those who were overweight at age 40 years lived about three years less and those who were obese at age 40 years lived 6 to 7 years less than those who were not.[18] In the same cohort, the relative risk in obese for vascular disease was higher for obese than for overweight adults.[19]

In our study, children with asthma combined with excessive body weight were more often treated with inhaled corticosteroids than asthmatic children without excessive body weight. Possible explanations for this phenomenon are a different perception of dyspnea by children, greater awareness of respiratory complaints by parents, or a different coping behavior with respiratory complaints in these children with excessive body weight.

To our knowledge, this is the first community-based study in children to evaluate the relationship between excessive body weight, asthma, and quality of life measured with a disease specific, validated and well-known quality of life questionnaire. Disease-specific questionnaires have a higher discriminative property and sensitivity to detect small differences for the disease of interest.[20-22] In contrast, general questionnaires on quality of life tend to be designed to assess moderate or severe impact of chronic conditions on children's quality of life, which make them less sensitive to small differences between groups.

The clinical interpretation of differences in quality of life is difficult because experience in their use is still limited. Juniper et al. proposed a difference of 0.5 or higher as being clinically relevant for the PAQLQ.[20] Knorr et al. studied the effect of treatment in 6 - 14 year old asthmatic children and observed a significant improvement in both FEV_1 and quality of life scores (with 0.4 for the emotional domain and 0.5 for the activity domain).[23] In light of these studies, our results suggest a clinically relevant impairment of quality of life in children with asthma with excessive body weight.

Our results suggest that treatment in children should be aimed at both asthma and excessive body weight. We know from adults that the response to different asthma medications is influenced by an increasing BMI.[24] The effect of placebo or corticosteroid treatment on asthma symptom-free days was lower in obese asthmatics, whereas this effect was not seen in treatment with leukotriene antagonists. Data on children with asthma combined with excessive body weight are still scarce. However, the combination of health problems makes it likely that a combined treatment for both conditions by a multidisciplinary team (including psychologist and dietician) is beneficial for the quality of life in these children. Caloric restriction and increasing energy expenditure are hallmarks in the treatment of excessive body weight. Ford et al suggested a need for weight-control programs among adults with asthma, because they found that many adults with asthma failed to employ recommended approaches of caloric restriction and adequate physical activity.[25] Further studies are needed to establish which strategy is best in children.

Until now, no reports are available about the influence of a reduction in excessive body weight on asthma severity in children and there are few evidence-based guidelines for intervention regarding excessive body weight in children.[26] In adults a reduction in excessive body weight by medical treatment and surgical procedures have resulted in a reduction of asthma symptoms, medication usage, and severity, and in improvement of lung function, indicating a possible causal relationship.[27-29]

When considering our results, some possible limitations of this study should be discussed. First, the ISAAC questionnaire used in this study depended on the recall of asthma symptoms by parents. Recall by parents can be faulty. Further, parents may not witness every asthma symptom a child experiences. Nonetheless, patient report of asthma symptoms has long been a key factor in physician's decision making, and the ISAAC questionnaire mimics the questions they pose as part of assessment. Second, misclassification of asthma is possible. However, we believe that using a combination of the well-known and validated ISAAC questionnaire and objective measures such as lung function reversibility and BHR resulted in the best possible clinical definition of asthma. Third, because of the cross-sectional design of this study we can not speculate on the causal relationship between asthma and excessive body weight and the effect on quality of life. Fourth, one might argue that asthma-specific quality of life questionnaires are inappropriate to be used in healthy controls. However, the PAQLQ also includes questions on the effect of respiratory symptoms without making reference to asthma. Therefore, we have considered them appropriate for use in children serving as healthy controls. Our observations of the highest scores in healthy controls that

approximated the maximum value may be considered a confirmation.

In conclusion, excessive body weight is associated with an additional decrease in quality of life in children with asthma. Clinicians should realize that children with asthma need extra attention if they also have excessive body weight. We therefore consider that treatment by specialized multidisciplinary teams will have the largest beneficial effect in these children.

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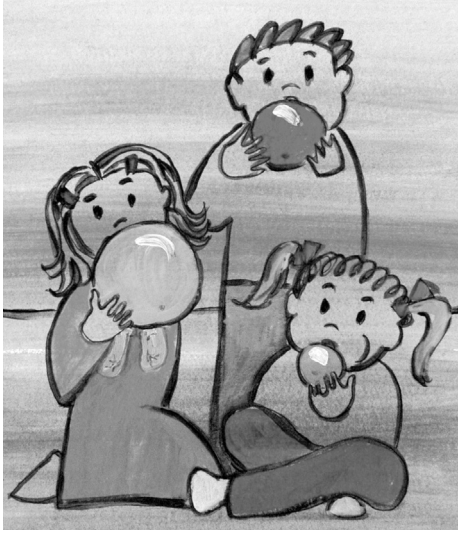

Chapter 5

No differences in physical activity in (un)diagnosed asthma and healthy controls

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Abstract

To establish whether asthma affects physical activity levels in children (aged 7 - 10 years) we evaluated physical activity levels in children with undiagnosed asthma, diagnosed asthma and healthy controls.

A cross-sectional community-based study was performed which included a parental questionnaire on their child's respiratory health, and testing of airway reversibility and bronchial hyperresponsiveness. Diagnosed asthma was defined as the parents' confirmation of a physician's diagnosis of asthma in the past 12 months. Undiagnosed asthma was defined by asthma symptoms combined with airway reversibility or bronchial hyperresponsiveness in children without a physician's diagnosis of asthma. Physical activity was measured during 5 days with an accelerometer and a diary, and with the habitual activity estimation scale which reviews the physical activity during the past 2 weeks.

The final study population comprised 1614 children of whom 81 (5%) had diagnosed asthma, 130 (8%) undiagnosed asthma, and 202 healthy controls. Baseline FEV_1 % predicted, was lowest in children with undiagnosed asthma (undiagnosed asthma FEV_1 94% predicted, diagnosed asthma FEV_1 98% predicted, healthy controls FEV_1 100% predicted). Using the three methods, no differences were found in the physical activity between children with undiagnosed asthma, diagnosed asthma and healthy controls.

Childhood asthma does not appear to be associated with a decreased level of daily physical activity in our study population.

Abbreviations

BHR	Bronchial hyperresponsiveness
DA	Diagnosed asthma
FEV_1	Forced expiratory volume in 1 second
HAES	Habitual Activity Estimation Scale
HC	Healthy controls
PAM	Physical Activity Monitor
UDA	Undiagnosed asthma

Introduction

Physical activity is an important part of both a healthy lifestyle and of a child's daily routine.[1] Development of good health and fitness habits in childhood is associated with physical fitness, and international guidelines recommend children to be active 60 minutes/day.[1,2] However, in modern society physical activity in children is declining, resulting in a higher prevalence of obesity and cardiovascular diseases.[3,4] Lower levels of activity in asthma seem to have more impact on physical fitness than the degree of airway obstruction.[5] Furthermore, high physical fitness seems to be associated with a reduced risk of asthma, and the amount of daily physical activity is associated with aerobic fitness.[5,6] Therefore, regular physical activity and participation in sports are considered to be important components in the overall management of asthma, and the American Academy of Pediatrics guidelines for sports medication states that "with proper medication and education, only athletes with the most severe asthma need to modify their participation".[7] However, in the AIRE study, 30% of the children appeared to be limited in their sporting activities.[8]

Since 1980 it has been suggested that asthma in children is underdiagnosed and subsequently undertreated.[9-15] Recent data show that underdiagnosis is still a problem. Chew et al. reported that 49% of all children with asthma-like symptoms had not been diagnosed with asthma, whereas Joseph et al. reported a prevalence of undiagnosed asthma of 11.7%.[16,17] The prevalence of exercise-induced asthma is as high as 90% in children with asthma and a majority of children report that the worst thing about their asthma is their inability to participate in sports.[18,19] Finally, asthma, whether undiagnosed or diagnosed, can have a negative effect on the level of physical activity in these children.

Therefore, the present study investigates whether asthma decreases the physical activity level in children. For this we compared physical activity levels in children (aged 7 - 10 years) with undiagnosed asthma (UDA), diagnosed asthma (DA) and in healthy controls (HC).

Materials and Methods

Population and study protocol

The study was conducted in 41 out of 44 primary schools in four cities in the Netherlands. We asked all children aged 7 - 10 years and their parents to participate in our study. All participating parents completed a questionnaire on respiratory symptoms, demographic and household characteristics. The questions about respiratory symptoms were identical to those of the well known International Study of Asthma and Allergies in Childhood the ISAAC questionnaire.[20] All participating children were invited for lung function testing with assessment of reversibility to salbutamol. Children with asthma symptoms in the past 12 months or reversible airway obstruction were invited for bronchial challenge with hypertonic saline. A child was considered to have diagnosed asthma if the parents confirmed that their child had physician-diagnosed asthma in the past 12 months. A child was considered to have undiagnosed asthma if the child had 1) no physician-diagnosed asthma in the past 12 months, 2) asthma symptoms (wheeze or dry cough at night apart form a cough associated with a cold or chest infection) in the past 12 months, and 3) either had reversible airway obstruction or bronchial hyperresponsiveness (BHR). For each child with asthma, a healthy control was randomly selected from the same classroom. Healthy controls had no asthma diagnosis, no asthma symptoms in the past 12 months, and no airway reversibility to salbutamol.

We obtained approval for the study from the central Committee on Research involving Human Subjects (The Hague, the Netherlands), from the Hospital Ethics Committee, and from the principals of the schools involved. Informed written consent was obtained from the parents of all children.

Questionnaire

Parents completed a questionnaire that included the ISAAC core questions on symptoms of asthma, rhinitis and eczema which have been reported elsewhere.[20] Additional data were collected on household characteristics such as parental education and passive smoking. Asthma symptoms were defined as wheeze or a dry cough at night in the past 12 months.

Spirometry and reversibility

Maximal flow-volume curves were measured using a hand-held spirometer (Vitalograph Ltd, Buckingham, UK) according to the ERS guidelines.[21] A minimum of two technically acceptable baseline flow-volume curves were performed and the highest of two reproducible (within 5%) measurements of forced expiratory volume in one second (FEV_1) was recorded as baseline FEV_1. Subsequently, 800 microgram of salbutamol was administered via a metered dose inhaler using a volumatic spacer (GSK, Uxbridge, UK). Airway reversibility was defined as an increase of FEV_1 of ≥ 10% of the predicted value 10 minutes after administration of salbutamol.[22]

Hypertonic saline testing

Bronchial hyperresponsiveness was assessed by inhalation challenge with nebulized hypertonic (4.5%) saline using an ultrasound nebulizer (Klava 2000/4000, Klava Eltromed, Bielefeld, Germany) according to the ISAAC protocol. BHR was assessed on a different day than the spirometry.[23] All children were asked to withhold all asthma medications for at least 12 hours beforehand. Children with a baseline $FEV_1 \leq 75\%$ predicted were excluded. The children inhaled the saline for periods of increasing duration: 0.5, 1, 2, 4, and 8 min. FEV_1 was measured 1 min after each inhalation period and the next inhalation period started after 3 min. Bronchial challenge was stopped if FEV_1 had fallen at least 15% from baseline or if the total inhalation period of 15.5 min had been completed. A child was defined as having BHR if FEV_1 had dropped by ≥ 15% from baseline during the inhalation challenge.

Daily Physical Activity

Physical activity was assessed in all participating children. We evaluated the physical activity with both an accelerometer and a diary during 3 week days and 2 weekend days, and with the habitual activity estimation scale (HAES), which is described in more detail below.

Physical Activity Monitor (PAM)

The daily physical activity level was assessed using the (PAM) accelerometer (type AM 100; Pam B.V., The Netherlands).The PAM is a small-sized (58x43x12 mm), light weight (28 g) accelerometer, which is worn on a belt at the hip. The PAM measures accelerations in two dimensions on the x and y axis. The PAM was worn during waking

hours except during showering and swimming. Validity and reliability are good.[24] At the end of the monitoring period data were downloaded into a personal computer. Measurements are expressed as PAM points, that is, the ratio between the amount of energy used while active and the amount of energy used in rest, multiplied by 100%. The output can also be expressed in min/day in different activity levels. Activity that burns 3 to 6 METs was defined as moderate-intensity activity and any activity that burns > 6 METs as vigorous-intensity activity. Data were averaged in 1 min. blocks.

]Activity diary

Children wrote down their activities (intensity and type of activity) during the day in blocks of 15 minutes.[25] Activities were categorized into nine levels from the lowest acitivity,1, representing sleep or rest in bed, to the highest level, 9, during very intense sport.

HAES

Physical activity was also assessed with the habitual activity estimation scale (HAES), designed to categorize daily physical activity (hours spent inactive, somewhat inactive, somewhat active, and active).[26] This scale reviews the subject's activity level for 1 week day and 1 weekend day during the previous 2 weeks. Each child was given a detailed explanation and demonstration how to use the different methods. The total percentage of time spent being active is presented.

Data analysis

All data of the questionnaires were double-entered into the database using Microsoft Access software. Chi-square tests and ANOVA with a Bonferroni post-hoc test were used to analyze differences in each of the three physical activity measurement groups. Data were analyzed using the statistical package SPSS version 13.0.

Results

Participants

Of 44 eligible schools, 41 participated in the study. Reasons for non-participation were recent involvement in another study (n = 2) and school policy never to participate

in medical studies (n = 1). We invited 2745 children and their parents to participate in the study in the period September 2002 to April 2005 of which 64% (n = 1758) gave informed consent to participate. We excluded 144 children from further analysis. Reasons for exclusion were missing questionnaire data (n = 60), refusal to participate in bronchial challenge testing (n = 31), inability to complete the bronchial challenge test due to nausea or coughing (n = 3), or inability to meet technical conditions (n = 50).

Diagnosis and demographics

The final study population comprised 1614 children of whom 81 (5%) had diagnosed asthma and 130 (8%) undiagnosed asthma according to our criteria. Of the remaining healthy controls, we randomly selected 202 children. Table 1 presents the characteristics of the study population. There were no differences between groups for gender, age or parental education. Children with diagnosed asthma more frequently had a father with asthma compared to the children with undiagnosed asthma and healthy controls, whereas having a mother with asthma occurred more frequently in children with both diagnosed and undiagnosed asthma.

Table 1: Characteristics of the three groups

	Undiagnosed asthma (n = 130)	Diagnosed asthma (n = 81)	Healthy controls (n = 202)
Sex, n (%)			
Male	73 (56)	47 (58)	100 (50)
Female	57 (44)	34 (42)	102 (50)
Mean age ± SD (years)	9.4 (0.7)	9.4 (0.8)	9.4 (0.7)
Mother asthma ever, n (%)	19 (17)	16 (23)	4 (2)
Father asthma ever, n (%)	7 (7)	11 (16)	12 (7)
Mother current smoker, n (%)	26 (20)	10 (14)	41 (22)
Father current smoker, n (%)	30 (26)	17 (24)	42 (22)
Mother's education			
Low, n (%)	17 (15)	14 (20)	33 (17)
Moderate, n (%)	56 (49)	34 (48)	95 (50)
High, n (%)	41 (36)	23 (32)	62 (33)
Father's education			
Low, n (%)	20 (20)	16 (24)	37 (20)
Moderate, n (%)	41 (40)	22 (32)	65 (35)
High, n (%)	40 (40)	30 (44)	82 (45)

Table 2: Clinical characteristics of the three groups

	Undiagnosed asthma (n = 130)	Diagnosed asthma (n = 81)	Healthy controls (n = 202)	p-value
Symptoms in last 12 months				
Wheeze, n (%)	72 (56)	70 (86)	0 (0)	< 0.001 [a,b,c]
Dry cough at night, n (%)	90 (71)	54 (70)	0 (0)	< 0.001 [a,b,c]
Lung function parameters				
Mean baseline FEV_1 % predicted	94	98	100	< 0.001 [b]
Mean baseline FVC % predicted	89	95	95	< 0.05 [a,b]
FVC after bronchodilation	94	97	95	
Change in FEV_1 after BD (%)	+ 9	+ 5	+ 2	< 0.001 [b]
Reversibility ≥ 10%, n (%)	67 (52)	19 (24)	0 (0)	< 0.001 [a,b,c]
BHR, n (%)	93 (73)	38 (47)	21 (11)	< 0.001 [a,b,c]
Inhaled corticosteroids, n (%)	12 (9)	60 (74)	0 (0)	

BD indicates bronchodilator; BHR indicates bronchial hyperresponsiveness
[a] *Significant difference between undiagnosed asthma and diagnosed asthma*
[b] *Significant difference between undiagnosed asthma and healthy controls*
[c] *Significant difference between diagnosed asthma and healthy controls*

Table 3: Daily physical activity in the three groups

	Undiagnosed asthma (n = 130)	Diagnosed asthma (n = 81)	Healthy controls (n = 202)
	Mean (95% C.I.)	Mean (95% C.I.)	Mean (95% C.I.)
PAM (score/day)	49 (44-54)	49 (42-56)	47 (43-50)
PAM: moderate intensity activity (min/day)	86 (76-95)	78 (66-90)	78 (71-85)
PAM: vigorous intensity activity (min/day)	22 (15-25)	21 (14-28)	20 (14-21)
Diary (minutes active/day))	110 (105-116)	112 (105-119)	111 (107-116)
HAES (minutes active/day)	109 (98-120)	111 (99-121)	113 (106-120)

Table 2 presents clinical characteristics of the three groups. Wheeze was reported for 56%, 86% and 0% of the children with respectively undiagnosed asthma, diagnosed asthma and healthy controls ($p < 0.001$ for all comparisons). Children with undiagnosed asthma had lowest baseline FEV_1, which showed the greatest increase after inhalation of salbutamol (9%, 5%, 2% respectively; UDA vs. HC; $p < 0.001$, UDA vs DA; $p = 0.07$). Furthermore, children with undiagnosed asthma more frequently had airway reversibility and BHR than children with diagnosed asthma and healthy controls.

Daily physical acitvity

We found no differences between the three study groups for daily physical activity measured by the three different methods (table 3). PAM scores were 49 for respectively undiagnosed asthma and diagnosed asthma and 47 for healthy controls. According to the diary and the HAES all diagnosis groups performed an average of 110 minutes of physical activities per day. Analyses of different intensity levels were performed for the PAM accelerometer, diary and HAES, but revealed no differences between the study groups.

Discussion

Mild asthma does not seem to affect physical activity levels in children aged 7 - 10 years, as we found no differences in daily physical activity or differences in intensity levels of physical activity between children with undiagnosed asthma, diagnosed asthma and healthy controls. Furthermore, on average, the children of all three groups meet the international guidelines that recommend participation in regular physical activity for children at least 30 minutes of moderate activity on at least five days per week, or 20 minutes of vigorous physical activity at least three times per week.[27]

Levels of FEV_1 were only mildly decreased in both groups with asthma, which shows that this study deals with mild asthma. Furthermore, FEV_1 in all groups is high enough to be able to participate in physical activities.[28] We found a higher frequency of BHR and a lower FEV_1 in children with undiagnosed asthma than children with diagnosed asthma. This might suggest that children with undiagnosed asthma had more severe asthma than those with a diagnosis of asthma, and this might be the result of proper treatment with inhaled corticosteroids after diagnosis. However, bronchial hyperresponsiveness and lung function reversibility was used in the definition of undiagnosed asthma, whereas bronchial hyperresponsiveness or lung function reversibility was not required in the definition of diagnosed asthma. Thus our definition selected for children with BHR. However only those with asthma symptoms were considered to have undiagnosed asthma.

Our results are in agreement with the results of Nystadt et al. who also found no differences between children with asthma and healthy controls, and with Pianosi et al. who found no differences in physical activity level in children with different asthma severity.[29,30] Our results are, however, not in agreement with Firrincieli et al. who

observed lower levels of physical activity in wheezing children as compared to healthy controls, and Lang et al. who also found that children with asthma were less active than healthy controls.[31,32] None of these studies, however, used an accelerometer according to the recommendations as suggested by Trost et al., which is known to be the only objective measurement of daily physical activity in field studies.[33] However, it remains to be said that differences between these studies and our study could also be due to different methodologies and inclusion criteria (i.e. definition of asthma, asthma severity and age) in our study.

To our knowledge no other studies have compared daily physical activity levels of children with undiagnosed asthma with those with diagnosed asthma and healthy controls. Moreover, the finding of equal physical activities in the three different groups was consistent with all used methods. Since the majority of children with asthma also have exercise induced asthma, we expected that children with undiagnosed asthma would have the lowest physical activity and that the children with diagnosed asthma would perform less physical activities than healthy controls. Our opposite findings could mean that asthma per se does not affect physical activity in asthma. In the undiagnosed asthma group this may have several explanations: i.e. poorer symptom perception, ignorance of symptoms, or not labeling symptoms to disease. In the diagnosed group this could be due to adherence to treatment regimes and the emphasis on recommendations for children with asthma to attend physical activities without restrictions.

Although we found no differences in physical activities between children with asthma and healthy controls, several studies showed that children had limitations with sport.[19,34,35] For instance the AIRE study showed that 30% of children had limitations with sport activities.[8] In that study the interviewers only asked whether children had activity limitations due to their asthma (i.e. information about perception), but they did not quantify the duration of daily physical activity. Perception of physical activities is an important limiting factor for physical activities in children with asthma; that is perceived competence in physical activity is associated with maximal aerobic power, but asthma severity in children does not correlate with physical activity.[30] This might explain the difference in results of our study compared with the AIRE study. In fact, the results of Pianosi et al. also suggest that asthmatic children can achieve a level of exercise performance similar to that of healthy children, provided that they have a comparable level of habitual physical activity.[30]

Some possible limitations of our study should also be addressed. First, measuring physical activity in children remains difficult. Children tend to have short burst of activities that are more difficult to measure than the more circumscribed activities in adults.[36] The gold standard for assessing physical activity in field studies is probably the double-labeled water method.[37] However, for use in a large population survey this method is expensive, does not provide information about activity patterns, and is limited due to parental reluctance about the ingestion of even a nonradioactive isotope. Second, accelerometers selectively record movement of the specific part of the body to which they are attached and thus differences in types of physical activities are mostly indistinguishable or unmeasured. Subsequently, some activities, such as swimming and cycling, can not be adequately measured.[38,39] Third, the diaries we used and the HAES questionnaire might have been subject to recall bias. We have, however, no reason to believe that this recall bias differed between the three study groups. A last comment addresses the definition of undiagnosed asthma. There is no golden standard for asthma diagnosis in childhood. To prevent misclassification we used the well known ISAAC questionnaire and included objective parameters (airway reversibility and BHR) for the definition of undiagnosed asthma. Comparisons of physical activity between the different study groups are valid, but our results might be more difficult to compare with other studies due to different asthma diagnosis in other studies.

In conclusion childhood mild asthma, whether diagnosed or not, does not seem to be associated with a decreased level of daily physical activity compared to healthy controls.

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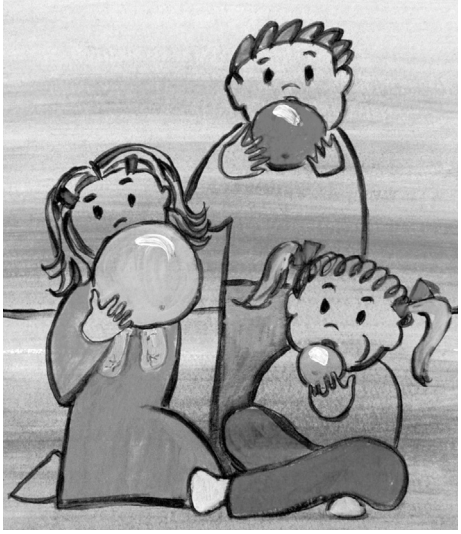

Chapter 6

Poor perception of dyspnea in children with undiagnosed asthma

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Eur Respir J 2007;30:1-6

Abstract

The aim of the present was to establish differences in dyspnea perception between children with undiagnosed asthma and diagnosed asthma.

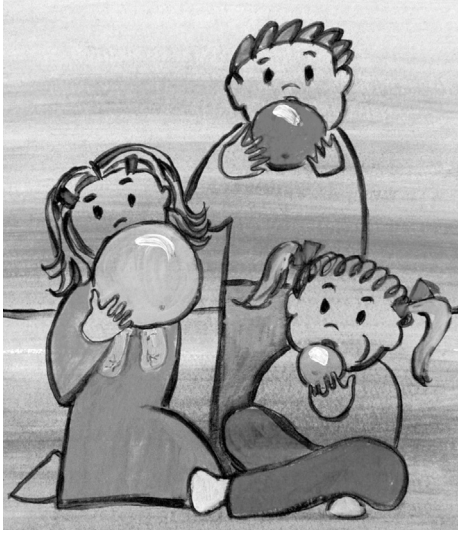
A cross-sectional community-based study was performed which included a parental questionnaire on their child's respiratory health and testing of airway reversibility and bronchial hyperresponsiveness (BHR). "Diagnosed asthma" was defined by a physician's diagnosis of asthma. "Undiagnosed asthma" was defined by the presence of asthma symptoms combined with either airway reversibility or BHR without a physician's diagnosis of asthma. Only children with a positive bronchial hyperresponsiveness test were selected for further analysis. Perception of dyspnea was assessed using the Borg scale and Visual Analogue Scale (VAS), plotted against the percent fall in forced expiratory volume in 1 second and expressed as the slope of the regression line (Slope-Borg and Slope-VAS).

Of the initial 1758 children, 70 children had undiagnosed asthma and 38 had diagnosed asthma. The Borg and VAS slopes in children with undiagnosed asthma were less steep than those of children with diagnosed asthma (Borg: 0.07 and 0.14, respectively; $p = 0.04$; VAS: 0.06 and 0.11, respectively; $p = 0.11$).

Among children with bronchial hyperresponsiveness, those without a parent's report of physician's diagnosis of asthma had a worse perception of dyspnea than children with diagnosed asthma.

Abbreviations

BHR Bronchial hyperresponsiveness
FEV_1 Forced expiratory volume in 1 second
PD 15 Cumulative dose of hypertonic saline resulting in a 15% decrease in FEV_1



Chapter 7

Adherence to follow-up recommendations in asthma

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Abstract

A cross-sectional study showed that 130 out of 1758 (8%) primary school children without a previous asthma diagnosis had undiagnosed asthma. Of the parents, 38% refused to visit a general practitioner for this disorder. Factors associated with refusal were high maternal education, mild symptoms and absence of airway reversibility.

Abbrevations

GP	General practioner
BHR	Bronchial hyperresponsiveness
FEV_1	Forced expiratory volume in 1 second

Introduction

Screening for asthma in children is controversial.[1] The success of screening programs is dependent on parental recognition and report of asthma symptoms, adherence to recommendations after a positive test and physician's recognition and management of asthma symptoms.[2] Easily accessible general practitioners are the first level of care in the Dutch health care system. The aim of this study was to assess the willingness of parents of children with possible asthma to visit their general practitioner (GP).

Methods

The study methods have been described previously.[3] Briefly, children aged 7 - 10 years and their parents in 41 primary schools were asked to participate. Participating parents completed the ISAAC questionnaire on respiratory symptoms.[4] Children with asthma symptoms in the past 12 months or reversible airway obstruction were invited for bronchial challenge with hypertonic saline. A child was considered to have "diagnosed asthma" if a physician diagnosed asthma in the last 12 months. A child was considered to have "possible asthma" if the child had 1) no physician-diagnosed asthma in the last 12 months, 2) asthma symptoms in the last 12 months, and 3) had either reversible airway obstruction or BHR.

Parents of children with possible asthma were sent a letter recommending medical evaluation by their GP. The GPs received a letter including telephone numbers for questions with the results of the questionnaire and lung function tests. A research nurse contacted parents to conduct a structured telephone interview concerning the response of the parents and the GP. Data were collected about adherence to the recommendation to visit a physician. Approval was obtained from the national Committee on Research involving Human Subjects. Informed consent was obtained from the parents of all participating children. Chi-square tests were used to analyze differences between the groups of children with possible asthma visiting and not visiting a physician. Univariate regression analysis was used to analyze predictors of non-adherence to the recommendation. Variables with a p-value < 0.1 were entered in a multivariate logistic regression model aiming at the analysis of independent predictors of non-adherence to the recommendation.

Results

Participants

The final study population has been described in detail elsewhere and comprised 1614 children.[3] Of the 2745 invited children, 1758 (64%) participated in the study, of whom 144 children were excluded from further analysis. According to our criteria 81 (5%) had diagnosed asthma and 130 (8%) possible asthma, which represented our study population. A follow-up interview was completed in 114 (88%). Table 1 presents the characteristics of the 114 children with possible asthma which completed the follow-up interview. Non-responders did not differ from responders with respect to sociodemographic characteristics (parental education, child's sex and age) and clinical parameters (asthma symptoms, lung function, airway reversibility and BHR).

Table 1: Characteristics of the study groups

	Visit to a physician n = 71	No Visit to a physician n = 43	p-value
Child characteristics			
Gender, n (%)			
Male	32 (46)	21 (47)	0.3
Mean age ± SD (years)	9.4 (0.7)	9.3 (0.8)	0.5
Symptoms in the last 12 months			
Wheeze, n (%)	36 (52)	25 (56)	0.8
Dry cough at night, n (%)	49 (71)	30 (70)	0.8
Lung function parameters			
Mean baseline FEV_1 % predicted	92	96	0.1
Mean baseline FVC % predicted	88	91	0.2
Mean change in FEV_1 after BD (%)	12	4	0.01
Reversibility ≥ 10%, n (%)	40 (58)	17 (39)	0.04
Bronchial hyperreactivity, n (%)	48 (71)	36 (80)	0.4
Inhaled corticosteroids, n (%)	5 (7)	3 (7)	
Family characteristics			
Mother asthma ever, n (%)	10 (16)	7 (18)	0.8
Father asthma ever, n (%)	2 (4)	3 (8)	0.5
Mother current smoker, n (%)	12 (19)	10 (26)	0.5
Father current smoker, n (%)	15 (24)	9 (23)	0.9
Education level			
Mother university or high vocational degree, n (%)	17 (27)	20 (51)	0.02
Father university or high vocational degree, n (%)	16 (30)	19 (54)	0.02
Current pet ownership	44 (73)	27 (69)	0.2

SD indicates standard deviation; BD indicates bronchodilation

Seventy-one (62%) children visited a physician (GP n = 69, pediatrician n = 2). Adherence to the recommendation to visit the GP was similar in parents with a lower level of education, i.e. 17% visiting and 11% non-visiting mothers, and 20% visiting and 14% non-visiting fathers. To increase statistical power, we combined low and moderate educational levels in subsequent analyses. Bivariate logistic regression yielded significant associations of airway reversibility (OR 2.2; 95% CI 1.1 - 4.7; p = 0.04) and a maternal university education degree (OR 0.4; 95% CI 0.2 - 0.9; p = 0.02) with willingness to follow-up the recommendations. Multivariate logistic regression did not change the results (airway reversibility: OR 2.1; 95% CI 0.9 - 5.1, p = 0.07 and for maternal education: OR 0.4; 95% CI 0.2 - 0.9, p = 0.02).

The main reason for parents not to visit a physician was absence or mildness of symptoms (63%, n = 27) (table 2). The majority of these parents stated in the interview that they would visit their GP if the symptoms worsened; 8 (20%) of the children had already made a visit to the GP in the last year and 7 of these children were using medication (1 inhaled corticosteroids, 6 bronchodilator on demand). Of the 7 already being treated children, 3 had highly educated parents. Reasons for not visiting the GP were not different between highly educated parents vs moderate/low educated parents (table 3). Of the children referred to a pediatrician, all received a prescription for asthma medication during the GP visit. Table 3 gives data on the result of the visit to the GP as reported by the parents.

Table 2: Main reason why parents (n = 43) did not visit a physician for their children with possible asthma

	n	%
Absence or mildness of symptoms	27	63
Visit to non-regular physician	1	2
Seasonal-based symptoms	1	2
Had already visited their GP	8	20
Child refused to visit GP	1	2
No priority	4	9
Was treated by GP for respiratory symptoms but had no asthma diagnosis	1	2

Table 3: Parental response in telephone interview of those visiting a GP (n = 69)

Action GP	**No 28 (40%)**	**Yes 41 (60%)**	**% of 69**	**% of 41**
Physical examination	n.a.	17	25%	41%
Allergy testing	n.a.	16	23%	34%
Lung function	n.a.	11	16%	25%
Peak flow	n.a.	6	9%	15%
Referred to a pediatrician	n.a.	15	22%	37%
Advice for new evaluation, if symptoms return	n.a.	14	20%	34%
Medication	**No 42 (61%)**	**Yes 27 (39%)**	**% of 69**	**% of 41**
Reliever	n.a.	26	38%	96%
Inhaled corticosteroids	n.a.	12	17%	44%
Other medications	n.a.	5	7%	18%

n.a. = not applicable

Discussion

Two thirds of parents visited a physician after they had been informed that their child might suffer from asthma. Willingness to follow-up the recommendations was higher for children with more severe airway reversibility, and if the mother was not highly educated. Previous studies reported parental initiated response rates ranging from 12% to 40%.[5-7] In addition, we demonstrated that parents underestimated the severity of current symptoms in their child.

A worse lung function in children visiting a physician might explain their visit because they experienced more symptoms, despite a similar prevalence rate of asthma symptoms. Alternatively, parents may have noticed more symptoms in retrospect, when confronted with the letter recommending medical evaluation by their GP, than before the start of the study period. Clark et al. showed that children with intermittent disease reported more symptoms after following an education program, probably because of a higher awareness of symptoms.[8] This suggests that knowledge about asthma symptoms is limited and that future health care programs might benefit from improving public recognition of asthma.[9] However, we did not collect data on parental symptom perception, and thus cannot conclude if recall bias occurred.

We found an inverse relation between educational level and visiting a GP. Butz et al found that lower education level of the caregiver was associated with the child more frequently receiving adequate preventive asthma care.[10] Other studies have shown that lower parental education is associated with medication underuse.[11,12] Highly educated parents might refrain from a physician's visit due to fear of medical or psychosocial consequences as pharmacologic side effects, limitations on social participation or stigmatization. Consequently, highly educated parents might be more confident in making health care decisions and undertake environmental sanitation or change their smoking behavior before seeking medical advice.

There are several explanations for the percentage (40%) receiving medical treatment. Parents and GPs might be convinced that at the moment of the visit there are too few symptoms to warrant treatment. The advice of the GP to return for evaluation, if the symptoms recur, takes the variability of asthmatic disease into account. Furthermore, the GPs limited knowledge about interpreting BHR tests might have influenced their response.

Refusal to visit a GP visit may represent a lack of confidence in our study's ability to identify problems, or a low expectation of asthma management.[13-16] Furthermore, the asthma symptoms might have represented intermittent asthma that had resolved by the time the parents received the recommendation letter.[17,18] However, this would be in contradiction to our previously results showing a lower quality of life and higher school absence in children with "possible" asthma than healthy controls.[3]

Loss to follow-up might have influenced our results. However, we have no reason to believe there was any systematic non-response. Symptom awareness and perception prior and after the report of "possible asthma" may have induced recall bias either by underreporting symptoms at the initial questionnaire, or excess report of symptoms after receiving the diagnosis of "possible" asthma. Selection bias might have influenced our results: i.e. parents who were aware of respiratory symptoms might be more likely to have their children participate in our study. As we have collected no data directly from the GP, parental interpretation of the visit might have influenced our results. Differences in knowledge about asthma and/or interpretation of the lung function tests between GPs might have influenced their response, since the GPs received no instructions about preferred behavior to possible asthma.

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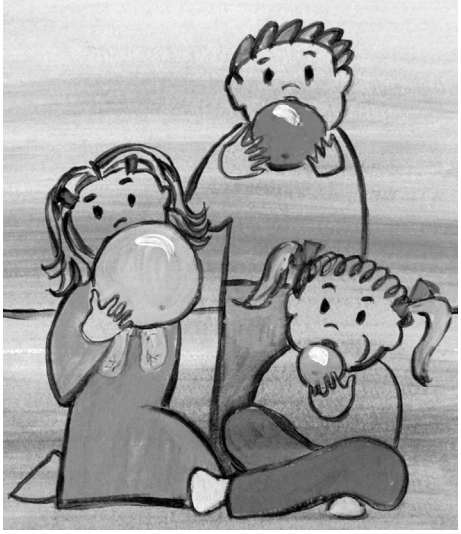

Chapter 8

Discussion and recommendations for further research

This chapter focuses on the main findings emerging from our studies, and directions for future research. The following questions were addressed in this thesis:

1) What is the prevalence of undiagnosed asthma?

In our population-based study conducted in the southern part of the Netherlands, we found a prevalence of 8% undiagnosed asthma. In the literature, the prevalence of undiagnosed asthma is reported to range from 3.9% in Dutch general practice, to 5% in a Danish survey, to 11.7% among urban schoolchildren in the USA.[1-3] Differences in reported prevalence might be an indication of real differences in the prevalence of undiagnosed asthma, or might also be caused by differences in the timing of the studies, population samples, methods used to classify undiagnosed asthma, variability of asthma symptoms, or in the medical care or health beliefs in the population studied. Because there is no universally applied objective set of diagnostic criteria for asthma, our diagnostic approach may identify a different subset of asthma patients than when applying other diagnostic methods. In our investigations, the diagnosis was mainly based on a symptom questionnaire and on lung function measurements.

Questionnaire

In our studied population, the use of a self-report questionnaire to diagnose asthma might have led to an underestimation or an overestimation of the true prevalence of undiagnosed asthma. The ISAAC questionnaire explores all recent symptoms of cough and wheeze, which might result in overestimation of the prevalence of childhood asthma.[4] It is known that self-report questionnaires can result in a large variability in response from both patients and their parents.[5-7] For example, symptom questionnaires might be biased due to recall bias. In addition, parents may not witness every asthma symptom that is experienced by their child. Although the ISAAC questionnaire has some limitations, it has the advantage that it allows to compare results obtained by different studies. In our study, a small group of the children with undiagnosed asthma used inhaled corticosteroids. A possible explanation for this might be that the parents misunderstood the asthma diagnosis that was made by the GP. In the asthma definition used in the current study we did not incorporate a minimum frequency of symptoms of undiagnosed asthma, which might have led to the inclusion of relatively more children with mild asthma. In addition, our data do not allow to classify the children according to their level of severity, which might comprise a priority for asthma treatment and education.

Lung function

In addition to the self-reported symptoms, we used objective parameters to characterize our study population. However, there is an ongoing debate concerning the actual value of these measurements in epidemiologic studies, because such measurements are both costly and time consuming. Although Toelle et al. concluded that bronchial hyperresponsiveness plus recent wheeze is the most useful definition to date for measuring the prevalence of clinically important asthma in populations, others did not agree with this.[3,8-10]

Table 1 shows the outcomes of different parameters tested against the gold standard of a physician's diagnosis of current asthma.[11] The bronchial hyperresponsiveness (BHR) test on its own has a high specificity (87 - 92%) but its sensitivity is low (36 - 47%), which may have led to underestimation of the actual prevalence of undiagnosed asthma. Further, the positive predictive value of the combination of the BHR test and the questionnaire is higher than that of the questionnaire alone (74% vs 64%), which increases the proportion of correctly classified undiagnosed children.[4] However, the lower negative predictive value of the combination of the BHR and the questionnaire compared to the questionnaire alone (84% vs 94%) may have led to a lower prevalence of undiagnosed asthma.

To decrease the proportion of children with 'missed' undiagnosed asthma, we added lung function reversibility to our definition of undiagnosed asthma. In addition, reversibility could be tested in children whose resting lung function was too poor to allow a BHR test. Addition of the lung function test to the diagnostic parameters may improve the precision of diagnosis, but might have affected our response rate (thereby increasing selection bias).

Table 1: Parameter estimates of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) between response to questionnaires, bronchial hyperresponsiveness (BHR) and hypertonic saline vs physician diagnosis of current asthma

	Sensitivity	Specificity	PPV	NPV
Questionnaire vs diagnosis	85%	81%	61%	94%
BHR vs diagnosis	54%	89%	64%	85%
Questionnaire + BHR vs diagnosis	47%	94%	74%	84%

Future studies

Future investigations should use the recently developed and validated asthma control questionnaires.[12] Also, in future studies some of the new diagnostic methods may be helpful in providing a more accurate diagnosis of asthma. Fraction of exhaled nitric oxide (FeNO) measurement is a relatively new non-invasive technique to quantify airway inflammation. Measurement of FeNO might be more appropriate for use in children than the more time-consuming BHR tests. Also, because most asthma cases in a population are mild, exhaled NO might be a more sensitive marker of asthma and allergy than spirometric indices, and might also be suitable as an adjunct to questionnaires in the evaluation of asthma in the general population.[13,14] Although FeNO can be used to titrate inhaled corticosteroids in the treatment of childhood asthma, it remains to be established whether a single FeNO measurement is sufficient to 'label' an individual child as asthmatic.[15] A recent community-based study investigating FeNO concludes that it is not a useful tool for identifying children with asthma, as increased levels did not discriminate between those with asthmatic and those with atopic symptoms.[16]

Exhaled breath condensate (EBC) is another relatively new non-invasive method to study airway inflammation and reflects the composition of the fluid lining of the airway. In children it might have an additional value to exhaled NO as a non-invasive inflammometer.[17] Although not specific to airway inflammation, detection of inflammatory markers in the urine might be an interesting and easily collectable parameter to explore. Furthermore, lung function impairment is inconsistently associated with airway remodelling and is easily obtained. By using the above-discussed endpoints, follow-up of the present study population might provide additional information about the natural history of asthma, remodelling, and the progression of asthmatic disease.

2) What is the impact of undiagnosed asthma on daily life?

Our study has shown that children with undiagnosed asthma have a lower quality of life, more frequent school absence, and a lower lung function (FEV_1) compared with healthy controls. In contrast, we did not find differences in physical activity between children with undiagnosed asthma, those with diagnosed asthma, and healthy controls. However, excessive body weight was found to be associated with additional loss of quality of life in children with asthma. This implies that children with both asthma and

excessive body weight might benefit from treatment for both conditions.

According to the ICF model (see Chapter 2, Figure 2) we can describe the consequences of undiagnosed asthma. Using the three components of function and of disability, the domain of body functions is a physician-centred outcome; i.e. changes in lung function are often not recognized by the patient, making it difficult to use this component as an outcome goal. The other two components of functioning and of disability can be categorized as patient-centred outcomes: i.e. activities (running, cycling) and participation (sport, social functioning, school, quality of life). The contextual factors of the ICF model, i.e. environmental factors (smoking, air pollution, asthma education) or personal factors (self-confidence, mood, coping, upbringing), emphasize the broader concept which is needed in asthma care.

Lung function

Our study shows that the lowest FEV_1 occurs in undiagnosed children compared with children with diagnosed asthma and healthy controls. This is in agreement with earlier studies reporting that undertreated asthmatics show a greater loss of FEV_1 than healthy subjects; this is comparable to the observed fall in FEV_1 in chronic pulmonary disease and cystic fibrosis and appears to be related to duration and severity.[18] In our study population we did not evaluate the response of lung function to treatment with inhaled corticosteroids. Some children may have already developed abnormalities of lung function early in the course of asthmatic disease, whereas others may have a progressive decline in lung function.[19-21]

Physical activity

In contrast to other studies, we found no differences in measured physical activity levels between children with undiagnosed asthma, those with diagnosed asthma, and healthy controls.

The lower scores measured in the physical domain of quality of life in children with undiagnosed and diagnosed asthma compared with healthy controls seem in contrast with the scores measured with the accerelometer, diary and the habitual activity estimation scale.

There are several possible explanations for this finding: 1) the methods used in our study to measure physical activity are not sensitive enough to show differences between

our three study groups; 2) although physical activity was found to be of the same duration in the three study groups, the intensity of activity might differ between groups and these latter differences might explain the differences in quality of life; and 3) the perception of physical activity is a broader component than merely being able to participate in physical activity. For instance, physical activity might be possible but only after inhalation of a reliever before that activity; consequently, children who may not like to use a reliever might experience a lower quality of life. Other issues that might influence a child's perception of physical activity include: no free choice in which sport the child may want to participate, the behaviour of parents regarding physical activities (e.g. restrictions), feeling different from peers during physical activity, etc.

Quality of life

The participation component in the ICF model can be evaluated with the quality of life questionnaires. Severity and control of asthma are independent contributors to quality of life.[22] In addition to a higher school absence among children with undiagnosed asthma, generic questionnaires might have provided supplemental information about general health status, e.g. about sleeping or gastrointestinal problems. Although we considered disease-specific quality of life questionnaires to be appropriate for our study, generic questionnaires might have yielded additional information about the decreased quality of life in the children with undiagnosed asthma. In addition, generic questionnaires would have made comparison with other chronic diseases possible. Overall health-related quality of life is reported to be lower in children with asthma than in healthy controls and comparable to other chronic diseases.[23]

In our study, excessive body weight is associated with an additional decrease in quality of life in children with asthma. There is an ongoing debate as to whether asthma leads to obesity or whether obesity leads to asthma.[24,25] Proponents of the former relationship propose that poor lung function leads to inactivity which then leads to excessive body weight. This latter view has been challenged by prospective evaluations in women that show that increased body mass index precedes development of asthma.[26] Although for some asthmatic children excessive body weight may indeed be caused by a decreased level of physical activity, we could not demonstrate differences in physical activity between children with asthma and healthy controls. Other mechanisms, such as the adipocyte influence on airway smooth muscle or shared genetic risks, might be responsible for the additional decrease in quality of life. Since both conditions occur frequently together in an estimated 40,000 children in the Netherlands, the effect of

these conditions on asthma care, disease severity and health care resources is substantial. The observation of weight loss leading to improvement of asthma, supports the importance of initiatives to reduce the increase in excessive body weight.[27]

Future studies

Although specific elements of long-term asthmatic airway inflammation, like remodelling, remain poorly understood and the clinical significance is still controversial, there is evidence that airway remodelling influences the clinical expression and natural evolution of asthma and that remodelling might begin in childhood.[28,29] The degree to which abnormal lung function and airway remodelling are reversible remains unclear.[29] Prevention of airway remodelling has the potential to decrease asthma severity in adulthood, to improve asthma control, and to prevent disease expression. Follow-up of our study population should provide additional information about the natural course of remodelling and the effect of treatment in these children.

Measurement of physical activity in children remains difficult. Children tend to have short bursts of activities that are more difficult to measure, in contrast to the more circumscribed activities in adults.[30] The use of accelerometers seems to be the most promising method for objective measurement of physical activity, because questionnaires or diaries are more dependent on the effort of children and parents to complete them. Physical activity has four components, i.e. intensity, type, duration and frequency. With regard to these aspects the current generation of accelerometers has some limitations: they selectively record movement of a specific part of the body to which the accerelometer is attached so that activities such as swimming and cycling can not be adequately measured, and accerelometers have limited power to differentiate between types and intensities of physical activity.[31,32] To study physical activities in more detail, more sophisticated and less expensive accelerometers are needed that can better differentiate between different types and intensities of physical activities. The next generation of accelerometers will likely provide more detailed information, because they will use multisensor devices applied at different body segments, or combine accerelometry with physiologic sensor(s) in a single device.[31]

In our study we did not evaluate components of contextual factors of the ICF model, i.e. environmental factors (air pollution, asthma education) or personal factors (self-confidence, mood, coping). Sufficient psychosocial coping resources (self-efficacy, self-esteem, and social support) and an adequate coping style (avoidant, rational and

emotional) may have a beneficial effect on quality of life, sport participation, and on recognizing asthma symptoms. Until now, little research has been directed at these associations and certainly not among patients with asthma. Some of the existing scales can be used for further research. The Child Behavior Checklist (CBCL) measures parent-reported evaluation of behavioural and emotional problems, social competence, and school competence. There are no standardized instruments to evaluate coping in children under the age of 12 years. In adolescents, coping mediates the negative relationship between severity of asthma and quality of life, suggesting that interventions based on changing coping strategies may be an approach to improve quality of life in adolescents.[33]

Further longitudinal studies are needed to explore coping behaviour and the effects of childhood asthma into adulthood; e.g. to what extent childhood asthma affects the final education level and adult employment.

What are possible explanations for undiagnosed asthma?

Our study has shown that children with undiagnosed asthma and bronchial hyperresponsiveness (BHR) have a worse perception of dyspnoea compared with children with diagnosed asthma and BHR. Although this might play a role in being undiagnosed, these results are not generalizable for all children with undiagnosed asthma.

From a theoretical point of view, a proper diagnosis of asthma is dependent on consecutive processes in which patients, caregivers, and physicians each play a role.

1. Patient perceives the respiratory symptoms
2. Patient or caretaker wonders whether it is a disease
3. Patient and caretaker decide to see their general practitioner
4. Physician accepts symptoms as being asthma-like
5. Physician tests asthma hypothesis
6. Physician chooses the right tests at the right time

In this study we focused on the first three steps of this process. Feelings of significant breathlessness result from a mismatch between central respiratory motor activity and the incoming information from receptors in the airways, lungs, and chest wall structures. However, dyspnoea, is merely a sensation which arises from multiple sources rather than from stimulation of a single neural receptor. Furthermore, the

severity of dyspnoea as well as the sensation of breathlessness varies widely among patients, and patients with prolonged airway obstruction perceive these symptoms less well.[34] Components of breathlessness include quality, intensity, duration, frequency, and the amount of distress or discomfort.

The recognition of and associating symptoms with asthmatic disease might be difficult for parents as well as for others who observe children in some capacity, e.g. teachers and sport trainers. Psychological variables (such as denial or defensive coping style), smoking behaviour, parent-child variables, and intelligence level may also affect the appraisal and interpretation of symptoms.[35-38] Miscommunication about observed symptoms between those involved in the daily life of children (e.g. teachers, daycare professionals, sport trainers) and their caretakers might be a barrier for recognizing symptoms.

Future studies

Failure to detect and treat symptoms can lead to emergency healthcare use, near fatal, and even fatal attacks.[39-42] Conversely, a child's oversensitivity to asthma may be associated with greater asthma morbidity. Poor perceivers require extra attention in order to make a proper diagnosis of asthma. Discrimination between poor and normal perceivers of dyspnoea might contribute to a treatment program tailored to the individual patient, i.e. improving their perception of dyspnoea or selecting other indicators (e.g. FeNO, BHR) to optimize asthma control. Perception of dyspnoea can be measured during a BHR test, although routine testing of BHR in children is not currently common practice. Instead, evaluating perception of dyspnoea during airway reversibility testing or office peak flow measurement is more convenient to use in children.

To prevent subsequent loss of lung function, poor perceivers might be provided with airway hyperresponsivness-driven asthma treatment.[43] Using FeNO as inflammometer seems attractive; however, the case for using FeNO to titrate steroids is not yet proven.[44] Moreover, low compliance of parents and children might be a barrier to implementing this type of physician-centred strategy. Improving dyspnoea perception in poor perceivers is possible by treating with inhaled corticosteroids, training of perceiving airflow obstruction, or feedback involving false sounds of wheezing.[45-47] Future studies exploring these different strategies should also evaluate cost-effectiveness, barriers for implementation in daily care, quality of life, symptom-free days, emergency room visits, and airway remodelling.

Should children with undiagnosed asthma be treated?

There is a gap between an asthma diagnosis based on epidemiologic criteria and the individual judgement of the general practitioner (GP). In our study, all children who were diagnosed as asthma were advised to visit their GP; the majority of parents did visit their GP for possible asthma in their child. Our data did not allow classification of the children by levels of severity, which might comprise a priority for asthma treatment and education. This may explain why some patents refused to visit the GP after a positive test. This phenomenon might also explain the low percentage of children for which parents and GPs felt that it was justified to treat these children.

Although we could not find a lower physical activity, we did find a lower quality of life and more school absence among children with undiagnosed asthma. However, these patient-centred factors did not translate into a need for asthma treatment in 60% of these children. Furthermore, poor perception of dyspnoea and subsequent unrecognized symptoms might play a role in treatment decisions; however, our study was not designed to evaluate differences in dyspnoea perception between treated and non-treated children.

Future studies

In the present study, the short follow-up period (2 months) might have had an effect on the percentage of treated children. Follow-up of the present study cohort could be used to evaluate the development and remission of asthma and asthma-related symptoms. The high prevalence and impact of undiagnosed asthma combined with available treatment options and the willingness of parents to visit the GP makes our study population suitable for a screening program. However, because this study was not designed to evaluate a screening program for undiagnosed asthma, the choice of the best screening instrument, the cost-effectiveness, and the timing of a screening program remain to be assessed.

Conclusion of this thesis

Our study shows that the majority of school children with asthma remain undiagnosed. The impact of undiagnosed asthma in daily life is substantial; i.e. children have a poorer lung function, lower quality of life scores and a higher school absence than their healthy peers. High suspicion of undiagnosed asthma is warranted in school-

age children with substantial school absence, respiratory symptoms, or less specific symptoms (i.e. fatigue or sleeping problems). Children, caregivers, physicians and others involved in the daily life of children can play an important role in recognizing asthma symptoms in the community. This might lead to important improvement of functioning and a decrease in the disability of schoolchildren.

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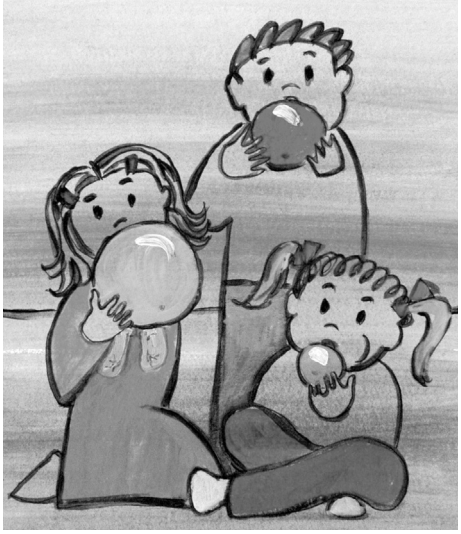


Chapter 9

Summary

Asthma is the most prevalent chronic disease in childhood. To study the actual prevalence and impact of undiagnosed childhood asthma in daily life (i.e. quality of life, participation in physical and school activities) we performed a survey in schoolchildren (aged 7 - 10 years) in the southern part of the Netherlands.

Broadening the instruments of asthma control to non-traditional areas might create opportunities to improve asthma control and minimize the impact of asthma on the health status of children. **Chapter 2** presents a description of the International Classification of Functioning, Disability and Health (ICF). This model gives a broader view on the global health status of children with asthma; i.e. it describes how people live with their health condition. In addition to components of body function (e.g. lung function or hyperreactivity), other important components of functioning and disabilities such as activities (running, cycling) and participation (sport, social functioning, school, quality of life) may be used to evaluate the impact of asthma on daily life. Chapter 2 describes some of these items (i.e. sport participation, social impact, school attendance and quality of life) in children with asthma.

Chapter 3 describes the impact of undiagnosed asthma on daily life. In the present study, we found a prevalence of 8% undiagnosed asthma and 5% diagnosed asthma. Diagnosed asthma was defined as the parents' confirmation of a physician's diagnosis of asthma. Undiagnosed asthma was defined by asthma symptoms combined with airway reversibility or bronchial hyperresponsiveness (BHR). Quality of life was measured with the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) for children, and with the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) for their caregivers. For both questionnaires the scores range from 1 to 7 (score 7 representing maximal quality of life). The PAQLQ consists of three domains, i.e. the emotions domain, activity domain and symptom domain. The PACQLQ consists of two domains, i.e. the emotions domain and activity domain.

Compared to healthy controls, quality of life scores among children and their caregivers were lower if the child had asthma ($p < 0.05$), with the lowest scores found in diagnosed asthma ($p < 0.05$). The scores for the combined domain were, respectively, 5.6 (95% CI; 5.4 - 5.9) for diagnosed asthma, 6.1 (95% CI; 5.8 - 6.3) for undiagnosed asthma, and 7.0 (95% CI; 6.9 - 7.0) for healthy controls. Quality of life scores in caregivers showed a similar pattern. The scores for the combined domain in caregivers were, respectively, 6.3 (95% CI; 6.1 - 6.5), 6.7 (95% CI; 6.6 - 6.8) and 7.0 (95% CI; 6.9 -7.0). Children with asthma reported more school absence ($p < 0.05$), with highest absence rates in those with diagnosed asthma. Children with undiagnosed asthma had the lowest baseline FEV_1 (respectively, 94% predicted for undiagnosed asthma, 98%

for diagnosed asthma, and 100% predicted for healthy controls; undiagnosed asthma vs. healthy controls, $p < 0.001$) which showed the greatest increase after inhalation of salbutamol (9% for undiagnosed asthma, 5% for diagnosed asthma, and 2% for healthy controls; undiagnosed asthma vs. healthy controls; $p < 0.001$, and undiagnosed asthma vs. diagnosed asthma; $p = 0.07$). In conclusion we have shown that children with undiagnosed asthma are impaired in their quality of life, which suggests that this group may benefit from being diagnosed and receiving treatment. This study also shows that in our study population, children with diagnosed asthma still do not meet optimal control even though proper treatment modalities are widely available in the Netherlands.

Since asthma and excessive bodyweight frequently co-exist, we hypothesized that excessive bodyweight may be related to an additional decrease in quality of life in children with asthma. The results of this study are described in **Chapter 4**. Asthma was considered as a possibility if one of the following two criteria was fulfilled: 1) a parent's report of asthma diagnosis, with or without airway reversibility or BHR, or 2) asthma symptoms in the past 12 months combined with airway reversibility or BHR. We found that, compared with the three other groups, children with asthma combined with excessive bodyweight had the lowest quality of life for all domains ($p < 0.01$). For the combined domain, scores were 5.2 (95% CI; 4.5 - 5.9) in children with asthma and excessive bodyweight, 6.0 (95% CI; 5.8 - 6.2) in children with asthma with normal weight, 6.9 (95% CI; 6.9 - 7.0) in healthy controls with excessive bodyweight and 7.0 (95% CI; 6.6 - 7.0) in healthy controls with normal weight ($p < 0.05$ for all comparisons, except between healthy controls with excessive bodyweight and with normal weight). Compared to healthy controls with normal weight, quality of life scores for the combined domain were, respectively, 14% lower in children with asthma and normal weight, and 1% lower in healthy controls with excessive bodyweight. Based on the separate effects for asthma and overweight we expected a 15% lower quality of life score; however, the score for the combined effect in overweight asthmatic children proved to be 25% lower. We conclude that excessive bodyweight is associated with an additional decrease in quality of life in children with asthma. This implies that clinicians should be aware of the interaction between asthma and excessive bodyweight on quality of life and should give extra attention to children with both conditions.

Literature concerning the reasons for having undiagnosed asthma in childhood is scarce; **Chapter 5** addresses this question. We hypothesized that perception of dyspnoea differs between children with undiagnosed and diagnosed asthma. To investigate this, in our study population we evaluated the perception of dyspnoea during

a positive BHR test. The severity of dyspnoea during the challenge test was assessed by both a Borg scale and a visual analogue scale (VAS). The slopes for the Borg/FEV_1 were twice as low in children with undiagnosed asthma compared to children with diagnosed asthma (0.07 and 0.14, respectively; $p = 0.04$). A similar trend was found for the VAS/FEV_1 slope (0.06 and 0.11, respectively; $p = 0.11$). Our results show that children whose parents do not report a physician's diagnosis of asthma appear to perceive bronchoconstriction less well than children with diagnosed asthma. For a number of children this might be an explanation for the delay in asthma diagnosis.

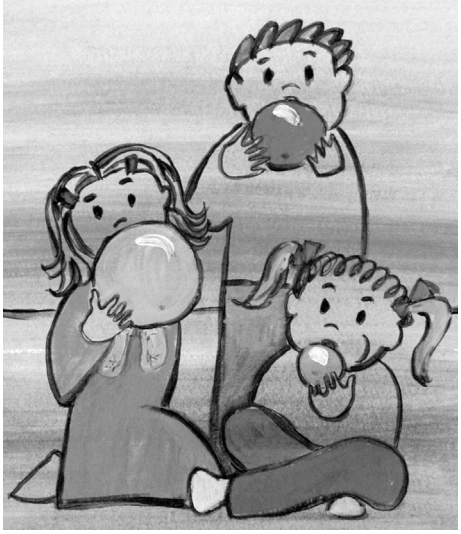
Chapter 6 addresses the question as to whether asthma decreases the physical activity level in children. To explore this we compared the physical activity levels of children with undiagnosed asthma in our study population with children with diagnosed asthma and with healthy controls. Physical activity was measured with both an accelerometer and a diary during three weekdays and during two weekend days, and also with the habitual activity estimation scale (HAES). We found no differences in daily physical activity or in intensity levels of physical activity between children with undiagnosed asthma, diagnosed asthma and healthy controls. Accelerometer scores were 49 for children with both undiagnosed asthma and with diagnosed asthma, and 47 for the healthy controls. According to the diary and the HAES, all three groups performed on average 110 minutes of physical activities per day. Analyses of different intensity levels were performed for the accelerometer, the diary and the HAES, but revealed no differences between the three groups. In conclusion, childhood mild asthma - whether diagnosed or not - does not seem to be associated with a decreased level of daily physical activity compared with healthy controls.

Furthermore, we were interested to explore how parents and general practitioners (GPs) would react to possible asthma in the studied children. Therefore, we assessed the willingness of parents of children with possible asthma to visit their GP - on our advice - and evaluated the actions undertaken by the GPs. **Chapter 7** describes the results of this study. We found a high level of willingness among parents to visit their GP, as two thirds of our parents visited a physician after they had been informed that their child might suffer from asthma. Factors associated with refusal were high maternal education, mild symptoms and absence of airway reversibility. At the end of the program, medical treatment for asthma was started in two out of five children.

This study answers questions about the influence of undiagnosed childhood asthma on daily life, and factors that contribute to underdiagnosis of asthma. However, new answers often generate new questions, or suggest new research topics and approaches.

Chapter 8 therefore focuses on these latter items.

In conclusion, our study shows that the majority of schoolchildren with asthma remain undiagnosed. The impact of undiagnosed asthma in daily life is substantial; i.e. children have a poorer lung function, lower quality of life scores and a higher school absence than their healthy peers. High suspicion of undiagnosed asthma is warranted in school-age children with substantial school absence, respiratory symptoms or less specific symptoms (e.g. fatigue or sleeping problems). Children, caregivers, physicians and others involved in the daily life of children can play an important role in recognizing asthma symptoms in the community. This might lead to important improvement of functioning and a decrease in the disability of schoolchildren.



Chapter 10

Samenvatting

Astma is de meest voorkomende chronische ziekte op de kinderleeftijd. Astma is een chronische ontsteking van de luchtwegen. Kinderen met astma of astmaklachten worden benauwd, ademen 'piepend' of moeten hoesten. In dit proefschrift wordt de huidige prevalentie (het aantal kinderen met astma op een specifiek moment) en de invloed van niet-gediagnosticeerd astma op het dagelijks leven (kwaliteit van leven, participatie in sport en schoolactiviteiten) bestudeerd met behulp van een bevolkingsonderzoek bij kinderen in de leeftijd van 7 - 10 jaar, in het zuidelijk deel van Nederland.

De behandeling van astma kan mogelijk verder worden verbeterd met behulp van niet traditionele instrumenten. **Hoofdstuk 2** beschrijft het ICF-model dat staat voor International Classification of Functioning, Disability and Health. De ICF is een begrippenkader waarmee het mogelijk is te beschrijven welke problemen mensen in hun functioneren ervaren en welke factoren op dat functioneren van invloed zijn. Met dit begrippenkader kan ook de ziekte astma verder worden beschreven. Het begrip "functies en anatomische eigenschappen" bevat bijvoorbeeld de traditionele testen longfunctie en hyperreactiviteit. Andere belangrijke begrippen in het beschrijven van de gezondheidtoestand zijn "activiteiten" (rennen, fietsen) en "participatie" (sport, sociaal functioneren, school, kwaliteit van leven). De begrippen "activiteiten" en "participatie" kunnen worden gebruikt bij het beschrijven van de invloed van astma op het dagelijks leven. Hoofdstuk 2 beschrijft een aantal van deze items; met name sportparticipatie, de invloed op het sociale functioneren, het functioneren op school en de kwaliteit van leven bij kinderen met astma.

Hoofdstuk 3 beschrijft de invloed van niet-gediagnosticeerd astma op het dagelijks leven van kinderen. In de huidige studie vonden we een prevalentie van 8% niet-gediagnosticeerd astma en 5% gediagnosticeerd astma. Een kind had gediagnosticeerd astma als de ouders bevestigden dat hun kind een door een arts vastgestelde diagnose astma had in de afgelopen 12 maanden. Een kind had niet-gediagnosticeerd astma als het kind geen door een arts vastgestelde diagnose astma had in de afgelopen 12 maanden en astmasymptomen had gecombineerd met een reversibele luchtwegobstructie of bronchiale hyperreactiviteit (BHR). De kwaliteit van leven werd gemeten met de Pediatric Asthma Quality of Life Questionaire (PAQLQ) voor kinderen en de Pediatric Asthma Caregivers Quality of Life Questionaire (PACQLQ) voor verzorgers. De PAQLQ bestaat uit 3 domeinen: het emotionele domein, het activiteitendomein en het symptomendomein. De PACQLQ bestaat uit 2 domeinen: het emotionele domein en het activiteitendomein. Kinderen met gediagnosticeerd of niet-gediagnosticeerd astma hadden een lagere kwaliteit van leven dan gezonde controles

voor alle domeinen. De kwaliteit van leven van kinderen met gediagnosticeerd astma was lager dan van kinderen met niet-gediagnosticeerd astma voor alle domeinen. De scores voor kwaliteit van leven van verzorgers toonden een vergelijkbaar patroon. Kinderen met astma hadden meer schoolverzuim, met de hoogste verzuimpercentages bij diegene met gediagnosticeerd astma. Kinderen met niet-gediagnosticeerd astma hadden de laagste FEV_1, die het meeste toenam na toediening van een luchtwegverwijder. In dit onderdeel van de studie hebben we aangetoond dat kinderen met niet-gediagnosticeerd astma een verminderde kwaliteit van leven hebben, hetgeen suggereert dat deze groep baat zou kunnen hebben bij een diagnose astma en zonodig een daarop volgende behandeling. Daarnaast worden de kinderen met gediagnosticeerd astma nog steeds niet optimaal behandeld, terwijl een goede behandeling van astma mogelijk is.

Omdat astma en overgewicht vaak samen voorkomen onderzochten wij of overgewicht een extra daling in kwaliteit van leven van kinderen met astma zou kunnen veroorzaken. De resultaten van deze studie worden beschreven in **hoofdstuk 4**. Voor deze studie werd de volgende definitie van astma gebruikt: 1) een door ouders gerapporteerde diagnose astma met of zonder luchtwegreversibiliteit of bronchiale hyperreactiviteit of 2) astmasymptomen in de laatste 12 maanden gecombineerd met luchtwegreversibiliteit of bronchiale hyperreactiviteit. Kinderen met astma en overgewicht hadden de laagste kwaliteit van leven in vergelijking met alle andere groepen van kinderen voor alle domeinen. Vergeleken met gezonde controles met normaal gewicht waren de scores voor kwaliteit van leven voor het gecombineerde domein respectievelijk 14% lager bij kinderen met astma en normaal gewicht en 1% lager bij gezonde controles met overgewicht. Op grond van de afzonderlijke effecten van astma en overgewicht verwachtten wij een 15% lagere score; echter de score voor de gecombineerde effecten van astma en overgewicht bleek 25% lager te zijn. Wij concluderen dat overgewicht is geassocieerd met een extra daling in kwaliteit van leven bij kinderen met astma. Artsen zouden zich moeten realiseren dat kinderen met astma extra aandacht verdienen als ze ook overgewicht hebben.

Er is weinig literatuur over oorzaken van niet-gediagnosticeerd astma op de kinderleeftijd. **Hoofdstuk 5** beantwoordt de vraag of de perceptie van benauwdheid verschillend is tussen kinderen met niet-gediagnosticeerd astma en gediagnosticeerd astma. Om dit in onze studiepopulatie te onderzoeken, evalueerden we de perceptie van benauwdheid gedurende een positieve BHR-test. De ernst van de benauwdheid gedurende de test werd gemeten met zowel een Borg-schaal als een visuele analoge schaal (VAS). De perceptie van benauwdheid bij kinderen met niet-gediagnosticeerd

astma was twee keer lager dan bij kinderen met gediagnosticeerd astma. Onze resultaten laten zien dat kinderen van de ouders die geen diagnose astma rapporteerden, een vernauwing van de luchtwegen minder goed voelen dan kinderen met gediagnosticeerd astma. Voor een aantal van deze kinderen kan dit een reden zijn voor een latere diagnose van astma

Hoofdstuk 6 beantwoordt de vraag of astma de hoeveelheid lichaamsbeweging vermindert bij kinderen. Hiervoor vergeleken wij de activiteitenniveaus van kinderen met niet-gediagnosticeerd astma in onze studiepopulatie met kinderen met gediagnosticeerd astma en gezonde controles. De hoeveelheid lichaamsbeweging werd gemeten met een versnellingsmeter en een dagboek gedurende 3 werkdagen en 2 weekenddagen en bovendien met de habitual activity estimation scale (HAES). Wij vonden geen verschillen in de hoeveelheid lichaamsbeweging of in niveaus van intensiteit van de hoeveelheid lichaamsbeweging tussen kinderen met niet-gediagnosticeerd astma, gediagnosticeerd astma en gezonde controles. Wij concluderen dat mild astma op de kinderleeftijd -gediagnosticeerd of niet-gediagnosticeerd- niet is geassocieerd met een verlaagd niveau van de dagelijkse hoeveelheid lichaamsbeweging vergeleken met gezonde controles.

Vervolgens onderzochten wij wat ouders en huisarts deden met informatie van mogelijk astma bij de onderzochte kinderen. Hiervoor evalueerden wij de bereidheid van ouders van kinderen met mogelijk astma om de huisarts te bezoeken (na ons advies) en evalueerden wij de acties die door de huisarts werden genomen. **Hoofdstuk 7** beschrijft de resultaten van deze studie. Wij vonden een hoge bereidheid van ouders om de huisarts te bezoeken; tweederde van de ouders bezocht de huisarts nadat zij waren geïnformeerd over de mogelijke astma van hun kind. Oorzaken die geassocieerd zijn met het niet bezoeken van de huisarts, waren een hoge opleiding van de moeder, milde symptomen en afwezigheid van luchtwegreversibiliteit. Uiteindelijk werd een behandeling gestart voor astma bij 2 van de 5 kinderen.

Deze studie beantwoordt vragen over de invloed van niet-gediagnosticeerd astma in het dagelijks leven en factoren die bijdragen tot onderdiagnose van astma. Echter, er worden ook nieuwe vragen opgeroepen en suggesties voor nieuw onderzoek.
Hoofdstuk 8 concentreert zich op deze items.

Concluderend toont onze studie aan dat de meerderheid van de schoolkinderen met astma niet wordt gediagnosticeerd. De invloed van niet-gediagnosticeerd astma op het dagelijks leven is groot: kinderen hebben een lagere longfunctie, lagere scores voor

kwaliteit van leven en een hoger schoolverzuim dan hun gezonde klasgenoten. Een hoge verdenking op niet-gediagnosticeerd astma is aangewezen bij schoolkinderen met meer dan normaal schoolverzuim, luchtwegklachten of minder specifieke problemen (vermoeidheid of slaapproblemen). Kinderen, verzorgers, artsen en anderen die betrokken zijn bij het dagelijks leven van kinderen kunnen een belangrijke rol spelen bij het herkennen van astmasymptomen in de bevolking. Herkenning, diagnose en behandeling kan leiden tot een belangrijke verbetering van het functioneren van kinderen en vermindering van de invloed van astma op schoolkinderen.

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Curriculum Vitae

René van Gent, geboren op 6 september 1966 te Schiedam, behaalde in in 1984 zijn diploma Gymnasium B aan het Stedelijk Gymnasium te Schiedam. Hierna studeerde hij geneeskunde aan de Erasmus Universiteit in Rotterdam, waar hij in 1991 het artsexamen behaalde.
Hij werkte achtereenvolgens als arts-assistent bij de afdeling kindergeneeskunde in het St. Elizabeth ziekenhuis te Leiderdorp en het Refaja ziekenhuis te Dordrecht.
Vanaf juli 1993 werkte hij eerst als AGNIO in het Sint Joseph ziekenhuis te Veldhoven, waar hij vanaf 1994 begon met de opleiding tot kinderarts (opleider Dr. E.J. Lommen). Hij vervolgde zijn opleiding in het Radboud ziekenhuis te Nijmegen (opleider Prof. dr. R.C.A. Sengers).
Aan het einde van zijn opleiding volgde hij een stage kinderlongziekten bij de afdeling kinderlongziekten van het Sophia Kinderziekenhuis te Rotterdam (Prof dr. J.D. de Jongste).
In januari 1999 werd hij geregistreerd als kinderarts en begon hij met zijn loopbaan als kinderarts in Máxima Medisch Centrum te Veldhoven. De eerste twee jaar liep hij 1 dag per week stage bij de afdeling kinderlongziekten van het Universitair Medisch Centrum te Utrecht (hoofd Dr. H.J.L. Brackel en later Prof. dr. C.K. van der Ent). In 2001 ontstond het idee voor dit promotieonderzoek. Zijn aandachtsgebieden zijn kinderlongziekten en acute kindergeneeskunde. Vanaf 2002 is hij instructeur voor de Advanced Paediatric Life Support cursus van de Stichting Spoedeisende Hulp bij Kinderen te Riel. René is getrouwd met Francisca Meyboom, samen hebben zij drie kinderen: Jelle (1998), Koen (2000) en Inge (2002).