"HAY FEVER" IN CHILDREN
- THE REAL STORY

Marit Westman

Stockholm 2014
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PREFACE

Symptoms from the upper airways, such as blockage of the nose, sneezing, runny nose, are common in the general population. When the symptoms extend over a longer period, and can no longer be explained by a common cold or some other acute infection, it is a common belief that allergy is the cause. On the other hand, among young children, rhinitis symptoms are often interpreted as a cold, “the kindergarten syndrome”. However, there may be several causes for chronic upper airway symptoms, even in childhood. Moreover, “hay fever” has been regarded as benign and harmless; something recent studies have proved not to be the whole truth. This thesis is an attempt to describe different chronic upper airway symptoms in children and adolescents from the aspects of prevalence, natural course, comorbidity, risk factors and quality of life. Hopefully, after reading this book, you will see a stuffy, runny, sneezing nose as more than just “harmless hay fever” or “kindergarten infection” and understand “the real story” about upper airway symptoms in children.

Marit Westman
Stockholm 2014
ABSTRACT

Rhinitis, allergic (AR) and non-allergic (NAR), and chronic rhinosinusitis (CRS) are different expressions of upper airway inflammation. Chronic upper airway symptoms are common in childhood and adolescence. There is a need for more epidemiologic data of these different entities of upper airway symptoms in the aspects of prevalence, natural course, co-morbidity and risk factors.

The aim of this thesis was to provide epidemiologic data from a pediatric general population for a better understanding of the different phenotypes of upper airway inflammation from childhood to adolescence. To do this, we used the BAMSE birth cohort with 4089 children followed from birth up to 16 years of age with repeated questionnaires and clinical follow-ups.

We found that AR was already common at 4 years (5.4%) and that the prevalence increased to 14% at 8 years. 87% of the 4-year-olds with AR had persistent disease up to 8 years. In contrast, among the 8.1% with NAR at 4 years, 74% had no rhinitis symptoms at 8 years. We also found that co-morbidity with asthma and eczema was common, not only for AR, but also for NAR. Oral allergy syndrome (OAS) was found among 31% of 8-year-olds and 63% of the 16-year-olds with allergic rhinitis to birch pollen.

Parental allergic disease increased the risk of the child of developing AR as well as NAR at 8 years of age. There was an increased risk of AR in particular if the parents had hay fever or if both parents were allergic. An increased risk of NAR was seen if one parent had two or more allergy-related diseases. We found no difference in risk between maternal and paternal heredity.

The prevalence of reported symptoms of allergic rhinitis to birch pollen (ARbp) increased from 2.5% at 4 years to 10.6% at 8 years and 17.8% at 16 years. Bet v 1-specific IgE was the most prevalent specific IgE against PR-10 allergen molecules and had the highest median levels. We found an increased probability for the onset of ARbp at 16 years with increasing levels of Bet v 1-specific IgE or increasing number of other IgE-reactive PR-10 proteins at 4 years. In addition we found that the levels of Bet v 1 at 4 years were associated with severity of ARbp at 16 years.

The prevalence of CRS at 16 years of age was estimated to be between 0.3% and 1.5%. Adolescents with CRS more often reported symptoms of allergic rhinitis and asthma and had a lower health-related quality of life than those without CRS.
In conclusion, the results from this thesis show that both AR and NAR in children are common, are associated with asthma and eczema and affected by parental allergy-related diseases. There are differences between AR and NAR regarding the prognosis and the pattern of heredity for allergic diseases. AR may possibly be predicted by the levels of Bet v 1-specific IgE or number of IgE-reactive PR-10 proteins in early childhood and by parental hay fever. The prevalence of OAS among individuals with birch pollen allergy seems to increase during childhood. The prevalence of CRS in adolescence seems to be low but for those affected, the symptoms may be bothersome.
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ORIGINAL PAPERS
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This thesis is based on the following four papers, three original articles and one letter to the editor, which will be referred to in the text by their Roman numerals:


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### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AR</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>AR\textsubscript{bp}</td>
<td>Allergic rhinitis to birch pollen</td>
</tr>
<tr>
<td>ARIA</td>
<td>Allergic Rhinitis and its Impact on Asthma</td>
</tr>
<tr>
<td>BAMSE</td>
<td>Barn/Children Allergi/Allergy Miljö/Environment Stockholm Epidemiologic study</td>
</tr>
<tr>
<td>CRS</td>
<td>Chronic rhinosinusitis</td>
</tr>
<tr>
<td>EPOS</td>
<td>European Position paper On Rhinosinusitis</td>
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<tr>
<td>GM</td>
<td>Genometric mean</td>
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<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>ISAC</td>
<td>Immuno-solid phase allergen chip</td>
</tr>
<tr>
<td>ISAAC</td>
<td>International Study of Asthma and Allergy in Childhood</td>
</tr>
<tr>
<td>ISU-E</td>
<td>ISAC standardized units for IgE-detection</td>
</tr>
<tr>
<td>MeDALL</td>
<td>Mechanisms for the Development of Allergies, EU founded project</td>
</tr>
<tr>
<td>NAR</td>
<td>Non-allergic rhinitis</td>
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<td>OAS</td>
<td>Oral allergy syndrome</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>PR-10</td>
<td>Pathogenesis related proteins 10</td>
</tr>
<tr>
<td>PROM</td>
<td>Patient reported outcome measure</td>
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<tr>
<td>95% CI</td>
<td>95% confidence interval</td>
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I INTRODUCTION

1.1 UPPER AIRWAY INFLAMMATION

Rhinitis is defined as an inflammation of the nasal epithelium and is characterized by symptoms including rhinorrhea, sneezing, nasal blockage and/or itching of the nose (1, 2). The inflammation may have different causes and different authors classify rhinitis somewhat differently, but basically there are three main groups; infectious rhinitis, allergic rhinitis, and non-allergic (non-infectious) rhinitis. The conditions are not always disjunctive groups, but may overlap. The most common form of rhinitis is infectious rhinitis, i.e. viral infections, a common cold. The most common form of non-infectious rhinitis is allergic rhinitis (AR) where the inflammation is caused by an IgE-mediated reaction after contact with an allergen (3). AR is very often complicated by ocular symptoms, and then the term allergic rhinoconjunctivitis is used. When rhinitis is not caused by infection or allergy the term non-allergic rhinitis (NAR) or non-allergic non-infectious rhinitis (NINA), is used (2-4). Non-allergic rhinitis is a heterogeneous group with some known causes, but in the majority of cases no cause is found and is then called idiopathic rhinitis (previously vasomotor rhinitis).

The term rhinosinusitis is used when the inflammation extends to the paranasal sinuses. Previously, the term sinusitis was used, but since sinusitis often starts as rhinitis and the two very often coexist the term rhinosinusitis is now the accepted term. (There are, however some exceptions, i.e. dental sinusitis). The typical symptoms are nasal congestion/blockage, nasal discharge, facial pressure/pain and/or loss of smell (5).

1.1.1 Allergic rhinitis

In the beginning of the 19th century John Bostock described a new phenomenon he gave the name catarrhus aestivus, or summer catarrh (6, 7). He had noticed that a number of patients (himself included) reported symptoms from the nose, eyes or even chest recurring at the same season of the year. The term hay fever soon became popular because of the symptoms’ correlation to the hay season, but it was not until 1873 that Blackley showed that pollen grains from hay could elicit the symptoms (8, 9) (Blackley CH, Experimental researches on the causes and nature of catarrhus aestivus (hay-fever or hay-asthma), London, Ballière, Tindall and Cox, 1873, not retrieved).

AR is defined as an inflammation in the nasal mucosa caused by an IgE-mediated reaction after contact with an allergen (3). Clinically the diagnosis of AR is made when specific IgE-antibodies are detected and symptoms are
elicited by the particular allergen that corresponds to the specific IgE. The characteristic symptoms of allergic rhinitis were defined by Hansel in 1929: “The nasal reactions occurring in allergy are manifested chiefly by three cardinal symptoms, namely, sneezing, nasal obstruction, and mucous discharge” (10). In addition about 90% of patients with AR have ocular symptoms of redness, itching or watery eyes, often referred to as allergic rhinoconjunctivitis (11). Importantly, other symptoms may be tiredness, sleep disturbances, dry cough, headache and oral symptoms after ingesting certain food items (12-14). AR has previously been regarded as a trivial disease but evidence is now adding up that shows a reduced quality of life and reduced productivity at work or school (12, 14).

1.1.1.1 The sensitization process and allergic reaction

The process in which an individual starts to produce specific IgE-antibodies is called sensitization. Why certain individuals become sensitized and others are not sensitized is still not fully understood but a family history of allergic disease in combination with lifestyle factors seem to play a role. The sensitization process starts with an allergen entering the barrier of the skin or mucosa of the airways or guts where it encounters the immune system (Fig 1). The allergen is taken up by antigen-presenting cells (APC). On encountering a foreign antigen, the APCs will decide whether the naïve CD4+ cells will proliferate into Th1, Th2, Th17 or T-regulatory cells (Treg). When this foreign antigen is an allergen the APCs will signal to the CD4+ cells to proliferate into Th2 cells and start to produce IL-4 and IL-13. This in turn stimulates B-cells to produce specific IgE-antibodies. The specific IgE-antibodies will then coat mast cells and basophils. The individual has become sensitized (15, 16).

The next time the sensitized individual encounters the allergen, it will be recognized by specific IgE-antibodies on the mast cells and basophils, which results in activation of the cells and release of inflammatory mediators, such as histamine, which causes the allergic reaction (Fig 2).

1.1.1.2 Prevalence and risk factors

By now, most people are aware that the prevalence of allergic rhinitis, as well as other allergic diseases, has increased in the industrialized part of the world, especially during the latter half of the 20th century. In Sweden, the prevalence of AR among conscripts (18-year-old males) increased from 4.4% to 8.4% between 1971 and 1981 (17), and in school children from 5.5% to 8.1% from 1979 to 1991 (18). A similar increase has been seen among American college students (19) and British adolescents (20). A more recent study is The International Study of Asthma and Allergies in Childhood (ISAAC) epidemiologic research program which compared the prevalence of allergy-related
"Hay fever" in children - the real story

**Figure 1:** The process of primary sensitization.

**Figure 2:** The allergic reaction.
diseases worldwide in two different age groups, 6-7 years and 13-14 years, 7 years apart (on average). They found that overall allergic rhinoconjunctivitis was still increasing especially in the younger age group, but there were differences between countries (21). In Sweden the prevalence remained at about the same level during the seven years (8.0-6.9 among the 6-7 year olds and 11.1-10.4 in the 13-14 year olds). Differences in prevalence of allergic rhinoconjunctivitis between countries was reported with figures as low as 2-4% in the 6-7 year age group, for example, in Iran, Nigeria and Estonia and 13% or more in Australia, Taiwan, Costa Rica and Poland (21). But there also seem to be differences between regions within countries (18, 22).

The relatively rapid increase in prevalence of AR over the last 30-40 years and the differences seen between countries, but also between different geographical regions within countries implicates that the prevalence is affected by the presence or absence of risk factors or protective factors (23). To study these environmental risk- or protective factors was the main aim for the foundation of the BAMSE cohort as well as other birth cohorts in Europe initiated during the 1980s and 1990s (24, 25).

One of the main hypotheses of these environmental factors is the hygiene hypothesis, expounded in 1989 by David Strachan, which postulates that infections are protective against allergy (26). The hypothesis has resulted in a multitude of studies of the protective as well as harmful effects of infections, day care attendance, number of siblings etc., but many findings are diverse (23). Several other environmental factors have been analyzed for rhinitis, e.g. socio-economic status (27, 28), dietary factors such as early fish intake (29, 30), ventilation rates in the home (31), breast feeding (32, 33) however with more or less convincing results. More convicing are the findings of a protective effect of certain lifestyles; living on a farm (34-36) and the anthroposophic lifestyle (37, 38). The underlying causes for this effect can be many and identification of these protective factors has proven to be difficult. Some existing theories are microbial exposure during early life, drinking unprocessed farm milk (39), prenatal factors through the pregnant mother (40) dietary habits, restrictive use of antibiotics and certain vaccines (34).

The diverse findings about environmental factors are probably due to a more complex picture than first thought, with timing and dose of exposure, gene-environmental interactions as possible explanations (23). It is not surprising that the strongest associations are seen for completely different lifestyles which provide the immune system with a diverse set of stimuli.

Probably the best established risk factor for allergic rhinitis is a family history of allergic disease (3). The association between parental allergy and allergy in the offspring is seen regardless of the ages studied, study design or region of origin. However, studies on the pattern of heredity are scarce. There
are some studies indicating that a family history of asthma is more important for asthma (41, 42) and a family history of allergic rhinitis for allergic rhinitis (42, 43).

It is well known that not all individuals sensitized to an airborne allergen have clinical symptoms of allergy (44, 45). Already in 1976 Hagy et al. found that a positive skin prick test among asymptomatic college students was associated with an increased risk for allergic rhinitis seven years later (19). More recent studies have confirmed this result (46, 47). However, other studies suspect rhinitis symptoms develop into allergic rhinitis (48, 49).

1.1.1.3 Co-morbidity

Different allergic diseases (allergic rhinitis, asthma, eczema and to some extent also food hypersensitivity) are frequently associated. In children the different diseases are more prevalent at different ages (50), they may coexist or one may follow the other. Historically this has been referred to as the atopic march (51, 52). Typically the atopic march starts with atopic eczema, followed by food hypersensitivity, asthma and finally allergic rhinitis (52). Atopic eczema in early childhood is a risk factor for asthma as well as allergic rhinitis (51-53).

Asthma and allergic rhinitis frequently co-exist both among children and adults, which is an observation that has led to the concept of “the United Airway”. In 1997, due to the better understanding of the two diseases that had evolved, Grossman proposed viewing asthma and allergic rhinitis not as separate entities but as “a continuum of inflammation involving one common airway” (54). The theory of “One Airway, One Disease” was born. This theory is thoroughly presented in the consensus document “Allergic rhinitis and its impact on asthma” (ARIA), which was first published in 2001 with an update in 2008 (3, 55). Between 15% and 40% of patients with allergic rhinitis also have asthma or bronchial hyper-reactivity (56, 57). Among adults, a majority of patients with asthma also have allergic rhinitis (56). Among asthmatic children the proportion with rhinitis seems to be related to age with lower proportions at preschool age than at school age or adolescence (50, 58). Rhinitis has shown to be an independent risk factor for asthma in both children and adults (59-63). Furthermore, allergic rhinitis has been found to be associated with poor asthma control and an increased risk of asthma hospitalization (64, 65), but whether this is an expression of a more severe disease or if treatment of rhinitis improves asthma, needs further investigation. The mechanisms behind these associations are still not fully understood. Some theories have been discussed: by-passing nasal function, systemic pathways, neuronal pathways and postnasal drip (micro-aspiration of nasal contents) (3, 5, 66). In conclusion, the association between asthma and rhinitis is no longer questioned, but there are still things left to explore in relation to underlying
mechanisms. More data is needed regarding the epidemiology of AR during childhood, since different studies have used different definitions of rhinitis and the proportion of the association must be better studied in different age groups.

1.1.1.4 Oral allergy syndrome and IgE cross reactivity

It has long been known that patients with pollen allergy often complain of symptoms of itching in the mouth, throat or ears or even a swollen feeling in the lips, tongue or throat after consuming certain fruits or vegetables (13, 67). This condition is called oral allergy syndrome (OAS) and is characterized by an IgE-mediated reaction restricted to the oro-pharyngeal mucosa (67, 68). The phenomenon is caused by cross-reactions from pollen allergens and is sometimes called pollen-food syndrome (68). It is estimated to affect around 70% of adults with AR to birch pollen (13, 69). The prevalence among children has been unknown.

Birch pollen allergy is a typical example where patients report symptoms when eating, for example, fresh apples, peaches or kiwis, or tree nuts or peanuts. The recently acquired knowledge from molecular-based allergy diagnostics about allergenic molecules (allergen components) can explain this and will be exemplified here by birch pollen. The birch pollen allergen actually consists of several different allergen components i.e. allergenic molecules; Bet v 1, Bet v 2 and Bet v 4 (abbreviations derive from the Latin term Betula verrucosa and the number refers to order of characterization). Bet v 1, which is a major birch pollen allergen component, belongs to a protein family called pathogenesis related proteins (PR)-10. In this family of proteins, there are also allergen components from, for example, apples (Mal d 1), peaches (Pru p 1) and peanuts (Ara h 8). The PR-10 proteins have a similar function and show structural similarity (homology). When a Bet v 1-sensitized individual ingests food items which contain proteins from the PR-10 group, the specific IgE on the mast cells in the oral mucosa will recognize and bind to these molecules followed by a release of inflammatory mediators and consequently symptoms. The reason for symptoms being restricted to the oro-pharyngeal area is that the PR-10 proteins are labile, i.e. they are unstable to digestion or heat (70).

1.1.2 Non-allergic rhinitis

Hansel who defined the typical allergic rhinitis symptoms in 1929, also noted that patients with rhinitis symptoms that were not obviously due to infection, did not always have a positive allergy skin test. He interpreted these cases as due to “reflex disturbances” (10).
Non-allergic rhinitis may be defined as a chronic inflammation in the nasal epithelium not caused by systemic IgE-dependent mechanisms and not by infection (2, 3, 71).

There are no specific diagnostic criteria for NAR (3, 72), and the diagnostics rely instead on symptoms of rhinitis in the absence of infection and the absence of sensitization. In adults, non-allergic rhinitis is known as an umbrella term for several different nasal conditions, where some of them have known causes, e.g. non-allergic rhinitis with eosinophilia syndrome (NARES), hormonal changes during pregnancy, occupational rhinitis, drug-induced rhinitis. But the majority of cases have no known cause, with the current term idiopathic rhinitis or non-infectious non-allergic rhinitis, NINA, (3, 4, 73). There are probably several different phenotypes of idiopathic rhinitis yet to be defined in relation to underlying pathophysiology (71). Although NAR is a common condition, in at least 25% of adult rhinitis patients (4, 74), little is known about the underlying mechanisms. However, there are some theories; e.g. neurogenic mechanisms (C-fibers, parasympathetic hyper-reactivity and/or sympathetic hypo-reactivity) glandular hyper-reactivity, vascular hyper-reactivity (73). Among children, data on NAR is even scarcer. So far, the focus for rhinitis research in children has been on allergic rhinitis. Phenotypes within the NAR group are not well studied in children although it is plausible that NAR consists of several conditions; e.g. caused by irritants, hormonal changes, specific medications or idiopathic rhinitis, just as in adults (2). Co-morbidity associated with non-allergic rhinitis symptoms has also not been well studied in children. Co-morbidity has been studied for allergic rhinitis and for rhinitis including both sensitized and non-sensitized subjects, but so far there are few studies for non-allergic rhinitis symptoms alone.

There are several conditions that mimic rhinitis symptoms in children which are not included in the term “non-allergic rhinitis” and they need to be mentioned: Adenoidal hypertrophy, rhinosinusitis, cystic fibrosis, primary ciliary dyskinesia, choanal atresia/stenosis, immunodeficiency, foreign bodies, cerebrospinal fluid leakage, encephalocele, septal deviation and coagulopathy (2).

1.1.3 Chronic rhinosinusitis

Rhinosinusitis is an inflammatory process which involves the mucosa of the nose and of one or more of the paranasal sinuses (5). The nasal and sinus mucosa is a continuum and therefore rhinitis (inflammation of the nasal mucosa) commonly coexists with sinusitis (inflammation of the sinus mucosa), hence the term rhinosinusitis. It is a multifactorial disease and some examples of contributing factors are infections, biofilm, allergy, mucociliary impairment
and environmental exposures (e.g. tobacco smoke). Rhinosinusitis is an entity that clinically is poorly defined and there has been a lack of uniformly accepted definitions (5). This makes it hard to compare studies and elaborate treatment guidelines. The first evidence-based position paper with well-defined diagnostic criteria, the “European Position Paper on Rhinosinusitis” (EPOS), was elaborated in 2005, with updates in 2007 and 2012 (5, 75, 76). EPOS recommends certain symptom criteria to be used in general medicine or in epidemiologic research: nasal blockage, nasal discharge, facial pain/pressure, reduction or loss of smell, (explained in detail in Section 1:2:4). The symptoms are to be affirmed either by nasal endoscopy or a CT scan to be used in clinical practice or clinical studies. Symptoms lasting for less than 10 days are classified as a common cold. Symptoms with duration for 10 days or more but less than 12 weeks are classified as acute rhinosinusitis. Symptoms lasting for twelve weeks or more are classified as chronic rhinosinusitis (CRS). There are two main groups of CRS; with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP). They are often considered as one disease entity, CRSwNP as a subgroup of CRS, because of the difficulties of differentiating between the two (5).

1.1.3.1 Prevalence

As a result of the disease being heterogeneous and because of a previous lack of consistent diagnostic criteria between studies, the prevalence of CRS is uncertain.

Among adults the estimates of prevalence of CRS range between 1-16% depending on which diagnosis criteria have been used (5, 77-79). It seems more common among females than males (77, 79). In children the prevalence of CRS is mostly based on CT or MRI studies looking at mucosal changes in the sinuses (80-82). From this data it seems as if the prevalence of CRS is high in preschool age and decreases during school age. Although the exact figures are uncertain and the clinical relevance of CT/MRI findings needs to be affirmed, there is reason to believe that CRS is not an uncommon disorder in preschool age and among adults (5). Even less is known about the prevalence in adolescence.

1.1.3.2 Co-morbidity

As described for allergic rhinitis, there is an association between disease in upper and lower airways as thoroughly presented in ARIA. Also CRS is associated with lower airway disease. It is estimated that asthma or bronchial hyper-reactivity may affect up to 50% of patients with CRS (5). Among patients with asthma there may be a proportion as high as 80% who have sinonasal symptoms. A special group of patients are those with the so-called Samter’s Triad who present with asthma, nasal polyps and aspirin-intolerance.
Treatment of CRS (medical or surgical) has shown to improve asthma in both children and adults (5, 84-86).

Epidemiologic data has shown CRS and allergic rhinitis to be frequently associated (5). It has been suggested that allergic rhinitis predisposes patients for both acute and chronic rhinosinusitis by the inflammation and the swelling of the nasal mucosa leading to obstruction of the sinuses. The evidence for this causal relationship is still inconclusive (3). There are studies showing atopy (sensitization) to be more common in populations with CRS than what would be expected in the general population, but the results are not convincing (5).

1.1.3.3 HRQoL

With the use of patient-reported outcome measures (PROM), (described in Section 1.4), CRS has been shown to have a negative effect on several aspects of patients’ quality of life. As a comparison, a greater impact on social functioning has been shown for adults with CRS than for chronic heart failure, angina or back pain (87). Also among children with CRS, a significant impairment in their quality of life has been noted, interestingly scoring lower than children with asthma, juvenile rheumatoid arthritis and epilepsy (88). Again, data from adolescents is scarce.

1.2 EPIDEMIOLOGIC DEFINITIONS OF UPPER AIRWAY SYMPTOMS

For practical reasons, large population-based studies often use questionnaires. To define a health outcome, one has to rely on the symptoms reported by the subjects (or in case of children, the subjects’ parents). Therefore it is of importance that the questionnaire is based on validated questions in order to know how to interpret the results and to be able to compare the results with other studies. There are several different epidemiologic definitions used in the literature, with different sensitivity, specificity and positive predictive value (PPV). This is important when designing a study and when interpreting results.

1.2.1 Current rhinitis and current rhinoconjunctivitis according to the International Study of Asthma and Allergy in Childhood (ISAAC)

The International Study of Asthma and Allergy in Childhood (ISAAC) epidemiologic research program was founded with the aim of standardizing questions in order to compare the prevalence of rhinitis, asthma and eczema between different parts of the world in two separate age groups, 6-7 year olds and 13-14 year olds (89). The principal aims were to distinguish between rhi-
rhinitis and non-rhinitis in the general population and to predict which subjects with rhinitis were likely to be atopic (allergic). The core questions include:

- **Current rhinitis**: “In the past 12 months, have you (has your child) had a problem with sneezing, or a runny, or blocked nose when you DID NOT have a cold or the flu?”
- **Current rhinoconjunctivitis**: “In the past 12 months, has this nose problem been accompanied by itchy, watery eyes?”
- **Seasonal symptoms**: In which of the past 12 months did this nose problem occur?
- **Hay fever ever**: Have you (has your child) ever had hay fever?

A validation study of the ISAAC core questions among Swiss school children (90) found the questions to be highly specific but with rather low sensitivity as compared to skin prick test. Current rhinitis seemed better at detecting children with rhinitis (higher sensitivity) than current rhinoconjunctivitis, seasonal symptoms and hay fever ever. On the other hand the positive predictive value for atopy was higher for current rhinoconjunctivitis, seasonal symptoms and “hay fever ever” than for current rhinitis.

### 1.2.2 Allergic rhinitis

Other questions with the aim of predicting allergic rhinitis are:

- Nasal symptoms/hay fever on exposure to an allergen
- Hay fever or nasal allergy diagnosed by a doctor

These two questions have shown to have similar PPV (75-76%) for detecting allergic rhinitis (with symptoms confirmed by a doctor in combination with specific IgE as the golden standard) in subjects aged 18-25 year (91). Hay fever diagnosed by a doctor had higher specificity (93% vs 87%) but symptoms on exposure to an allergen had higher sensitivity (87% vs 52%). In children aged 1-17 years, standardized questions to the parents for aggravation of their children’s symptoms in contact with the allergen had a high accuracy >95% compared with the question being asked by an experienced allergologist (92). In this study, symptoms from both upper and lower airways were analyzed together and the range of ages was 1-17 years.

### 1.2.3 Non-allergic rhinitis

There are no specific questions for non-allergic rhinitis since it is a diagnosis of exclusion. Most epidemiologic studies of non-allergic rhinitis are based on rhinitis symptoms in the absence of cold or flu (current rhinitis according to ISAAC), with a negative test of sensitization (skin prick test or specific IgE) (93-95).
1.2.4 Chronic rhinosinusitis (CRS)

The symptom-based criteria for CRS developed by the European Position Paper on Rhinosinusitis (EPOS) are the following:

Two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
- ± facial pain/pressure,
- ± reduction or loss of smell,

with a duration of symptoms of 12 weeks or more.

This will not enable distinction between CRS with or without nasal polyps. For this, as well as for clinical studies and clinical practice nasal endoscopy will have to be performed (5).

1.3 WHEN QUESTIONNAIRES ARE NOT SUFFICIENT

Questionnaires can detect subjects with nasal symptoms, but the distinction between AR, NAR and rhinosinusitis may be difficult and an accurate diagnosis often requires more than a questionnaire answer (71).

1.3.1 Tests of allergic sensitization

To better distinguish allergic rhinitis from a non-allergic one should use a sensitization test. There are several ways to test whether a subject is sensitized or not and against which allergen(s). The two most commonly used are skin prick tests and blood samples analyzed with ImmunoCAP. The skin prick test analyzes the reaction in the skin (occurrence and size of a weal) after application of standardized solutions of the allergens (96). The ImmunoCAP technology analyzes specific IgE reactivity in serum from a blood sample. Over the last few years it has become more and more common with molecular-based diagnosis with multiplex platforms.

1.3.1.1 ImmunoCAP

**Specific IgE**: IgE-reactivity can be measured for a wide variety of allergens, both for allergen extracts (such as birch) and allergenic molecules (such as Bet v 1). The ImmunoCAP technology measures one allergen per assay, and is considered positive at a level of 0.35 kU/l.

**Phadiatop®**: The Phadiatop test is a screening test of sensitization, with a mix of the eight most common inhalant allergens in our region (birch, timothy, mugwort, cat, dog, horse, Cladosporium herbarum and Dermatophagoides pteronyssinus) (Thermo Fischer Scientific, Uppsala, Sweden) The test adds the levels of specific IgE for the different allergens and is considered positive at a level of 0.35 kU/l. The intensity of reaction in the Phadiatop test
has shown to correlate well with both skin prick test and the concentration of specific IgE to the same allergens measured with CAP-RAST (97).

1.3.1.2 Microarray Immunoassay
Molecular-based allergy diagnosis is used to determine sensitization at a molecular level, i.e. IgE-reactivity to specific allergen components. For this purpose one can use either singleplex platforms (such as ImmunoCAP) or multiplex platforms based on microarray technology. In contrast to the singleplex platform, the multiplex platform can analyze several different allergen extracts or allergen components simultaneously with only a small amount of serum. Moreover, the singleplex platforms determine IgE-binding under conditions of an excess of immobilized allergen whereas the multiplex platform uses low amounts of immobilized allergen which allows for competition between IgE and other allergen specific antibodies, e.g. IgG (70).

The commercially available multiplex platform is called ISAC (Immunosolid phase allergen chip).

The MeDALL chip (MeDALL – Mechanisms for the development of allergies, an EU funded project): The MeDALL chip is based on the ISAC chip but has been elaborated to suit large birth cohorts where the amount of serum for analysis is often scarce. It is modified from ISAC in outlay and with an increased number of allergens analyzed (98).

1.3.2 Olfactory threshold
Nasal chemosensory function can be tested for different aspects; olfactory threshold, discrimination of odors and identification of odors. Olfactory threshold measures at which level (concentration) a subject can detect a certain odor. There are several tests for olfactory threshold, e.g. CCCRC, Combined Olfactory test, T&T Olfactometer and Sniffin’ sticks.

1.3.2.1 Sniffin’ sticks
“Sniffin’ sticks” is a validated test of nasal chemosensory function that is based on pen-like odor dispensing devices (99). It consists of tests for odor threshold, discrimination, and identification. Test results are age dependent. The highest scoring age group, 16-35 years, is set as a reference group. Odor detection decreases with age but is also lower than the reference group in subjects aged 5-15 years. Hyposmia is defined as the 10th percentile of the age group 16-35 years, which for olfactory threshold corresponds to a value of 6.25. A high score on the test indicates high function (detecting odors at low concentrations).
1.4 HEALTH-RELATED QUALITY OF LIFE (HRQoL)

Measures of quality-of-life that are self-rated and reported by the patient/subject him/herself are called Patient Reported Outcome Measures (PROMs). These instruments are often questionnaires rating health in different domains, but may also be a graded scale or a visual analog scale. Most of the existing instruments define HRQoL within two main domains; physical function and psychosocial function. There are two different types of PROMs, the disease-specific instruments and the general instruments, also called generic. Generic instruments assess the general health and can be used to compare different conditions or to compare with the general population. Examples of widely used generic instruments are SF-36 and EQ-5D. Disease-specific instruments are developed for specific conditions and thus contain questions specific for that disease. Examples of disease-specific instruments validated for CRS are SNOT-22 and RSOM-31 (5).

1.4.1 EQ-5D

EQ-5D™ is a well-established and widely used generic instrument for the assessment of health-related quality of life (HRQoL) (100, 101). It has previously been widely used for assessment of the general self-reported health in different chronic conditions and recently also in CRS (102). It consists of two parts. The first part collects information from 5 separate domains, with one question for each domain. In the second part, called EQ-VAS, the respondent evaluates his or her state of health by indicating a position on a visual analog scale, from 0=worst health state imaginable to 100=best health state imaginable. The advantage of this instrument is that it is short (5 questions + VAS-scale) and therefore suitable to add in an extensive questionnaire as in a birth cohort.

1.4.2 SNOT-22

The 22-item Sino Nasal Outcome Test (SNOT-22) is a disease-specific instrument validated for adults with CRS (103) and translated into Swedish (104). It contains questions about physical functions (symptoms) and psychosocial functions and is widely used for CRS. The respondent scores each of the 22 questions from 0 to 5. The total score can have a value between 0=no symptoms to 110=maximum symptoms.

1.5 AIMS

The main aim of this thesis was to contribute with epidemiologic data from a pediatric general population on rhinitis and rhinosinusitis from childhood to adolescence.
Specific aims:

**Study I:** To investigate different phenotypes of non-infectious rhinitis in children, 4 and 8 years old, in the aspect of natural course of disease and comorbidity with other allergy related diseases.

**Study II:** To examine how maternal and paternal hay fever, asthma and eczema affect the risk of allergic rhinitis (AR) and non-allergic rhinitis (NAR) at 8 years of age.

**Study III:** To investigate if IgE-reactivity to allergenic molecules of the PR-10 protein family in childhood was associated with occurrence, incidence, and persistence of AR to birch pollen up to 16 years of age. Secondary aims were to assess the association between IgE-reactivity to PR-10 proteins and severity of AR to birch pollen and the occurrence of oral allergy syndrome (OAS) at 16 years.

**Study IV:** To estimate the prevalence of CRS in adolescence and evaluate the burden of symptoms.

## 2 MATERIAL AND METHODS

### 2.1 STUDY SUBJECTS

#### 2.1.1 The BAMSE cohort

All the papers are based on material from the prospective, population based birth cohort BAMSE (Barn/Children Allergi/Allergy Miljö/Environment Stockholm Epidemiologi/Epidemiology). This cohort was planned in the early nineties to study environmental risk- or protective factors associated with allergic diseases. Children born between 1994 and 1996 in four distinct areas in greater Stockholm were identified through a community population register. The districts were chosen to cover urban as well as suburban environments with a mix of living conditions and socio-economy representative of the Swedish population. 7221 children were born in these areas during 1994 and 1996 (Fig 3). Exclusion criteria were families who planned to move within a year, children with very severe chronic diseases or a sibling already included in the cohort. 477 families were never reached, 897 families never answered the inclusion questionnaire, 1256 families were excluded, and 502 families declined participation. In the end 4089 children were included in the cohort (Fig 3). The average age of inclusion was 2 month. At this time point (baseline) the families filled out questionnaires regarding background characteristics such as living conditions, education and employment, number of people in the household, pet ownership, smoking and parental allergy related diseases.
Families who did not want to participate were sent a short questionnaire of background characteristics for the purpose of comparison to the families included (25).

2.1.2 Follow-ups

The cohort has been followed up with questionnaires at 1, 2, 4, 8, 12 and 16 years of age (Fig 4). At 4, 8 and 16 years everyone who had completed the questionnaire was invited for a clinical follow up including blood samples for IgE-testing. Blood samples were obtained from 2614 children at 4 years, 2480 children at 8 years and 2558 children at 16 years. The number of children with blood samples from all 3 time points was 1699. Of the 1699 children 800 were randomly selected for IgE-testing with microarray. 5 of the 800 children did not have sufficient serum for microarray analysis and were thus excluded.

Figure 3: Description of the recruitment of children to the BAMSE cohort.

Figure 4: Periods of data collection in the BAMSE cohort (indicated by yellow fields) and number of participants for each follow-up.
2.2 STUDY POPULATIONS (I-IV)

For Study I we included 2024 children with completed questionnaires and results from blood tests at both 4 and 8 years of age.

For Study II we included 2413 children who had complete answers for maternal and paternal hay fever, asthma and eczema at baseline as well as result from blood tests and complete answers for the rhinitis questions at the 8 year follow up.

For Study III we used the subgroup of children who were tested for IgE-reactivity with microarray and who had complete answers in the parental questionnaires of rhinitis symptoms after exposure to birch pollen at 4, 8 and 16 years of age (N=764).

Study IV is based on 3112 children who answered the questions regarding chronic rhinosinusitis at the 16-year-follow-up. Everyone who fulfilled the EP3OS criteria (for explanation see Table 3) (76) for chronic rhinosinusitis was contacted by phone (n=48) and the symptoms were confirmed or rejected by a structured interview (Fig 5). The median time between questionnaire and interview was 16 months. 27 children fulfilled the CRS symptom criteria and had ongoing symptoms and were invited for clinical examination. 23 children were examined. 22 children still fulfilled the symptom criteria for CRS after the clinical examination.

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**Figure 5**: Flow chart of study IV.
2.3 DEFINITIONS OF BACKGROUND VARIABLES

Background characteristics, collected at baseline, were used to compare the study populations with the original cohort in order to interpret the generalizability of the results and potential selection bias. These background characteristics were demographic data as well as potential risk factors for allergic disease. The definitions are presented in Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental allergy</td>
<td>Mother and/or father with doctor’s diagnosis of asthma and asthma medication and/or doctor’s diagnosis of hay fever in combination with allergy to furred animals and/or pollen at the time of Q0.</td>
</tr>
<tr>
<td>Parental hay fever</td>
<td>Mother and/or father reported symptoms of allergic rhinitis at the time of Q0</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>Socioeconomic status for the household according to dominance, in four classes: blue collar worker, lower white collar worker, higher white collar worker, other. At the time of Q0.</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>For the household according to dominance. Blue collar worker.</td>
</tr>
<tr>
<td>Birth month</td>
<td>Birth month of the child in four categories: Dec-Feb, Mar-May, Jun-Aug, Sep-Nov.</td>
</tr>
<tr>
<td>Young mother</td>
<td>Mothers age below 26 years of age at birth of the child.</td>
</tr>
<tr>
<td>Older siblings</td>
<td>Any older siblings in the household/family.</td>
</tr>
<tr>
<td>Parent born outside Scandinavia</td>
<td>Father and/or mother born outside of Scandinavia, i.e. outside of Sweden, Finland, Norway or Denmark.</td>
</tr>
<tr>
<td>Exclusive breast feeding</td>
<td>The child has been exclusively breast fed at least 4 months.</td>
</tr>
<tr>
<td>Furred animals at home</td>
<td>Furred animal at home at the time of Q0.</td>
</tr>
<tr>
<td>Mother smoking</td>
<td>The mother smoked at least one cigarette/day at the time of Q0 and/or at any point during the pregnancy.</td>
</tr>
<tr>
<td>Smell of mildew in the home</td>
<td>Smell of mildew in the home at the time of Q0.</td>
</tr>
<tr>
<td>Moisture damage in the home</td>
<td>Any type of moisture damage in the home at the time of Q0.</td>
</tr>
<tr>
<td>Acute media otitis &lt;1 year</td>
<td>Up to age 1 year the child has had at least one acute media otitis treated with antibiotics. Q1</td>
</tr>
<tr>
<td>Use of antibiotics &lt;1 year</td>
<td>Up to age 1 year the child has been treated with antibiotics at least once. Q1</td>
</tr>
<tr>
<td>Day care attendance &lt;2 years</td>
<td>The child has attended day care center less than two years of age. Q2</td>
</tr>
<tr>
<td>RSV infection &lt; 1 year</td>
<td>Before age 1 years the child has had a respiratory syncytial virus infection. Q1</td>
</tr>
<tr>
<td>Early fish intake</td>
<td>Before age 1 year the child ate fish 2-3 times/months or more.</td>
</tr>
</tbody>
</table>
2.4 DEFINITION OF EXPOSURES

2.4.1 Risk factors (II)

In Study II we analyzed different aspects of parental allergy related diseases in the aspect of risk of developing allergic or non-allergic rhinitis at 8 years of age. The definitions of the parental allergic diseases are presented in Table 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal hay fever</td>
<td>Mother reported “yes” to the question: “Do you have or have you previously had allergic rhinitis (hay fever)?” at time of Q0.</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>Mother reported “yes” to the question: “Do you have or have you previously had asthma?” at time of Q0.</td>
</tr>
<tr>
<td>Maternal eczema</td>
<td>Mother reported “yes” to the question: “Do you have, or have you previously had eczema?”</td>
</tr>
<tr>
<td>Paternal hay fever</td>
<td>Father reported “yes” to the question: “Do you have or have you previously had allergic rhinitis (hay fever)?” at time of Q0.</td>
</tr>
<tr>
<td>Paternal asthma</td>
<td>Father reported “yes” to the question: “Do you have or have you previously had asthma?” at time of Q0.</td>
</tr>
<tr>
<td>Paternal eczema</td>
<td>Father reported “yes” to the question: “Do you have, or have you previously had eczema?”</td>
</tr>
<tr>
<td>Hay fever only</td>
<td>Mother and/or father reported “yes” to the question of hay fever as above. Parents with positive answers to asthma or eczema were excluded.</td>
</tr>
<tr>
<td>Asthma only</td>
<td>Mother and/or farther reported “yes” to the question of asthma as above. Parents with positive answers to hay fever or eczema were excluded.</td>
</tr>
<tr>
<td>Eczema only</td>
<td>Mother and/or farther reported “yes” to the question of eczema as above. Parents with positive answers to hay fever or asthma were excluded.</td>
</tr>
<tr>
<td>Any allergic disease</td>
<td>Mother and/or father reported “yes” to any of hay fever, asthma or eczema.</td>
</tr>
<tr>
<td>No heredity</td>
<td>Reference category: both mother and father needed to have answered “no” to hay fever, asthma and eczema.</td>
</tr>
</tbody>
</table>

The variables analyzed for potential confounding were; sex, socioeconomic status, maternal smoking, furred animals in the home, older siblings, early fish intake, birth month, mothers age, breast feeding, home dampness as defined in Table I.
2.4.2 IgE-reactivity (I, III)

In Study I IgE-reactivity was considered present at a specific IgE-level of 0.35 kU/L measured with ImmunoCAP.

In Study III IgE-reactivity was measured with micro array and considered present at a specific IgE-level of ≥0.3 ISU-E. Apart from positive/negative responses analyses of IgE-levels were also used. For longitudinal analyses of incidence or persistence of ARbp, the number of IgE-reactivities to PR-10 proteins was classified into 4 categories at 4 and 8 years: 1) No IgE-reactivity, 2) IgE-reactivity to Bet v 1 only, 3) IgE-reactivity to Bet v 1 and up to the median number of other recognized PR-10 proteins, 4) IgE-reactivity to Bet v 1 and above median number of other PR-10 proteins.

2.5 DEFINITIONS OF HEALTH OUTCOMES

The health outcomes used are all validated variables, except for non-allergic rhinitis. Definitions of all variables used are presented in Table 3.

Table 3: Definitions of health outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Used in Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current rhinitis (ISAAC-rhinitis)</td>
<td>Sneezing, runny or blocked nose in the last 12 months without common cold or flu, according to the International Study of Asthma and Allergy in Children (ISAAC)</td>
<td>I, IV</td>
</tr>
<tr>
<td>Current rhinoconjunctivitis (ISAAC-rhinoconjunctivitis)</td>
<td>Sneezing, runny or blocked nose in the last 12 months without common cold or flu, accompanied by itchy, watery eyes (ISAAC)</td>
<td>I</td>
</tr>
<tr>
<td>Symptoms at exposure to an allergen Sensitization</td>
<td>Sneezing, runny or blocked nose, or itchy, red eyes after contact with pollen or pets. Positive result of the Phadiatop® test (≥ 0.35 kU/L)</td>
<td>I, II</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Nasal symptoms; ISAAC-rhinitis and/or symptoms at exposure to an allergen in combination with sensitization.</td>
<td>I, II</td>
</tr>
<tr>
<td>Non-allergic rhinitis</td>
<td>Nasal symptoms; ISAAC-rhinitis and/or symptoms at exposure to an allergen without sensitization.</td>
<td>I, II</td>
</tr>
<tr>
<td>Allergic rhinitis to birch pollen (ARbp)</td>
<td>Reported symptoms of sneezing, runny or blocked nose or itchy eyes after exposure to birch pollen.</td>
<td>III</td>
</tr>
<tr>
<td>Chronic rhinosinusitis (CRS)</td>
<td>At least two symptoms of the following during ≥ 12 weeks: 1) blockage/congestion of the nose, 2) runny nose/postnasal discharge, 3) facial pain/pressure or 4) loss of smell; where one symptom had to be number 1 or 2 (according to the EPPOS criteria).</td>
<td>IV</td>
</tr>
</tbody>
</table>
2.6 DEFINITIONS OF CO-VARIABLES

The co-variables used in the different studies are presented in Table 4.

**Table 4: Definitions of co-variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Used in Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>At least 4 episodes of wheezing, or at least 1 episode of wheezing among patients that had received a prescription for inhaled steroids, in the last 12 months</td>
<td>I</td>
</tr>
<tr>
<td>Asthma – GA2LEN</td>
<td>At least two of the following: wheeze during the last 12 month, doctor’s diagnosis of asthma ever or asthma medication.</td>
<td>IV</td>
</tr>
<tr>
<td>Eczema</td>
<td>Dry skin in combination with itchy rash for 2 or more weeks, at typical localizations, within the last 12 months and/or doctor’s diagnosis of this disorder</td>
<td>I</td>
</tr>
<tr>
<td>Food hypersensitivity</td>
<td>At least 1 specific symptom (of the nose or eyes, or itchy mouth, breathing problems, urticaria, vomiting or diarrhea, eczema or avoiding specific foods because of symptoms) after eating at least 1 specific food item (milk, egg, fish, wheat, soy, apple, peach, kiwi, avocado, banana, raw carrot, peanut, or tree nuts)</td>
<td>I</td>
</tr>
<tr>
<td>Oral allergy syndrome at 8 years of age</td>
<td>Itchy mouth from apple, peach, kiwi, banana, or raw carrot. No reported systemic reactions were allowed.</td>
<td>I</td>
</tr>
<tr>
<td>Oral allergy syndrome at 16 years of age</td>
<td>Itch in mouth, throat or ears, and/or swollen feeling in mouth or throat after consumption of PR-10 allergen-containing plant food.</td>
<td>III</td>
</tr>
</tbody>
</table>

2.7 CLASSIFICATION OF SEVERITY

Classification of severity of allergic rhinitis was used in Study III. Severity was classified according to the ARIA document into **mild**: no impact on daily activities or sleep, **moderate/severe**: impact on daily activities and/or sleep (3).

2.8 HRQoL INSTRUMENTS

In Study IV we wanted to measure the health-related quality of life among adolescents with CRS. We used the generic instrument EQ-5D VAS which is a visual analogue scale from 0-100 where the respondent indicates his or her current state of health (102). EQ-VAS was answered at the time of the BAMSE 16 year follow up, a median time of 16 month before the clinical examination.
We also used the disease-specific instrument Sino Nasal Outcome Test 22 (SNOT-22) consisting of 22 parameters on symptoms and disease-related quality of life which the respondent scores from 0 to 5. The total score can take a value between 0=no symptoms to 110=maximum symptoms (103).

2.9 MEASUREMENT OF ALLERGIC SENSITIZATION

In the BAMSE cohort, measurements of allergic sensitization were performed from blood samples with ImmunoCAP, both the screening test PhadiaTop® which is a mix of the 8 most common inhalant allergens (birch, timothy, mugwort, cat, dog, horse, Cladosporium herbarum and Dermatophagoides pteronyssinus) (Thermo Fischer Scientific, Uppsala, Sweden) and single allergen specific IgE. In a subgroup of children randomized from those who had blood samples at all three time points analyses of IgE-reactivity to allergen components were performed with micro array technique.

2.9.1 PhadiaTop® (I, II, IV)

The PhadiaTop test was used to define children as sensitized or not in Study I, II and IV. A technical cut off was set at ≥0.35 kU/l according to recommendations of the manufacturer. IgE-levels up to 100 kU/l were measured.

2.9.2 Specific IgE (I)

Presence of sensitization to specific IgE was analyzed in Study I. Just as for PhadiaTop, a technical cut off was set at ≥0.35 kU/l and values up to 100 kU/l were measured.

2.9.3 Micro-array (III)

In Study III measurements of sensitization, IgE-reactivity profiles and levels of the different PR-10 proteins (Bet v 1, Mal d 1, A1n g 1, Cor a 1.04, Ara h 8, Pru p 1, Api g 1, Act d 8, Gly m 4), were performed with the MeDALL chip which is based on the ISAC microarray platform (Phadia Multiplexing/Thermo Fisher Scientific, Uppsala, Sweden) (98). Briefly, aliquots of 35 μl of serum were incubated on the microarray and after 120 min of incubation at room temperature, slides were washed, and fluorescence-labelled anti-IgE antibodies (Thermo Fisher) were added and incubated for 30 min. Chips were then washed, dried and analyzed using a Laser Scan Confocal microarray reader (LuxScan 10K/A; Capital-Bio, Beijing, China). The results were evaluated using Phadia Microarray Image Analysis (MIA) software and are reported in ISU-E. A technical cut off was set at ≥0.3 ISU-E (ISAC Standardized Units for IgE-detection) according to recommendations of the manufacturer.
2.10 NASAL ENDOSCOPY (IV)

In Study IV 23 of the 27 adolescents who fulfilled the symptom criteria of CRS underwent examination with nasal endoscopy. The endoscopy was performed by two specialists in Ear- Nose- and Throat Diseases (M Westman, M Holmström). Before application of topical anesthesia (nafazolin-lidocain spray) inspection by anterior nasoscopy was performed, and afterwards endoscopy with a 0° rigid endoscope and in some cases fiber optic endoscope was performed. Endoscopic signs of CRS according to the EP³OS criteria were considered; nasal polyps, mucopurulent secretion or edema/mucosal obstruction mainly in the middle meatus (76).

2.11 OLFACTORY THRESHOLD (IV)

In Study IV we wanted an objective measure of the odor threshold on the 23 adolescents who attended the clinical follow up. For this purpose the validated test “sniffin’ sticks” was used (99).

2.12 STATISTICAL ANALYSES

All analyses were conducted using STATA Statistical Software (College Station, Texas, USA), version 11 (Study I, II) or version 13.1 (Study III, IV).

2.12.1 Confidence intervals (I, II, III, IV)

To compare the study populations used in the different studies with the original cohort regarding background characteristics we used proportions presented with a 95 % confidence interval (95 % CI). Non-overlapping confidence intervals were considered statistically significant. In Study III we calculated p-values for the differences with finite population correction, as a complement.

2.12.2 Chi² test of independence (I, II, III, IV)

The chi² test of independence was used in Study I-IV to analyze associations between two dichotomous variables. Fisher’s exact test was used when the number in any group was 5 or less. A p-value <0.050 was considered as statistically significant.

2.12.3 Student t-test (I)

T-tests were used in Study I to analyze levels of specific IgE between time points and the association to persistent allergic rhinitis. Since the distributions of IgE-levels are skewed and not normal, they were analyzed with a previous logarithmic transformation. Levels of IgE are expressed as geometric means.
2.12.4 Logistic regression (II, III)

In Study II logistic regression models were used to analyze the effect of parental allergic disease on the risk of AR and NAR at 8 years. First, we explored differences between maternal and paternal heredity. We used categorical variables, where “Reported hay fever” was stratified into” mothers”, “fathers” or “both“ and analyzed with “no heredity” as reference category. To not reduce the number in the analysis, the other two diseases, asthma and eczema, were allowed. The same principle was used for asthma and eczema. Then we compared the three diseases and combinations of diseases. One combined variable was used and analyzed with “no heredity” as reference category. In both models potential confounders were introduced stepwise. The variables tested (sex, socioeconomic status, maternal smoking, furred animals in the home, older siblings, early fish intake, birth month, mothers age, breast feeding, home dampness) changed the OR less than 2 % why the final models were kept unadjusted.

In Study III logistic regression was used as the base of the fitted predicted probability curves used to present the probability of symptoms in relation to the levels of specific IgE to Bet v 1 for AR or the corresponding PR-10 protein for OAS. When analyzing the probability to report symptoms of OAS in relation to the corresponding PR-10 protein, allergen components (other than PR-10) known to give severe reactions were excluded from the analyses. For example for OAS in relation to levels of Ara h 8-specific IgE, Ara h 2 and Ara h 6 were excluded.

2.12.5 Cluster analysis (II)

Cluster analysis is a so called unsupervised method where it is not decided beforehand how to group the exposure variables. Instead you let the data itself form the groups (clusters). Since co-occurrence between allergy related diseases is common and may exist in one or both parents there are many possible patterns of parental allergic disease. Therefore, in Study II we used cluster analysis with the k-means method as a complement to the logistic regression models to search for latent phenotypes of heredity that are likely to be associated with AR and NAR. The k-means method is a frequently used method for clustering of large datasets (105-107). We tested 3-, 4-, 5- and 6-cluster models. The 10 variables clustered were reported hay fever, reported asthma, reported eczema, reported pollen allergy and reported allergy to furred animals in mothers and in fathers respectively. When a cluster-model was found, proportions of the outcome variables AR and NAR were calculated for the different clusters. After repeated trials we chose the cluster solution with the most commonly appearing clusters.
2.12.6 Quantile regression (III, IV)

To compare continuous variables not normally distributed between two groups one either has to perform a logarithmic transformation and use geometric means or one can use quantile regression. With quantile regression you do not have to assume that the variable is normally distributed and you compare medians without logarithmic transformation. This is easier to interpret from a clinical perspective. There is also the possibility of comparing any percentile of the distribution besides the median. In paper III we compared the median of IgE-levels between different PR-10 proteins, Bet v 1-specific IgE levels between symptomatic and asymptomatic children and between time points. We also used quantile regression to compare Bet v 1 specific IgE levels in relation to severity of allergic rhinitis to birch pollen and then compared median values as well as 25th and 75th percentiles. In Study IV we compared the median values of EQ-VAS scores between adolescents with and without CRS.

2.12.7 Spearman correlation test (III)

Correlation between levels of Bet v 1-specific IgE and the number of other IgE-reactive PR-10 proteins was assessed with Spearman’s correlation test.

2.12.8 General estimated equations, GEE (IV)

GEE was used in study IV to analyze the risk for incident symptoms of AR_{bp} in relation to number of IgE-reactive components, longitudinally. We analyzed the 4 categories among children without symptoms of AR_{bp} at the current time point or before. At 4 years we calculated the overall odds ratio for incident symptoms after 4 years as well as odds ratios at 8 and 16 years separately. At 8 years the odds ratio for incident symptoms at 16 years was calculated. With two time points only, GEE gives the same result as a logistic regression.

2.12.9 Absolute risks (III)

Absolute risks were used as a complement to GEE when assessing onset or persistence of AR_{bp} in relation to number or IgE-reactive PR-10 proteins. It was calculated as the number of children with the exposure (specific IgE ≥0.3 ISU-E) and the outcome (AR_{bp}) at 8 or 16 years, respectively, divided by the total number of children with the exposure at baseline. 95% confidence intervals were calculated with the binomial test of statistical significance.

2.13 ETHICAL APPROVAL

All studies (I-IV) were derived from the BAMSE cohort which has been approved by the Regional Ethical Review board at Karolinska Insti-
tutet, Stockholm, Sweden throughout the study years (93:189, 98:175, 02:420, 2010:1474-31/3). Specific permissions were obtained for Study IV (2012:1620-32, 2012:1943-32) also from the Regional Ethical Review board at Karolinska Institutet. Parents gave informed consent for each follow up.

3 RESULTS

3.1 PREVALENCE OF UPPER AIRWAY SYMPTOMS (I, III, IV)

An important part of this thesis was to estimate the prevalence of different types of upper airway symptoms at different ages.

The prevalence of rhinitis symptoms increased from preschool age up to adolescence regardless of which definition was used (Fig 6-8). The prevalence of current rhinitis (ISAAC) increased from 12.0% to 15.3% to 25% at 4, 8 and 16 years and reported symptoms of AR at exposure to an inhalant allergen increased from 4.1% to 15.2% to 25% at corresponding ages (Fig 6 and Fig 8).

![Figure 6: Prevalence of sensitization and reported symptoms of rhinitis at 4 and 8 years of age, respectively.](image)
In Study I we used sensitization to an inhalant allergen to allow for calculation of allergic and non-allergic symptoms. When combining rhinitis symptoms with sensitization to an inhalant allergen we found a prevalence of allergic rhinitis at 4 years of 5.4% that increased to 14% at 8 years. The prevalence of non-allergic rhinitis symptoms decreased from 8.1% to 6.3% during the same period (Fig 6).

In Study III we looked specifically at reported symptoms of allergic rhinitis to birch pollen. These are reported symptoms, only including birch pollen and no other allergens and not combined with sensitization as above. The prevalence at 4 years of age was low, 2.5% but increased up to 8 years (10.6%) and 16 years (17.8%) (Fig 7).

**Figure 7:** Prevalence of reported symptoms on exposure to birch pollen from the upper and lower airways, respectively, and IgE reactivity to Bet v 1 at ages 4 (N=764), 8 (N=763) and 16 (N=686).

**Figure 8:** Prevalence of reported upper airway symptoms at 16 years of age (N=3112).
In Study IV we estimated the prevalence of CRS according to the EPOS criteria, as answered at the BAMSE 16-year questionnaire, to be 1.5% which accounted for only a very small part of the total prevalence of upper airway symptoms at 16 years of age (Fig 8). After clinical examination the prevalence of CRS was only 0.3-0.8%. The true prevalence was estimated to be more than 0.3% but lower than 1.5%.

3.2 PREVALENCE OF SENSITIZATION (I, III, IV)

Just as symptoms of rhinitis, the prevalence of sensitization to inhalant allergens increased over time.

3.2.1 Phadiatop and specific IgE (ImmunoCAP) (I, IV)

The prevalence of sensitization to inhalant allergens in the population measured with Phadiatop, (a mix of 8 common inhalant allergens) was 16% at 4 years of age, 26% at 8 years (Fig 6) and, as seen in Study IV, at 16 years as high as 44%. As seen in Study I the most common sensitizing allergen in the population was birch, at both 4 (10%) and 8 (16%) years, followed by timothy (6% at 4 years, 15% at 8 years) and cat (6% at 4 years, 13% at 8 years). Among children with allergic rhinitis the same proportion, 78-79% had specific IgE to birch at both 4 and 8 years while the proportion of children with specific IgE to timothy increased from 44% to 69% from 4 to 8 years of age.

3.2.2 PR-10 allergen components (Microarray) (III)

Sensitization to Bet v 1, the major birch allergen component, increased from 12% at 4 years to 17% at 8 years and 25% at 16 years (Fig 9A). In the PR-10 group, IgE-reactivity to Bet v 1 was most common and also had the highest levels of specific IgE (Fig 9B).

The median ISU-E levels of Bet v 1 were significantly higher in all age groups among children with symptoms of ARbp compared to asymptomatic children (19.9 vs 3.2 at 4 years, 28.3 vs 1.8 at 8 years, and 32.7 vs 2.3 at 16 years). IgE-reactivity to the other PR-10 proteins seemed to follow a certain order of occurrence; Bet v 1 > Mal d 1 > Cor a 1.04 > Ara h 8 > Pru p 1 > Aln g 1 > Api g 1 > Act d 8 > Gly m 4 (Fig 9). There also seemed to be a hierarchy of IgE-reactivity within the PR-10 protein group where IgE-reactivity to the more common PR-10 proteins almost always was present when IgE-reactivity to the less common PR-10 proteins were seen. This was seen at 4, 8 as well as 16 years of age.
As an example, among 16-year olds with IgE-reactivity to the most common PR-10 protein, Bet v 1, 79% also had IgE-reactivity to the next PR-10 protein in order, Mal d 1, but only 19% to the least common PR-10 protein Gly m 4 (Table 5). On the other hand, among children with IgE-reactivity to the least common PR-10 protein Gly m 4 100% had IgE-reactivity to Bet v 1, Mal d 1 and Cor a 1.04 (Table 5). The levels of Bet v 1 specific IgE correlated well with the number of IgE-reactivities to the other PR-10 proteins analyzed at 4, 8 as well as 16 years of age (rho=0.87-0.90).

Table 5: Number of children with IgE-reactivity to the different PR-10 proteins (left column) and percentages with additional IgE-reactivity to other PR-10 proteins. Green= high degree of IgE cross reactivity, Red= Low degree of IgE cross reactivity.
3.3 DEVELOPMENT OF DISEASE OVER TIME (I, III)

Another important aspect of the thesis was to study the development of rhinitis symptoms and sensitization over time. In Study I we found that 87% of the children with allergic rhinitis had persistent symptoms up to 8 years. In contrast, among children with non-allergic rhinitis symptoms 74% remitted, i.e. had no symptoms of rhinitis, up to 8 years. Among children with sensitization but without rhinitis symptoms 56% developed allergic rhinitis up to 8 years (Fig 10). When other allergic diseases (asthma, eczema and food hypersensitivity) were excluded from the analysis of children with sensitization still 49% developed allergic rhinitis up to 8 years of age compared to 3% in the reference group (no sensitization and no rhinitis). Only 9% of children sensitized to an inhalant allergen at 4 years lost their sensitization up to 8 years.

In Study III we performed a complementary analysis which was not included in the final manuscript. We wanted to investigate how the Bet v 1-specific IgE levels were related to the duration of disease. Among children at 16 years of age with ARbp, the levels of Bet v 1-specific IgE were higher the longer (4-16, 8-16 or at 16 years only) they had been sensitized. The median IgE-level among children sensitized at 16 years, but not at 4 or 8 years was 6.5 ISU-E, compared to 41.1 ISU-E for children who were sensitized at all three time points (Fig 11).
3.4 PREDICTION OF DISEASE (I, II, III)

3.4.1 Parental allergic disease as risk factor for allergic and non-allergic rhinitis (II)

Parental allergic disease, or an atopic constitution, is a well-known risk factor for allergic rhinitis as well as other allergic diseases. In Study II we wanted to investigate if there was a difference in risk of allergic- as well as non-allergic rhinitis depending on type of parental allergic disease or between heredity from the mother or the father. Among children with maternal heredity for any allergic disease the OR for AR at 8 years was 1.8 (95% CI 1.3–2.5) and among children with paternal heredity for any allergic disease 1.9 (95% CI 1.3–2.6). With double heredity, i.e. from both mother and father, for any allergic disease the OR was 4.3 (95% CI 3.1–5.9). This pattern, with a similar OR between mother and father but an increase with double heredity was seen for both parental hay fever and parental asthma, although not for parental eczema when double heredity did not seem to have impact on the OR (Fig 12). For non-allergic rhinitis the OR remained roughly the same for maternal, paternal and double heredity (OR 2.0-2.4).

**Figure 11:** Bet v 1-specific IgE levels among 104 children with AR_{top} at 16 years: A) De novo IgE-reactive after 8 years of age (n=20), B) IgE-reactive since 8 years of age (n=21), C) IgE-reactive since 4 years of age (n=63). M=median level (ISU-E).
When analyzing the different diseases separately, there was an increased risk for AR at 8 years with parental hay fever (OR 2.2, 95% CI 1.6-3.2), but not for parental asthma or eczema. No single disease, but 2 or more diseases in combination, increased the odds for non-allergic rhinitis (Fig 13).
The cluster analysis we performed as a complement confirmed the results from the logistic regression. We did not find a stable model, but there were some clusters that tended to reappear several times when trying different models. The model that best explained these often reappearing clusters was the following 6-cluster model:

*Cluster 1:* Both parents reported hay fever and pollen allergy.
*Cluster 2:* The mother had hay fever and pollen allergy.
*Cluster 3:* The father had hay fever and pollen.
*Cluster 4:* The father had hay fever, pollen allergy, and eczema.
*Cluster 5:* Low proportions of allergy related diseases among both parents except for eczema among fathers.
*Cluster 6:* Low proportions of allergy related diseases among both parents.

Cluster 1, in which both parents had hay fever and pollen allergy, was the cluster with the highest proportion of children with allergic rhinitis (38%). The highest proportion of non-allergic rhinitis was seen in Cluster 4 where one parent had hay fever, pollen allergy and eczema (11%), (Fig 14).

![Figure 14: Proportions of the 8-year-old children’s allergic and non-allergic rhinitis for each of the 6 clusters in the cluster analysis, presented as percentages (%).](image-url)
3.4.2 Sensitization as predictor of allergic rhinitis (I, III)

In Study I we found that children with persistent disease had higher levels of specific IgE to birch than children who had transient symptoms from 4 to 8 years (GM 13.9 vs 3.8, p=0.039) or new cases at 8 years (GM 26.1 vs 15.0, p=0.025). To analyze this further, in Study III, we used Bet v 1, a major birch allergen molecule. We found that the possibility of predicting both incidence and persistence of symptoms increased with increasing levels of Bet v 1-specific IgE (Fig 15).

Figure 15: Probabilities for incident or persistent AR from 4 to 16 years of age, in relation to Bet v 1-specific IgE levels (ISU-E) at 4 and 8 years, respectively.

In addition, the overall odds ratio for incidence of symptoms also increased with increasing number of IgE-reactive PR-10 proteins. For IgE-reactivity to Bet v 1 only the OR was 7.1 (95% CI 3.3-15.3), for Bet v 1 and 1-2 other PR-10 proteins the OR was 26.2 (95% CI 13.1-52.3) and for Bet v 1 and 3 or more other PR-10 proteins 45.1 (95% CI 21.3-95.5), with p for trend <0.001. There were too few children to perform GEE for persistence of symptoms. Instead we calculated absolute risks, which is rather similar to positive predictive values. At 4 years of age no child with symptoms had IgE reactivity to Bet v 1 only. Among symptomatic children with IgE-reactivity to Bet v 1 in combination with 1-3 other PR-10 proteins 67% had persistent
symptoms up to 16 years of age. Among children with IgE-reactivity to Bet v 1 and 4 or more other PR-10 proteins the absolute risk of persistent disease reached 100%. In Study III we also analyzed the levels of Bet v 1 at 4 years of age in relation to severity of ARbp at 16 years. We found that among adolescents with severe ARbp at 16 years, the levels of specific IgE to Bet v 1 at 4 years were higher than among adolescents with mild ARbp (Fig 16).

![Figure 16: Bet v 1-specific IgE levels (ISU-E) at 4 years among children with mild ARbp compared to moderate/severe ARbp at 16 years, where the box plots show the median levels and 25th and 75th percentiles.](image)

3.5 COMORBIDITY (I, III, IV)

3.5.1 Allergic and non-allergic rhinitis (I, III)

In study I we found that asthma, eczema and food hypersensitivity were associated with both allergic and non-allergic rhinitis. The prevalence of asthma in the population was a little more than 7% at both 4 and 8 years of age. Among children with allergic rhinitis, asthma was found in 26-28% and among children with non-allergic rhinitis 11-13% (Fig 17). The prevalence of eczema was higher at 4 years (21%) than at 8 years (17%). Among children with allergic rhinitis eczema was found in 50% at 4 years and 32% at 8 years. The corresponding proportions among children with non-allergic rhinitis were 30% and 28%.
Regarding food hypersensitivity 28% of children with allergic rhinitis at 4 years reported to have any kind of adverse reaction to any kind of food. This proportion increased to 51% at 8 years. At 8 years half of this proportion consisted of children reporting oral allergy syndrome (25%). Restricted to children with allergic rhinitis and specific IgE to birch, 31% reported symptoms of OAS. Non-allergic rhinitis was associated with food hypersensitivity but not with oral allergy syndrome.

At 8 years of age, children with allergic rhinitis already since age 4, had higher rates of comorbidity than incident cases of AR at 8 years (asthma 36% vs 21%, p=0.008, food hypersensitivity 73% vs 40%, p<0.001, OAS 38% vs 18%, p<0.001). Children with allergic rhinitis at 4 years of age with persistent disease up to 8 years, more often had food hypersensitivity (but not asthma or eczema) than those who had transient symptoms up to 8 years (42% vs 8%, p=0.023).

Oral allergy syndrome was analyzed in Study III for allergen components belonging to the PR-10 protein family. At 16 years of age in our population based cohort, 63% of adolescents with symptoms of allergic rhinitis to birch pollen and IgE-reactivity to Bet v 1 reported symptoms of OAS to any of the food items apple, hazelnut, peanut, peach, kiwi or soy. The most commonly reported food item was apple (47%). The probability of reporting symptoms of OAS increased with increasing specific IgE-levels of the corresponding PR-10 protein (Fig 18).
Figure 18: Cross sectional probabilities of reporting symptoms of OAS to any food item in relation to Bet v 1-specific IgE levels, or to specific food items in relation to levels of IgE specific for the corresponding PR-10 protein, at 16 years of age.

Figure 19: Proportions of allergic rhinitis symptoms, asthma, chronic cough, eczema and sensitization, among adolescents with CRS (n=22) vs. without CRS (n=3090) *p-value <0.05.
3.5.2 Chronic rhinosinusitis (IV)

In Study IV we found that adolescents with CRS more often had symptoms of allergic rhinitis (57.1% vs 28.1%, $p=0.003$), asthma (25.0% vs 11.0%, $p=0.047$) and chronic cough (13.6% vs 3.4%, $p=0.008$) compared to those without CRS. There was no difference between the groups regarding sensitization to inhalant allergens or eczema (Fig. 19).

3.6 HRQoL (IV)

Health-related quality of life was analyzed for CRS in Study IV. We used both the generic EQ-VAS and the disease-specific SNOT-22. Among adolescents with CRS symptoms ($n=22$) the median EQ-VAS score was significantly lower than among adolescents without CRS symptoms ($n=3090$) ($M=80$ vs $M=90$, $p=0.024$) (Fig 20). When stratifying for sex the difference in median EQ-VAS score was larger among girls ($M=75$ vs $M=87$) than among boys ($M=85$ vs $M=90$). The mean value of SNOT-22 among adolescents with symptoms of CRS was 38. Among the subgroup of adolescents with CRS who also had endoscopic signs of CRS ($n=9$) the mean value of SNOT-22 was 44. In addition we performed an objective measure of olfactory threshold where the mean value among adolescents with CRS symptoms was 6.08 and in the subgroup of adolescents with CRS symptoms and endoscopic signs 6.33.

Figure 20: EQ-VAS scores among adolescents with CRS symptoms vs. without CRS symptoms. Box plots show the median values and 25th and 75th percentiles
4 DISCUSSION

Since the discovery that allergic diseases have increased and now constitute one of the most common health problems in the industrialized part of the world, research within the field of allergy-related diseases has almost exploded. When starting the work with this thesis, my impression was that the majority of these studies concerned lower airway symptoms, “allergy” or sensitization. Large, longitudinal studies where rhinitis was the main focus were scarce. Therefore, the main aim of this thesis became to provide epidemiologic data on upper airway symptoms during childhood and up to adolescence. My work has resulted in estimations of the prevalence of allergic- and non-allergic rhinitis as well as chronic rhinosinusitis, the comorbidity of these diseases, and the risk factors and predictors of rhinitis. Over these years I have noticed that the number of studies on rhinitis has started to increase. A discussion of our main findings in relation to other studies as well as methodological considerations will follow here.

4.1 MAIN FINDINGS

4.1.1 Prevalence and natural course of rhinitis

In Study I we noticed that the prevalence of rhinitis symptoms rose with increasing age and that this increase was due to the rise in prevalence of AR. This increase in AR symptoms with age was also seen in Study III for birch pollen allergy. This was consistent with our expectations and that which has been found by several others (21, 108, 109). Despite the total increase of rhinitis symptoms, NAR symptoms decreased slightly from 4 to 8 years. Consequently, the proportion of NAR among children with rhinitis was higher at 4 years (60%) than at 8 years (31%). Among adults the proportion of NAR among rhinitis patients is estimated to be between 25%-50% (4, 74, 110). The few population-based studies among children show rates of NAR at 5 years of 50% (111), at 7 years of 64% (94) and at 10 years 27% (93).

74% of the children with NAR in our study at 4 years remitted up to 8 years of age. One possible explanation for the higher prevalence at preschool age and the many remitting cases could be that children at preschool age have an enlarged adenoid with symptoms mimicking rhinitis. The adenoid reaches its maximum size around 5-6 years of age and normally decreases in size during school age, which parallels the finding of remitting cases in our study from 4 to 8 years. Another explanation could be that frequent upper respiratory viral infections at preschool age, less frequent at school age, are misinterpreted as non-infectious rhinitis. However, we cannot exclude that non-allergic, non-infectious rhinitis exists and is common in preschool age.
It is most likely, just as in adults, that there are several causes for children to present with non-allergic rhinitis symptoms and this will need to be further investigated.

4.1.2 Comorbidity of AR and NAR

4.1.2.1 Asthma and eczema

In Study I we found that AR was associated with both asthma and eczema at both 4 and 8 years of age, which is a finding consistent with similar studies from other birth cohorts (93, 94, 111). We also found that the children with AR at 8 years with the onset of the disease already before 4 years more often had co-morbid diseases than the incident cases at 8 years. A more surprising finding was that NAR symptoms were associated with not only asthma, but also eczema indicating a non IgE-mediated association between these diseases. Others have shown an association of NAR with asthma, but studies of a possible association with eczema have shown conflicting results (93, 94). In longitudinal studies both AR and NAR have been found to be risk factors for asthma (60, 62, 63). Even though there is a lot more to find out about different phenotypes of NAR symptoms in children, it seems as if having rhinitis, allergic or non-allergic, is vitiated with an increased risk of comorbidity with other allergy related diseases.

4.1.2.2 Oral allergy syndrome (OAS)

OAS is common among adults with pollen allergy with an estimated proportion around 70% among patients with birch pollen allergy (13, 69). In Study I we estimated the prevalence of OAS among 8-year-old children with AR to birch pollen to be 31%. In Study III we found that among 16-year olds, 63% reported symptoms of OAS to any of the food items analyzed. Moreover, the probability of reporting OAS symptoms increased with increasing levels of Bet v 1-specific IgE. The most frequently reported food item was apples, which is consistent with studies among adults (112, 113). However, the proportions for OAS in general as well as for specific food items were lower than for adults. One explanation may be that the specific IgE-levels are different between the populations studied. One supplementary finding from Study IV was that the levels of Bet v 1-specific IgE among the 16-year-olds with AR were higher the longer they had been sensitized. Most previous studies have been performed at allergy clinics and one may assume that, on average, these patients have had their disease longer than in the general population. Another explanation could be that the population studied may differ in sensitization patterns and intake habits of food items causing OAS. Moreover, the definition of OAS and which food items have been included may differ between studies. However, the proportion of reported symptoms of OAS among individuals with AR to birch pollen may also be age-dependent.
4.1.3 Chronic rhinosinusitis

4.1.3.1 Prevalence

Although Study IV is a quantitatively small part of this thesis, I believe that our estimation of prevalence of CRS in adolescence was an important contribution to current knowledge in this field. Even among the adult population the prevalence of CRS, based on the EPOS criteria, has been little known until recently published papers.

The estimate of prevalence of CRS in our study was based on both questionnaire answers and clinical follow-ups. We used the validated EPOS criteria to identify individuals with CRS (114). However, the EPOS criteria have not been validated in the age group of 16 year olds. Therefore we wanted to compare questionnaire data results with a structured telephone interview and secondly by using nasal endoscopy. In the telephone interviews 13 subjects did not fulfill the criteria for CRS currently or at the time of the BAMSE 16 year questionnaire. Consequently, the questionnaire-based definition was probably an overestimation. This has also been shown in other studies (114, 115). During the 16 months between questionnaire and interview, eight children remitted, and were excluded from clinical examination. This may have led to an underestimation of the prevalence of CRS at the clinical follow-up. Furthermore, we did not examine control adolescents, i.e. subjects who were negative according to the questionnaire. Since the prevalence of CRS was low, one would not expect to find more than a few with a positive endoscopy among those who were negative according to the questionnaire. For ethical reasons we did not perform CT scans as proposed by EPOS, since we were studying growing individuals. In conclusion, the prevalence of CRS in adolescence is probably more than 0.3% but less than 1.5%. This is much lower than the almost 11% that was seen in a European population-based survey, based on the EPOS criteria, of 15-74 year old subjects (11.5% in the 15-24 year age group) (116). In a Korean study based on clinical symptoms and nasal endoscopy of subjects of all ages (0 - >85), the prevalence was found to be 1.0% (78) (1.1% in the 15-19 year age group). No age differences were seen but in both the studies mentioned geographical differences were noted. Differences in the estimation of prevalence may also be explained by differences in response rate between studies. A low response rate may result in a higher prevalence if those with the disease are more inclined to respond than those without the disease. More studies using well-defined criteria for CRS will be needed in order to understand the epidemiology of CRS at different ages.

4.1.3.2 Symptom severity and HRQoL

Although the prevalence of CRS among the 16 year olds was low the symptoms seemed bothersome. The HRQoL measured with generic as well as disease-specific instruments was reduced. The median score of EQ-VAS
was significantly lower than seen among adolescents without CRS. Girls have been shown to score lower on HRQoL measurements than boys (117, 118). We had 68% girls in our group of adolescents with CRS compared to 51% among adolescents without CRS. However, this did not explain the difference found. When stratifying for gender, the difference in median EQ-VAS score between those with CRS compared to those without CRS was more pronounced among girls than among boys.

SNOT-22 has been validated among adults where a mean value for healthy patients has been found to be 9.3 (95% CI 7.5-11.1) (103). Among the adolescents with CRS in our study the mean value was 38.2-44.2, which is level with what can be found for adults with CRS prior to sinonasal surgery (103). Furthermore, the mean value for olfactory threshold (6.08) was lower than reported for the age group 16-35 years (9.32) in a multicenter study of over 3,000 healthy subjects (119). Hyposmia has been defined as a value below the 10th percentile of the age group 16-35 years which corresponds to a value of 6.25 (99, 119). The 4 subjects who did not come to clinical examination may have had milder symptoms and thus skew the results to appear more severe. However, when the 4 drop-outs from clinical examinations were included in the analyses of EQ-VAS and current co-factors, there was no effect on the results. Furthermore, the delay between questionnaire and clinical examination may have resulted in finding the more severe cases, i.e. those with persistent disease.

4.1.4 IgE-reactivity

In Study III we described IgE-reactivity to allergen proteins within the PR-10 group. To our knowledge, this had not been described before at a population level. The most prevalent IgE-reactivity was seen for Bet v 1. Bet v 1-specific IgE was also found to have the highest median levels. IgE-reactivity to the other PR-10 proteins seemed to follow a certain hierarchical order where IgE reactivity to the more prevalent PR-10 proteins was almost always present when IgE-reactivity to the less common PR-10s was seen. These findings are in line with results from inhibition studies indicating Bet v 1 to be the primary sensitizing allergen among the PR-10 proteins in a birch-prevalent area (120, 121). The order of IgE-reactivity to the other PR-10 proteins may reflect the proteins’ degree of homology to Bet v 1, different allergenicity and/or routes and amounts of allergen exposure. One has to bear in mind that the pattern of IgE-reactivity found was in a population frequently exposed to birch pollen. The patterns of IgE-reactivity in other areas, for example, the Mediterranean area where birch pollen is not the driving allergen in the sensitization process, have shown to be very different (122, 123).
4.1.5 Can allergic rhinitis be predicted?

4.1.5.1 Parental hay fever as a risk factor of allergic rhinitis

A family history of allergy has proven to be an important risk factor for allergic rhinitis (3). However, in order to make better clinical assessments and to better understand the genetic basis of atopy, further investigations of the hereditary patterns of allergic diseases need to be performed. In Study II, both in the logistic regression analyses and the cluster analysis, we found parental hay fever (with pollen allergy) in particular if both parents reported such a disease, to be the most important risk factor for the child to develop allergic rhinitis. For parental asthma and eczema, no increased risk of AR was found. This was in accordance with previous cross-sectional (42, 43) and longitudinal (124) findings. A recent, longitudinal cohort study also confirms this result (125). There are other longitudinal studies showing that the risk of the child developing asthma is greater for parental asthma than for other parental allergic diseases (41, 126). In our study, when stratifying AR for co-morbid asthma, parental asthma increased the odds of AR with asthma, but not for AR without asthma. Taking these facts into consideration, it seems as if specific allergy-related diseases among parents may be more important for the child’s risk of developing a certain allergic disease than just “family history of allergy”. In genetic studies on asthma, eczema and rhinitis both shared- and unique pathways for the development of these diseases have been found (127, 128). Our results support a theory of both shared and specific pathways. The finding that parental hay fever, but not asthma or eczema, was associated with AR at 8 years, indicates that genes specific for rhinitis may be of importance. On the other hand, the co-morbidity between asthma, eczema and hay fever among the parents was associated with an even higher risk of AR, suggesting that shared genetic factors are also likely to influence disease development.

4.1.5.2 Preclinical sensitization

In Studies I and III, we found that a large proportion of children sensitized to inhalant allergens (Phadiatop) or to Bet v 1 specifically did not report symptoms. The presence of IgE sensitization without clinical symptoms is well known (44, 45, 129). As seen in Study III the Bet v 1-specific IgE-levels, at all three time points, were higher among children with symptoms of AR\textsubscript{bp} than asymptomatic children; a finding in accordance with previous studies (44, 45, 129). In Study I the majority of children with sensitization to inhalant allergens but without rhinitis symptoms at 4 years developed allergic rhinitis up to 8 years of age. Sensitization to inhalant allergens as a predictor of development of AR has also been shown by others (47, 130). Thus, it seems as if sensitization to inhalant allergens may predict AR later in life. On the other hand, sensitization is common and not all children will develop symptoms.
In an attempt to better predict symptoms, than just being sensitized or not, we analyzed allergen components within the PR-10 protein family in relation to symptoms of AR_{bp} (Study III). We found that the levels of Bet v 1-specific IgE, as well as the number of sensitizing PR-10 protein allergen components at 4 years, were associated with the onset of symptoms of AR_{bp} from 4 years up to 16 years of age. Moreover, moderate/severe AR_{bp} at 16 years of age was associated with high levels of Bet v 1-specific IgE at 4 years compared to mild AR_{bp}.

Considering both the aspects mentioned above of predicting AR, a recent study from the MAS cohort in Germany shows that pre-clinical IgE to grass pollen is a strong risk factor for the development of AR to grass pollen and that this risk is reinforced by a history of parental hay fever (125). This supports our findings that parental hay fever, levels of specific IgE, and in the case for birch pollen, number of IgE-reactive PR-10 proteins, need to be taken into consideration in future prediction models.

4.1.5.3 Predicting persistence of symptoms

In Study III we found that from 8 to 16 years of age the probability of having persistence of symptoms of AR_{bp} was already high at limited levels of Bet v 1-specific IgE. A further analysis of Bet v 1-specific IgE-levels or IgE-reactivity to other PR-10 proteins did not seem to provide much added value for predicting persistence. An explanation may be that the eight-year-old children, previously sensitized to birch pollen and already presenting with symptoms, were no longer in their early phase of disease, but had rather developed a persistence of disease (129). If this holds true, such knowledge may be of importance when intervention treatment of allergen-specific immunotherapy, ASIT is considered. Furthermore, it has been reported that ASIT may prevent the progression of allergic rhinitis to asthma (132). On the basis of our results and others (129, 131) it is tempting to speculate on ASIT as a future preventive intervention treatment in the early phase of allergic sensitization when there is still plasticity of the IgE response.

4.2 STRENGTHS AND LIMITATIONS

The major strength of this thesis is that the studies are based on data from a prospective, population-based cohort. The cohort has a relatively large number of participants with a high response rate from baseline over the years. The possibility of using a blood test for determining allergic sensitization enabled us to distinguish between allergic- and non-allergic rhinitis symptoms, which is an advantage not always available in large population-based studies. Moreover, the fact that in Study IV we were able to interview every case who fulfi-
led the criteria of chronic rhinosinusitis according to the questionnaire and we not only relied on the questionnaire answers for the estimation of prevalence, must be regarded as a strength. The potential weaknesses of the studies in this thesis are mostly of the type that may occur in observational studies and will be discussed below.

4.3 METHODODOLOGICAL CONSIDERATIONS

Epidemiologic studies may be afflicted by error (133). An error in a study is when the estimated value differs from the “correct” (and unknown) value in the population. The actual error can never be determined so the causes of errors occurring must be known and taken into consideration throughout the study, from study design, to analyzing data and interpreting the results. There are two different types of error, random error and systematic error (bias).

4.3.1 Systematic error (bias)

There are basically three different types of bias: selection bias, information bias and confounding. Selection bias may occur when those included in the study (the study population) differ from the target population in such a way that affects the results. In a prospective cohort a potential difference between those included and those not included may result from non-participation or loss to follow-up. Information bias (or misclassification) may occur if the variables have not been correctly measured. Misclassification may affect the exposure as well as the outcome and may be differential or non-differential. The term “non-differential misclassification of exposure” is used if the misclassification of exposure is not related to the outcome and the term “differential misclassification of exposure” is used if the misclassification of exposure is related to the outcome. In the same way the term “non-differential misclassification of outcome” is used when the misclassification of outcome is not related to the exposure and the term “differential misclassification of outcome” is used when the misclassification of outcome is related to the exposure.

Confounding occurs when another variable than the one studied affects the association between the exposure and the outcome.

4.3.1.1 Selection bias

Non-participation in prospective cohort studies may result in differences in frequencies of exposure and/or outcome between the cohort and the target population which would result in the cohort not being a representative sample of the population studied. However, this is unlikely to bias the associations between exposure and outcome since the outcome has not yet occurred at the time of inclusion and the comparison is made within the cohort. In the
BAMSE cohort 75% of the target population was included. At baseline, a short questionnaire was sent to non-participants for the purpose of comparing background characteristics. The non-participants were found to have a higher proportion of smokers than the participants, but no other differences between background characteristics were found including the family history of allergic diseases (25). Thus, the cohort is fairly representative of the target population and it is unlikely that non-participation would affect the associations seen in our studies. Possible selection bias may have instead been caused by loss to follow-up. Loss to follow-up may bias the estimates of prevalence as well as the associations between exposure and outcome. Regarding prevalence, it may be more likely that children without disease are inclined to leave the cohort than children with disease. We cannot exclude the possibility that we may have overestimated the prevalence of AR and NAR in Studies I and II and AR_b, in Study III, as compared to the target population. Regarding the association between parental allergy and AR and NAR in Study II, when comparing those included in the study (59%) with those not included (41%) we found that the study population had a somewhat higher proportion of allergic parents (32% vs 27%, p<0.001). Since non-allergic parents were more likely to leave the cohort and if children without disease are more likely to leave, this would result in a higher proportion of AR and NAR among those without a family history of allergic disease and rather underestimate the observed association (the observed relative risk, OR, would be lower than expected). However, the difference of parental allergy found between those included and those not included was small and is not likely to have had a major impact on the observed association. In Study III the study population differed from the cohort in socio-economic status and birth months. These differences were small and we performed a sensitivity analysis which showed that the differences in socio-economic status and birth months did not seem to have any effect on the observed associations between the levels of Bet v 1-specific IgE and AR_b. The high ORs seen also imply that the association between levels of IgE and AR_b is strong and not likely to be explained solely by this small selection.

4.3.1.2 Information bias (misclassification)

In Study I any possible misclassification would refer to AR, NAR and sensitization not being properly defined or reported. We have used validated questions and the use of sensitization as part of the outcome definition of allergic rhinitis (in Studies I and II) probably reduced the risk of misclassifying non-allergic subjects as allergic. The Phadiatop test has shown to correlate well to both the skin prick test and specific IgE measured with CAP-RAST (97), which is why it is likely that we have been able to distinguish children
with AR from NAR.

In Study II the possible misclassification of exposure (parental allergic disease) is not likely to be differential because of the prospective design (the exposure data was collected before the outcome had occurred). A non-differential misclassification of exposure may have occurred since we relied on self-reported allergic diseases. For comparison we restricted the analyses in two different ways. Firstly, we restricted the analyses to those who reported they had a doctor’s diagnosis of an allergic disease, and secondly, to those where both parents had filled out the questionnaire. No major differences were seen in both situations. In Study II there was also a possibility of a differential misclassification of the outcome. One could suspect that parents with hay fever might recognize rhinitis symptoms in their child more easily which may bias the results towards an association between parental hay fever and rhinitis symptoms in the children. Because of this suspicion, we performed the analysis of parental hay fever but used sensitization (without rhinitis symptoms) as the outcome, for comparison. We found that there was also an association with sensitization (without symptoms) and concluded that the association found between parental hay fever and rhinitis in the offspring was not only a result from parents with hay fever being more inclined to report symptoms.

In Study III the parents or children were not given the results of the micro-array analyses and thus any misclassification of the outcome would be non-differential. To reduce the risk of non-differential misclassification, we used the validated question of symptoms on exposure to birch pollen (91).

In Study IV the amount of a possible non-differential misclassification of outcome was hard to determine since the EPOS questions had not been validated among 16 year olds. That was the reason for corroborating the questionnaire answers with telephone interviews and a nasal endoscopy. Other aspects of the estimation of prevalence of CRS have been discussed above (Section 4.1.3.1).

4.3.1.3 Confounding

The cohort design with inclusion at birth and follow-ups at specific time-points controlled for age as a confounder. In Study I, asthma or eczema as potential confounders for the association between sensitization at 4 years and incident AR at 8 years was checked for by excluding asthma and eczema from the analysis (restriction). In Study II we checked for confounding by a step-wise introduction of the potential confounding variables into the logistic regression models. The different variables changed the OR <2%, which is why we kept the final models unadjusted. In Study III we analyzed asthma and eczema as potential confounders both by adjusting for them in the GEE
model and by stratification. No major differences were seen. In Study IV we adjusted for gender as a potential confounder in the quantile regression analysis of median EQ-VAS scores. The p-value for the difference was affected which is why we stratified on gender and found that the difference seen was more pronounced among girls. Consequently gender was rather an effect modifier than a confounder.

4.3.2 Random error

The random error is basically the variability in the data that cannot be readily explained. The random error will be reduced by increasing the size of the study population (133). The confidence intervals reflect the amount of random error. The original BAMSE cohort is relatively large and the study populations for Studies I, II and IV consist of more than 2 000 children. In the main analyses the confidence intervals are rather narrow reflecting good precision. For some of the sub-analyses, the number of subjects in the analyses is small and the confidence intervals become wide, for example in Study III when analyzing persistent symptoms. In these cases we have tried to be cautious when interpreting the results.

4.3.3 Generalizability

Generalizability means whether the results can be generalized to endure in a broader context. With the population-based design of the cohort, the limited selection bias and relatively good precision one could assume that the associations found are fairly generalizable to a western, urban pediatric population in a birch-prevalent area.
5 CONCLUSIONS

The results from this thesis show that symptoms of upper airway inflammation are common in childhood and adolescence. Allergic rhinitis, non-allergic rhinitis and chronic rhinosinusitis show similarities, but also differences, which points to the importance of distinguishing these entities both from a clinical perspective and in research. The conclusions drawn from the different studies are the following:

• There seem to be different prognoses for 4 year olds with allergic and non-allergic rhinitis, up to 8 years of age. Children with allergic rhinitis are more likely to have persistent disease than children with non-allergic rhinitis, who seem to remit.
• Sensitization to inhaled allergens at an early age (4 years) precedes the development of allergic rhinitis, whereas symptoms of rhinitis do not.
• Both AR and NAR are associated with asthma and eczema. The prevalence of oral allergy syndrome among children with AR seems to increase with age during childhood. The likelihood of reporting symptoms of OAS increases with increasing levels of Bet v 1-specific IgE.
• Parental allergy-related disease may be an important risk factor for NAR as well as AR. The risk is comparable for maternal- and paternal allergy. There seem, however, to be different hereditary patterns for AR and NAR. Parental hay fever (with pollen allergy) seems to be the dominating hereditary risk factor for AR, while for NAR one parent with several diseases seems to be the most important risk factor.
• Bet v 1 seems to be the dominating allergen in the PR-10 protein group in a birch-prevalent area.
• The risk of onset or persistence of symptoms of AR bp increases with increasing levels of Bet v 1-specific IgE or increasing number of recognized PR-10 proteins at 4 years.
• High levels of Bet v 1-specific IgE at 4 years are associated with severe AR bp at 16 years.
• In adolescence CRS exists even though the prevalence is low. For those affected the symptoms may be bothersome.

5.1 CONCLUDING REMARKS

Knowledge in epidemiology is of importance for the understanding of disease development and morbidity. This may be useful in a clinical setting when meeting patients, when giving information to patients and their parents about the disease, but also for generating hypotheses for research.
Based on the results from Study I, I believe that rhinitis in children should not be neglected. Already at preschool age 1 child out of 20 in the population has allergic rhinitis. A child with allergic rhinitis at this age will most likely continue to have the disease for several years. Moreover, a large proportion of these children will also have asthma, eczema or oral allergy syndrome. In Study I we found that also non-infectious non-allergic rhinitis is common among children and that these children more often report asthma, eczema and food hypersensitivity than children without rhinitis. Non-allergic rhinitis symptoms among children will need to be better investigated. An important investigation would be to examine these children with nasal endoscopy in order to better understand possible phenotypes.

As seen in Study IV upper airway inflammation is common also among adolescents. Although CRS symptoms constitute a small part of upper airway symptoms in adolescence, those with CRS are important to identify and treat, since they seem to have bothersome symptoms. The prevalence of CRS needs to be further explored both among children, adolescents and adults.

The work with Study I and III has given me a better understanding of the natural course of allergic rhinitis. The improved understanding is based on our findings in combination with findings of others as previously discussed. It seems as if the disease starts with preclinical sensitization with low levels of specific IgE. Thereafter the IgE-levels start to increase and at some point the child will start to present symptoms. After the symptoms have occurred the IgE-levels continue to increase and the pattern of sensitization becomes more complex. As the disease continues, other allergy related diseases develop and oral allergy symptoms become more common. It seems as if the disease may develop from “simple” to “complex” and become more and more manifest during childhood. In the light of this I believe it would be of importance to investigate allergen specific immunotherapy (ASIT) as a potential preventive measure, at an early phase of disease, or even before it has presented at all. This would require a way of identifying those with early sensitization or predicting the course of those with early onset of allergic rhinitis in order to know who would possibly benefit from such a preventive treatment. Our findings, of parental hay fever (rather than parental asthma or eczema) and preclinical levels of specific IgE to be predictive of allergic rhinitis, seem plausible. However, defending ASIT as a preventive treatment from an ethical and cost-benefit perspective would require a lot more data.

In this thesis I have tried to describe at least a part of the reality regarding upper airway inflammation in children, as the title implies. To find the truth, however, we will have to keep on searching...
6 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund
Besvär från näsa eller bihålor drabbar uppskattningsvis ca en tredjedel av den vuxna befolkningen och kan räknas som en av våra folksjukdomar. Näs- och bihålebesvär är vanligt även hos barn och har visat sig kunna påverka både livskvalitet och skolprestation. Trots detta finns det mycket som är outforskat vad gäller uppkomst, förekomst i olika åldrar, naturlförlopp och samband till andra allergirelaterade sjukdomar.


Syfte
Syftet med den här avhandlingen var att belysa olika aspekter av inflammation i näsa och bihålor (som inte beror på förkylning) hos barn och ungdomar i befolkningen vad gäller förekomst, sjukdomsutveckling över tid, riskfaktorer och samband till andra allergirelaterade sjukdomar.

Metod
Av resultaten skulle jag vilja lyfta fram följande:

Både hösnuva och icke allergisk snuva var vanligt hos barn, men de två typerna av snuva hade olika prognos. 5,4 % hade hösnuva redan vid 4-års ålder. Nästan 9 av 10 fortsatte att ha sin sjukdom upp till 8 års ålder. Många nya barn insjuknade mellan 4 och 8 år då förekomsten var 14,0 %. Icke allergisk snuva var ännu vanligare än hösnuva vid 4 år (8,1 %) men i motsats till de med hösnuva tillfrisknade 7 av 10 barn upp till 8 år. Nya barn insjuknade varpå 6,3 % hade icke allergisk snuva vid 8 år.

Inte bara barn med hösnuva utan även de med icke allergisk snuva hade oftare astma och eksem än barn utan snuva. Förekomsten var dock något lägre än bland barn med hösnuva.

Något som tidigare inte varit känt är förekomsten av oralt allergisyndrom hos barn. Hos vuxna uppskattas ca 70 % av björkpollenallergiker ha OAS. Vi fann att vid 8 års ålder hade 31 % av barnen med allergisk snuva orsakad av björkpollen OAS och vid 16 års ålder 63 %. Förekomsten verkar således stiga med ökande ålder.

Risken för att få hösnuva kan möjlichen förutsägas. Vi fann att risken för att insjukna i hösnuva ökade vid ärftlighet för hösnuva (snarare än ärftlighet för astma eller eksem).

Risken var ännu högre om båda föräldrarna var sjuka. Vad gäller björkpollenallergi så fann vi att sannolikheten för att insjukna i hösnuva vid 8 eller 16 års ålder ökade med ökande nivåer av allergiantikroppar mot björkpollen i blodet vid 4 år. Även antikropparnas grad av korsreaktivitet mot födoämnen som ger upphov till OAS kunde förutsäga insjuknande av allergisk rinit. På liknande sätt ökade risken för fortsatt sjukdom bland de som redan hade hösnuva. Nivåerna av allergiantikroppar i blodet verkade också kunna förutsäga om man fick svår eller lindrig sjukdom.

Förekomsten av kronisk bihåleinflammation hos ungdomar uppskattade vi till mellan 0.3 % och 1.5 % beroende på hur sjukdomen definierades. Detta är en låg förekomst om man jämför med förekomsten av t ex hösnuva (25 %) i samma ålder. Ungdomarna med kronisk bihåleinflammation hade oftare symtom på hösnuva, astma och kronisk hosta, hade sämre luktsinne och lägre livskvalitet än de utan bihåleinflammation.
Slutsatser

Resultaten från denna avhandling har bidragit med epidemiologisk kunskap om olika typer av inflammation i näsa och bihålor hos barn och ungdomar. Denna kunskap är viktig både för förståelse av tillstånden och för fortsatt forskning. Vi har sett likheter mellan hösnuva och icke allergisk snuva men även skillnader vilket belyser vikten av att skilja dessa tillstånd åt. De som fått hösnuva i tidig ålder kommer med största sannolikhet att ha sin sjukdom i många år och vissa dessutom att ha symtom på astma, eksem eller oralt allergisyndrom. Det vore därför önskvärt att kunna förutsäga insjuknande och prognos. Till viss del verkar hösnuva kunna förutsägas med hjälp av ärftlighet för hösnuva eller med hjälp av nivåerna i blodet av allergiantikroppar mot björk. Kronisk bihåleinflammation är hos ungdomar inte särskilt vanligt, men de som drabbar är viktiga att identifiera och behandla eftersom de verkar ha svåra symtom.
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REFERENCES


100. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.


