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SEVERE ASTHMA AND ASTHMA CONTROL IN SCHOOLCHILDREN

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ABSTRACT

Background: Asthma is a major health problem in children and most troublesome during severe or persistent symptoms. Children with problematic severe asthma have a disproportionate consumption of health care, despite high-dose treatment with inhaled corticosteroids (ICS). Little is known about children with impaired asthma control or problematic severe asthma in regards to prevalence in a normal population, characterisation and classification, and health effects measured as health-related quality of life (HR-QoL).

Aim: The overall aim of this doctoral thesis was to evaluate the burden of symptoms and factors associated with impaired asthma control in schoolchildren.

Materials and Methods: The study population consisted of 3 015 children up to 12 years of age from the prospective birth cohort BAMSE, and children from the Severe asthma study with problematic severe asthma (n = 56) and, for comparison, controlled asthma (n = 39). Parental questionnaires collected data on environmental exposures, asthma symptoms and treatments. In the BAMSE study, asthma control was classified based on parental reports and according to a modified GINA classification. The prevalence of severe asthma with dispensed high-dose ICS was estimated through the Swedish drug register. Evaluations with component-resolved allergy diagnostics, exhaled nitric oxide (FeNO), bronchial hyperresponsiveness to methacholine (BHR), blood count of eosinophils and HR-QoL were applied in the Severe asthma study.

Results: In the BAMSE cohort, a high proportion of children with asthma were classified as impaired in their asthma control (partly or uncontrolled) at 8 years, 84% of 323, and at 12 years, 53% of 329, ($p < 0.001$). Parental report of symptoms varied in these children, with more activity limitation (66% vs. 48%, $p < 0.001$) and wheeze $\geq$ 4 times in last year (52% vs. 38%, $p = 0.002$) at 12 years compared with at 8 years, but fewer with nocturnal symptoms (36% vs. 82%, $p < 0.001$) and less acute healthcare utilization (15% vs. 34%, $p < 0.001$) at 12 years. Severe asthma was prevalent in 0.4% of children in a normal urban population at age 12, or 4% among children with asthma.

Children with impaired asthma control at both 8 and 12 years in the BAMSE cohort (n = 91) and children with problematic severe asthma had more often a family history of allergic disease and comorbidity of rhinitis than children with controlled asthma.

Multi-sensitization to animal-derived components was more pronounced in problematic severe asthma than in controlled asthma, 25% vs. 8% ($p = 0.03$), and was associated with increased eosinophil inflammation as compared with children sensitized to fewer animal-derived components, FeNO 38 ppb vs. 25 ppb ($p = 0.002$), blood eosinophils 0.65 vs. 0.39 ($p = 0.021$), and BHR 112 vs. 28 ($p = 0.002$).

Children with problematic severe asthma were more impaired in HR-QoL than children with controlled asthma 5.4 vs. 6.7 ($p < 0.001$).

Conclusion: A high proportion of schoolchildren reported impaired asthma control. Children with problematic severe asthma have impaired HR-QoL, with effects of limitations in daily activities and reduced emotional well-being. Common factors associated with children having impaired asthma control at both 8 and 12 years and problematic severe asthma were family history of allergic disease and comorbidity of rhinitis.

Key words: Asthma control, Children, Component-resolved allergy diagnostics, Health-related quality of life, Problematic severe asthma

LIST OF PUBLICATIONS

The thesis is based on the four following papers, which will be referred to in the text by their Roman numbers.

I. **Nordlund B**, Melén E, Schultz E, Grönlund H, Hedlin G, Kull I.
Severe asthma and asthma control among schoolchildren: study from the BAMSE birth cohort. Submitted

II. Konradsen JR, **Nordlund B**, Lidegran M, Pedroletti C, Grönlund H, van Hage M, Dahlen B, Hedlin G; In cooperation with the Swedish Network of Pediatric Allergists, Severe Asthma Network. Problematic severe asthma: A proposed approach to identifying children who are severely resistant to therapy. Pediatr Allergy Immunol. 2011 Feb;22(1 Pt 1):9-18.

III. **Nordlund B**, Konradsen JR, Kull I, Borres MP, Önell A, Hedlin G, Grönlund H.
IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobin are markers of bronchial inflammation in severe childhood asthma. Allergy. 2012 May;67(5):661-9.

IV. **Nordlund B**, Konradsen JR, Pedroletti C, Kull I, Hedlin G.
The clinical benefit of evaluating health-related quality of life in children with problematic severe asthma. Acta Paediatr. 2011 Nov;100(11):1454-60.

ADDITIONAL PAPERS

Konradsen JR, **Nordlund B**, Nilsson OB, van Hage M, Nopp A, Hedlin G, Grönlund H.
High basophil allergen sensitivity is associated with severe allergic asthma.
Pediatr Allergy Immunol. 2012 Jun;23(4):376-84.

Orsmark Pietras C, James A, Konradsen JR, **Nordlund B**, Söderhäll C, Pedroletti C, Kere J, Dahlén SE, Hedlin G, Melén E.
Genome wide transcriptome analysis suggests novel mechanisms in severe childhood asthma.
ERJ. 2012

Konradsen JR, James A, **Nordlund B**, Reinus L, Melén E, Söderhäll C, Wheelock Å, Lödrup Carlsen K, Lidegran M, Verhoek M, Boot R, Dahlén B, Dahlén SE, Hedlin G.
Chitinase are markers of airway remodeling in children with therapy resistant asthma.
Submitted.

CONTENTS

1 Introduction 1
2 Background 2
2.1 Asthma – a global health problem 2
2.2 Asthma severity 3
2.2.1 Asthma control 3
2.2.2 Severe asthma 4
2.3 Allergy 6
2.4 Health-related quality of life 7
3 Aim 9
4 Materials and methods 10
4.1 Study Design 10
4.1.1 BAMSE birth cohort 10
4.1.2 Severe asthma study 10
4.2 Study population 13
4.3 Questionnaires 14
4.3.1 Parental health questionnaires 14
4.3.2 Asthma control test 14
4.3.3 Health-related quality of life 14
4.4 Clinical measures 14
4.4.1 Conventional allergy diagnostics 14
4.4.2 Component-resolved allergy diagnostics 15
4.4.3 Inflammation 15
4.4.4 Lung function and bronchial hyperresponsiveness 15
4.5 Definitions and outcomes 16
4.6 Study ethics 17
4.7 Statistics 17
5 Results 19
5.1 Asthma disease in the BAMSE cohort 19
5.1.1 Asthma control 19
5.1.2 Prevalence of severe asthma 20
5.2 Factors in children's history 21
5.2.1 Severe difficult-to-treat asthma 21
5.2.2 Asthma triggers 22
5.3 Lung function and bronchial hyperresponsiveness 23
5.4 Allergy diagnostics 24
5.4.1 Conventional allergy diagnostics 24
5.4.2 Component-resolved allergy diagnostics 25
5.4.3 Animal-derived sensitization and bronchial inflammation 27
5.4.4 Cross-reactivity between lipocalin components 28
5.5 Health-related quality of life 28
6 Discussion 31
6.1 Asthma control 31
6.2 Severe asthma 33
6.3 Factors in children's history 34
6.3.1 Socio-economy and health literacy 34

6.3.2 Family history of allergic disease 35
6.3.3 Rhinitis 35
6.3.4 Triggers 36
6.4 Lung function and bronchial hyperresponsiveness 37
6.5 Conventional allergy diagnostics 38
6.6 Utilizing component-resolved allergy diagnostics 38
6.7 Health-related quality of life 39
6.7.1 Sex differences 40
6.8 Strengths and weaknesses 40
7 Conclusions 42
8 Future perspectives 43
9 Sammanfattning på svenska 45
10 Acknowledgements 49
11 Financial support 52
12 References 53

LIST OF ABBREVIATIONS

ACT	Asthma control test
ATS	American Thoracic Society
AUC	Area under the curve
BAMSE	Swedish abbreviation for Children Allergy Milieu Stockholm Epidemiology
BHR	Bronchial hyperresponsiveness
BMI	Body-Mass-Index
C-ACT	Childhood-asthma control test
CI	Confidence interval
CRD	Component-resolved diagnostics
DRS	Slope of the dose-response curve for the methacholine challenge
EIA	Exercise-induced asthma
ERS	European Respiratory Society
FeNO	Fraction of exhaled nitric oxide
FEV1	Forced expiratory volume in one second
GERD	Gastro-oesophageal reflux disease
GINA	Global Initiative for Asthma
HR-QoL	Health-related quality of life
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
ISAAC	International study of asthma and allergies in childhood
ISAC	Immunosolid-phase allergen chip
ISU	ISAC independent units
LABA	Long-acting beta-2 agonist
LTRA	Leukotriene receptor antagonist
OR	Odds ratio
PAQLQ(S)	Paediatric asthma quality of life questionnaire
PEF	Peak expiratory flow rate
SD	Standard deviation
SPT	Skin prick test
TLA	Temperature-controlled laminar airflow
ROC	Receiver operating characteristic analysis
RV	Rhinovirus
WBC	White blood cell count

1 INTRODUCTION

Throughout the world, asthma is a common disease, especially in children [1]. The pathophysiology of asthma is characterised by airway inflammation and bronchial hyperresponsiveness, which subsequently cause symptoms of wheezing, breathlessness, chest tightness and coughing [2]. There seems to be a combination of genetic predisposition and environmental factors involved in development of asthma symptoms [3-5]. A family history of allergic diseases increases the risk for development of sensitization and persistent asthma [6, 7], but nevertheless, as a part of the complexity of asthma and other allergic diseases, it has been suggested that other non-allergic mechanisms also play a part [8]. Demonstration of inflammation in children with asthma symptoms provides support for the diagnosis of current asthma [9, 10].

Anti-inflammatory treatment improves symptom control and decreases the risk for exacerbations in patients with asthma [11]. According to the Global Initiative for Asthma (GINA) a child's asthma is under control when he or she can play without troublesome symptoms or limitations, sleep without awakening from coughing and avoid serious attacks or declined lung function [12]. For some the asthma symptoms remit during childhood while others have life-long symptoms with health effects. The persistency of symptoms is related to underlying severity. The severity is assessed by the patient's requirement for treatment to achieve good control of symptoms [13]. Those who do not respond to standard therapy appear to have increased burden of symptoms, disproportional consumption of health care [14], and poorer health-related quality of life (HR-QoL) [15]. Asthma severity appears to inversely correlate with children's HR-QoL, including psychological and social wellbeing [16]. In clinical practice, measurement of HR-QoL facilitates identification of the children with the greatest need for improved asthma treatment. For children with persistent symptoms and severe asthma there is an obvious need to improve understanding of poorer response to given treatment and asthma care. It has been demonstrated that psychosocial factors in the family history have effect on health disparities [17]. The patient's and caregiver's abilities to understand and follow basic health information are of major importance for treatment of chronic diseases such as asthma, and defines the skills of health literacy [18]. For health care professionals family limitations in health literacy is a major challenge and requires an individualized approach to offer health care based on the children's and parents' skills to obtain and follow health information.

The clinical guidelines for managing asthma include four essential components of asthma care: assessment and monitoring, patient education, control of environmental and comorbidity factors that affect asthma, and drug treatment. The aim of this thesis was to assess schoolchildren with impaired asthma control and provide knowledge on how to better approach these children with asthma care. The present thesis was based on children in two different cohorts: the population based BAMSE birth cohort with a longitudinal study design and the multi-centre cross-sectional Severe asthma study with a selected material of patients.

2 BACKGROUND

2.1 ASTHMA – A GLOBAL HEALTH PROBLEM

Worldwide, asthma constitutes a major health problem and economic burden [19]. Over 300 million people worldwide are affected by asthma [20], with great variation between countries [21], Figure 1. European studies in schoolchildren estimate an asthma prevalence of 10% [22-24]. In recent years the prevalence seems stationary, but increases in Africa, Latin America and parts of Asia [25].

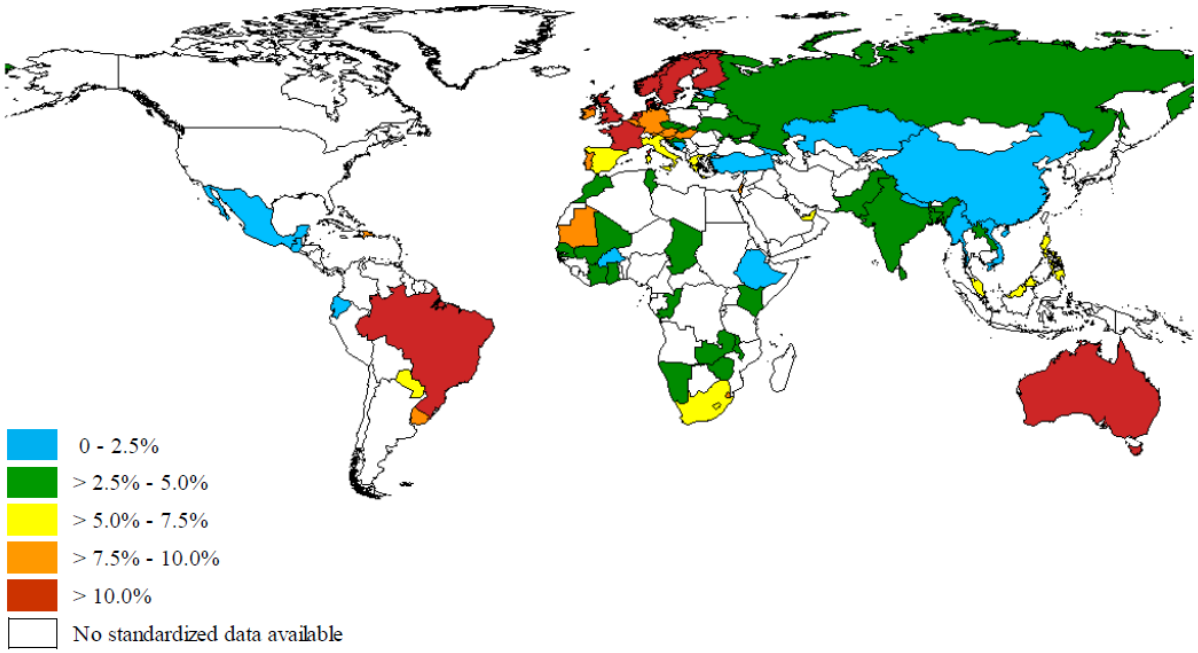

Figure 1. Prevalence of clinical asthma throughout the world based on doctor's diagnosis or intake of asthma medication [21].

Indicators of increased health cost of asthma like e.g. health utilization, medication and lost school/work days are associated with severe and uncontrolled asthma [26]. In undeveloped countries with limited economic resources the proportion of severe symptoms seems to be much higher than in wealthy countries, despite respiratory symptoms of e.g. current wheeze being more common in the wealthy world [27]. In addition, studies have shown that patients with lower socio-economic status are associated with more impaired asthma control [28-30], and further attention is needed to assist patients with impaired asthma control through better management strategies and more effective and cheaper medication.

Literacy can be defined as the skills required for functioning in society, developing knowledge and achieving personal and professional goals. Health literacy has been defined as the degree to which individuals have the capacity to obtain, process, and understand the basic health information and services needed to make appropriate health decisions [31]. Asthma care for patients who have limited health literacy has been shown to be very costly [32], and is more common in certain groups in the society i.e. ethnic minorities, immigrants

and in those with limited education [33]. Adult caregivers with low health literacy are likely to exhibit negative health behaviours that affect their children's health, and the children are likely to use more health care [34]. Possible effects of poorer health literacy in children with severe asthma remain unknown.

2.2 ASTHMA SEVERITY

Asthma is presented in different severities. The severity is influenced by the patient's underlying pathophysiology as well as on environmental exposures and trigger factors [6]. International guidelines recommend stepwise and standardised asthma treatment. The definition of severity is based on the intensity of treatment required for a patient to achieve good asthma control [13]. Schoolchildren from 5 years of age have mild asthma if the asthma is characterized by clinical improvements on low-dose inhaled corticosteroids (ICS), while moderate asthma requires higher doses, up to 400 microgram (budesonide), in combination with long-acting beta-2 agonist and/or leukotriene antagonist [35]. Schoolchildren are classified with severe asthma on basis of a required high-dose of $\geq$ 800 microgram budesonide or equivalent to achieve symptom control [36, 37]. If control is not possible in spite of such high-dose treatment, asthma is classified as problematic severe asthma.

2.2.1 Asthma control

The ultimate goal for all patients is to achieve asthma control. There are various tools for evaluating a patient's asthma control, one is to use validated questionnaires e.g. Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ) [38, 39], another is to evaluate symptoms in patient history based on recommended characteristics from the Global Initiative for Asthma (GINA) [12]. These characteristics emphasize optimal asthma control as no symptoms, undisturbed sleep, no severe exacerbations, no emergency visits, normal lung function and no limitations in daily activities, Table 1. Although the GINA guidelines are not validated, the characteristics are widely used as the golden standard for both clinical research and for asthma care [40, 41]. Based on a patient's number of characteristics, GINA classifies asthma as controlled, partly controlled or uncontrolled [42]. The GINA guidelines include two domains for assessment, the first is the evaluation of symptoms and the second is the patient's future risk for adverse events. Few population-based studies have assessed asthma control during childhood with a focus on different age groups. Treatment and diagnosis may be affected by how children's symptoms are presented and likewise occurrence of specific symptoms may vary during childhood.

Asthma is, as far as we know, a non-preventable disease in children, often requiring regular treatment and health care. The response to treatment differs between patients and the underlying reason for that is largely unknown [14, 43]. Factors in patient's history or environment are recognised to worsen or increase the risk for morbidity i.e. sensitization to allergens, tobacco smoke, family history for disease and comorbidities [3, 44, 45], Effects of psychosocial factors affecting mental health may also have a substantial impact on a child's asthma [46, 47]. The clinical challenge is to support children and caregivers to handle or, if possible, solve or avoid critical health factors. Specific factors associated with persistent asthma in children are largely unknown. In this thesis, children with severe or persistent

symptoms will be compared with children having controlled asthma in order to identify relevant factors that can be highlighted and implemented in children's health care.

Table 1. Characteristics and classification of asthma control according to GINA [12].

	Controlled	Partly controlled	Uncontrolled
A. Characteristics	All of the following	Any measure presented	Three or more features of partly controlled asthma
Daytime symptoms	None (twice or less/week)	More than twice/week	
Limitation of activities	None	Any	
Nocturnal symptoms/awaking	None	Any	
Need for reliever/rescue inhaler	None	More than twice/week	
Lung function (PEF or FEV_1)	Normal	< 80% predicted or personal best (if known)	
B. Future risk assessment ǂ			

ǂ Features that are associated with increased risk of adverse events in the future include: poor clinical control, frequent exacerbations in the past year, admission to critical care for asthma, low FEV_1, exposure to cigarette smoke, high dose medications.

Ï An exacerbation in any week makes that an uncontrolled asthma week and should prompt review of maintenance treatment to ensure that it is adequate.

2.2.2 Severe asthma

Although most children with asthma respond well to given treatment [11], patients with severe asthma appear to be therapy-resistant with an increased risk for exacerbations despite high-dose anti-inflammatory treatment [37]. This heterogeneous group of patients suffers increased burden of symptoms including lost school/work days, increased health care utilization and impaired lung function [19, 48, 49]. Attempts to identify clinical biomarkers for predicting the risk of severe asthma or asthma exacerbation have unfortunately failed. Paediatric health care requires more knowledge on how to improve the health for children with severe asthma. Increased awareness about the burden of symptoms of severe asthma and the effect on children's daily life could facilitate development of health care programs.

There is an obvious need to investigate severe asthma and identify reasons for poor treatment response. To reduce the risk for misclassification when analysing this patient group, the terminology of severe asthma has been revised during the last decade. Problematic severe asthma is an international designation term which is used in the present thesis [50, 51], this definition is adapted to countries where treatment is available and affordable. The term

'problematic severe asthma' refers to first confirming the diagnosis of asthma in children [51], and then subdividing children into two different groups, each carrying different health messages and challenges. The first level is to identify patients with *difficult-to-treat asthma* according to identified aggravating factors that might explain symptoms e.g. untreated comorbidities, poor adherence or environmental factors. For this group it is recommended to approach these aggravating factors before applying novel or advanced therapies [50, 52]. Such a distinction is important so that side effects of ineffective or unnecessary treatment are avoided. The second level is *therapy-resistant asthma*, which despite long-term, high-dose treatment with ICS, is insufficiently controlled, Figure 2. The nomenclature of problematic severe asthma has never been approached clinically in patients. The World Health Organization (WHO) has also adapted the nomenclature of problematic severe asthma with extension to patients in low-income countries having *untreated severe asthma* due to undiagnosed asthma or unavailability of therapy, and for patients which asthma only can be maintained only with the highest level of recommended treatment [53]. In this thesis, two definitions of severe asthma were approached; in the BAMSE study the WHO definition was used for estimation of children with severe asthma in a normal population. The term problematic severe asthma was applied in the Swedish Severe asthma study.

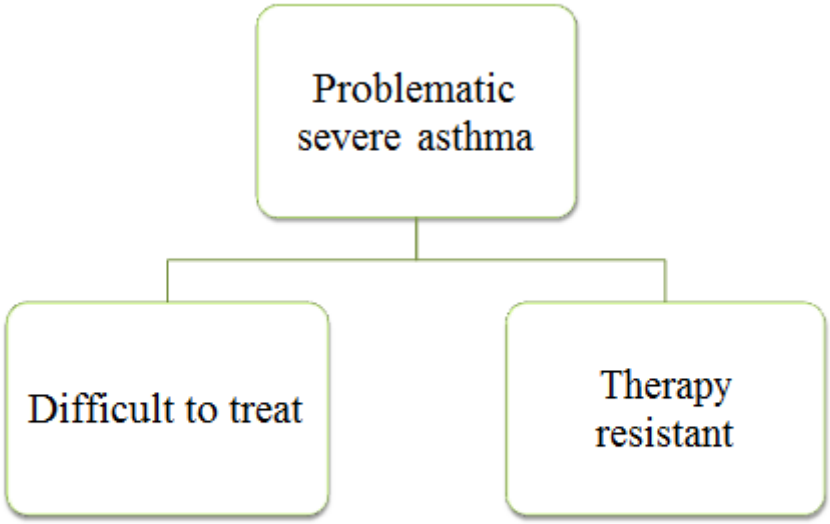

Figure 2. The term problematic severe asthma refers to confirmation of asthma diagnosis and separates patients with difficult-to-treat asthma according to identified aggravating factors from those with severe therapy-resistant asthma [50].

The prevalence of severe asthma is largely unknown, although this patient category has yielded a lot of research interest in recent years [54-56]. The majority of studies published to date have analysed a selected group of patients. A population-based study may improve estimation of prevalence and add generalizable information about this morbidity.

2.3 ALLERGY

According to S.G.O. Johansson et al. *"Atopy is a personal and/or family tendency, usually in childhood or adolescents, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema"* [57]. The term atopy is thus reserved for describing a person's genetic predisposition to become IgE-sensitized to allergens. Development of allergic symptoms and sensitization is more common in children with family history of atopy [58, 59]. Association between asthma and sensitization to primary aeroallergens is common in children with asthma [24, 60]. To define allergy in children with asthma a positive skin prick test or presence of IgE in serum is required [61].

The nomenclature describes allergy as a hypersensitivity reaction initiated by specific immunological mechanism [57]. Sensitization to allergens is common in schoolchildren with asthma [44]. The sensitization starts in the mucosa when antigen-presenting cells uptake allergen and present it to naïve T cells, Figure 3. T cells differentiate into Th2 cells and induce naïve B cells to switch and become IgE-producing B cells and memory B cells.

IgE-mediated reactions to harmless antigens or allergens induce immunological responses and cause immediate allergic symptoms e.g. rhinitis, asthma or anaphylaxis. The immediate allergic reaction induces degranulation release of histamine upon allergen cross-linking of surface-bound IgE on mast cells and basophils. A late-phase response causing increased allergic inflammation occurs at the site of the allergen exposure, initiated by allergen-presenting Th2 cells. Activated Th2 cells signal for cellular recruitment of eosinophils, activated to release inflammatory mediators, chemokines and cytokines.
Conventional diagnostics of sensitization recommend *in vivo* use of the skin prick test (SPT) [62], or *in vitro* measuring specific IgE antibodies in serum [63]. In this thesis, a positive SPT response or specific IgE antibodies towards any of the tested allergens was designated as sensitization. However, traditional diagnostics have limitations in their concordance and in the quantification of sensitization [61, 64]. Thus, as extract-based diagnostics contains the whole nature of an allergen, various specific IgE antibodies could react to the same single allergen, containing different allergenic components. In clinical practice, this poses a limitation in determination of patient's primary sensitization. Component-resolved diagnostics (CRD) is a new method for measuring specific IgE towards single allergen components *in vitro*, the measurement can be either singleplex or multiplex, e.g. by using an allergen microarray chip [65]. The clinical usefulness is under validation, but the main advantage of using CRD is that it enables the identification of cross-reactivity or species-specific components and components associated with mild/local reactions to severe/systemic reactions [60, 66-68]. To date, the practical use and identification of clinically relevant allergenic components among schoolchildren with problematic severe childhood asthma has not yet been proven.

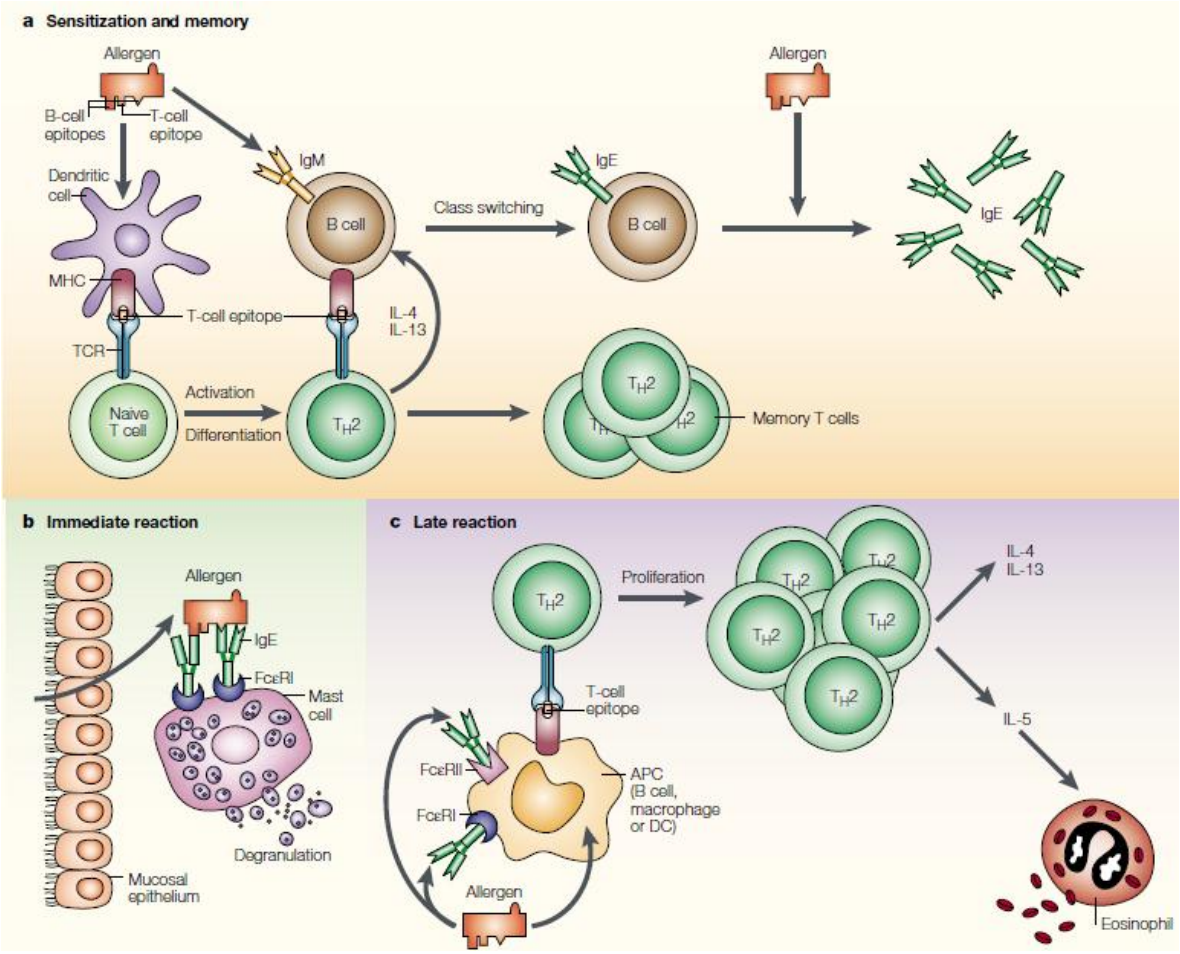

Figure 3. Overview of the allergic immune response, with permission from [69]. (A) Sensitization and memory of allergen initiated by antigen-presenting cells (e.g. dendritic cells) in mucosa presenting allergen to naïve T cells. T cells differentiate into Th2 cells that induces a class switch from naïve B cells to IgE-producing B cells. (B) Immediate allergic reaction causing degranulation of mast cells and release of histamine. (C) Inflammatory late-phase reaction initiated by allergen-presenting Th2 cells recruiting eosinophils and activating release of inflammatory mediators, chemokines and cytokines.

On-going exposure to aeroallergens is associated with increased bronchial inflammation and risk of exacerbations in severe allergic childhood asthma [70]. In order to define relevant strategies for allergen avoidance and treatments, analysed IgE may be used to visualize sources of exposure and identify underlying sensitization [71]. Defining sensitization in problematic severe asthma is complex, due to extensive multiple sensitizations, and thus the protocol recommends the use of several diagnostic methods in children with problematic severe asthma [72].

2.4 HEALTH-RELATED QUALITY OF LIFE

For the purpose of collecting valuable information about the patients' own perceived health, validated questionnaires of health-related quality of life (HR-QoL) could be used. The broad definition of HR-QoL covers different aspects and dimensions of health. By agreement this includes general health, physical functioning, physical symptoms, emotional functioning, cognitive functioning, role functioning as well as social wellbeing and functioning [73]. Since there is a wide variation of aspects, different instruments address quality of life in

different ways. There are some generic instruments which cover several aspects of the conditions with the advantage of enabling comparison of scores between patients with various diseases or against general population. These generic instruments may fail to have enough sensitivity to detect differences of particular concern in specific patient groups. Therefore, disease-specific instruments have been developed. As young children may have difficulties in understanding questions, parents need to add important information on their child's behalf. To overcome children's difficulties with literacy, Juniper et al. have constructed an interview-based instrument to assist these children [74]. Importantly, aspects of health experiences may vary between children and parents [75], and such differences may be captured with HR-QoL assessment.

Paediatric studies have found association between asthma severity and impairment in HR-QoL [76, 77]. and suggested that children with poor HR-QoL would benefit from psychological evaluation and support [78]. Few studies have evaluated HR-QoL in children with asthma longitudinally, but Sundell et al. found improvements over time in adolescents, especially in females performing regular physical activity [79]. For children with the most severe disease, as patients with problematic severe asthma, the health situation is poorly described and needs further analysis.

3 AIM

The overall aim of this doctoral thesis was to evaluate the burden of symptoms and factors associated with impaired asthma control in schoolchildren. In particular it set out to:

- Estimate the prevalence of severe asthma and evaluate asthma control in childhood asthma based on a prospective Swedish birth cohort (paper I).

- Identify factors in patient history or clinical measures associated with impaired asthma control and/or problematic severe asthma as compared with controlled asthma (paper I and II).

- Utilize component-resolved allergy diagnostics in children with problematic severe asthma and controlled asthma (paper III).

- Evaluate health-related quality of life in children with problematic severe asthma and controlled asthma (paper IV).

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

The doctoral thesis is based on two different cohorts; the population-based longitudinal birth cohort BAMSE (paper I), and the cross-sectional Swedish multicentre cohort of the Severe asthma study (paper II, III and IV).

4.1.1 BAMSE birth cohort

All children born between February 1994 and November 1996 in a predefined area of Stockholm, Sweden were invited to participate in the cohort. The recruitment area was selected to represent both urban and suburban environments with a representative variation of buildings and socio-economy

A total of 7 221 children were born during the relevant period, of these 477 were unreachable due to incorrect address, 1 399 never answered or declined participation and 1 256 children were actively excluded. Exclusion was done if the family planned to move within 1 year of study enrolment, in case of insufficient language skills in Swedish and if the child was seriously ill or an older sister or brother was already included in the study. This resulted in a final cohort of 4 089 new born infants.

To analyse if the non-respondents and the actively excluded children differed in relation to key exposures such as parental history of allergic disease, and exposure to parental smoke, a short questionnaire was sent by mail to 1 418 families with a response rate of 67%. The result revealed that parental history of allergic disease was comparable between the included and not included children, although parental smoking was more prevalent among not included children.

Children in the BAMSE cohort were followed from study enrolment, and after 1, 2, 4, 8 and 12 years. Almost 84% (n = 3 431) were evaluated at 8 years and 82% (n = 3 346) at 12 years [24].

4.1.2 Severe asthma study

An invitation to participate in the Severe asthma study was sent to paediatric allergists at 27 paediatric clinics throughout Sweden. The clinics were represented by members in the Swedish severe asthma network. A mobile team consisting of two researchers, Jon Konradsen and Björn Nordlund, visited all the 15 participating clinics and conducted data collection on site, bringing along and utilizing the same equipment, to ensure a standardized data collection of biological samples and measurements, Figure 4.

Skellefteå, n = 1
Umeå, n = 1
Sundsvall, n = 1
Falun, n = 1
Uppsala, n = 7
Karolinska Universitetssjukhuset, n = 52
Sachsska barnsjukhuset, Stockholm, n = 5
Jönköping, n = 1
Växjö, n = 2
Trollhättan, n = 3
Karlstad, n = 2
Göteborg, n = 6
Helsingborg, n = 2
Malmö, n = 10
Linköping, n = 2

Figure 4. Localisation of paediatric clinics and numbers of children from each respective clinic in the Swedish Severe asthma study, n = 96.

Schoolchildren and adolescents 6 to 18 years with problematic severe asthma and controlled mild-moderate asthma were recruited. Children with problematic severe asthma used daily high-dose of ICS (≥ 800 µg budesonide or equivalent) and children with controlled asthma daily low-to-medium dose of ICS (100 – 400 µg budesonide or equivalent). The patients with problematic severe asthma and controlled asthma were age-matched to within 12 months. Inclusion criteria are listed in Table 2. The study was open for inclusion from January 2007 to June 2009. Patients were referred by participating clinics or by review of journal charts by Björn Nordlund. The children referred in this manner were invited by mail, telephone or verbally in connection with a clinical visit. In addition, acceptable medical adherence was required and defined as regular scheduled visits to the doctor and not having missed more than three doses of control medication per week (as documented in report provided by child/parent). Study exclusion criteria were other lung diseases than asthma, such as vocal cord dysfunction, cystic fibrosis and immune deficiency or serious neurological diseases or major lung surgery as well as premature birth (< 36 weeks of gestation age).

Table 2. Inclusion criteria for patients of the Severe asthma study.

Problematic severe asthma	Controlled mild-moderate asthma
Major criteria: (all required)	**Major criteria: (all required)**
▪ Physician-diagnosed asthma	▪ Physician-diagnosed asthma
▪ Daily high-dose (≥ 800 µg/day budesonide equivalent) ICS treatment in combination with LABA and/or LTRA[†]	▪ Daily low- to medium-dose (≥100 and ≤ 400 µg/day) ICS treatment[‡]. Either LABA or LTRA use accepted.
Minor criteria within preceding 12 months (minimum one required)	**Minor criteria within preceding 12 months (all required)**
▪ ≥1 emergency hospitalisation	▪ No hospitalisation
▪ ≥ 2 emergency out-patient visits	▪ No emergency out-patient visits
▪ ≥1 course of oral corticosteroid treatment*	▪ No oral corticosteroid treatment
▪ ≥ 12 exacerbations** of asthma / year or continuous symptoms during ≥ 3 months	▪ ≤ 4 exacerbations of asthma
▪ Asthma symptoms limiting daily activity (including sport or leisure activities) > 2 times a week for ≥ 3 consecutive months.	▪ Only occasional activity-related asthma symptoms during heavy exercise, otherwise without symptoms
▪ Nocturnal asthma symptoms > 2 times a week for ≥ 3 consecutive months.	▪ No nocturnal symptoms
General exclusion criteria for problematic severe asthma and controlled asthma:	
▪ Other lung diseases[×]	
▪ Serious neurological diseases	
▪ Major lung surgery	
▪ Premature birth < 36 weeks of gestation age	

ICS: Inhaled corticosteroid; LABA: long-acting β-2 agonist; LTRA: leukotriene receptor antagonist

[†] High-dose ICS > 6 months preceding year; previous use of LABA or LTRA accepted if discontinued due to no benefit or unacceptable side effects. [‡] ICS dosage increase < 2 weeks during asthma exacerbations. * Oral-steroid bursts were in principle prescribed by a physician. ** Exacerbations of asthma were defined as periods with significantly increased asthma symptoms and (self-administered) increase in medication. [×] Other lung diseases are e.g. vocal cord dysfunction, cystic fibrosis and immune deficiency.

4.2 STUDY POPULATION

The study population of this thesis consisted of children from two cohorts:

- Children of the BAMSE cohort who were prospectively evaluated at age 0 to 12 years with complete data on definition of asthma disease (definition presented in 4.5) at age 8 and 12, n = 3 015. Children in the BAMSE study (n = 3 015) were representative for the original BAMSE cohort at enrolment (n = 4 089) with regard to sex, parental history of allergic disease, socio-economy and tobacco exposure. Mean ages at 8- and 12-year follow-ups were 8.2 years (±0.5 years) and 12.9 years (±0.8 years), respectively.

- Children of the Severe asthma study with problematic severe asthma (n = 56) and controlled asthma (n = 39). Information about recruitment and exclusion of patients is presented in Figure 5. At the time for arrangement of paper II and IV, data were collected from 54 patients with problematic severe asthma. Children with problematic severe asthma and controlled asthma were similar with regard to age (mean 13.2 vs. 13.8 years, p = 0.34), proportion of girls (41% vs. 41%, p = 0.99), Caucasian ethnicity (82% vs. 92%, p = 0.16) and BMI (mean 63 vs. 55 percentile, p = 0.17).

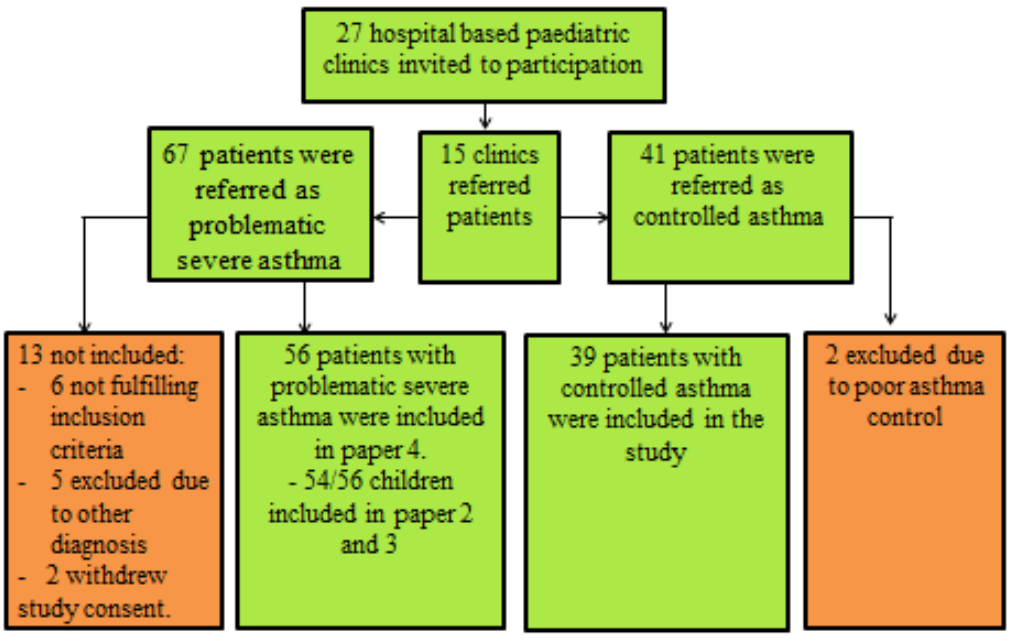

Figure 5. Flow chart over included and excluded patients in the Severe asthma study.

4.3 QUESTIONNAIRES

4.3.1 Parental health questionnaires

In the BAMSE study, data were obtained by parental questionnaire at the time for enrolment (mean age 2 months) to collect information on each child's history of environmental exposures, parental history of allergic disease and life style factors. Information about asthma symptoms, asthma medication, comorbidities and life style factors were obtained by parental questionnaires when children were aged 8 and 12. Body mass index (BMI) kg/m^2 was calculated and cut-off for overweight BMI was set to the 85th percentile of BMI based on children in the BAMSE study, taking sex and age into account [80].

In the Severe asthma study, patients and their parents were interviewed with use of a standardized health questionnaire to obtain information about the children's history of environmental exposures, family history of allergic disease, lifestyle, asthma symptoms, asthma medication, comorbidity and adherence to prescribed medication. In addition, the child's inhalation technique was observed in relation to intake of beta-2 agonist prior to and after lung function testing.

4.3.2 Asthma control test

Validated self-reported asthma control tests were employed for assessment of children's asthma control in the Severe asthma study, the Childhood Asthma Control test® (C-ACT) in the children up to 11 years of age [38], and the Asthma Control Test® (ACT) for children 12 years or older [81]. The scores grade from 0-25 for ACT and 0-27 for C-ACT. Independent of the test used, a score ranging between 0-19 is considered to reflect uncontrolled asthma, whereas controlled asthma is defined by a score of 20 or above.

4.3.3 Health-related quality of life

HR-QoL was evaluated by interviewing patients in the Severe asthma study. The validated Swedish version of the Juniper Paediatric Asthma Quality of Life Questionnaire® (PAQLQ(S)) was applied [82]. This questionnaire has been validated for children aged 7-17, but it was decided to use it for the two 18-year-old subjects as well. The PAQLQ(S) consists of 23 questions divided into three domains termed symptoms, activity limitation, and emotional function. The scores range from 1-7 where 1 represents the greatest impairment possible and 7 represents the least.

4.4 CLINICAL MEASURES

4.4.1 Conventional allergy diagnostics

In the BAMSE study, blood sampling was included in the clinical examination of 2 226 children (74%) at the 8-year follow-up, and in all subjects of the Severe asthma study (n = 95). Serum was analysed for specific immunoglobulin E (IgE). Tests provided by Phadia AB, Uppsala, Sweden, were Phadiatop® containing inhalant allergens of birch, grass, cat, dog, horse, mould, house dust mite and mugwort and Fx5® including food allergens of cow's milk, egg white, peanut, soy, cod and wheat [83, 84]. An IgE level of $\geq$ 0.35 kU_A/l

designated patients with sensitization. In the Severe asthma study, total IgE (kU/l) was also analysed.

In the Severe asthma study, a positive SPT response was considered when the wheal diameter was ≥ 3 mm. The tested allergens included inhalant allergens of birch, timothy, mugwort, dermatophagoides pteronyssinus, dog, cat, rabbit, cladosporium, alternaria, and food allergens of egg, milk, cod, rye, wheat, almond, hazelnut and peanut (Soluprick® SQ, obtained from ALK Abelló, Hörsholm, Denmark).

4.4.2 Component-resolved allergy diagnostics

Serum samples (n = 95) in the Severe asthma study were analysed using an experimental research ISAC prototype (Phadia AB, Sweden) containing 111 allergen components (all components of the ImmunoCAP ISAC 112 chip version except Ara h 6). The chip contained allergens derived from 51 sources, and required 30 µl of serum per test. Details of the tested perennial, inhalant and food components are listed in Figure 13. Positive sensitization was defined by a level of ≥ 0.30 ISAC independent units (ISU).

4.4.3 Inflammation

Markers of airway inflammation were analysed in the Severe asthma study, fraction of exhaled nitric oxide (FeNO) was determined by a chemiluminescence method using NIOX® equipment (Aerocrine AB, Solna, Sweden). Settings were in accordance with European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [85]. Samples of venous blood were collected, and numbers of white blood cell count (WBC, 10^9 x L^{-1}), neutrophils (10^9 x L^{-1}) and eosinophils (10^9 x L^{-1}) were analysed.

4.4.4 Lung function and bronchial hyperresponsiveness

In the BAMSE birth cohort, assessment of lung function was performed at the 8-year follow-up using dynamic spirometry (2200 Pulmonary Function Laboratory; Sensormedics, Anaheim, CA, USA) including forced expiratory volume in one second (FEV1%) in 1 841 children (61%), and peak expiratory flow rate (PEF, Ferraris Medical Limited, London, UK) in 2 318 children (77%). The predicted reference values based on the BAMSE population were adjusted for sex, height and age [86].

In the Severe asthma study, patients were evaluated with dynamic spirometry (Vitalograph® 2120 Ennis of Ireland) utilizing ERS/ATS guidelines. ERS/Polgar reference values were applied for estimation of predicted FEV1 values, adjusted for sex, height and weight [87]. Bronchial hyperresponsiveness (BHR) was evaluated by a challenge with methacholine (delivered by the Spira® Elektro 2 Dosimeter; Respiratory Care Center Ltd., Hämeenlinna, Finland) [88] in accordance with ATS guidelines [89]. Patients withheld their asthma medication prior to both methacholine challenge and baseline lung function testing. The decrease in FEV1 as a response to the cumulative inhaled dose of methacholine was calculated using the dose-response slope (DRS) [90].

4.5 DEFINITIONS AND OUTCOMES

The study definition of asthma at 8- and 12-year follow-ups in the BAMSE study required fulfilment of at least two of the following criteria [22, 91].

- Wheeze (at least one episode) in the last 12 months prior to the date of assessment.
- Intake of asthma medication regularly or occasionally in the last 12 months prior to the date of assessment.
- A doctor's diagnosis of asthma (ever).

Parental reported asthma control in the BAMSE cohort was analysed in the last 12 months prior to the date of assessment in children fulfilling the asthma criteria at 8 and/or 12 years, using symptom features of *limitation in daily activity* and *nocturnal asthma* from GINA [12], in combination with features of severe wheezing (*wheeze ≥ 4 times in the last year*) from the ISAAC protocol [92] and *healthcare utilization due to acute asthma symptoms* (emergency visit or hospitalization). In addition, *lung function* less than 80% of predicted in PEF or FEV_1 was included in the 8-year follow-up [12]. A child's asthma control was classified as follows:

- *Impaired* when at least one feature was fulfilled.
- *Controlled* (0 features).
- *Partly controlled* (1-2 features).
- *Uncontrolled* (≥ 3 features).

Severe asthma was defined as presence of asthma (according to the definition above) and pharmacy-suspended prescription of daily high-dose inhaled corticosteroids (ICS) of at least ≥ 800 microgram budesonide or equivalent steroid (≥ 500 µg fluticasone) in combination with treatment with a long-acting beta-2 agonist (LABA) according to WHO definition [53]. Pharmacy-delivered high-dose ICS was identified during a ± 1.5-year period before and after the date of each child's 12-year follow-up, through the Swedish prescribed drug register. The register lists all prescription drugs dispensed to Swedish residents since July 2005 and was only accessible at the time of 12-year follow-up [93].

Asthma triggers, e.g. cold air and physical activity, were evaluated as history of symptoms of whistling, wheeze, shortness of breath and troublesome cough induced by the trigger in question. While the time period for the trigger in question was defined in the BAMSE study as the past 12 months, no time period was specified in the Severe asthma study.

Continuous anti-inflammatory treatment included > 2 months use of regular treatment with ICS at 8- and 12-year follow-ups or > 2 months of treatment with montelucast at 12-year follow-up (BAMSE).

Rhinitis was defined as symptoms of prolonged sneezing or runny or blocked nose without common cold in the last 12 months (BAMSE) [94]. The Severe asthma study defined symptoms of rhinitis and/or conjunctivitis.

Airflow limitation was based on less than 80% of predicted in FEV1 (Severe asthma study and BAMSE) or PEF (BAMSE). Reference values in each respective cohort are presented in section 4.4.4.

Socio-economic background in children included in the Severe asthma study was defined based on total parental income and parental education. Annual income in Swedish kronor was defined on a four-point scale (< 350 000, 350 000 – 560 000, 560 000 – 750 000 and > 750 000) and parental education on a five-point scale (< 9 years, = 9 years, = 12 years, ≤ 3 years of high school or university, ≥ 4 years of high school or university).

4.6 STUDY ETHICS

All studies included in the thesis were approved by the ethics committee at Karolinska Institutet, Stockholm, Sweden. The longitudinal birth cohort BAMSE was approved at baseline, 8-year and 12-year follow-ups with the respective reference numbers; 93:189, 02-420 and 2007/1634-31. Reference numbers with relation to the Swedish Severe asthma study were; 2006/1324-31/1, 2007/443-32. Informed consent was obtained from all subjects.

4.7 STATISTICS

Statistical analyses were performed with STATA statistical software (release 11.1; Stata Corp, College Station, TX, USA) or IBM SPSS statistics software versions 16 to 19 (Chicago, IL, USA). Binary data was presented as frequencies and percentages and continuous variables as means with standard deviation (SD). Differences between normally distributed continuous data were analysed using the independent t-test, while non-parametric data were assessed using the Mann-Whitney U test. Differences in binary variables were analysed in percent with 95% confidence interval (95% CI) or with the chi-square test. A p-value < 0.05 was considered significant. Relationships between linear variables were examined using Pearson's correlation and non-linear using Spearman correlation coefficient.

Determinant factors associated with impaired asthma control at 8 and 12 years or problematic severe asthma were analysed with multiple logistic regression (presented as odds ratio (OR) with 95% CI) and as univariate analyses adjusted for age, sex and ethnicity. Reference populations were children with controlled asthma in each respective cohort. Factors in the children's history were analysed on the basis of previous known association with asthma symptoms [86, 95, 96]. Definitions of these factors in the BAMSE study were; *parental smoking* - any of the parents smoked at least one cigarette per day at the day of study enrolment, *family history of allergic disease* - mother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of hay fever in combination with furred animal or pollen allergy at the time of study enrolment, and *socio-economy* – status for the household at study enrolment, blue collar, white collar (university

graduate jobs) or other (e.g. student, housewife/man, person on a disability pension or unemployed).

Receiver operating characteristic (ROC) analysis was performed to estimate the area under the curve (AUC), and identify optimal thresholds of sensitivity and specificity for PAQLQ(S) and the asthma control test to differentiate problematic severe asthma from controlled asthma. The ROC analysis was conducted as a non-parametric test.

5 RESULTS

5.1 ASTHMA DISEASE IN THE BAMSE COHORT

In the population-based cohort BAMSE, 11% of the children fulfilled the study definition of asthma at 8 and 12 years respectively (n = 323 / n = 329), which corresponded to 15% (n = 458) at either 8 or 12 years, and 6% (n = 194) at both 8 and 12 years. The asthma incidence between the ages of 4 and 12 was 9.78 per 1000 person-years.

Children with asthma at both 8 and 12 years were more often boys (61% vs. 50%, $p < 0.001$) and had family history of allergic disease (46% vs. 29%, $p < 0.001$), compared with children without asthma. Sensitization to common inhalants or food allergens at 8 years was also more common in children with asthma (64% vs. 29%, $p < 0.001$). In addition, tobacco exposure at enrolment was more prevalent among children with asthma at 8 years (24% vs. 19%, $p = 0.03$), but not at 12 years (22% vs. 20%, $p = 0.24$). The proportion of overweight was comparable between children with and without asthma at age 8 (21% vs. 21%, $p = 0.89$), but higher among children with asthma at age 12 (16% vs. 11%, $p = 0.015$). Any type of asthma medication in the last 12 months was taken by 96% of the children with asthma at 8 years and by 94% at 12 years ($p = 0.12$), however, continuous ICS was to a larger extent used in children with asthma at 12 years than at 8 years, 31% vs. 23% ($p = 0.04$).

5.1.1 Asthma control

Characteristics of asthma control were analysed in children with asthma at 8 and/or 12 years and independently of asthma treatment in the BAMSE study. The frequency of impaired asthma control (partly or uncontrolled) was higher at 8 years than at 12 years, 85% vs. 53% ($p < 0.001$). At 8 years, 27% of 323 children with asthma were uncontrolled and 58% were partly controlled. The corresponding proportions at age 12 were 7% with uncontrolled asthma and 46% with partly controlled (of 329 children with asthma). Activity limitation occurred in 66% at 12 years versus 48% at 8 years ($p < 0.001$) and severe wheezing ($\geq$ 4 times in last year) in 52% versus 38% ($p = 0.002$). In contrast, nocturnal asthma was less frequent at 12 years, 36% versus 82% ($p < 0.001$), as was healthcare utilization due to acute symptoms, 15% versus 34% ($p < 0.001$), Table 3. Lung function was assessed at age of 8 years and 13% (n = 25) of the children with asthma had < 80% of predicted in FEV1 or PEF, four of these children fulfilled no other criteria of impaired asthma control.

Table 3. Frequency of controlled asthma (0 features) and impaired asthma control (≥ 1 features) at age 8 and 12 years, measurement of lung function is not included.

	8 years		12 years	
	Controlled n = 52	Impaired control n = 271	Controlled n = 155	Impaired control n = 174
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Prevalence	16 (12.1-20.1)	84 (79.9-87.9)	47 (41.7-52.5)	53 (47.5-58.3)
Limitation in daily activities	0	48 (42.4-54.3)	0	66 (59.0-73.2)
Nocturnal asthma *	0	82 (76.9-86.2)	0	36 (28.4-42.8)
Wheeze ≥ 4 times †	0	38 (31.8-43.4)	0	52 (44.8-59.8)
Health care utilization ¡	0	34 (28.6-40.0)	0	15 (9.6-20.3)

* Sleep disturbance in relation to cough or asthma symptoms. † Last 12 months prior to assessment. ¡ Hospitalization or emergency visits due to asthma symptoms.

Among all children with impaired asthma control (n = 358) at age 8 or 12 years, 25% reported impaired at both 8 and 12 years, 51% were impaired only at 8 years and 23% only at 12 years, Figure 6.

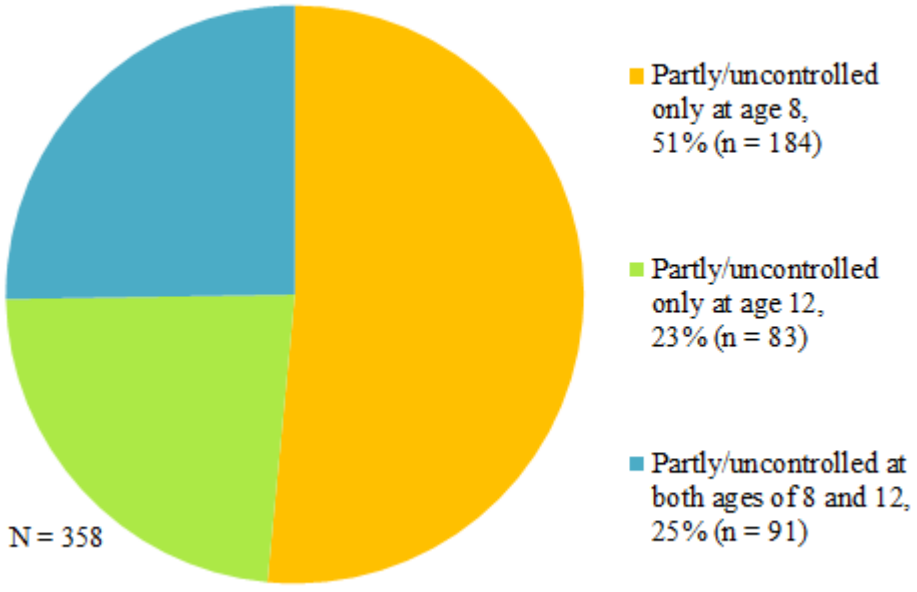

Figure 6. Proportions of children with impaired asthma control at 8 and 12 years in the BAMSE cohort.

5.1.2 Prevalence of severe asthma

At 12 years, 0.4% (n=13) of 3 015 children from the BAMSE cohort fulfilled the definition of severe asthma, corresponding to 4 % among children with asthma.

5.2 FACTORS IN CHILDREN'S HISTORY

In the BAMSE cohort, children's history and comorbidities were analysed among children reported as having impaired asthma at both 8 and 12 years (n = 91) and compared with children with controlled asthma at ages 8 or 12 years (n = 48 and n = 155, respectively). Compared with controlled asthma at 8 years, family history of allergic disease OR-adj. 3.3 (95% CI, 1.35-8.19) and rhinitis OR-adj. 2.8 (95% CI, 1.07-7.26) were associated with impaired asthma at 8 and 12 years. At 12 years, boys were overrepresented in the group with impaired asthma at 8 and 12 years as compared with in controlled asthma OR-adj. 2.0, (95% CI, 1.03-4.00). Treatment of continuous ICS did not differ significantly between children with impaired asthma at 8 and 12 years and children with controlled asthma, 38% vs. 32% (p = 0.27). Of children with impaired asthma at 8 and 12 years and rhinitis 68% were untreated with nasal steroids the last year prior to the 12-year follow-up

In the Severe asthma study, family history demonstrated that family history of parental asthma OR-adj. 3.5 (95% CI, 1.18-10.10) and lower parental education (no formal education beyond high school) OR-adj. 3.6 (95% CI: 1.07-12.17) were more associated with problematic severe asthma as compared with controlled asthma. Univariate analyses, with adjustment for sex, ethnicity and age, showed that a smoking family member OR 2.7 (95% CI, 1.01-7.10) and that patient history of rhino-conjunctivitis OR 3.7 (95% CI, 1.20-12.00) were also associated with problematic severe asthma, Figure 7.

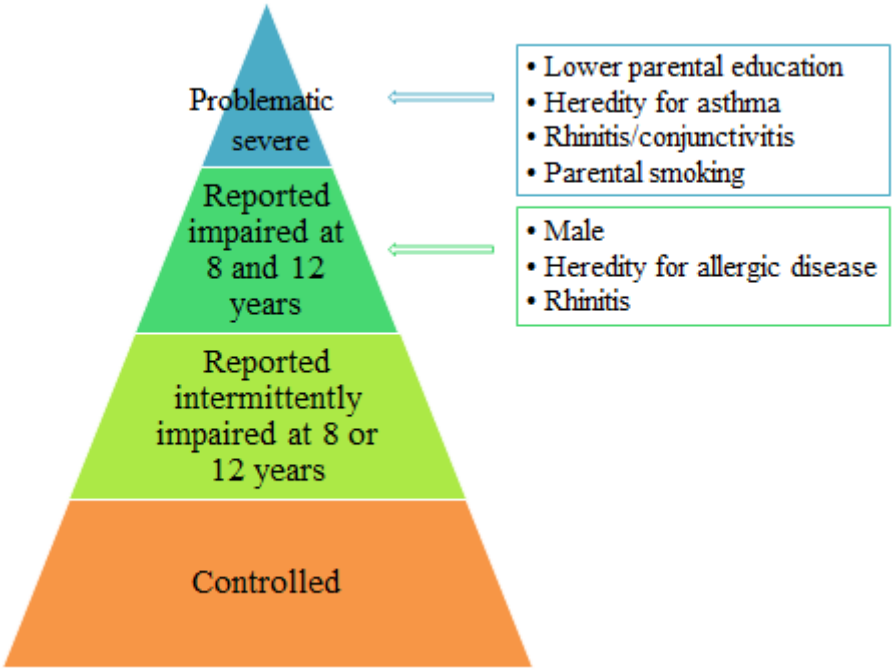

Figure 7. Factors and comorbidities associated with problematic severe asthma (Severe asthma study) and impaired asthma at 8 and 12 years (BAMSE cohort) as compared with controlled asthma in the respective cohorts.

5.2.1 Severe difficult-to-treat asthma

Starting with the problematic severe asthma group (the Severe asthma study), patients were further differentiated to be severely therapy-resistant or difficult-to-treat. Aggravating factors

in the children's history were identified through the health questionnaire and designated the subgroup of children with difficult-to-treat asthma. Identified factors were untreated symptoms of rhinoconjunctivitis (n = 4), current exposure to tobacco (n = 12), untreated symptoms of GERD (n = 5), presence of pets in the household despite sensitization to such pets (n = 3) and sensitization to moulds in combination with reported exposure of mould or humid and problematic indoor climate in a child's home (n = 4). Thirty-three patients (61%) remained classified as therapy-resistant after exclusion of difficult-to-treat asthma (n = 21), Figure 8. Children with difficult-to-treat asthma revealed lower parental income on a four-point scale, median 1 vs. 3 (p = 0.002) and a lower proportion parents with education beyond high school, 28% vs. 70% (p = 0.004), compared with children with therapy-resistant asthma.

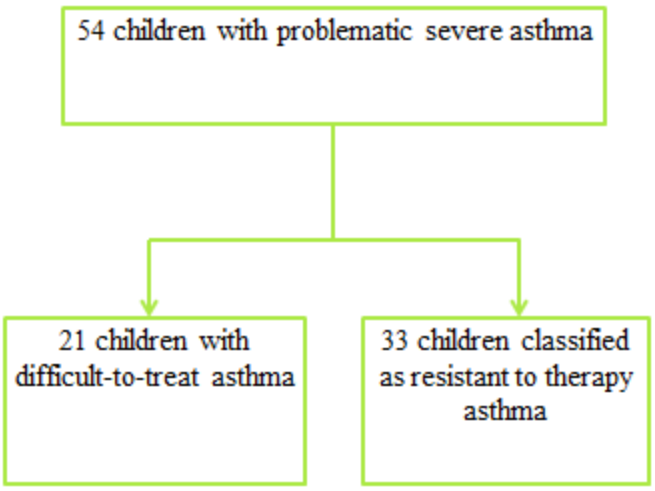

Figure 8. Number of patients with problematic severe asthma that were differentiated as having difficult-to-treat or therapy-resistant.

5.2.2 Asthma triggers

Reported asthma triggers in the BAMSE cohort were limited to the past 12 months at the 12-year follow-up, as opposed to the Severe asthma study where no such time limit was defined. The most common triggers reported as inducing asthma symptoms among children with both impaired asthma at 8 and 12 years and problematic severe asthma were physical activity (84% and 86%, respectively) and viral infections (88% and 93%). In comparison, viral infections occurred more often in both impaired asthma at 8 and 12 years and problematic severe asthma compared with in controlled asthma in each respective cohort, Table 4. In addition, triggers from pollen allergens, cold air and tobacco smoke were also more pronounced among impaired asthma at 8 and 12 years and problematic severe asthma, whereas furred animal exposure and food allergens were equally distributed between the groups.

Table 4. Asthma triggers in reported impaired asthma at both 8- and 12-year follow-ups and in problematic severe asthma compared with controlled asthma in the respective cohorts.

	BAMSE			Severe asthma study		
	Impaired at 8 and 12 yr.	Controlled	p - value	Problematic severe	Controlled	p - value
	n = 91	n = 155		n = 56	n = 39	
Asthma triggers †	n (%)	n (%)		n (%)	n (%)	
Physical activity	76 (84%)	75 (48%)	< 0.001	48 (86%)	33 (85%)	0.89
Viral infections	78 (88%)	41 (27%)	< 0.001	52 (93%)	30 (77%)	0.026
Cold air	46 (51%)	28 (18%)	< 0.001	34 (61%)	10 (26%)	0.001
Pollen ¶	45 (49%)	39 (25%)	< 0.001	39 (74%)	19 (49%)	0.020
Furred animal ×	28 (31%)	38 (25%)	0.29	34 (64%)	24 (63%)	0.92
Tobacco smoke	13 (14%)	6 (4%)	0.003	28 (53%)	11 (29%)	0.023
Food	5 (3%)	4 (3%)	0.24	19 (34%)	9 (23%)	0.25

† Asthma triggers were evaluated in the BAMSE cohort as history of symptoms of whistling, wheeze, shortness of breath and troublesome cough induced by the trigger in question in the last 12 months. In the Severe asthma study no time limit was defined. ¶ Grass and birch allergens. × Cat, dog and horse allergens.

5.3 LUNG FUNCTION AND BRONCHIAL HYPERRESPONSIVENESS

The lung function of children in the BAMSE study was measured at 8 years. Airflow limitation (< 80% of predicted in PEF or FEV1) was more common in children with asthma compared with children without asthma at 8 years, 8% vs. 4% ($p = 0.009$), and at 12 years, 10% vs. 4% ($p < 0.001$). In children with defined asthma at 12 years, a higher proportion of wheeze during common cold was presented in children with airflow limitation at 8 years than in children with normal lung function at that age, 70% vs. 50% ($p = 0.035$). In contrast, wheeze without common cold at 12 years revealed no such difference with regard to airflow limitation at 8 years and normal lung function, 67% vs. 50% ($p = 0.07$). The proportion of children with air flow limitation at 8 years was comparable between children with impaired asthma at both 8 and 12 years and controlled asthma at 12 years, 13% vs. 10% ($p = 0.49$).

Airflow limitation was more common among children in the Severe asthma study than in children with asthma at 8 years in the BAMSE study, 38% vs. 8% ($p < 0.001$). In addition, in the Severe asthma study, children with problematic severe asthma more often displayed airflow limitation than children with controlled asthma, 48% vs. 23% ($p = 0.013$), Figure 9.

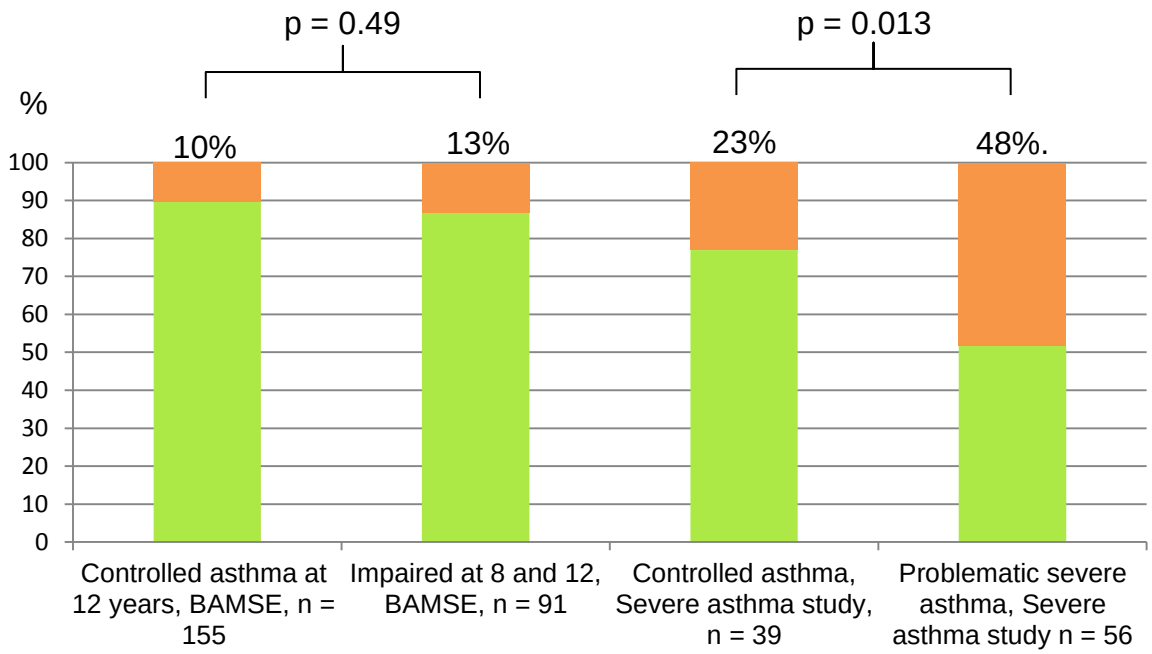

Figure 9. Proportions of airflow limitation (< 80% of predicted FEV1 or PEF at 8 years) in children at age 12 years with controlled asthma or impaired asthma at both 8 and 12 years in the BAMSE cohort, and in the Severe asthma study comparing controlled asthma with problematic severe asthma.

Bronchial provocation with methacholine revealed more pronounced BHR in patients with problematic severe asthma (n = 34) compared with controlled asthma (n = 39), DRS mean 51 vs. 17 (p = 0.01). Twenty children with problematic severe asthma were unable to undergo the provocation due to low baseline FEV1 < 70%, or difficulties in withdrawing their medication, in addition two children were not challenged owing to technical difficulties with installation of nebulizer. Five children with problematic severe asthma were negative to the methacholine provocation, defined as less than 20% reduction in FEV1.

5.4 ALLERGY DIAGNOSTICS

5.4.1 Conventional allergy diagnostics

In the BAMSE cohort, sensitization to Phadiatop and/or Fx5 was seen in 65% of children with controlled asthma and in 71% (p = 0.82) of children with impaired asthma at both 8 and 12 years. In multivariate analysis, no increased risk of sensitization was seen in children with impaired asthma at both 8 and 12 years OR-adj. 0.7 (95% CI, 0.28-1.98) compared with controlled asthma. The proportion of children with sensitization was higher in the Severe asthma study compared with children with asthma at 8 years in the BAMSE cohort 82% vs. 64% (p = 0.027) but not at 12 years (based on sensitization at 8 years) 82% vs. 70% (p =0.82). In the Severe asthma study alone, sensitization was equal in positive response to SPT, Phadiatop and Fx5 between problematic severe asthma and controlled asthma 82% and 82% (p = 0.94), as well as to three or more allergens (data not shown).

5.4.2 Component-resolved allergy diagnostics

Taking into account both groups of children with problematic severe asthma and controlled asthma in the Severe asthma study, IgE-sensitization with multiplex component-resolved diagnostics (CRD) was detected in 80% of 95 children. Fifty-one percent were sensitized to pollen, food and perennial aeroallergens, with equal distribution between problematic severe asthma and controlled asthma, Figure 10. The most common allergen sources among sensitized individuals were cat - 76% (rFel d 1 and 4), birch - 64 % (nBet v 1) and timothy grass - 64% (rPhil p 1, 2, 5, 6 and 11). In the food panel, the predominant sensitization was to peanut, 42% (rAra h 1, 2, 3 and 9).

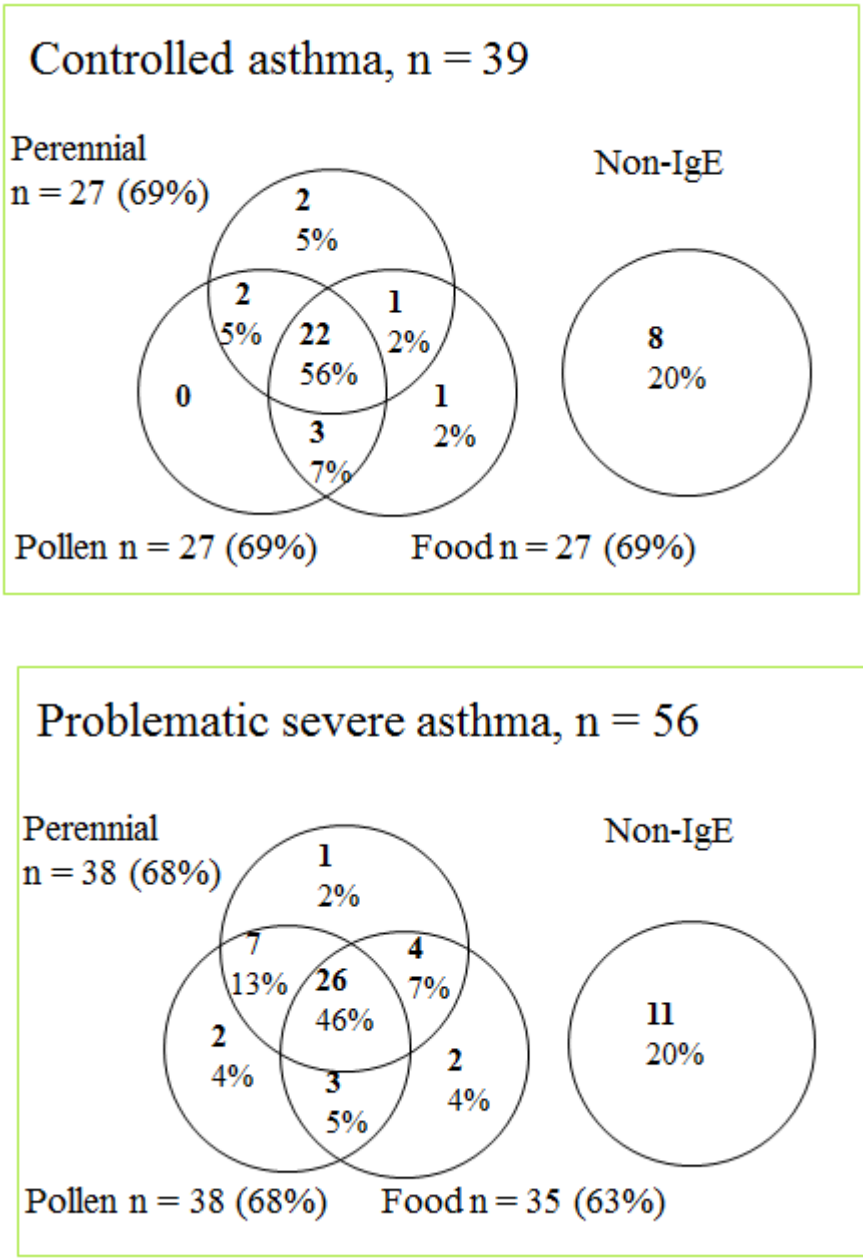

Figure 10. Sensitization to perennial aeroallergen components (1), pollen allergen components (2) and food allergen components (3) among children with problematic severe asthma and controlled asthma.

1. Perennial aeroallergen components: Dog (rCan f 1, 2, 3, 5), horse (rEqu c 1, 3), cat (rFel d 1, 2, 4), mouse (nMus m 1) house dust mites (rBlo t 5, nDer f 1, rDer f 2, nDer p 1, rDer p 2, 10, rLep d 2, rEur m 2), cockroach (rBla g 1, 2, 5, 7), Alternaria (rAlt a 1, 6), Aspergillus (rAsp f 1, 3, 6) and Cladosporium (rCla h 8), sum=28.

2. Pollen allergen components: Bermuda grass (nCyn d 1), Timothy (rPhl p 1, 2, 4, 5, 6, 11), Alder (rAln g 1), Birch (nBet v 1), Hazel (rCor a 1.0101), Japanese cedar (nCry j 1), Cypress (nCup a 1), Olive (nOle e 1, 7, 9), Plane (rPla a 1, 2, 3), Ragweed (nAmb a 1), Mugwort (nArt v 1, 3), Goosefoot (rChe a 1), Wall pellitory (rPar j 2), Plantain (rPla l 1), Saltwort (nSal k 1) and cross-reactive markers of polcalcin (rBet v 4 and Phl p 7) and profilin (Latex rHev b 8, Birch rBet v 2, Timothy rPhl p 12 and Annual mercury rMer a 1), sum=31.

3. Food allergen components: Kiwi (nAct d 1, 2, 5, 8), Celery (rApi g 1), Apple (rMal d 1), Peach (rPru p 1, 3), Cashew nut (rAna o 2), Brazil nut (rBer e 1), Hazel nut (rCor a 1.0.0401, 8, 9), Walnut (nJug r 1, 2, 3), Sesame seed (nSes i 1), Peanut (rAra h 1, 2, 3, 8, 9), Soy (rGly m 4, 5, 6), Buckwheat (nFag e 2), Wheat (rTri a 14, a 19, nTri aA_TI), Cow's milk (nBos d 4, 5, 6, 8, lactoferrin), Cod (rGad c 1), Egg (nGal d 1, 2, 3, 5), Shrimp (nPen m 2, 4), and cross-reactive components of tropomyosin (Anisakis rAni s 3, Shrimp nPen m 1, sum=43.

With regard to multi-sensitization to more than three positive components of animal-derived lipocalin (nMus m 1, rEqu c 1, rFel d 4, rCan f 1, 2), kallikrein (rCan f 5) and secretoglobin (rFel d 1), this were more common in children with problematic severe asthma than in the controlled asthma group 25% vs. 8% (p = 0.03), Figure 11.

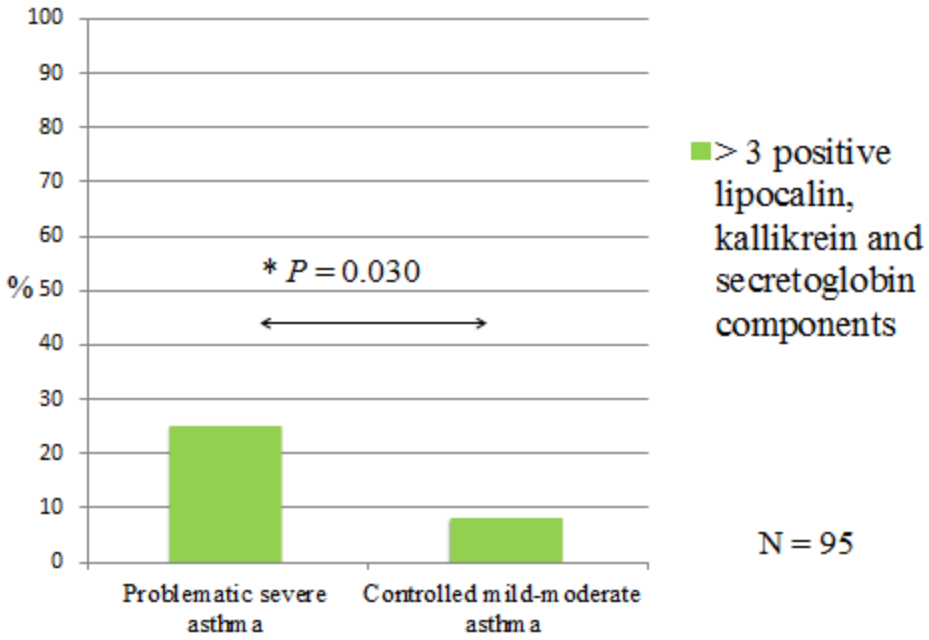

Figure 11. Sensitization to more than three animal-derived lipocalin, kallikrein and secretoglobin components in patients with problematic severe asthma (n = 56) and controlled asthma (n = 39). The components consisted of rCan f 1, 2, 5 (dog); rEqu c 1(horse); nMus m 1(mouse); rFel d 1, 4(cat).

5.4.3 Animal-derived sensitization and bronchial inflammation

In the Severe asthma study, patients with multi-sensitization to more than 3 single lipocalin, kallikrein or secretoglobin components (n = 17) were more likely to have increased bronchial inflammation of exhaled nitric oxide (FeNO), higher blood count of eosinophils and BHR to methacholine compared with those positive to fewer lipocalin/kallikrein/secretoglobin components (n = 78), Table 5. HR-QoL and higher total IgE were also associated with this multi-sensitized group. No differences were found in furred animal ownership or tobacco exposure (parental smoking in the household) between the two groups.

In the problematic severe asthma group alone, multi-sensitization to animal-derived components showed more impairments compared with patients sensitized to fewer animal components, in FeNO 38 ppb vs. 25 ppb, (p = 0.021), blood eosinophils 0.65 vs. 0.39, (p = 0.021), BHR 112 vs. 28, (p = 0.002) and in total IgE 1279 vs. 331, (p = 0.006). In contrast, no association with reduced HR-QoL was present, but a tendency towards increased numbers of exacerbations treated with oral steroids in the past year was shown, mean 3.50 vs. 2.49, (p = 0.051).

Table 5. Distribution of covariates by sensitization to more than 3 positive animal-derived lipocalin/kallikrein/secretoglobin components in the total cohort of patients with problematic severe asthma (n = 56) and controlled asthma (n = 39).

	Sensitized to > 3 animal-derived lipocalin/kallikrein/secretoglobin components		
	Yes n = 17	No n = 78	p - value
Furred pet owner, no (%)	2 (12%)	12 (15%)	0.70
Smoke exposure ¶ no. (%)	2 (12%)	14 (18%)	0.54
Serum total IgE (kU/L, mean, ± SD)	1090 ± 953	464 ± 601	0.041
FeNO (ppb, mean, ± SD)	34 ± 23	24 ± 20	0.022
Blood count of eosinophils (10^9 x L^{-1}, mean, ± SD)	0.56 ± 0.50	0.33 ± 0.32	0.025
Lung function (predicted FEV_1%, mean, ± SD)	86 ± 16	85 ± 17	0.80
DRS of methacholine (% decrease of FEV_1, mean, ± SD)	(n = 12) 85 ± 105	(n = 61) 22 ± 33	0.004
Negative methacholine PD-20,† no. (%)	1 (8%)	16 (26%)	0.18
Baseline FEV_1% < 70% * no, (%)	2 (12%)	13 (17%)	0.62
PAQLQ(S) - total score ,mean, ± SD)	5.5 ± 0.9	6.0 ± 0.9	0.014

5.4.4 Cross-reactivity between lipocalin components

Specific IgE levels of lipocalin components correlated in sensitized individuals in the Severe asthma study; rFel d 4 and rEqu c 1 ($r = 0.850$, $p < 0.001$), rFel d 4 and nMus m 1 ($r = 0.751$, $p < 0.001$) and rEqu c 1 and nMus m 1 ($r = 0.683$, $p < 0.001$).

5.5 HEALTH-RELATED QUALITY OF LIFE

HR-QoL was only assessed in children of the Severe asthma study. All subjects (n = 93), except one, were able to answer the interview-based PAQLQ(S) questionnaire. The average PAQLQ-score (including the three sections covering symptoms, activity limitation and emotional function) was significantly lower for children with problematic severe asthma than for those with controlled asthma, Table 6.

Table 6. Assessments of health-related quality of life and asthma control in problematic severe asthma and controlled asthma, n = 93.

	Problematic severe	Controlled	P-value
	mean (SD±)	mean (SD±)	
PAQLQ(S) – total	5.4 (± 0.8)	6.7 (± 0.3)	< 0.001
PAQLQ(S) – symptoms	5.1 (± 0.9)	6.5 (± 0.4)	< 0.001
PAQLQ(S) – activity limitation	5.3 (± 0.9)	6.5 (± 0.4)	< 0.001
PAQLQ(S) – emotional function	5.9 (± 0.8)	6.9 (± 0.2)	< 0.001
Asthma control test, ACT	17.0 (± 3.3)	22.9 (± 1.7)	< 0.001

The HR-QoL experienced by girls with problematic severe asthma was significantly lower than for boys with problematic severe asthma (5.1 versus 5.6, $p = 0.02$). Furthermore, all girls with problematic severe asthma reported use of short-acting beta-2 agonist more than twice per week compared with 66% of the boys ($p = 0.03$). No other differences were found with regard to factors in child's history, BMI, lung function, inflammation of FeNO or WBC or in numbers of exacerbations (data not shown). For children with controlled asthma, no difference in HR-QoL or asthma control test was observed between girls and boys (data not shown).

Analysis of how well PAQLQ(S) and the asthma control test (ACT or C-ACT) discriminate between patients with problematic severe asthma and controlled asthma was performed. Receiver operated characteristics (ROC) analysis estimated area the under the curve (AUC) for PAQLQ(S) to 0.96 ($p < 0.001$) and 0.95 ($p < 0.001$) for the asthma control test, Figure 12a. The AUC for each subdomain of PAQLQ(S) was also analysed; symptoms 0.93 ($p < 0.001$), activity limitation 0.92 ($p < 0.001$) and emotional function 0.90 ($p < 0.001$), Figure 12b. Optimal thresholds for PAQLQ(S) to discriminate between patients with problematic severe asthma controlled asthma were < 6.2 for PAQLQ (85%

sensitivity and 97% specificity) and < 20 for the asthma control test (79% sensitivity and 94% specificity). Thresholds for PAQLQ(S)'s subdomains were < 6.1 for symptoms (81% sensitivity and 82% specificity), < 6.1 for activity limitation (85% sensitivity and 87% specificity) and < 6.7 for emotional function (81% sensitivity and 87% specificity).

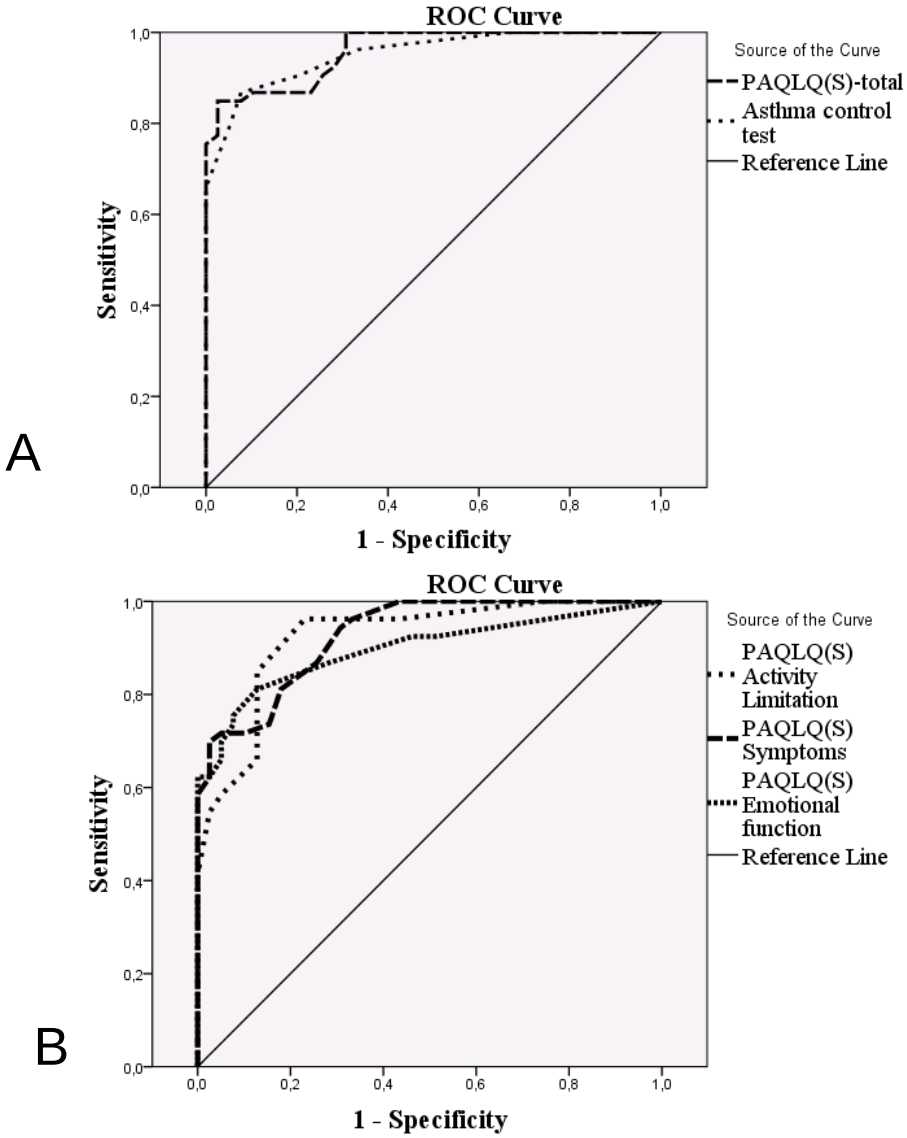

Figure 12a and b. The ability of PAQLQ(S) – total score, ACT or C-ACT (A), and subdomains of PAQLQ(S) – symptoms, activity limitation and emotional function (B), to differentiate problematic severe asthma from controlled asthma analysed using receiver operating characteristic curves.

In the Severe asthma study, the results of the asthma control test strongly correlated with the HR-QoL ($r = 0.8$, $p < 0.001$), Figure 13. The figure displays concordance between measurements based on the estimated optimal thresholds to differentiate between the patients with problematic severe asthma and controlled asthma, for PAQLQ(S), < 6.2 on the y-axis, and for the asthma control test (score below 20 vertical line on x-axis).

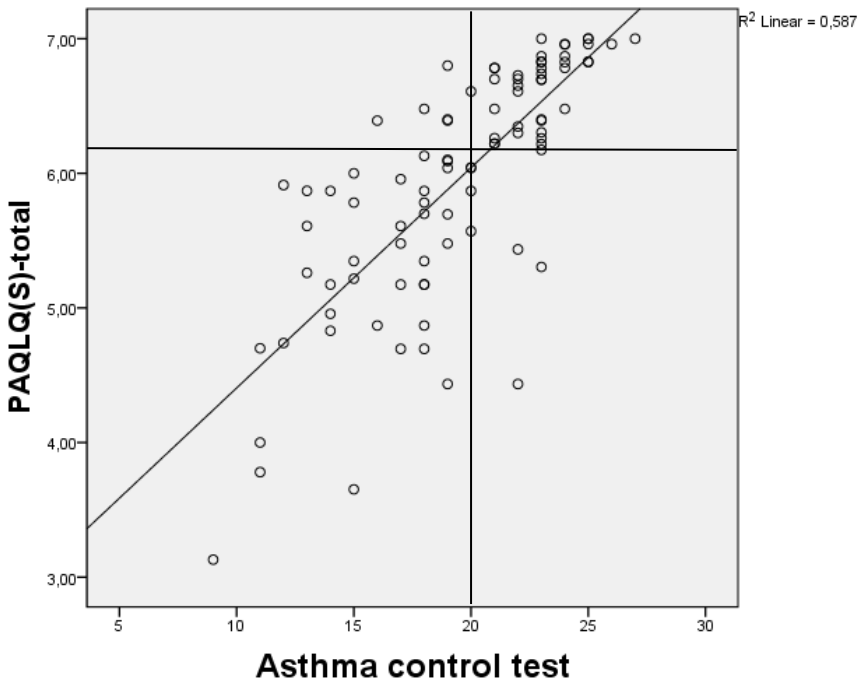

Figure 13. Correlation of PAQLQ(S) and the asthma control test (ACT and C-ACT) scores from children with problematic severe asthma and controlled asthma ($r = 0.8$, $p < 0.001$, $n = 93$). The horizontal line displays the optimal threshold of < 6.2 to differentiate children with problematic severe asthma and controlled mild-moderate asthma, and the vertical line shows the optimal threshold of < 20 for ACT and C-ACT.

6 DISCUSSION

The aim of this thesis was to assess the burden of symptoms and factors associated with impaired asthma control in schoolchildren. A high burden of symptoms was found in children with asthma in the prospective birth cohort BAMSE, and about one in five children with asthma was defined as having impaired asthma control at both 8 and 12 years. Children with problematic severe asthma in the Severe asthma study suffered from impaired quality of life with essential effects on daily activities and emotional function compared with children with controlled asthma.

Children with impaired asthma control at 8 and 12 years and problematic severe asthma were further analysed regarding factors associated with children's history and clinical measures compared with children with controlled asthma. Factors associated with impaired asthma control were parental history of allergic disease and comorbidity of rhinitis. Among children with problematic severe asthma, limited health literacy was another factor found in children classified with difficult-to-treat asthma, based on concurrent failure to prevent children from having asthma symptoms. Sensitization was a common feature among all children with asthma in the study population (both in the BAMSE and Severe asthma study cohorts). In children with problematic severe asthma, multi-sensitization to animal derived components was more pronounced than in children with controlled asthma. Furthermore, children with such multi-sensitization demonstrated evidence of more severe eosinophil inflammation than children with sensitization to fewer animal-derived components**.**

6.1 ASTHMA CONTROL

The ultimate goal of asthma therapy is to allow patients to achieve control over their symptoms. In spite of that, a high burden of symptoms was present among schoolchildren with asthma in the BAMSE study. One in five children with asthma was classified with impaired asthma (partly or uncontrolled) at both age 8 and 12 years.

There are various ways to classify asthma control in children and according to GINA two domains are included [12], the first domain reflects burden of symptoms and reduced lung function and the second the risk for exacerbations as well as persistent decline in lung function. Classification of the first domain in the BAMSE cohort included parental assessment of activity limitations, nocturnal asthma, and severe wheezing four or more times in the last year (criterion adopted from the ISAAC protocol [92]), as well as reduced lung function (at 8 years only). The second domain assessed hospitalization and emergency visits due to acute symptoms in the last year. If possible, it would have been preferable to assess other features as well in this domain, e.g. treatment frequency with oral steroids. Another difference was that asthma control reflected a period of the last 12 months in contrast to GINA's recommended 4 weeks. Moreover, reduced lung function is an important outcome associated with reduced asthma control [11], unfortunately, the assessment was not included in the 12-year follow-up. When classifying asthma control among schoolchildren it is an obvious risk that some children with absence of symptoms have remittent asthma rather than controlled asthma. In the CAMP trial, Covar et al. defined remission of asthma based on

absence of any asthma activity (asthma medication or symptoms) in the last year prior to follow-up [97]. In comparison with the BAMSE study, the risk for misclassification of children with asthma remission should be low, since asthma control was only assessed in children with defined asthma, which means presence of asthma activity; both wheeze or medication in the last 12 months, or only one asthma activity (wheeze or medication) in addition to a doctor's diagnosis of asthma.

In the BAMSE study, age-related differences in children's asthma control were observed, corresponding to more acute health care utilization and nocturnal asthma at age 8, and more activity limitations and wheeze ($\geq$ 4 times last year) at age 12. Moreover, fewer children fulfilled the criteria of controlled asthma at age 8 compared with at age 12. In spite of that, the overall asthma control cannot automatically be interpreted as improved at 12 years. Reasons for this discrepancy may exist, one is that the GINA criterion may not be perfectly suited for defining asthma control in childhood asthma due to the natural course of childhood asthma including changes over time in symptoms e.g. in comparison to wheeze during common cold and allergic asthma. Another is longitudinal changes in parental perceived asthma control compared with children's, mainly underestimation of children's asthma symptoms (39,80). Kuehni et al. also found that parental acceptance of poor asthma control was higher than that outlined in guidelines [40]. Taken together, these findings emphasize why asthma control should be evaluated with reliable and validated instruments to avoid unforeseen changes in health outcomes. Asking children directly, using validated HR-QoL or asthma control tests, puts more focus on the child's own perceived disease burden compared with GINA guidelines [98, 99], and should as often as possible be incorporated in paediatric healthcare, certainly with older schoolchildren, Figure 14.

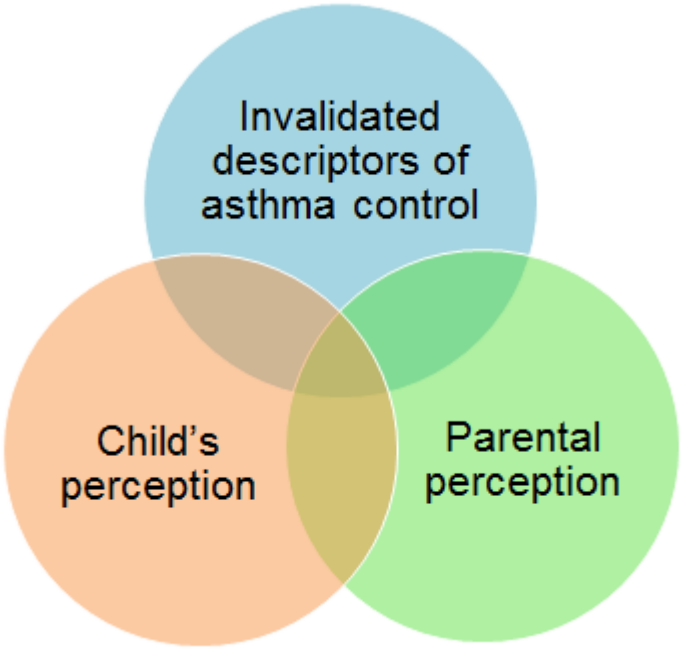

Figure 14. Factors with influence on the outcomes of asthma control in children.

A high burden of asthma symptoms was present in the BAMSE study. This finding emphasizes the importance of well-functioning asthma care. One reason for poor asthma control is wrong diagnosis. If a patient's symptoms do not respond as expected to treatments, the first step before increasing the dose of therapy should be to confirm the diagnosis. Ideally, asthma is confirmed on evidence of reversible airway obstruction using spirometry or through bronchial provocation [100]. Furthermore, an essential component of successful asthma care is patient education. Treatment goals should be established in partnership with the child and parents. The patient education needs to address the influence of avoidable aggravating factors as triggers in home or school environment [101, 102], and effect of comorbidities e.g. rhinitis or GERD [103-105]. Patient adherence to therapy is easily overestimated [106], and another critical challenge for paediatric health care. Observed inhalation techniques in combination with the right inhaler are important considerations in paediatric health care. Metered-dose inhalers may be incorrectly used [107], and some children do not have sufficient force or depth when inhaling medication through a dry powder device, so the medication fails to enter the lungs [108, 109]. There are devices to aid children in performing proper inhalation technique such as whistles giving sound at the required inhalation rate and devices designed to release a dose only when the required inhalation rate is achieved [110].

6.2 SEVERE ASTHMA

In spite of a growing interest for research in patients with severe asthma, the majority of studies have analysed selected materials which can be regarded as a limitation. In this thesis the severe asthma prevalence was analysed in a prospective population-based Swedish birth cohort, combined with information of dispensed high-dose ICS from records in the Swedish prescribed drug register.

The pharmacy information of dispensed ICS was collected at ± 1.5 years before and after the children's 12-year follow-up, this could be considered a limitation for estimating the prevalence of severe asthma. While no standards are available for defining the optimal time periods of suspended medications in a drug register in connection with follow-up data in a birth cohort, the time period of ± 1.5 years was used, based on the maximum time period for children not requiring a doctor's issuance of new medication prescriptions. It is possible that children's asthma treatment may be changed to high-dose ICS without the requirement of pharmacy suspension of new medication, certainly if old medications are still provided. Severe asthma is a heterogenic disease and various underlying factors may exist with effect on the estimated prevalence, including wrong diagnosis, psychosocial factors, socio-economy, poor adherence, comorbidities, and environmental exposures [50]. Severe asthma among schoolchildren seems to be rare. The prevalence of 0.4% corresponded to 4% of all children with asthma at 12 years. This rate is comparable with a Norwegian study [111] as well as with a British study in which 4.6% of adults with asthma received step 4 or 5 treatment according to British guidelines [112].

Studies regarding severe asthma in the last decade are difficult to compare due to various nomenclatures and definitions. This stresses the importance of using a global definition that facilitates assessments and health care of severe childhood asthma. Ideally, the clinical

usefulness of a proposed definition should be analysed in regards to real life data, which is rarely done. In this thesis, two different definitions of severe asthma were used, one in the BAMSE study and one in the Severe asthma study. Both definitions agreed on treatments with high-dose ICS, which the majority of proposed nomenclatures agree on [37, 113]. Another major criterion to consider is the level of asthma control, the term 'problematic severe asthma' emphasizes uncontrolled symptoms while in BAMSE no such criteria were applied. One of the reasons for that was that the two most recent proposed nomenclatures seem to disagree on the level of achieved asthma control in severe asthma [53, 113]. According to the WHO definition, it is acceptable that *treatment-resistant severe asthma* is subdivided into uncontrolled or controlled asthma, since controlled asthma would refer to patients whose asthma can only be controlled with the highest level of ICS. In the BAMSE study, the broader definition regardless of children's asthma control was used when estimating numbers of children with severe asthma.

6.3 FACTORS IN CHILDREN'S HISTORY

Although several risk factors are known for development of asthma morbidity, the current understanding of factors and characteristics associated with impaired asthma control is limited. Main factors associated both with children designated as having impaired asthma at 8 and 12 years in the BAMSE study and with children with problematic severe asthma in the Severe asthma study were family history of allergic disease, comorbidity of rhinitis, and triggers of virus, cold air, pollens and tobacco smoke. In patients with problematic severe asthma, additional associated factors was lower socio-economy.

6.3.1 Socio-economy and health literacy

In this thesis, children with problematic severe asthma were more often associated with parents not having education beyond high school, as compared with children with controlled asthma. In addition, among patients with problematic severe asthma, lower parental education and income were more pronounced among children with difficult-to-treat-asthma compared with patients with therapy-resistant-asthma. The large proportion of children with difficult-to-treat-asthma (39%) was defined upon characteristics in children's history of environmental exposures to tobacco smoke, keeping furred animal at home despite sensitization and problematic indoor climate with visible mould or perceived odour of mould in spite of sensitization to mould. Untreated comorbidities of GERD and rhinitis were other characteristics in children with difficult-to-treat asthma. All these factors were assessed only on the basis of patient and parental reports and without visiting the home environment. Home visits would probably improve the assessment and result in a larger proportion of patients with difficult-to-treat-asthma. In support, Bracken et al. analysed modifiable factors in patients with problematic severe asthma by visiting their homes, in 79% of children aggravating factors were found that contributed to more severe disease such as environmental exposures, psychosocial factors and poor adherence [114]. Traditional patient education in clinical practice may not overcome family barriers to follow asthma management due to psychological distress. A randomised home-based family intervention evaluated the efficacy of targeting asthma management and stressors in low-income children with asthma [115]. Outcomes of emergency visits and hospitalizations were improved after one year intervention. A similar and promising home-based study with improved asthma

control in children with atopic asthma was made by Morgan et al., conducting intervention with reduction of environmental exposures and family education [116]. Taken together, an individual approach with home visits addressing medical and psychosocial needs is probably beneficial for patients with problematic severe asthma.

Failure to understand or follow health information may result in poor adherence, untreated and unrecognised comorbidities, not avoiding trigger factors and poor recognition of signs of asthma worsening. These aspects are included in the definition of limited health literacy [18]. Although there are major gaps in the current knowledge of what brings low health literacy, there is an association to general literacy skills [117]. Low health literacy is more common in certain groups in the society, such as members of ethnic minorities, immigrants, the poor and those with limited education [117]. Aspects of parental health literacy need to be approached in children with problematic severe asthma, especially in those defined as "difficult-to-treat". In a large Swedish study, children in families with social adversity were seen to have an increased risk for exacerbations and for hospital admissions because of asthma [118]. It is also relevant to consider that poor health literacy has larger health effects on children with more severe disease than on children with e.g. mild asthma. Importantly, limited health literacy emphasizes challenges in targeting both patients and parents with tailored education [32], and with information to health care professionals to optimize their communication skills. Health education has proven to be effective on disease management in patients with low health literacy [119].

6.3.2 Family history of allergic disease

Family history of allergic disease was a distinguishing factor in both children with impaired asthma at 8 and 12 years in the BAMSE study and in problematic severe asthma in the Severe asthma study. The findings elucidated the children's inherited relation to increased asthma severity. There are few genetic studies performed in children with severe asthma and the genetic causes of enhanced asthma severity remain unresolved. Analysis of gene expression is complex, with different levels of mechanisms in relations to various triggers from the environment. The DNA sequence is a template for transcription of messenger RNA which further determines the translation and production of proteins with effect on the pathophysiology of asthma. To enable proper analysis of genetic variants, well-characterized patients are a requirement. Specific gene expressions of bitter taste transduction (TAS2Rs) has been found in patients from the Severe asthma study with severe therapy-resistant asthma in addition to controlled asthma and healthy individuals [120]. The bronchodilatory bitter taste receptors are suggested as new targets for therapy.

6.3.3 Rhinitis

Comorbidity of rhinitis was more common in both children with impaired asthma at 8 and 12 years in the BAMSE study and in those with problematic severe asthma in the Severe asthma study. A surprisingly high proportion of children with impaired asthma at 8 and 12 years and rhinitis (68%) were untreated with nasal steroids at 12 years. Importantly, asthma and rhinitis are represented as the same entity of allergic diseases and need to be evaluated and treated simultaneously [24, 121]. Studies have found links between asthma control and severe nasal

disease in children [103], even though the majority of studies are focused on adults [122, 123]. To date, few randomised control studies have proven any effect of nasal treatment on asthma control in children. Kersten et al. found that intranasal corticosteroid treatment of allergic rhinitis ameliorated EIA symptoms in children with asthma [124]. Pedroletti et al. saw no effect of reduced FeNO in children treated with nasal mometason furoate for perennial rhinitis, but signs of nasal and systemic eosinophil inflammation were improved [125]. Measurements of rhinitis include symptom scores, visual analogue scale scores [126], quality of life assessments [127, 128], and should be incorporated in a patient's asthma care.

6.3.4 Triggers

Viruses and physical activity were the most troublesome triggers reported in all children with asthma in both BAMSE study and Severe asthma study. Symptoms during physical activity are of major concern as the current recommendations are that all children with asthma should be able to engage in regular physical activity. In the BAMSE study, children with impaired asthma at both 8 and 12 years more often revealed symptoms during physical activity than children with controlled asthma. The important pathogenic role of exercise-induced symptoms (EIA) is bronchial inflammation and for optimal control of EIA, anti-inflammatory treatment is required [129]. A surprisingly low number, 38% of all children with impaired asthma at both 8 and 12 years, used ICS continuously (minimum period of 2 months) in the last year prior to the 12 year follow-up. Implications of these findings need to be highlighted in clinical practice. EIA should be managed and diagnosed at an early stage in order to avoid recurrent symptoms of uncontrolled asthma or other diagnoses. The diagnosis of EIA is best confirmed through a standardized exercise test [130], the test has high specificity and also indicates how well the child masters physical activity. Alternative methods are other measurements of bronchial hyperresponsiveness, such as bronchial challenges [131] and lung function testing with reversibility test. Triggers of cold air and physical activity are closely related since both triggers induce symptoms through the combined mechanisms of water and heat loss through respiration, which cause bronchoconstriction in bronchial smooth muscle [132, 133]. Children with impaired asthma at 8 and 12 years and with problematic severe asthma reported more symptoms in relation to cold air exposure than children with controlled asthma. This was associated with more severe bronchial hyperresponsiveness, which was confirmed through the methacholine provocation conducted in patients with problematic severe asthma and controlled asthma.

Viruses were significantly associated with impaired asthma at both 8 and 12 years and problematic severe asthma as compared with controlled asthma. Rhinoviruses (RV) are often the primary cause of common cold [134], and severe exacerbations of chronic respiratory disease [135]. Unlike many other viral infections that sometimes confer lifelong protection, the RV can occur throughout the year and may infect the same individual several times each year [136]. Recent findings in immune responses towards RV have identified proteins that map to antibody responses and explain a misdirection of antibody responses in RV-infected humans, these findings are a crucial first step towards development of a vaccine against RV [137]. An effective vaccine against RV is an elusive goal and would extensively reduce the burden of respiratory symptoms and exacerbations in respiratory health care.

Pollen was another trigger causing more symptoms among children with impaired asthma at both 8 and 12 years and problematic severe asthma, emphasizing the role of sensitization to common aeroallergens in symptomatic asthma. Sensitization is one of the strongest risk factors for asthma but *per se* rarely leads directly to persistent impaired asthma [6, 138]. In support, children with impaired asthma at 8 and 12 years and problematic severe asthma were comparable in specific IgE to children with controlled asthma in each respective cohort. Instead, studies have demonstrated synergism between allergens and viruses in severe exacerbations [139, 140], most notably is that viral infections drive the disease development. For high risk individuals, such as children with problematic severe asthma, new prophylactic antiviral treatments during seasons of RV would open for prevention against severe exacerbations, meanwhile early immunotherapy in appropriately selected children is also useful for disease prevention [141].

Tobacco smoke was a significantly more common trigger in impaired asthma at both 8 and 12 years and in problematic severe asthma than in children with controlled asthma. It is well-known that tobacco smoke reduces the sensitivity to ICS [142], and increases the risk for hospital admission and morbidity compared with the risk among non-smokers with asthma [143, 144]. As with active smoking, exposure to passive smoke has a number of severe effects on asthma control and severity in children [145]. Therefore smoking cessation in relation to childhood asthma is absolutely crucial. Children's health status would benefit if parents and children quit smoking.

6.4 LUNG FUNCTION AND BRONCHIAL HYPERRESPONSIVENESS

Assessment of airflow limitation less than 80% of predicted in FEV1 or PEF was greater in the Severe asthma study compared with among children with asthma in the BAMSE study. Airflow limitation was most predominant in children with problematic severe asthma. Despite that, airflow limitation at 8 years in the BAMSE cohort was associated with more wheezing during viral infections in children with asthma at 12 years than in children with asthma and normal lung function. This finding indicates that children with airflow limitation are prone to more severe effects from viral infections than children with normal lung function. Thus, controlled randomised interventions have to prove this hypothesis, as children with airflow limitation could to a larger extent benefit from preventive treatments and interventions against viral infections than children with normal lung function.

Although children with controlled asthma in the Severe asthma study were included as a reference group to children with problematic severe asthma, these children also revealed more airflow limitation than children with asthma in the BAMSE study. This indicates that all these children, in spite of reported symptom control and continuous treatment with ICS, were not sufficiently controlled in their asthma. However, findings of airflow limitation among children with problematic severe asthma is comparable with other studies [111, 146, 147], and raise concerns about long-term health effects. Few studies have evaluated persistent airflow limitation longitudinally in patients with severe asthma. In the TENOR study, risk factors in adults were older age, male sex, black ethnicity, current or past smoking and longer asthma duration [148], whereas higher education was a protective factor. The

clinical implication of these results for paediatric health care is health education preventing children and adolescents from taking up smoking.

It is noteworthy that, although more pronounced BHR was seen in children with problematic severe asthma, five children were negative to bronchial provocation with methacholine. This raises a question about these children's asthma diagnosis, and required additional asthma diagnostics.

6.5 CONVENTIONAL ALLERGY DIAGNOSTICS

Sensitization to specific IgE of common inhalant and food allergens remained almost comparable between children in the Severe asthma study and children with asthma in the BAMSE study. No differences were found in the respective cohorts in relation to the children's level of asthma control or severity. Sensitization as measured with conventional allergy diagnostics is a common comorbidity in children with asthma, the risk for impaired asthma control seems to be more dependent on the background of sensitization in combination with other triggers than sensitization alone.

6.6 UTILIZING COMPONENT-RESOLVED ALLERGY DIAGNOSTICS

In the Severe asthma study, sensitization was analysed utilizing component-resolved allergy diagnostics (CRD). IgE-profiles with more than three single animal-derived lipocalin, kallikrein and secretoglobin components differentiated children with problematic severe asthma from children with controlled asthma. Furthermore, markers of BHR and eosinophilic bronchial and systemic inflammation were more pronounced among children with multi-sensitization to lipocalin, kallikrein and secretoglobin components. In multi-sensitized children with problematic severe asthma, a tendency was revealed toward an increased number of treated exacerbations with oral corticosteroids in the last year.

Taken together, CRD added new information about children's sensitization and asthma severity compared with conventional diagnostics. CRD also identified a pattern of cross-reactivity within the lipocalin family. This improves the knowledge of how sensitization to different species of furred animals are related. It also enables health care professionals to be more specific about which species of furred animals should be avoided in order to prevent or ameliorate patient symptoms. Exposure and sensitization to domestic animals are common among children [149, 150]. The effects of indoor exposures on allergy development have been debated, in a recent meta-analysis of pet ownership in infancy the risk in children was neither increased nor reduced for development of allergic symptoms later during school-age [151]. In sensitized individuals allergic symptoms to domestic furred animals are a health problem difficult to avoid, especially for children [152]. Indirect allergen exposures in a school environment with many cat owners have been associated with increased burden of asthmatic symptoms [102].

The effect of sensitization in preschool children has been demonstrated through the use of quantitative analysis of numbers of positive sensitizers and IgE-levels, correlating with increased probability of asthma symptoms and reduced lung function [153, 154]. Subsequent studies have followed this field and investigated the association between exposures and

asthma severity. Matsui et al. found that allergen levels in the environment (although not cat allergen levels) correlated with IgE-levels and that high IgE-levels were associated with more severe asthma (5). Multi-sensitization has demonstrated evidence of a role in relation to persistent [97] and severe asthma [147]. Allergen exposure drives increased inflammation in mucosa and reduces barrier function, which promotes development of symptoms and sensitization. In vitro, basophil CD-sensitivity response measured additive dose-response of CD63 from a combined challenge with cat, timothy and mite allergens compared with a single or double challenge with the same allergens in the same patients [155], this experiment showed more severe immune responses in multi-sensitized individuals.

Today's use of crude allergenic extracts in allergen-specific immunotherapy (SIT) will in future be tailored with recombinant allergen-based vaccines [156]. New vaccines based on recombinant proteins with less allergenic activity are being developed, with the aim to make them free from side effects and with prophylactic action against allergic symptoms. Meanwhile, new therapies are being developed, treatment with temperature-controlled laminar airflow (TLA) shows promising effects [157]. A TLA device is placed beside the patient's bed and reduces inhalant exposure during sleep, and randomised, placebo-controlled intervention improved the patients' HR-QoL and reduced bronchial inflammation and cat-specific IgE [158]. Additionally, for patients with severe allergic asthma treatment with omalizumab, a humanized monoclonal anti-IgE antibody, is recommended to reduce exacerbations and symptoms [52].

6.7 HEALTH-RELATED QUALITY OF LIFE

In the present thesis, children with problematic severe asthma were found to have more impaired HR-QoL compared with children with controlled asthma. This finding indicates that children with problematic severe asthma have essential health effects on daily activities and emotional function. Children with severe asthma to a larger extent experience feelings of exclusion and dissatisfaction compared with children with controlled asthma. Such feelings are easily overlooked in clinical practice, and therefore it is recommended to evaluate requirements for psychological support to patients with severe asthma. In addition, psychological educational programs with family therapy have shown positive effects in terms of symptom-related outcomes [159], which potentially could improve the prognosis of severe asthma.

Children's HR-QoL assessed with PAQLQ(S) correlated strongly with the asthma control test, indicating a strong impact of asthma control on children's HR-QoL. Both measurements showed high probability to differentiate between problematic severe asthma and controlled asthma. Measurements of HR-QoL are not always included in guidelines for management of severe childhood asthma [72], which diminished evaluation and support of children's psychological health status. In the present study, to facilitate use of PAQLQ(S) and ACT in clinical practice, reliable cut-offs were analysed through ROC curve analysis. Both the PAQLQ(S) and the asthma control test can assist the management of problematic severe asthma towards closer achievement of controlled asthma. In comparison, the conduct of PAQLQ(S) is more time-consuming for patients and health care professionals than the asthma control test, but the PAQLQ(S) adds more information about both asthma control and

psychological wellbeing. Furthermore, in paediatric health care, HR-QoL assessments have proven to be beneficial to the communication between patient and clinician [160], as well as between child and caregiver [75].

6.7.1 Sex differences

It is well known that boys before puberty to a higher degree than girls are identified to have asthma [161], but after puberty, a shift is seen with higher prevalence of female asthma [162], which is due to both increased incidence and decreased remission of asthma in females compared with males [163]. In line with these observations presence of asthma was more common in boys up to the age of 12 years in the BAMSE study. In addition, among children with reported impaired asthma at both 8 and 12 years compared with controlled asthma, boys occurred more frequently, emphasizing that asthma control, as defined in the BAMSE study, was more impaired in boys compared with girls up to the age of 12 years.

The assessment of HR-QoL in the Severe asthma study showed that girls with problematic severe asthma had significantly lower HR-QoL than boys. Moreover, all of the girls but only 66% of the boys inhaled rescue of short-acting β-2 agonist more than twice a week. No other data indicated that underlying severity of asthma was worse among these girls with problematic severe asthma. In support, sex differences in HR-QoL have also been observed in children with other diseases than asthma [164]. The interpretation of these findings is that girls' more impaired HR-QoL probably reflects differences in girls' and boys' perceptions of symptoms, which is supported by Killian et al., demonstrating more intense dyspnoea in females during bronchoconstriction induced by methacholine provocation compared with in males [165]. According to Osborne et al., sex differences could reflect different psychological responses to asthma, rather than actual differences in the disease itself [166]. It is possible that non-adherence to therapy to a larger extent is shown in patients suffering poor perception of symptoms. A population-based birth cohort from New Zealand analysed risk factors for hospital admission for asthma up to the age of 26 years and one determinant was male sex [167]. The group of subjects with hospital admission suffered impaired lung function and increased bronchial responsiveness to methacholine. These impairments were associated with undertreatment since only 10% and 21% reported use of ICS and short-acting beta-2 agonist, respectively. There is limited knowledge about how to manage patients with poor symptom perception, bronchial provocation may somewhat improve patients' perception and diagnosis of underlying BHR [168], but the long-term effect is unknown. To improve perception of asthma symptoms patients could use action plans which include self-monitoring of symptoms or PEF for treatment of exacerbations [169]. Intervention with parental support and education have shown promising effects on improved perception in parents [170].

6.8 STRENGTHS AND WEAKNESSES

The present thesis was based on children in two different cohorts: the BAMSE birth cohort with a longitudinal study design and the multi-centre cross-sectional Severe asthma study with a selected material of patients. The population-based design of the BAMSE study allows us to generalize findings and compare children's asthma characteristics with healthy individuals. The BAMSE study has a prospective design, with relatively small losses of

subjects since study start, the study also includes well defined exposures permitting comprehensive analyses of disease and symptoms. A general limitation concerning large population-based cohorts is that they are less suitable for studying rare diseases. For this thesis, the study population of BAMSE was too small for extended analyses of children with severe asthma. The 12-year follow-up included only questionnaire data, which without other objective measures of asthma is a clear limitation. Although children with impaired asthma at both 8 and 12 years and children with problematic severe asthma were compared with controlled asthma in each respective cohort, the reference population with controlled asthma was differently constituted in asthma severity between BAMSE and the Severe asthma study as regards ICS treatment. In the Severe asthma study, all children with controlled asthma were selected on the basis of continuous ICS, whereas 32% of children in the BAMSE cohort revealed continuous ICS treatment.

The multi-centre design of the Severe asthma study was required to ensure as many children as possible, 15 paediatric clinics throughout Sweden referred 56 patients with severe asthma. Strength with the Severe asthma study was the comprehensive clinical protocol, making a detailed characterization of problematic severe childhood asthma possible. Furthermore, inclusion and examinations of all subjects were performed by two of the researchers, Jon Konradsen and me, Björn Nordlund, using the same equipment and standardised assessments, and thereby providing a uniformity that is uncommon for multicentre studies. Limitations with the Severe asthma study are a small population of children to study and the cross-sectional design which hampers analysis of finding robustness. Despite intense efforts, we were not able to include a group of children with controlled asthma equally large as the group with problematic severe asthma. The reasons for that were stringent criteria for children with controlled asthma group, such as age-matching to patients with problematic severe asthma. Children with controlled asthma may also have experienced less motivation to participate since the advantages involved were less pronounced. Another factor is that all inclusion was performed in paediatric specialist clinics for allergy or pulmonology, the number of children with controlled asthma is limited in these clinics, especially when the asthma is under control and no other comorbidities exist the patient is likely to be transferred to primary health care.

7 CONCLUSIONS

The burden of symptoms was high among schoolchildren with asthma, about one in five children reported impaired asthma control at both age 8 and 12 years. The most common factors of impaired asthma control were family history of allergic disease and comorbidity of rhinitis.

- Age-related differences in parental reports of children's asthma control were seen, underlining the importance of using validated measures of asthma control in paediatric health care, with a focus on the patient's own perception.

- The prevalence of severe asthma is 0.4% in a Swedish urban population and 4% among children with asthma.

- Children with problematic severe asthma were to a high degree classified as difficult-to-treat, based upon characteristics in these children's history as regards environmental exposures and untreated comorbidities. Family history of children with difficult-to-treat asthma was associated with lower socio-economy. Further studies are needed to improve the knowledge on how to manage these children in paediatric health care.

- In comparison to conventional allergy diagnostics, component-resolved allergy diagnostics revealed that children with problematic severe asthma were associated with multi-sensitization to animal-derived components of secretoglobin, lipocalin and kallikrein. These children showed evidence of more severe eosinophilic bronchial inflammation than children sensitized to fewer animal-derived components. Component-resolved allergy diagnostics may prove useful in asthma severity evaluation.

- Children with problematic severe asthma suffer from more impaired health-related quality of life than patients with controlled asthma, including essential effects on daily activities and emotional well-being. A difference was observed in reports from children with problematic severe asthma, with girls perceiving a more impaired health-related quality of life than boys. Children's quality of life needs to be included in asthma severity assessment.

8 FUTURE PERSPECTIVES

Findings of this thesis show that paediatric health care has challenges in reducing the burden of symptoms in schoolchildren with asthma and improving the quality of life in children with severe asthma. Additional research is needed to involve health care professionals in managing underlying and associated factors in children with impaired asthma control and poor treatment response. An increased involvement would facilitate design and implementation of new asthma care programs in paediatric health care.

In order to follow up the high proportion of children suffering from impaired asthma control at 8 and 12 years in the BAMSE cohort, a proximal evaluation has been done in children at 16 years. Clinical examination with measurements of lung function, bronchial inflammation and blood analysis were applied, together with questionnaires containing information about children's history of allergic diseases. A major advantage of the 16-year follow-up is a larger extent of objective measurements of asthma severity than at the 12 years' assessment. Extensive data collection provides new study opportunities relating to factors associated with asthma control. Particularly interesting areas to study are the role of sensitization to animal-derived allergen components in adolescents with asthma. Another opportunity is to analyse factors associated with airflow limitation and inflammation among adolescents with asthma. Findings in the BAMSE study demonstrated evidence of a great impact of viral infections on asthma control. New diagnostics are being developed for analysing effects of rhinovirus on asthma control and sensitization.

Proposals for randomised controlled trials exist based on the findings of the present thesis. In particular, one identified topic for further studies is the effect of nurse-led home visits to explore aggravating factors that inhibit improvements in children's asthma control. The intervention should include family support with education and actions against identified barriers in children's homes, such as environmental exposures, poor adherence or psychosocial factors that hinder families from obtaining and following health information.

Another clinical challenge is comorbidity of rhinitis, which was a common feature among children with impaired asthma control at 8 and 12 years and with problematic severe asthma. The association of rhinitis to asthma control seems to be more pronounced in patients that have never received nasal corticosteroids [103]. A randomised clinical trial could further clarify the effectiveness of nasal steroids on asthma control in children.

Primary prevention with allergen avoidance is difficult to perform in real life, but is possible through nocturnal temperature laminar airflow (TLA) treatment [158]. TLA treatment is used during the patient's sleep and has no side effects on patient health. A future perspective is to analyse the effectiveness of treatment with TLA on development of sensitization and exposure. Preschool children with severe wheezing and family history of allergic diseases are a group of particular interest. It is worth noting that primary prevention studies investigating the effect of allergen avoidance on the development of allergic diseases are long-term and therefore costly.

Respiratory diseases other than asthma need further clinical evaluation in paediatric health care. The purpose is to improve the overall understanding of the health effects of lung diseases in children. Long-term effects in children born with e.g. bronchopulmonary dysplasia (BPD) are largely unknown and poorly defined in schoolchildren. Our research team has recently collected data from children with diagnosed BPD and asthma to conduct an analysis with two comparable age- and gender-matched groups. Although respiratory diseases of BPD and asthma occur differently, the perception and psychological responses on health-related quality of life may be similar in these diseases. Other aspects of BPD and asthma are inflammatory markers that could be analysed in relation to children's disease burden and responses to treatment. To date, long-term requirements related to health care for children with BPD are unknown and need to be explored.

Finally, longitudinal data in children with asthma is lacking. Health registers with data from children with asthma could provide a foundation for generating greater understanding about health needs. A national asthma register is planned in Sweden. Potentially, the register could provide important information to all actors in the health system, from health care providers to health care professionals and patients. Patients should be able to use the register for their own purposes, to better control their asthma. Health care providers could benefit by taking part of information for planning and distributing resources to the health care system. The benefit for health professionals would be to gain more specific information about patients, which could be applied in the health care system, and researchers could obtain data from the health register in a more efficient way than through managing large cohort studies.

9 SAMMANFATTNING PÅ SVENSKA

Astma är en global sjukdom som förekommer hos cirka tio procent av alla barn i Sverige. Astma är en inflammatorisk luftvägssjukdom som kännetecknas av en överkänslighet och en sammandragning av luftrören. Detta orsakar hosta, andningsbesvär och täthetskänsla i bröstet. Några av de vanligaste utlösande orsakerna till astmasymtom hos barn är virusinfektioner, ansträngning och allergier.

Astma bör klassificeras för att tydliggöra och underlätta bedömningen av barns och ungdomars behov av vård och behandling. Astmakontroll kan definieras som den grad av symtom som påvisas hos patienten, tillsammans med den samlade riskbedömningen för att patienten ska drabbas av symtom eller försämrad lungfunktion. För att utvärdera astmakontroll på kliniken finns olika metoder. En är att fråga förälder och barn, en annan att använda validerade frågeformulär som patienten själv fyller i. Dessa formulär kan på ett standardiserat sätt underlätta utvärderingen av patientens astmakontroll. Målsättningen med astmavård är att patienten ska uppnå god kontroll av sin sjukdom utan allvarliga medicinska biverkningar eller försämrad livskvalitet. Välfungerande vård med patientutbildningen är en förutsättning för att behandlingsmålen ska uppnås. Barn och familj behöver kunskap om hur man tar sina läkemedel på rätt sätt, de behöver även informeras om vad som utlöser symtom och försämringar, samt hur dessa undviks. En lyckad patientutbildning förutsätter en bra kommunikation mellan vårdgivare och patient. En annan viktig faktor är patientens och familjens förmåga att ta till sig hälsoinformation och följa den. Studier har visat att nedsatt förmåga att följa hälsoinformation resulterar i sämre astmakontroll och ett ökat behov av sjukvård.

När det gäller astmans svårighetsgrad kan den definieras efter patientens erforderliga dos av läkemedel för att uppnå astmakontroll. Hos de flesta varierar svårighetsgraden över tid, en kontinuerlig astmavård underlättar bedömningen av vilken typ av behandling som är nödvändig.

Svår astma hos barn kännetecknas av bristande astmakontroll trots hög dosering med antiinflammatoriska läkemedel. Barn med svår astma har stort behov av sjukvård och sjukdomen riskerar att leda till frånvaro från skola eller förskola. Den orsakar inskränkningar och begränsningar i barnets och familjens dagliga liv. Förhållandevis lite forskning finns på patientgruppen barn och ungdomar med svår astma, och många aspekter av sjukdomen är okända.

Allergier är särskilt vanliga hos barn och ungdomar med astma. Detta ger upphov till ökad inflammation i luftrören och ökade besvär vid exponering av allergen som patienten är överkänslig mot. I astmavården är det därför viktigt att diagnostisera allergier för att kunna ge råd om hur exponering ska kunna undvikas vid påvisad allergi. Effekter av astma på barns och ungdomars livskvalitet är viktiga att belysa för att på bästa sätt stödja och underlätta barns liv med en kronisk sjukdom. Särskilt lite kunskap finns om hur barn med svår astma mår, vilka begränsningar sjukdomen orsakar och vilka psykologiska aspekter

som är viktiga för sjukvården att åtgärda.

Målet med den här avhandlingen var att studera förekomsten av symtom och faktorer som är associerade med bristande astmakontroll hos skolbarn, med särskild vikt på att:

- Analysera förekomsten av svår astma hos skolbarn i normalbefolkningen.
- Identifiera faktorer i barnens sjukdomshistoria som är relaterade till bristande astmakontroll och svår astma i jämförelse med lindrig astma.
- Utnyttja komponentbaserad allergidiagnostik och jämföra allergier mellan barn med svår och lindrig astma.
- Utvärdera livskvalitet hos barn med svår astma i jämförelse med lindrig.

Den här avhandlingen baseras delvis på den populationsbaserade födelsekohorten BAMSE där 3 015 barn i åldrarna 8 och 12 år analyserats. Studiepopulationen bestod ursprungligen av 4 089 barn som inkluderats från Stockholmsregionen under åren 1994 till 1996. Enkätdata är insamlade sedan nyföddhetsperioden med bakgrundsfaktorer som ärftlighet för allergisjukdom, exponering för tobaksrök, livsstil mm. Därefter har data samlats in via enkäter rörande möjliga astmasymtom, sjukvård och miljöfaktorer. Information om ordinerade läkemedel och uthämtade läkemedel finns i det Svenska läkemedelsregistret. I registret finns information om alla uttag av läkemedel som gjorts åt barnen i BAMSE-studien. Detta gör det möjligt att identifiera antalet barn med hög-dos behandling med antiinflammatoriska läkemedel som kan klassificeras som svår astma. Astmakontroll baserades på föräldrarnas rapportering av symtom hos barnen vid 8 och 12 års ålder.

Avhandlingen innehåller också barn och ungdomar från den nationella studien om svår astma. Från 15 kliniker har 56 barn inkluderats med svår astma och jämförts med 39 barn med lindrig astma. Information om barnens sjukdomshistoria har precis som i BAMSE-studien samlats in. I tillägg har barnen rapporterat sin hälsorelaterade livskvalitet med hjälp av frågeformulär, tillsammans med mätningar av lungfunktion, inflammationsmätningar i luftrören och i blodet. Allergitester har gjorts för att studera förekomst av IgE-antikroppar.

Bland barn med astma i BAMSE-studien var förekomsten av bristande astmakontroll vid 8 år hela 84 procent, och vid 12 år 53 procent. Tydliga skillnaderna sågs i föräldrarnas rapportering med högre andel barn med nedsatt astmakontroll vid 8 år än vid 12 år. Även andelen med symtom varierade i stor utsträckning, med mer aktivitetsbegränsningar på grund av astma och ökade episoder av väsande andning vid 12 år än vid 8 år. Nattliga astmasymtom och akuta sjukvårdsbesök på grund av astma var däremot vanligare vid 8 år. Resultaten understryker att även om astmasymtom ser ut att minska vid 12 år kan detta inte automatiskt tolkas som en klar förbättring, snarare tydliggörs behovet av att utvärdera barnens upplevelse av symtom i stället för föräldrarnas. Det föreligger en klar risk att föräldrarna underskattar barnens astmakontroll. I BAMSE-studien var 13 barn identifierade med svår astma med hjälp av det Svenska läkemedelsregistret, vilket motsvarar 0,4 procent av normalbefolkningen och 4 procent bland alla barn med astma runt 12 års ålder.

Hos 91 skolbarn med bristande astmakontroll vid 8 och 12 års ålder i BAMSE-studien samt 56 barn med svår astma från Svår astma-studien utvärderades faktorer i barnens sjukdomshistoria, nästäppa och snuva och förälder med allergisk sjukdom var vanligare

hos de barnen i jämförelse med lindrig astma. I övrigt var 68 procent av barnen i BAMSE-studien obehandlade trots symtom med nästäppa och snuva, bland barn med svår astma endast 7 procent.

Bland 39 procent av barnen med svår astma fanns faktorer i barnens sjukdomshistoria som ökade risken för astmabesvär och gjorde barnen mer svårbehandlade. Dessa faktorer var bland annat obehandlade besvär av nästäppa och snuva samt gastrit, exponering av rökning från föräldrarna eller ungdomen själv och förekomsten av pälsdjur i hemmet trots att barnet påvisats med allergi mot samma djur, samt problem med mögel i bostaden trots påvisad allergi mot mögel. Gemensamt hos de här skolbarnen var lägre socioekonomi (föräldrarnas utbildningsnivå och årsinkomst) i jämförelse med övriga barn med svår astma. Resultaten tolkas som att familjerna har en bristande förmåga att följa hälso-sjukvårdens råd att förebygga symtom och därigenom minska effekterna av astmasjukdomen. Ökat fokus på patientutbildning och hembesök föreslås kunna stärka de här familjernas förmåga att förbättra barnens hälsa.

Majoriteten av barnen med astma i BAMSE- och Svår astma-studien hade en allergisk läggning när vi analyserade IgE-antikroppar i deras blod. Inga tydliga skillnader var presenterade mellan bristande astmakontroll vid 8 och 12 års ålder, svår astma eller lindrig astma med traditionell allergidiagnostik. I traditionell allergidiagnostik finns alla proteiner från testade allergen i samma extrakt, till skillnad från komponentupplöst allergidiagnostik som baseras på specifika proteiner från varje allergen. Med komponentupplöst diagnostik fanns skillnader mellan svår och lindrig astma. Flera olika IgE-antikroppar mot pälsdjur från katt, hund, häst och mus var vanligare bland en större del av skolbarnen med svår astma, 25 procent respektive 8 procent. Dessutom hade barnen med flera olika antikroppar mot pälsdjur i större utsträckning ökade tecken på luftvägsinflammation än de som analyserats med färre av dessa IgE-antikroppar. Detta öppnar upp för att minska exponering och effekten av pälsdjursallergen hos barn med svår allergisk astma. Nya behandlingsmetoder finns att tillgå som luftrenare som bara används på natten när barnet sover och injektioner med anti-IgE behandling som minskar effekten av den allergiskareaktionen. Besök av hem och skola kan möjliggöra identifiering av källor av allergen exponering, viket bör undersökas i framtida studier.

Hos barnen med svår astma var livskvaliteten tydligt försämrad i jämförelse med dem som hade lindrig astma. Det betyder att skolbarn med svår astma i ökat omfång upplever begränsningar i dagliga aktiviteter och upplever fler känslomässiga problem på grund av astma än hos barn med lindrig astma. I vården av barn med svår astma bör också barnens emotionella välbefinnande observeras och stödjas. Kommande studier bör undersöka och identifiera välfungerande och lämpliga strategier för barn med svår astma. Ett annat fynd hos barnen med svår astma var att flickorna rapporterade betydligt sämre livskvalitet än pojkarna med samma sjukdom. Detta fynd belyser att flickor och pojkar upplever sjukdom på olika sätt, trots att inga data i övrigt visade att flickornas sjukdom var svårare än pojkarnas. Snarare bör dessa fynd tas i beaktning när man utvärderar behov och effekter av stärkande åtgärder för skolbarn med svår astma.

I konklusion visar den här avhandlingen att bristande astmakontroll är vanligt bland skolbarn, och att barn med svår astma har betydligt sämre livskvalitet är dem med lindrig astma. De vanligaste faktorerna i sjukdomshistorien hos barn med bristande astmakontroll vid 8 och 12 år och svår astma var snuva och nästäppa samt ärftlighet för allergisk sjukdom.

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