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PO Box 117
221 00 Lund
+46 46-222 00 00

The Voice of the Patient

Patient-reported outcomes in respiratory allergic disease,
with special focus on health-related quality of life

Hampus Kiotseridis



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DOCTORAL DISSERTATION

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Title and subtitle The Voice of the Patient Patient-reported outcomes in respiratory allergic disease, with special focus on health-related quality of life		
<p>Abstract</p> <p>Allergic diseases, which constitute a global health problem, have been defined as one of the epidemics of the twenty-first century. Since there are no cures for allergic diseases today, the goal of treatment is to get the disease under control so that the patient can live a normal life with optimal chances of development. Patient-reported outcomes for control assessment have been a focus of attention since no laboratory test or physical examination can do this alone in a reliable manner.</p> <p>The aim of this thesis was to develop patient-reported outcomes (PRO) for clinical evaluation in regard to respiratory allergic disease.</p> <p>Two PROs were validated. The first questionnaire was a disease-specific, health- related quality of life questionnaire that had been developed in England for children with multiple allergic diseases. The questionnaire was translated into Swedish and validated for children with a grass pollen allergy. The second instrument is a novel tool for asthma assessment in primary care developed with the goal of structuring asthma review in primary care. The result showed that it can be useful for assessing asthma control as well.</p> <p>The burden of allergic disease was assessed in children with a grass pollen allergy during pollen season. The result showed that the health-related quality of life was impaired and that the patients were affected both physically and mentally. We also propose new limits for pollen prognosis that would be easy for children to understand, in this case presented as a traffic light model with green, yellow and red lights.</p> <p>In conclusion, this thesis shows that respiratory allergies can affect the health-related quality of life. We believe, since the goal of our treatment is to improve the patient's daily life, that PRO measurements can be helpful both in research and in clinical practice.</p>		
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Hampus Kiotseridis



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Faculty of Medicine
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To my family

*“There are two ways to be fooled.
One is to believe what isn’t true;
the other is to refuse to believe what is true.”*

-Søren Kirkegaard

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ABBREVIATIONS

PRO: Patient-reported outcome

QOL: Quality of life

HRQL: Health-related quality of life

RQLQ: Rhinitis quality of life questionnaire

PRQLQ: Pediatric rhinitis quality of life questionnaire

MiniRQLQ: Mini-rhinitis quality of life questionnaire

PADQLQ: Pediatric allergic disease quality of life questionnaire

IgE: Immunoglobulin E

APC: Antigen-presenting cell

WAO: World Allergy Organization

ACQ: Asthma control questionnaire

MID: Minimal important difference

ICC: Intra-class correlation

AQLQ: Asthma quality of life questionnaire

PAQLQ: Pediatric asthma quality of life questionnaire

ALMA: Active life with asthma

FDA: Food and Drug Administration

VAS: Visual analogue scale

FEV: Forced expiratory volume

ACT: Asthma control test

OTC: Over-the-counter

ASIT: Allergen-specific immunotherapy

POPULÄRMEDICINSK SAMMANFATTNING

Allergiska besvär från luftvägarna utgör ett stort och växande folkhälsoproblem. Det finns idag ingen bot mot dessa sjukdomar och de kan, om de inte behandlas, utgöra ett betydande hinder i vardagen.

Även om dagens mediciner i de allra flesta fall kuperar symtomen väl, vet man, att många patienter är odiagnostiserade eller saknar behandling trots diagnos. Målet med behandlingen är symtomlindring så att patienten kan ha en normal vardag. Särskilt för barn och ungdomar är detta av största vikt, så att de får möjlighet att utvecklas optimalt utifrån sina förutsättningar. Metoder såsom laboratorieprov eller röntgenundersökningar kan idag inte visa hur patienten mår eller hur välkontrollerad sjukdomen är. Därför behövs andra metoder som också tar hänsyn till patientens upplevelse.

Målet för vårt arbete har varit att utveckla bedömningsinstrument för att utvärdera sjukdomsaktivitet utifrån patientens upplevelse, s.k. patientrapporterade utfall samt att utvärdera hur barn med pollenallergiska besvär påverkas under pollensäsong.

I delarbete I har vi översatt och kvalitetssäkrat ett hälsorelaterat livskvalitetsformulär som utvecklats i England för barn med allergiska besvär.

98 barn inkluderades i undersökningen och följdes över en sommar. Barnen fick redovisa sina besvär i en dagbok. Utöver detta fick de regelbundet fylla i livskvalitetsformuläret. Detta har uppfattats som enkelt att använda och visat sig fungera väl för att skilja barn med olika grad av besvär. Formuläret som vi valt att kalla "Livskvalitet vid luftvägsallergi" (LILA) fungerade också väl för att följa sjukdomsförloppet över tid.

I delarbete IV utvecklade vi ett bedömningsinstrument för astmapatienter som är tänkt att användas i primärvården. Vår strävan har varit, att få med alla viktiga aspekter av sjukdomen så att instrumentet kan fungera som en "minneslapp" för primärvårdsläkaren. Frågeformuläret utvecklades tillsammans med astmapatienter för att försäkra oss om att allt som upplevdes som väsentligt för patient och läkare kom med. Vi fann, att detta instrument hade bra tillförlitlighet och kunde med precision värdera graden av astmakontroll hos denna patientgrupp.

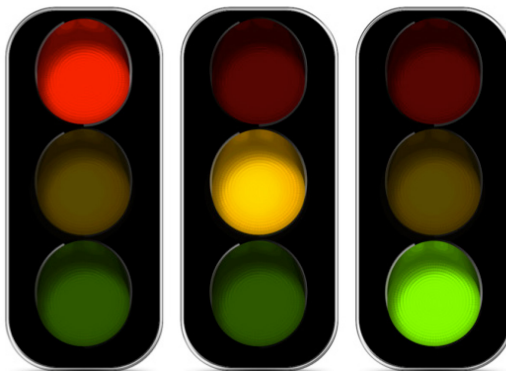
I delarbete II undersöktes hur gräspollenallergiska barn påverkades i sin livskvalitet under gräspollenssäsongen. Förutom vårt LILA-formulär använde vi ett etablerat livskvalitetsinstrument som tidigare har använts för barn med kroniska sjukdomar. Det visade sig att livskvaliteten är sänkt för dessa barn under pollenssäsongen. De upplevde både fysisk och mental påverkan, som t.ex. trötthet och sömnbesvär. De kände sig också mer nedstämda. De barn som led av både astma och hösnuva hade sämre livskvalitet än de barn som bara hade hösnuva. Livskvaliteten var jämförbar med den hos barn med andra kroniska sjukdomar.

I delarbete III undersökte vi hur symtomen påverkades dag för dag under pollenssäsongen. Det visade sig att symtomen fanns kvar i flera dagar efter pollenexponering.

För att kommunicera pollenprognoser med barn föreslår vi en trafikljusmodell.

Grön – inga problem, gul – var försiktig, röd – hög risk.

Sammanfattningsvis visar resultatet av vårt arbete, att luftvägsallergi kan påverka livskvaliteten hos barn. Vi har också visat att patientrapporterade metoder är bra instrument för att värdera detta. Eftersom målet med vår behandling är att förbättra patientens vardag och livskvalitet är vår övertygelse att sådana mätningar kan vara till hjälp både i forskning och i sjukvårdens vardag.



LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals.

- I **Hampus Kiotseridis**, Corrado M. Cilio, Leif Bjermer, Magnus Aurivillius, Helene Jacobsson and Alf Tunsäter.

Translation and Validation of the Pediatric Allergic Disease Quality of Life Questionnaire (PADQLQ)

Acta Paediatrica. 2011 Feb, 100(2):242-7

- II **Hampus Kiotseridis**, Corrado M. Cilio, Leif Bjermer, Magnus Aurivillius, Helene Jacobsson, Åslög Dahl, and Alf Tunsäter.

Quality of life in children and adolescents with respiratory allergy, assessed with a generic and disease specific instrument

Clin Respir J. 2013 Apr, Vol. 7 Issue 2, pp. 168-175

- III **Hampus Kiotseridis.**, Corrado M.Cilio, Leif Bjermer, Helene Jacobsson, Alf Tunsäter and Åslög Dahl.

Grass pollen allergy in children and adolescents-symptoms, health related quality of life and the value of pollen prognosis

Clin Transl Allergy. 2013 Jun, 3:19 (22 June 2013)

- IV **Hampus Kiotseridis**, Leif Bjermer, Eva Pilman, Björn Stållberg, Kerstin Romberg and Alf Tunsäter.

ALMA, a new tool for the management of asthma patients in clinical practice: development, validation and initial clinical findings.

Prim Care Respir J. 2012 Jun, 21(2):139-44

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INTRODUCTION

In modern medicine, assessing the severity of disease and changes over time has traditionally been evaluated by laboratory tests, functional tests and physical examination.

While these are important in the evaluation, and especially in the diagnosis of diseases as we have defined them, they are not fully sufficient when trying to cover the importance of the disease for the individual patient. In chronic diseases like allergic diseases, the most important part when trying to treat them is to help the patient function in their everyday life so that they can live the life they want to live. Children that are developing should especially not be inhibited by their disease but instead should be given the possibility to develop optimally – physically, mentally and socially. This is actually how the World Health Organization (WHO) defines health: "A state of complete physical, mental, and social well-being and not merely the absence of disease".

The quality of life concept refers to the definition of health offered by the WHO, as quoted above. Quality of life, when referring to an individual's health, is called health-related quality of life (HRQL). HRQL is the subjective impact of health on the life domains perceived as being relevant. To give patients with allergic diseases the optimal chance of living the life they want to live, we have to assess the burden of disease with measures also including this subjective experience of disease.

Patient-reported outcomes (PRO) are clinical instruments that use the patient's experiences of the disease as a clinical outcome measure for the evaluation of the disease's status. The nature of the PRO can vary. Some are just symptom scores in regard to certain aspects of interest, and others are more multidimensional HRQL questionnaires.

In the present thesis, two patient-reported outcome instruments are introduced. The first tool is a disease-specific questionnaire that has been translated into Swedish and validated in regard to children and adolescents with a grass pollen allergy. The second patient-reported outcome tool is a novel clinical tool for asthma assessment in primary care. We present below the development and

validation processes of the tool. We have furthermore explored the use of symptom scoring in order to assess the significance and duration of the effects of pollen exposure in pollen-allergic patients and the use of generic questionnaires to detect non-disease specific complaints in allergic patients.

BACKGROUND

The basics of allergy

Allergy can be described as an inappropriate response of the immune system after exposure to substances normally tolerated by healthy people. These substances, known as antigens, are presented in the interface between the outside and the inside of the body. This can be the mucosa in the nose and lungs, or the gastrointestinal tract. The antigens are picked up by the antigen-presenting cells (APC) that then present the antigen to the T-cell in the neighbouring lymph node. The APC becomes the reporter and is important in the decision-making process of the immune system in regard to how to react to the antigen [1]. Mature and activated APC stimulates naïve T-cells to differentiate into more specified T helper cells (TH). Allergic disease is associated with the activation of the T helper cell known as the Th2 cell (TH2). This cell secretes cytokines, such as IL-4, IL-5 and IL-13, that are important for the differentiation of the B-cell into an IgE-producing plasma cell (PC) and for the stimulation of eosinophils [2].

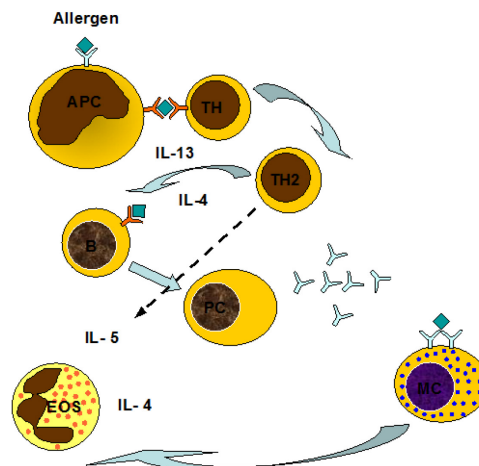


Figure 1. Presentation of the allergen to the immune system leading to sensitization. By the next exposure, mast cells are activated, leading to the release of histamine and other inflammatory mediators causing the allergic reaction.

Mast cells, resident in many tissues throughout the body, play a key role in the inflammatory process. The binding of the antigen to the receptor on the mast cell will then elicit activation which subsequently leads to an allergic reaction. The early response happens immediately when the allergen binds to the IgE. This binding activates the mast cells, and this then leads to degranulation and the release of mediators such as histamine and prostaglandins. This release of mediators is associated with increased vascular permeability and increased blood flow as well as with resulting oedema. The symptoms of wheezing, sneezing and urticaria are dependent upon the target organ of the allergic reaction or, in the worst case, a systemic reaction: the development of an anaphylactic reaction. The late phase response, starting within hours of exposure, is dominated by the recruitment of eosinophils.

It seems that allergic diseases are complex genetic diseases where interaction with the environment is crucial for the outcome [3]. No allergy gene explaining everything has been found. Instead, many genes are associated with weak correlations to allergic diseases. These genes code for proteins involved in all parts of allergic immune responses [4, 5]. One indication of the importance of environmental factors is the increase in incidence in the last decades. This quick rise in incidence cannot be explained by genes alone since they have virtually not changed in the population during this short period of time. Instead, the hygiene hypothesis has evolved to explain why the allergy prevalence is increasing. The hygiene hypothesis was first proposed by Strachan who found that siblings with older brothers and sisters had a lower risk of developing allergic disease with the proposed mechanism of being exposed to more infections early in life [6]. A strong body of epidemiological evidence supporting this hypothesis has been amassed since then, although the mechanisms still need to be elucidated further. Proposed factors are early airway infections, early antibiotic use, vaccinations, bacterial gut flora, exposure to pets and endotoxins [7-10].

Aeroallergens

Aeroallergens are airborne particles that induce allergic reactions in sensitized subjects and can cause respiratory, cutaneous, or conjunctival allergies. Aeroallergens are a subset of diverse forms of aerosols ranging from submicronic particles to relatively larger pollen grains, fungal spores and animal emanations.

To be clinically significant, aeroallergens first must be airborne, present in significant concentration, and allergenic. In general, insect-pollinated plants produce sticky pollens that do not become airborne. Wind-pollinated plants can reach high concentrations, remain airborne for days, and can be carried hundreds

of miles from their points of origin [5]. There are more than 600 genera and 10,000 species of grasses (Poaceae) in the world. Most of the allergenically important grass species belong to the subfamily Pooideae, where timothy belongs. Among the allergenically important trees, the most commonly found in Sweden is the birch, which belongs to the Betulaceae family.

Atmospheric pollen counts are considered to be positively correlated with allergic symptomatology. Pollen warnings are meant to be part of a guided self-management program aiming to prevent system aggravation and help allergy sufferers take control of their conditions. They increase awareness about the disease and its connection to ambient aeroallergen levels and thus act in the interests of patient education, which is essential, as is stressed by the World Allergy Organization. It has been suggested that pollen warnings should be presented to the public in a structured, easily understandable way. The delimitation of these categories varies from country to country. In Sweden, the categories used in the public warning system were delimited in the 1970's, referring to "clinical experience". There is a need for clinically relevant threshold levels that also can be easy to understand.

Manifestations of allergy

Atopy is a Greek word meaning "out of place": a reaction that is not meaningful. In medicine, atopy is defined as the tendency to excessively produce IgE in response to antigens usually tolerated by humans and to develop allergic diseases, usually with strong hereditary traits. The allergic diseases that we usually refer to are food allergies, eczema, asthma and rhinoconjunctivitis.

In the atopic child, diseases usually debut at different ages. This is usually called the allergic march. In small children, eczema and food allergies are common. Later, when the child grows older, allergic asthma and rhinoconjunctivitis debut. Asthma is also a common disease in pre-schoolers, but this is only to a minor degree associated with allergic sensitization and atopy. Rhinoconjunctivitis with sensitization to environmental antigens like pollen or mould usually precedes the development of allergic asthma. Thus, if you have a child with one allergic disease, there is a high risk for the development of other allergic diseases, and this makes it important to be observant for symptoms and signs in order to be able to treat them properly or, if possible, to prevent them. This could, for example, be done in children with allergic rhinoconjunctivitis where treatment with allergen-specific immunotherapy has been shown to prevent the development of allergic asthma[11].

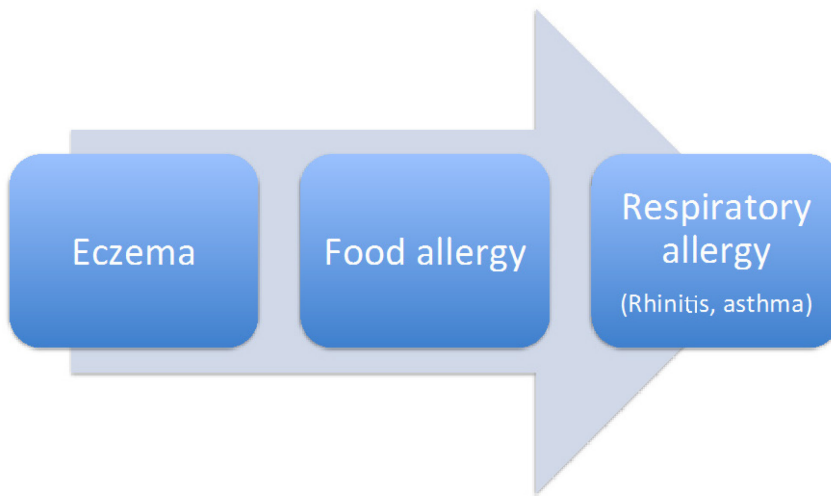


Figure 2. The allergic march.

Allergic rhinitis

Rhinitis is characterized by an inflammation in the nasal mucosa. This inflammation gives rise to characteristic symptoms, i.e., nasal obstruction (blocked nose), runny nose, itching and sneezing [12]. If prolonged, it can also affect the sense of smell [13]. The most common cause of rhinitis is probably viral infection (the common cold). Allergic rhinitis is defined as an allergen-induced inflammation characterized by eosinophilic infiltration [14, 15]. The allergic inflammation in the nose is often associated with an ocular mucosal inflammation. This gives rise to symptoms affecting the eyes, including tearing, redness and itching. The state is then referred to as rhinoconjunctivitis [12].

Allergic rhinitis is a global health problem although the prevalence differs radically in different parts of the world at different points in time. The diagnostic criteria are also of importance for the resulting prevalences. Generally, symptom-based questionnaires give higher prevalences than physician-diagnosed rhinitis.

The International Study of Asthma and Allergies in Childhood (ISAAC), an initiative to describe the global burden of allergic diseases, found an overall prevalence of 1.4 to 39.7 % among 13 to 14-year-old children [16]. The prevalence in Sweden was 11-12 %. Other questionnaire-based studies have

shown higher figures, but with smaller patient populations [17]. Among adults, several studies have found a prevalence of about 20 % [18-20].

Since the middle of the twentieth century, the prevalence of rhinitis has increased [12]. Among Swedish conscripts, the prevalence more than tripled in children born between 1952 and 1981[21] According to the ISAAC follow-up study conducted ten years after the initial study, there was an increase in prevalence in a majority of the countries globally although there was no further increase in 25 % of the countries, including Sweden [22].

Classification

Traditionally, allergic rhinitis has been divided into seasonal and perennial diseases: seasonal, meaning for a short period, is usually caused by a single type of pollen while perennial is usually a result of exposure to house dust mites, furred animals, and mould. Since patients with seasonal rhinitis often have long periods with symptoms caused by multiple types of pollen and patients with perennial allergies might be asymptomatic for long periods, this system of classification became impractical and a new one has since been suggested [12]. This classification is based partly on the duration of symptoms and partly on how the symptoms affect everyday life. Symptoms lasting less than four weeks are called intermittent and those lasting for longer than four weeks are called persistent. If the symptoms affect sleep, school/work performance, sport/leisure activities or if the symptoms are experienced as troublesome then the rhinitis is classified as moderate/severe. If none of these is affected, it is classified as a mild disease [12]. Several studies have shown that more than 50 % of cases are classified as moderate/severe [23, 24].

Allergic Rhinitis Classification

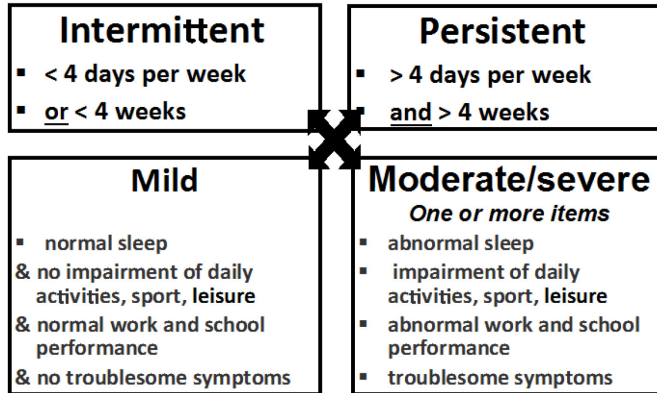


Figure 3. Classification of rhinitis.

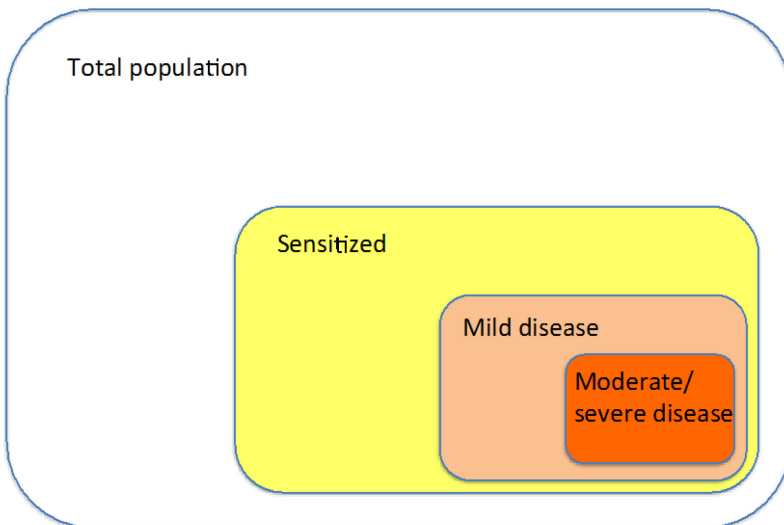


Figure 4. The clinical panorama in pollen sensitized individuals

Diagnosis and treatment

Diagnosis is to a large extent based on medical history. Symptoms are sneezing, itching, and blocked nose, and when these are associated with exposure to an allergen then the diagnosis is clear. Objective testing can help confirm eliciting agents. Sometimes, further investigation is needed to rule out differential diagnosis like polyps, tumours and, in the case of children, foreign bodies.

Treatment is based on local and systemic treatment with antihistamines. The effect of nasal steroids has been shown to exceed the effect of antihistamines and is therefore indicated in moderate/severe disease. There are now also combinations of antihistamines and corticosteroids available on the market. Allergen-specific immunotherapy (ASIT) is a well-established treatment with good efficacy both in children and adults. The multiple injections needed during treatment make it suitable only for patients with residual symptoms despite ordinary pharmacotherapy. ASIT has been shown to protect against asthma development and is supposed to slow down the allergic march [11]. ASIT is also available as a sublingual tablet, but in Sweden it is still only available for grass pollen.

Asthma

Asthma is defined by its clinical, physiological and pathological characteristics.

The definition of asthma given by the Global Initiative for Asthma (GINA) is as follows:

”A chronic inflammatory disorder in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment” [25].

Asthma in clinical practice is a heterogeneous disease with many different phenotypes that can be classified further. The status of atopy, type of inflammation and reactivity during exercise are some factors among others. In young children, the diagnosis is only symptom-based [25].

Asthma is a global health problem with varying prevalence in different parts of the world. In Northern Europe, the epidemiologic studies have found the current prevalence of asthma to be around 10 % in children from ten years of age as well

as in adults [26] [27]. In the first years of life, the prevalence seems higher, but this is probably not attributed to an allergy but rather to a viral infection, and this phenotype is to a large extent outgrown before reaching six years of age [28, 29]. This is also indicated by the lower prevalence between four and eight years of age found in Swedish cohorts [30, 31].

The prevalence of asthma has risen in the last half of the former century [21], but in the last decade, no further increase has been seen in Sweden, and the prevalence seems to have reached a plateau [22].

Asthma-symptom onset usually occurs in youth, although it can appear at any age. The symptoms include dyspnea, especially in relation to exercise, coughing and wheezing. The characteristic eosinophilic inflammation is triggered in allergic asthma by aero-allergens. Also, unspecific triggers such as smoke, perfume, cold air, etc., can lead to symptoms, especially if there is an inflammation.

The basis of therapy consists of preventer medication, such as inhaled corticosteroids and antileukotrienes. They can dampen the inflammation and prevent clinical exacerbations [32]. Bronchodilators, work as a reliever medication in the case of acute obstructive symptoms. Long acting bronchodilators can also be used as a complement to the preventer medication. Other steps include allergen-specific immunotherapy and anti-IgE treatment [33].

The concept of the united airways

The upper and lower airways share many features. The mucosa of the upper and lower airways has a high histological resemblance. Also, the diseases that arise in these organs covariate greatly. More than 80 % of asthma patients have rhinitis, and 20-50 % of rhinitis patients have symptoms from the lower airways [34, 35]. In fact, many of those patients with asthma who do not complain about having nasal symptoms also have inflammation in the nose to the same degree as the rhinitis patients [36]. The functional interaction has also been shown where provocation in the nose leads to a reduction in lung function and an increase of eosinophils in the lower airways [37].

The interactions between the upper and lower airways are probably complex. Rhinitis leads to deteriorated nasal functioning. These functions include smell, humidification and filtration of air. Bypassing the nose by the mouth if the nose is blocked can thus lead to the inhalation of more particles and also the inhalation of cold and dry air which can then lead to bronchial obstruction and asthma symptoms [38-40]. In addition to these mechanisms, there is also evidence for a systemic interaction possibly mediated through IL-5.

The clinical implication is twofold. First, the rhinitis patients should be thoroughly evaluated, including testing lung function, as part of the clinical routine in an effort toward early detection of symptoms and signs of asthma. Second, in patients with asthma the nasal airways should become part of the clinical assessment and be treated properly when needed.

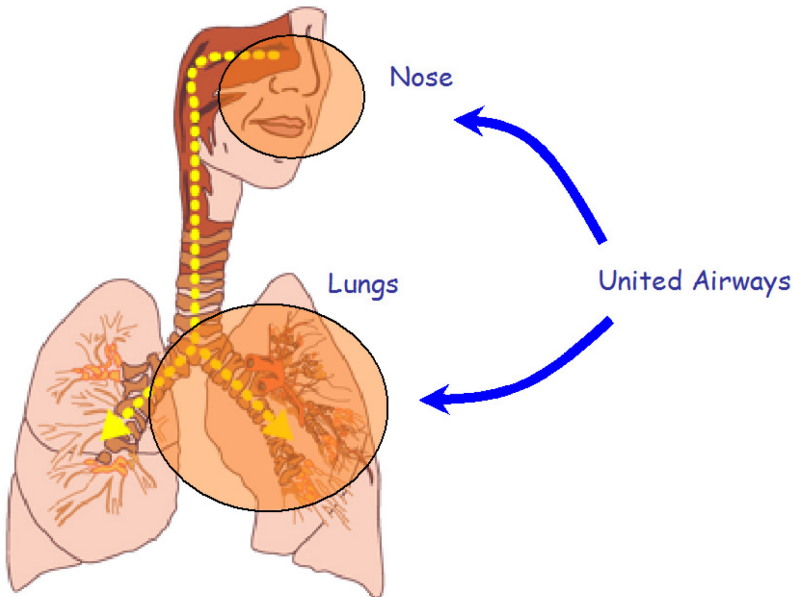


Figure 5. The upper and lower airways.

Patient-reported outcomes

The term patient-reported outcomes (PRO) addresses the source of the report rather than the content. PRO is a useful term as an organizing tool for the many concepts and applications of self-reports in treatment evaluations. These outcomes may include symptoms, health status, reports of activities, quality of life, adherence to treatment recommendations and satisfaction with treatment. PROs are important for measuring the impact of disease and treatment. They are also important for evaluating health and social policies.

Health-related quality of life

It is important to take the patient's perspective into account for healthcare services, for example, when considering new treatments or evaluating old ones. As we have discussed above, the World Health Organization (WHO) defines health as "A state of complete physical, mental, and social well-being not merely the absence of disease". This underlines for us not only the importance of taking the symptoms of disease into consideration when treating patients but also the importance of taking into account the mental status and the social situation of that patient. The quality of life concept tries to capture these aspects.

Most of us have a common sense of the meaning of the term quality of life. It could mean different things to different people. It could also mean different things for a person at different times in their life. For some people, it might be materialistic things like cars and money, and for others it might be the view from their home or the proximity to parks. The WHO defines quality of life as "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". This definition stresses two important aspects. First, it is the individual feeling of where you are and what you do, and the second important aspect is that it refers to the individuals own goals. From the health-care perspective, it can be quite paradoxical because it means that the QOL can be raised in two ways: one is by improving aspects that are important for the QOL, and the other is by lowering expectations or goals. This is not a practical way to handle QOL issues, but it points to the importance of setting realistic goals. This implies the importance of education, i.e., to be sure that the patient knows what to expect and what not to expect. To be more useful in healthcare, the term health-related QOL (HRQL) has been developed. With this term, the concept tries to tighten the meaning of the QOL so that it includes that which has to do with health and disease. For making the measurement useful in healthcare, both in research and in clinical practice, the way we measure needs to be valid and reliable, and the results need to be understandable. The measurement needs to respond to changes over time so that it can be used to measure any effect of treatment.

Different types of HRQL instruments

Generic instruments

Health-related quality of life instruments could be divided into generic and specific instruments. Generic instruments attempt to measure all important aspects of HRQL. They include items that are not specific for a single disease and can be used irrespective of the underlying condition. The sickness impact profile [41], the Nottingham health profile [42], and the SF-36 [43] are among the most widely used in regard to adults. There are also numerous HRQL instruments for the pediatric population [44]. Pediatric Quality of Life Inventory (PedsQL) and child health questionnaire (CHQ) are widely used questionnaires for the pediatric population [45, 46]. The PedsQL consists of 23 items covering the domains of physical, emotional and social functioning [46]. Because generic instruments apply to a variety of populations, they allow for broad comparisons of the relative impact of various healthcare programs. Generic profiles may, however, be unresponsive to changes in specific conditions.

Utility measures are a type of generic instrument that reflect the preferences of patients and are recommended for use in cost-utility analyses. The usefulness of utility measures in economic analysis is important when healthcare providers are asked to justify the resources devoted to treatment. EQ-5D developed by the EuroQoL group, is globally used and is recommended for use in regard to this purpose [47, 48].

Generic instruments have been used in asthma patients. The results show an affect both in terms of physical, emotional and social functioning [49-51]. Generic questionnaires have been used to a lesser extent in connection to rhinitis. In adult patients with a perennial allergy, the HRQL was affected in the physical, emotional and social domains [52, 53]. There are to our knowledge no studies on generic HRQL performed on children with rhinitis and pollen allergy.

Disease-specific instruments

The second basic approach to HRQL measurement focuses on aspects of health status that are specific to the area of primary interest. The rationale for this approach lies in the potential for increased sensitivity that may result from including only important aspects of HRQL that are relevant to the patients being studied. In addition to the likelihood of improved sensitivity, specific measures have the advantage of relating closely to areas routinely analyzed by clinicians. The rhinitis quality of life questionnaire, RQLQ, is the most extensively used disease-specific instrument for upper airways; it was developed by Elisabeth Juniper[54]. The items for this questionnaire were generated by the investigators and were subsequently checked by patients with known rhinoconjunctivitis. This

questionnaire consists of 28 items in seven domains (activity limitations, sleep impairment, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional problems). Since the validation, the questionnaire has been translated into multiple languages and has been used extensively both in research and clinical practice. The development of a pediatric version of the questionnaire showed that the problems were almost similar [55]. The adolescent version (12 – 16 years) indicated that the teenagers were more bothered by difficulties concentrating in school [56]. All of these questionnaires were validated on patients with just rhinitis or rhinoconjunctivitis. The patients with asthma were excluded from the validation studies. A new HRQLQ called the “Pediatric allergic disease quality of life questionnaire” (PADQLQ) has been developed [57, 58]. This questionnaire has been developed for assessing the multisystem effects of allergic disease on HRQL and takes into account aspects regarding the eyes, nose, lungs, skin, emotions and everyday activities. Roberts et al. used unstructured interviews for the item generation in patients with rhinitis, asthma and eczema [57]. The resulting item generation was as expected more diverse, highlighting also problems from non-eye/non-nose organs. The questionnaire consists of 26 questions and is answered by the children themselves. It takes less than ten minutes to answer [57]. It has also been shown to correlate well with allergic inflammation and allergenic load [58].

No disease-specific questionnaire in Swedish validated for children with rhinitis and pollen allergy has been available.

Development of Patient-reported outcomes (PRO)

Although some heterogeneity exists among guidelines for the development and validation of PRO, all emphasize the importance of validity, reliability and responsiveness as crucial aspects [59, 60]. The FDA guidelines highlight important aspects of the validation process[61].

The first step in the process is to explain the underlying rationale for the instrument. Next is the item generation phase, usually including both patient and expert input. The questions (or items) will then be reviewed and a preliminary questionnaire version will be made. This preliminary questionnaire needs to undergo a validation process in order to secure certain basic properties[62]. These properties are fundamental for an HRQL instrument and are therefore explained in detail.

Validity

Validity refers to the question of if the instrument measures what it intends to measure. The instrument needs to cover (contain) all important aspects of the underlying concept. This is called content validity [62]. This process is mainly secured during the development phase, including both expert and patient input as well as literature research. During the evaluation process, healthcare workers, researchers and patients should perceive the questionnaire as being relevant and sensible. This is called face validity.

The construction (and the underlying hypothetical model) of the questionnaire then has to be confirmed (construct validity). This is done by testing the questionnaire on the target population. Often, the testing involves using the new questionnaire together with another well-established method or questionnaire, a so-called golden standard, with which the new questionnaire can be compared. The questionnaire should also be able to differentiate between known groups with anticipated different severity and prognosis, for example, mild vs. severe disease.

The results of the different items and domains should also correlate as hypothesised. Domains suspected to be closely related should have high correlations and vice versa, i.e., domains that are mirroring different aspects should have low correlations.

Reliability

Reliability means that the measurements show consistent and reproducible results. This means that the results should be the same for repeated measurement if the patient's condition has not changed. Reliability is often analyzed when the measurements are repeated over time (test-retest reliability) where it is tested together with other markers of the underlying condition. The smaller the variation in the group with no other signs of changes, the better the reliability.

Sensitivity

Sensitivity is the ability of an instrument to detect differences between groups with presumed different HRQL, for example, patients with severe disease compared to mild disease.

Responsiveness

Responsiveness is the ability of an instrument to detect changes over time, e.g., detect improvement after a new therapy or perhaps the progression of the disease.

Both sensitivity and responsiveness are crucially important aspects for an instrument to be useful both in research and clinical practice.

Challenges with HRQL

Response shift

Response shifts are about the challenge in interpreting the answer “Pretty good-considering” to the question “How are you?”.

What is the reference value from which you decide how you feel? Is it compared to an ideal human being? Is it compared to someone else in your age or with your disease? Is it a comparison of how you were before you got ill or a comparison of how you expected to feel?

It is a well-known but paradoxical fact that patients with obvious severe disease sometimes score their HRQL equal or better than the healthy population [63, 64]. This response shift is defined as “a change in the meaning of ones self-evaluation of HRQL as a result of changes in internal standards, values and conceptualization” [65]. Thus, a major change in health status leads to behavioural and cognitive processes necessary for accommodating the new health status. These processes can change the internal standards and values and thus the HRQL. The magnitude of the response shift seems to be dependent upon the patient’s personal characteristics, such as personality and coping strategies, and external factors, such as social and family support and compensation by medical rehabilitation and society.

To summarize, the HRQL concept tries to capture important aspects of the patient’s life and not just merely symptoms or disabilities. The difficulties are obvious, not least because of the subjective nature of HRQL. Many of the quality of life questionnaires do not include what the public thinks is important for the perception of HRQL [66]. Even so, a practical approach, one defining the HRQL by the content of the questionnaire, can be useful for capturing a broader perspective of the patient and the effect of the disease on that individual.

The concept of disease control

Disease control means different things for different people. The patient might think of disease control as a cure or remission. The concept has been most widely used in asthma care, and only recently has it been introduced in rhinitis management [67]. In asthma care, it refers to control of manifestations of disease [33]. This includes control over clinical manifestations, such as night-time waking, coughing, wheezing, but it also means minimizing the limitations of daily activities. It should also take into account medications and the potential side effects of medications. The control of these factors should lead to a lower risk for future exacerbations.

Different instruments have been developed for asthma-control assessment. HRQL questionnaires can be used. They are well-suited for capturing personal limitations but are many times extensive and time consuming to complete and as such are not easy to use in clinical practice [68]. The Global Initiative for Asthma (GINA) guidelines use five items: daytime symptoms (two times or more per week), limitations in activity (any), nocturnal symptoms (any), need for rescue medication (more than twice a week) and lung function (FEV1 less than 80% of that which is predicted). If one or two parameters are affected, then the asthma is defined as partly controlled, and if three or more parameters are affected, the asthma is defined as uncontrolled. The ACT (asthma control test), which is widely used, uses five items (asthma restricts your activity at work/home, self-rated asthma control, shortness of breath, night-time wakings/symptoms and the need to use rescue medication [69]. Every item is answered on a five-point Likert scale and asks how you have felt during the last four weeks. ACQ, another control questionnaire, uses similar questions but also includes lung function and the appearance of wheezing [70]. This questionnaire has a version without reference to lung function. The recall time for ACQ is one week, and the items are answered on a seven-point Likert scale. These short instruments have the advantage of being easy to use when, for example, screening for uncontrolled asthma. The shortcoming is that they do not include everything that is important in an asthma review.

Modern medication has been proved to be effective in clinical trials [71]. Despite this, many surveys have shown that in real life, a large number of patients have little control of their disease [72, 73]. There are many different reasons for poor control. One underlying cause is the genetic and phenotypic characteristics of the asthma disease. Comorbidity, like rhinitis, has been shown to be associated with poor asthma control [74]. Other important factors are the care given and interest displayed by the doctor. Does the doctor have the right knowledge? Does the patient receive the right treatment, and is the treatment appropriately evaluated?

Cross-sectional surveys have shown that patients seeing a specialized doctor were more likely to follow guidelines and use preventer medications than patients seeing a doctor not specialized in allergy and asthma care [75]. Education of healthcare providers in asthma treatment and communication skills showed a significant effect on emergency department visits, asthma symptoms and the use of preventer medications [76, 77].

Further important aspects are the patient's thoughts, beliefs and concerns. Is the patient educated? Does the patient have knowledge about the disease and the signs and symptoms of poor asthma control? Self-management programs have been shown to improve symptoms, HRQL and adherence to therapy [78, 79].

The control of disease is defined by us, the healthcare professionals. Patients might have other preferences. They are not necessarily interested in using preventer medications which means taking medication every day, especially if it is a medication that they think has dangerous side effects. Non-adherence is complex and can be both intentional and non-intentional [80]. Intentional non-adherence can be improved by understanding the patient's perspective. A tool that is easy to use, one which covers all important areas of asthma assessment, including asthma control, could help in this patient communication. Such an instrument could also help in the communication between healthcare providers and serve as an aid for the doctor securing comprehensiveness of the asthma review and the evaluation of the patient.

AIMS OF THE PRESENT INVESTIGATIONS

The overall aim of this thesis was to develop patient-reported outcomes for clinical evaluation of respiratory allergic disease.

The specific aims are:

- to validate a disease-specific, health-related quality of life questionnaire (HRQLQ) in Swedish for children with respiratory allergic disease,
- to validate a clinical tool for asthma assessment including the evaluation of asthma control.
- to, by the use of patient-reported outcomes (PRO), evaluate the burden of disease in children with a grass pollen allergy, and
- to evaluate the effect of pollen exposure on symptom duration and validate the threshold levels in the current national pollen warning system.

METHODS AND SUBJECTS

The studies in this thesis emanate from two cohort groups. First, we describe the grass pollen study (Papers I, II, and III) and then the Active Life with Asthma study –ALMA (Paper IV).

Grass pollen study (Papers I, II, and III)

This was an observational cohort study. The inclusion criteria were children aged 7-18 with a grass pollen allergy. The diagnosis of a grass pollen allergy was, in addition to the clinical history, ascertained by a positive skin prick test or by the presence of allergy-specific IgE in the blood. An exclusion criterion was other allergies causing symptoms during grass pollen season. The patients were consecutively included if they met the inclusion criteria and did not meet the exclusion criteria. The majority of patients included in the study lived at the time in the inner city of Malmö, but some patients also lived in the suburban areas. Most of the children were seeing a pediatrician because of their allergy. Subject characteristics are shown in Table 1.

Table 1. Subject characteristics, percentages or median values.

Subject characteristics	
Children with a	%
<hr/>	
Grass pollen allergy (n=89)	
Age (7–18)	13
Rhinitis	89.8
Food allergy	39.1
Asthma	60.2
Eczema	37.2
<hr/>	

The patients completed one PADQLQ before grass pollen season (April). Beginning in June, they kept a diary for symptoms and medication every day. Once a week, they filled out the PADQLQ until mid-July (high grass pollen season). On the same occasions, the children completed a visual analogue scale (VAS) for symptoms. After the season (August-September), patients were asked to fill out a PADQLQ modified on the timescale (How troubled have you been during the pollen season?) in order to get a retrospective estimation of HRQL during pollen season. In total, eight PADQLQ questionnaires were completed.

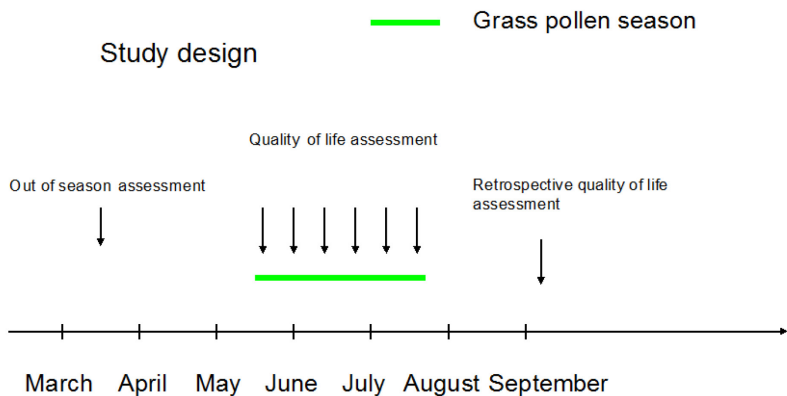


Figure 6. The study design in the grass pollen study.

Instruments used

PADQLQ

The PADQLQ already described in the introduction covers three domains: a practical one (Q1-7, 26), a physical one (Q8-22) and an emotional domain (Q23-25). Each question was answered using a seven-point Likert scale where zero means “not troubled at all” and six means “extremely troubled”. The questionnaire was self-administered.

The translation was performed according to the guidelines discussed further in the result and discussion section.

Generic HRQLQ – DISABKIDS

DISABKIDS Chronic Generic Module (DCGM-37) was developed as an EU-funded collaboration in seven European countries: the European DISABKIDS project [81]. The instrument was constructed to measure HRQL in children with chronic conditions from a general perspective. This is the first time it has been used in connection with a pediatric pollen-allergic disease population. The questionnaire consists of 37 items assigned to three domains:

1. Mental, including dimensions concerning independence and emotions
2. Physical, including dimensions concerning limitations and treatment
3. Social, including social inclusion and exclusion.

The scores of the domain can be combined to produce a general score. Each item is answered on a five-point Likert scale ranging from one (never) to five (very often). The items refer to the four previous weeks. The DCGM-37 has shown satisfactory psychometric properties [82]. Reference values for other chronic diseases are available [83].

Diary

For the correlation with pollen exposure, we used a diary for symptoms from the eyes, nose, and lungs. Every question was answered on a zero to three-point scale (not at all, mild, moderate, severe). This scale has been widely used in allergic research and has been found to be sufficiently sensitive in order to detect changes after treatment [84].

Visual analogue scale (VAS)

For the cross-sectional validity, we compared the results of the PADQLQ with the results from the visual analogue scales (VAS) which have been used in rhinitis both for severity assessment and in the follow-up of treatment and are recommended by the World Allergy Organization (WAO) guidelines [85-87]. We chose symptoms that had been shown to be relevant for rhinoconjunctivitis and asthma [88]. We used four nasal symptoms (obstruction, sneezing, watery and itching), three eye symptoms (watery, itching and redness) and four asthma symptoms (coughing, wheezing, difficulty breathing and difficulty breathing while running) and one question for a global assessment (How troubled have you been because of your allergy?). Patients were asked to answer the question for the past week.

Pollen counts

Daily atmospheric pollen counts for the Malmö area, comprising mainly urban and agricultural land in the Northern European nemoral vegetation zone, were monitored during the pollen season of 2009 using a Burkard seven-day volumetric spore trap, situated on a roof top about 25 m above ground at Skåne University Hospital (SUS), 55°60'N, 13°00'E. The exposed tapes were analyzed by Botaniska Analysgruppen i Göteborg AB. The counts are representative for an area with a radius of 30 km from the trap, encompassing the residence of all subjects in the study.

Study period – pollen season

The first grass pollen was registered on 26 April 2009 (Fig. 7). From 5 May, grass pollen was registered for five days in a row, defining the start of the pollen season. On 25 May, the grass pollen count was four pollen grains per cubic meter, but afterwards counts started to increase, and on 31 May, the day before the start of the study period, the pollen count was 30 pollen grains per m³. During the study period, the pollen counts varied between one and 242 pollen grains/m³. The total number of registered pollen during the study period was 2,930, i.e., 79 % of the total pollen index (3,700) during the entire grass flowering period. The study period encompassed most of the anthesis of species belonging to the subfamily Pooideae, which are the main provokers of grass pollen induced allergy in Sweden. The peak occurred at 13 June, the day after a heavy rain, and counts then did not decrease below 50 pollen grains per cubic meter until 5 July.

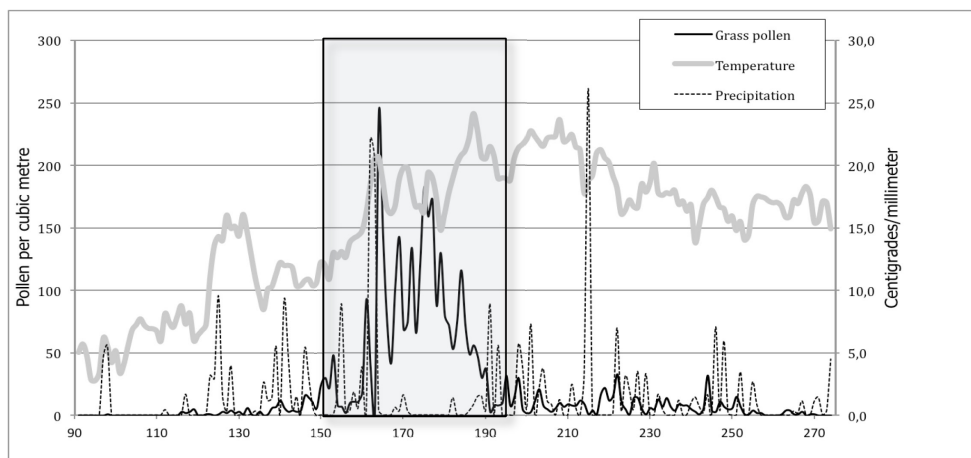


Figure 7. The grass pollen season of 2009. The study period is greyed.

Statistical methods

Paper I

Descriptive statistics are given as a number, median with min-max values or valid percentage. To estimate the internal consistency of the PADQLQ, looking at all the items and the items in each domain, the Cronbach's coefficient α was calculated. Spearman's rho statistic, ρ_s , was used to test the cross-sectional validity between the PADQLQ scores (total and domain) and the VAS score and also to test the responsiveness to change between the change in PADQLQ scores (total and domain) and the change in VAS score. The Kruskal-Wallis test was performed to test both the discriminative property and the responsiveness to change. To assess reliability, the intra-class correlation (ICC) was calculated by the repeated PADQLQ measurements.

Paper II

Spearman's rho statistic, ρ_s , was performed to assess the correlation between different scores. The Mann-Whitney U test or the Fisher's Exact test was used to test differences between groups, and the Wilcoxon Signed Ranks test was performed to test for differences between two repeated measurements. To assess the relationship between DISABKIDS and symptoms (nose, eyes and lungs) adjusted for age group, gender, asthma and hay fever, multiple linear regressions were used.

Paper III

To estimate the association between pollen count symptoms, HRQL and lag effects, mixed models on repeated observations were performed. Three different symptoms (nose, eyes and lungs), the mean of the three different symptoms (total) and HRQL were used as outcomes. The outcomes were all on ordinal scales: the three symptoms 0-3, the mean of the three different symptoms 0-10, and quality of life 0-6. The pollen counts were tested as fixed effect and were analyzed both as continuous and categorical variables (threshold levels). Lag effects were also tested. The analyses were performed on the whole period (day 1-42) and on three sub-periods (day 8-17, day 18-27 and day 28-37). The change in reactivity to pollen exposure during pollen season was analysed for two periods (day 1-7 and day 36-42). Periods (1 = day 1-7 and 2 = day 36-42) were added to the model. The estimates were obtained by the procedure GENMOD in SAS.

Breaking points for the symptom score (nose, eyes, lungs and total) were obtained by the fitting method Loess in SPSS. Fifty percent of points to fit and kernel Epanechnikov were used.

The statistical analyses were performed in SPSS Statistics 18 for Windows (IBM Corporation, Somers, NY, USA) and SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). A p-value below 0.05 was considered statistically significant.

The ALMA study (Paper IV)

The aim of the ALMA study was to develop and validate a clinical tool for asthma assessment in primary care that would be useful in monitoring asthma including the evaluation of asthma control.

The developmental process of the questionnaire is shown in Figure 8.

First, discussion groups composed of up to eight asthma patients and chaired by an asthma specialist got together to discuss everyday life with asthma, with a focus on issues related to the disease. The patients were recruited from primary care and were equally distributed concerning gender and age. The patients were divided into two age groups: younger (19 – 35) and older (>50). The aim was to find unmet needs reflecting real-life problems for asthmatics. The discussions resulted in a set of questions. After reconciliation by the studying committee, 25 questions were reduced to 19. The questions excluded were considered irrelevant to this questionnaire (for example, the need for asthma education) although they were used for the basis of our educational program.

A pilot questionnaire was run to make sure that the questions were perceived correctly (step 2). Ten primary care health centers were enrolled for this purpose, with 10 patients participating at each center, making it a total of 100 patients that went through the questions together with the asthma nurse. The questions were subsequently evaluated and modified (minor wording changes) in collaboration with experienced asthma specialists, and a draft version was established. The resulting questionnaire consisted of all in all 19 questions: 16 questions with four alternative answers (often, sometimes, seldom, never), two questions with yes/no answers, and one question about as-needed medication. The paper-based form was filled in by the patient or by the medical staff at an interview and took about five minutes to complete.

ALMA Tool Development

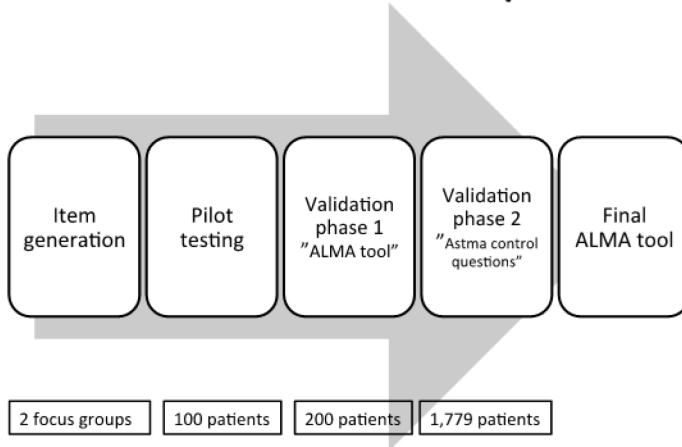


Figure 8. The study design of the ALMA study.

Validation

In order to validate the questionnaire, the results of the 16 questions with four answer alternatives were compared with the answers of ACQ (step 3). Three questions in ALMA did not have an ordinal scale and were not used for the comparison (Q17-Q19). The result of the questionnaires were expected to correlate positively.

The questionnaire was sent out twice, two weeks apart, for assessing the test-retest reliability. The questionnaire was sent out to 200 consecutive patients in primary care with doctor-diagnosed asthma.

To further validate the questionnaire with a larger patient sample, a database was constructed (step 4). In addition to the questionnaire results, questions by a medical specialist about smoking habits, current asthma medications, inhalation technique, spirometry, evaluation of treatment control and actions taken were added and entered into a web-based application, an ALMA database, with password-protected access. Each form covers information from three visits with variable time periods in between reflecting the regular visit schedule. Patients over 18 years of age with a diagnosis of asthma are qualified to fill in the questionnaire, and the healthcare staff selects the eligible patients. ALMA was optional to use for both primary care centers and patients. The resulting database was then used for further validation of the questionnaire by factor analysis.

Statistical methods

For computational reasons, the 19 questions were numerically coded: 1 - 4 (questions 1 - 16), 1 - 2 (questions 17 - 18) or 1 - 3 (question 19). Descriptive statistics were calculated for each question and numerical background variables. Correlation coefficients between questions and lung function variables were also calculated. For cross-sectional validity, we compared the results to the ACQ results. For internal validity, the Cronbach's alpha coefficient was used.

Test-retest reliability was calculated by Pearson's correlation coefficient.

An exploratory factor analysis was undertaken to investigate the structure among the 19 questions and to explore if there were groupings (factors) among them indicating different domains. The applied extraction method was axis factoring. A scree plot was constructed. Since the correlation matrix suggested correlation between factors, we used an oblique rotation.

The statistical tests were performed in SPSS Statistics 18 for Windows (IBM Corporation, Somers, NY, USA). A p-value below 0.05 was regarded as statistically significant.

RESULTS

Paper I – Translation and validation of the PADQLQ

In the first part of this project, we aimed to translate and validate a disease-specific quality of life questionnaire for children suffering from allergic disease.

Translation

The original English version was translated by two professional English teachers with Swedish as their native language. After reconciliation (Hampus Kiotseridis, HK and Alf Tunsäter, AT), the Swedish version was translated back into English by a (native) English-speaking medical physician fluent in Swedish. This was then reviewed (HK and AT). There were no conceptual differences found compared to the original English version.

After working with the design in order to make it easy to use, a cognitive debriefing was done on six consecutive patients (HK), and in the review after the cognitive debriefing (HK and AT), only minor changes were made (see appendix).

Validation

The internal consistency of the PADQLQ was tested by Cronbach's α . For the total score, the Cronbach's α was 0.96. For the practical, physical and emotional domains, the Cronbach's α was 0.90, 0.93 and 0.78, respectively.

Cross-sectional validity was tested by comparing the PADQLQ score (total and domain) and the VAS score. All domains as well as the total score in the PADQLQ were significantly correlated to the VAS scores.

The discriminative property was tested by dividing children into groups according to their VAS score. The HRQL differed significantly between the groups (Figure 9).

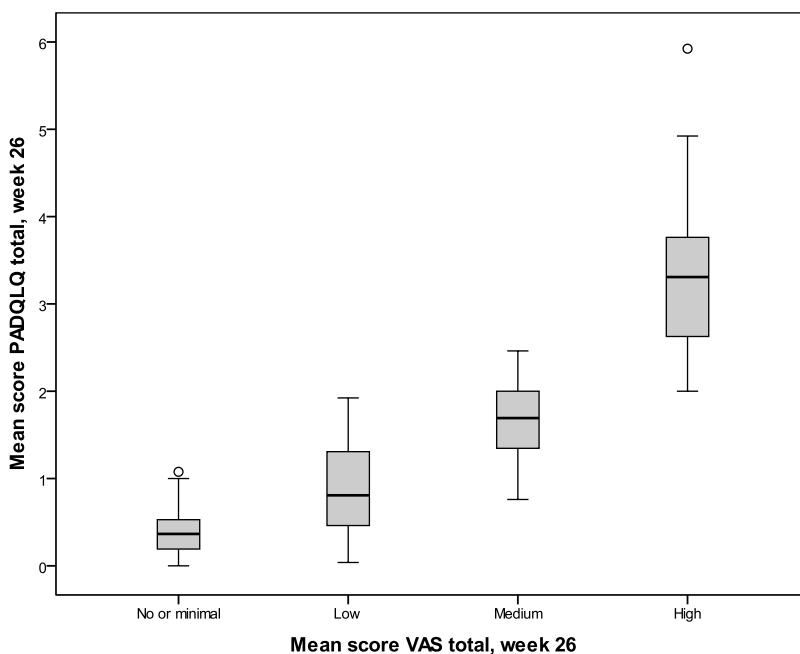


Figure 9. Discriminative property: The quality of life was significantly different in the patient groups with different VAS scores. Patients were grouped according to their VAS in four groups. VAS 0-1 (None or minimal), VAS1-3 (low), VAS 3-5 (medium) and VAS 5-10 (high). The group differences were tested with the Kruskal-Wallis test, and the QOL were all significantly different ($P < 0.001$).

The responsiveness to change was tested by comparing change in PADQLQ and the change in VAS between two different occasions in and out of grass pollen season. There was a good correlation between changes both in the total score and the domains.

The patients were divided according to their change in VAS (better, worse or unchanged). The PADQLQ score was significantly different in the groups (< 0.001).

The minimal important difference (MID) is defined as the smallest change in patient-reported outcome (PRO) perceived as beneficial for the patient or that would result in a change in treatment. In our study, the MID was 0.42, using the $\frac{1}{2}$ SD rule[89].

PAPER II – HRQL in grass pollen allergic children

Quality of life during pollen season

A large proportion of the studied population was affected during pollen season. Many of the items in the PADQLQ were shown to be bothersome (Figure 10). This was also the case for the DISABKIDS questionnaire.

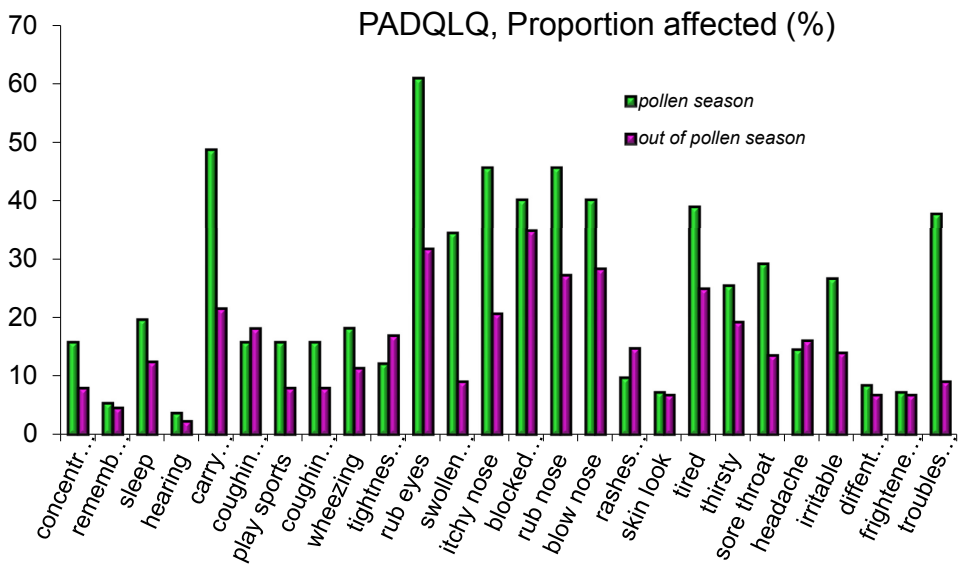


Figure 10. PADQLQ. The proportion of patients affected (per cent) defined by a score of three or more on a seven- point Likert scale, in grass pollen season (green) and out of pollen season (purple).

The quality of life score was significantly decreased during pollen season when measured with the disease-specific as well as the generic questionnaire. In the generic questionnaire, there were significant differences in the physical domain ($p=0.00093$) and the emotional domain ($p=0.034$), but no differences were found in the social domains (social relations, feeling left out) (Figure 11).

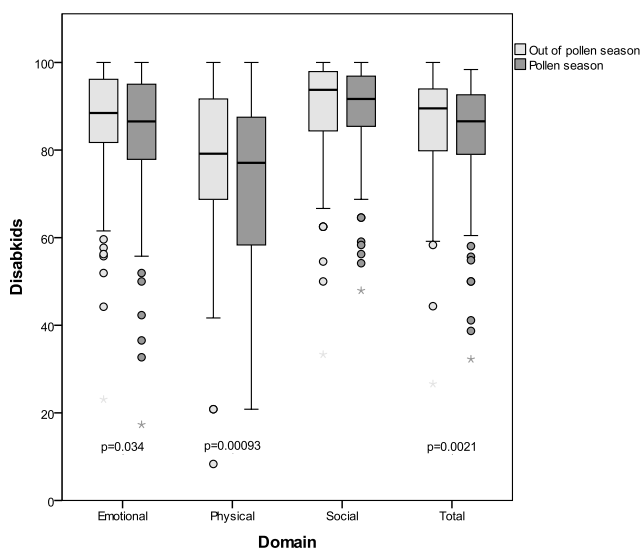


Figure 11. DISABKIDS. Generic HRQL assessed with DISABKIDS questionnaire. The results are shown with median and quartiles for total score and emotional, social and physical domains. The results during pollen season and out of pollen season are presented. The PADQLQ differed significantly in regard to physical ($p=0.0003$) and practical domains ($p=0.0024$) but not the emotional ones.

Gender and age differences

There was a significantly lower score among girls when compared to boys in the DISABKIDS physical domain. The total HRQL also differed in the same direction, but this was not significant ($p=0.088$). There were no differences in the PADQLQ and symptoms scores between girls and boys.

There were no differences in symptoms or HRQL between different age groups (7-12 and 13-18).

Severity, co-morbidity and the effect on HRQL

Patients with persistent rhinitis had lower scores in HRQL than patients with intermittent rhinitis. This was shown both with DISABKIDS and PADQLQ. Patients with both rhinitis and asthma had a lower quality of life score than children only suffering from rhinitis. This was shown with DISABKIDS ($p = 0.010$) and PADQLQ ($p = 0.041$). The relationship between symptoms (nose, eyes and lungs) and the DISABKIDS score, adjusted for age group, gender, asthma and hay fever, showed that symptoms from the eyes, nose, lungs all had strong and

equal impact on HRQL (standardized coefficient -0.47, -0.47 and -0.46, respectively).

Results compared with other diseases

The DISABKIDS quality of life total score for the study population was 81.5, which is comparable to the reference value for an asthma population (80.15). For the children with more severe symptoms (total mean VAS >5), the results (68.0) were comparable to the reference of severe chronic disease (66.2).

PAPER III - Relationship between pollen count and symptoms

The breaking points for total symptom aggravation were visually inferred from a Loess curve (Fig. 12). We found two sharp inflexion points at 30 and 80 pollen grains per cubic meter and a less clear one at 150 pollen grains per cubic meter.

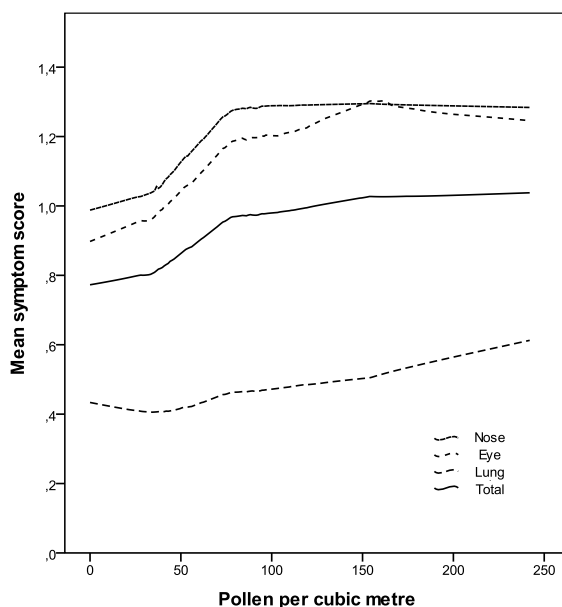


Figure 12. The relationship between symptom scores and pollen grains during the study period 1 June–12 July in Malmö, 2009, evaluated with locally weighted regression (LOESS).

There was a significant relationship for the continuous dependence of total symptom scores on pollen counts when calculated for the entire study period

($p < 0.0001$), for the period comprising study days 8-17 ($p < 0.0001$), and for the period comprising study days 28-37 ($p = 0.037$).

Nose symptom scores increased continuously and linearly with pollen counts from concentrations of 0-30 pollen grains per cubic meter, wherefrom symptom severity increased faster until about 80 pollen grains per cubic meter. At higher pollen concentrations, the severity of symptoms did not appear to increase.

Eye-symptom scores increased with pollen counts in a way similar to nose symptoms, but symptom severity continued to increase beyond concentrations of about 70 pollen grains per cubic meter and did not level out until about 140-150 pollen grains per cubic meter. Two lower inflexion points of the curve were located at pollen concentrations of about 30 and about 80 pollen grains per cubic meter.

Lung symptom scores related to increasing pollen counts in a pattern different from that of the nose and the eyes. There was no apparent change in symptom severity until levels above 50 pollen grains per cubic meter. From levels above about 70 pollen grains per cubic meter, the increase appeared almost linear.

Lag effects, accumulation of exposure effects and symptom severity

Pollen exposure had a significant effect on nose, eye and lung symptoms. With an increasing lag of 1-3 days, significance levels decreased. For lung symptoms, the effect was nearly significant (OR 0.999, $p = 0.0546$) for a lag of one day but with two or three days, there was none. For nose and eye symptoms, the effect of exposure three days before symptom registration was still significant, but significance levels had decreased from $p < 0.0001$ for a lag of 0-2 days to $p = 0.0021$ for the nose and $p = 0.0007$ for the eyes. For total symptoms, the significance level at a lag of three days decreased to $p = 0.0014$.

If the day when symptoms were registered was excluded and only the accumulated pollen sum during the three days preceding this date was included, there was still a strongly significant effect on the nose, eye and total symptoms ($p < 0.0001$) but none on the lung symptoms. With an extension of five days before registration day, the effect remained strongly significant for eye symptoms and significant to a lower degree for the nose and total symptoms ($p = 0.0004$ and $p = 0.0001$, respectively).

Reactivity late and early in pollen season

The change in reactivity to pollen exposure during pollen season was analyzed with a generalized linear model. The change in symptom severity by pollen exposure did not change significantly during the season either for nose, eye, lung and total symptom score.

Threshold levels

We considered the total symptom score and the nose, eye and lung symptom scores separately and related the symptom scores to Swedish and British/Danish pollen warning threshold levels. We related them to a three-level alert system defined from the visual inference of the Loess curve (Fig. 13), which we call the “traffic light system”.

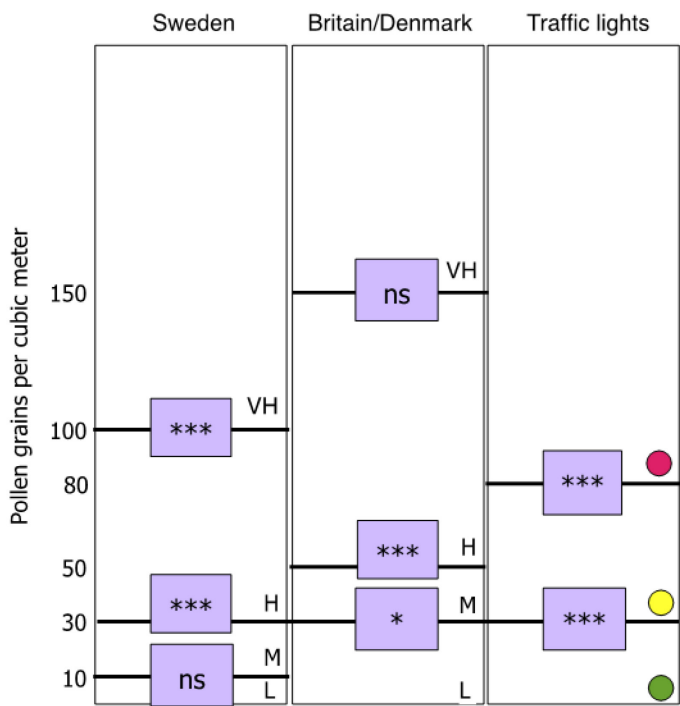


Figure 13. Threshold levels in Sweden and Britain/Denmark (Low, Medium, High and Very High), and the traffic light model (Low, Medium and High).

PAPER IV – ALMA – Active life with asthma

Both the ALMA and the ACQ questionnaires were sent out to 200 consecutive patients (114 women) and the median age was 41 years (range 18-76). One hundred and thirty-one patients (62 women) answered the first questionnaire. The second questionnaire, sent to patients who answered the first questionnaire, was answered by 77 patients (47 women). There was no difference in age or gender in the non-answering group. The mean ACQ score (Range 0-4) did not change during the two-week test period (ACQ mean 0.78 and 0.8, respectively).

The correlation between ALMA and ACQ was 0.71. The internal validity measured with Cronbach's alpha was 0.91, and the test-retest reliability was 0.93.

Factor analysis of the subset of control questions

After exploring different solutions, we found a three-factor solution most appropriate with three logical domains: a physical, a mental and an environmental domain. The correlation matrix showed correlations between the factors suggesting an oblique rotation as most appropriate. The rotated factor pattern showed that the 14 items loaded onto one of the three factors with a value >0.4 . The Cronbach's α was 0.88 for the whole scale (0.86 for the physical factor, 0.59 for the mental factor, and 0.51 for the environmental factor). The correlation for the questions and the ACQ score was 0.72. The test-retest coefficient was 0.93 (0.92 for the physical factor, 0.88 for the mental factor, and 0.81 for the environmental factor).

Results from ALMA tool database (1,779 patients):

Figure 14 illustrates the responses from 1,779 patients to the ALMA questions on the first visit. Two-thirds of the patients (62 %) reported chest tightness on a regular basis (defined as often or sometimes). Many patients had asthma aggravations when exposed to dust, pollen, furred animals (61 %), tobacco-smoke, strong odors (62 %) and cold weather outdoors (68 %). Presence of a cold aggravated the asthma for a majority of the patients (84 %). Physical activity, such as walking, heavy work and sports, affected about half of those questioned (48 %, 50 % and 53 %, respectively), and one-third reported nocturnal wakings (30 %). Forty-five percent of the patients reported asthma breakthrough, defined as having asthma symptoms despite prescribed intake of asthma medication. Few patients

(15 %) experienced adverse medication effects. During the past year, 21 % of the patients had an emergency room visit due to asthma, but only 2.5% had been hospitalised. As-needed medication above recommended dosage guidelines was used by 25 %.

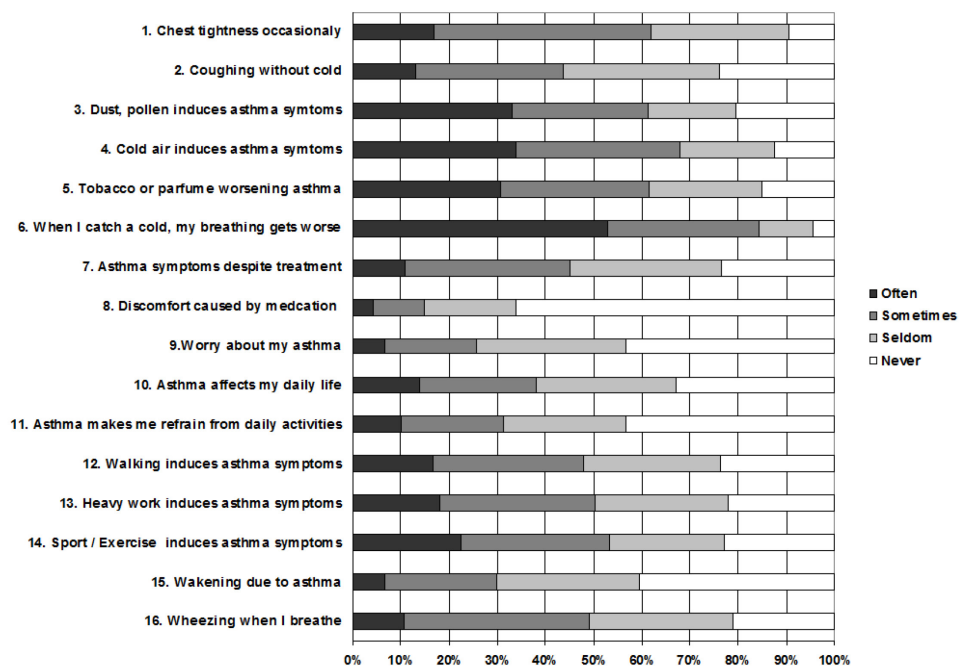


Figure 14. Results on the individual questions in the ALMA questionnaire on the registered patients (age range 18-89) in the database so far.

DISCUSSION

The discussion is divided into two parts. The first part is about the validation process of the Swedish version of the PADQLQ and ALMA, and the second part is about the effects of pollen exposure on symptoms and HRQL in children with pollen allergy.

Instruments for clinical assessment in allergic disease

PADQLQ

In allergic diseases where objective parameters only correspond moderately to subjective measures, there is a need for a validated instrument covering these aspects. In Sweden, there was no such instrument for children with respiratory allergic disease. We have in this study translated and validated the pediatric allergic disease quality of life questionnaire (PADQLQ).

There were no major difficulties in the translation and cultural adaptation of the PADQLQ. We have used a multistep approach including two forward translations and one backward translation as recommended by guidelines [90-94]. The process of cross-cultural validation is essential since results might otherwise lead to wrong conclusions [95, 96]. Differences can exist between cultures in their concepts of health and illness, levels of literacy, concordance between written and spoken versions of language, taboo subjects, and social desirability effects. There can be great differences in health perception between cultures [97]. There are fewer differences between European languages than there are between European and Arabic or Asian languages. We found no conceptual differences in the translations, and we believe that the culture differences are minor in the light of this disease-specific questionnaire.

Semantic equivalence is obtained when items mean the same thing to people from different groups and in the target and source languages. Operational equivalence ensures that standardized methods of survey administration are appropriate for the target culture. The cognitive debriefing of the resulting questionnaire showed that

the questions were easy to understand for the children and were relevant. They also found the questionnaire easy to complete.

The content validity has been ascertained in the original development [57]. In clinical studies where one is interested in evaluating a new rhinitis medication, it is logical to include only symptoms involving the nose and eyes as is the case with the PRQLQ, but in clinical practice it is not that obvious. Traditionally, allergic rhinitis has been classified as a disease on its own or as rhinoconjunctivitis if it occurs in conjunction with allergic conjunctivitis. Studies show high co-morbidity in allergic disease. More than 80 % of asthma patients have rhinitis and 20-50 % of rhinitis patients have symptoms from the lower airways [34, 35]. In our study, more than 60 % had asthma. In the light of the concept of united airways, we believe that it is appropriate to include symptoms from both upper and lower airways. From the results, it became clear that all organ involvement per se contributes to the total PADQLQ score.

The PADQLQ showed a good cross-sectional validity and a high reliability. The questionnaire showed also very high sensitivity, and a good responsiveness to change.

As such, the PADQLQ developed for the multi-allergic child can be used for a wide range of patients in both longitudinal and cross-sectional studies. It is well suited for assessment when, for example, evaluating systemic treatment with expected effect on many different organs. The good discriminant properties make the questionnaire useful in cross-sectional studies, for example, when studying other important factors like treatment strategies and environment.

We have also shown that the PADQLQ has good reliability in the assessment after grass pollen season with an ICC of 0.81. Although included in the guidelines for immunotherapy, the retrospective estimation is an issue of debate [98]. Röder et al. showed only moderate correlation between the retrospective estimation of symptoms during pollen season compared to the assessment during pollen season, but no explanation is given concerning when the retrospective estimation was done[99]. Mallin et al. did a retrospective analysis of the diary results using a 0-3 scale (none, mild, moderate, severe) and they found while using the mean score during pollen season some over-rating [100]. The correlation to the worst weeks seemed to be better, but was because of a small sample size not eligible for statistical analysis. Earlier studies had shown that the retrospective feeling of well-being was correlated to the symptom score during pollen season[101]. This is in line with our result where we find a good correlation between the PADQLQ score of the worst week and the retrospective estimation. We believe that the instrument might be useful in clinical practice as the patient often comes after pollen season seeking help for the next season.

ALMA

Describing the burden of asthma is complex. Historically, classification focuses on the severity of the disease. This has led to a lack of distinction between the severity of the underlying disease and the current level of asthma control. Disease severity is a quite stable characteristic of the individual that may change slowly over time, whereas the level of control reflects current functioning and may change markedly over relatively short time frames.

While measures of both the severity and the level of control are correlated, both concepts are important and conceptually distinct. For example, mild asthmatics will occasionally suffer from acute exacerbations during which their level of control may be very poor. Similarly, individuals with moderate to severe asthma require more intensive pharmacotherapy to control their symptoms, and yet with proper therapy and good compliance they can experience good symptom control. From the perspective of the practicing clinician, the level of control may be the more relevant measure, because the objective of therapy will be to control symptoms and minimize the impact of the disease on patient functioning. From the perspective of population-based disease management, asthma control could also serve as a good barometer of the adequacy of healthcare being provided to a population as well as serving as an indicator of patients who may benefit from more aggressive management.

In Paper IV, the objective was to develop a tool to be useful in clinical practice as a follow-up instrument in asthma care. The evaluation of the new ALMA tool and the validation of the subset of asthma-control questions demonstrated that the items selected cover key areas in an auditable structure for primary care asthma reviews, e.g., physical restrictions, environmental triggers, psychological function and healthcare utilization. These are important aspects when assessing patients with asthma, and we believe that the use of the ALMA tool helps structure this evaluation.

The three domains found in the ALMA subset of control questions covers aspects of asthma measured by other instruments (AQLQ, Mini-AQLQ) and are comprehensive for clinical follow-up. The AQLQ and Mini-AQLQ quantify HRQL and some measures for asthma control in a clinical trial setting [102]. Still, these asthma-control and HRQL instruments are not fully optimal for a real-life setting, as none of them cover the complete evaluation of an asthma patient's daily life to be considered in primary care. ALMA, although its principal use is supposed to be an auditing tool to structure primary care asthma reviews, also covers important areas for the clinical assessment of asthma control. As such, it can be used to assess the changes since the last visit and the possible need for a change in treatment. The ALMA tool also provides a useful educational

complement for both patients and doctors/healthcare nurses with data summaries on the individual level. It can also be used on the regional level in order to give feedback on asthma care.

We chose in regard to the ALMA questionnaire to not have a specified recall period. There is no gold standard for the recall time period, and different items might have different timeframes, depending upon the nature of the item [103, 104]. A short time period might give a more accurate recall for that period, but in clinical practice, when the patient sees the doctor a few times every year, to have an open time frame gives the patient the possibility of assessing and capturing a broader range of experiences.

In this study, a large proportion of the patients still present signs of suboptimal treatment with chest tightness, nightly wakings and asthma aggravations caused by environmental triggers, which also has been observed in earlier studies [73, 105-107]. There was a weak correlation between the objective lung function measurements, such as FEV1, and the HRQL according to ALMA, which is consistent with previous findings [108-110].

Clinical measures, such as FEV1, provide useful information but fall short in their ability to capture the broad impact of asthma on quality of life. A broad-based self-report measure that permits integration of multiple disease effects can fulfil some important requirements for a follow-up instrument in clinical practice.

Patient-reported outcomes in clinical practice

Can these questionnaires be used in clinical practice?

PROs have to a large extent been developed to be useful in clinical studies in order to also find out if it is effective on these subjective parameters, but what about the usefulness on the individual level? Theoretically, it could be useful in many ways. Widening the parameters of benefit, indicating a need for supportive interventions, aiding decision-making and informing healthcare policy are some such ways, but are these communication tools helpful in reality? Some studies have shown that treatment decisions are unaffected by the provision of HRQL information [111, 112]. Others have shown some effect in emotional well-being [113]. Velikova et al. compared three groups of patients in a randomized controlled trial to determine which actions related to using PROs from individual patients have effects [114]. In the intervention group, patients filled out HRQL questionnaires just before visiting the doctor, and their responses were then given to the doctor. In the attentioncontrol group, patients filled out the HRQL questionnaires, but the

information was not given to the doctor. In the control group, patients did not fill out the questionnaires. Related to collecting the PROs, the results showed that both the intervention and attention control groups had better symptom control than the control group.

Another controlled study conducted in community primary care practices demonstrated that the use of a HRQL instrument led to patients receiving more assistance with limitations in physical and daily activities and greater patient understanding [115].

The general intent of using PROs in clinical practice is to characterize a patient's experiences of a health situation so that the information can then be shared with clinicians and/or other patients. It seems, therefore, reasonable to consider the clinical use of PROs as communication events. Where in this communication could the PRO be useful?

Communication in brief as explained by Feldman-Stewart et al. is based on a framework including four components [116]. First is the drive of the communication, i.e., what the goal is for each participant. The second component consists of the five key attributes underlying each person's participation and goals for the communication: their needs, beliefs, values, skills, and emotions. The third component of the framework is the communication process, which includes each person both conveying messages and receiving messages. The messages can be verbal or non-verbal. Finally, the fourth component of the framework is the environment in which the communication occurs. It includes both the current physical setting and the world beyond, including social and cultural dimensions.

Guided by the framework, Feldman-Stewart et al. hypothesize, for example, that filling out the forms improves patients' skills regarding describing their symptoms, such as the skills related to identifying and classifying their symptoms. This will in turn give a better picture to the doctor about the problems, thus facilitating both the second and the third component of communication. Also, the interest one shows as a doctor by asking the patient to fill out the instrument will possibly help the patient feel that the doctor is committed and thus also help the fourth component of communication.

Studies have shown that the doctor underestimates the burden of disease in allergic rhinitis. In an American survey of children and adults with rhinitis, the patient-reported incidence of severe symptoms was two to three fold compared to the doctor's assessment [117]. They also concluded that the doctor's impression of the disease is likely reflected by the symptom profile at consultation. A questionnaire can help the doctor to better understand the burden during pollen season.

What characteristics are needed in order to be useful in clinical practice? In addition to being valid and reliable, the PRO needs some further characteristics.

We need a clear indication (is it valid for that patient in that situation?). Further, we need interpretable results (do the patient and the doctor understand the results?). Moreover, the burden of completing the questionnaire should be considered. It should be easy for the patient to complete and easy for the doctor to analyze.[118]

We have shown both ALMA and the PADQLQ to have good reliability and validity with a good responsiveness to change. The high test-retest reliability shows that the ALMA and the PADQLQ instruments are very stable which makes them suitable as a follow-up instrument [119]. We believe that the questionnaires are easy to complete and, that the results are interpretable. We believe that both ALMA and the PADQLQ could be used as communication tools helping the communication between the patient and provider. They can furthermore be used as communication tools between healthcare providers, for example, in association with referral to specialist care or as a part of a national registry. Both ALMA and PADQLQ need further validation for use in clinical practice and especially as an aid in the decision-making process.

Effect of pollen exposure on symptoms and HRQL

About one out of five school-age children are sensitized to grass pollen. In sensitized children, these pollen allergens elicit an allergic reaction in the target organ and give rise to a systemic inflammation [120, 121]. Atmospheric pollen count has been found to be positively correlated with allergic symptoms, drug consumption for allergic rhinitis and/or conjunctivitis [122-125], emergency room visits because of asthma [126-130], and hospitalizations because of asthma [131-133]. Moreover, most studies have so far not investigated if the reactions change with time and either focus on one target organ or lump symptoms from several organs together. In the present study, we investigated the effect of pollen exposure on symptoms from different organs and HRQL during pollen season. We have found a strong relation between symptoms and grass pollen exposure. We have also shown that the HRQL is impaired during pollen season.

Effect of pollen exposure on symptoms

We found a strong relation between symptoms and grass pollen exposure. Different organs react differently when pollen concentrations change and also with regard to the effect of exposure one to three days before assessment day. There is a lag effect of the preceding days upon eye and nose but not upon lung symptoms. We did not find any signs of aggravation nor of symptom relief over time that

could not be related to increasing or decreasing pollen levels on the assessment day or during the preceding three-day period.

Citizens who are well informed of factors in their environment, e.g., the presence of aerosols with a possible adverse effect on health, are able to take measures in order to protect themselves from these negative effects. Information about registered and forecasted amounts of allergenic and airborne pollen helps the allergy sufferer to identify his or her disease and relate it to ambient concentration levels. The allergic person can avoid activities that enhance exposure risk or demand a high level of concentration and precision, and may take appropriate medication to reduce the effects of exposure. Thus, he or she may take control of the disease, enjoying increased performance and quality of life.

In many countries and regions, this information service is already running. Pollen concentration is measured on a daily basis, and the registered numbers and/or short-term forecasts are usually presented in media and special websites, usually translated into categories. The delimitation of these categories varies from country to country. They may either be determined according to the number of individuals that experience symptoms at a certain ambient pollen load [134], according to the severity of symptoms in an “average” allergic person, or to the general abundance of the pollen types [135]. In Malmö and other parts of Sweden, the categories used in the public warning system were delimited in the 1970’s, referring to “clinical experience”. In the capital of Denmark, Copenhagen, which is situated only a few kilometres from Malmö, other threshold levels are used in public communication [136]. From an educational point of view, this situation is not desirable; firstly, the threshold levels should be clinically relevant, and secondly, the information given should not be confusing.

In the children in our study group, we found three relevant levels reflecting the reaction towards grass pollen: at 0-30 pollen grains per cubic meter, giving no or minor symptoms; at 30-80 pollen grains per cubic meter, giving intermediate symptoms; and then at more than 80 pollen grains per cubic meter, causing severe symptoms. We found that the Swedish system has an unnecessary limit between “low” and “moderate” values at 10 pollen grains/m³ and that the British/Danish system includes a limit between “high” and “very high” levels that does not reflect any significant differences in symptom severity. We found that symptoms reached a plateau at 80 pollen grains/m³, and we do not believe that it is clinically meaningful to further categorize into very high levels. A similar plateau beyond 80-90 pollen grains was found in France and Switzerland, which suggests that the pollen limits found in our study might be applicable to Northern and Central Europe [137].

Most studies on the effects of bio-aerosols on health focus on asthma exacerbations, measured as emergency room visits or hospitalizations, or on rhinoconjunctivitis. Fewer consider symptoms from several organs at one time. We studied total symptom scores and nose, eye and lung symptoms separately and found that the two former and the latter vary with pollen concentration in different ways. The curves describing nose and eye symptoms are steeper and have a number of more or less sharp inflexion points, whereas the lung symptoms do not increase until pollen concentration reaches about 70 pollen grains per cubic meter, and the symptom scores were fairly low throughout our study. It is possible that pollen counts must be higher in order to have a clear effect on lung symptoms or that exacerbations of such symptoms are associated with special meteorological conditions, such as humid conditions and thunderstorms, that may cause the pollen grains to burst. Epidemiological studies have shown an association between even lower levels of pollen concentrations (less than 30 pollen grains) and hospital admissions, which suggests that these levels might have an effect on susceptible individuals [138]. During the present study, there was little precipitation, with the exception of one day just before the pollen peak, and the connection between heavy rains and lung symptoms could not be evaluated. But pollen-derived debris and small particles can be associated with pollen allergens, and since they are much smaller than the intact grains are themselves, they are able to penetrate into the lower airways so as to induce asthma [139]. Furthermore, asthma is a complex disease with many different phenotypes where pollen allergy is only one of many factors influencing asthma control [140].

We found a lag effect of up to five days. This is in line with results from two other studies [141, 142]. We could not find any difference in reactivity between the beginning and the end of pollen season. As early as in the 1960's, repeated pollen challenges were shown to increase nasal sensitivity to other allergens in experimental models. This was called Connell's priming effect [143]. De Weger et al. [144] found that that allergic rhinitis symptoms at similar grass pollen concentrations were more severe in the early flowering season as compared to those in the late flowering season. They suggested that there is a natural potential to down-regulate the allergic response after repeated allergen exposure, similar to the effects of successful immunotherapy. In contrast to the results of that study, we could neither find evidence of symptom relief nor of aggravation during the course of the study period that could not be related to changes in pollen levels. The strength of our design is that we do not have symptom aggravation in early grass pollen season due to actual other allergen exposure (e.g., birch pollen) since birch-sensitized children were excluded.

HRQL during pollen season

We have shown that the HRQL is impaired during pollen season. This was shown with both generic and disease-specific questionnaires.

The magnitude of the change was, as expected, larger with the disease-specific questionnaire. In the present study, the most marked impairment shown was in the physical functioning. In children with symptom score of five or higher, on a visual analogue scale, the physical limitations were greatly pronounced and comparable to the results of children with cerebral palsy. The children felt tired and also had more trouble falling asleep. Rhinitis is known to affect nocturnal sleep and cause daytime sleepiness. The impaired sleep may be related to nasal congestion which leads to sleep-disordered breathing and micro-arousals [145]. Also, parents to allergic children reported more sleeping problems than other parents did [146]. Daytime fatigue is a logical result of sleep disruption, but other studies have shown that the daytime sleepiness is an independent consequence of the allergic rhinitis itself, possibly through systemic affect [147]. A good quality of sleep is of great importance because lack of sleep has consequences both for social functioning and for school performance [148].

The PADQLQ captures the effects on daily activity. A pilot study using the patient preference for activities of children (PAC) showed that the rhinitis patients had lower preference for activities both of a physical (including sports) and social (including going to parties, hanging out with friends, etc.) nature [149]. In the pediatric allergies in America survey, they found effects on outdoor activities. Such activities were three to four times more limited in rhinitis patients than in their healthy peers. They speculate that this could contribute to the high prevalence of obesity [146, 150]. This might affect the acquisition of the personality and of health behaviors and as such become a future risk factor for metabolic/cardiovascular disease [151].

The negative effect on physical domain was more pronounced in girls. This has also been shown before in studies concerning asthma [152, 153]. Girls and boys seem to adapt to a chronic disease in different ways. Williams et al. [154] found in their interview-based study concerning children with chronic diseases that girls showed a greater adaptation and acceptance while boys had a tendency to deny their problems and to try to keep the disease separate from their identity. The clinical implication might be that the girls have a tendency to lower HRQL and boys tend to deny their symptoms. Both of these should be taken seriously.

We found that not only was physical functioning affected but that psychological well-being was affected as well. The children felt unhappier during pollen season because of their allergy, and they felt that they could not do the things they wanted to do because of their allergy. Also, in the American allergy survey, they found the patients to feel more miserable, irritable, depressed and embarrassed [150]. Using

an instrument screening for psychiatric symptoms, Baybek et al. found in patients with seasonal and perennial rhinitis an effect on all subscales including depression and anxiety, and they found in general an overall distress higher than what they found in the control group [155].

Majani et al. investigated the HRQL in young adults with seasonal allergic rhinitis and found that they were affected during pollen season but did not report a change in the satisfaction profile measured with the life satisfaction profile (SAT-P)[156]. They argue that adults cognitively are aware of the transient nature. Our result suggests that this might not be case for children since they were affected in the emotional domain including worries about the future. This important question could be further studied, comparing the HRQL in an unselected patient population comparing healthy and allergic children. In adults, it has been shown that the HRQL out of pollen season did not differ when compared to the healthy control group [147].

The quality of life was affected in the study group assessed with both the generic and disease-specific questionnaires. The children with both asthma and rhinitis had poorer HRQL than the children with only rhinitis. The rhinoconjunctivitis symptoms seem to be as important as the asthma symptoms for the HRQL. This is in line with studies concerning adults [157]. Organ-specific questionnaires do not capture these aspects and might underestimate the real burden of disease. Petersen et al. showed that HRQL scores assessed with an organ-specific questionnaire did not differ in adults with co-morbid asthma and rhinitis, but HRQL differences could be identified with a generic HRQL questionnaire [158]. The assessment of a patient with a pollen allergy need not only take symptoms from the nose and eyes into consideration but also other symptoms that are relevant for the child with a pollen allergy, for example, symptoms from the lungs. In our study, both DISABKIDS and PADQLQ capture the additional burden on quality of life due to having both asthma and rhinitis. This highlights the problems with the atopic children that often suffer from more than one allergic disease. The burden of diseases adds to each other and impairs the children's daily lives. In a recently published study from Sweden, the HRQL measured with EQ-5D (parental form) was affected in rhinitis, asthma and eczema [159]. This is an interesting finding although parents and children do show some differences in their perception on HRQL [160].

Generic HRQL questionnaires capture aspects of children's lives not captured by disease-specific questionnaires. In our study, there was a moderate correlation between the generic and disease-specific HRQL. This is in line with results from other studies [161]. They seem to cover different aspects where the disease-specific questionnaire covers the organ-specific manifestations shown with a high correlation between symptoms involving the lungs, nose and eyes and the HRQL.

We have shown that the symptoms involving the nose, lungs and eyes are equally important for the HRQL outcome.

The generic HRQL assessed with DISABKIDS captures the emotional impact of the allergic disease and can thus be used as a complement in epidemiological surveys capturing also the emotional impact of disease. It can also be used for comparison with other diseases and for socioeconomic studies. These aspects are important in times of limited resources.

The DISABKIDS quality of life total score for the study population was 81.5 (0-100), which is comparable to the reference value for an asthma population (80.15). For the children with more severe symptoms (total mean VAS >5), the results (68.0) were comparable to the reference of severe chronic disease (66.2). The response shift needs to be taken into account when interpreting these data. The response shift due to reconceptualization or recalibration can affect the result moderately [162]. The effect of a pollen allergy in children when not exposed needs to be addressed using a generic instrument applicable to a healthy control group.

The importance of PRO measurements

There are at least two important reasons to estimate the burden of disease in allergic disease. The first reason we have already discussed above, namely to aid communication between patient and provider in order to better treat the individual patient. The second important reason is to increase understanding about this highly prevalent disease. In Sweden, about one million people suffer from respiratory allergic disease. Are they treated appropriately or is there still room for improvement? The cost for society is tremendous since it is such a prevalent disease. Adults with rhinitis have an estimated work loss of 25 % on days with rhinitis. Most of this is due to of presenteeism, i.e., being at work but doing less [163]. The indirect cost of rhinitis in the USA was calculated to be 1.7 to 9.7 billion USD each year [164]. In Sweden alone, the indirect cost for rhinitis (both allergic and infectious) was calculated to be 2.7 billion Euros, or 653 Euro per person, each year [165]. In regard to children, there is a substantial amount of school absenteeism and presenteeism. This leads to learning impairment that has long-term effects both on the patient and on society [166, 167].

We know that effective treatment exists. Both pharmacotherapy and immunotherapy have been shown to have an effect on symptoms and HRQL [168-172]. In addition to this, immunotherapy also has been shown to prevent asthma development in children with rhinitis [11]. Do we know that patients are

satisfactorily treated? We know from other studies that many patients are still under-diagnosed and under-treated [173] and many of the patients despite receiving treatment do not have control of their symptoms. In the disease-specific program (DSP) run in 2006 in the USA, 50 % of the rhinitis patients with seasonal allergic rhinitis did not have good control of their symptoms despite taking medication, and in patients with both season and perennial allergic rhinitis, this was even less [117].

The doctor's attitude toward the disease is also important for patients' adherence to therapy and disease control. Allergic rhinitis is sometimes viewed more like a common cold than a disease affecting symptoms and well-being, which is in contrast with how the patient perceives the disease [174]. One difficulty is the clinical signs that do not correlate with the impact of disease, especially the patient goes to the doctor's office during a period when he or she feels better. Scadding et al. found in their survey that general practitioners considered allergic rhinitis to be relatively easy to manage and as being of low priority [175]. They also found that knowledge in primary care is sometimes limited in regard to how to treat and monitor these patients [176].

Many parents buy OTC drugs for their children but do not meet any doctor in order to discuss treatment options, expected treatment goals, etc. This leads to sub-optimal compliance to medication regimens. In an American pediatric survey, more than 50 % reported using OTC medications for their allergy [150]. Nearly all parents and providers answered that there was at least a moderate to a strong need for improved education for parents of children with AR in the same survey, and this could be expected to be the same in Sweden where no guidelines for patient education exist. Improved educational resources should provide an understanding of the burden of AR, its symptoms and available treatment options, and reasons for poor adherence and reduced efficacy of prescription nasal sprays.

In our study, many of the patients' diseases were not satisfactorily controlled. Larger epidemiological studies including assessment of HRQL will give the possibility of understanding how these patients are affected in their daily lives and if they are treated properly. Results from such studies might be the basis of new recommendations with respect to the treatment and monitoring of pollen allergic children.

Improvement in care would not only save money for society but it would also help patients to improve their HRQL and optimize their chances to develop physically, emotionally and socially.

Strength and limitations of the studies

The strength of the grass pollen study (Papers I, II and III) is the careful monitoring of the patients using multiple PROs for evaluation. The high compliance as well as the concordance in the results gives a good degree of reliability to the study.

The use of a validated questionnaire for generic HRQL has to our knowledge not been done before and this creates an opportunity to make comparisons with other chronic diseases.

A weakness of the study is that patients are consecutively registered, and a majority of the patients were recruited from the allergy department. Hence, it is unlikely that our study population is representative of the pollen allergy population. We have, however, not selected patients according to their severity, and all the patients fulfilling the inclusion criteria were offered the opportunity to participate. We believe that the patient population studied is representative for the population seeking help for their grass pollen allergy and thus usually having moderate/severe rhinitis.

In this study, the patients are their own controls. It would have been preferable to have a healthy control group, especially when comparing HRQL. Also, the reference values for other diseases are just presented with means and cannot be subject to further analysis when comparing different chronic diseases in childhood. Although our data indicates that the children with pollen allergies have the same level of HRQL as other chronic diseases, controlled studies including children with different diseases should be performed in order to evaluate these aspects. Also, the effects of a pollen allergy out of pollen season have to be investigated with a healthy control group and with a generic instrument also eligible for healthy controls.

Another weakness of the study is that we have used only PROs as outcome parameters. It would have been preferable to also have objective parameters for outcome comparison, but the results are in line with the results of the original English version where they found good correlation between the HRQL score and the airway inflammation (17).

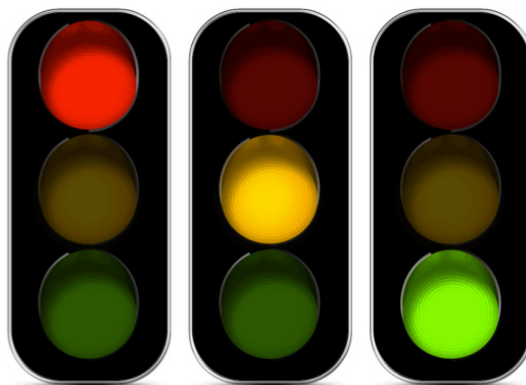
The strengths of the ALMA study are its development and validation which has been done in three steps, all including real-life patients to ensure its usefulness in a clinical setting. The validation of the asthma control questions included 1,779 patients, which is also a strength of the study

The correlation between ALMA and ACQ was high (0.72), which indicates that ALMA covers the asthma control aspects. It would have been preferable to also have other scales for comparison in the validation process.

Another limitation of the study is that only a small part of the asthma patients in the region were included, which might introduce a selection bias, e.g., asthma patients with more severe asthma may be registered and those with milder disease may not be included. The ALMA needs further validation, especially for the use in clinical practice. Hopefully the introduction of a web-based version will enable this.

CONCLUSIONS

1. The Swedish version of PADQLQ is highly valid as a patient-reported outcome measure for children with a respiratory allergy useful both for cross-sectional and longitudinal purposes.
2. The asthma tool ALMA was developed for monitoring asthma. It has been shown to be valid, reliable and to reflect the degree of asthma control and as such is suggested to be used for follow up both on the individual and group level.
3. The health-related quality of life is affected in children with a grass pollen allergy both physically and mentally. This was shown both with generic and disease-specific instruments. The instruments seem to complement each other..
4. Grass pollen symptoms are highly correlated to the dose of pollen exposure. Threshold levels need to be revised. We suggest a traffic light model for public pollen warnings directed at children, where green signifies “no problem”, yellow signifies “can be problems, especially if you are sensitive” and red signifies “alert – take action”.



IMPLICATION AND FUTURE DEVELOPMENT

PROs can be used for different purposes. For example, they can be used for differentiating between individuals with different perceived problems. This is very important especially in highly prevalent diseases such as asthma and rhinitis. Not all patients can be monitored by a specialist clinic. Most of the patients are actually taken care of in primary care settings. PRO tools should help the primary care physician make the right decisions and refer the right patient to the specialist. They should also help screen for potential problems and ascertain that the patient is treated properly. PROs in primary care should also be useful for communication between different levels of healthcare.

Another potential use of PRO is in clinical governance. Do the same patients get the same treatment everywhere in the country? Are the patients equally controlled or do the results differ in different parts of the country? A PRO as part of a national registry can help answer these questions.

For healthcare, it is a great challenge to give equal care to everyone, especially in the case of allergic diseases where some patients are treated by primary care physicians and some by specialists. Guidelines tell us that, for example, indication for immunotherapy treatment (allergy vaccination) is residual symptoms despite optimal pharmacological treatment. But what does this mean? Does it mean the same thing for every doctor or do they judge this differently? Do the patients get the right treatment or are they under-treated ?

Our instrument provides a possibility to investigate these aspects. An epidemiological survey including medication and HRQL could help us to better understand not only how prevalent the diseases are but also how they affect daily life and HRQL. We will also be able to investigate if the patients have received the optimal treatment and as such if the healthcare system gives the right care to this patient population. In fact, our results show that a large proportion of patients in our study had a symptom score on a visual analogue scale (VAS) over 5, which is a limit that has been used to define uncontrolled allergic disease [177].

Further, the validation of the PADQLQ has shown good discriminant properties and also sensitivity to change. Can we also use it in clinical studies to show effects on new treatment regimes? This is planned for an immunotherapy study with the HRQL as an outcome parameter.

Moreover, can patient-reported outcomes help us in the care of the allergic patient? Can we, with the use of patient-reported outcomes, better select patients for the right treatment? This can be addressed by using the HRQL as a discriminate marker to select a patient for referral to a specialist where immunotherapy is a possibility.

For ALMA, we will do a translation into English and in the next phase explore the use in clinical practice and, if possible, improve the assessment and care of this particular patient population. Hopefully, it will also be included in the Swedish national airway registry.

Lastly, one goal for the patient living with a chronic disease is to make daily live function optimally. We need good tools to correctly judge if we have reached this goal or have to take new steps in treatment. Patient-reported outcomes are essential for this purpose both in research and clinical practice.

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REFERENCES

1. Kaiko, G.E., et al., *Immunological decision-making: how does the immune system decide to mount a helper T-cell response?* Immunology, 2008. **123**(3): p. 326-38.
2. Clutterbuck, E.J., E.M. Hirst, and C.J. Sanderson, *Human interleukin-5 (IL-5) regulates the production of eosinophils in human bone marrow cultures: comparison and interaction with IL-1, IL-3, IL-6, and GMCSF.* Blood, 1989. **73**(6): p. 1504-12.
3. Ober, C. and E.E. Thompson, *Rethinking genetic models of asthma: the role of environmental modifiers.* Curr Opin Immunol, 2005. **17**(6): p. 670-8.
4. Van Bever, H., B. Lane, and J. Common, *Gene defects and allergy.* BMJ, 2009. **339**: p. b1203.
5. Adkinson, N.F. and E. Middleton, *Middleton's allergy : principles & practice.* 7th ed2009, Philadelphia, PA: Mosby/Elsevier.
6. Strachan, D.P., *Hay fever, hygiene, and household size.* BMJ, 1989. **299**(6710): p. 1259-60.
7. von Mutius, E., *Infection: friend or foe in the development of atopy and asthma? The epidemiological evidence.* Eur Respir J, 2001. **18**(5): p. 872-81.
8. Alm, B., et al., *Neonatal antibiotic treatment is a risk factor for early wheezing.* Pediatrics, 2008. **121**(4): p. 697-702.
9. Penders, J., et al., *The role of the intestinal microbiota in the development of atopic disorders.* Allergy, 2007. **62**(11): p. 1223-36.
10. Ege, M.J., et al., *Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children.* J Allergy Clin Immunol, 2006. **117**(4): p. 817-23.
11. Jacobsen, L., et al., *Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study.* Allergy, 2007. **62**(8): p. 943-8.
12. Bousquet, J., P. Van Cauwenberge, and N. Khaltaev, *Allergic rhinitis and its impact on asthma.* J Allergy Clin Immunol, 2001. **108**(5 Suppl): p. S147-334.
13. Guilemany, J.M., et al., *Persistent allergic rhinitis has a moderate impact on the sense of smell, depending on both nasal congestion and inflammation.* Laryngoscope, 2009. **119**(2): p. 233-8.
14. Linder, A., P. Venge, and H. Deuschl, *Eosinophil cationic protein and myeloperoxidase in nasal secretion as markers of inflammation in allergic rhinitis.* Allergy, 1987. **42**(8): p. 583-90.
15. Meyer, P., et al., *Alpha2-macroglobulin and eosinophil cationic protein in the allergic airway mucosa in seasonal allergic rhinitis.* Eur Respir J, 1999. **13**(3): p. 633-7.

16. *Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee.* Lancet, 1998. **351**(9111): p. 1225-32.
17. Aberg, N., et al., *Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991.* Clin Exp Allergy, 1995. **25**(9): p. 815-9.
18. Bjornsson, E., et al., *Symptoms related to asthma and chronic bronchitis in three areas of Sweden.* Eur Respir J, 1994. **7**(12): p. 2146-53.
19. Lundback, B., *Epidemiology of rhinitis and asthma.* Clin Exp Allergy, 1998. **28 Suppl 2**: p. 3-10.
20. Montnemery, P., et al., *Prevalence of nasal symptoms and their relation to self-reported asthma and chronic bronchitis/emphysema.* Eur Respir J, 2001. **17**(4): p. 596-603.
21. Braback, L., A. Hjern, and F. Rasmussen, *Trends in asthma, allergic rhinitis and eczema among Swedish conscripts from farming and non-farming environments. A nationwide study over three decades.* Clin Exp Allergy, 2004. **34**(1): p. 38-43.
22. Asher, M.I., et al., *Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys.* Lancet, 2006. **368**(9537): p. 733-43.
23. Ibero, M., et al., *Diagnosis and treatment of allergic rhinitis in children: results of the PETRA study.* Allergol Immunopathol (Madr), 2012. **40**(3): p. 138-43.
24. Jauregui, I., et al., *Validation of ARIA (Allergic Rhinitis and its Impact on Asthma) classification in a pediatric population: the PEDRIAL study.* Pediatr Allergy Immunol, 2011. **22**(4): p. 388-92.
25. Bateman, E.D., et al., *Global strategy for asthma management and prevention: GINA executive summary.* Eur Respir J, 2008. **31**(1): p. 143-78.
26. Lodrup Carlsen, K.C., et al., *Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study.* Allergy, 2006. **61**(4): p. 454-60.
27. Norrman, E., et al., *Prevalence and incidence of asthma and rhinoconjunctivitis in Swedish teenagers.* Allergy, 1998. **53**(1): p. 28-35.
28. Martinez, F.D., et al., *Asthma and wheezing in the first six years of life. The Group Health Medical Associates.* N Engl J Med, 1995. **332**(3): p. 133-8.
29. Mallol, J., et al., *International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources.* Thorax, 2010. **65**(11): p. 1004-9.
30. Goksor, E., et al., *Asthma symptoms in early childhood--what happens then?* Acta Paediatr, 2006. **95**(4): p. 471-8.
31. Ronmark, E., et al., *Different pattern of risk factors for atopic and nonatopic asthma among children--report from the Obstructive Lung Disease in Northern Sweden Study.* Allergy, 1999. **54**(9): p. 926-35.
32. Szeffler, S.J., et al., *Characterization of within-subject responses to fluticasone and montelukast in childhood asthma.* J Allergy Clin Immunol, 2005. **115**(2): p. 233-42.
33. (GINA), G.I.f.A., *Global strategy for asthma management and prevention, 2012:* Ginasthma.com.

34. Vignola, A.M., et al., *Relationships between rhinitis and asthma*. Allergy, 1998. **53**(9): p. 833-9.
35. Leynaert, B., et al., *Association between asthma and rhinitis according to atopic sensitization in a population-based study*. J Allergy Clin Immunol, 2004. **113**(1): p. 86-93.
36. Gaga, M., et al., *Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis*. Clin Exp Allergy, 2000. **30**(5): p. 663-9.
37. Braunstahl, G.J., et al., *Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways*. J Allergy Clin Immunol, 2001. **107**(3): p. 469-76.
38. Shturman-Ellstein, R., et al., *The beneficial effect of nasal breathing on exercise-induced bronchoconstriction*. Am Rev Respir Dis, 1978. **118**(1): p. 65-73.
39. Zeballos, R.J., et al., *The role of hyperventilation in exercise-induced bronchoconstriction*. Am Rev Respir Dis, 1978. **118**(5): p. 877-84.
40. McLane, M.L., et al., *Integrated response of the upper and lower respiratory tract of asthmatic subjects to frigid air*. J Appl Physiol, 2000. **88**(3): p. 1043-50.
41. Bergner, M., et al., *The Sickness Impact Profile: development and final revision of a health status measure*. Med Care, 1981. **19**(8): p. 787-805.
42. Hunt, S.M., et al., *The Nottingham Health Profile: subjective health status and medical consultations*. Soc Sci Med A, 1981. **15**(3 Pt 1): p. 221-9.
43. McHorney, C.A., J.E. Ware, Jr., and A.E. Raczek, *The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs*. Med Care, 1993. **31**(3): p. 247-63.
44. Solans, M., et al., *Health-related quality of life measurement in children and adolescents: a systematic review of generic and disease-specific instruments*. Value Health, 2008. **11**(4): p. 742-64.
45. Raat, H., et al., *Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population*. Qual Life Res, 2002. **11**(6): p. 575-81.
46. Varni, J.W., M. Seid, and C.A. Rode, *The PedsQL: measurement model for the pediatric quality of life inventory*. Med Care, 1999. **37**(2): p. 126-39.
47. Rasanen, P., et al., *Use of quality-adjusted life years for the estimation of effectiveness of health care: A systematic literature review*. Int J Technol Assess Health Care, 2006. **22**(2): p. 235-41.
48. *EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group*. Health Policy, 1990. **16**(3): p. 199-208.
49. Sawyer, M.G., et al., *The relationship between asthma severity, family functioning and the health-related quality of life of children with asthma*. Qual Life Res, 2000. **9**(10): p. 1105-15.
50. Sundell, K., et al., *Quality of life in adolescents with asthma, during the transition period from child to adult*. Clin Respir J, 2011. **5**(4): p. 195-202.
51. Vila, G., et al., *Psychopathology and quality of life for adolescents with asthma and their parents*. Psychosomatics, 2003. **44**(4): p. 319-28.

52. Bousquet, J., et al., *Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire*. J Allergy Clin Immunol, 1994. **94**(2 Pt 1): p. 182-8.
53. Meltzer, E.O., et al., *Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis*. Ann Allergy Asthma Immunol, 1999. **83**(4): p. 311-7.
54. Juniper, E.F. and G.H. Guyatt, *Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis*. Clin Exp Allergy, 1991. **21**(1): p. 77-83.
55. Juniper, E.F., et al., *Measuring quality of life in children with rhinoconjunctivitis*. J Allergy Clin Immunol, 1998. **101**(2 Pt 1): p. 163-70.
56. Juniper, E.F., G.H. Guyatt, and J. Dolovich, *Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials*. J Allergy Clin Immunol, 1994. **93**(2): p. 413-23.
57. Roberts, G., C. Hurley, and G. Lack, *Development of a quality-of-life assessment for the allergic child or teenager with multisystem allergic disease*. J Allergy Clin Immunol, 2003. **111**(3): p. 491-7.
58. Roberts, G., et al., *Impairment in quality of life is directly related to the level of allergen exposure and allergic airway inflammation*. Clin Exp Allergy, 2005. **35**(10): p. 1295-300.
59. Guyatt, G.H., B. Kirshner, and R. Jaeschke, *Measuring health status: what are the necessary measurement properties?* J Clin Epidemiol, 1992. **45**(12): p. 1341-5.
60. Lohr, K.N., et al., *Evaluating quality-of-life and health status instruments: development of scientific review criteria*. Clin Ther, 1996. **18**(5): p. 979-92.
61. Speight, J. and S.M. Barendse, *FDA guidance on patient reported outcomes*. BMJ, 2010. **340**: p. c2921.
62. *Assessing health status and quality-of-life instruments: attributes and review criteria*. Qual Life Res, 2002. **11**(3): p. 193-205.
63. Allison, P.J., D. Locker, and J.S. Feine, *Quality of life: a dynamic construct*. Soc Sci Med, 1997. **45**(2): p. 221-30.
64. Stensman, R., *Severely mobility-disabled people assess the quality of their lives*. Scand J Rehabil Med, 1985. **17**(2): p. 87-99.
65. Sprangers, M.A. and C.E. Schwartz, *Integrating response shift into health-related quality of life research: a theoretical model*. Soc Sci Med, 1999. **48**(11): p. 1507-15.
66. Bowling, A., *What things are important in people's lives? A survey of the public's judgements to inform scales of health related quality of life*. Soc Sci Med, 1995. **41**(10): p. 1447-62.
67. Fonseca, J.A., et al., *Control of Allergic Rhinitis and Asthma Test (CARAT) can be used to assess individual patients over time*. Clin Transl Allergy, 2012. **2**(1): p. 16.
68. Horne, R., et al., *Can asthma control be improved by understanding the patient's perspective?* BMC Pulm Med, 2007. **7**: p. 8.
69. Nathan, R.A., et al., *Development of the asthma control test: a survey for assessing asthma control*. J Allergy Clin Immunol, 2004. **113**(1): p. 59-65.

70. Juniper, E.F., et al., *Development and validation of a questionnaire to measure asthma control*. Eur Respir J, 1999. **14**(4): p. 902-7.
71. Bateman, E.D., et al., *Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study*. Am J Respir Crit Care Med, 2004. **170**(8): p. 836-44.
72. Demoly, P., et al., *Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years*. Eur Respir Rev, 2012. **21**(123): p. 66-74.
73. Rabe, K.F., et al., *Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study*. Eur Respir J, 2000. **16**(5): p. 802-7.
74. de Groot, E.P., et al., *Allergic rhinitis is associated with poor asthma control in children with asthma*. Thorax, 2012. **67**(7): p. 582-7.
75. Diette, G.B., et al., *Comparison of quality of care by specialist and generalist physicians as usual source of asthma care for children*. Pediatrics, 2001. **108**(2): p. 432-7.
76. Clark, N.M., et al., *Impact of education for physicians on patient outcomes*. Pediatrics, 1998. **101**(5): p. 831-6.
77. Clark, N.M., et al., *Long-term effects of asthma education for physicians on patient satisfaction and use of health services*. Eur Respir J, 2000. **16**(1): p. 15-21.
78. Janson, S.L., et al., *Individualized asthma self-management improves medication adherence and markers of asthma control*. J Allergy Clin Immunol, 2009. **123**(4): p. 840-6.
79. Thoonen, B.P., et al., *Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial*. Thorax, 2003. **58**(1): p. 30-6.
80. Horne, R., *Compliance, adherence, and concordance: implications for asthma treatment*. Chest, 2006. **130**(1 Suppl): p. 65S-72S.
81. Bullinger, M., S. Schmidt, and C. Petersen, *Assessing quality of life of children with chronic health conditions and disabilities: a European approach*. Int J Rehabil Res, 2002. **25**(3): p. 197-206.
82. Simeoni, M.C., et al., *Field testing of a European quality of life instrument for children and adolescents with chronic conditions: the 37-item DISABKIDS Chronic Generic Module*. Qual Life Res, 2007. **16**(5): p. 881-93.
83. Schmidt, S., et al., *The DISABKIDS generic quality of life instrument showed cross-cultural validity*. J Clin Epidemiol, 2006. **59**(6): p. 587-98.
84. MacKenzie, C.R. and M.E. Charlson, *Standards for the use of ordinal scales in clinical trials*. Br Med J (Clin Res Ed), 1986. **292**(6512): p. 40-3.
85. Bousquet, P.J., et al., *Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines*. Allergy, 2007. **62**(4): p. 367-72.
86. Canonica, G.W., et al., *Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce*. Allergy, 2007. **62**(3): p. 317-24.
87. Remington, M., et al., *Comparative reliability of categorical and analogue rating scales in the assessment of psychiatric symptomatology*. Psychol Med, 1979. **9**(4): p. 765-70.
88. Pfaar, O., C. Anders, and L. Klimek, *Clinical outcome measures of specific immunotherapy*. Curr Opin Allergy Clin Immunol, 2009. **9**(3): p. 208-13.

89. Norman, G.R., J.A. Sloan, and K.W. Wyrwich, *Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation*. Med Care, 2003. **41**(5): p. 582-92.
90. Guillemin, F., C. Bombardier, and D. Beaton, *Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines*. J Clin Epidemiol, 1993. **46**(12): p. 1417-32.
91. Acquadro, C., et al., *Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials*. Value Health, 2008. **11**(3): p. 509-21.
92. Bullinger, M., et al., *Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International Quality of Life Assessment*. J Clin Epidemiol, 1998. **51**(11): p. 913-23.
93. Bullinger, M., et al., *Developing and evaluating cross-cultural instruments from minimum requirements to optimal models*. Qual Life Res, 1993. **2**(6): p. 451-9.
94. Flaherty, J.A., et al., *Developing instruments for cross-cultural psychiatric research*. J Nerv Ment Dis, 1988. **176**(5): p. 257-63.
95. Bjorner, J.B., et al., *Differential item functioning in the Danish translation of the SF-36*. J Clin Epidemiol, 1998. **51**(11): p. 1189-202.
96. Mkoka, S., et al., *The pitfalls of translation--a case study based on the translation of the EQ-5D into Xhosa*. S Afr Med J, 2003. **93**(4): p. 265-6.
97. Kleinman, A., L. Eisenberg, and B. Good, *Culture, illness, and care: clinical lessons from anthropologic and cross-cultural research*. Ann Intern Med, 1978. **88**(2): p. 251-8.
98. Malling, H.J., *Current status of allergen-specific immunotherapy*. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M, 1994(87): p. 169-77; discussion 178-80.
99. Roder, E., et al., *The relevance of patient-reported outcomes in a grass pollen immunotherapy trial in children and adolescents with rhinoconjunctivitis*. Pediatr Allergy Immunol, 2013. **24**(1): p. 39-48.
100. Bodtger, U., L.K. Poulsen, and H.J. Malling, *Retrospective assessment of seasonal allergic symptoms: over-rating but useful*. Clin Exp Allergy, 2003. **33**(4): p. 496-500.
101. Bodtger, U., et al., *The safety and efficacy of subcutaneous birch pollen immunotherapy - a one-year, randomised, double-blind, placebo-controlled study*. Allergy, 2002. **57**(4): p. 297-305.
102. Vollmer, W.M., et al., *Association of asthma control with health care utilization and quality of life*. Am J Respir Crit Care Med, 1999. **160**(5 Pt 1): p. 1647-52.
103. Stull, D.E., et al., *Optimal recall periods for patient-reported outcomes: challenges and potential solutions*. Curr Med Res Opin, 2009. **25**(4): p. 929-42.
104. Norquist, J.M., et al., *Choice of recall period for patient-reported outcome (PRO) measures: criteria for consideration*. Qual Life Res, 2012. **21**(6): p. 1013-20.
105. Stallberg, B., et al., *Living with asthma in Sweden--the ALMA study*. Respir Med, 2003. **97**(7): p. 835-43.
106. Partridge, M.R., et al., *Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study*. BMC Pulm Med, 2006. **6**: p. 13.
107. Haughney, J., et al., *The Living & Breathing Study: a study of patients' views of asthma and its treatment*. Prim Care Respir J, 2004. **13**(1): p. 28-35.

108. Juniper, E.F., et al., *Relationship between quality of life and clinical status in asthma: a factor analysis*. Eur Respir J, 2004. **23**(2): p. 287-91.
109. Ehlers, P.O., H. Aberg, and K. Larsson, *Quality of life in primary care asthma*. Respir Med, 2001. **95**(1): p. 22-30.
110. Ehlers, P.O., B.M. Sundblad, and K. Larsson, *Quality of life and inflammatory markers in mild asthma*. Chest, 2006. **129**(3): p. 624-31.
111. Espallargues, M., J.M. Valderas, and J. Alonso, *Provision of feedback on perceived health status to health care professionals: a systematic review of its impact*. Med Care, 2000. **38**(2): p. 175-86.
112. Calkins, D.R., et al., *Functional disability screening of ambulatory patients: a randomized controlled trial in a hospital-based group practice*. J Gen Intern Med, 1994. **9**(10): p. 590-2.
113. Rubenstein, L.V., et al., *Improving patient quality of life with feedback to physicians about functional status*. J Gen Intern Med, 1995. **10**(11): p. 607-14.
114. Velikova, G., et al., *Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial*. J Clin Oncol, 2004. **22**(4): p. 714-24.
115. Wasson, J.H., et al., *A randomized trial of the use of patient self-assessment data to improve community practices*. Eff Clin Pract, 1999. **2**(1): p. 1-10.
116. Feldman-Stewart, D., M.D. Brundage, and C. Tishelman, *A conceptual framework for patient-professional communication: an application to the cancer context*. Psychooncology, 2005. **14**(10): p. 801-9; discussion 810-1.
117. Schatz, M., *A survey of the burden of allergic rhinitis in the USA*. Allergy, 2007. **62 Suppl 85**: p. 9-16.
118. Reeve, B.B., et al., *ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research*. Qual Life Res, 2013.
119. Bland, J.M. and D.G. Altman, *Cronbach's alpha*. BMJ, 1997. **314**(7080): p. 572.
120. Traidl-Hoffmann, C., et al., *Impact of pollen on human health: more than allergen carriers?* Int Arch Allergy Immunol, 2003. **131**(1): p. 1-13.
121. Traidl-Hoffmann, C., et al., *Lipid mediators from pollen act as chemoattractants and activators of polymorphonuclear granulocytes*. J Allergy Clin Immunol, 2002. **109**(5): p. 831-8.
122. Takasaki, K., et al., *Relationship between airborne pollen count and treatment outcome in Japanese cedar pollinosis patients*. Eur Arch Otorhinolaryngol, 2009. **266**(5): p. 673-6.
123. Zeghnoun, A., et al., *Short-term effects of airborne pollen on the risk of allergic rhinoconjunctivitis*. Arch Environ Occup Health, 2005. **60**(3): p. 170-6.
124. Fuhrman, C., et al., *Short-term effect of pollen exposure on antiallergic drug consumption*. Ann Allergy Asthma Immunol, 2007. **99**(3): p. 225-31.
125. Breton, M.C., et al., *Relationship between climate, pollen concentrations of Ambrosia and medical consultations for allergic rhinitis in Montreal, 1994-2002*. Sci Total Environ, 2006. **370**(1): p. 39-50.
126. Heguy, L., et al., *Associations between grass and weed pollen and emergency department visits for asthma among children in Montreal*. Environ Res, 2008. **106**(2): p. 203-11.

127. Tobias, A., et al., *Short term effects of airborne pollen concentrations on asthma epidemic*. Thorax, 2003. **58**(8): p. 708-10.
128. Tobias, A., I. Galan, and J.R. Banegas, *Non-linear short-term effects of airborne pollen levels with allergenic capacity on asthma emergency room admissions in Madrid, Spain*. Clin Exp Allergy, 2004. **34**(6): p. 871-8.
129. Tobias, A., et al., *Point-wise estimation of non-linear effects of airborne pollen levels on asthma emergency room admissions*. Allergy, 2009. **64**(6): p. 961-2.
130. Carracedo-Martinez, E., et al., *Effect of short-term exposure to air pollution and pollen on medical emergency calls: a case-crossover study in Spain*. Allergy, 2008. **63**(3): p. 347-53.
131. Dales, R.E., et al., *Tree Pollen and Hospitalization for Asthma in Urban Canada*. International Archives of Allergy and Immunology, 2008. **146**(3): p. 241-247.
132. Rosas, I., et al., *Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City*. Allergy, 1998. **53**(4): p. 394-401.
133. Dales, R.E., et al., *Influence of outdoor aeroallergens on hospitalization for asthma in Canada*. J Allergy Clin Immunol, 2004. **113**(2): p. 303-6.
134. Stewart, M.G., *Identification and management of undiagnosed and undertreated allergic rhinitis in adults and children*. Clin Exp Allergy, 2008. **38**(5): p. 751-60.
135. Burge, H.A., *Monitoring for airborne allergens*. Ann Allergy, 1992. **69**(1): p. 9-18.
136. Davies, R.R. and L.P. Smith, *Forecasting the start and severity of the hay fever season*. Clin Allergy, 1973. **3**(3): p. 263-7.
137. Caillaud, D.M., et al., *Nonlinear short-term effects of airborne Poaceae levels on hay fever symptoms*. J Allergy Clin Immunol, 2012. **130**(3): p. 812-814 e1.
138. Erbas, B., et al., *Do levels of airborne grass pollen influence asthma hospital admissions?* Clin Exp Allergy, 2007. **37**(11): p. 1641-7.
139. Bacsi, A., et al., *Subpollen particles: carriers of allergenic proteins and oxidases*. J Allergy Clin Immunol, 2006. **118**(4): p. 844-50.
140. Bush, A. and A. Menzies-Gow, *Phenotypic differences between pediatric and adult asthma*. Proc Am Thorac Soc, 2009. **6**(8): p. 712-9.
141. Taudorf, E. and L. Moseholm, *Pollen count, symptom and medicine score in birch pollinosis. A mathematical approach*. Int Arch Allergy Appl Immunol, 1988. **86**(2): p. 225-33.
142. Roberts, G., et al., *Longitudinal study of grass pollen exposure, symptoms, and exhaled nitric oxide in childhood seasonal allergic asthma*. Thorax, 2004. **59**(9): p. 752-6.
143. Connell, J.T., *Quantitative intranasal pollen challenges. 3. The priming effect in allergic rhinitis*. J Allergy, 1969. **43**(1): p. 33-44.
144. de Weger, L.A., et al., *Difference in symptom severity between early and late grass pollen season in patients with seasonal allergic rhinitis*. Clin Transl Allergy, 2011. **1**(1): p. 18.
145. Meltzer, E.O., *Introduction: Stuffy is also related to Sleepy and Grumpy--the link between rhinitis and sleep-disordered breathing*. J Allergy Clin Immunol, 2004. **114**(5 Suppl): p. S133-4.

146. Meltzer, E.O., et al., *Burden of allergic rhinitis: results from the Pediatric Allergies in America survey*. J Allergy Clin Immunol, 2009. **124**(3 Suppl): p. S43-70.
147. Stuck, B.A., et al., *Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial*. J Allergy Clin Immunol, 2004. **113**(4): p. 663-8.
148. Baiardini, I., et al., *Sleep disturbances in allergic diseases*. Allergy, 2006. **61**(11): p. 1259-67.
149. Engel-Yeger, B., A. Engel, and A. Kessel, *Differences in leisure activities between children with allergic rhinitis and healthy peers*. Int J Pediatr Otorhinolaryngol, 2010. **74**(12): p. 1415-8.
150. Meltzer, E.O., et al., *Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys*. Allergy Asthma Proc, 2012. **33 Suppl 1**: p. S113-41.
151. Gidding, S.S., et al., *Understanding obesity in youth. A statement for healthcare professionals from the Committee on Atherosclerosis and Hypertension in the Young of the Council on Cardiovascular Disease in the Young and the Nutrition Committee, American Heart Association. Writing Group*. Circulation, 1996. **94**(12): p. 3383-7.
152. Wijnhoven, H.A., et al., *Gender differences in health-related quality of life among asthma patients*. J Asthma, 2003. **40**(2): p. 189-99.
153. Warschburger, P., et al., *Health-related quality of life in children and adolescents with asthma: results from the ESTAR Study*. J Asthma, 2004. **41**(4): p. 463-70.
154. Williams, C., *Doing health, doing gender: teenagers, diabetes and asthma*. Soc Sci Med, 2000. **50**(3): p. 387-96.
155. Bavbek, S., et al., *Psychological status of patients with seasonal and perennial allergic rhinitis*. J Investig Allergol Clin Immunol, 2002. **12**(3): p. 204-10.
156. Majani, G., et al., *Health-related quality of life assessment in young adults with seasonal allergic rhinitis*. Allergy, 2001. **56**(4): p. 313-7.
157. Leynaert, B., et al., *Quality of life in allergic rhinitis and asthma. A population-based study of young adults*. Am J Respir Crit Care Med, 2000. **162**(4 Pt 1): p. 1391-6.
158. Petersen, K.D., et al., *Quality of life in rhinoconjunctivitis assessed with generic and disease-specific questionnaires*. Allergy, 2008. **63**(3): p. 284-91.
159. Covaciu, C., et al., *Childhood allergies affect health-related quality of life*. J Asthma, 2013. **50**(5): p. 522-8.
160. Upton, P., J. Lawford, and C. Eiser, *Parent-child agreement across child health-related quality of life instruments: a review of the literature*. Qual Life Res, 2008. **17**(6): p. 895-913.
161. Wilke, S., et al., *Correlations between disease-specific and generic health status questionnaires in patients with advanced COPD: a one-year observational study*. Health Qual Life Outcomes, 2012. **10**: p. 98.
162. Razmjou, H., et al., *Response shift in outcome assessment in patients undergoing total knee arthroplasty*. J Bone Joint Surg Am, 2006. **88**(12): p. 2590-5.
163. Blaiss, M.S., et al., *Patient and healthcare-provider perspectives on the burden of allergic rhinitis*. Allergy Asthma Proc, 2007. **28 Suppl 1**: p. S4-10.

164. Reed, S.D., T.A. Lee, and D.C. McCrory, *The economic burden of allergic rhinitis: a critical evaluation of the literature*. Pharmacoeconomics, 2004. **22**(6): p. 345-61.
165. Hellgren, J., et al., *Allergic rhinitis and the common cold--high cost to society*. Allergy, 2010. **65**(6): p. 776-83.
166. Richards, W., *Preventing behavior problems in asthma and allergies*. Clin Pediatr (Phila), 1994. **33**(10): p. 617-24.
167. Simons, F.E., *Learning impairment and allergic rhinitis*. Allergy Asthma Proc, 1996. **17**(4): p. 185-9.
168. Bousquet, J., et al., *Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire*. J Allergy Clin Immunol, 1996. **98**(2): p. 309-16.
169. Milgrom, H., et al., *Comparison of ipratropium bromide 0.03% with beclomethasone dipropionate in the treatment of perennial rhinitis in children*. Ann Allergy Asthma Immunol, 1999. **83**(2): p. 105-11.
170. Ratner, P.H., et al., *A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis*. J Fam Pract, 1998. **47**(2): p. 118-25.
171. Calderon, M.A., et al., *Allergen injection immunotherapy for seasonal allergic rhinitis*. Cochrane Database Syst Rev, 2007(1): p. CD001936.
172. Radulovic, S., et al., *Systematic reviews of sublingual immunotherapy (SLIT)*. Allergy, 2011. **66**(6): p. 740-52.
173. Nolte, H., S. Nepper-Christensen, and V. Backer, *Unawareness and undertreatment of asthma and allergic rhinitis in a general population*. Respir Med, 2006. **100**(2): p. 354-62.
174. Meltzer, E.O., *Allergic rhinitis: the impact of discordant perspectives of patient and physician on treatment decisions*. Clin Ther, 2007. **29**(7): p. 1428-40.
175. Scadding, G.K., D.H. Richards, and M.J. Price, *Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis*. Clin Otolaryngol Allied Sci, 2000. **25**(6): p. 551-7.
176. Ryan, D., et al., *Management of allergic rhinitis in UK primary care: baseline audit*. Prim Care Respir J, 2005. **14**(4): p. 204-9.
177. Bousquet, P.J., et al., *Uncontrolled allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial*. J Allergy Clin Immunol, 2010. **126**(3): p. 666-8 e1-5.