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Allergic Disease among Adolescents

IgE-sensitisation, Health-Related Quality of Life and physical activity

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FACULTY OF MEDICINE | LUND UNIVERSITY





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Allergic Disease among Adolescents

IgE-sensitisation, Health-Related Quality
of Life and physical activity

Therese Sterner



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DOCTORAL DISSERTATION

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<p>Abstract: Background: Allergy, asthma and atopic dermatitis have been found to be the most common chronic diseases among young children and adolescents, which makes it vital to identify influencing factors. Allergic sensitisation is a strong risk factor for the development of allergic disease, thus knowledge of the sensitisation occurrence and its time trends in the population is important. It is known that children with allergic disease have an impaired Health-related Quality of Life and their physical activity can be affected. It is of importance to study these factors also during adolescence due to that it can be a critical period in their life.</p> <p>Aims: The overall aim of this thesis was to increase knowledge about self-reported allergic disease in adolescence, with regard to symptom occurrence, contributing factors, sensitisation profile, impact on physical activity and Health-Related Quality of Life.</p> <p>Methods: The present thesis is based on a cross-sectional cohort of adolescents in southern Sweden. The design of the studies was based on both quantitative Studies (I, II & III) and a qualitative Study (IV) with 36 interviews. The international ISAAC questionnaire was used as well as questions regarding physical activity and Health-Related Quality of Life in Study I, II & III. In Study II, the IgE sensitization was examined by means of both extract-based and component-based tests.</p> <p>Results: Of all adolescents 32% reported at least one allergic disease. 67% reported one allergic disease and 33% reported more than one. No allergy-related disease were reported by 68%. Sensitization to airborne allergens was significantly more common than sensitization to food allergens, 43% vs. 14%, respectively. IgE response was significantly higher in airborne allergens among adolescents with rhinoconjunctivitis ($p < 0.001$) and eczema ($p < 0.01$). Among 53 adolescents with self-reported allergic disease, 60% were sensitized. Sensitization to food allergens was found among those with rhinoconjunctivitis, but only to PR-10 proteins. There were no noticeable differences in physical activity among adolescents with and without allergic disease ($p \geq 0.3$ in all comparisons). Clear differences in HRQoL were observed depending on current or previous symptoms. The findings in the qualitative study suggested that; Being physically active when suffering from an allergic disease means becoming aware of the symptoms and thus what strategies are needed.</p> <p>Conclusions: A high number of affected adolescents were identified. The major grass pollen allergen Phl p 1 was the main sensitizer, followed by Cyn d 1 and Phl p 2. Sixty-one percent reporting any allergic disease were sensitized, and the allergen components associated with wheeze and rhinoconjunctivitis were Fel d 4, Der f 2 and Can f 5. The noticeable impaired HRQoL during pollen season in relation to self-reported symptoms observed in the present study warrants further attention by health care. The participants in this study are quite physically active but have to struggle with symptoms, medications and try out which activity that suits them. The care of adolescents with allergic disease needs to be improved from both in the perspective of nursing and that of medical care.</p>		
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Allergic Disease among Adolescents

IgE-sensitisation, Health-Related Quality
of Life and physical activity

Therese Sterner



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MADE IN SWEDEN 

*Two roads diverged in a wood, and I –
I took the one less travelled by,
And that has made all the difference.*

Robert Frost.

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Abstract

Background: Allergy, asthma and atopic dermatitis have been found to be the most common chronic diseases among young children and adolescents, which makes it vital to identify influencing factors. Allergic sensitisation is a strong risk factor for the development of allergic disease, thus knowledge of the sensitisation occurrence and its time trends in the population is important. It is known that children with allergic disease have an impaired Health-related Quality of Life and their physical activity can be affected. It is of importance to study these factors also during adolescence due to that it can be a critical period in their life.

Aims: The overall aim of this thesis was to increase knowledge about self-reported allergic disease in adolescence, with regard to symptom occurrence, contributing factors, sensitisation profile, impact on physical activity and Health-Related Quality of Life.

Methods: The present thesis is based on a cross-sectional cohort of adolescents in southern Sweden. The design of the studies was based on both quantitative Studies (I, II & III) and a qualitative Study (IV) with 36 interviews. The international ISAAC questionnaire was used as well as questions regarding physical activity and Health-Related Quality of Life in Study I, II & III. In Study II, the IgE sensitization was examined by means of both extract-based and component-based tests.

Results: Of all adolescents 32% reported at least one allergic disease. 67% reported one allergic disease and 33% reported more than one. No allergy-related disease were reported by 68%. Sensitization to airborne allergens was significantly more common than sensitization to food allergens, 43% vs. 14%, respectively. IgE response was significantly higher in airborne allergens among adolescents with rhinoconjunctivitis ($p < 0.001$) and eczema ($p < 0.01$). Among 53 adolescents with self-reported allergic disease, 60% were sensitized. Sensitization to food allergens was found among those with rhinoconjunctivitis, but only to PR-10 proteins. There were no noticeable differences in physical activity among adolescents with and without allergic

disease ($p \geq 0.3$ in all comparisons). Clear differences in HRQoL were observed depending on current or previous symptoms. The findings in the qualitative study suggested that; Being physically active when suffering from an allergic disease means becoming aware of the symptoms and thus what strategies are needed.

Conclusions: A high number of affected adolescents were identified. The major grass pollen allergen Phl p 1 was the main sensitizer, followed by Cyn d 1 and Phl p 2. Sixty-one percent reporting any allergic disease were sensitized, and the allergen components associated with wheeze and rhinoconjunctivitis were Fel d 4, Der f 2 and Can f 5. The noticeable impaired HRQoL during pollen season in relation to self-reported symptoms observed in the present study warrants further attention by health care. The participants in this study are quite physically active but have to struggle with symptoms, medications and try out which activity that suits them. The care of adolescents with allergic disease needs to be improved from both in the perspective of nursing and that of medical care.

Original papers

This thesis is based on the following papers:

- I Sterner T, Uldahl A, Svensson Å, Björk J, Svedman C, Nielsen C, Tunsäter A, Bruze M, Kiotseridis H (2018) The Southern Sweden Adolescent Allergy-Cohort: Prevalence of allergic diseases and cross-sectional associations with individual and social factors. *J Asthma* 2019 Mar;56(3):227-235. doi.org/10.1080/02770903.2018.1452033
- II Sterner T, Uldahl A, Svensson Å, Borres MP, Sjölander S, Tunsäter, A, Björk J, Svedman C, Bruze M, von Kobyletzki L, Kiotseridis H (2019) IgE-sensitisation in a cohort of adolescents in southern Sweden and its relation to allergic symptoms. *Clin Mol Allergy* 2019;17:6
doi: 10.1186/s12948-019-0110-6
- III Sterner T, Uldahl A, Svensson Å, Tunsäter A, Svedman C, Bruze M, Von Kobyletzki L, Kiotseridis H, Zakrisson AB, Björk J
Physical activity and health-related quality of life in relation to allergic disease among adolescents – results from a cross-sectional study. In manuscript
- IV Sterner T, Björk J, Svensson Å, von Kobyletzki L, Zakrisson A-B.
Physical activity among adolescents with allergic disease; a five-year qualitative follow-up study. In manuscript.

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Abbreviations

ABISS	Allergiska Barn I Södra Sverige (Allergic Children in southern Sweden)
AD	Atopic Dermatitis (Eczema)
ALADDIN	Assessment of Life-style and Allergic Disease During Infancy
ARIA	Allergic Rhinitis and its Impact on Asthma
BAMSE	Barn Allergi Miljö Epidemiologi (Children, Allergy, Milieu, Stockholm, Epidemiology)
GINA	Global Initiative for Asthma
HRQoL	Health-Related Quality of Life
ISAAC	The International Study of Asthma and Allergies in Childhood
IgE	Immunoglobuline E
ISAC	Immuno Solid phase Allergen Chip
OAS	Oral Allergy Syndrome
OLIN	Obstructive Lung disease in Northern Sweden
PADQLQ	Paediatric Allergic Disease Quality of Life Questionnaire
RC	Rhinoconjunctivitis
SPT	Skin Prick Test
WHO	World Health Organisation

Preface

Since the beginning of 2000, I have worked as an Allergy adviser nurse in the province of Skåne, Sweden. I was accepted as a PhD student at Lund University in May 2014 after two years a Logistics in the Allergic Children in southern Sweden (ABISS) project.

When I started work as an Allergy adviser nurse, I had little experience of respiratory allergy but was very familiar with atopic dermatitis after having worked as a nurse at a department of dermatology. My work as an Allergy adviser nurse includes providing information and education to children, their parents and family members, day care centres, schools and teachers, school canteen chefs and staff. This is a very important task and I often feel happy after meeting this “audience”. I love to inspire and present a lecture in an interesting way so that the audience grasps and remembers the message. After several years I realized that schools were requesting more and more help with allergy education. I sometimes received reports that 30% of the children had some kind of allergy and/or asthma and that many had a medical certificate exempting them from all forms of physical activity (PA) due to their asthma. I asked myself and my colleagues if it could be the true that such a large number of children suffer from severe allergic disease and whether there are more such children who have not come to the attention of the healthcare system. We felt the need for increased knowledge about the prevalence and severity of allergic disease among children and adolescents in the general population in the southern part of Sweden.

The research presented in this thesis focuses on the population based prevalence of self-reported severity of allergic disease. The hope is that the thesis will provide some valuable knowledge about symptom prevalence, sensitisation, Health-Related Quality of Life (HRQoL) and PA among adolescents to be used by healthcare staff and allergy professionals like myself but with the overall aim of improving the health and well-being of those suffering from allergic disease.

Introduction

Allergic diseases have increased worldwide in recent decades, although a stagnation has lately been seen in the western world^{1, 2}. Allergy, asthma and atopic dermatitis have also been found to be the most common chronic diseases among young children and adolescents, which makes it vital to identify different influencing factors. In Sweden some cohorts of children were established many years ago to study the risk factors and variations in incidence, but to date there has been no such cohort in the southern part of Sweden, see fig 1.

The ongoing cohorts are;

The Obstructive Lung Disease in Northern Sweden (OLIN) studies since 1985 and two child cohorts since 1996 (n=3,430) and 2006 (n=2,585) and 2017 (n=2,712). Data collection is through questionnaires, blood samples and skin prick test (SPT). Research has shown that children growing up with pets are not at any greater risk of developing asthma or allergies, which finding has been taken account of in healthcare.

The Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE) study is an ongoing prospective, longitudinal, population-based birth cohort study including 4,089 children born between 1994 and 1996. Data collection is through questionnaires, blood samples, SPT and physical examinations. Research has contributed to knowledge about how lifestyle, hereditary factors and the environment might affect allergy, asthma and lung development.

The Swedish prospective, longitudinal Children of Western Sweden Study comprises a birth-cohort of >4,000 children born in 2003. Data collection is through questionnaires, SPT and physical examination. The study has contributed knowledge about the association between eating fish in childhood and allergy, but also about the link between overweight and allergy.

The Assessment of Life-style and Allergic Disease During Infancy (ALADDIN) study, is an ongoing prospective birth cohort of 330 children, since 2004. The study focuses on the impact of lifestyle during pregnancy and

early childhood and development of allergic disease in a community with an anthroposophical lifestyle.

Differences in climate (north to south) and air pollution from the countries south of the Baltic Sea might affect the development and occurrence of allergic diseases. In a study from Finland it was found out that asthma-related symptoms were similar in the southern and northern parts of the country, but that other respiratory symptoms were more common in the southern part. These results support the view that environmental factors have a substantial effect on respiratory symptoms, but less effect on the prevalence of asthma ³. Geographic differences in asthma prevalence were also demonstrated in the International Study of Asthma and Allergies in Childhood (ISAAC), suggesting that the environment and epigenetics might have a crucial role in patients with asthma ⁴.

Allergic sensitisation is the first step in allergy development and is therefore a very strong risk factor for the development of allergic disease, thus knowledge of the sensitisation occurrence and its time trends in the population is important ⁵⁻⁷.

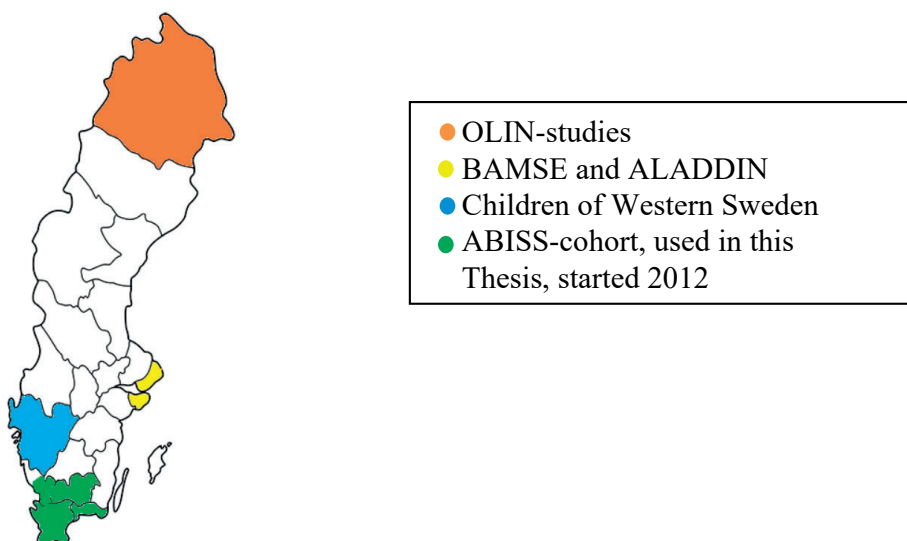


Figure 1. Ongoing child-cohorts for allergic disease in Sweden

Studies have revealed that many of the children and adolescents with allergic disease have symptoms that may affect their HRQoL⁸⁻¹³. These symptoms could be caused by uncontrolled allergic disease due to ineffective medication, wrong medication or an adherence problem¹⁴. Adolescence is a sensitive period of life and allergic disease may be difficult to treat due to poor adherence to treatment. Adolescents may not prioritize the energy required to manage multiple chronic diseases due to focusing on social interaction, academic work, sports and other extracurricular activities. However, sport activities and exercise lead to symptoms such as cough, tiredness, itchy skin due to heat and sweating as a result of physical exertion¹⁵. Adolescents may feel embarrassed when dry and/or inflamed skin sets them apart from their friends, which may lead to social isolation. In addition, the academic challenges of school admissions could cause increased sleep and psychological pressure that can worsen their allergic disease. It is important for healthcare professionals to discuss how they work with adolescents as individuals in order to provide high quality care. They have to decide if something in the team process needs to be changed to enhance opportunities for engagement between nurses and patients. In addition, such discussions can enable healthcare professionals to challenge beliefs and values pertaining to practice and create a shared vision of person-centered care. This should facilitate the development of multidisciplinary clinical teams and enhance the effectiveness of staff relationships, thus making them better able to identify practice developments and inform patients about results of diagnostic tests^{16, 17}.

Human beings have the ability to make appropriate choices and adapt their lifestyle if they obtain the knowledge and tools to do so¹⁷. Person-centred care gives the patients greater opportunities to influence their treatment and take responsibility for self-care, while at the same time leading to reduced costs due to fewer healthcare visits¹⁷.

The lack of data from southern Sweden about allergic disease among adolescents in the general population was the starting point for a new cohort entitled Allergic Children in Southern Sweden (ABISS), 2012.

Background

Adolescents

The world has more young people than ever before and, according to UNICEF, of the 7.78 billion people worldwide, about 1.2 billion are in the 10 -19 year age group¹⁸. Adolescence is a critical period when young people transition from childhood to adulthood¹⁹. They go through different phases with changes in biological, emotional, cognitive and social dimensions. This also affects their relationship with parents, siblings and other relatives¹⁹. The period also influences their way of thinking about life, which they do in a different manner than in childhood²⁰. It is an age when they become independent individuals, forge new relationships and learn skills and behaviour that will last for the rest of their lives. It can also be one of the most challenging periods in terms of their health. Studies have shown that living with asthma involved living with physical limitations, a feeling of being different, and an increased risk of morbidity²¹⁻²³. A challenge for adolescents with atopic dermatitis is adherence to daily treatment^{24, 25}.

Improving adolescents' health is a worthwhile investment, as it will not only improve health and survival in the short term, but provide benefits for future generations²⁶.

Allergic disease

The terms allergic diseases and allergy-related diseases are not well defined. Atopic dermatitis is the first clinical manifestation of atopy and the so called atopic march²⁷ with progression different atopic manifestations also named atopic diseases^{27, 28}.

Thus, in this thesis allergic disease refer to atopic dermatitis (AD), asthma, food-allergy, rhinitis and rhinoconjunctivitis (RC). Allergic contact dermatitis is excluded. In most diseases, there is a link between hereditary factors,

environment and lifestyle, which is especially relevant in terms of allergy. Allergy-related disease affects a huge proportion of the paediatric population during the first 12 years of life²⁹. The development of AD, asthma and rhinitis is a dynamic process, although both new cases and remission are common throughout childhood^{16, 29-31}. Using self-reported data is an easy way to obtain information about a population.

IgE-sensitisation

IgE antibodies are markers of and major contributors to many allergic reactions, which is known as sensitisation³². Sensitisation can be described as an inappropriate response of the immune system when exposed to substances (allergens) normally tolerated by healthy people. The sensitisation is achieved by the trapping of the allergen from the mucosa of antigen-presenting cells, which transport the allergen to the lymph nodes where activation of T helper cells occurs, a Th2-dominant response. The IgE antibodies thus formed may be directed against the genuine allergen (mostly a protein) or secondarily bind to molecules with similar epitopes on their surface, causing the phenomenon of cross-reactivity³³. The antibodies bind to receptors on mast cells and basophils. Upon renewed allergen exposure, cross-links between the allergen and two IgE molecules occur on the mast cell or basophil. Mast cells reside in vascularized tissues throughout the body and particularly within tissues that are in contact with the external environment³⁴. The prevalence of allergic sensitisation has increased in Sweden during recent decades to around 30% among children^{5, 35}. Sensitisation in childhood is a predictor of the development of RC at a later stage among adolescents³⁶. The sensitisation can be mono, (sensitisation to one allergen source) oligo (sensitisation to more than one allergen source) or poly (sensitisation to a large number of different biological sources)³². The allergic profile is important, although IgE antibodies against perennial allergens is related to new-onset asthma whereas IgE sensitisation against seasonal (pollen) aeroallergens has been shown to be more related to rhinitis than asthma in both cross-sectional and longitudinal studies^{32, 37}. It has been shown that children with multimorbid asthma and rhinitis have a polysensitised IgE pattern to several allergen sources³⁷. There are also geographical differences concerning which allergic profile is most clinically relevant for asthma and airway inflammation³². IgE sensitisation is also found among individuals without allergy-related diseases³⁸. Sensitisation can be verified by different kind of in vivo and in vitro techniques; Provocation, the SPT, the S-IgE test (Phadiatop or Fx5) or ImmunoCap ISAC. ISAC is to be

seen as a supplement the basic extract-based test, due to the component-resolved IgE antibody determination³⁹. The various allergenic components are grouped into protein families, based on their structure and biological function³².

Atopy

The distinction between atopy and atopic disease can in some cases be important⁴⁰. Atopy refers to the presence of clinical symptoms that occur following an interaction between allergen-specific IgE and exposure to an allergen (a common normally harmless protein)^{28, 41}. Although specific IgE is necessary for a reaction to be classified as allergic, other mechanisms can cause similar symptoms, making it necessary to test for the antibodies for diagnosis. A child with atopy produces specific IgE antibodies after exposure to common environmental allergens and is said to be sensitised to one or several of these allergens. Common allergens are proteins in pollens, house dust mites, animal dander and foods. IgE-mediated atopic diseases should be perceived as different manifestations of an immunological disease^{42, 43}. The association between atopy and atopic dermatitis, asthma and RC appear to be weaker in developing countries than in industrialized nations⁴³.

Allergic comorbidity

Allergic disease with different symptoms coexist in many children, termed allergic or atopic comorbidity^{16, 28, 29}. For example, in the ISAAC international study almost 15% of asthmatic children aged 6–7 years and 40% of those aged 13–14 years also had allergic rhinitis⁴⁴. Coexistence of AD, rhinitis and asthma in the same child is more common than expected by chance alone, both in the presence and absence of IgE sensitisation, suggesting that these diseases share causal mechanisms^{16, 28, 42}. Comorbidity at preschool age has been shown to increase the risk of comorbidity regardless of IgE sensitisation⁴⁵. AD occurring in the first few months of life is the first manifestation of the allergic march, and numerous investigations support the existence of atopic diseases that comprise the atopic march^{27, 46-48}. The link between the presence of early AD in childhood and the development of food allergy, especially peanut, egg and milk allergies, is rather well-documented^{28, 49}. In a longitudinal study from western Sweden it was found that in children who had two or more of any allergic manifestations in infancy, more than half had some form of allergic disease at eight years of age⁴⁵. Furthermore, the more allergic manifestations a

child had in infancy, the greater the risk of allergic disease and comorbidity at eight years of age, data also confirmed by other studies ^{42, 45}. Thus it is important to understand that the presence of AD in early childhood increases a child's risk of developing asthma later during childhood compared to a child without AD ^{28, 46}. Moreover, the risk is further increased by the presence of comorbid atopy or wheezing ⁴⁶.

Asthma

Asthma is one of the most common non-communicable chronic diseases among children worldwide, with a worldwide prevalence of 12% ^{50, 51}. It is characterized by chronic airway inflammation defined by a period of respiratory symptoms; wheeze, cough, shortness of breath and chest tightness. These symptoms can vary over time and in intensity ⁵². Children who wheeze are at increased risk of developing asthma and allergies, but not all children with wheeze have asthma. The first symptom often starts in childhood, although it can also develop in adults and affects people of all ages ⁵³. Asthma is divided into different phenotypes and can be allergy related as well as non-allergy related. More than 80% of patients with asthma also have RC ^{54, 55}. It is well known that psychological comorbidity in adolescents with asthma increases with the severity of the asthma ^{10, 56, 57}. Children with asthmatic symptoms are more often given the diagnosis of asthma than is the case with adolescents presenting similar problems. The differences between wheeze and asthma is not totally clear and both can be used in studies. Although asthma is usually used after a diagnosis by a doctor, the presence of airway symptoms can also be defined as four or more wheezing episodes during the past year or at least one episode of wheezing combined with corticosteroids treatment ⁵⁸. Asthma prevalence estimates vary across time and region but can be useful for healthcare resource planning purposes, while prediction models are mainly developed for clinical applications ^{59 60}.

Atopic dermatitis

Atopic dermatitis (AD) or eczema is a chronically relapsing, inflammatory skin disease with pruritus ^{51, 61, 62}. The word eczema is of Greek origin and its original meaning is "to boil over" ⁶¹. It is a genetically determined skin disease characterized by dry skin, intense itching and recurrent eczematous lesions ⁶³. The dry skin and tendency to develop itchy rashes typically begin in childhood but persistency into adulthood is common and in some cases can be lifelong ²⁴.

⁶⁴. Even if the AD has apparently resolved, it can re-appear at any stage during life and most certainly during adolescence due to parents no longer supervising skin care and washing practices. The prevalence among children is 15-30% in developed countries and has increased during the past 50 years ^{63,65}. For 20% the disease can persist throughout childhood into adolescence, leading to fatigue due to the extra effort required to care for dry skin and the necessity of daily moisturizing and application of medications to rashes ^{24,63}. AD is the most common non-fatal health burden attributable to skin diseases and places a substantial psychosocial burden on patients and their relatives. It also increases the risk of food allergy, asthma, allergic rhinitis, other immune-mediated inflammatory diseases and mental health disorders ⁶³.

Allergic Rhinoconjunctivitis

Allergic rhinitis (AR) is a symptomatic disorder of the nose induced by an IgE-mediated inflammation of the membranes of the nose after allergen exposure and the overall prevalence, among children under 18 years, worldwide is 13% ^{51,66,67}. This inflammation causes some characteristic symptoms such as; nasal obstruction, runny nose, nasal itching and sneezing ^{66,68}. When the eyes are involved, the term allergic rhinoconjunctivitis (RC) is used, the symptoms of which can include itchy, red, watery and/or swollen eyes ⁶⁹. Intermittent disease means symptoms for less than 4 days a week and less than 4 weeks a year, while persistent disease means symptoms for more than 4 days a week for more than 4 weeks a year ⁷⁰. Studies have shown that 20-50% of patients with RC also have lower airway symptoms ^{54,55}. RC can be seen as a global health problem with increasing prevalence ^{1,71}. However it is not well known how adolescents cope with RC.

Food hypersensitivity

The World Allergy Organisation (WAO) defines food hypersensitivity as conditions that cause objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. Food allergy is defined as a hypersensitivity reaction initiated by proven or strongly suspected immunologic mechanisms, often IgE-mediated ⁴¹. In early life, food-related symptoms but no IgE sensitisation are much more common than food allergy ⁷². Food allergy as well as food hypersensitivity can abate before or in adolescence. There are studies suggesting that consumption of food allergen induces oral tolerance and that environmental exposure to allergen through the

skin can cause sensitisation⁷³. Food hypersensitivity can be caused by cross allergies, with Oral Allergy Syndrome (OAS)⁷⁴.

Self-management and allergic disease

In the self-management process the patient must be involved in every step to understand and identify self-management strategies, which are dependent on many factors due to the disease itself but also the person's own life situation and coping ability^{75, 76}. Adherence to treatment is a major problem in allergic disease, and management includes mediation as well as education and support for self-management strategies^{20, 77, 78}. A prerequisite for self-management is patient involvement and support in real-life situations^{20, 76}. This also encompasses system-focused changes in the primary care environment,⁷⁹ as those who introduce and support patient education must be prepared and have knowledge and interest to inspire and involve the patient. There is evidence that supports the implementation of practice strategies that are conducive to self-management and improved outcomes among chronically ill patients^{76, 80}. A study from Finland highlighted the importance of moving from professionally-led education and counselling towards an educational relationship in which the professional and patient are equals and represent different kinds of expertise⁸¹. Furthermore, patient education should be developed to promote person-centredness and self-management support⁷⁵. The Finnish allergy programme with six important strategies for reducing severe asthma and allergy⁸¹ by means of simple and pragmatic allergy guidelines to healthcare professionals has also increased awareness among children of the need for adherence to treatment. A comprehensive self-management asthma education programme in Switzerland improved asthma control and patients' perception of the asthma care and of self-management support received⁸². Professionals should motivate patients to attend allergic disease education in order to become active partners in managing their condition^{20, 83}. However, it is also essential to take account of this age group as adolescents require treatment programmes that are uniquely tailored to them⁸⁴. Finally, there must also be a written action plan to facilitate self-management and adherence to treatment^{85, 86}. In accordance with the person-centred process, this action plan should involve the patients' own goals⁷⁵.

Impact on Health Related Quality of Life and physical activity

Health-Related Quality of Life and allergic disease

Health is defined by the WHO as: “A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” ²⁶. HRQoL is multi-dimensional and includes physical, psychological, functional and social domains related to human beings’ perception of quality of life in relation to their health status. HRQoL is an important variable in clinical practice when evaluating treatment or considering new treatment, which could have significant consequences for patients and families ⁸⁷. Poor asthma control among adolescents has been shown to reduce HRQoL, especially among young females ¹³. Children with both asthma and RC or more than one allergic disease have lower HRQoL than children with only one disease⁹.

In order to measure HRQoL in the population, two type of instrument can be used, generic or disease specific. Generic instruments measures all aspects of HRQoL regardless of the disease or underlying condition. Disease specific instruments are mainly employed to focus on aspects of the health status in a specific condition or disease due to their greater sensitivity. The use of disease specific instrument were therefore suitable in the study.

Physical activity and allergic disease

The Swedish national guidelines for prevention and treatment in unhealthy living⁸⁸ and the WHO ⁸⁹ state that adolescents should perform at least 60 minutes of moderate to vigorous PA every day (or at least five days a week). This recommendation is aimed at generating positive effects on health and HRQoL, although it is known that only 20% of the world youth population actually achieves this goal ⁹⁰. Studies have shown that children and adolescents with allergic disease could benefit from PA ^{91, 92}. However there are also indications that children and adolescents with severe allergic disease are at higher risk of sedentary behaviour and decreased PA ⁹³. PA is used as an overall term for different forms of leisure activity including sports, games, gymnastics, exercise and outdoor life ⁸⁹.

Quantitative and Qualitative methods

Various methods are used in medical research depending on the research question. Irrespective of the method employed, the goal is the advancement of scientific knowledge by means of critical reflection⁹⁴. Inductive methods are often employed to study a large number of outcomes or occurrences from which empirical data can be generalised. Deductive method mean exploring one or more assumptions to establish whether they are true on the basis of which logical conclusions can be reached. Different methods can be divided into two approaches, a hermeneutic approach and a positivistic approach:

A hermeneutic approach is subjective and can be used for;

- In-depth interviews
- Observations
- Focus group discussions
- Case studies
- Narratives

A positivistic approach is objective and can employ;

- Statistical sampling
- Measurement and scaling
- Questionnaires

The benefits of employing both quantitative and qualitative methods are set out below.

In the quantitative research questions one asks Whether? and How much? The methods involve systematic investigations of an objective measured or compared by statistical or numerical analysis of data collected through questionnaires, surveys, or pre-existing data to explain data and predict other data.

Using qualitative methods in combination is a way to further understand existing or new data. It is also a way of describing rather than to predict a phenomenon⁹⁴. In qualitative research questions one asks How? and What? In order to understand the Why. People's own perceptions, attitudes, experiences or interactions of a phenomenon are explored through interviews.

Some of the most common methods for analysing data are described by Malterud, Creswell and Brinkman/Kvale⁹⁴⁻⁹⁶ and those most frequently used

in nursing research are, content analysis, grounded theory, ethnography, narrative research, systematic text condensation and phenomenology.

The qualitative analysis quantify the phenomena by counting words and phrases to describe the phenomenon. Cavanagh has developed this and believes that content analysis can also be used to gain a deeper understanding of the meaning of a communication and interaction⁹⁷. Content analysis can sometimes be confused with Grounded Theory (GT) and phenomenology⁹⁶. These methods may be similar, but GT and phenomenology go beyond content analysis to develop a theory or to understand the meaning of lived experience⁹⁶.

Study of perceptions and experiences involving many individuals. We have identified a potential problem, which is according to the quantitative data from Study I, that many adolescents suffer from allergic disease, something that also needs to be explored in a qualitative analysis to understand and describe the phenomenon. Content analysis was considered suitable, as it is a method used to systematically analyse verbal as well as written communication and a descriptive way of understanding the meaning of a phenomenon⁹⁸. The method focuses on identifying similarities and differences within the text, which results in categories and themes⁹⁹. The findings generated from content analysis are based on the participants' unique perspectives and grounded in the data. Both manifest and latent content analysis were applied to find the deeper meaning of the experience of PA in adolescents with allergic disease¹⁰⁰. Several authors have described qualitative content analysis as revealing the manifest content, which is the most obvious and visible content in the text^{99, 101}, while the latent content concerns the underlying and deep structural meaning of the text. Manifest and latent meaning are described by themes⁹⁴ after analysing codes and categories. The meaning of the latent content is analysed, that which is close to as well as distant from the text but yet close to the underlying meaning^{99, 100}.

GT and phenomenology were judged to not be usable because those methods not intend to develop a theory and that there is such a high degree of pre-understanding⁹⁶. Content analysis can be used to describe patterns or models of participants' experience / experience about how their behaviour has changed, how they view things and what they expect from the future. In short, participants can be asked to describe themselves and their social world and in this thesis, physical activity when suffering from allergic disease.

Aims

The overall aim of this thesis was to increase knowledge about self-reported allergic disease in adolescence, with regard to symptom occurrence, contributing factors, impact on physical activity and Health-Related Quality of Life.

Specific aims

To assess the prevalence of self-reported allergic diseases in an unselected cohort of adolescents aged 13–14 years living in southern Sweden (Study I)

To analyse the sensitisation profile in a representative sample of the adolescent population and to relate patterns of allergens and allergen components to allergic symptoms (Study II)

To determine the association between self-reported physical activity and allergic disease among adolescents (Study III)

To evaluate Health-Related Quality of Life in a group of adolescents with self-reported symptoms during the pollen season (Study III)

To explore adolescents' experience of physical activity and impact of allergic diseases (Study IV)

Ethical considerations

The research in this thesis was approved by the Regional Ethics Board in Lund, Sweden (No. 2011/753 for the quantitative studies in Papers I, II and III and with the amended No. 2017/120 for the qualitative study in Paper IV). The principles of the Helsinki Declaration were followed.

All participants were given both verbal and written information about the aim, utility and confidentiality of the study. Participants in this cohort gave their written informed consent, as did their parents or guardians, thus allowing the adolescents to participate in the research project. Parents or guardians could consent to their children participating in both the questionnaire and blood sample, or only the questionnaire.

Participants in Study IV were given additional written information about the study before being contacted for interview. All participants were informed that they could withdraw from the study at any time without giving a reason. The location of the interview in a city, the nearest hospital or by phone, was chosen by the participants in order to provide an environment where they would feel relaxed and safe as well as a suitable time.

The results of all four studies are presented at group level, which rules out the possibility of identifying a specific individual.

Raw data, personal IDs and code-keys pertaining to the studies are kept confidentially in accordance with the General Data Protection Regulation (GDPR) and stored on a secure server at Clinical Studies Sweden, Forum South. Only pseudonymized data were processed in Studies I-III in the present thesis. In Study IV the code-keys were used to identify persons to invite for interview and the recorded interviews were stored on the same secure server as described above.

Material and methods

Overview of the design of the studies

Both quantitative and qualitative methods were used in this thesis.

Table 1. Overview of design, participants, recruitment and data collection in the thesis.

	Study I	Study II	Study III	Study IV
Design	Quantitative, cross-sectional	Quantitative, cross-sectional	Quantitative, cross-sectional	Qualitative, descriptive
Sample	1333	195	1181 (HRQoL 181)	36
Data collection	<i>Questionnaires:</i> ISAAC and clinical questionnaires	<i>Questionnaires:</i> ISAAC <i>Blood tests:</i> Phadiatop, fx5 and ISAC 112	<i>Questionnaires:</i> ISAAC, Questions on PA and PADQLQ	<i>Individual interviews</i>
Data analysis	Parametric and non-parametric analysis	Parametric analysis (cluster analysis)	Parametric and non-parametric analysis	Content analysis (manifest and latent)

The cohort was established in 2012 from a random sample of schools in 13 of 52 municipalities (300 schools for the selected age group) in the four southernmost provinces of Sweden; Blekinge, the southern part of Halland, Kronoberg and Skåne, with a total of 1, 875, 900 inhabitants, Fig 2. Stratified sampling was conducted in order to obtain data from small, large, costal and urban and rural municipalities. The location of the school was used as a proxy for place of residence (large city, city and countryside), as in Sweden most children live close to their elementary.

Participants

In 2012, information on the study was sent to the principals and school nurses of 104 schools. Each principal was contacted personally by telephone in order to elicit the school's participation in the study, resulting in the participation of 51 schools (230 classes in grade 7 and 8). Written information about the study was distributed to the adolescents at school as well as sent home to their parents. Written informed consent from their guardians was required in order to participate, which was obtained for 2,568 (46%) of the 5,622 eligible adolescents attending the participating schools, Fig 2. The web-based survey used in this study was completed during school hours in the autumn term under the supervision of the school nurse or a teacher.

Five school were randomized for adolescents participating in the clinical part of Study II.

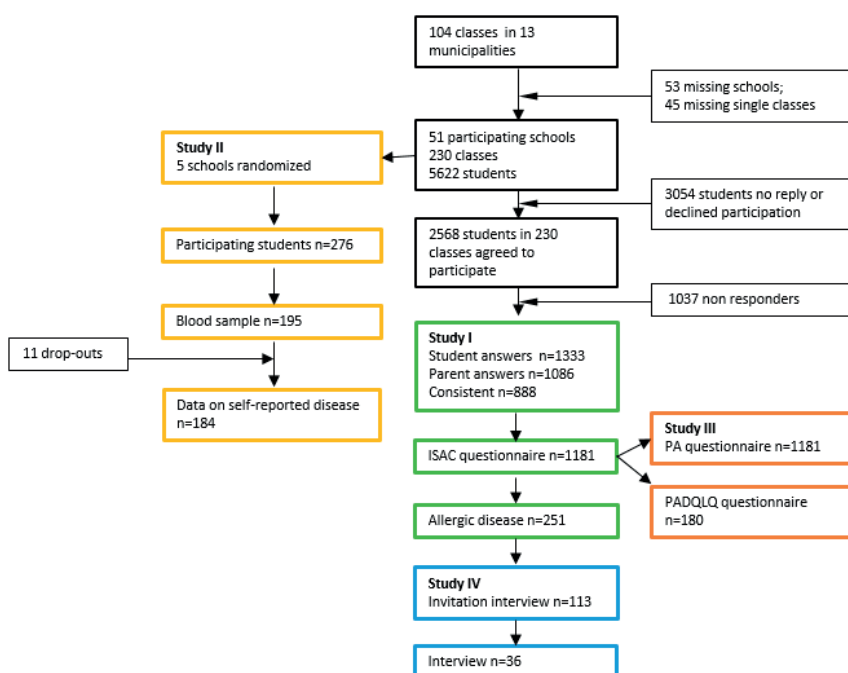


Figure 2. Flowchart for all four studies.

Participants (Studies I and III)

All students who answered the questionnaire became study participants (n=1,333). Their guardians were asked to answer the questionnaire at home (n=1,086) of which n=888 questionnaires matched.

Participants (Study II)

A subpopulation of 756 children from five schools who agreed to participate were selected for this study. Of these, 276 students received permission from their parent/guardian to participate. Of these, 276 students, 195 were at school at the time of the study examination i.e. providing blood samples and undergoing epicutaneous testing with a modified baseline series, followed by a clinical skin examination by a dermatologist.

Participants and settings (Study IV)

A letter with information about the study, was sent to 113 adolescents and their parents during June 2017, five years after they had filled in the questionnaire. One to two weeks later they were contacted by telephone to explain the study and invite them to participate. A total of 63 agreed to participate and 36 interviews were conducted (21 girls and 15 boys), nine by telephone and 27 face-to-face. The participants were spread across the four counties of southern Sweden (n=22 Skåne, n=8 Blekinge, n=4 Kronoberg and n=2 Halmstad).

Data collection

Questionnaires (Studies I-III)

ISAAC (Study I-III)

The International Study of Allergies and Asthma in Childhood (ISAAC) questionnaire is a widely used standard for determining outcomes from allergic diseases in epidemiologic studies¹⁰². The ISAAC questionnaire for atopic dermatitis was also used in combination with questions validated in the Swedish context: Have you had hand eczema on any occasion during the past

12 months?; Did you have childhood eczema? and Are you hypersensitive or allergic to nickel?¹⁰³.

Questions concerning food hypersensitivity (Studies I, II)

The main questions were; Did you ever have any reaction to food? And Have you had any food reaction during the past year?

Questionnaire PADQLQ (Swedish LILA) (Study III)

In order to assess HRQoL, we used the Swedish version (LILA) of the disease-specific and validated Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ) ⁹. This questionnaire was only answered by those who reported any pollen related symptoms. The PADQLQ has 26 questions in three domains:

- 1) Practical domain with questions about symptoms that affect concentration, sleep, hearing, breathing and physical activity.
- 2) Physical domain with questions about physical allergy symptoms on airways, eyes, nose and skin or in the form of tiredness and thirst.
- 3) Emotional domain with questions about burden and fear of having an asthma attack.

Each question was answered on a 7-point Likert scale where 0 denotes “not troubled at all” and 6 “extremely troubled”. A mean score (range 0-6) was calculated for every participant in each of the three domains in the PADQLQ.

Questions concerning physical activity (Study III)

Three questions about PA designed by the research group specifically for this study were used:

- 1) Think of what you have done during break time at school over the past seven days; How many of those days were you hot and sweaty after physical activity?
- 2) Think of what you do after school; How many times a week do you exercise and become hot and sweaty?
- 3) Think of the last three days that were not school days; How many of those days did you exercise so that you became hot and sweaty?

Interviews (Study IV)

The interviews which lasted 10-35 minutes, were digitally recorded and transcribed verbatim after the last interview by the author. They took place in settings chosen by the participants so that they would feel comfortable. An interview guide with semi-structured, open-ended questions was used to make it possible to ask probing questions to explore and follow-up the participants' answers.

- What does physical activity mean to you?
- Can you explain further? and/or Tell me more
- Do you still have respiratory problems and/ or allergy?
- What kind of symptoms? Are they related to allergy/asthma?

Analysis

Statistical analysis (Studies I-III)

Statistical analysis (Studies I-III) was conducted using SPSS Statistics 25.0 for Windows (SPSS Inc., Chicago, IL, USA). P-values below 0.05 were considered statistically significant.

Non-parametric analyses were mainly performed due to the nature of the sample, which comprised ordinal data. Prevalences, differences and relationship were analysed. Differences in binary and categorical sociodemographic and lifestyle characteristics across groups with and without asthma and rhinoconjunctivitis were tested with Fisher's exact test and the Chi square test. ANOVA was used to test differences between groups.

In Study III differences in PA between symptom groups were tested by means of the Mann-Whitney test. This test is used to explore statistically significant differences between two unpaired groups¹⁰⁴. The Spearman's rank-correlation coefficient was calculated as a measure of the association between the total PA score and PADQLQ.

Parametric analysis in Study II all statistical tests were two-sided and a significance level of < 0.05 was regarded as statistically significant. Fisher's exact test was used to compare prevalences across groups. A cluster analysis (see below) was performed on the IgE binding categories for all samples.

Serological analysis (Study II)

IgE sensitisation

All statistical analyses were performed using the SAS® statistical software system version 9.3 (SAS Institute Inc., Cary US) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Clustering was performed using sparse hierarchical clustering with complete linkage, as implemented in the R package *sparcl*, where the tuning parameter controlling the number of features was determined as the value providing the largest Gap statistic ¹⁰⁵.

Blood samples were collected during the period January– March 2013 and stored frozen until analysis. Serum from 194/195 children was used for serological analysis.

Specific IgE testing (s-IgE) was performed with two allergen panel tests i.e. Phadiatop™ Europe and fx5™ (Thermo Fisher Scientific, Uppsala Sweden. Serum was also tested for IgE reactivity to 112 allergen components (ISAC 112, Thermo Fisher Scientific, Copenhagen, Denmark).

Qualitative analysis (Study IV)

The NVivo software analysis tool was employed to sort the text material ¹⁰⁶. Meaning units related to the aim of the study were condensed, coded and sorted into categories. Creating categories is the core feature of content analysis with the purpose of providing means and descriptions in order to deepen understanding and generate further knowledge ¹⁰⁷.

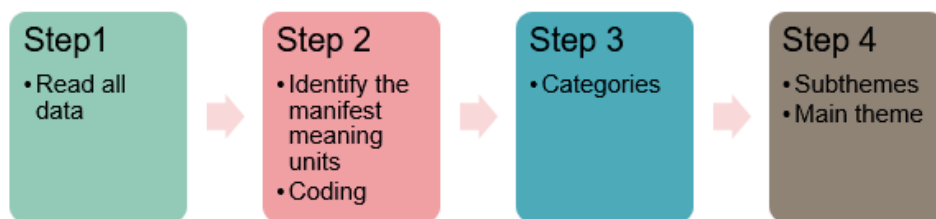


Figure 3. The content analysis process.

The categories were then grouped, from which subthemes and a main theme emerged, which formed the latent analysis. The theme is our interpretation of the underlying meaning of categories and subthemes and the analysis process, this is presented in Fig. 3. All interviews were read several times as Step 1. There after meaning units were identified in Step 2, and then coding of the text in relation to these meaning units. In Step 3, categories were found after merging codes into groups. These categories then formed the subthemes in Step 4, leading to the main theme.

Results and comments

The findings will illuminate several different aspects of allergic disease among adolescents based on the definitions of allergic disease used in the studies included in this thesis, Table 2.

Table 2. Definitions of self-reported allergic disease in this thesis

Current asthma	If the respondent answered yes to wheeze, at any time in her/his life and during the past year
Current RC	If the respondent answered yes to rhinitis (sneezing, runny or blocked nose without a cold) and conjunctivitis (itchy and/or watery eyes) at any time in her/his life and during the past year
Previous asthma and/or RC	If the respondent answered yes to wheeze and or rhinitis/conjunctivitis, at any time in her/his life but not during the past year.
Current AD	If the respondent answered yes to itching, rash/eczema for at least six months at any time during her/his life
Food hypersensitivity	If the respondent answered yes to a reaction to food at any time in her/his life and during the past year

Basic characteristics of the main cohort, are presented in Table 3. Gender balance equal in all groups but not among current food hypersensitivity with 70% females. Around 40% had pets at home and prevalence of smoking in the family were 7-11%. There was a significant difference between heredity of allergy from one/two parents than from none of the parents, $p < 0.001$.

Table 3. Basic characteristics of the study population.

		All n= 1333 %	Current asthma n=131 %	Current RC n=170 %	Current AD n=144 %	Current food hypersensitivity n=163 %
Gender	Female	51	46	50	58	70
	Male	49	53	50	42	30
School location	Large city	24	23	22	22	24
	City	49	51	52	54	46
	Rural area	27	26	26	24	30
Furry pet	Yes	44	34	30	40	35
Smoking in family	Yes	9	11	7	10	7
Birth order *	1	29	27	32	29	30
	2	25	26	24	31	29
	3	9	10	7	14	10
	4	2	0.7	0	2	0
	5	0.6	0	0	0.7	0.6
Heredity	Mother or Father	25	32**	32**	37**	27
	Both	7	9 **	11 **	13 **	10
	None	68	59	57	50	63

*missing 34%, **significantly

Prevalence of self-reported allergic diseases (Study I)

Out of 1,333 participants, 33% reported at least one allergic disease, of whom 67% (291) mentioned one allergic disease and 33% (142) more than one allergic disease. The comorbidity can be seen in Fig. 4. No atopic comorbidity was in 44-51% of the adolescents in any disease.

Current asthma was reported by 10% and current RC by 13%. Food hypersensitivity was reported by 12% and AD by 11%.

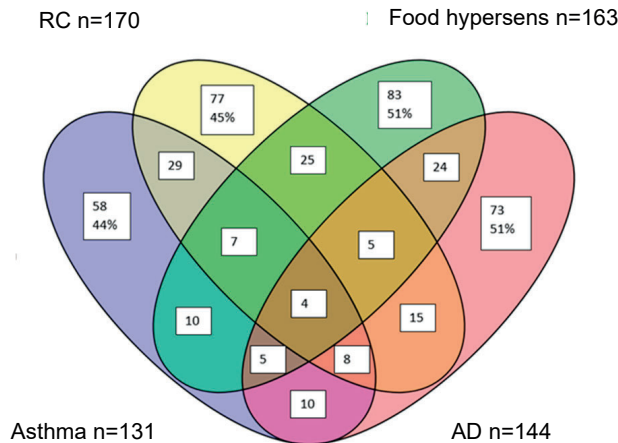


Figure 4. Comorbidity of the cohort

Allergic diseases diagnosed by a doctor;

- Current asthma n=67/131 (51%)
- Current RC n=93/170 (55%)
- Current AD n=73/144 (51%)
- Current Food allergy n=59/163 (36%) (Lactose n=48 Coeliac disease n=16)

Severity

- One to three wheezing attacks were reported by 55%, and 40% reported more than four attacks of wheezing in the preceding year.
- RC symptoms lasting for more than four weeks a year were reported by 52%, and 48% reported symptoms on more than four days a week. Symptoms during the pollen season were reported by 52%, while 28% reported an impact on their daily activities.
- A prescribed Adrenaline auto injector was reported by 10 adolescents of which seven didn't report any food hypersensitivity.

There was a significant relationship between current asthma and current RC ($p<0.0001$) and in these groups, children had a significantly higher prevalence of AD, 19% vs 9% ($p<.001$) and food allergy, 24% vs 10% ($p<.001$), compared to children without current asthma and RC.

Correlations between IgE sensitisation and symptoms of allergic diseases (Study II)

Positive IgE in Phadiatop among those with at least one allergic disease was 58% compared to 34% for children without any allergic disease (n=117). 85% of those with self-reported RC were positive to airborne allergens. There were significantly higher IgE-levels among airborne allergens than food allergens ($p<0.001$). In the fx5 the highest prevalence figures was found in the asthma group (33%). No participants with only AD showed positive s-IgE sensitisation, but four of them exhibited positive reactions in the ISAC test. The level of IgE was also significantly higher for airborne allergens in both current RC ($p<0.001$) and AD ($p<0.01$). A positive s-IgE response to airborne allergens was seen in 43% (83/194) of the participants while s-IgE response to the most important food allergens (fx5) was only detected in 14% (27/194). Furthermore it was demonstrated that among children with self-reported food allergy the prevalence of food-allergens was much lower than to airborne allergens.

Sensitisation to various allergens (Study II)

The ISAC-test revealed that, 48% of the children were positive to at least one component, while no IgE-binding to any allergen component was observed in the remaining 101 children. The number of IgE responses is summarized in Table 4. Out of the 112 allergen components, 94 exhibited IgE binding with at least one serum. Polysensitisation was shown in 31% of the participants.

Table 4. Sensitisation patterns for the 195 children included in the analysis

Total number of tests evaluated	n=195 (%)
No response, for any component	101 (52)
Monosensitised	14 (7)
Oligosensitised, response to 2-3 components	19 (10)
Polysensitised, response to ≥ 4 components	61 (31)

The allergen components were sorted into allergen groups for analysing the severity of the sensitisation, the type of allergen. According to Table 5.

Table 5. Allergen component sorted by source, type and group.

Allergen component	Allergen source	Type of allergen*	Allergen group
Pol d 5	Paper wasp	Antigen 5	Venoms
Ves v 5	Common wasp	Antigen 5	
Ara h 8	Peanut	PR-10	Foods
Cor a 1	Hazelnut	PR-10	
Gly m 4	Soybean	PR-10	
Mal d 1	Apple	PR-10	
Pru p 1	Peach	PR-10	
Der f 1	<i>Dermatophagoides farinae</i>	Cysteine protease	House dust mite
Der f 2	<i>Dermatophagoides farinae</i>	NPC2 family	
Der p 1	<i>Dermatophagoides pteronyssinus</i>	Cysteine protease	
Der p 2	<i>Dermatophagoides pteronyssinus</i>	NPC2 family	
Can f 1	Dog	Lipocalin	Furry animals
Can f 2	Dog	Lipocalin	
Can f 5	Dog	Prostatic kallikrein	
Equ c 1	Horse	Lipocalin	
Fel d 1	Cat	Uteroglobin	
Fel d 4	Cat	Lipocalin	
Mus m 1	Mouse	Lipocalin	grass/tree pollen
Aln g 1	Alder	PR-10	
Bet v 1	Birch	PR-10	
Cyn d 1	Bermuda grass	Grass group 1	
Phl p 1	Timothy grass	Grass group 1	
Phl p 2	Timothy grass	Grass group 2	
Phl p 4	Timothy grass	Grass group 5	
Phl p 5	Timothy grass	Grass group 4	
Phl p 6	Timothy grass	Grass group 6	
Phl p 11	Timothy grass	Grass group 11	

In the RC group a majority of the most common 20 food components are related to the PR-10 and venoms are only seen in the AD group. The proportion of IgE bindings is much higher in the RC (median 9) than in the AD and asthma groups (median just over 2). Table 6. The RC group has both a higher quantitative IgE value (Phadiatop - significant) and IgE against more allergenic components, this could be a suggested phenotype.

Table 6. Number of individuals with IgE reactivity to the 20 most common allergens components within three symptom groups (asthma, RC and AD)

Asthma (n=18)		RC (n=28)		AD (n=16)	
Allergen component	n(%)**	Allergen component	n(%)**	Allergen component	n(%)**
Phl p 1	6(33)	Phl p 1	15(54)	Der f 1	7(44)
Fel d 1		Cyn d 1	14(50)	Der p 1	6(38)
Cyn d 1	5(28)	Phl p 4	13(46)	Der f 2	5(31)
Fel d 4		Phl p 5		Der p 2	
Der f 1		Fel d 1	12(43)	Fel d 1	4(25)
Bet v 1		Bet v 1		Phl p 1	3(19)
Aln g 1	4(22)	Phl p 2	11(39)	Fel d 4	
Can f 5		Phl p 6		Can f 5	
Equ c 1		Aln g 1		Equ c 1	
Der p 1		Der f 2		Bet v 1	
Cor a 1		Der p 2		Cyn d 1	2(13)
Phl p 2	3(17)	Cor a 1		Phl p 4	
Phl p 4		Mal d 1		Phl p 5	
Phl p 5		Pru p 1***	9(32)	Aln g 1	
Phl p 6		Ara h 8***		Can f 1	
Can f 1		Der f 1	7(25)	Can f 2***	
Mus m 1***		Phl p 11***	6(21)	Pol d 5***	
Der f 2		Can f 5		Ves v 5***	
Der p 2		Der p 1		Cor a 1	
Mal d 1		Gly m 4***		Mal d 1	

**Number/percentage of individuals with IgE reactivity to the allergen component within each disease group

***Allergen components only found within one of the disease group

Clustering was performed on the response to allergen components and showed three clusters with 195 sera on the x-axis and most common allergens on the y-axis Fig. 5. A positive response to a component was defined as IgE binding ≥ 0.3 ISU/l, and further classified into semi-quantitative categories; low (0.3–3 ISU-yellow), moderate (3–15 ISU-orange) and high (15–150 ISU-red). The largest cluster contained samples with no IgE or IgE to 1-5 allergen components at a low or moderate level. The other two clusters contained samples with IgE reactivity to many allergen components. One of these clusters was dominated by allergen components from the grass pollen family, Phleum Pratense (Phl p) Table 5. The second cluster was dominated by

moderate/high IgE responses to allergens from the mite family, *Dermatophagoides pteronyssinus* and *farinae* (Der p och Der f) and the major cat allergen, *Felix domesticus* (Fel d). In the case of *Canis* (Can f5), at least two sub-clusters were found within the pollen-dominated cluster; one in which sera reacted strongly with allergens from the mite family (Der f 2 and Der p 2) and another containing the major birch pollen allergen, *Betula verucosa* (Bet v 1) and related allergens (Cor a 1, Aln g 1 and Mal d 1). A similar sub-cluster was found within the mite cluster, with sera also responding to Bet v 1 and related allergens (Cor a 1, Aln g 1 and Mal d 1) Fig. 5. Tree and grass allergens dominated in all three groups with asthma, RC and AD, while foods and venoms were less represented also seen in table 6.

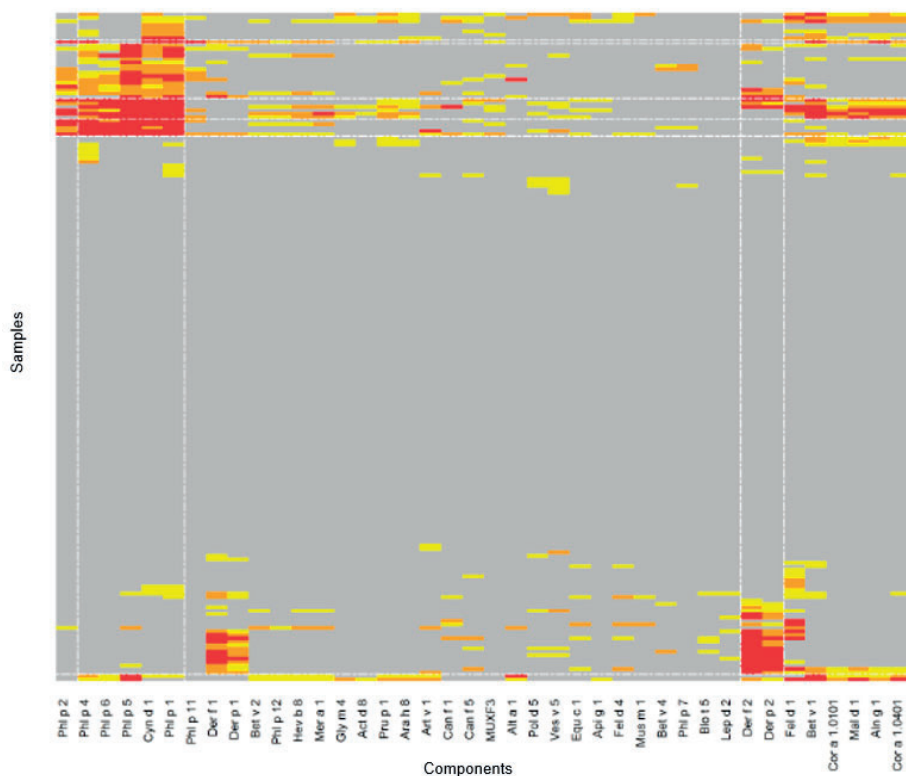


Figure 5. 112 Unsupervised clustering performed with 40 allergen components yielding at least 4 positive results across the 195 sera. The Colors represent the level of sensitization on the semi-quantitative ISAC scale.

Allergic diseases and impact on Health-Related Quality of Life (Study III)

The study comprised 180 participants with allergic symptoms during the pollen season who answered the PADQLQ about HRQoL. The ANOVA test showed strong empirical evidence for differences in all three dimensions of HRQoL related to current or previous symptoms ($p \leq 0.004$) Table 7. Likewise, there was strong empirical evidence suggesting that adolescents with both current asthma and RC ($n=29$) had lower HRQoL in all three domains compared to those with only one or no current symptom ($n=152$; $p \leq 0.005$).

Table 7. HRQoL scores obtained from the PADQLQ-questionnaire in relation to self-reported current or previous allergic symptoms

<i>n=180</i>	Current asthma only	Current RC only	Both current asthma and RC	Previous asthma and/or RC	p-value
<i>*Likert scale 0-6</i>					
<i>n</i>	18	62	29	71	
Practical domain mean (range)	1.62 (0.30-4.50)	1.56 (0.4-1.3)	2.24 (0.4-7.5)	0.93 (0.5-5.0)	<0.001
Physical domain mean (range)	2.12 (0.4-4.40)	2.39 (0.36-4.67)	2.63 (0.4-8.7)	0.99 (0.4-7.3)	0.004
Emotional domain mean (range)	1.29 (0.4-0.0)	1.04 (0.0-4.33)	1.51 (0.0-5.0)	0.47 (0.6-6.0)	0.001

* 0 = "not troubled at all" and 6 = "extremely troubled"

Allergic diseases and impact on physical activity (Studies III and IV)

Boys were more physically active than girls (mean total PA score 6.47 vs. 5.98, range 3-9). However, there were no noticeable in PA among adolescents with and without allergic disease ($p \geq 0.3$ in all comparisons) and this was true also when the analysis was conducted separately for boys and girls. The proportion of participants reporting PA classified as high was 19% for school breaks, 67% after school and 29% for school-free days. Only 29% of the boys and 22% of the girls reported PA classified as high both after school and during school-free days.

The interviews in Study IV deepened the understanding of the quantitative data about PA in Study III. The interpretation of the adolescents' experiences of PA when suffering from allergic disease resulted in one main theme:

Being physically active when suffering from an allergic disease means becoming aware of the symptoms and thus what strategies are needed. The findings consist of nine categories, three subthemes and one main theme Table 8. Awareness included reflections about wellbeing, information, symptoms of allergic disease, medication and all kinds of exercise and training.

Table 8. Interpretation of adolescents' experiences of PA when suffering from an allergic disease

Theme	Being physically active when suffering from an allergic disease means becoming aware of the effects of the disease and thus what strategies are needed.								
Subthemes	PA when suffering from an allergic disease and asthma means being aware of the situation				PA when suffering an allergic disease means learning to cope with the symptoms			Inadequate information and knowledge about symptoms might cause low PA	
Categories	Having a positive experience of PA	Being influenced by something or someone	Finding suitable forms of exercise	Being active in the future	Experiencing symptoms when performing PA	Dealing with the disease and medication	Feeling the effects of medication	Not wishing to be physically active	Being in need of information and knowledge

Being aware of the situation meant to having positive experiences of PA but also being influenced by someone. In addition, it could also mean finding suitable forms of exercise as well as being active in the future. The adolescents described PA as something enjoyable, fun and relaxing. Some mentioned that it was beneficial for their health and made them feel good. Others said that it was important for staying healthy and could be a fun thing to do.

The influence of friends is something many of the participants highlighted as an incentive to start exercising. Several spoke about the “thing” of doing activities together in a group.

Learning to cope with the symptoms meant dealing with them in order to perform PA. They described difficulties with outdoor exercise due to cold, dry or humid and foggy weather, which could cause symptoms leading to breathing difficulties. Some mentioned that it would probably be possible to run a little faster if it was not for the asthma. Several participants stated that their ability to exercise was impaired due to losing their breath and the need for rest. They talk about losing the breath, which led to the need to rest. They also had to deal with the disease and medication, such as taking medication before, during and after training. Most of them considered that the medication relieved their symptoms to some extent.

Inadequate information and knowledge about symptoms might cause low PA, as several stated that nobody told them why PA could be beneficial.

They also said that health care should provide information every time, not only once. They mentioned that teachers and the school nurse talked about daily

activity. Some had asked healthcare professionals for written information about the medication and how and when to use it.

The findings reveal different levels of awareness of the impact of PA on allergic disease and the possibilities to alleviate symptoms. An inability to achieve maximum PA due to asthma/allergic symptoms was also revealed as well as lack of knowledge about the disease and the positive impact of PA. The adolescents expressed a degree of commitment when talking about PA and how they used different facilitating strategies. Most of them were positive to PA but reported challenges in dealing with symptoms and medication.

Discussion

The overall aim of this thesis was to increase knowledge about self-reported allergic disease in adolescence, with regard to symptom occurrence, contributing factors, impact on PA and HRQoL.

The cross-sectional Study I, employs the first population-based cohort of adolescents in southern Sweden. The majority (67.5%) of children with allergy, reported only one allergic disease. The prevalence proportions for asthma (10%) and rhinoconjunctivitis (13%) were in accordance with other European population-based studies¹⁰⁸ ⁶. Our study couldn't confirm the geographical differences in respiratory symptoms as in the finish study³ but according to IgE sensitisation the national geographical differences are confirmed in high frequencies of mite and grass-sensitisation in southern part of Sweden but not up north^{35, 38}.

In Sweden, most children see physicians in primary healthcare and may never attend a specialist clinic unless they experience severe symptoms. This factor could contribute to the fact that in our study only 51% reported a doctor's diagnosis despite pronounced symptoms.

Prevalences

The prevalence in self-reported food hypersensitivity are higher if self-reported than with a doctors diagnoses, shown in several studies^{109, 110}. It is well known that self-reported food hypersensitivity is higher than the number of diagnoses by doctors, which could be due to OAS from cross-reactivity allergens¹¹¹.

Other birth-cohort studies shows higher prevalence of RC among adolescents (32.8.35%) than in our study, whereas the prevalence of asthma was similar (13%) ⁶. Although studies from the Swedish cohort^{111, 112} shows likewise results as in the present study^{35, 113, 114}. Thus, it is of importance for healthcare professionals to be aware of prevalence data in order to prepare and take care of children and adolescents in good time and not wait until the symptoms increase, leading to a worse feeling of illness. These divergent trends in

prevalence of symptoms of allergic diseases form the basis for further research¹.

Sensitisation

Our results show that wheeze is associated with sensitisation to the lipocalin protein group and that allergic RC is associated with sensitisation to the PR-10 component and *Phleum pratense* (grass pollen). The highest frequency of non-sensitisation, 40%, was found among adolescents with asthma, which is an important finding to consider when choosing treatment for these children. Those with food hypersensitivity formed the largest group, with no sensitisation to the major allergens, but to PR-10 cross-reactive allergens. This is of importance because many children, parents and people in general find Oral Allergy Syndrome (OAS) troublesome due to cross-reactivity and how and when to use treatment with antihistamine. For example, in Study II only two adolescents responded to Ara h2 (peanut) and one to walnut, but with no relation to the allergic disease. IgE sensitisation to perennial aeroallergens seems to have the greatest clinical impact on asthma³². This may be because asthma is associated with increased IgE and sensitisation to indoor perennial allergens, mostly from cats and mites³². The cross-reactive allergen components can explain many sensitisations and clinical symptoms. Component-based analysis facilitates the understanding of primary sensitisations and decreases the risk future severe allergic reactions. This can improve the selection of appropriate patients for immunotherapy or food challenges. However, the geographical differences in the distribution and prevalence of various sensitisation patterns and disease expression should be taken into account to achieve better health care.

Physical activity

There were no noticeable differences in PA among adolescents with or without allergic disease. Our results support the importance of directing health care measures towards promoting PA among adolescents with allergic disease as part of their treatment. The findings reveal different levels of awareness of the impact of PA on allergic disease and the possibilities to alleviate symptoms. An inability to achieve maximum PA due to asthma and or allergic symptoms was also revealed as well as lack of knowledge about the disease and the positive impact of PA. The participants expressed a degree of commitment when talking about PA and how they used different facilitating strategies.

Our study identifies several important factors that may limit the possibilities for adolescents with allergic disease to perform PA. One is the poor knowledge of both the disease and medication.

Interviews with participants who reported any allergic disease, although revealed that such diseases are not only a biological condition but something experienced and with reduced well-being. Experience can be on different levels as, after exercise and/or training, physiological and behavioural functional exercise capacity, asthma symptoms and quality of life are significantly improved. The efficacy of exercise training programmes is demonstrated by a study with a 3-year follow up, in which patients choose to be more PA when exercise program were supervised by healthcare professionals¹¹⁵. In recent decades there has been a reduction in school sports or physical education in favour of academic subjects. In Sweden, school sports and physical education have been reduced from 20% to 7.5% during the past three decades. Our results reflect this in some ways as the self-reported PA at school was very low in all groups. The overall data on PA in our study indicate that there is a need for implementation of existing guidelines. The PA pattern during adulthood seems to moderately reflect PA behaviour during childhood¹¹⁶⁻¹¹⁸, providing a sufficient argument for an increased level of PA in children and adolescents. Some studies infer that PA may have direct positive effects on the nervous system by increasing brain volume and blood flow to the brain, both of which are involved in different aspects of perception, cognition, memory and attention¹¹⁹⁻¹²². Other studies suggest that PA has positive effects on psychological parameters such as self-esteem, motivation, social engagement and communication, all of which are important for learning outcomes¹²³. The qualitative study also confirms these findings as the adolescents described PA as enjoyable, fun and relaxing. Some mentioned that it was beneficial for their health, made them feel good and could be a fun thing to do. This is another reason why guidelines should be implemented to increase PA during school hours as well as during leisure time. The Swedish National Board of Health and Welfare¹²⁴ recommends that healthcare professionals should engage in a person-centred dialogue with the patient aimed at supporting a change in behaviour to increase PA and reduce sedentary habits⁸⁸. The need of information and support from healthcare professionals also emerged in the interviews in Study IV.

Adolescents who are not physically active should be asked which PA they can perform in order to start a dialogue. If no activity is mentioned the next question should be how she/he can start to increase activity or movement. A

further question could be; What do you need to become motivated? And Do you need more education or information about PA and medication?²⁰ A written treatment plan should be used^{85, 124} in accordance with national guidelines and studies pointing at the benefits. The dialogue ought to be documented to enable follow-up at the next visit with question; How did it go? It is of essential to encourage any progress and highlight positive health-enhancing effects. Information should also be provided to parents.

Health-Related Quality of Life

Differences in HRQoL in all three domains, were observed in relation to current or previous symptoms. In particular, adolescents with both current asthma and RC scored lower in terms of HRQoL than their peers without these two allergic symptoms. Suggesting that they might be more negatively influenced by the disease than they care to admit. These results confirm what we expected and shows the importance of including issues of quality of life in the diagnostics as well as in treatment of children and adolescents with allergic disease. Symptoms of dyspnea during exercise are common in asthma and are associated with lower HRQoL also confirmed in various studies^{9, 11, 125}. HRQoL are considered to have a psychological impact on allergic disease during school age¹¹.

Self-management

There are as described in the background several studies regarding the importance about patient education to promote person-centredness and self-management support. The results from the questionnaires tell us that 12% reported food hypersensitivity and that none of them were sensitised to any severe allergen but to PR-10, meaning probably OAS. It is not known if the participants know anything about this. Furthermore in Study I it is described low frequencies of medication both among RC and Asthma, which gives questions of why? Findings from the interview tell us that the participants need more information and knowledge about their disease and that they have to cope with the situation but at the same time they don't seem to know about proper treatment. Self-management doesn't come by itself but with help and introduction from healthcare professional.

Methodological considerations

The following considerations will be addressed in:

- Sample selection and participants
- Methods and analysis
- Trustworthiness and validity

The combination of quantitative and qualitative studies to explain the allergic disease condition in adolescents while the same time trying to understand the experience of the condition provides valuable data for research. The quantitative studies are based on self-reported symptom data and blood samples, while the qualitative employs interviews aimed at gaining a deeper understanding.

Sample selection and participants

The participation rates were rather low, which was mainly caused by technical difficulties at the schools or that the head master at the end didn't give time for questionnaires during school time without informing the research team. The students are not to be claimed for this bias.

Today, eight years later, it might have been possible to employ another form of sampling method, my means of some kind of App or other technical devices. However, the sample gave us useful answers with the possibility of follow-up.

Choice of methods and analysis

The ISAAC questionnaire should be used in a specific manner according to the research programme found on the www.isaac.auckland.ac.nz¹²⁶ webpage.

The definition of allergic disease used in our studies and this thesis was constructed to take account of the fact that the data are self-reported. In order

to adhere to the instructions for interpretation of the ISAAC questionnaire, we decided to combine lifetime symptoms with those of the previous 12 months. However, self-reported data on allergic disease can be interpreted in different ways as described in the data collection section. The "ever wheeze" question is often used to compare asthma prevalence between countries. We are aware of that whistling/whistling and/or wheeze at some stage in combination with whistling and/or wheeze during the past year may not be asthma. As is mostly the case internationally the numbers of unknown asthmatic children are included in the definition of asthma, although wheezing appears to be the symptom most often used ¹⁰². For international studies, a symptom-based definition is less subject to bias than a diagnosis-based definition and therefore the GINA guidelines are used ⁷⁷. According to the ISAAC questionnaire, development and validation are set to include symptoms ranging from relatively mild to more severe.

Using a combination of different web-based questionnaires might render the validity of the responses weak. We also included questions that had not been validated, which could also weaken validity.

Sensitisation

The cooperation with the industry in this part was useful for proper testing and help in interpreting the test results. The ImmunoCap ISAC gives results that must be carefully reviewed in order not to make incorrect conclusions.

Physical activity and Health-Related Quality of Life

We are aware that the questions about PA could be more detailed for deeper information. Using some technology as for example accelerometer, to measure daily steps, individually, could have given useful data.

Another limitation is that the PADQLQ was only answered by those with any symptoms during the pollen season, which meant that we did not obtain a generic HRQoL score from all participants.

Qualitative part

Qualitative methods are part of the hermeneutic knowledge tradition and intended to interpret the meaning of different human experiences. In some ways the information from all narratives contained in the interviews depends on the interpretation, which is based on the descriptions provided ⁹⁴. However, the interpretation was not biased by our pre-understanding, as two of the authors independently identified meaning units and performed coding.

Ensuring trustworthiness and validity

Trustworthiness in the qualitative study was strengthened by using and reflecting on the following criteria; credibility, dependability and transferability¹²⁷. Credibility was enhanced by providing information about sampling, data collection strategies and analysis technique. The data correlate well with other allergy cohort studies and should be considered valid.

Dependability was ensured by using an interview guide and a software analysis tool, making it easier to move between the raw data and the emerging categories and themes. To increase the trustworthiness we present the findings by showing the process of transforming meaning units to categories and themes, thus giving the reader an opportunity to find alternative interpretations⁹⁹. Although the findings of qualitative studies cannot be generalised, they can be transferred to provide increased understanding of similar situations in a new context. To remain neutral and minimize our impact on the data interpretation, two of the authors were involved in the qualitative analysis process, the identification of meaning units and coding.

Transferability is possible when qualitative findings can be transferred to other groups with the same basic criteria.

Aspects of trustworthiness such as striving for credibility, dependability and transferability throughout the whole study process, strengthen the study¹²⁸. Interviewing an unselected cohort of adolescents from different parts of southern Sweden about their experiences of PA strengthens transferability. However, when discussing the validity of the study and generalizing our results there could be a limitation due to the fact that the adolescents no longer remembered answering the questionnaire five years previously nor their symptoms at that stage. Nevertheless, we obtained deeper knowledge of experiences of PA when suffering from allergic disease, which findings may be transferable to other adolescents with allergic disease and could be useful when discussing treatment alternatives.

Conclusions

Based on the results of this thesis, the care of adolescents with allergic disease needs to be improved from both in the perspective of nursing and that of medical care.

- The prevalence in southern Sweden based on self-reported data is at the same level as in other cohorts in Sweden and various European countries.
- The IgE-sensitisation revealed more mite and grass allergens than in northern Sweden. However, the low sensitisation to peanut and nuts was surprising and not in line with other population based studies.
- Self-reported PA was low overall, but not related to allergic disease.
- HRQoL among adolescents having current allergic disease were significantly lower during pollen season, compared to those with no current disease.
- Being physically active when suffering from an allergic disease means becoming aware of the effects of the disease and thus what strategies are needed.

Clinical implications

Principles of treatment, education and follow up

- There is a gap between the healthcare provided to children/adolescents and the national recommendations and guidelines.
- Adolescents with allergic disease need proper and reliable information to identify and adhere to self-management strategies for coping with the disease.
- Allergic disease have an impact on PA. Adolescents struggle with their symptoms because they are deemed “normal”. Healthcare professionals should ask specific questions and employ objective measurement methods to analyse the problem and provide treatment and follow-up.

Studies on AD among adolescents show that they develop their own way of using topical treatment and that they ask for more information about the principles of topical treatment to ensure correct use and follow up²⁵. Studies on asthma in adolescents revealed that there is frustration among parents and adolescents due to lack of knowledge about treatment and the absence of communication with healthcare professionals^{129, 130}. This was also found in the present thesis and is an aspect that healthcare professionals must bear in mind. Healthcare professionals should devote more time to discussing environmental asthma triggers and control strategies as part of the treatment. They should also educate both children/adolescents and parents as it might lead to increased adherence to medication^{131, 132}. My recommendation is for healthcare professionals to use the “Summary of optimal healthcare for adolescents with allergic disease in healthcare”, Fig 6. Identifying the child’s needs and goals is a challenge for healthcare professionals and caregivers^{75, 86}. Using educational technology seems to be a winning concept¹³³.

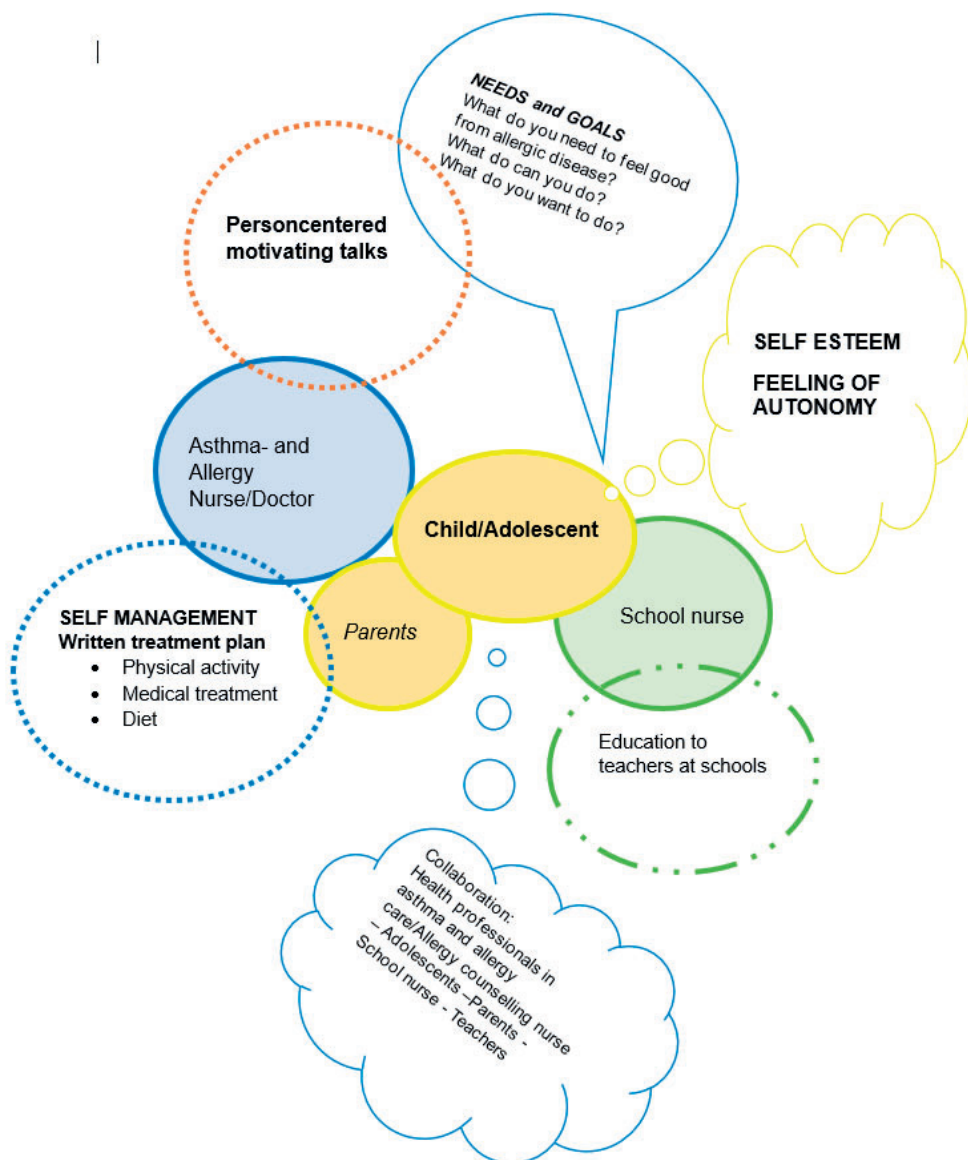


Figure 6. Summary of optimal healthcare for adolescents with allergic disease.

Different aspects of team processes that need to be changed, such as the necessity to adjusting shift patterns to enhance opportunities for engagement between nurses and patients, require attention. In person-centred healthcare it is paramount to understand the meaning of shared decision-making in a busy general medical ward. Furthermore, it is essential to facilitate the development of multidisciplinary clinical teams to enhance the effectiveness of staff relationships and identify possible ways to communicate diagnostic test results to patients ⁷⁵.

This thesis can in a way summarize the importance of involving the patient in both the diagnosis as well as selected treatment. To give the patient an understanding of the disease overall and the symptoms specific in order to let the patient identifying self-management strategies to use prescribed treatment. The patient should have a possibility of reflecting and discuss the life situation and possibilities to manage to cope with the situation.

Future research – how to proceed

Population based allergy-studies are important for verifying the epidemiology that includes the prevalence and associated risk factors for allergic diseases. Without population-based studies it would be impossible to know if chronic diseases in a hospital setting is also widespread in the general population. Patient reported outcomes are therefore useful tools to assess whether the healthcare system provides correct diagnosis and good treatments.

This cohort with results at baseline gives rich opportunities for register-based follow-up after 10-20 years to get valuable information about development of allergic diseases in adulthood and during life.

Populärvetenskaplig sammanfattning

Det övergripande syftet med denna avhandling är att öka kunskapen om självrapporterad allergisk sjukdom i tonåren, avseende förekomst av symtom, sensibiliseringsprofil, hälsorelaterad livskvalitet och fysisk aktivitet.

Allergisk sjukdom är idag några av de mest förekommande kroniska sjukdomarna hos barn och tonåringar i Sverige och har ökat världen över under de senaste decennierna, vilket innebär att det är av stor betydelse att identifiera och förstå olika påverkande faktorer. Allergisk sensibilisering, d.v.s. när immunförsvaret bildar s.k. IgE antikroppar mot ett allergen, är en stark riskfaktor för utveckling av allergisk sjukdom. Därför är kunskap om förekomst av IgE sensibilisering i den allmänna populationen viktig. En faktor som påverkar de som redan har astma är bl. a. fysisk aktivitet något som har visat sig kunna vara förebyggande mot astmaförsämring men det är inte känt hur det ser ut i tonårsgruppen med just fysisk aktivitet. Den hälsorelaterade livskvaliteten är påverkad vid allergisk sjukdom men den är inte generellt studerat hos tonåringar under pollensäsong.

Det som är känt är att tonåringar är i en känslig fas i livet vilket kan påverka deras sjukdomsinsikt. Därför är det av vikt att tala med som har allergisk sjukdom för att få vet hur de ser på sjukdom och fysisk aktivitet.

Den här avhandlingen är baserad på ett tvärsnitt av ungdomar, från en kohort i södra Sverige (Blekinge, södra Halland, Kronoberg och Skåne) i åldrarna 13-14 år. Det internationella ISAAC-frågeformuläret användes samt frågor om fysisk aktivitet, matöverkänslighet och hälsorelaterad livskvalitet.

I delstudie I framkom att av alla ungdomar (n=1333) rapporterade 32% minst en allergisk sjukdom medan 67% rapporterade en allergisk sjukdom och 33% rapporterade mer än en. De som inte rapporterade någon allergisk sjukdom var 68%. De rapporterade också en mycket låg förekomst av medicinering.

I delstudie II var fokus att se hur många som hade förekomst av IgE-antikroppar i förhållande till självrapporterad allergisk sjukdom. IgE-sensibilisering undersöktes hos 195 tonåringar med hjälp av både extraktbaserade och komponentbaserade test. IgE-antikroppar mot luftburna allergener var signifikant vanligare än IgE antikroppar mot matallergener, 43% respektive 14%. IgE-antikroppar mot luftburna allergen var signifikant högre bland ungdomar med rinokonjunktivit ($p < 0,001$) och eksem ($p < 0,01$). Av 53 ungdomar med allergiska symtom hade 60% IgE-antikroppar. IgE-antikroppar mot livsmedelsallergener sågs hos de med rinokonjunktivit, men endast för de allergen som betecknas som korsallergen, PR-10-proteiner. IgE-antikroppar som var mest förekommande var gräspollenallergen, Phleum pratense (Phl p 1).

Delstudie III och IV fokuserade på själv rapporterad fysisk aktivitet generellt och i relation till allergisk sjukdom både genom frågor om daglig fysisk aktivitet och under fritiden samt genom intervju med 36 tonåringar. Generellt visade resultatet på en låg fysisk aktivitet i förhållande till Socialstyrelsens rekommendationer men det var inte någon skillnad i grupperna med allergisk sjukdom eller inte. Resultaten i den kvalitativa studien visade på; Att vara fysiskt aktiv när man lider av en allergisk sjukdom innebär att bli medveten om symtomen och därmed vilka strategier som behövs. De intervjuade tonåringarna är relativt fysiskt aktiva men berättar att de måste kämpa med symtom, mediciner och testa sig fram för att hitta en aktivitet som passar dem.

I Delstudie III undersöktes även den hälsorelaterade livskvaliteten under pollensäsong. Signifikanta skillnader i den hälsorelaterade livskvaliteten observerades beroende på nuvarande eller tidigare symtom. Den märkbart nedsatta livskvaliteten under pollensäsong i förhållande till självrapporterade symtom som observerats i den här studien visar på vikten av att sjukvården ger dessa tonåring den uppmärksamhet som krävs.

Sammanfattningsvis visar avhandlingen på att ett stort antal tonåringar med allergisk sjukdom i södra Sverige. Livskvaliteten är påverkad under pollensäsong och många får kämpa för att kunna vara fysiskt aktiva. Detta är tydliga tecken på att vård och behandling av ungdomar med allergisk sjukdom måste förbättras främst avseende ökad kommunikation och information både med och till ungdomarna både gällande medicinering, preventiva åtgärder, fysisk aktivitet och omgivande faktorer.

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