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Breathe in...breathe out...

How difficult can it be in patients with asthma or allergy ?

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Breathe in…breathe out…

Breathe in...breathe out...

How difficult can it be in patients with asthma or allergy ?

Georgia Papapostolou

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 10th of October date of month at 09.00 in Segerfalk Hall, Department of Clinical Sciences, Sölvegatan 17, 223 62 Lund, Sweden

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Breathe in...Breathe out...How difficult can it be in patients with asthma or allergy?

Abstract

Background: Clinicians face challenges starting from evaluating the disease burden, both with regards to symptoms and quality of life, in order to make decisions on when to start treating, what kind of treatment and to which degree. To understand the degree to which patients experience symptoms due to their disease and on what level is their quality of life affected we applied methods that are widely used in everyday clinical practice but even methods that are less widely used but believed to be more accurate.
Aims: This PhD project focused on investigating the symptoms and quality of life in patients with asthma and allergic rhinitis. We aimed to highlight unsolved problems regarding the evaluation of disease burden in asthmatics and allergic patients, focusing on cognitive dysfunction during the pollen season, patients' perspectives on living with severe asthma and peripheral airways obstruction.
Methods: We focused on both symptoms and quality of life, using standard validated questionnaires, specific for the diseases such as ACT, but even non-specific such as Nijmegen, while introducing less commonly used techniques (cognitive tests, in-depth interviews and Forced Oscillation Technique), examining different populations in order to investigate the problem from different aspects and thus acquiring an overall understanding of the existing limitations.
Results: In Paper I, allergic children performed worse during the season in cognitive tests in comparison to out-of-season, but also in comparison to non-allergic participants In Paper II, in-depth interviews showed that only a small part of the problems that these patients faced in their everyday life was captured by the questionnaires and important information, such as limitations, fears, mental health and impact on their families, was revealed. In Paper III+IV, we found that measurements during exhalation were more informative than during inhalation. Some questionnaires correlated better with peripheral lung obstruction than others even though they were not very specific for evaluating asthma. In addition, when using the most popular questionnaire to assess asthma control, the score reflecting whether the disease is under control or not did not provide adequate results with regards to small airway engagement.
Conclusion: By partly questioning several methods, mainly patient reported outcomes, and comparing them side by side with more objective but less used tools (cognitive tests, in-depth interviews and Forced Oscillation Technique) could be the beginning of a better understanding on how these diseases affect patients' lives.

Key words: asthma, allergy, symptoms, quality of life, cognitive dysfunction, pollen season, in-depth interview, severe asthma, forced oscillation technique, resistance, reactance

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How difficult can it be in patients with asthma or allergy ?

Georgia Papapostolou

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To all my patients and to my little sister…

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Papers included in the thesis

This thesis is based on the following papers, hence referred to as Paper I-IV:

Paper I: Papapostolou G, Kiotseridis H, Romberg K, Dahl Å, Bjermer L, Lindgren M, Aronsson D, Tunsäter A, Tufvesson E. Cognitive dysfunction and quality of life during pollen season in children with seasonal allergic rhinitis. *Pediatr Allergy Immunol. 2021 Jan;32(1):67-76. doi: 10.1111/pai.13328. Epub 2020 Aug 31. PMID: 32767782; PMCID: PMC7818136.*

Paper II: Papapostolou G, Tunsäter A, Binnmyr J, Telg G, Roslind K. Patient perspectives on living with severe asthma in Denmark and Sweden. *Eur Clin Respir J. 2020 Dec 16;8(1):1856024. doi: 10.1080/20018525.2020.1856024. PMID: 33414901; PMCID: PMC7751392.*

Paper III: Peripheral airway obstruction in association with symptoms and quality of life asthma. Georgia Papapostolou, Abir Nasr, Linnea Jarenbäck, Kerstin Romberg, Alf Tunsäter, Jaro Ankerst, Leif Bjermer, Ellen Tufvesson. (Manuscript)

Paper IV: Nasr A, Papapostolou G, Jarenbäck L, Romberg K, Tunsäter A, Ankerst J, Bjermer L, Tufvesson E. Expiratory and inspiratory resistance and reactance from respiratory oscillometry defining expiratory flow limitation in obstructive lung diseases. *Clin Physiol Funct Imaging. 2024 Jun 14. doi: 10.1111/cpf.12895. Epub ahead of print. PMID: 38873744.*

Other Papers

Eriksson G, Radner F, Peterson S, Papapostolou G, Jarenbäck L, Jönsson S, Ankerst J, Tunsäter A, Tufvesson E, Bjermer L. A new maximal bicycle test using a prediction algorithm developed from four large COPD studies. *Eur Clin Respir J. 2019 Nov 20;7(1):1692645. doi: 10.1080/20018525.2019.1692645. PMID: 31839909; PMCID: PMC6882496.*

Tufvesson E, Radner F, Papapostolou G, Jarenbäck L, Jönsson S, Nihlén U, Ankerst J, Tunsäter A, Peterson S, Bjermer L, Eriksson G. Reduced Variability of Endurance Time in New Protocols for Exercise Tests in COPD. *Int J Chron Obstruct Pulmon Dis. 2020 Nov 19;15:3003-3012. doi: 10.2147/COPD.S268894. Erratum in: Int J Chron Obstruct Pulmon Dis. 2021 May 20;16:1413. doi: 10.2147/COPD.S318908. PMID: 33239872; PMCID: PMC7682444.*

Tufvesson E, Radner F, Simonsen A, Papapostolou G, Jarenbäck L, Jönsson S, Nihlen U, Tunsäter A, Ankerst J, Peterson S, Bjermer L, Eriksson G. A new protocol for exercise testing in COPD; improved prediction algorithm for *WMAX* and validation of the endurance test in a placebo-controlled double bronchodilator study. *Ther Adv Respir Dis. 2021 Jan-Dec;15:17534666211037454. doi: 10.1177/17534666211037454. PMID: 34590519; PMCID: PMC8488527.*

Abbreviations

ACOS	Asthma COPD overlapping syndrom
ACT	Asthma Control Test
ACQ	Asthma Control Questionnaire
ARIA	Allergic Rhinitis and its Impact on Asthma
ATS	American Thoracic Society
AQLQ	Asthma Quality of Life Questionnaire
BD	Bronchodilator
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
EAACI	European Academy of Allergy and Clinical Immunology
EFL	Expiratory Flow Limitation
ERS	European Respiratory Society
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 sec
FOT	Forced Oscillation Technique
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital Anxiety and Depression Scale
ICS	Inhaled Corticosteroids
IL	Interleukin
IOS	Impulse Oscillometry System
LABA	Long-acting Beta-agonists
LAMA	Long-acting Muscarinic Antagonists
MOT	Motor Screening Test
OCS	Oral Corticosteroids
PADQLQ	Paediatric Allergic Disease Quality of Life Questionnaire
PAL	Paired Associates Learning
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Tests
R5	Resistance at 5 Hz
R19	Resistance at 19 Hz

Rexp	Expiratory flow resistance of the airways
Rinsp	Inspiratory flow resistance of the airways
Rtot	Total flow resistance of the airways
RTI	Reaction Time
RV	Residual Volume
RVP	Rapid Visual Information Processing
RQLQ	Rhinoconjuctivitis Quality of Life Questionnaire
SABA	Short-acting Beta-agonists
SCIT	Subcutaneous Immunotherapy
SGRQ	St George's Respiratory Questionnaire
SLIT	Sublingual Immunotherapy
SNOT22	Sino-nasal outcome test
SWM	Spatial Working Memory
TLC	Total Lung Capacity
TNFα	Tumor Necrosis Factor alpha
VAS	Visual Analogue Scale
WHO	World Health Organisation
WPAI	Work Productivity and Activity Impairement
X5	Respiratory reactance at 5 Hz
Xtot	Total respiratory reactance
Xexp	Expiratory reactance
Xinsp	Inspiratory reactance

Introduction

*When you **breath in** (inhale), air enters your lungs, and oxygen from that air moves to your blood. At the same time, carbon dioxide, a waste gas, moves from your blood to the lungs and is **breathed out** (exhaled). This process is essential to life. How well this process functions is essential to quality of life.*

This thesis was inspired by the observation that in several studies, previously performed in the field of allergy and asthma by the Research Unit of Lung and Allergy Department, SUS, Lund, had one common red thread. This thread was the evaluation of symptoms and quality of life from several perspectives, serving as part of the studies but not set as the main focus despite the fact that this aspect is fundamental for the patients suffering from asthma or allergic rhinitis.

Background

I. The Respiratory System- Upper and lower airways

The respiratory system is essential for gas exchange, enabling the body to take in oxygen and expel carbon dioxide. It is divided into two main parts: the upper airways and the lower airways. Each section plays a crucial role in ensuring efficient respiration and protecting the body from environmental hazards. Understanding the anatomy and physiology of these airways is crucial for diagnosing and treating respiratory conditions. Common disorders affecting the upper and lower airways, such as rhinitis, asthma, and COPD, have significant clinical implications. Effective diagnostic and therapeutic approaches are essential for managing these conditions and improving patient outcomes. By maintaining a comprehensive understanding of the respiratory system, healthcare providers can better address the challenges associated with respiratory diseases and enhance the quality of life for affected individuals.

The upper airways include the nasal cavity, pharynx, and larynx. The lower airways include the trachea, bronchi, bronchioles, and alveoli.

A specialized epithelium, lining the airways from the nasal cavity continuing to the trachea, bronchi and bronchioles, is composed of different cell types. Three major cell types represent the majority of the cells: basal, secretory and multi-ciliated cells. While multi-ciliated cells main function is to remove the mucus upwards, away from the alveoli, serving a mechanical protective purpose, a far more complex mechanism exists to defend the lungs against pathogens or exposure to toxins, pollutants, irritants and allergens. This mechanism consists of an inflammatory response during which numerous types of inflammatory cells are activated. The type-2 inflammation has been increasingly investigated over the past years considered to be a key factor in the underlying mechanism of several diseases of the airways.

A common disorder of the upper airways is **rhinitis**, an inflammation of the nasal mucosa, commonly caused by allergies or infections. Symptoms include nasal congestion, runny nose, and sneezing.

Common Disorders of the Lower Airways include:

- **Asthma**: a chronic inflammatory disease of the airways, characterized by episodes of bronchoconstriction, wheezing, and shortness of breath. Asthma can be triggered by allergens, exercise, or infections.
- **Chronic Obstructive Pulmonary Disease (COPD)**: a group of disease characteristics, including chronic bronchitis and emphysema, that cause airflow obstruction and breathing difficulties. COPD is often associated with smoking and long-term exposure to irritants.

II. Asthma

Asthma is a chronic respiratory condition characterized by inflammation and narrowing of the airways, leading to difficulty breathing, wheezing, and other respiratory symptoms. Affecting millions of people worldwide, asthma is a significant public health concern due to its impact on quality of life and the potential for severe, sometimes life-threatening exacerbations.

History

Asthma received its modern name by Hippocrates around 450 BC from the Greek verb aazein, meaning panting.

ἆσθμα

It was already recognised in Ancient Egypt and throughout the centuries people tried to understand the nature of this condition, attributing the cause to both psychological and physical factors. It is believed that the first time a respiratory distress was recorded, it was in China around 2600BC (1). While it is a well-recognized

condition, globally affecting hundreds of millions of people, there are still difficulties to agree upon a universal definition.

1905 Epinephrine was first referred in the treatment of asthma

1950s Oral corticosteroids began to be used to treat asthma

1950s Pressurized metered-dose inhaler were developed

1960s Inhaled corticosteroids and selective short-acting beta agonists

Treatment attempts are thought to have begun in ancient Egypt with an incense drinkable mixture, known as kyphi. A surviving manuscript from the 14-century indicates that there were medications for asthma in traditional Chinese medicine. From the use of Belladonna alkaloids in 1905 until the use of systemic corticosteroids, almost half a century later, to the inhaled corticosteroids and the development targeted asthma treatments, such as cromones, antileukotrienes and anti-IgE, over the last 40 years, one can conclude that asthma has been the target of several treatment attempts.(2)

"Asthma cigarettes" were sold commercially for asthma treatment until just before the middle of the 20th century. In the *Lancet* in 1910, dramatic positively responses to adrenaline injections were described and approximately in 1947 it was described in the bibliography that epinephrine could be given by inhalation to relieve asthmatic bronchoconstriction. An early nebulizer was marketed at that time. By the mid-1950s, metered-dose inhalers appeared, and they were devised for the delivery of epinephrine and isoproterenol, a relatively specific β-adrenergic agonist.

The Global Initiative for Asthma (GINA)

When looking back into the history of the disease, one essential dichotomous timepoint is the before and after era of the Global Initiative for Asthma. GINA was established approximately 30 years ago, in 1993, by the National Heart, Lung and Blood Institute and the World Health Organization (WHO) in an attempt to reduce asthma prevalence, morbidity and mortality. Since 2001, in order to raise awareness for asthma in the society and educate patients, families and healthcare professionals about effective asthma care, World Asthma Day has been organised annually. The first GINA Strategy Report, Global Strategy for Asthma Management and Prevention, was published in 1995 but it was in 2002 that the guide started being updated annually by the GINA Science Committee.

The ERS/ ATS Task Force

The European Respiratory Society (ERS) was founded in 1990 in the field of respiratory medicine. It is a non-profit organization with the goal to "promote lung health in order to alleviate suffering from disease and drive standards for respiratory medicine globally". The American Thoracic Society (ATS), also a non-profit organization, was established in 1905 and it was previously named American Sanatorium Association or later known as American Trudeau Society but changed its name to the modern version in 1960. The ATS focuses on improving care for pulmonary diseases. The two organizations have repeatedly joined their forces with the aim to produce official guidelines, statements and technical standards on the field of asthma.

Definition of asthma

It is widely agreed that defining asthma has been a challenge despite the fact that it was recognised as a troublesome condition that needed to be treated since the ancient years. There are obvious limitations when trying to accurately define such a heterogeneous disease, with a not yet completely understood underlying mechanism.

> Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow limitation. (GINA, 2024)

The above-mentioned definition was reached by consensus. The characteristics that are typical of asthma before initiating treatment with inhaled corticosteroids (ICS) and that distinguish asthma from other respiratory conditions are taken into consideration, although it is widely accepted that airflow limitation can become persistent even in asthma, and therefore this definition is not completely accurate.

Genetic Predisposition

Asthma often runs in families, indicating a genetic component to the disease. Children with parents who have asthma or other allergic conditions are at a higher risk of developing asthma. Research has identified several genes associated with the immune response and inflammation that may contribute to asthma development.(3)

Phenotypes of asthma

The more we learn about asthma based on research advances through the years the less we rely upon the description of the phenotypes that we have been using as clinicians in the past 3 decades(4-6). Clinical characteristics of the disease or etiologic factors have been used in an attempt to classify the different types of asthma.

The terms mild-moderate-severe asthma have been revised plenty of times and it is still difficult to set boundaries between the terms and fully define them.

It is far more comprehensive to understand the terms allergic or non-allergic asthma, deriving from the state in which asthma is partially or mainly triggered by allergens. However, even in this case such a phenotype becomes rather complicated on whether we can prove or not an IgE-mediated reaction. Infectious asthma or aspirin-exacerbated asthma are terms that are also easy to comprehend, however nowadays far less patients receive such diagnoses. Infections can interfere with any kind of asthma and especially in untreated asthma this is a common phenomenon. It is far more common nowadays to set a diagnosis for acetylsalicylic acid (ASA) or nonsteroidal anti-inflammatory drugs (NSAID) hypersensitivity and expect even symptoms from the lower airways in case a patient is exposed to these substances instead of calling this entity for aspirin-induced asthma.

Previously, in an attempt to categorise asthma, mostly in children, the terms intermittent and persistent were widely utilised. As intermittent it was frequently referred the kind of seasonal asthma, mostly during pollen season, and as persistent the version of asthma that existed all year round.

According to some authors, asthma debuting in childhood and persisting through adulthood should be a distinguished entity from asthma starting in adulthood(7). However, from a clinician's point of view, it is rather difficult to always rely on the clinical history regarding the onset of asthma as reported by the patients if no medical records are available. A significant number of asthma patients will claim that they never had a diagnosis of asthma during childhood but when penetrating the medical history, it is quite common to discover that the patient was suffering from frequent infections that were lasting longer than expected and severe coughing occurred during these periods or that they were prescribed as children's inhalers to use as-needed alongside with exercise. Difficulties to diagnose or reluctance to treat asthma with ICS during childhood may have resulted into a grey zone from childhood into adulthood making it harder to define a clear onset point.

More recent attempts to subdivide asthma in different phenotypes (8) have an approach based on phenotypes a) associated with environmental exposures (cigarette smoke, air pollution, etc), b) associated with specific symptoms or clinical characteristics (cough variant asthma, obesity, etc)(9), and c) associated with biomarkers. This last approach, the phenotypes based on biomarkers, is considered

to be promising and more relevant into identifying underlying mechanisms so that the phenotyping will be better targeted when selecting appropriate treatment and the disease outcomes will be further improved.

Diagnosis of asthma

Medical History and Physical Examination

The diagnosis of asthma begins with a thorough medical history and physical examination. Healthcare providers will ask about the patient's symptoms, their frequency and severity, and potential triggers. A family history of asthma or allergies is also relevant. During the physical examination, doctors will listen to the patient's breathing for signs of wheezing or other abnormal sounds.

Pulmonary Function Tests

Pulmonary function tests (PFTs) are essential for diagnosing asthma and assessing lung function. The most common PFTs include:

- **Spirometry:** Key parameters include Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1). A reduced FEV1/FVC ratio suggests obstructive airway disease.
- **Peak Expiratory Flow (PEF):** Measures the highest speed at which air can be expelled from the lungs. Variability in PEF readings can indicate asthma.
- **Bronchoprovocation Test:** Involves inhaling a substance that cause a bronchial constriction in the airways, followed by spirometry, or even oscillometry when available, to assess airway hyper responsiveness(10). There are several provocation challenges, direct or indirect. Metacholine or mannitol provocations are widely used in clinical practice nowadays as well as specific allergen or histamine provocations, mainly in studies. In addition, other less common technics consisting of eucapnic voluntary hyperventilation or cold-air provocations should be mentioned and are sometimes used as surrogates for exercise challenge.

Variable expiratory airflow limitation

To well-establish a diagnosis of asthma, besides a history of typical respiratory symptoms, a variable expiratory airflow limitation has to be confirmed. The spirometry should be preferred according to the guidelines (11) but other methods are considered to be sufficient in case there is no access to spirometry or if the

spirometry despite all efforts cannot verify the clinical suspicion. In the first case, Peak Expiratory Flow (PEF) can be assessed or in the second case a bronchial challenge test should be used. The variability is better evaluated before the initiation of treatment with ICS. Although in some diffuse cases, the evaluation is performed before and after initiation of ICS-treatment. It is suggested that the evaluation should be performed after 4 weeks of treatment but quite often this is a very short period, especially in patients that have never before used an inhaler, both due to compliance and correct technique. It is still unclear what the best method to diagnose an obstruction in the small airways with significant expiratory airflow limitation variability would be.

The sufficient difference in order to confirm a variability in expiratory airflow limitation is summarised below:

1.Positive bronchodilator (BD) responsiveness (reversibility) test with spirometry

Increase from baseline in FEV1 or FVC of ≥ 12% and ≥ 200 ml

2.Positive bronchodilator (BD) responsiveness (reversibility) test with PEF

Increase in PEF ≥ 20%

3.Excessive variability in twice-daily PEF over 2 weeks:

Average daily diurnal PEF variability > 10%

4.Increase in lung function after 4 weeks of treatment

Increase from baseline in FEV1 by ≥ 12% and ≥ 200 ml (or PEF by ≥ 20%) after 4 weeks of daily ICS-containing treatment.

5.Positive bronchial challenge test

Fall from baseline in FEV1 ≥ 20% with standard doses of methacholine or ≥ 15% with mannitol challenge.

Treatment of asthma

Medications for asthma are categorized into long-term control medications and quick-relief medications.

Long-Term Control Medications

These are taken daily to maintain control of chronic symptoms and prevent exacerbations. They include:

- **Inhaled Corticosteroids (ICS)**: The most effective long-term control medication, reducing inflammation and preventing symptoms.

- **Long-Acting Beta-Agonists (LABAs)**: Bronchodilators that help keep airways open, often used in combination with inhaled corticosteroids.
- **Long-Acting Muscarinic Antagonists (LAMAs):** Bronchodilators that reduce mucus production and help open the airways (anticholinergics).
- **Leukotriene Modifiers**: Oral medications that block the action of leukotrienes, inflammatory molecules involved in asthma.
- **Biologics**: Injectable medications targeting specific pathways in the immune system, used for severe asthma not controlled by other treatments.

Quick-Relief Medications

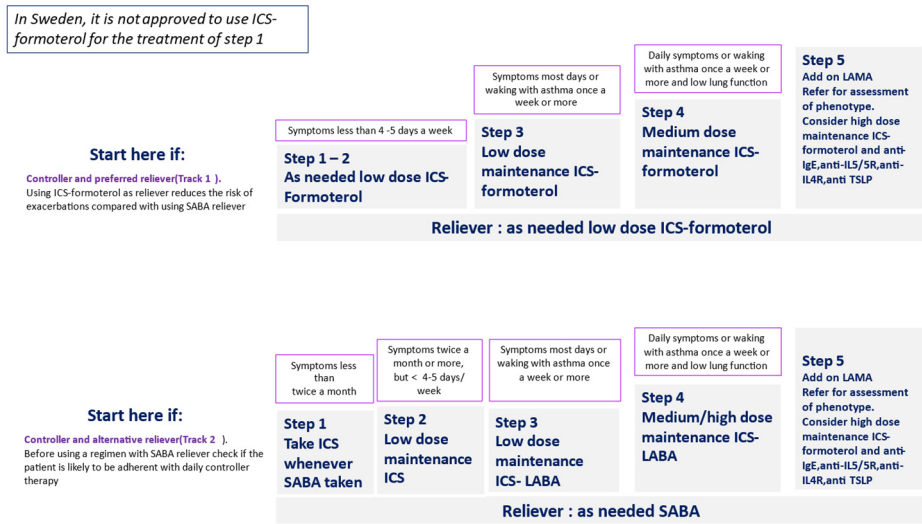
Used to relieve acute symptoms and prevent attacks. They include:

- **Short-Acting Beta-Agonists (SABAs)**: Bronchodilators that provide rapid relief of symptoms by relaxing the muscles around the airways.
- **Oral Corticosteroids**: Used for short-term treatment of severe exacerbations to reduce inflammation quickly.

Treatment recommendations according to GINA (2024)

According to the revised recommendations on treatment, there are very significant differences on how asthma treatment should be approached. There is no longer the recommendation of SABA alone as a treatment. The treatment of choice, for all adults and adolescents, even in mild asthma is from the very beginning an ICS-containing controller treatment. This should be delivered either daily as a regular treatment or as needed. There are two treatment tracks based on choice of reliever:

- Track 1 Low dose ICS-formoterol
- Track 2 SABA (alternative if track 1 is not feasible)



Classification of asthma according to severity

The ATS/ERS Task Force recommends assessing asthma severity retrospectively based on how difficult the patient's asthma is to treat and on the level of treatment required to achieve control on symptoms and exacerbations.(12-14). This practically means that at the time of diagnosis, it is impossible to label the severity of the disease. Therapy has to be initiated and after reaching a stable state of controlled disease, the severity can be first assessed based on the number of medications that were necessary to reach and maintain this stable state.

- **Mild asthma** is asthma that is well-controlled with *low-intensity treatment*. As low intensity treatment is considered low-dose ICS-formoterol or low-dose ICS plus as-needed SABA.
- **Moderate asthma** is asthma that is well-controlled with daily low or medium dose ICS-LABA
- **Severe asthma** is asthma that remains uncontrolled despite optimized treatment with daily high dose of ICS-LABA or asthma that requires daily high dose of ICS-LABA to prevent it from becoming uncontrolled(15).

Mild asthma= a retrospective label

Classification of asthma according to GINA steps (2024)

Different treatment strategies exist worldwide, and approaches may differ not only on international or national level but even on a regional one. The GINA guidelines of treatment, presented on the image above and nowadays consisting of 2 different tracks, and the retrospective classification of asthma according to these guidelines can be summarised into the following, according to the so-called treatment step:

- Step 1-2 = mild asthma when well controlled
- Step 3-4 = moderate asthma when well controlled
- Step 4 (Track 2) -Step 5 (Track 1+2) = severe asthma

Uncontrolled-Difficult to treat- Severe asthma

When referring to asthma as **uncontrolled**, according to GINA report of 2023 "Difficult-to-treat & Severe Asthma", one or both of the following is included:

- Poor symptom control (meaning frequent symptoms or frequent need for reliever use, activity limited by asthma, night waking due to asthma)
- Frequent exacerbations requiring OCS (≥ 2/ year) or serious exacerbations requiring hospitalization (≥ 1/year)

The term uncontrolled asthma may include various sub-categories within a range from mild asthma that is not properly treated up until asthma that cannot be controlled despite significant efforts to treat it.

Difficult-to-treat asthma is a term for asthma that remains uncontrolled despite medium- to high-doses of ICS plus a second controller (usually LABA) or with maintenance OCS, or asthma that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations. Due to a number of modifiable factors, such as comorbidities, smoking, poor adherence or incorrect inhaler technique, there may be the impression that asthma is difficult-to-treat.

Severe asthma is a category of difficult-to-treat asthma and by definition closer to an uncontrolled state. Severe asthma is uncontrolled despite adherence with maximal optimised high-dose ICS-LABA combination and management of contributing factors or worsens when high-dose treatment is decreased.

Severe asthma= a retrospective label

Perception of asthma severity from a patient's point of view

Patient reported outcomes are essential when it comes to evaluation of symptoms and quality of life in asthmatics(16).A situation, that often occurs due to a subjective point of view as well as a lack of awareness for the disease, is when patients themselves underestimate the asthma severity. Patients often perceive their asthma as mild if they have symptoms that are easily relieved by SABA or symptoms that are not frequent(12, 13). Even when it comes to severe asthma, there is still a challenge in understanding how the patients are perceiving their condition and the limitation derived from it. (17, 18)

Perception of asthma severity in epidemiological studies and clinical trials

There is a tendency to classify asthma as mild-moderate-severe based on the prescribed treatment by GINA, regardless of factors such as symptoms, compliance or exacerbations. It is important to take into consideration when interpreting the results since the assumption is in this case that the treatment is sufficient for the patients' needs.

Goals of asthma management according to GINA (2024)

On a population level, the goals focus on preventing deaths from asthma and minimizing the burden of asthma on individuals(19), families, communities, healthcare systems as well as the environment. On an individual level, the goals are focusing on achieving the patient's best possible long-term outcomes. In order to make these goals more concrete, GINA report focuses on long-term asthma symptom control and asthma risk minimization. As asthma symptom control is suggested a state of few/no symptoms, no sleep disturbances and unimpaired physical activity(20). As risk minimization it is described a state in which there are no side effects due to medication, no requirements for maintenance OCS, no exacerbations and improved or stable for the individual best lung function(21-23).

Regarding the asthma risk minimization, it is easier to quantify whether the goal is reached since it is easier to measure whether a patient is suffering from exacerbations or not, whether there is a need for maintenance OCS or if the individual is suffering from the well-known side effects of the asthma medication.

There is though a remaining difficulty in defining the best lung function for the individual based upon the methods of choice, that are available and reasonably advanced, to measure the lung function.

However, with regards to symptom control, there is a greater obstacle in quantifying whether the goal is achieved. Are we completely aware of the range of asthma symptoms as health care professionals and what are the tools that we are applying in order to identify the symptoms? Are the patients completely aware of their range of symptoms and therefore the severity? Or is it because asthma is a chronic disease, that the patients experiencing limitations from it, are prone to adjust their lifestyles and lack the ability to define what unimpaired physical activity involves for the individual since they cannot directly compare themselves to their healthy version?

It is emphasized in the latest GINA Strategy Report that the assessment of symptoms should not be limited to the past 4 weeks, as suggested by the most used tool to evaluate asthma control, the Asthma Control Test.

III. Allergic rhinitis due to pollen

Pollen allergies, also known as allergic rhinitis or hay fever, are a widespread condition affecting millions of people worldwide(24). Pollen allergy, that affects both the upper and lower airways, is often debilitating and has a complicated impact on the human body. Even though there are multiple causes to airborne allergies, such as exposure to house dust mite, pets and on extreme situations even food allergens, this thesis will only focus on pollen allergy. This kind of allergy occurs when the immune system overreacts to pollen grains from trees, grasses, and weeds, leading to various symptoms that can significantly impact the quality of life. Understanding the causes, symptoms, diagnosis, and treatment options is essential for managing this condition effectively. By adopting avoidance strategies, using appropriate medications, and considering advanced treatments like immunotherapy, individuals with pollen allergies can significantly reduce their symptoms and improve their quality of life.

Ongoing research and public health initiatives are crucial for addressing the growing prevalence of pollen allergies and their impact on society. Through continued efforts, we can better understand and manage pollen allergies, ultimately enhancing the well-being of those affected.

What is Pollen?

Pollen is a seed meal produced by plants during their reproductive cycle. It is carried by the wind, insects, or other animals from one plant to another, enabling fertilization. The types of pollen that most commonly cause allergic reactions are from trees, grasses, and weeds. Each type of plant has its own pollen season, which can vary by geographic location and climate.

History

A paediatrician from Vienna, named Clemens von Pirquet, introduced the term allergy when he noticed that patients reacted faster and more severe when injected with either horse serum or smallpox vaccine for the second time. He was inspired by the ancient Greek word allos meaning “other” and ergon meaning “work”.

ἄλλος + ἔργον

Symptoms however that could be attributed to allergy are mentioned in ancient sources and it is suspected that 3 members of the Roman Julio-Claudian dynasty had a family history of atopy. Up until the four types of hypersensitivity, type I to type IV, were described by Gell and Coombs in 1963 there was a tendency to classify all hypersensitivities as allergies. After 1963, the word allergy was classified as a type I hypersensitivity.

A few years later, the immunoglobulin E was discovered in 1966-67 simultaneously by two independent groups. The Ishizaka team in Denver, USA, and Johansson and Bennich in Uppsala, Sweden. These two groups published a joined paper in 1969. This was a key in understanding the mechanisms of allergy that was now classified as type I hypersensitivity, characterized by rapidly developing reactions involving IgE antibodies.

Long before that, already in 1911, two British physicians, Noon and Freeman, were the first researchers to test pollen allergen immunotherapy and publish their findings in the *Lancet.* In the 1930s allergen immunotherapy for hay fever was part of mainstream medical practice.

Defining a pollen season

When conducting research into the pollen allergy field, there is one severe obstacle that needs to be overcome, that randomly changes its characteristics in severity and duration from year to year, the pollen season. To begin with, there are difficulties in defining a pollen season. Two different methods have gained interest and been suggested as tools to help in the definition of the season throughout the recent years. The first one is based on defining a percentage of the annual or seasonal pollen index as start and end day. The second consists of defining a certain threshold, meaning a certain daily pollen concentration with or without a certain sum over a defined period, as start and end day.(25)

Defining pollen exposure times

Defining the pollen season is not the solemn challenge when conducting studies within this field. Pollen exposure times need to be defined in order to be able to objectify the results as much as possible, especially in clinical trials(26). An EAACI position paper published in 2017 has suggested specific definitions on the terms "pollen season", "peak pollen period" and "high pollen days" for different pollen types.

According to this paper, the **grass pollen season start day** is defined as the 1st of 5 days (out of 7 consecutive days), each of these 5 days with ≥3 pollen/m^3 and with a sum of these 5 days of ≥30 pollen/m^3 and the **end day** of the season as the last day of series of 5 days (out of 7 consecutive days) with ≥3 pollen/m^3 and with a sum of these 5 days of ≥30 pollen/m^3.

Peak pollen period start for the grass is defined as the 1st day of 3 consecutive days, each with at least ≥50 pollen/m^3 and end of the peak pollen period is defined as the last day of at least 3 consecutive days, each with ≥50 pollen/m^3.

As **high pollen days** are considered the day(s) with at least 50 pollen/m^3. (26)

The validity of the above definitions remains to be tested in future studies.

Pollen season in Sweden

The Palynological Laboratory, Swedish museum of Natural History, Stockholm, Sweden performs analyses daily during the pollen season every year, providing reports and forecasts that can be followed through the site www.pollerapporten.se.

According to the reports from the Palynological Laboratory, the definition of the levels of pollen varies from low to very high. In specific for the grass pollen, levels

from 1-10 pollen/m^3 are considered low, 11-30 as moderate, 31-80 as high and >80 as very high.

Symptoms of allergic rhinitis due to pollen

"More than just a stuffy nose"

Several studies have been focusing on understanding the symptoms caused by pollen allergy, both physical and mental.

The physical symptoms of pollen allergies can range from mild to severe and typically include:

- Sneezing: A frequent and often uncontrollable reaction to pollen inhalation.
- Runny or Stuffy Nose: Nasal congestion and discharge are common symptoms.
- Itchy Eyes, Nose, and Throat: Itching can be intense and persistent, leading to discomfort.
- Watery Eyes: Increased tear production is a common response to allergens.
- Postnasal Drip: Excess mucus can lead to a sensation of mucus dripping down the throat.
- Coughing: Irritation from postnasal drip or throat itching can cause a persistent cough.

Allergic rhinitis and its impact on asthma has also been studied thoroughly(27, 28). The concept of the united airways is widely known, meaning that the nose and the lungs are linked and that allergic rhinitis and asthma are both manifestations of a single inflammatory process(29).

Allergic rhinitis is believed to have a more complicated phenotype, beyond the symptoms from the nose and eyes, affecting mental functions possibly on the same extend as physical ones(30, 31). It has been a common complain among patients suffering from allergic rhinitis that during the season they experience difficulties to concentrate(32) and several studies have been focusing on school performance during the pollen season(33).

Diagnosis of allergic rhinitis due to pollen

Medical History

Diagnosis typically begins with a detailed medical history. The healthcare provider will inquire about the patient's symptoms, their frequency and duration, and any potential triggers.

Physical Examination

Even though it is thought that the healthcare provider will also perform a physical examination, focusing on the nose, eyes, throat, and lungs this is not always the case. Mostly due to practical reasons, it is not uncommon that the patients who are referred to a specialist unit treating allergies are meeting a physician outside the pollen season and thus they have no symptoms at that moment. Furthermore, a physical examination would be of value in case of nasal polyposis that could interfere with the symptoms during the season. However, rhinoscopy is not always available and in clinical practice it is not considered to be necessary to perform this examination in every patient that is diagnosed with allergic rhinitis, except from severe cases that do not respond to medications.

Allergy Testing

To confirm the diagnosis and identify sensitisation to specific allergens, allergy testing may be conducted through:

Skin Prick Test: Small amounts of various allergens are introduced into the skin using a tiny needle. A raised bump or reaction indicates an allergy to that specific substance.

Blood Test: Blood tests measure the level of specific IgE antibodies to different allergens in the bloodstream.

Treatment of pollen allergic rhinitis

Avoidance Strategies

Avoiding exposure to pollen is a hard-to-follow method, restricting severely the outdoor activities of the patients and having questionable results with regards to how quality of life is affected when trying to avoid pollen on the highest possible level. Examples of what most strategies include are listed below:

- **Stay Indoors During Peak Pollen Times:** Pollen counts are usually highest in the early morning and on windy days.
- **Keep Windows Closed:** Using air conditioning with a HEPA filter can help reduce indoor pollen levels.
- **Shower and Change Clothes:** After spending time outdoors, shower and change clothes to remove pollen.
- **Use Pollen Masks:** Wearing a mask designed to filter pollen can help reduce inhalation of allergens during outdoor activities.

Medications

Various medications can help manage pollen allergy symptoms:

- **Antihistamines:** These medications block histamine receptors, reducing sneezing, itching, and runny nose. They are available over-the-counter and by prescription in forms such as tablets, liquids, and nasal sprays.
- **Nasal Corticosteroids**: These prescription nasal sprays reduce inflammation in the nasal passages and are highly effective in controlling symptoms.
- **Eye Drops**: Antihistamine or natrium cromoglycate eye drops can relieve itchy, watery eyes.

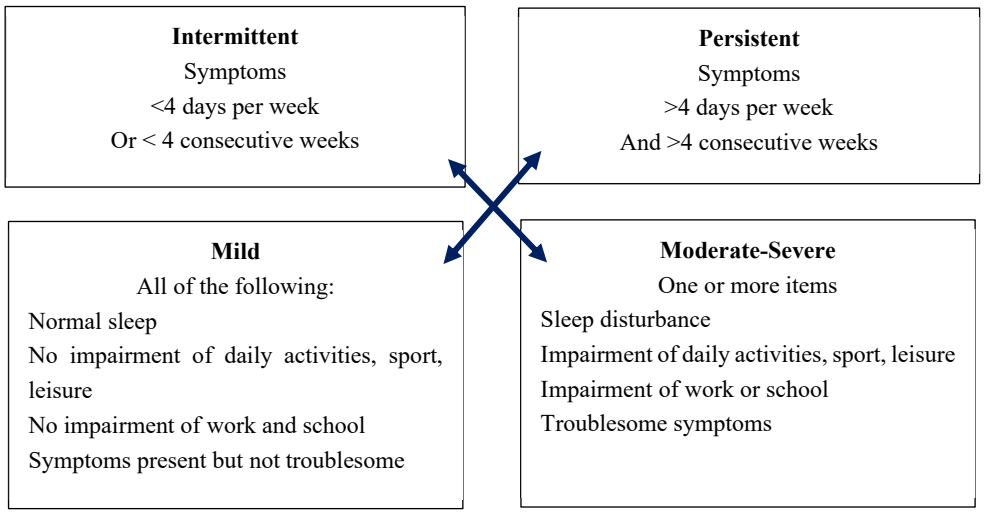
Immunotherapy

For individuals with severe allergies or those who do not respond well to medications, immunotherapy may be recommended:

- **Subcutaneous Immunotherapy (SCIT):** Regular injections of gradually increasing amounts of the allergen can desensitize the immune system over time.
- **Sublingual Immunotherapy (SLIT):** Allergen tablets or drops are placed under the tongue and absorbed. This method is less invasive than injections and can be done at home.

ARIA

ARIA (Allergic Rhinitis and its Impact on Asthma) is a non-governmental organization which collaborates with the World Health Organization (WHO) through the Global Alliance Against Chronic Respiratory Diseases (GARD). It is an integrated part of EUFOREA. According to ARIA guidelines on rhinitis(27), the grade of severity can be briefly assessed as, intermittent or persistent causing mild or moderate to severe symptoms.



IV. COPD

Another obstructive lung disease, that should be mentioned since it has served in this project as a condition being compared to asthma, is Chronic Obstructive Pulmonary Disease (COPD). COPD is a progressive respiratory condition characterized by persistent airflow limitation and chronic respiratory symptoms. COPD primarily includes two conditions: chronic bronchitis and emphysema. It is a major cause of morbidity and mortality worldwide, significantly impacting patients' quality of life. Smoking is the leading cause of COPD. Approximately 85-90% of COPD cases are directly attributed to cigarette smoking. The harmful chemicals in tobacco smoke damage the airways and alveoli, leading to inflammation, airway obstruction, and destruction of lung tissue(34, 35).

Initial symptoms on a mild stage may resemble asthma and it can be occasionally difficult to diagnose. During the past decades, there has been a term suggesting an overlap of these two obstructive lung diseases, named ACOS (Asthma-COPD-

overlap syndrome)(36-39). Several studies have been focusing on healthy smokers in an attempt to detect early changes that could be a precursor of COPD(38, 40).

Symptoms in COPD mainly consist of cough, usually productive, and dyspnoea. The disease is diagnosed with spirometry when in general a ratio of FEV1/FVC < 0.70 is present alongside with smoking history and typical symptoms(41). The GOLD classification based on symptoms assessed by the COPD assessment test (CAT) and exacerbations has been recently and repeatedly revised, suggesting that the initial pharmacological treatment should be guided by algorithms(42, 43). According to the 2024 GOLD report, the treatment strategies are different based on which group (A, B or E) each and every patient belongs to, starting from either short- or long- acting bronchodilators as needed or daily, adding up to long-acting muscarinic antagonists (LAMA) or even inhaled corticosteroids (ICS)(44).

V. Pulmonary function tests interpretation

A significant part, with regards to symptoms and quality of life of asthmatics, that is often taken for granted and therefore can affect the outcomes on a more subtle direction is the interpretation of the pulmonary function tests. Tests assessing the lung function, such as spirometry, diffusing capacity and lung volumes, have been used over several decades to diagnose lung diseases as well as monitor disease progression and treatment response. Standardisation of the pulmonary function tests has been revised thoroughly and several technical documents have been published (45-48).

Interpretation of the results, however, should take into account factors that create uncertainty(49-51). For example, how representative are the obtained results at the time of testing. Besides the quality of the individual's effort during the testing, it should be taken into consideration if the test was performed during a period with troublesome symptoms, especially in patients with seasonal worsening of the disease. The appropriate threshold for each individual, in order to classify the observed values as within/outside the normal range, should be considered alongside with the probability of disease based on the clinical suspicion. Reference populations should always be taken into consideration, but it is still a question on whether they are valid for each and every individual. (49)

Another important question is to which extent the available pulmonary function tests can capture all possible phenotypes of the disease and whether some phenotypes exist and cause troublesome symptoms despite normal pulmonary function tests results(52-54).

VI. Central vs peripheral airways

Asthma and Chronic Obstructive Pulmonary Disease (COPD) have two prevalent respiratory conditions characterized by airflow obstruction. Understanding the differences in central and peripheral airway resistance in these diseases is crucial for diagnosis, management, and treatment(55-61) .

The Peripheral Airways: Importance and Challenges in Detection

The peripheral airways, often referred to as the "silent zone" of the lungs, consist of the smallest bronchi and bronchioles with diameters less than 2 mm. These airways account for a significant portion of the lung's surface area and play a crucial role in gas exchange. Despite their importance, these airways are often overlooked in standard pulmonary function tests, including spirometry, because early pathological changes in the peripheral airways might not significantly affect the spirometric indices like FEV1 or FVC.

Pathophysiology of Peripheral Airway Diseases

Peripheral airway diseases, such as small airway disease (SAD), are characterized by inflammation, obstruction, or narrowing of the small airways. These changes can occur due to various factors, including chronic inflammation (as seen in asthma and COPD), exposure to toxins, smoking, or occupational hazards.

In the early stages of peripheral airway diseases, these changes may not be detected by spirometry because the larger airways continue to function relatively normally, maintaining overall lung volumes and flow rates. However, as the disease progresses, the small airway dysfunction can contribute to airflow limitation, hyperinflation, and gas exchange abnormalities, eventually leading to symptoms like dyspnoea (shortness of breath), wheezing, and chronic cough.

Advances in Assessing Peripheral Airways

Several methods have been developed to assess the peripheral airways more accurately(62, 63):

1. **Forced Oscillation Technique (FOT):** FOT measures the impedance of the respiratory system by applying external oscillations during breathing. It is a non-invasive method that can detect early changes in the small airways, providing valuable information about peripheral airway function. Impulse oscillometry system (IOS), delivering pulses in a frequency range of 5-35

Hz has been used in several studies to evaluate the obstruction in the peripheral airways.

2. **Multiple-Breath Nitrogen Washout (MBNW):** This technique measures the distribution of ventilation in the lungs. It is sensitive to ventilation heterogeneity in the small airways and can detect early dysfunction before spirometry shows abnormalities.
3. **Computed Tomography (CT) Scanning:** High-resolution CT scans can visualize the airways directly and detect structural changes in the peripheral airways, such as wall thickening, air trapping, and small airway narrowing.
4. **Exhaled Nitric Oxide (FeNO):** FeNO or exhaled nitric oxide is a marker that can determine inflammation in the lung associated with asthma. While not a direct measure of airway function, it provides complementary information about airway inflammation. It simply measures the levels of nitric oxide in the breath. FeNO originates primarily in the bronchial epithelium and is produced in large quantities by the enzyme inducible nitric oxide synthase (iNOS). The sensitivity of FeNO measurement for diagnosing asthma is 35% at the cut-off >50 ppb, and specificity is 95%. If the clinical symptoms 'allergic rhinitis' and 'wheezing' are present, the positive predictive value of FeNO >33 ppb is at least 70% (validation of the diagnostic algorithm10). A FeNO of 25-50 ppb in adults (20-35 ppb in children) is considered an intermediate range. Numbers in this range should be matched with the medical history and testing. FeNO numbers of over 50 ppb in adults (over 35 ppb in children) are considered high and indicate airway inflammation. Measurement of exhaled nitric oxide levels using different flow rates can indicate inflammation in the peripheral airways, in asthma, in an indirect way when estimating the bronchial and alveolar NO, separately.

Central Airway Resistance

Central airway resistance refers to the opposition to airflow in the larger airways, including the trachea and main bronchi. These airways have a larger diameter and contribute significantly to the total airway resistance, especially during high airflow rates such as forced expiration.

Peripheral Airway Resistance

Peripheral airway resistance involves the smaller airways, typically those with a diameter of less than 2 mm, including the bronchioles and smaller bronchi. These airways contribute to a substantial portion of total airway resistance, particularly during quiet breathing and at lower flow rates.

Central Airway Resistance in Asthma

- **Increased Resistance:** In asthma, central airway resistance increases due to bronchoconstriction and mucus plugging. During an asthma attack, the larger airways constrict, significantly increasing resistance and leading to symptoms like wheezing and shortness of breath**.**
- **Reversibility:** One hallmark of asthma is the reversibility of airflow obstruction. Bronchodilator therapy can effectively reduce central airway resistance, leading to rapid improvement in symptoms**.**

Central Airway Resistance in COPD

- **Moderate Increase:** Central airway resistance in COPD is moderately increased due to chronic bronchitis, which involves inflammation and thickening of the larger airways, as well as mucus hypersecretion**.**
- **Less Reversible:** Unlike asthma, the increase in central airway resistance in COPD is less reversible. Bronchodilators can provide some relief, but the structural changes in the airways limit the extent of reversibility**.**

Peripheral Airway Resistance in Asthma

- **Subclinical Involvement:** Peripheral airways are often involved in asthma, even in the absence of the most common symptoms. Inflammation and remodelling in these smaller airways contribute to increased resistance and can be detected using techniques like the Forced Oscillation Technique (FOT) or impulse oscillometry.
- **Persistent Changes:** In some patients, peripheral airway resistance remains elevated despite treatment, contributing to persistent symptoms and decreased lung function.

Peripheral Airway Resistance in COPD

- **Significant Contribution:** Peripheral airway resistance is markedly elevated in COPD, primarily due to emphysema. Destruction of alveolar walls leads to loss of elastic recoil, airway collapse, and significant narrowing of the smaller airways.

- **Dynamic Hyperinflation:** Peripheral airway obstruction in COPD results in dynamic hyperinflation, where air trapping occurs, especially during exertion. This leads to increased lung volumes, dyspnoea, and reduced exercise capacity.
- **Persistent Inflammation:** Chronic inflammation in the peripheral airways contributes to ongoing remodelling and fibrosis, further increasing resistance and reducing airflow.

In Asthma, identifying and differentiating central and peripheral airway resistance can aid in the diagnosis of asthma and help tailor treatment. For instance, measuring peripheral resistance can detect early changes that are not apparent with traditional spirometry. In COPD, distinguishing between central and peripheral resistance helps in understanding the extent of disease progression and the predominant underlying pathology (e.g., chronic bronchitis vs. emphysema). This can guide treatment decisions and management strategies.

VII. The burden of allergy and asthma

The World Health Organisation (WHO) reports that asthma affected 262 million people in 2019 and caused 455 000 deaths(64, 65). In Sweden, the average annual costs in were estimated at SEK 15919 per subject with asthma in the ages between 25 and 56 years, resulting into a total cost for society at approximately 3.7 billion SEK for this age range(66). The costs per subject with severe asthma were significantly higher estimated at an amount of SEK 74 000(67).

Approximately 100 million people in Europe suffered from allergic rhinitis in 2015(68, 69). The estimated avoidable indirect costs for insufficiently treated allergy in the EU ranged between 55 billion and 151 billion euro per annum. If patients were treated appropriately with available cost-effective treatments, average savings of 142 billion euro per annum could be realised according to the European Academy of Allergy and Clinical Immunology, Advocacy Manifesto, 2015(24, 70).

VIII. Unsolved problems

Throughout this introduction, several issues have been analysed with regards to symptoms and quality of life in patients suffering from asthma or allergic rhinitis. From difficulties to define asthma or to evaluate symptom control up to difficulties of understanding the real burden of an apparently trivial condition, such as runny nose during the pollen season, the unsolved problems are challenging. On all the

previously mentioned factors, one very important should be added; the lack of specialist physicians in this field. The result is that the vast majority of this group of patients is going to be treated within the primary health care, with limited access to diagnostic tools and experience. Even though the GINA reports try to point out the significance of being referred to a specialist department when asthma is uncontrolled, practical issues make this task almost impossible. It is a great question to understand how many patients are suffering from uncontrolled asthma that is being unnoticed, since it is classified as controlled, both due to lack of resources in primary health care, but even due to lack of awareness among general practitioners. In Sweden, according to reports, many patients with severe asthma are not seen by specialists(71) and also patients can suffer from frequent exacerbations and still wait for several years before they are referred to specialist care(67, 72). Even though, advanced treatments such as biologicals for severe asthma and immunotherapy for pollen allergy are available, the access to such treatments is restricted(71, 73, 74).

Aims

The aim of this project was to study symptoms and quality of life in patients with asthma or allergy, meaning diseases affecting the airways. We aimed to highlight unsolved problems regarding the evaluation of disease burden in asthmatics and allergic patients. In an attempt to comply with the international guidelines about treatment and disease control goals, the clinicians face challenges starting from evaluating the disease burden, both with regards to symptoms and quality of life, in order to make decisions on when to start treating, what kind of treatment and to which degree. A struggle exists in defining a pre- and post- intervention evaluation of the disease burden with a number of available tools that seem to have severe limitations. We focused on both symptoms and quality of life, using standard validated questionnaires while introducing less commonly used techniques (CANTAB, in-depth interviews and Forced Oscillation Technique), examining different populations in order to investigate the problem from different aspects and thus acquiring an overall understanding of the existing limitations. We aimed specifically to:

-investigate objective methods in evaluating symptoms that are commonly mentioned from pollen allergic patients, other than the usual nasal symptoms, during the season such as cognitive dysfunction.

- explore customizable methods adjusted to the disease severity that are potentially more appropriate in order to evaluate the burden of the disease, in severe asthma, other than the questionnaires that are currently applied to every asthma patient regardless of the disease phenotype.

-assess advanced technical methods to evaluate the burden of the obstruction in the peripheral airways, other than spirometry that is currently the most common method to diagnose and evaluate disease control in asthma.

Methods

I. Study population and study design

Paper I

A total of 69 children and adolescents, 8-17 years old (mean age 12 years), were included. Children with grass pollen allergy (n=43) and age- and sex-matched non-allergic controls (n=26) were recruited consecutively in a paediatric clinic and a primary health care unit. During previously scheduled appointments, participants and their parents were informed about the study and asked whether they were interested to participate. The allergic group experienced troublesome symptoms during previous grass pollen seasons despite a combination treatment of non-sedative oral antihistamines and nasal steroids daily. All participants completed questionnaires, undertook cognitive tests and blood samples twice, once during the pollen season and once outside the season. The off-season visit was performed outside the pollen season, either before (March-April 2015) or after (November-December 2015).

Paper II

A total of 93 patients, 73 in Sweden and 20 in Denmark (mean age 48 years, 80% females) were included in the study. Adult patients with severe asthma, defined as treatment per GINA step 5 or having uncontrolled disease despite treatment in GINA step 4, were included. The study consisted of two parts: a quantitative web survey and a qualitative In-Depth Interview. The screening period and recruitment started on the 9th of April and was completed on the 27th of December 2019. Several sites were participating in the recruitment, both in Sweden and Denmark. Study participants were identified among those asthma patients that contacted the participating sites for health-related issues or by advertisement via the Swedish Asthma- and Allergy patient association. All participants responded to the Web survey. After the web survey they were able to indicate their interest in taking part in the in-depth interviews. The interviews were conducted over the phone by trained moderators employed at an independent Life Science research company with previous experience in this field. Each interview had an approximate duration of one hour, following a semi-structured interview guide.

Paper III+IV

Data for these studies were collected from the BREATHE cohort, a cross-sectional study of real-life patients with asthma and/or COPD in Denmark and Sweden. A total of 319 asthma patients were included in paper III. In paper IV, a total of 471 subjects were included (311 with asthma, 96 with COPD, 30 healthy smokers and 34 healthy never-smokers). The patients answered to questionnaires and underwent spirometry and Resmon Pro Full measurements. The Resmon Pro measurements were systematically performed before spirometry. All subjects were asked to refrain from short- and long-acting bronchodilators for >4 and >12 hours respectively, before the examination. The participants were enrolled from two sites in Skane, Sweden, the Research Unit for Respiratory Medicine and Allergology at Skane University Hospital and the Primary Health Care Centre, Näsets Läkargrupp, Höllviken.

II. Ethical considerations

All studies were performed according to the declaration of Helsinki. In Paper I, caregivers and children received both oral and written information about the studies and signed parental informed consents were obtained before inclusion. All children gave oral informed consent.

All studies were reviewed and approved by the Regional Ethical Review Board in Lund, with the following diary number for Paper I 2014/927, for Paper II 2018/1110, for Paper III+IV 2016/1069.

Paper II was also reviewed and assessed as out of scope for ethics approval by the Region South Ethics Committee in Denmark (project ID:S-20190029).

III. In-depth interviews

Each interview had an approximate duration of one hour, following a semi-structured interview guide with focus on domains/questions regarding patients' experiences of living with severe asthma and free-flowing responses. The interview guide was developed by input of clinicians with experience in the field. Interviews were recorded and transcribed by a transcription agency, using Express Scribe Transcription software. All interviews were conducted in the respondent's local language (Swedish, Danish) over the telephone. All interviews were conducted by qualified medical interviewers employed at an independent Life Science research company with previous experience from this field (Sweden: Assistant nurse, Denmark: qualified nurse). If patients' responses indicated need for psychological support, the moderators followed a predefined procedure.

IV. Questionnaires

Paper I

DISABKIDS

A generic health-related quality of life questionnaire that can be used in every chronic disease. It was developed by the European DISABKIDS group in 2002.It is divided into mental, social and physical sections. It is consisted of 12 questions and there are 5 possible answers to each (never, rarely, sometimes, often, always). A higher score reflects better quality of life. It was applied to estimate the quality of life and the level of distress during the past 4 weeks caused by allergy as a chronic disease.(75)

DISABKIDS
1. Känner du dig som alla andra trots ditt hälsotillstånd?
2. Kan du leva det liv du vill trots ditt hälsotillstånd?
3. Är ditt liv styrt av ditt hälsotillstånd?
4. Stör ditt hälsotillstånd dig när du leker eller håller på med andra aktiviteter?
5. Är du olycklig pga ditt hälsotillstånd?
6. Får ditt hälsotillstånd dig att känna dig nere?
7. Känner du dig ensam på grund av ditt hälsotillstånd?
8. Känner du dig annorlunda jämfört med andra barn/ ungdomar?
9. Tycker du att du kan göra det mesta lika bra som andra barn/ ungdomar?
10. Tycker dina kompisar om att umgås med dig?
11. Stör det dig att ta medicin?
12. Hatar du din medicin?

LILA

LILA is the Swedish version of PADQLQ (Paediatric Allergic Disease Quality of Life Questionnaire)(76, 77). It is a disease specific questionnaire for allergic children and adolescents to assess impact on quality of life during pollen season. The questionnaire can be divided into practical, physical, and emotional sections and a lower score reflects a better quality of life. It consists of 26 statements that the

participants are requested to choose how they are affected from. Scoring from 0-6 reflects a range between “not at all affected” and “very much affected”. Higher scores reflect worse quality of life. It evaluates quality of life during pollen season but not during a more defined period of time.

LILA
Hur mycket har du besvärats av följande på grund av din allergi, under pollensäsong?
1. Jag har inte kunnat koncentrera mig
2. Jag har inte kunnat komma ihåg saker jag har lärt mig i skolan
3. Jag har inte kunnat somna eller sova gott på natten
4. Jag har inte kunnat höra bra
5. Jag har inte klarat mig utan att ha med mig eller använda mina mediciner, inhalatorer eller salvor
6. Jag har hostat eller haft "pip" i bröstet, när jag har sprungit eller lekt
7. Jag har inte kunnat sporta utomhus
8. Jag har hostat på natten
9. Jag har hostat eller haft ”pip” i bröstet
10. Jag har känt mig andfådd eller haft svårt att andas/tryck över bröstet
11. Jag har behövt gnugga mina ögon
12. Jag har haft svullna ögon
13. Jag har haft klåda i näsan
14. Jag har haft täppt näsa
15. Jag har behövt gnugga näsan
16. Jag har behövt snyta mig
17. Jag har haft hudutslag
18. Jag har oroat mig över hur min hud ser ut
19. Jag har känt mig trött eller sliten
20. Jag har känt mig törstig
21. Jag har haft torr, kliande hals eller ont i halsen
22. Jag har haft huvudvärk
23. Jag har känt mig irriterad eller frustrerad
24. Jag har känt mig annorlunda än mina kamrater
25. Jag har varit rädd för att få ett 25 astmaanfall
26. Tänk nu de aktiviteter som du deltagit i under en vecka under pollensäsong. Hur mycket tycker du, att din allergi har påverkat dig när du utövat dessa aktiviteter?

VAS

The global visual analogue scale (VAS) was applied to estimate the perceived degree of symptoms of various organs (eyes, nose, lungs), the subjects’ general condition and cross-reactivity to oral and stomach symptoms.(78)

Paper II

ACT

The Asthma Control Test (ACT) is evaluating the control of the disease during the last 4 weeks. It consists of 5 questions, scoring from 1-5 for each question. A total of 25 indicates a well-controlled disease, a score between 20-24 indicates partially controlled disease and under 20 poorly controlled disease(79, 80). Scores under 16 indicate very poorly controlled asthma (81).

ACT
1. During the last 4 weeks, how much of the time has your asthma kept you from getting as much done at work, school or home?
2. During the last 4 weeks, how often have you had shortness of breath?
3. During the last 4 weeks, how often have your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) woken you up at night or earlier than usual in the morning?
4. During the last 4 weeks, how often have you used your rescue inhaler or nebuliser medication (such as Salbutamol)?
5. How would you rate your asthma control during the last 4 weeks?

SGRQ

The St. George's Respiratory Questionnaire (SGRQ) was designed to measure the impact of obstructive lung diseases on several areas including overall health, daily life and perceived well-being. It consists of 2 parts. In Part 1 there is a symptoms component (frequency & severity) and in Part 2 there are questions about activities that cause or are limited by breathlessness and questions about impact components (social functioning, psychological disturbances resulting from airways disease). Rather complicated scaling of the different items. The scores range from 0 to 100, with higher scores indicating more limitations.

SGRQ
Part I
Please describe how often your respiratory problems have affected you over the past 3 months (scale 0-5)
1. Over the past 3 months, I have coughed
2. Over the past 3 months, I have brough up phlegm (sputum)
3. Over the past 3 months, I have had shortness of breath
4. Over the past 3 months, I have had wheezing attacks
5. How many times during the past 3 months have you suffered from severe or very unpleasant respiratory attacks? (more than 3 times, 3 times, 2 times, 1 time, none of the time)
6. How long did the worst respiratory attack last? (a week or more, 3 or more days, 1 or 2 days, less than a day)
7. Over the past 3 months, in a typical week, how many good days (with few respiratory problems) have you had?
8. If you wheeze, is it worse when you get up in the morning? (yes or no)
Part II
Section 1
9. How would you describe your respiratory condition?
10. If you have ever held a job:
Section 2 (true-false)
11. What activities usually make you feel short of breath these days? (sitting or lying still, washing or dressing yourself, walking around the house, walking outside on level ground, walking up a flight of stairs, walking up hills, playing sports or other physical activities)
Section 3 (true-false)
12. Questiona about your cough and shortness of breath these days (coughing hearts, coughing makes me tired, I am short of beath when I walk, I am short of breath when I bend over, my coughing or breathing disturbs my sleep, I get exhausted easily)
Section 4 (true-false)
13. Questions about other effects that your respiratory problems may have on you these days (My cough or breathing is embarrassing in public, my respiratory problems are a nuisance to my family, friends or neighbours, I get afraid or panic when I cannot catch my breath, I feel that I am not in control of my respiratory problems, I do not expect my respiratory problems to get any better, I have become frail or an invalid because of my respiratory problems, exercise is not safe for me, everything seems too much of an effort)
Section 5 (true-false)
14. Questions about your respiratory treatment (My treatment does not help me very much, I get embarrassed using my medication in public, I have unpleasant side effects from my medication, my treatment interferes with my life a lot)
Section 6 (true-false)
15. Questions about how your activities might be affected by your respiratory problems (I take a lot time to get washed or dressed, I cannot take a bath or shower or I take a long time to do it, I walk slower than other people my age or I stop to rest, jobs such as household chores take a long time or I have to stop to rest, if I walk up a flight of stairs I have to go up slowly or I have to stop if I hurry or walk fast I have to stop or slow down, my breathing makes it difficult to do things such as walk up hills-carry things upstairs-light gardening such as weeding-dance-bowl-play golf), my breathing makes it difficult to do things such as carry heavy loads-dig in the garden-shovel snow-jog or walk briskly-play tennis-swim, my breathing makes it difficult to do things such as very heavy manual work-ride a bike-run-swim fast-play competitive sports)
Section 7 (true-false)

16. How your respiratory problems affect your daily life (I cannot play sports or do other physical activities, I cannot go out for entertainment or recreation, I cannot go out of the house to do the shopping, I cannot do household chores, I cannot move far from my bed or chair)
17. Please write in any other important activities that your respiratory problems may stop you from doing
18. Check the box (only one) that you think best describes how your respiratory problems affect you (it does not stop me from anything I would like to do, it stops me from doing 1 or 2 things I would like to do, it stops me from doing most of the things I would like to do, it stops me from doing everything I would like to do)

WPAI

The Work Productivity and Activity Impairment (WPAI) questionnaire is a well validated instrument to measure impairments in work and activities. The questionnaire is a 6-item instrument to measure impairments over the last 7 days in both paid work and unpaid work due to one's health.

WPAI
1. Are you currently employed (working for pay)?
2. During the past seven days, how many hours did you miss from work because of your health problems?
3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
4. During the past seven days, how many hours did you actually work?
5. During the past seven days, how much did your health problems affect your productivity while you were working
6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

Study-specific questionnaire (VOICE)

A study specific questionnaire was created for the purposes of these study in order to gather as much information as possible for the participants. The questions concerned mainly the treatment, contacts with physicians (planned or emergency), sick leaves, impact of asthma on choices about career, hobbies, residence.

Study-specific questionnaire (VOICE)
1. Which drugs are you currently taking for the management of your asthma?
2. Are oral steroids part of your asthma treatment?
3. Do you take oral steroids daily, or as needed based on your symptoms?
4. How often (approximately) do you take courses with oral steroids?
5. What type of physician is the main decision maker for your asthma treatment, i.e. who do you normally see for asthma related problems and who normally issues prescriptions of asthma drugs?
6.(Approximately) how often do you have contact with the health care due to your asthma, on average?
7. [Asked all having accounted for emergency visits:] Q What happened after the very latest acute physician visit that you made?
8. Have you ever been examined by a specialist (pulmonologist, allergist or similar) due to your asthma?
9, Whom do you perceive to take the greatest responsibility for your asthma treatment*, you yourself or your GP?
10. Has your asthma in any way had an impact on your choice of career?
11. Has your asthma in any way had an impact on where you've chosen to live?
12. Has your asthma in any way had an impact on your hobbies and how you spend your spare time?
13. During a normal year, how many times (approximately) do you need to take longer sick leaves, for more than 1-2 days, due to your asthma?
14. During a normal year, how many times (approximately) do you need to take shorter sick leaves, 1-2 days at a time, due to your asthma?

Papper III+IV

ACT

The ACT questionnaire was used also in Papper III+IV

ACQ

The Asthma Control Questionnaire (ACQ) is used to assess symptoms during the past week. It has a different version based on the total number of questions. Some of the questions resemble the ones in ACT but the answer options are differently formulated. The total score is the sum of the separate points from the questions (0-6 points) divided by the number of the questions. The 5 questions version of the ACQ was used (=ACQ-5) with a scoring from 0-6 where 6 is most symptoms (maximum number=30 and thereafter divided by the number of questions giving a maximum score of 6). An ACQ score <0.75 indicates well-controlled asthma and > 1,5 indicates poorly controlled asthma(82).

ACQ-5
I genomsnitt under den gånga veckan:
1. Hur ofta har du väckts på natten av din astma?
2. Hur svåra har dina astma symtom varit när du vaknat på morgonen?
3. Hur begränsad har du varit i dina aktiviteter pga din astma?
4. Hur mycket andfådd har du känt pga din astma?
5. Hur stor del av tiden har det pipit i bröstet?

Nijmegen

The Nijmegen questionnaire is used for the evaluation of patients with dysfunction breathing such as hyperventilation syndrome. A score ≥24 suggests a positive diagnosis of hyperventilation syndrome. For every item, in total 16, there is a rating from never= 0 points up to very often=4 points(83, 84), giving a total score that ranges from 0-64.

Nijmegen
1.-chest pain
2.-feeling tense
3.-blurred vision
4.-dizzy spells
5.-feeling confused
6.-faster/deeper breathing
7.-short of breath
8.-tight feelings in the chest
9.-bloated feeling in the stomach
10.-tingling fingers
11.-unable to breathe deeply
12.-stiff fingers or arms
13.-tight feelings around the mouth
14.-cold hands or feet
15.-palpitations
16.-feeling of anxiety

HADS

The Hospital Anxiety and Depression Scale (HADS) consists of 14 questions, half of them focus on anxiety and half of them on depression. HADS includes 14 questions scoring 0-3, where 3 is most anxiety/depression (maximum score=42). Scores >10 indicate high risk for either anxiety or depression that may be requiring

a physicians evaluation, 7-10 indicate mild to moderate problems with anxiety or depression from 0-6 indicate that there is probably no anxiety or depression(85).

HADS
Å Jag känner mig spänd och nervös
D Jag uppskattar fortfarande saker jag tidigare uppskattat
Å Jag har en känsla av att något hemskt kommer att hända
D Jag kan skratta och se det roliga i saker och ting
Å Jag bekymrar mig över saker
Å Jag bekymrar mig över saker
Å Jag kan sitta stilla och känna mig avslappnad
D Allting känns trögt
Å Jag känner mig orolig, som om jag hade fjärilar i magen
D Jag har tappat intresset för hur jag ser ut
Å Jag känner mig rastlös
D Jag ser med glädje fram emot saker och ting
Å Jag får plötsliga panikkänslor
D Jag kan uppskatta en god bok, ett TV- eller radioprogram

Snot22

Snot22
1. Need to blow nose
2. Sneezing
3. Runny nose
4. Cough
5. Postnasal discharge (dripping at the back of your nose)
6. Thick nasal discharge
7. Ear fullness
8. Dizziness
9. Ear pain/pressure
10. Facial pain/pressure
11. Difficulty falling asleep
12. Waking up at night
13. Lack of a good night's sleep
14. Waking up tired
15. Fatigue during the day
16. Reduced productivity
17. Reduced concentration
18. Frustrated/restless/irritable
19. Sad
20. Embarassed
21. Sense of taste/smell
22. Blockage/congestion of nose

The Sino-nasal Outcome Test (Snot22) consists of 22 questions, both about symptoms and social/emotional consequences due to nasal disorder, and the evaluation concerns the past 2 weeks. For every question there are 6 possible answers, scoring from 0-5, where 0=no problem and 5=problem as bad as it can be(86). Maximum score=110.

MiniAQLQ

The mini version of the Asthma Quality of Life Questionnaire consists of 15 questions in the same domains as the original AQLQ (symptoms, activities, emotions, environment). It can be answered in a shorter time than the AQLQ. Every item is assessed in a seven-point scale from one to seven. A higher value indicates better HRQL. The mean score is calculated by the total score/the number of items. The domain scores are calculated as the total score/the number of items for respective domain. The period being assessed is the past 2 weeks(87).

MiniAQLQ
I allmänhet, hur stor del av tiden under de senaste 2 veckorna har du:
1. Känt dig andfådd pga din astma
2. Känt dig besvärad eller varit tvungen att undvika damm i omgivningen
3. Känt dig frustrerad pga din astma
4. Känt dig besvärad av hosta
5. Känt dig rädd för att inte ha din astma medicin tillgänglig
6. Haft en åtstramande känsla eller tryck över bröstet
7. Känt dig besvärad av eller varit tvungen att undvika cigarettrök i omgivningen
8. Haft problem om att sova gott om natten pga din astma
9. Känt dig bekymrad över att du har astma
10. Har det pipit i bröstet
11. Har du känt dig besvärad av eller varit tvungen att undvika gå ut pga vädret eller luftföroreningar
Hur begränsad har du varit pga din astma under de senaste 2 veckorna:
12. ansträngande aktiviteter (som att skynda sig, träna, springa upp för trappor, sporta)
13. måttligt ansträngande aktiviteter (som att promenera, utföra hushållsarbete, trädgårdsarbete, handla, gå upp för trappor)
14. sociala aktiviteter (som att prata, leka med husdjur/barn, besöka vänner)
15. arbetsrelaterade aktiviteter

MiniRQLQ

The mini version of the Rhinoconjuctivitis Quality of Life Questionnaire (RQLQ) is a disease-specific questionnaire for adults with allergic rhinoconjuctivitis. It is the shorter version of RQLQ and has 14 questions in various domains (physical, emotional, social). It evaluates the patient's condition during the past week(88).

MiniRQLQ
Hur mycket har du besvärats under den senaste veckan på grund av symtom från näsa/ögon
1. Regebundna aktiviteter hemma och på arbetet
2. Rekreationsaktiviteter
3. Sömn
4. Att behöva gnugga näsan/ögonen
5. Att behöva snyta sig ofta
6. Nyssningar
7. Täppt näsa
8. Rinnande näsa
9. Klåda i ögonen
10. Svidande ögon
11. Rinnande ögon
12. Trötthet och/eller bristande energi
13. Törst
14. Känt mig lättretlig

CAT

The COPD Assessment Test (CAT) is a validated, short (8-item) patient completed questionnaire, developed for use in clinical practice to measure the health status of patients with COPD. For every question there are 6 possible answers, scoring from 0-5, and the total score ranges from 0-40. A difference or change of 2 or more units over 2-3 months suggests a clinically significant difference or change in health status (89). Based on the total score the impact of the disease is categorized as very high if CAT>30, high >20, medium if 10< CAT<20 and low <10.

CAT
1. I never cough… I cough all the time
2. I have no phlegm (mucus) in my chest at all…My chest is completely full of phlegm (mucus)
3. My chest does not feel tight at all…My chest feels very tight
4. When I walk up a hill or a flight of stairs I am not breathless… When I walk up a hill or a flight of stairs I am very breathless
5. I am not limited doing anyactivities at home…I am very limited doing activities at home
6. I am confident leaving my home despite my lung condition… I am not confident at all leaving my home despite my lung condition
7. I sleep soundly… I don't sleep soundly because of my lung condition
8. I have lots of energy…I have no energy at all

CCQ

The Clinical COPD Questionnaire (CCQ) measures health status and can be used to assess health-related quality of life during the past week. It consists of 10 items

(each scored between 0=never and 6=almost all the time), divided into three domains (symptoms, functional, mental).(90)

CCQ
1. Short of breath at rest
2. Short of breath doing physical activities
3. Concerned about getting a cold or your breathing getting worse
4. Depressed because of your breathing problems
5. How much did you cough
6. Did you produce phlegm
7. Strenuous physical activities
8. Moderate physical activities
9. Daily activities at home
10. Social activities

V. CANTAB

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was invented by the University of Cambridge in the 1980s.The original purpose was to bridge a translational gap between basic neuroscience and classical neuropsychological assessment. Over 1,100 publications have used CANTAB since 2013. The test is provided for commercial use by Cambridge Cognition and is a computer-based cognitive assessment system consisting of a battery of neuropsychological tests, administered to subjects using a touch screen computer. Even though it was not specifically developed for patients with allergic rhinitis, there were several factors that favoured this test in our study of an allergic group consisting of children and adolescents. The test can be repeated without the risk of learning effects, making it possible to assess subjects more than once, during the season and outside the season. There was a total of 25 different cognition tests, enabling us to choose the ones assessing specific cognitive functions that appeared to be affected according to previous studies. It is suitable for young and old subjects and aims to be culture and language independent through the use of non-verbal stimuli in the majority of the tests. The 25 tests in CANTAB examine various areas of cognitive function, including:

- general memory and learning
- working memory and executive function
- visual memory
- attention and reaction time (RT)

- semantic/verbal memory
- decision making and response control

For our project we selected 5 tests, with the first one consisting of a screening test for visual, movement and comprehensive difficulties as well as serving the purpose of familiarization.

CANTAB test	Cognitive Domains	Task Format
Motor Screening Test (MOT)	General assessment of whether sensorimotor deficits or lack of comprehension, will limit the collection of valid data from the participant.	Coloured crosses are presented in different locations on the screen, one at a time. The participant must select the cross on the screen as quickly and accurately as possible.
Paired Associates Learning (PAL)	Assessment of visual memory and new learning.	Boxes are displayed on the screen and are "opened" in a randomised order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time and the participant must select the box in which the pattern was originally located. If the participant makes an error, the boxes are opened in sequence again to remind the participant of the locations of the patterns. Increased difficulty levels can be used to test high-functioning, healthy individuals.
Spatial Working Memory (SWM)	Working memory. Strategy use. Spatial Working Memory requires retention and manipulation of visuospatial information. This self-ordered test has notable executive function demands and provides a measure of strategy as well as working memory errors.	A number of coloured squares (boxes) appears on the screen. The aim of this test is that by selecting the boxes and using a process of elimination, the participant should find one yellow 'token' in each of a number of boxes and use them to fill up an empty column on the right-hand side of the screen. Depending on the difficulty level used for this test, the number of boxes can be gradually increased until a maximum of 12 boxes are shown for the participants to search. The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.
Reaction Time (RTI)	Reaction Time provides assessments of motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy and impulsivity.	The participant must select and hold a button at the bottom of the screen. Circles are presented above (one for the simple mode, and five for the five-choice mode.) In each case, a yellow dot will appear in one of the circles, and the participant must react as soon as possible, releasing the button at the bottom of the screen, and selecting the circle in which the dot appeared.
Rapid Visual Information Processing (RVP)	Attention test: Visual sustained attention. Rapid Visual Information Processing is a measure of sustained attention	A white box is shown in the centre of the screen, inside which digits from 2 to 9 appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8). When the participant sees the target sequence, they must respond by selecting the button in the centre of the screen as quickly as possible. The level of difficulty varies with either one- or three-target sequences that the participant must watch for at the same time.

VI. Spirometry

Spirometry manoeuvres were performed according to the standards recommended by the American Thoracic Society/ European Thoracic Society.(46)

Spirometry is a fundamental tool in the assessment of pulmonary function and is widely used in the diagnosis, management, and monitoring of respiratory diseases(45, 46). It provides a simple, non-invasive way to measure how much air a person can inhale and exhale, as well as how quickly they can do so. The data obtained from spirometry can offer valuable insights into the presence and severity of various lung conditions, particularly those affecting the larger, central airways. However, spirometry has limitations, especially in assessing the peripheral airways, which are crucial in the early detection and management of obstructive airway diseases like asthma and COPD.

Spirometry measures the volume and the flow of air exhaled or inhaled by a patient over time, providing several key parameters that are crucial in evaluating lung function:

- **Forced Vital Capacity (FVC):** The total amount of air a person can forcibly exhale after taking the deepest breath possible. This measurement reflects the lung's capacity to hold air.
- **Forced Expiratory Volume in One Second (FEV1):** The amount of air that can be forcibly exhaled in the first second of a forced breath. FEV1 is a critical parameter for diagnosing and assessing the severity of obstructive lung diseases.
- **FEV1/FVC Ratio:** This ratio helps in differentiating between obstructive and restrictive lung diseases. A reduced ratio typically indicates obstructive airway diseases.
- **Peak Expiratory Flow (PEF):** The highest flow rate achieved during the forced exhalation. It gives an indication of the patient’s maximal ability to exhale, though it is less specific than FEV1.
- **Flow-Volume Loop:** This graphical representation of the rate of airflow against the volume of air exhaled provides a visual insight into the dynamics of airflow during forced breathing manoeuvres. It is particularly useful in identifying upper airway obstructions and other abnormalities.

Limitations of Spirometry in Detecting Peripheral Airway Dysfunction

Spirometry is the gold standard for diagnosing obstructive and restrictive lung diseases, but it has significant limitations in detecting early peripheral airway dysfunction:

1. **Insensitivity to Early Changes:** Spirometry primarily reflects the function of the larger, central airways. The early pathological changes in the peripheral airways often do not cause a significant reduction in FEV1 or FVC, making spirometry relatively insensitive to these changes.
2. **Effort Dependence:** Spirometry requires maximum effort from the patient to produce accurate results. Inconsistent effort can lead to variability in the measurements, potentially masking subtle changes in the peripheral airways.
3. **Global Lung Function Assessment:** Spirometry provides a global assessment of lung function, which can dilute the impact of localized abnormalities in the small airways, particularly when the larger airways are unaffected.
4. **Flow-Volume Curve Interpretation:** While the flow-volume curve can sometimes indicate peripheral airway obstruction (e.g., through a "scooped-out" appearance), this sign is not specific and may not be present until the disease is advanced.

VII. Forced Oscillation Technique

The study of respiratory mechanics is crucial in understanding how the lungs function and how various respiratory conditions affect this function. Traditional methods, such as spirometry, have been widely used to assess lung function. However, these methods often require active cooperation from the patient, which can be challenging in certain populations, such as young children, elderly individuals, or patients with severe respiratory conditions. This is where the Forced Oscillation Technique (FOT) comes into play, offering a non-invasive, effort-independent means of assessing respiratory mechanics. This method enables also measurements performed during inspiration and exhalation separately. The expiratory flow limitation (EFL) can be evaluated, among various methods, by means of estimating the difference of expiratory and inspiratory resistance.

What is the Forced Oscillation Technique?

The Forced Oscillation Technique (FOT) is a diagnostic method used to assess respiratory mechanics noninvasively(91, 92). This technique involves the

application of external oscillatory pressures at the mouth during normal breathing, which induces oscillations in the airflow. These oscillations are typically in the range of 5 to 35 Hz, and they help in characterizing the mechanical properties of the lungs and airways.

Oscillation techniques have gained prominence(93) due to the ability to provide detailed information on lung function with minimal patient effort. Patients only need to breathe normally while the oscillatory signals are applied, making the test easy to perform and well-tolerated. Traditional lung function tests, like spirometry, require significant patient effort and coordination, which can be challenging for young children and elderly patients, patients with physical limitations or cognitive impairments. FOT, being effort-independent, is particularly advantageous for these populations, allowing for accurate and reliable lung function assessment without the need for forced manoeuvres. FOT can detect subtle changes in lung function that might not be apparent in conventional tests. This sensitivity makes it a valuable tool for early detection of lung diseases, potentially leading to earlier intervention and better outcomes.

There are however some limitations when using the Forced Oscillation Technique. The need for specialized equipment and trained personnel to operate the device and interpret the results accurately limits its accessibility in low-resource healthcare units. Although one could argue that FOT requires less resources in means of personnel and significantly less training in comparison to spirometry. FOT measurements can be sensitive to artifacts such as upper airway shunts, glottic closure, and leaks around the mouthpiece. These artifacts can affect the accuracy of the measurements, necessitating careful technique and sometimes repeated assessments to ensure reliability. Interpretation challenges have also been a significant limitation. While FOT provides detailed data, interpreting this data can be complex. The clinical implications of specific patterns in resistance and reactance require thorough understanding and experience. Standardization of interpretation criteria is needed to enhance its clinical utility.

The Forced Oscillation Technique operates on the principle of superimposing external oscillatory signals onto the normal breathing of a patient. These oscillations, typically in the form of pressure waves, are applied at the mouth, and the resulting pressure and flow signals are measured. The relationship between these signals helps in determining the mechanical properties of the respiratory system, such as resistance and reactance.

FOT provides several key parameters. FOT measures the respiratory system's impedance, which is a complex quantity comprising two components: resistance (R) and reactance (X). Resistance reflects the opposition to airflow, mainly due to the airways, while reactance includes contributions from both the elastic and inertial properties of the respiratory tissues and the air within the lungs.

- Resistance (R): Represents the opposition to airflow in the airways.
- Reactance (X): Represents the elastic and inertial properties of the lung and chest wall.

Frequency Dependence: FOT measurements are conducted across a range of frequencies. IOS devices deliver signals at a range between 5-35 Hz while other devices can deliver signals with specific frequencies. The frequency-dependent nature of the measurements allows for the differentiation between central and peripheral airway obstructions, as different parts of the respiratory system respond differently to varying frequencies.

Resmon Pro Full

For the purposes of our project, we used Resmon Pro Full, a commercial respiratory oscillometry device that delivers composite sinusoidal pressure waves with specific frequencies of 5, 11 and 19 Hz and analyses reflected signals. The signals reflected at a low frequency (5 Hz) are a proposed measure of the total resistance and reactance of the respiratory system while the signals reflected at a high frequency (19 Hz) measure the resistance in the central airways. The resistance R5-R19 is proposed as a measure of the peripheral airway resistance.

Understanding Resistance and Reactance in the Forced Oscillation Technique

Two parameters measured by FOT are resistance and reactance. Understanding these parameters is essential for interpreting lung function and diagnosing respiratory conditions.

Resistance

Resistance (R) refers to the opposition to airflow within the airways during breathing. It is measured by applying an oscillatory pressure wave to the airway opening and assessing the resulting airflow. Resistance is calculated by analysing the pressure-flow relationship, specifically focusing on the in-phase component of the oscillatory signal. Its clinical significance can be summarized into the following:

- **Airway Obstruction**: Increased resistance typically indicates airway obstruction. Conditions such as asthma and chronic obstructive pulmonary disease (COPD) often show elevated resistance, particularly in the lower frequency ranges. This increase is due to the narrowing or blockage of the airways, which impedes airflow.
- **Central vs. Peripheral Airway Resistance**: The frequency dependence of resistance helps differentiate between central and peripheral airway obstructions. At lower frequencies (around 5 Hz), resistance reflects the behaviour of the entire respiratory system, while higher frequencies (20-35 Hz) primarily reflect central airways. A significant increase in resistance at low frequencies suggests peripheral airway involvement. Resistance at 5 Hz minus resistance at 19 Hz (R5-R19) is considered to represent the resistance in the peripheral airways.

Reactance

Reactance (X) in FOT represents the combined effects of the elastic and inertial properties of the respiratory system. It is derived from the out-of-phase component of the oscillatory pressure-flow relationship. Reactance consists of two components: 1) **Elasticity (Elastance)**: Reflects the elastic properties of the lung and chest wall. It indicates the ability of the respiratory system to return to its original shape after being deformed by airflow. 2) **Inertia**: Represents the mass of the air and tissues that must be moved during breathing. It is more significant at higher frequencies. Its clinical significance consists of the following:

- **Elastance and Compliance**: Negative reactance values (observed at lower frequencies) are associated with the elastic recoil of the lungs and chest wall. High negative reactance indicates decreased compliance, which might reflect stiffer lungs.
- **Resonant Frequency**: The point where reactance crosses zero (shifts from negative to positive) is known as the resonant frequency. It provides valuable information about the balance between elastic and inertial properties of the respiratory system. Changes in this frequency can indicate alterations in lung mechanics due to disease.
- **Dynamic Hyperinflation**: In diseases like COPD, positive reactance values at low frequencies can indicate dynamic hyperinflation, where air trapping leads to increased lung volumes and altered respiratory mechanics.

Challenges and Limitations of FOT

Despite its many advantages, FOT is not without limitations. One challenge is the interpretation of the results, particularly in complex cases where multiple factors may be influencing respiratory mechanics. Additionally, while FOT is highly sensitive, it may not always be specific, meaning that abnormal results can sometimes be difficult to attribute to a specific underlying cause without further testing. Moreover, FOT is still less commonly used than spirometry, and there may be a lack of familiarity with the technique among clinicians. This can lead to underutilization in clinical practice, despite its potential benefits.

Recent Advances and Future Directions

Recent advances in FOT technology have focused on improving the accuracy and ease of use of the technique(94-96). This includes the development of more sophisticated analysis algorithms and the integration of FOT with other diagnostic tools to provide a more comprehensive assessment of respiratory health.

There is also ongoing research into the use of FOT in a wider range of respiratory conditions, including interstitial lung diseases and pulmonary fibrosis. These studies are exploring how FOT can be used to detect early changes in lung function in these diseases, potentially leading to earlier diagnosis and treatment.

As technology continues to advance and our understanding of respiratory mechanics deepens, FOT is likely to become an increasingly important part of the clinical toolkit for respiratory assessment(97). Its potential for early diagnosis, monitoring treatment efficacy, and improving patient care is significant, making it a technique worth understanding and utilizing in the clinical setting(98-100).

VIII. Biomarkers

In paper I, serum samples were collected at the same days as the children performed the cognitive tests. Inflammation biomarkers (IL-13, TNF-α, TGF-β) and stress biomarkers (cortisol and catecholamines) were analysed(101-104). IL-13 was used as a biomarker of the type-2 response while TNF-α and TGF-β as a marker to reflect systemic inflammation that could be present due to allergen-induced stress status. Cortisol and catecholamine levels were analyzed based on the hypothesis that biologic stress during the season would induce higher levels of these biomarkers. These specific biomarkers were chosen based on previous studies performed in the field.(101, 102) It should be mentioned that daily use of nasal corticosteroids by the participants may have affected the results.

IX. Pollen level measurements

During the pollen season 2015 in the Skane Region, Sweden, daily pollen measurements, provided by the Palynological laboratory, were taken into account in paper I. The measurements provided us information about the pollen levels in the region, enabling us to precisely estimate how many patients undertook cognitive tests during low-moderate-high-very high pollen levels.

X. Data analyses

All statistical calculations were performed using SPSS for Windows. Due to non-normally distributed data, all statistical analyses were done using non-parametric tests. Mann-Whitney U test for unpaired data was used to compare two independent groups and Wilcoxon signed-rank test was used for paired data. Kruskal-Wallis test with Dunn's post hoc was used for multiple comparisons between separate groups. Chi-square test was used for categorical variables and number comparisons, with Fisher's correction when low numbers. Correlations were calculated by Spearman's correlation test. Linear regression was used when needed to adjust for age, sex etc. A $p < 0.05$ (two tailed) was considered significant.

Results

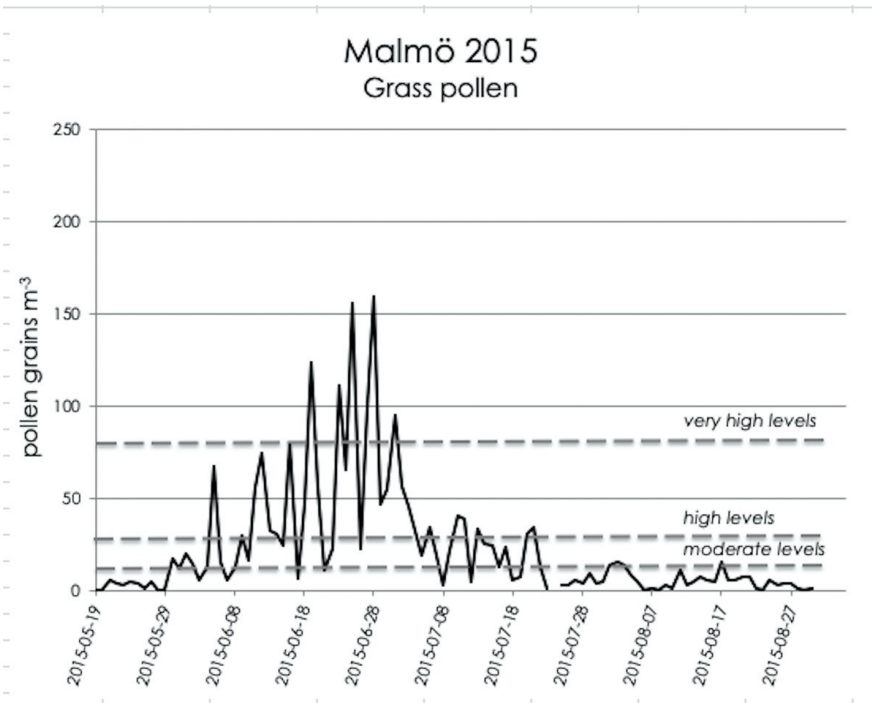
Paper I:

PAPER I: Papapostolou G, Kiotseridis H, Romberg K, Dahl Å, Bjermer L, Lindgren M, Aronsson D, Tunsäter A, Tufvesson E. Cognitive dysfunction and quality of life during pollen season in children with seasonal allergic rhinitis. Pediatr Allergy Immunol. 2021 Jan;32(1):67-76.

In the first project, we aimed to examine whether specific cognitive functions were affected during the grass pollen season in allergic children and whether the potential degree of cognitive impairment was related to symptoms, quality of life and biomarkers.

A total of 69 children were included, of which 43 had troublesome symptoms despite a combination treatment of antihistamines and nasal steroids daily. The remaining 26 participants were the control group and had a negative skin prick test or Phadiatop and no clinical history of allergy or other conditions that could interfere with the study.

During the pollen season in 2015, there was a maximum of two consecutive days with very high levels of grass pollen (>80.000 pollen grains per m^3). In total, very high levels were observed for only five days during the whole season. Of the total of 46 allergic participants, only 20 undertook the test during very high (4 participants) or high levels (16 participants) of grass pollen. In the picture below, the levels of grass pollen are presented throughout May-August 2015 in Malmö, Sweden:



Specific cognitive functions were affected during the season in allergic participants. The more symptoms the allergic participants had, the longer the reaction time for simple movement. In tests examining the Spatial Working Memory, the allergics made significantly more errors during the season compared to non-allergics, even though in the end they achieved similar results. In the table below, the results are summarized as results in the CANTAB test, correlation to questionnaires of symptoms and quality of life as well as correlation to the pollen levels.

Regarding quality of life, as investigated with the DISABKIDS questionnaire, a mental, social and physical impairment was exhibited in the group of the allergic children when compared to the control group during the season. The difference between the 2 groups remained even outside the season. When using a disease-specific questionnaire in order to examine quality of life (LILA), impairment was also revealed during the season in the group of the allergic children. As expected, when using the VAS method to evaluate symptoms, allergic children had significantly higher scores in comparison with the control group.

The examined biomarkers did not differ between the groups neither during the season nor off-season.

CANTAB TEST	Spatial Working Memory	Reaction Time	Rapid Visual Information Processing	Paired Associates Learning
Cognitive function	Executive function test	Attention and psychomotor speed test		Memory test
Administration time	4-6 minutes	3 minutes	7 minutes	8 minutes
Outcomes measures	-errors -strategy	-reaction time -movement time Simple and Five-choice	-latency (speed of response) -total false alarms -sensitivity	-errors
Results	Allergics made significantly more errors compared to the non-allergic group during the season.	Reaction time (speed of response) and speed of movement, a tendency for the allergics to be slower in comparison to the control group (during and outside the season) but also themselves.	No difference	No difference
Correlation with questionnaires	-	Reaction time for simple movement correlates negatively to DISABKIDS and positively to LILA the poorer quality of life the allergic children had, the longer the reaction time for simple movement.	-	-
Correlation with pollen levels	-	A significant correlation between grass pollen levels and change in five choice reaction time compared to off-season in the allergic group.	-	-

Paper II:

PAPER II: Papapostolou G, Tunsäter A, Binnmyr J, Telg G, Roslind K. Patient perspectives on living with severe asthma in Denmark and Sweden. Eur Clin Respir J. 2020 Dec 16;8(1):1856024.

The aim of this study was to investigate how severe asthma patients experience their symptoms and their quality of life and on what degree the impairment due to the disease is captured by standard questionnaires and in-depth interviews.

A total of 93 patients, 73 in Sweden and 20 in Denmark, were included in the study. All patients participated in a web survey and those that indicated interest continued with the second part of the study, the in-depth interviews. In the second part, 33 patients, 25 from Sweden and 8 from Denmark, were interviewed through the telephone by trained moderators following a semi-structured interview guide.

During the web survey, the patients completed the ACT, SGRQ, WPAI and a study specific questionnaire. When answering to ACT, the results appeared to be as in the following pictures, with the vast majority having uncontrolled asthma (77%). In a typical week, a 59% had 4 or less good days. Shortness of breath on ground level was reported by 50% and exercise was considered as "not safe" by half of the patients. Severe attacks occurred at least 2 times over the last 3 months for the majority of patients and in between the worsening periods, six out of ten patients had less than 3-4 good days/week. The perception of current health as a question of the SGRQ, was considered as poor or very poor in only 1/3 of the participants, almost 40% described their current health as fair and approximately 25% as good.

The statements deriving from the in-depth interviews provided a more detailed picture of the problem. The actual level of impact of severe asthma on patients' quality of life was revealed as well as the individuals' adaptations due to limitations deriving from the disease but even in order to avoid disease worsening.

One of the patients' spontaneous comments regarding the limitations of a web-survey and standardised questionnaires as experienced by the participants, described the challenges when trying to answer as accurate as possible to questions by choosing among specific answers:

> "It is difficult to choose an answer for what I CAN and CANNOT do due to my breathing. For example, I CAN eat, but not unless I nebulize before having the meal, because then I'd pass out. Does that mean that I CAN eat, or that I CANNOT eat? It was difficult to select in many questions."

Restrictions on daily life, such as travelling, involvement in social life and household chore, need of planning to avoid anything that could lead to disease deterioration was reported by all patients participating in the in-depth interviews. A 70% reported impact on family and 45% stated that the disease had impacted and restricted their choice of professional career. Longer sick leaves were reported due to asthma by 1/3 and shorter sick leaves were equally common, occurring at least 2-3 timer per year.

"When I get this severe breathlessness, then I get anxious. When I can't get any air. But it only happens a few times per month, these severe attacks that feels like they're not passing even though I take plenty of medication. And it causes anxiety, you become stressed and sad and… yes. Anxious."

"For me, what's worst is the infections season, when it's cold, in the winter. All the people going to work or school and moving around in public when they are sick and contagious, it can be devastating for me – and also, it becomes expensive. It's not just the fact that you get very sick, but also that it's expensive to stay home from work for 2-3 weeks when you're sick."

"I must have had it for… Well, it's been at least ten years, because I've been through a lung x-ray and all tests and everything you can imagine. I had cough medicine for maybe three years until a physician at the health care centre stopped it and asked why I was taking so much cough medicine."

"I claim that it doesn't affect my life, but it does. It's a constant jigsaw puzzle."

"My lack of energy affects the family; I'm more tired than others and I can't do everything I'd like to do with the children and the family. I let the children play by themselves instead of joining them, and my husband has to take care of sports trainings and all that."

"To constantly having to plan everything. 'Oh, there are stairs over there, what should I do to handle that, can I walk around them instead' – you see, I'm constantly planning. If I know I have to walk up a long staircase, then I perhaps take my inhalation in the car, and then I stand outside for a while in order to get used to the colder temperature before I walk up the staircase."

"And I've been quite worried, and I've been thinking a lot about how things will turn out. That I might not be able to work full time, and that I don't… I don't know if I'll be able to have a family."

"I used to be a politician, and… I can't do that anymore, stand up and speak in front of a group or be part of discussions, because I can't get enough air."

Paper III

PAPER III: Peripheral airway obstruction in association with symptoms and quality of life asthma. Georgia Papapostolou, Abir Nasr, Linnea Jarenbäck, Kerstin Romberg, Alf Tunsäter, Jaro Ankerst, Leif Bjermer, Ellen Tufvesson. (Manuscript)

In this study, we aimed to investigate how inspiratory and expiratory resistance and reactance in the central and peripheral airways, measured by FOT, was associated with various symptoms and quality of life.

From a total of 319 asthma patients included, 212 patients had a controlled disease (ACT ≥ 20) of which 53 subjects had totally controlled disease (ACT=25). The remaining 107 patients had an uncontrolled disease (ACT<20) of which 29 patients had a poorly controlled disease (ACT<16). When investigating the ACQ-5, only 141 patients had a total score <0.75, a score that indicates well-controlled asthma, 98 patients had ACQ-score between 0.75-1.5 indicating a partly controlled asthma, while 80 patients had a total score >1.50, which indicates poorly controlled asthma. As expected, there is a high agreement between ACT and ACQ-5, but not fully.

Scores from all questionnaires correlated well with each other when investigating the group of patients as a whole. The ACT, ACQ and MiniAQLQ questionnaires showed strong correlations to each other. Nijmegen score and MiniRQLQ showed moderate correlations to asthma symptoms, while HADS, Nijmegen and Snot22 only showed weak correlations to asthma symptoms. The correlations remained when examining subjects with a controlled asthma based on ACT. However, in subjects with uncontrolled disease, the correlations remained within asthma symptoms, Nijmegen score and quality of life.

When dividing patients into 2 groups, applying a cut-off at 20, there was no statistically significant difference in the FOT measurements between the groups. However, when different cut-off points were applied with ACT score at 16, 20 and 25 we could exhibit a higher total (R5) and peripheral resistance (R5-R19) as well as reactance (X5) with increasing symptoms. The results are presented in figure 1.

We also investigated subgroups that were created by using an ACQ-5 cut-off at 0.75 and 1.5. In those groups, statistically significant differences could be captured in total resistance (R5) and reactance (X5). When even creating 2 different subgroups based on a Nijmegen cut-off at 24, there were differences in total (R5) and central resistance (R19).

Total scores from most questionnaires (except for HADS and Snot22) correlated with many of the FOT results, as shown in Table 1, but there were different patterns

of correlation between airway obstruction and symptoms in uncontrolled and controlled asthma.

In addition, separate questions were found to be associated to airway obstruction. Peripheral resistance (R5-R19) correlated with limited activity (ACTq1), night symptoms (ACQq1) and wheeze (ACQq5) when investigating the asthma group as a whole.

Even questions in the Nijmegen questionnaire, that would not be directly recognised as symptoms related to asthma, correlated with some of the FOT measurements as seen in Table 2. In the group with uncontrolled asthma, some questions correlated even stronger to R5 and R19 than in the asthma group as a whole. These were blurred vision, feeling confused and bloated feeling in the stomach, and R19 additionally correlated to feeling tense, dizzy spells and shortness of breath. Only the question regarding the bloated feeling in the stomach correlated with X5 in this group.

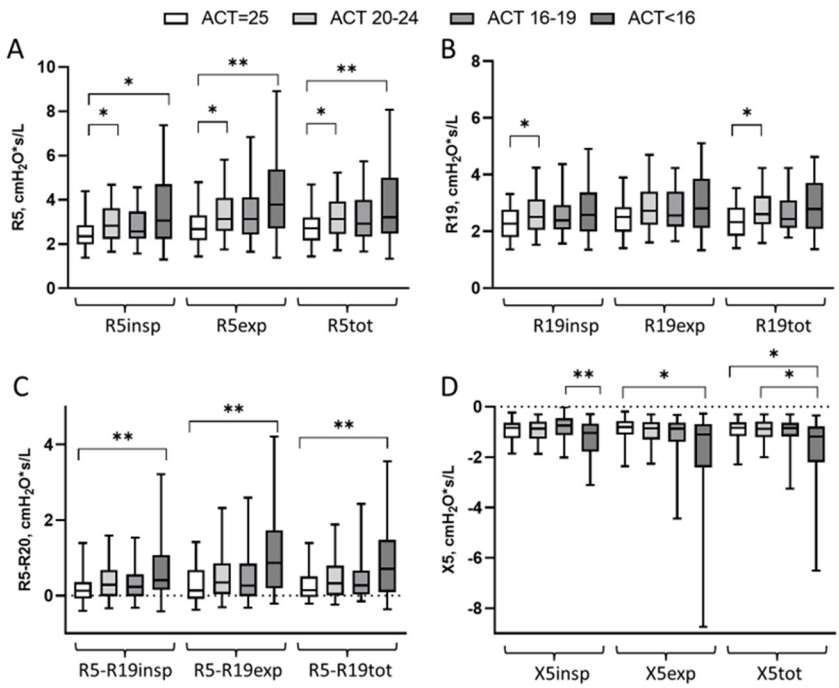


Figure 1. Subjects divided into four patient groups (ACT score = 25, 20-24, 16-19 and <16) and differences resistance and reactance among the groups

Correlation of questionnaires and FOT measurements													
		R5			R19			R5-R19			X5		
		Insp	Exp	Tot	Insp	Exp	Tot	Insp	Exp	Tot	Insp	Exp	Tot
ACT	All	**.008**	**.002**	**.004**	**.038**	**.047**	**.045**	**.037**	**.011**	0.82	.788	**.009**	**.042**
	C	**.004**	**.003**	**.003**	**.004**	**.002**	**.001**	.248	.302	.275	.517	.334	.593
	U	.265	.104	.233	.501	.573	.432	**.049**	**.042**	.136	.063	.109	.073
ACQ	All	**.016**	**<.001**	**.003**	.187	.104	.124	**.023**	**.002**	.037	.086	**<.001**	**<.001**
	C	**.047**	**.007**	**.014**	.179	.088	.081	.231	**.038**	.196	.240	**.030**	.122
	U	.085	**.022**	.065	.501	.265	.277	**.022**	**.033**	0.51	**<.001**	**.003**	**<.001**
Nijmegen	All	**.003**	**<.001**	**<.001**	.384	.145	.458	**.009**	**.007**	**.003**	**<.001**	**<.001**	**<.001**
	C	**.011**	**.004**	**.002**	**.008**	**.004**	**.003**	.955	.238	.463	**.002**	**.019**	**.011**
	U	.125	**.026**	**.046**	**.011**	**.001**	**.003**	.955	.915	.978	.066	.606	.189
HADS	All	.538	.197	.235	.070	.082	.096	.107	.640	.189	.189	.505	.175
	C	.905	.832	.863	.189	.434	.344	.731	.123	.025	.376	.409	.975
	U	.635	.095	.102	.338	.086	.210	.731	.906	.849	.168	.325	.117
Snot22	All	.160	.108	.118	.364	.247	.290	.410	.144	.418	**.036**	.180	.170
	C	.099	**.004**	**.010**	.115	**.041**	.066	.643	**.010**	.450	**.018**	.055	**.017**
	U	.517	.712	.881	.900	.816	.795	.643	.547	.689	.276	.860	.761
AQLQ	All	**.006**	**<.001**	**.003**	.103	.121	.145	**.019**	**.003**	**.035**	**.010**	**<.001**	**<.001**
	C	**.015**	**.006**	**.008**	.072	.092	.076	.330	**.023**	.088	**.002**	**.003**	**.004**
	U	.233	.112	.201	.474	.282	.290	.330	.559	.441	**.024**	**.101**	**.020**
RQLQ	All	**.018**	**.007**	**.017**	**.028**	.055	**.048**	.175	.020	.290	.284	.128	.070
	C	.113	.070	.097	.077	.178	.137	.376	.171	.743	.407	.697	.447
	U	.210	.062	.152	.146	.092	.096	.376	.112	.586	.107	.249	.108

Table 1. Data is shown as p-value (p). ACT= Asthma Control Test. ACQ= Asthma Control Questionnaire. Nijmegen=self-reporting symptoms attributed to hyperventilation syndrome. HADS= Hospital Anxiety and Depression Scale. Snot22= Sino-nasal outcome test. AQLQ=Asthma Quality of Life questionnaire. RQLQ= Rhinokonjuktivitis Quality of Life questionnaire. C=Patients with partially or fully controlled disease based on ACT≥ 20 (N=212). U=Patients with uncontrolled disease based on ACT<20 (N=107). All= all patients (N=319). Insp= Measurement during inspiration. Exp= Measurement during expiration. Tot= Measurement as a total of the inspiratory and expiratory phase of the breath.

Correlation of separate questions in the Nijmegen questionnaire and FOT measurements													
		$R5_{in}$	**$R5_{exp}$**	**$R5_{tot}$**	**$R19_{in}$**	**$R19_{exp}$**	**$R19_{tot}$**	**$R5\text{-}R19_{in}$**	**$R5\text{-}R19_{ex}$**	**$R5\text{-}R19_{tot}$**	**$X5_{in}$**	**$X5_{exp}$**	**$X5_{tot}$**
Q1-chest pain	p	.678	.418	.355	.660	.365	.514	.861	.831	.657	.395	.831	.589
	r	.023	.046	.053	.025	.052	.038	.010	.012	.025	-.048	-.012	-.031
Q2-feeling tense	P	.099	**.006**	**.004**	**.026**	**.002**	**.006**	.633	.329	.537	**.009**	.076	**.014**
	r	.093	.158	.163	.126	.174	.158	.027	.056	.035	-.147	-.101	-.141
Q3-blurred vision	p	**.009**	**.001**	**.002**	**<.001**	**.002**	**.001**	.277	**.022**	.354	.184	.086	.054
	r	.146	.185	.178	.186	.177	.182	.061	.131	.052	-.075	-.098	-.110
Q4-dizzy spells	p	**.003**	**<.001**	**<.001**	**.006**	**.004**	**.004**	.182	.133	.177	**.022**	**.013**	**.010**
	r	.164	.193	.196	.154	.163	.165	.075	.086	.076	-.128	-.141	-.147
Q5-feeling confused	p	**.023**	**.004**	**.003**	**.002**	**.001**	**<.001**	.973	.383	.904	.384	.283	.429
	r	.128	.164	.167	.172	.187	.191	-.002	.050	.007	-.049	-.061	-.045
Q6-faster/deeper breathing	p	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	.209	.079	.392	.114	.062	.053
	r	.201	.217	.206	.221	.209	.222	.071	.101	.048	-.089	-.106	-.111
Q7-short of breath	p	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**.036**	**.007**	.092	**.009**	**<.001**	**<.001**
	r	.233	.250	.238	.193	.197	.212	.119	.153	.095	-.146	-.230	-.218
Q8-tight feelings in the chest	p	.749	.549	.614	.504	.313	.401	.564	.986	.584	.227	.595	.522
	r	.018	.034	.029	.038	.058	.048	-.033	.001	-.031	-.068	-.030	-.037
Q9-bloated feeling in the stomach	p	.114	**.011**	**.018**	.421	.091	.148	.061	**.021**	.156	.101	**.015**	**.023**
	r	.089	.145	.135	.046	.097	.083	.106	.132	.080	-.092	-.139	-.130
Q10-tingling fingers	p	.061	.038	**.050**	**.028**	**.016**	**.015**	.191	.205	.244	.107	.181	.117
	r	.105	.118	.112	.124	.138	.139	.074	.073	.066	-.091	-.076	-.090
Q11-unable to breathe deeply	p	**.001**	**.001**	**.001**	**.007**	**.010**	**.006**	.596	.313	.554	.061	**.003**	**.007**
	r	.181	.180	.181	.153	.148	.157	.030	.058	.033	-.105	-.167	-.153
Q12-stiff fingers or arms	p	.104	**.021**	**.045**	.287	.331	.333	**.005**	**<.001**	**.016**	.075	**.003**	**.008**
	r	.091	.131	.114	.060	.056	.056	.157	.188	.135	-.100	-.168	-.152

Q13-tight feelings around the mouth	p	.940	.976	.860	.771	.545	.671	.666	.884	.871	.993	.798	.989
	r	-.004	.002	.010	.016	.035	.024	-.024	-.008	-.009	.001	.015	.001
Q14-cold hands or feet	P	.455	.441	.282	**.025**	**.002**	**.007**	.059	**.014**	.141	.121	.425	.742
	r	.042	.044	.062	.126	.178	.153	-.107	-.140	-.083	-.087	.046	-.019
Q15-palpitations	p	.133	.339	.299	.322	.358	.288	.085	.444	.176	.055	.628	.354
	r	.084	.055	.059	.056	.053	.061	.097	.044	.076	-.108	-.028	-.053
Q16-feeling of anxiety	p	.286	**.012**	**.021**	**.035**	**.003**	**.009**	.223	.927	.331	.153	.104	.076
	r	.060	.143	.131	.119	.172	.149	-.069	.005	-.055	-.080	-.093	-.101

Table 2. Data is shown as p-value (p) and Spearman's correlation coefficient (r). R5=Resistance at 5Hz, R19=Resistance at 19Hz, X5=Reactance at 5 Hz, in=inspiratory, exp=expiratory. The Nijmegen questionnaire is used to screen patients with dysfunctional breathing such as hyperventilation syndrome. There are 16 items, Q1-Q16, (related to symptoms of hyperventilation syndrome) to be answered on a 5-point scale ranging from 'never' (0) to 'very often' (4).

Paper IV:

PAPER IV: Nasr A, Papapostolou G, Jarenbäck L, Romberg K, Tunsäter A, Ankerst J, Bjermer L, Tufvesson E. Expiratory and inspiratory resistance and reactance from respiratory oscillometry defining expiratory flow limitation in obstructive lung diseases. Clin Physiol Funct Imaging. 2024 Jun 14.

In this study we wanted to examine delta values between expiratory and inspiratory resistance and reactance and its correlation with air trapping, symptoms and quality of life in 4 different groups. We included 96 patients with COPD, 311 with asthma, 30 healthy smokers and 34 healthy subjects never-smokers. The last 2 groups were aimed to match COPD (healthy smokers) and asthma patients (healthy never-smokers) as control groups.

A pattern was noticed for higher expiratory than inspiratory values in both total (R5) and central resistance (R19) but not in reactance (X5) in asthmatics. When comparing asthmatics with the other groups, baseline measurements of expiratory and inspiratory total resistance (R5) were lower than in the COPD group. Expiratory total resistance (R5) was however higher in asthmatics than healthy never-smokers. Further examination of expiratory versus inspiratory measurements between the groups, showed that expiratory peripheral resistance (R5-R19) was also higher in asthma compared to healthy never-smokers, but lower in comparison to the COPD group, in both inspiratory and expiratory peripheral resistance (R5-R19). Regarding the central resistance (R19), there were no differences noticed among the groups. Reactance (X5) on the other hand, both inspiratory and expiratory, was more negative in patients with COPD than asthma.

Delta values between expiratory and inspiratory variables were used as an estimate of expiratory flow limitation. Delta values in total resistance (ΔR5) was lower in asthmatics compared to COPD and healthy smokers. Delta values of peripheral resistance (ΔR5-R19) were also lower in asthmatics in comparison to COPD. More negative delta values in reactance (ΔX5) were seen in COPD than asthmatics.

As a measure of air trapping, the RV/TLC ratio was investigated and its correlation to delta values between expiratory and inspiratory measurements. There was no correlation in the asthma group, when examined separately.

Delta values, however, regarding total and peripheral resistance and reactance correlated with symptoms (ACT and ACQ) and quality of life questionnaires (AQLQ) in the asthmatics while it was only delta values of reactance that correlated in the COPD group with symptoms (CAT) and quality of life questionnaires (CCQ).

Delta values of the central resistance did not show any correlation with the questionnaires in neither asthma nor COPD group (Table 3).

Correlations between delta-FOT-variables and questionnaires (after adjustment for age and sex)						
			ΔR5	ΔR19	ΔR5-R19	ΔX5
Asthma	ACT	p	**0.021**	0.21	**0.007**	**<0.001**
		β1	**-0.73**	-0.39	**-0.847**	**1.15**
	ACQ	p	**0.001**	0.062	**0.002**	**<0.001**
		β1	**1.24**	0.68	**1.145**	**-1.37**
	AQLQ	p	**0.003**	0.63	0.23	**0.007**
		β1	**-3.185**	0.42	-1.31	**2.51**
COPD	CAT	p	0.94	0.15	0.53	**<0.001**
		β1	-0.056	-0.97	0.61	**-1.30**
	CCQ	p	0.97	0.20	0.28	**<0.001**
		β1	-0.030	-1.05	1.29	**-1.89**
Healthy Smokers	CAT	p	0.33	**0.035**	0.80	**0.038**
		β1	0.96	**1.36**	0.35	**-3.39**
	CCQ	p	0.16	0.10	0.48	**0.020**
		β1	1.44	1.13	1.03	**-3.92**

Table 3. FOT-variables are presented as pre-bronchodilator delta-values between expiratory and inspiratory measurements. Data is shown as p-value (p) and linear regression coefficient (β1). R5= Resistance at 5 Hz, R19= Resistance at 19 Hz, X5= reactance at 5 Hz, ACT= Asthma Control Test, ACQ= Asthma Control Questionnaire, AQLQ= Asthma Quality of Life Questionnaire, CAT= COPD Assessment Test, CCQ= COPD Control Questionnaire

Discussion

Various questions arise when it comes to the assessment of symptoms and quality of life in chronic diseases affecting the upper and lower airways. Although there is a number of objective methods to assess the lower airways' function, with regards to asthma, the options for the upper airways, when it comes to pollen allergic rhinitis, are limited. Efforts to create guidelines and therefore an international consensus on when to treat, what is the goal of treatment and how we measure whether we have achieved the goal or not, are ongoing by international committees. It is nowadays widely accepted that patients suffering from asthma or allergic rhinitis have a significantly decreased quality of life(69, 105, 106) and the socioeconomic burden of these chronic diseases are of such degree that it is difficult to ignore. However, our increasing knowledge of the disease mechanisms and the development of advanced treatments have not been followed by a simultaneous evolution in the field on how to assess the disease burden for the individuals, regarding the symptoms and quality of life. Patient reported outcomes has been the method of choice for allergic rhinitis and in combination with lung function tests, mostly spirometry, in asthma. Standardised questionnaires have been widely used, securing somehow basic rules on how to assess the problem. Nevertheless, the questionnaires were developed in times when we did not have as much knowledge about the different phenotypes of the diseases as we have now(107, 108). They were developed before the most recent and advanced treatments emerged, such as sublingual immunotherapy for pollen allergy and biological treatments for asthma. The asthma questionnaires were mainly validated towards lung function tests such as spirometry, that lacks in the ability to capture the peripheral lung dysfunction in its whole.

So, how do patients perceive their condition? How bothersome are symptoms and how is everyday life and work productivity affected? Do patients have a tendency to under- or overestimate the problem? How is disease control defined? What are the goals with the treatment?

Allergic rhinitis is considered to cause significant work productivity loss and according to reports resulting into costs that are even larger than those incurred by asthma. The evaluation of the disease severity is clinical, based on physicians' perception and patient reported outcomes. Objective methods to evaluate the symptoms are lacking, not only regarding the symptoms from eyes and nose but even when it comes to patients reporting fatigue, difficulties to concentrate and to

perform their tasks(109). Recent reports from Norway exhibit a problem that affects students during the pollen season. Spring is an examination time and secondary students in Norway undertake tests, the results of which are important when pursuing higher education. The findings of the study suggested that random increases in pollen counts could result into a reduction of the scores for allergic pupils relative to their non-allergic peers. Study opportunities are therefore potentially limited for allergic pupils since they compete with non-allergic pupils for university slots on the basis of grades(33, 110-112).

In the first project, we included children and adolescents suffering from severe pollen allergic rhinitis as described according to ARIA classification, meaning troublesome symptoms affecting everyday life. In this study we decided to include participants that were treated daily with a combination of non-sedative antihistamines and nasal steroids in an attempt to evaluate whether such a group could exhibit a cognitive dysfunction despite the treatment. Even though the particular pollen season may not have been as representative as a researcher would have wished for, i.e. having several days with low pollen counts in between the higher peaks, it was still possible to exhibit an impairment in a significant function such as Spatial Working Memory as well as a general tendency for more errors before accomplishing the correct results in tests regarding strategy use, speed of response and movement. The questionnaires that were used regarding quality of life, correlated well with the Reaction Time test.

It is difficult to conclude, due to weaknesses and limitations of such a project with regards to random pollen levels from day to day that cannot be predicted beforehand, whether there were only some cognitive functions that were impaired while others could remain intact despite the season or whether a longer exposure to higher pollen levels was necessary in order to notice a defect in all cognitive functions examined.

There was a debate in Sweden, a couple of years ago on whether the pollen measurements should be seized as it was considered to be a not particularly cost-effective data source. It should be definitely mentioned that projects as the one performed as part of this PhD, would have been impossible to conduct if there were not any data about the pollen levels.

Moving on to the next project and investigating the problem from a different perspective, the one coming from the patients, it was no longer the issue to prove whether the patients were being affected by their disease using objective methods. Towards setting treatment goals(113) and creating international guidelines in order to define control disease and achieve a stable state that will be the least troublesome for patients(114) and improve their quality of life, one has to examine practical difficulties concerning the groups involved, the sufferers from one side, meaning the patients, and the health care providers, making the decisions and evaluations. Our main concern was to investigate whether impact on quality of life and the degree of symptoms could be captured by standardised questionnaires, a quantitative

method. Furthermore, we aimed to examine in depth the patients' perspective in an attempt to map the difficulties when healthcare givers and patients have to communicate towards goals set for treatment and disease control. Therefore, we selected a severe asthma group, focusing this time on the lower airways, in an attempt to ensure that all participants were having such a degree of symptoms that should not be overlooked.

In the beginning of this project, we already had the knowledge from previous studies that there was an overestimation of asthma control within primary health care(115, 116), several challenges occurring from the existing models of care(116) and in particular in Sweden that many patients are not seen by specialists(71) and that patients can suffer for several years with an uncontrolled disease before being referred to specialist care(67).

With regards to symptoms and quality of life in this particular group, several questions were attempted to be answered by this project. Do patients and physicians perceive differently the burden of the disease? Is this perception affected by lack of structured patient education and disease awareness? Are standardised questionnaires sufficient to capture the problem? Are limitations impacting the quality of life as measured by the questionnaires and to what degree?

Indeed, the questionnaires revealed impaired quality of life and poor disease control. However, the actual degree of impairment, restrictions, need for adaptations was fully revealed by the in-depth interviews. It then became apparent that poor disease awareness as well as an increased acceptance of limitations through the years, since "there was not so much to be done about it", affected significantly answers to important questions included in ACT or SGQR.

When being asked how they perceive their current health a surprising 38% answered fair at the same time when a 26% answered good, one could wonder how this is possible when based on the ACT score approximately 77% had uncontrolled disease in this severe asthma group. Could it be because, after all, the disease does not have a significant symptom burden or maybe because quality of life is not so much impaired by severe asthma? Or could it be explained by a vast gap created when participants had to choose from a given number of answers in combination with the fact that they had given up after all these years of living with a severe disease? While a web survey allows for a consistent way of presenting results, it also limits the nuances of the responses given and forces respondents to select an answer without explaining their rationales.

Even though one can argue that giving up and learning to live with a health problem due to a significant amount of adaptations may indicate that the problem itself is somehow manageable, reports on costs due to productivity loses among individuals with severe asthma and increased risk of unemployment among adults with severe asthma and frequent symptoms, indicate a problem that has a vast impact for society and not only the individuals suffering from the disease.

Once again in an attempt to approach this topic from several angles, in our goal to understand the problem on a detailed level, we decided to investigate a quite large group suffering from asthma(117). In the third study we aimed mainly to understand how obstruction in the peripheral airways could be correlated with symptoms and quality of life. We chose to examine the peripheral airways since this area of the lungs is frequently overlooked, partly due to lack of advanced techniques being used by the health care system in Sweden. Spirometry is widely used when diagnosing asthma and also as an instrument to evaluate treatment and disease control. But is it possible to achieve disease control and improve quality of life, the main concern of the international guidelines, when using methods that cannot fully evaluate a significant area of the respiratory system?

The most important finding in this project was that originally when the whole group of patients was divided into 2, using a cut-off point at ACT>20, that is very well known among clinicians, defining a group of well or partially controlled disease versus a group with uncontrolled disease, there was no statistically significant difference in the FOT measurements between the groups. This observation created the need to question whether the ACT captured controlled and uncontrolled disease when the obstruction was located in the peripheral airways. According to the hypothesis that uncontrolled disease affects even the peripheral airways, one would have expected to see a difference in the FOT measurements between the groups. This was not however the case. It appeared as though a significant number of patients with peripheral untreated obstruction was categorised as controlled according to the ACT. The results changed significantly when more than one cut-off points were used, depicting in a better way the differences between patients having different grades of symptoms.

Even though one would have expected that the ACT and ACQ scores would provide similar results regarding the correlation to FOT measurements, the separate questions in the ACQ correlated better than the ones in the ACT. It is still unclear whether this phenomenon resulted from the different period of time that is evaluated with the ACT (4 weeks) and the ACQ (1 week) or because of the slightly different formulation of both the questions and the answer options in ACQ.

One more surprising result was that a questionnaire that was not specific for asthma, Nijmegen, seemed to correlate relatively well with both total and central resistance and reactance no matter if the disease was controlled or not. This is a field that is interesting for further investigation, but the preliminary assumption is that Nijmegen contains questions similar to the tool developed by the ATLANTIS study with the purpose to evaluate the small airways in a more specific way(118, 119).

In ACT and ACQ there are still many questions that contribute to the total score of the questionnaires that seem to be less and less relevant as asthma research advances and a better understanding of the disease is achieved. Although there is a version of ACQ that is taking into account results from spirometry, biomarkers are neglected.

Several biomarkers that are proven to be of great importance in asthma, such as FeNO, eosinophils and cytokines should maybe also be taken into account.

In an attempt to understand the burden of asthma in particular that is correlating to the peripheral airways, we proceeded to the next project and included also patients with COPD as well as healthy smokers. The within-breathe difference in R5 (ΔR5) did not correlate at all with symptom or quality of life questionnaires for COPD patients but it did correlate with questionnaires used to evaluate asthmatics. However, ΔX5 correlated both with COPD and asthma questionnaires about the symptoms and quality of life. Even though it appears as if in both diseases there is a peripheral airways obstruction, the underlying mechanism resulting into symptoms cannot be easily understood. Symptoms and quality of life in COPD as evaluated by the existing questionnaires do not reflect a problem in the peripheral airways. It would have been of interest to use non-specific questionnaires such as Nijmegen also in COPD patients.

CONCLUSIONS/ VALUE OF THIS THESIS

Exploring widely used methods in assessing symptoms and quality of life in patients with asthma and allergic rhinitis from a different angle has been the main focus of this project. By partly questioning several methods, mainly patient reported outcomes, and comparing them side by side with more objective but less used tools (CANTAB, in-depth interviews and Forced Oscillation Technique) could be the beginning of a better understanding on how these diseases affect patients' lives. Coming closer into proving a cognitive dysfunction, attributed to pollen exposure, besides the reported one by the patients, it could be the beginning of a series of changes to improve the life of several students undertaking exams during the season. Understanding the burden of the disease, for each and every severe asthma patient separately, by using methods beyond the standard questionnaires, could potentially lead into improvement of the services provided by the existing health care system, better disease control and therefore improvement of the quality of life. Further on, investigating in detail the resistance and reactance during inspiration and expiration and how FOT measurements correlate with both specific and non-specific questionnaires for asthma and COPD could be the reason why we should reconsider widely used cut-off points when defining asthma as controlled. We hope that this project has enabled the reader to better understand how difficult it can be to perform simple functions, usually taken for granted, such as breathing in and breathing out, if you are allergic or asthmatic.

Future perspectives

The procedure of understanding the limitations of the projects included in this thesis as well as the questions emerging when analysing the results lead naturally into thoughts regarding future perspectives and new projects that could derive from this one.

In an attempt to further investigate the effects of grass pollen season on cognitive function, the following suggestions/future projects emerge:

- Examine how grass pollen allergic patients perform in CANTAB tests but this time with a much more controlled exposure to the allergen. Provocation procedures should be used having a standardised exposure to pollen. The results could be examined after a shorter and a longer exposure period.
- Examine how patients with untreated pollen allergy versus treated pollen allergy perform during and outside the season. Is available medication such as antihistamines and nasal steroids having a statistically significant effect on cognitive dysfunction?
- Examine how patients perform before and after immunotherapy. Can the cognitive dysfunction by treated?

With regards to severe asthma and evaluation of symptoms and quality of life in this group, the following questions/future projects could be of great interest:

- Severe asthma: Before and after treatment with biologics. How is the effect of the biologics captured by standardised questionnaires versus in-depth interviews?
- Severe asthma versus mild asthma: Is the problem really so mild if patients are interviewed in-depth?

Although peripheral airway obstruction in asthmatics is a vast field of study, the following question could be the beginning of a future project, highly connected to Paper III+IV:

- Forced Oscillation Technique: Why does not the CAT and CCQ questionnaires in patients with COPD correlate with the measurements? How do their separate questions correlate with FOT? Would FOT correlate with CAT if the number of exacerbations per year was taken into account?

Populärvetenskaplig sammanfattning

Syftet med projektet var att undersöka symptom och livskvalitet hos patienter med astma eller allergisk rinit. Vi fokuserade på att förstå i detalj hur patienterna upplever sina symptom och på vilket sätt deras livskvalitet påverkas. Vi använde olika sorters metoder, både de vanligaste som används just nu för att utvärdera symtomen och livskvalitet men även lite mera avancerade metoder som inte används så ofta men som vi trodde att var mer pålitliga.

Första studien fokuserade på kognitiv påverkan hos barn och tonåringar med pollenallergi. Vi försökte ta reda på hur mycket deltagarna påverkades under pollensäsong av deras allergi. Det är väletablerat att pollenallergi orsakar symtom från näsa och ögon men vi ville undersöka om det fanns en påverkan på olika hjärnfunktioner. Många allergiker rapporterar uttalad trötthet och svårigheter att koncentrera sig under pollensäsong. Just nu har vi inga metoder att dokumentera problemet i detalj förutom olika frågeformulär som patienterna kan svara på och som läkare använder för att utvärdera situationen. I vår studie använde vi en metod som utvecklades av Cambridge universitet och som heter CANTAB. Med hjälp av en pekskärm gjordes olika tester och viktiga funktioner utvärderades under och utanför pollensäsong. På grund av relativ låga pollenhalter under sommaren 2015, året då studien genomfördes, hade vi svårt att se mycket tydliga resultat i alla tester. I vissa tester kunde vi däremot se att allergiker presterade sämre jämfört med kontrollgruppen under pollensäsongen, men även jämfört med sig sina egna resultat som de presterade när det inte var pollensäsong.

Nästa projekt fokuserade på svår astma. Vi inkluderade cirka 100 patienter från Sverige och Danmark. De fick först fylla i olika frågeformulär och cirka en tredjedel av alla patienter tackade ja till att fortsätta den andra delen av studien där de blev intervjuade. Vi kunde notera att endast lite av problemen påvisades med hjälp av frågeformulären, medan en helhetsbild framkom när patienterna intervjuades. Flertalet begränsningar påvisades och vi kunde se mer i detalj hur mycket dessa patienter faktiskt anpassade sitt liv på grund av sin svåra astma. Sjukdomen påverkade familje- och det sociala livet kraftigt och även den mentala hälsan. Det fanns en risk att dessa problem gick obemärkt förbi sjukvården eftersom de var knappt märkbara.

Tredje och fjärde arbetet fokuserade på nya metoder som skulle kunna användas för att utvärdera obstruktion i de små luftvägar hos astmatiker och hur denna

obstruktion korrelerade med symptomen och livskvaliteten. Vi inkluderade många patienter med astma, men även patienter med KOL, friska rökare och friska aldrig-rökare. Ett problem idag är att det är svårt att diagnostisera problem i de små luftvägarna med de vanliga metoderna, såsom spirometri, som finns tillgänglig på de flesta vårdcentraler. Vår metod som heter Forced Oscillation Technique kunde möjliggöra att mäta olika obstruktionsnivåer både vid inandning och utandning. Mätningarna som gjordes vid utandning korrelerade bättre med symtom och livskvalitet. Dessutom kom vi fram till att de flesta befintliga frågeformulär som används för att utvärdera astma inte är specifika för symtom som kopplas till de små luftvägarna och en risk finns att problemet underskattas. Vi upptäckte att även frågeformulär som inte var så specifikt kopplade till astma symtom var också av betydelse eftersom de korrelerade väl med mätningarna av lungfunktionen. Dessutom, noterade vi att poänggränserna som används nuförtiden för att bedöma om astman är kontrollerad eller inte, tyvärr inte är så användbara när det finns försämring långt ute i de små luftvägarna.

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When you breath in (inhale), air enters your lungs, and oxygen from that air moves to your blood. At the same time, carbon dioxide, a waste gas, moves from your blood to the lungs and is breathed out (exhaled). This process is essential to life. How well this process functions is essential to quality of life.

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