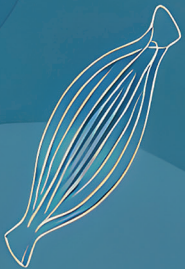
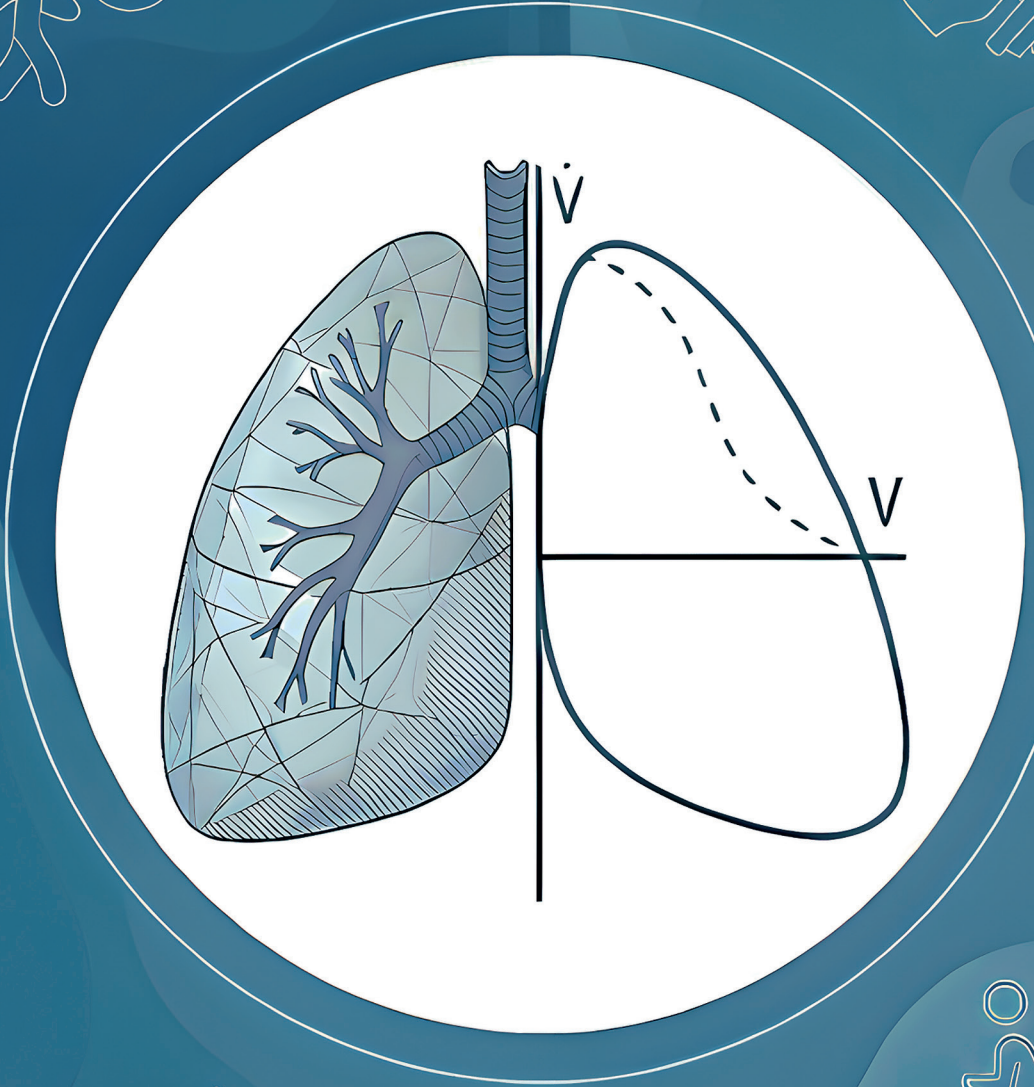


Extrapulmonary features of patients with asthma

Roy Meys



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Roy Silverius Agnes Meys

The research presented in this thesis was conducted at Ciro in Horn. The work was carried out in close collaboration with the Research Institute of Nutrition and Translational Research in Metabolism (NUTRIM) in Maastricht. This research was supported by a grant from the Lung Foundation Netherlands (#5.1.18.232). Data from the U-BIOPRED consortium were used in this study.

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Design: Proefschrift AIO | Guus Gijben

Cover: Tess Beurskens, Bente Brauwerts & OpenAI

Printing: Proefschrift-aio.nl

ISBN: [ISBN]

DOI: 10.54195/[ISBN]

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Printing of this thesis was financially supported by Maastricht University, Stichting Astma Bestrijding and Lung Foundation Netherlands (Longfonds).

Extrapulmonary features of patients with asthma

PROEFSCHRIFT

voor het behalen van de graad van Doctor aan de Universiteit Maastricht,
onder gezag van Rector Magnificus, prof. dr. Pamela Habibović,
overeenkomstig met het besluit van het College van Decanen,
te verdedigen in het openbaar op donderdag 28 mei 2026, om 16:00 uur

door

Roy Silverius Agnes Meys

Promotores

Prof. dr. M.A. Spruit, Universiteit Maastricht

Prof. dr. F.M.E. Franssen, Universiteit Maastricht

Beoordelingscommissie

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Dr. E.J. Weersink, Amsterdam UMC

Em. Prof. dr. G. Wesseling, Universiteit Maastricht

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1. Performing only one six minute walk test in patients with asthma results in underestimation of their functional exercise capacity. *(this dissertation)*
2. In order to assess low muscle mass in obese patients with asthma, physiological determinants (age, sex and BMI) must be taken into account. *(this dissertation)*
3. The wide variety of problematic activities of daily living and the absence of a strong association with clinical determinants emphasize the need for using individualized interview-based performance measures in patients with asthma. *(this dissertation)*
4. Asthma exacerbations cannot adequately be predicted from disease-specific patient-reported outcome measures or clinical variables such as age and lung function. *(this dissertation)*
5. Management of asthma requires not only optimal pharmacotherapies, but also a broader, trait-based approach focused on restoring functioning and wellbeing. *(this dissertation, impact paragraph)*
6. Based on patient history and spirometry testing, primary care clinicians are able to reliably differentiate between asthma and COPD in persons with suspected chronic airways disease. *(Bouwens, npj Prim. Care Respir. Med, 2022)*
7. Current diagnostic and severity classifications in clinical practice poorly differentiate between clinical phenotypes of obstructive airways diseases that may have specific risks and treatment implications. *(Reddel, Eur Respir J, 2021)*
8. Patients with obstructive airway disease categorized as 'can't do, don't do' require a different treatment approach than patients in other categories of physical capacity and activity, as their clinical management must prioritize a more extensive cluster of extrapulmonary and behavioral treatable traits. *(Guerrero, ERJ Open Res, 2024)*
9. The real voyage of discovery consists not in seeking new landscapes but in having new eyes. *(Marcel Proust)*
10. Geneet van 't laeve, zolang este kins. *(Opa Huub/Sjef Diederren)*

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CHAPTER 1

General Introduction

Asthma

Asthma is a common, chronic respiratory condition affecting a substantial proportion of the worldwide population. The Global Initiative for Asthma (GINA) defines asthma as *"a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a 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"* (1). According to the World Health Organization (WHO), an estimated 262 million people were affected by asthma in 2019, and the disease was responsible for approximately 455,000 deaths (2). To this day, asthma remains a major global health concern across all age groups. Its prevalence continues to rise and varies significantly across countries, ranging from 1% to 29% of the population (1). These differences are influenced by factors such as environmental exposures, genetic predisposition, age distribution and socioeconomic conditions.

Asthma is also highly prevalent in the Netherlands. As of 2023, approximately 577,500 individuals were diagnosed with asthma (3). The impact of asthma extends beyond personal health, placing a significant burden on healthcare systems and society through increased costs and reduced productivity. In 2019, healthcare expenditures related to asthma in the Netherlands exceeded €444 million (3), with medication, hospitalizations, and primary care services being the main contributors to these costs.

A key aspect of asthma burden is the occurrence of exacerbations, which represent a change in symptoms and/or pulmonary function from the patient's usual status (e.g. "flare-ups"). Exacerbations may vary in severity, from mild events that can be managed at home or in primary care with increased use of reliever medication to more severe episodes requiring oral corticosteroids (OCS), emergency care, or hospitalization (1). Preventing asthma exacerbations is a primary goal of asthma management, and their frequency is a critical measure of how well asthma is controlled at both the individual and population level.

Asthma severity

Given the high prevalence and societal impact of asthma, it is important to consider the varying levels of disease control and severity. Asthma is a heterogeneous condition characterized by a broad spectrum of clinical presentations, ranging from

well-controlled disease with minimal symptoms to severe, persistent forms that are difficult to manage and associated with significant morbidity. A key distinction is that of *uncontrolled asthma*, which refers to poor symptom control and/or frequent exacerbations (≥ 2 /year) requiring OCS or serious exacerbations (≥ 1 /year) requiring hospitalization. When asthma remains uncontrolled despite treatment with medium- or high-dose inhaled corticosteroids (ICS) in combination with a long-acting beta-agonist (LABA) or with maintenance OCS to maintain symptom control, it is classified as *difficult-to-treat asthma*. Within this group, a smaller subset meets the criteria for *severe asthma*, defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA and management of contributing factors, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled (1). Data from the Netherlands indicate that approximately 4% of asthma patients meet the criteria for severe asthma (4), which places a large physical, mental, emotional, social and economic burden on patients. However, the impact of asthma is not determined by severity or control alone. Recent work in Dutch referral populations has shown that ‘treatable traits’ are common across the entire spectrum of asthma, including in patients with controlled disease, with only a small minority having none (5). The ‘treatable traits’ framework has been proposed to better account for the complexity of chronic respiratory diseases (6). This approach categorizes individuals based on “potentially modifiable elements” that influence symptoms and prognosis. These findings emphasize the need to look beyond severity classifications and highlight the importance of identifying and addressing traits in all patients.

Pulmonary traits of asthma

Given its widespread prevalence and impact, understanding the clinical manifestations of asthma is vital for unraveling its pathophysiology and developing effective management strategies. Asthma is primarily defined as a respiratory disease characterized by distinct pulmonary traits that reflect the underlying pathophysiological processes. These traits, airway inflammation, variable airflow limitation, bronchial hyperresponsiveness, and airway remodeling, are central to the clinical manifestations of asthma (7).

Airway Inflammation

Chronic airway inflammation is a hallmark of asthma, involving various immune cells such as eosinophils, mast cells, T-helper type 2 (Th2) lymphocytes, and cytokines. This inflammatory process leads to swelling of the airway walls and increased

mucus production, contributing to the characteristic symptoms of wheezing, coughing, and shortness of breath. Asthmatic inflammation varies in severity and patterns, often exacerbated by exposure to allergens, irritants, or respiratory infections, causing episodic worsening of symptoms (i.e. asthma exacerbations) (8).

Increasing focus has been placed on identifying inflammatory phenotypes, which reflect the dominant immune pathways driving the disease and help guide personalized treatment approaches. The two principal inflammatory phenotypes are Type 2 asthma and non-Type 2 asthma, each associated with specific immunological features, biomarker profiles, and treatment responsiveness.

Type 2 asthma, driven by Th2 cells and innate lymphoid cells type 2 (ILC2), is characterized by eosinophilic airway inflammation, elevated fractional exhaled nitric oxide (FeNO), and often IgE-mediated sensitization to environmental allergens. Patients with this phenotype typically respond well to ICS and may benefit from targeted biologic therapies. In contrast, non-Type 2 asthma is often non-eosinophilic, with neutrophilic or paucigranulocytic airway inflammation, and is less responsive to corticosteroids. Despite exciting advances in treatments for Type 2 asthma, there are limited therapeutic options available for management of non-Type 2 asthma (9).

Variable Airflow Limitation

Another central pulmonary feature of asthma is variable airflow limitation, traditionally characterized by episodic airway narrowing that is at least partially reversible, either spontaneously or following bronchodilator administration. This reversibility has long been a key clinical criterion to distinguish asthma from other chronic respiratory diseases, particularly chronic obstructive pulmonary disease (COPD) (1). However, recent large-scale observational studies, including NOVELTY, have highlighted substantial heterogeneity and overlap in pulmonary function patterns across asthma, COPD, and asthma-COPD overlap (ACO) populations, challenging the traditional dichotomy based on bronchodilator responsiveness.

An analysis of baseline characteristics in the NOVELTY population demonstrated marked heterogeneity within and considerable overlap between physician-assigned diagnoses of asthma and/or COPD. The NOVELTY study showed that persistent airflow limitation, defined by post-bronchodilator FEV1/FVC ratio below the lower limit of normal, was present in only around 64% of these patients with COPD. Interestingly, approximately 23% of patients diagnosed with asthma also exhibited persistent airflow limitation, indicating that fixed obstruction is not

exclusive to COPD. Additionally, bronchodilator responsiveness was observed in 13% of patients with COPD, as well as in those with ACO (19%) and asthma (16%), with responsiveness increasing alongside physician-assessed disease severity (10).

Bronchial Hyperresponsiveness

Asthma is also defined by an increased sensitivity of the airways, also known as bronchial hyperresponsiveness (BHR). Clinically, BHR testing can be useful for confirming variable airflow limitation when spirometry results are inconclusive. A negative test, particularly in a patient not currently using ICS, can help rule out asthma with reasonable confidence. However, a positive test is not specific for asthma and must be interpreted in context, as BHR can also be present in other conditions such as allergic rhinitis, cystic fibrosis, bronchopulmonary dysplasia, and COPD (11).

Airway Remodeling

In persistent asthma, repeated cycles of inflammation and repair can lead to structural changes in the airways, a process known as airway remodeling. These changes include thickening of the airway wall, subepithelial fibrosis, increased smooth muscle mass, and glandular hypertrophy, which can result in a fixed component of airflow limitation, reducing the reversibility of symptoms. Hence, airway remodeling contributes to chronic symptoms and reduced responsiveness to standard asthma treatments over time, making it a crucial target in the management of severe asthma cases (6).

Although patients with asthma can present in different ways, and these variations can partly be explained by disease severity, this does not fully capture the well-known heterogeneity of the disease. Viewing asthma solely as a pulmonary condition overlooks its broader complexity and limits individualized care. Increasing attention to extrapulmonary features and comorbidities reinforces the importance of the treatable traits approach, which encourages assessment beyond the airways and aims to identify measurable and modifiable factors in each patient, as described before.

Assessing extrapulmonary features in patients with asthma

Within the treatable traits framework, traits are grouped into three domains: pulmonary, extrapulmonary, and behavioral or risk factors. Among these, extrapulmonary traits are increasingly recognized for their significant impact

on disease burden (6). These may include, but are not limited to, skeletal muscle dysfunction, nutritional abnormalities, anxiety and depression, cardiovascular comorbidities, osteoporosis, and systemic inflammation (12). Accurate identification and assessment of these traits are critical for delivering individualized and effective interventions (1). This section will focus on the assessment of key extrapulmonary traits that are critical for improving patient-centered outcomes in asthma.

Deconditioning and exercise performance

Deconditioning refers to the decline in physical function and physiological reserve due to prolonged inactivity or illness (13). In chronic respiratory disease deconditioning is both a consequence and a driver of symptom burden, most notably dyspnea and fatigue, leading to a self-perpetuating cycle of inactivity and further functional decline (14). Exercise performance, therefore, becomes a critical measure of disease impact and a core target for interventions. It reflects the integrated functioning of multiple systems, including the cardiopulmonary, neuromuscular, metabolic, and psychological domains, and is highly sensitive to the presence of extrapulmonary features like skeletal muscle dysfunction and cardiometabolic comorbidities.

To assess deconditioning and exercise performance, various field-based and laboratory tests are used, each with specific advantages. Field walking tests, such as the 6-minute walk test (6MWT), are low-cost and easy to administer, providing an effective measure of functional capacity and response to interventions (15). While widely used in COPD and heart failure, the 6MWT's application in asthma is less defined (16). The need for further research into its reproducibility, responsiveness, and clinical relevance in asthma is critical to improving its use in assessing functional status and guiding exercise interventions in this population.

Externally paced field walking tests, such as the Incremental Shuttle Walk Test (ISWT) and Endurance Shuttle Walk Test (ESWT), are more standardized than the 6MWT, as the walking speed is set, reducing the influence of patient motivation or self-selected pacing. The ISWT measures maximal exercise capacity, while the ESWT evaluates endurance at a constant speed. Both tests are valuable tools for assessing exercise limitations and monitoring response to pulmonary rehabilitation, as they are less affected by patient motivation, making them highly useful for evaluating functional capacity in various respiratory conditions (15, 16).

Laboratory-based tests, such as treadmill and cycle ergometer tests, allow for controlled, incremental, or constant-load testing with detailed physiological

monitoring (17). These tests provide valuable insights into exercise performance, including measures like peak aerobic capacity, heart rate response, and ventilatory limitations. Like the treadmill, the cycle ergometer requires less space than field walking tests, allows more complex physiological data to be routinely recorded, and is suitable for both incremental and endurance protocols. The cycle ergometer provides a more stable platform than the treadmill and may be less affected by obesity than walking (17). However, some argue that cycling may not be familiar to many individuals with chronic respiratory disease, making it less relevant to daily activities. Both tests are highly reproducible and useful for assessing functional capacity, with the choice between them often depending on the patient's condition, resources, and specific clinical context (17).

Physical activity

Physical inactivity is common in individuals with chronic respiratory diseases, including asthma, and can contribute to worsened outcomes, independent of lung function abnormalities (18). Like COPD, inactivity in asthma may be linked to increased symptom burden, decreased exercise capacity, and a heightened risk of comorbidities such as obesity and cardiovascular diseases (19). In asthma, physical activity is often limited by symptoms such as shortness of breath, wheezing, and fatigue, which can create a cycle of deconditioning. This can lead to further deterioration in exercise performance and exacerbate the overall disease burden. Despite the importance of physical activity, studies have shown mixed results when it comes to the relationship between exercise capacity and physical activity levels (20). While interventions like bronchodilators or oxygen therapy improve exercise capacity in asthma patients, they do not always translate into increased daily physical activity (20). Physical inactivity and deconditioning in asthma can significantly reduce an individual's ability to engage in daily physical activities, including activities of daily living (ADLs), which in turn complicates overall disease management.

Functional status

Functional status refers to an individual's ability to complete activities necessary for meeting basic physical, psychological, and social needs (21). Measurement of functional status can be multidimensional; functional capacity assesses an individual's maximal potential to perform activities, functional performance measures what a person actually does in daily life. In individuals with asthma, difficulty performing basic daily activities, such as bathing, walking the stairs and household activities will often drive them to seek healthcare advice (22). However, given the significant variability in individual goals and physical limitations, daily

activities may vary greatly in terms of importance to each patient. The complexity of daily activities involves multiple factors, including frequency, duration, difficulty, and satisfaction with performance, which are not adequately reflected in any one instrument (23).

Functional status scales typically include a predefined list of activities commonly deemed problematic, where patients rate their ability to complete these tasks. Examples of these scales include the Manchester Respiratory Activities of Daily Living Scale (24), the Pulmonary Functional Status and Dyspnea Questionnaire (25), and the London Chest Activity of Daily Living (24). An alternative to these standardized scales is the Canadian Occupational Performance Measure (COPM), a semi-structured interview that assesses an individual's functional performance. The tool has proven to be reliable and sensitive to changes, for example after pulmonary rehabilitation (PR) in patients with COPD (26, 27). The COPM, albeit more time intensive to complete, captures challenges in ADLs that may not be reflected by general tests or questionnaires, offering a more comprehensive view of a patient's functional status. Given the variability in how asthma affects daily life, it is reasonable to hypothesize that patients with asthma may identify a broad range of problematic ADLs that are not fully addressed by standard questionnaires with predefined tasks. Further exploring problematic ADLs in asthma patients using the COPM could provide valuable insights into the specific functional limitations they face, allowing for more tailored interventions that address the unique challenges of managing asthma in daily life.

Body weight and composition abnormalities

Abnormalities in body weight and composition, including obesity and sarcopenia, play a significant role in the clinical presentation of chronic diseases, including asthma. These abnormalities can have a profound impact on symptom severity, disease progression, and overall health outcomes (28).

Obesity is now recognized not only as a comorbidity but also as a risk factor for the development of asthma. Epidemiological data consistently show that individuals with obesity have an increased risk of asthma, particularly non atopic forms. Beyond increased incidence, a distinct “obese asthma” phenotype has been identified, characterized by greater symptom burden, poorer disease control, and a diminished response to standard anti-inflammatory therapies. This phenotype is often associated with a non-eosinophilic inflammatory profile, indicating distinct underlying pathophysiological mechanisms (29, 30).

Traditional anthropometric measures, such as body mass index (BMI) and waist circumference, have been used to assess obesity and fat mass in asthma patients. However, these metrics often fail to capture critical aspects of body composition, such as lean muscle mass (LM), potentially masking the presence of sarcopenia in overweight or obese individuals. To overcome this limitation, more refined indices have been introduced that differentiate between fat and muscle compartments. One such measure is the appendicular lean mass index (ALMI), which expresses lean mass in the limbs relative to height and can help detect low muscle mass even in individuals with a high BMI (31).

Sarcopenia, characterized by a progressive loss of muscle mass and strength, is another body composition abnormality seen in obstructive pulmonary disease (32), particularly in patients with ongoing systemic inflammation or prolonged corticosteroid use (33, 34). The concurrent presence of obesity and sarcopenia, referred to as sarcopenic obesity (SO), has been linked to greater functional decline and increased morbidity and mortality in the general population (35). Recent studies have highlighted the potential role of SO in asthma (35), yet the prevalence and functional consequences of low muscle mass and SO in asthma patients are not well understood. Given the high prevalence of obesity among asthma patients, comprehensive assessment of body composition, including indices such as ALMI, is essential to better understand the interplay between fat accumulation, muscle loss, and functional outcomes in this population.

Patient-Reported Outcome Measures (PROMs)

PROMs are essential tools in asthma care, providing direct insight into the patient's perspective on health status, symptom burden, functional impairment, and emotional well-being (36). Unlike physiological or clinical indicators, PROMs capture subjective experiences that are often not detectable through standard diagnostic tests, yet critically influence disease perception, treatment adherence, and overall quality of life.

Health-Related Quality of Life (HRQoL) is frequently impaired in individuals with asthma, even in those with mild disease (37). PROMs such as the Asthma Quality of Life Questionnaire (AQLQ) and its shorter version (Mini-AQLQ) are widely used and validated instruments that assess domains including symptoms, activity limitation, emotional function, and environmental exposure (38). These tools have been instrumental in evaluating the effectiveness of both pharmacological and non-pharmacological interventions (39).

Symptom burden in asthma, including shortness of breath, wheezing, chest tightness, and cough, can fluctuate over time and may be influenced by both physiological and psychosocial factors. PROMs like the Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT) are commonly used to quantify symptom control and guide treatment decisions (40, 41). These instruments allow clinicians to track changes over time and align management strategies with patient-reported needs. Psychological distress, including anxiety and depression, is highly prevalent in asthma and is often underrecognized (42). These symptoms can negatively impact asthma control, worsen quality of life and increase healthcare utilization (43). Instruments such as the Hospital Anxiety and Depression Scale (HADS) or the Patient Health Questionnaire (PHQ-9) offer a reliable means to identify and monitor psychological symptoms (44, 45). Addressing these aspects is crucial, as untreated anxiety and depression are associated with poor asthma outcomes, including reduced adherence to medication and higher risk of exacerbations (46).

Since traditional metrics like FEV₁ correlate only weakly with how patients experience their condition, there is a clear need for a more holistic, patient-centered approach. PROMs offer a unique window into the lived experience of asthma, capturing aspects of the disease burden that cannot be assessed by clinical tests alone. However, their application in routine clinical care remains limited. Investigating how PROMs change over time in response to real-world events such as exacerbations, and whether they can predict such events, may enhance individualized care and support clinical decision-making in patients with severe asthma.

Treatment of asthma

Asthma management aims to control symptoms, prevent exacerbations, and improve quality of life. Ultimately, remission of asthma is the aim of treatment: a state where the disease's signs and symptoms are significantly reduced or eliminated, though it doesn't mean a complete cure. Clinical remission is typically defined as the absence of asthma symptoms and exacerbations for at least 12 months, a stable or optimized lung function, and no need for oral corticosteroids (OCS). Some definitions include additional criteria like low inflammatory markers for "biological remission" (1). The treatment approach includes a variety of strategies, ranging from inhaler medications and biological therapies to non-pharmacological interventions such as pulmonary rehabilitation (PR). These strategies can either be implemented independently or in combination, depending on disease severity.

Medication

The pharmacological management of asthma aims to control airway inflammation, reduce bronchoconstriction, and prevent exacerbations, thereby improving overall pulmonary function and quality of life. Various classes of medications are employed, each targeting specific pathophysiological mechanisms involved in asthma.

ICS are the cornerstone of asthma management due to their potent anti-inflammatory effects by inhibiting the transcription of pro-inflammatory genes, reducing the release of cytokines, and suppressing the infiltration of inflammatory cells, such as eosinophils and T lymphocytes, into the airway. The combination of formoterol (or alternative LABAs) with ICS is particularly effective in reducing the frequency of exacerbations and improve asthma control over time (47).

Bronchodilators are primarily used to alleviate acute symptoms by relaxing bronchial smooth muscle and improving airflow. Short-acting beta-agonists (SABAs) exert their effects through the activation of beta-2 adrenergic receptors, leading to rapid bronchodilation. LABAs, such as formoterol, provide sustained bronchodilation over extended periods of time and are commonly prescribed in conjunction with ICS. Nowadays, GINA recommends that low-dose ICS-formoterol is preferred to SABA as reliever therapy in asthma, across the range of asthma severity (1).

Leukotriene modifiers, such as Montelukast, are oral medications that target leukotrienes, pro-inflammatory lipid mediators derived from arachidonic acid. Leukotrienes contribute to airway inflammation, bronchoconstriction, and mucus hypersecretion in asthma. By inhibiting the leukotriene receptor, these agents reduce the inflammatory cascade and provide symptomatic relief, particularly in patients with neutrophilic asthma or those with concomitant allergic rhinitis. However, the indication for leukotriene modifiers is very limited and mainly considered for patients with contraindications to inhaled ICS (48).

Oral corticosteroids are typically reserved for the management of adults with severe asthma (49). Agents such as prednisone rapidly suppress airway inflammation through genomic and non-genomic mechanisms, including the inhibition of pro-inflammatory cytokine production and the reduction of immune cell activity. However, due to their significant side-effect profile with long-term use, oral corticosteroids are only recommended for short-term use and are generally employed during acute exacerbations of asthma or in patients with poor-symptom control (50).

For patients with severe asthma that is inadequately controlled by conventional pharmacotherapy, *monoclonal antibody (mAb) therapies* (“biologics”) offer a targeted approach by modulating the immune system. Biological therapies have shown to significantly reduce asthma exacerbations, improve lung function, and decrease the need for oral corticosteroids (51).

Omalizumab is an anti-IgE mAb that binds to free IgE, preventing its interaction with high-affinity IgE receptors on mast cells and basophils. This inhibition reduces the release of inflammatory mediators and cytokines involved in allergic reactions. Omalizumab is particularly effective in patients with allergic asthma and elevated IgE levels (52).

mAbs targeting type 2 inflammation include *Mepolizumab*, *Reslizumab*, and *Benralizumab*, which inhibit interleukin-5 (IL-5) and reduce eosinophil-driven airway inflammation, a hallmark of eosinophilic asthma. *Dupilumab* blocks interleukin-4 (IL-4) and interleukin-13 (IL-13), key cytokines in Th2-mediated pathways that regulate IgE production, eosinophilic inflammation, and airway remodeling. These biologics are effective in patients with severe Type 2 asthma and often those with associated atopic conditions (51).

In contrast, *Tezepelumab* targets thymic stromal lymphopoietin (TSLP), a cytokine involved in initiating broader inflammatory pathways. By inhibiting TSLP, Tezepelumab addresses both eosinophilic (Type 2) and non-eosinophilic (non-Type 2) inflammation, making it a promising treatment for severe asthma patients across inflammatory phenotypes, including those less responsive to corticosteroids (53).

Pulmonary Rehabilitation

A comprehensive approach to asthma management recognizes the essential role of both pharmacological and non-pharmacological interventions in optimizing patient outcomes. While pharmacological therapies primarily target the underlying inflammation and bronchoconstriction, non-pharmacological strategies have increasingly been recognized for their complementary benefits. Recent studies have highlighted the importance of incorporating these interventions alongside traditional pharmacological treatments to improve overall disease management, particularly in patients with severe asthma. Non-pharmacological interventions such as smoking cessation, weight loss interventions, as well as promoting regular physical activity and adherence to therapy, constitute fundamental components of asthma management. These strategies aim to reduce asthma symptoms, improve lung function, and decrease the frequency of exacerbations aimed at improving

asthma control. These measures represent essential initial steps to reduce symptoms and prevent exacerbations by targeting modifiable risk factors. However, they differ from multidisciplinary approaches such as PR.

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) define PR as *“a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors”* (54).

Similar to COPD, asthma presents as a complex disease with varying pulmonary and extrapulmonary manifestations and frequently associated comorbidities. PR is a targeted intervention, not indicated for all patients with asthma but specifically for those with difficult-to-treat or severe asthma in whom multiple (>2) treatable traits contribute to persistently poor asthma control and/or recurrent exacerbations (55). It represents a valuable component of the management plan for patients whose limitations persist despite optimal standard care.

By integrating PR into asthma management, patients can improve their exercise capacity, reduce anxiety and depression, and achieve better asthma control. These benefits, alongside the reduction of bronchial inflammation, align with the aims of integrated care, ultimately improving both physical and psychological health outcomes for patients with asthma. Both in asthma and COPD, health behavior change plays a critical role in optimizing treatment outcomes and maintaining long-term benefits. PR might help to facilitate these changes by not only improving physical functioning (e.g. physical capacity) through tailored exercise programs but also providing education on asthma self-management, inhaler technique, and trigger avoidance. This holistic approach encourages patients to actively engage in their care, which enhances adherence to pharmacological treatments and reduces asthma-related symptoms, exacerbations, and hospitalizations.

One of the key outcomes of PR is the enhancement of *physical functioning*. Through aerobic and strength training exercises, patients with asthma experience improvements in exercise capacity, endurance and muscle strength. To date, it remains inconclusive whether and to what extent an increase in physical functioning following exercise-based PR can improve asthma control and disease-specific quality of life. While some studies have reported improvements in these outcomes, others have not. A recent systematic review by Hansen et al. did, however,

demonstrated a significant improvement in the asthma control (measured by ACQ) in patients with asthma following supervised exercise training (56). In patients with COPD, enhancing physical capacity alone has been shown to be insufficient for improving patients' physical activity (57). While improvements in physical capacity may reflect better physiological performance, they do not necessarily translate into increased daily physical activity levels (58). Factors such as motivation, behavior, and environmental influences also play a critical role in sustaining physical activity, highlighting the need for comprehensive interventions beyond just improving physical capacity.

Beyond physical functioning, PR has been shown to significantly improve *asthma control* and *quality of life* (59-61). Structured PR programs that include education on asthma management strategies, proper inhaler techniques, and trigger avoidance empower patients to better self-manage their condition. This education also fosters increased adherence to pharmacological treatments and helps in reducing the frequency and severity of asthma exacerbations. Furthermore, PR is associated with a decrease in the emotional burden of asthma, such as *symptoms of anxiety and depression*, which are commonly experienced by individuals with chronic respiratory conditions. The psychological support provided through PR programs can improve overall well-being and reduce the sense of helplessness that often accompanies poorly controlled asthma.

In conclusion, integrating pulmonary rehabilitation into the asthma management plan offers substantial benefits in improving clinical outcomes. However, the lack of well-defined Minimally Important Differences (MIDs) in asthma presents a challenge in evaluating the true effectiveness of treatments like PR. MIDs represent the smallest change in a clinical outcome that patients perceive as meaningful, and they are essential for determining the "real-world impact" of interventions (61). However, to date, the establishment of MIDs for various outcomes remains insufficiently researched in asthma.

While improvements in clinical metrics may be statistically significant, it is the MID that provides insight into whether these changes are meaningful from the patient's perspective. In the absence of clear MIDs, it is difficult to draw reliable conclusions about how interventions translate into tangible improvements in patients' daily lives. Further research is needed to establish MIDs for asthma-specific outcomes to guide clinical decision-making, tailor individualized treatment plans, and improve the overall management of asthma.

Aim and outline of this thesis

The main aim of this thesis is to expand existing knowledge regarding the extrapulmonary features of asthma, with a particular focus on their assessment and the impact of pulmonary rehabilitation.

In **Chapter 2**, the measurement properties of the 6MWT, a widely used field walking test to assess functional exercise capacity in patients with respiratory diseases, are examined. This chapter focuses on its reliability, construct validity, and the determinants of the 6MWD in patients with asthma.

Body composition abnormalities as extrapulmonary manifestations of asthma are investigated in **Chapter 3**, specifically focusing on the prevalence and functional consequences of low ALMI and SO in patients attending PR.

Self-reported limitations in ADLs among asthma patients are described in **Chapter 4**. This chapter highlights the most frequently reported problematic ADLs using the COPM and analyzes their associations with clinical determinants.

Chapter 5 presents an analysis of PROMs in adult patients with severe asthma, with a particular emphasis on how asthma exacerbations affect changes in PROMs over time and the ability of asthma-specific PROMs to predict future exacerbations.

The development of MIDs for clinical outcomes of PR in patients with asthma is explored in **Chapter 6**. This chapter also examines how MIDs vary based on baseline characteristics.

Finally, **Chapter 7** presents a general discussion, outlining the clinical implications of this thesis and exploring future perspectives.

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2

CHAPTER 2

Test-retest reliability, construct validity and determinants of 6-minute walk test performance in adult patients with asthma

Meys R, Janssen SMJ, Franssen FME, Vaes AW, Stoffels AAF, van Hees HWH, van den Borst B, Klijn PH, Burtin C, van 't Hul AJ, Spruit MA.

Pulmonology. 2023 Nov-Dec;29(6):486-494.

Doi: **10.1016/j.pulmoe.2022.10.011.**

Abstract

Introduction and Objectives: Current knowledge regarding the measurement properties of the 6-minute walk test (6MWT) in patients with asthma is limited. Therefore, the aim of this study was to assess the test-retest reliability, measurement error and construct validity of the 6MWT and identify determinants of 6-minute walk distance (6MWD) in patients with asthma.

Patients and Methods: 201 asthma patients referred for pre-pulmonary rehabilitation assessment, were retrospectively analyzed (age 61 ± 12 years, 42% male, FEV1 $78 \pm 27\%$ predicted). Patients performed two 6MWTs on subsequent days using a 30-meter straight walking course. Other measurements included resting dyspnea, maximal exercise capacity, body composition, pulmonary function, pulmonary and quadriceps muscle strength and symptoms of anxiety and depression. Measurement error (absolute reliability) was tested using standard error of measurement (SEM), minimal detectable change at 95% confidence interval (MDC95%) and Bland and Altman 95% limits of agreement, whereas test-retest reliability (relative reliability) and construct validity were assessed using the intra-class correlation coefficient ($ICC_{2,1}$) and correlations, respectively.

Results: The 6MWD showed excellent test-retest reliability ($ICC_{2,1}$: 0.91). The mean change in 6MWD after the second 6MWT was 18m (95%CI 11-24m), with 73% of the patients walking further in the second test. The SEM and MDC95% for the 6MWT were 35 m and 98 m, respectively. The best 6MWD correlated strongly with peak oxygen uptake during CPET and resting dyspnea ($r = 0.61-0.64$) and had no-to-moderate correlations with body composition, pulmonary function, respiratory and quadriceps muscle strength and symptoms of anxiety and depression ($r = 0.02-0.45$). Multiple linear regression was able to identify maximal workload, BMI, rollator use, maximal expiratory pressure, FEV₁ and DL_{CO} as independent determinants of the best 6MWD ($R^2 = 0.58$).

Conclusions: The 6MWT was considered to be reliable and valid in patients with asthma, which strengthens its clinical utility. However, the majority of patients demonstrated a considerable learning effect in the second 6MWT, providing a strong rationale for performing two 6MWTs.

Introduction

Asthma is a chronic respiratory disease with variable expiratory airflow limitation, usually characterized by chronic airway inflammation, that affects many individuals worldwide and inflicts a great burden on society (1). Due to its complex and heterogeneous nature, asthma typically presents with a variety of respiratory and non-respiratory symptoms (2, 3) and is associated with significant comorbidity and an increased mortality risk (4, 5). Currently, asthma management is primarily focused on respiratory symptoms (i.e. pharmacotherapy) (6), potentially overlooking the impact of extra-pulmonary manifestations, including exercise limitation and decreased physical activity, which are commonly reported irrespective of impairments in pulmonary function (7-9). Considering the fact that impaired physical functioning is a common feature in patients with chronic respiratory disease (10, 11), it is essential for healthcare professionals and clinical scientists to use valid and reliable measures when assessing functional exercise capacity. Tests with good measurement properties are needed to ensure patient progress is well-monitored and above all, accurate. Moreover, daily practice requires tests that are quick and easy to perform in order to guard time management and to retest patients and monitor changes efficiently.

The 6-minute walk test (6MWT) is an easy-to-administer, generally well tolerated and safe field walking test, commonly used as a clinical indicator of functional exercise capacity and a predictor of morbidity and mortality across a wide range of cardiopulmonary diseases (12, 13). The reliability and construct validity of the 6MWT have been demonstrated in several patient populations, such as chronic obstructive pulmonary disease (COPD) (14), chronic heart failure (15) and idiopathic pulmonary fibrosis (16). Despite the fact that the 6MWT can provide insights in functional limitation in chronic respiratory disease, current knowledge regarding its measurement properties (e.g. reliability, construct validity) in patients with asthma is limited. A considerable learning effect of the 6MWT has been previously established in patients with COPD (13, 14), with the majority of individuals showing an increase in 6-minute walk distance (6MWD) when a second test is performed without any intervention or alteration in clinical characteristics. Information regarding this learning effect in patients with asthma is highly limited (17). It seems reasonable to hypothesize that the test-retest reliability of the 6MWT will be good in patients with asthma, since a systematic review by Singh et al. (2014) examining field walking tests in chronic respiratory disease stated that intra-class correlation coefficients (ICC's) ranged from 0.82 to 0.99 (13). However, the limits of agreement reported in the included studies were large, indicating that there is a

certain amount of measurement error and the results from the first test may not be able to predict the outcome of the second test. Therefore, the current study aimed 1) to investigate the measurement error and test-retest reliability of the 6MWT, quantifying a potential learning effect between tests; 2) to evaluate the construct validity of the 6MWT; and 3) to identify the clinical determinants of the best 6MWD in a large cohort of patients with asthma.

Methods

In a retrospective observational study, 217 adult patients with asthma referred for a pre-pulmonary rehabilitation assessment at Ciro (Horn, the Netherlands) between September 2015 and January 2019, were screened for eligibility. Patients were included in the current analysis if they met the following criteria: respiratory physician-based diagnosis of asthma, based on an initial identification of both a characteristic pattern of symptoms and variable expiratory airflow limitation according to national and international guidelines (1), clinical stability at the time of the assessment (absence of current asthma attack); and two 6MWTs performed on subsequent days. The medical ethics committee of Maastricht University stated that the Medical Research Involving Human Subjects Act (WMO) did not apply for this study and that an official approval of this study by the committee was not required (METC azM/UM 2019-1081).

6MWT

Two 6MWTs were performed according to the official European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (12, 18) on subsequent days using a 30-meter straight walking course using cones as turnaround points. Use of walking aids (cane, rollator, etc.) was allowed during the 6MWTs and patients were instructed to take all usual medications. Patients were instructed to walk as far as possible and the distance walked (6MWD) was registered after each test. All tests were supervised by a trained and qualified technician who walked behind the patient, providing them with standardized phrases for encouragement every minute and informing them about the remaining time of the test. Patients were permitted to stop (if required) during the test, but were instructed to resume walking once they were able to. Heart rate (beats/min) and oxygen saturation (SpO_2) as measured by pulse oximetry were assessed before, during and at the end of the 6MWTs and perceived dyspnea and leg fatigue (modified Borg scale; range 0-10) were assessed at the start (at rest) and at the end (at peak exertion) of the test. Oxygen supplementation was used if required, and oxygen desaturation

during the 6MWT was defined as a drop of $\geq 4\%$ in SpO_2 and an end- SpO_2 of $< 88\%$. The predicted 6MWD reference values of Troosters et al. were used (19).

Other measurements

Demographics, anthropometrics, medication use (including maintenance oral corticosteroids (OCS)), smoking status, asthma attack/hospitalization frequency and the use of oxygen and/or walking aids (rollator or cane) were assessed, as part of standard care. To characterize patients with eosinophilic asthma, blood eosinophils were measured as part of the complete blood count plus differential, using cut-off values of both ≥ 150 cells/ μL and ≥ 300 cells/ μL (20). The modified Medical Research Council (mMRC) scale was used to evaluate the level of functional limitation due to dyspnea in activities of daily living. The mMRC is a five-point scale, ranging from 0 (dyspnea only with strenuous exercise) to 4 (too dyspneic to leave the house or breathless when getting dressed), in which a higher grade indicates higher functional disability due to dyspnea (21).

Pulmonary function (Masterlab®, Jaeger, Würzburg, Germany) was measured according to ATS/ERS guidelines using spirometry, with forced expiratory volume in the first second (FEV_1) and FEV_1 /forced vital capacity (FVC) ratio as primary outcomes (22), and whole-body plethysmography, providing residual volume (RV), total lung capacity (TLC) and the RV/TLC ratio (23). Furthermore, respiratory muscle strength, using maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) measurements, was determined (24).

Whole-body dual energy X-ray absorptiometry (DEXA) provided information about body composition, by means of lower-limb lean muscle mass (LL-LMM) and calculating fat-free mass (FFM) based on the sum of both lean and mineral bone mass (25). Subsequently, body mass index (BMI) and FFM index (FFMI) was calculated as body weight (kg) and FFM (kg) divided by height squared (m^2), respectively. Mood status was assessed with the 14-item Hospital Anxiety and Depression Scale (HADS), in which higher scores are equivalent to more symptoms of anxiety or depression (26). Maximal exercise capacity was evaluated with a symptom limited incremental ($+10$ W/min) cardiopulmonary exercise test (CPET) performed on a cycle ergometer (Carefusion, Houten, The Netherlands; Oxycon β , Jaeger, Würzburg, Germany), of which maximal power output (W_{max}) and peak oxygen consumption ($\text{VO}_{2\text{peak}}$ in mL/min/kg) were the main outcomes (27, 28). Isokinetic quadriceps muscle strength, defined as the highest peak torque in Nm ($\text{PT}_{\text{quadriceps}}$), was determined using a computerized dynamometer (Biodex System 4 Pro, Biodex Medical Systems, New York, USA) (29, 30).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, USA) and GraphPad Prism 9.0 (GraphPad Software Inc., California, USA). Descriptive statistics are used to present the data, as appropriate. The data was screened for extreme outliers, after which none were identified. Continuous variables were tested for normality using the Shapiro-Wilk test. The measurement properties of the 6MWT have been assessed according to the taxonomy developed by the COSMIN initiative (31). Accordingly, measurement error (as a measure of absolute reliability) was analyzed using standard error of measurement (SEM; $SD \cdot (\sqrt{1-ICC})$), the minimal detectable change at 95% confidence interval (MDC95%; $1.96 \cdot SEM \cdot \sqrt{2}$) and Bland and Altman 95% limits of agreement (31). The two-way random ICC with single measures (ICC2,1) (32) was calculated to assess the test-retest reliability (as a measure of relative reliability) of the 6MWT (31). Furthermore, the reproducibility of the 6MWT was studied after stratification for sex, age and smoking status. Logistic regression models adjusted for age, sex and BMI were used to identify predictive factors of a change in 6MWD of at least 27 m, which is the minimal clinically important difference (MCID) in patients with asthma (33), between the two 6MWTs.

Construct validity was verified according to the COSMIN guidelines by testing convergent, discriminant and known-groups validity (31). Convergent validity concerns the degree to which a measure is related to other measures of similar constructs, while discriminant validity considers the degree to which a measure can be differentiated from measures of conceptually distinct constructs (34). To investigate convergent and discriminant validity, Pearson or Spearman correlation coefficients were calculated. It was hypothesized that the best 6MWD would show moderate to strong (positive) correlations ($r = 0.40-0.79$) (35) with measures of maximal exercise capacity, as measured with CPET (i.e., W_{max} and VO_{2peak} ; absolute values), which would support convergent validity. Regarding discriminant validity, we expected only weak to moderate associations ($r = 0.20-0.59$) (35) with absolute values of pulmonary function, body composition, $PT_{quadriceps}$ and symptoms of anxiety and depression (HADS-A and HADS-D). The ability of the 6MWT to discriminate between clinically diverse groups (known-groups validity) was assessed with analyses of variance (one-way ANOVA) with Tukey-HSD *post hoc* in patients grouped by mMRC score. It was hypothesized that patients with higher mMRC scores would have a lower mean 6MWD. Finally, a stepwise multiple linear regression model was built to identify independent determinants of the best 6MWD. Only explanatory variables with a significant correlation coefficient ($p < 0.05$) were used in the model (in absolute values). In case of singularity or multicollinearity (i.e., $r \geq 0.70$) between

two independent variables, only the variable with the strongest association with the best 6MWD was kept in the model. *A priori*, the level of significance was set at $p < 0.05$.

Results

Characteristics Two patients were not able to perform a 6MWT and 14 patients only performed one 6MWT (due to medical or administrative reasons) and were excluded accordingly. Demographic and clinical characteristics of 201 included patients with asthma (42% male; mean age 61 ± 12 years) are summarized in Table 1. The vast majority of patients (80%) showed abnormal BMI values, with more than half of the sample being obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). The proportion of patients on maintenance OCS was 19% (Supplemental Data, Table 1). Based on a blood eosinophil count $\geq 300 \text{ cells}/\mu\text{L}$, 32% and of the patients could be characterized as having eosinophilic asthma. Mean FEV_1 was $78 \pm 27 \%$ predicted and 79% of the patients had a mMRC dyspnea severity score of 2 or higher. Eighteen percent of the patients used a rollator and 2% used a cane as walking aid. Rollator use was significantly higher in females than in males ($p < 0.05$; Table 1). Forty-four percent of the patients never smoked, whereas 9% was a current smoker.

Table 1. Patient characteristics

<i>Characteristic</i>	<i>Total group</i>		<i>Females</i>		<i>Males</i>	
	<i>N</i>	<i>Value</i>	<i>N</i>	<i>Value</i>	<i>N</i>	<i>Value</i>
Age, years	201	61 ± 12	117	59.3 ± 12.3	84	$63.1 \pm 10.7^*$
Weight, kg	201	87.4 ± 22.0	117	83.8 ± 20.8	84	$92.4 \pm 22.7^*$
BMI, kg/m^2	201	31.0 ± 7.1	117	31.7 ± 7.3	84	30.1 ± 6.6
BMI $< 18.5/18.5$ – 24.99/25–29.99/ $\geq 30 \text{ kg/m}^2$, n (%)	201	2 (1)/41 (20)/52 (26)/106 (53)	117	0 (0)/24 (21)/28 (24)/65 (56)	84	2 (2)/17 (20)/24 (29)/41 (49)
LL-LMM, kg	201	16.6 ± 4.2	117	14.8 ± 3.2	84	$19.0 \pm 4.2^*$
FFM, kg	201	51.4 ± 11.1	117	45.7 ± 7.8	84	$59.2 \pm 10.2^*$
FFMI, kg/m^2	201	18.1 ± 2.8	117	17.3 ± 2.5	84	$19.3 \pm 2.8^*$
Smoking status (current/former/ non-smoker), n (%)	195	17 (9)/ 92 (47)/ 86 (44)	113	8 (7)/47 (42)/58 (51)	82	9 (11)/ 45 (55)/ 28 (34)
Blood eosinophil count, $\text{cells}/\mu\text{L}$	189	278 ± 244	108	252 ± 213	81	314 ± 277

Table 1. Continued

<i>Characteristic</i>	<i>Total group</i>		<i>Females</i>		<i>Males</i>	
	<i>N</i>	<i>Value</i>	<i>N</i>	<i>Value</i>	<i>N</i>	<i>Value</i>
Blood eosinophil count ≥ 150 cells/ μ L, n (%)	189	129 (68.3)	108	67 (57.3)	81	62 (73.8)*
Blood eosinophil count ≥ 300 cells/ μ L, n (%)	189	60 (31.7)	108	31 (26.5)	81	29 (34.5)
mMRC ≥ 2 , n (%)	201	159 (79.1)	117	97 (82.9)	84	62 (73.8)
Rollator, n (%)	201	37 (18.4)	117	30 (25.6)	84	7 (8.3)*
Cane, n (%)	201	4 (2.0)	117	1 (0.9)	84	3 (3.6)
FEV ₁ , L	201	2.08 $\pm$ 0.87	117	1.91 $\pm$ 0.73	84	2.33 $\pm$ 0.99*
FEV ₁ , % pred	201	78 $\pm$ 27	117	81 $\pm$ 26	84	74 $\pm$ 29
FEV ₁ /FVC ratio, %	201	60 $\pm$ 16	117	63 $\pm$ 15	84	56 $\pm$ 17*
RV, L	197	2.30 (1.89-2.94)	115	2.13 (1.75-2.63)	82	2.83 (2.16-3.23)*
RV, % pred	197	111 (89-133)	115	111 (92-139)	82	115 (88-131)
RV/TLC ratio, %	197	41 $\pm$ 10	115	42 $\pm$ 11	82	40 $\pm$ 8
TLC, L	197	5.98 $\pm$ 1.38	115	5.20 $\pm$ 0.90	82	7.06 $\pm$ 1.18*
TLC, % pred	197	104 $\pm$ 17	115	105 $\pm$ 17	82	103 $\pm$ 17
MIP, kPa	200	7.85 $\pm$ 2.57	116	6.92 $\pm$ 2.30	84	9.15 $\pm$ 2.36*
MIP, % pred	200	92 $\pm$ 27	116	95 $\pm$ 30	84	86 $\pm$ 22*
MEP, kPa	169	11.40 $\pm$ 3.92	107	10.32 $\pm$ 3.73	62	13.26 $\pm$ 3.54*
MEP, % pred	169	72 $\pm$ 25	107	76 $\pm$ 28	62	67 $\pm$ 18*
HADS-A, points	191	7 (4-10)	113	8 (5-10)	78	6 (4-10)
HADS-D, points	191	7 (4-10)	113	7 (4-10)	78	7 (3-9)
W _{max} CPET, watts	184	90 (68-115)	105	87 (66-101)	79	99 (69-129)*
VO _{2peak} CPET, ml/min/kg	172	16.4 $\pm$ 5.2	100	15.3 $\pm$ 4.5	72	17.8 $\pm$ 5.7*
VO _{2peak} CPET, % pred	168	79 (62-104)	96	92 (74-117)	72	64 (50-79)*
PT _{quadriceps} , Nm	146	101 $\pm$ 38	84	81 $\pm$ 25	62	127 $\pm$ 37*
PT _{quadriceps} , % pred	146	71 $\pm$ 19	84	69 $\pm$ 19	62	73 $\pm$ 19

Summary variables are presented as n (%) for discrete variables, mean $\pm$ standard deviation for quantitative variables or median (Interquartile range) for skewed variables. * $p < 0.05$ females vs. males. *Abbreviations.* BMI: body mass index; LL: lower-limbs; LMM: lean muscle mass; FFM: fat-free mass; FFMI: fat-free mass index; mMRC: modified Medical Research Council; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; HADS-A: Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale, Depression subscale; W_{max}: maximal achieved workload; CPET: cardiopulmonary exercise test; VO_{2peak}: peak oxygen consumption; PT_{quadriceps}: isokinetic peak torque of the quadriceps muscle.

Test-retest reliability and measurement error of the 6MWT

On average, patients walked 392 m (95% CI 376-408 m) in the first 6MWT and 410 m (95% CI 393-427 m) in the second 6MWT. The mean change in 6MWD was 18 m (95% CI 11-24 m) or 5% ($p < 0.001$). Seventy-three percent of the patients improved their 6MWD in the second test, with 39% having an increase of at least 27 m (MCID of the 6MWT in patients with asthma)(33). 11% of the patients decreased their 6MWD with ≥ 27 m. After stratification for sex, age and smoking status, no differences in terms of reproducibility of the 6MWT between these subgroups were shown (Supplemental Data, Table 2).

Test-retest reliability between the two 6MWTs was excellent, with an ICC value of 0.91 (95%CI 0.86-0.94; $p < 0.001$). The SEM and MDC95% for the 6MWT were 35 m and 98 m, respectively. Bland and Altman plots confirmed that the majority of patients increased their 6MWD during the second 6MWT (average difference: 18m; Figure 1). The limits of agreement between first and second 6MWTs ranged from -75 to 110 m. Logistic regression models showed that none of the specific patient characteristics were associated with a lower or higher likelihood of having a meaningful increase in 6MWD (≥ 27 m(33)) in the second 6MWT (Supplemental Data, Table 3).

On average, the change in oxygen saturation (ΔSpO_2) during the first and second 6MWT was -1.9% and -2.0% (Supplemental Data, Table 4). Of the 201 patients, 20 patients (10.0%) showed a desaturation in 6MWT1 and 25 patients (12.4%) in 6MWT2. The reliability of ΔSpO_2 when two 6MWTs were performed was only modest (ICC 0.68; $p < 0.001$). When comparing the change in heart rate and Borg symptom scores, relative reliability was modest with ICC's ranging from 0.44–0.57 ($p < 0.001$, Supplemental Data, Table 4).

Construct validity of 6MWD

The mean 6MWD on the best test was 418 m (95% CI 402-435 m) or 68% of the predicted values (95% CI 65-70% predicted). In Table 2, correlation coefficients between the best 6MWD and other outcomes are presented. A strong correlation was found with $\text{VO}_{2\text{peak}}$ ($r = 0.61$) and mMRC score ($r = -0.64$), whereas W_{max} presented a moderate correlation ($r = 0.50$). Regarding pulmonary function, FEV_1 , RV and FEV_1/FVC ratio showed very weak correlations ($r = 0.08$ -0.19), and TLC and RV/TLC ratio weak correlations ($r = 0.26$ and -0.21) with best 6MWD. Very weak-to-moderate correlations were found with age, measures of body composition (BMI, FFM, and LL-LMM), MIP/MEP, $\text{PT}_{\text{quadriceps}}$, HADS-A and HADS-D (i.e., $r = 0.02$ –0.45; Table 2). Mean 6MWD decreased as functional impairment attributable to dyspnea (mMRC scores) increased, supporting known-groups validity (Figure 2). ANOVA

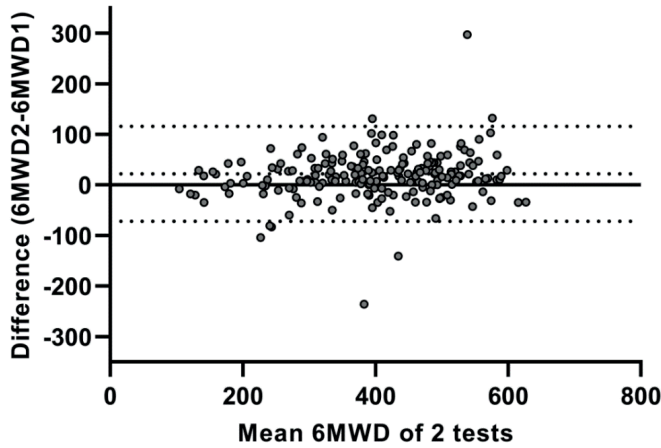


Figure 1. Bland and Altman plot illustrating the difference in six-minute walking distance (6MWD; in meters) between two 6-minute walk tests (6MWTs) conducted on a 30 m straight point-to-point course, plotted against the mean value of these two tests in patients with asthma. The central continuous line represents the zero line; the central dotted line corresponds to the average difference (bias) between the two 6MWTs (18 m); and the lower and upper dotted lines correspond to the lower 75 m) and upper (110 m) limits of agreement, respectively.

Table 2. Correlations between best 6-minute walk distance and other outcome measures in patients with asthma.

Outcome measure	<i>n</i>	Pearson <i>r</i>	<i>p</i> -value
Age, years	201	-0.15	0.037
Weight, kg	201	-0.25	<0.001
BMI, kg/m ²	201	-0.38	<0.001
LL-LMM, kg	201	-0.03	0.664
FFM, kg	201	-0.02	0.832
FFMI, kg/m ²	201	-0.18	0.013
mMRC score, points	201	-0.64	<0.001
FEV ₁ , L	201	0.19	0.006
FEV ₁ /FVC ratio, %	201	-0.08	0.242
RV, L	197	0.08 [*]	0.297
TLC, L	197	0.26	<0.001
RV/TLC ratio, %	197	-0.21	0.004
MIP, cmH ₂ O	200	0.45	<0.001
MEP, cmH ₂ O	169	0.37	<0.001
HADS-A, points	191	-0.15	0.040
HADS-D, points	191	-0.22	0.002
W _{max} CPET, watts	184	0.50 [*]	<0.001
VO ₂ peak CPET, ml/min/kg	172	0.61	<0.001
PT _{quadriceps} , Nm	146	0.31	<0.001

See **Table 1** for definition of abbreviations. ^{*} Spearman's ρ correlation coefficient

showed a significant overall difference ($p < 0.001$) in best 6MWD among mMRC groups, with non-significant Tukey-HSD *post hoc* mean differences between mMRC score 0 and 1-2 and between mMRC score 3 and 4 (Figure 2).

Determinants of the best 6MWD

All the variables with a significant correlation coefficient ($p < 0.05$) were considered in a stepwise multiple linear regression model (Table 3). Weight had to be excluded due to *singularity* with BMI and VO_{2peak} had to be excluded due to *multicollinearity* with W_{max} (i.e., $r > 0.70$). As there was a significant difference in best 6MWD between male (463 ± 105 m) versus female patients (386 ± 119 m), sex was included as an independent variable in the model. In addition, the use of a rollator during the 6MWT was added to the regression model, since additional analyses showed that several patient characteristics and 6MWT performance were statistically different between patients who required a rollator and patients who did not (Supplemental Data, Table 5). Subsequently, the following variables were included in the model assessing the best 6MWD: age, sex, rollator use, BMI, FFMI, mMRC, FEV_1 , RV/TLC ratio, TLC, MIP, MEP, $PT_{quadriceps}$, HADS-A and HADS-D scores, and W_{max} . Out of these, W_{max} , rollator use, MEP, BMI and FEV_1 were shown to be independent determinants of the best 6MWD, explaining 58.4% of the variability (Table 3).

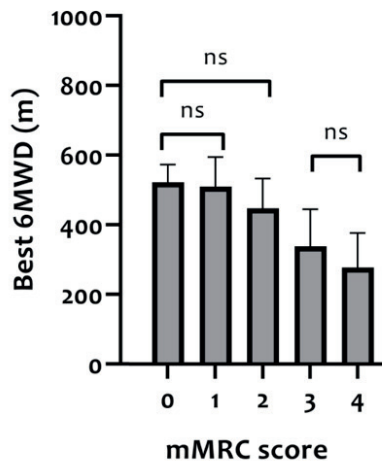


Figure 2. Distance covered in the 6MWT (best 6MWD) stratified according to modified Medical Research Council (mMRC) resting dyspnea severity scores in patients with asthma. The ability of the 6MWT to discriminate between clinically diverse groups (known-groups validity) was assessed with analyses of variance (one-way ANOVA) with Tukey-HSD *post hoc*. ns = non-significant difference between groups.

Table 3. Stepwise multiple linear regression analysis with the best 6MWD as the dependent variable.

(R ² = 0.584)						
	Unstandardized coefficients		Standardized coefficients		95%CI for B	
	B	Standard error	Beta	p-value	Lower Bound	Upper Bound
(Constant)	455.031	37.132	N/A	N/A	381.352	528.710
W _{max} CPET	1.469	.236	.609	<0.001	1.001	1.937
Rollator use	-87.277	24.634	-.255	0.001	-136.157	-38.397
MEP	6.344	1.715	.251	<0.001	2.941	9.746
BMI	-4.941	1.124	-.303	<0.001	-7.170	-2.711
FEV ₁	-34.906	11.555	-.289	0.003	-57.834	-11.979

See **Table 1** for definition of abbreviations. Variables entered in model: age, sex, rollator use, BMI, FFMI, mMRC, FEV₁, TLC, MIP, MEP, PTquadriceps, HADS-A and HADS-D scores, and Wmax.

Discussion

The 6MWT showed good test-retest reliability in patients with asthma when two tests were performed on subsequent days. Nevertheless, in the majority of patients the distance walked in the second test improved, indicating a consistent learning effect. As a matter of fact, about four in every ten patients increased their 6MWD in the second test with at least 27 meters, which is considered the MCID of the 6MWT in patients with asthma(33). This was supported by Bland and Altman analyses, presenting limits of agreement largely exceeding this 27 m cutoff. Our results also show that there is a large interval (MDC95% of 98 m) within which a patient’s true score will lie with repeated testing, 95% of the time, which suggests important within-participant variability on repeated testing in this population. Interestingly, none of the possible determinants were able to predict a clinically important increase in the second 6MWT in this patient population. Consequently, it is recommended to test all patients with asthma twice.

Numerous studies have reported a learning effect when repeated 6MWTs are performed in patients with COPD, with a pooled mean improvement of 26.3 m (13). To date, there is only one study available supporting a learning effect in asthma when two 6MWTs are performed on the same day (17). The learning effect of 19 m (95% CI 11–27 m) or 4%, with 80% of the patients walking further in the second test, is in line with the 18 m (or 5%) reported in our study, in which 73% of the patients improved their 6MWD in the second test. This is consistent with the general assumption that the learning effect is most probably present in different chronic respiratory diseases and even in healthy subjects (13, 36-38). The few

studies reporting exercise intolerance in patients with asthma using the 6MWT, all state that 6MWTs were performed in accordance with international guidelines, without specifying the use of a second test, hampering the interpretation of these results (3, 7, 39, 40). The learning effect established in the current study indicates that the vast majority of patients could have an underestimation regarding their baseline functional exercise capacity if only one 6MWT was performed. This is supported by the magnitude of the measurement error of the 6MWT in this study, which suggests that there is important within-patient variability on repeated testing. Thus, the well-known learning effect on the second 6MWT (13) is demonstrated for the first time in a large sample of asthmatics and our data provide a strong rationale for performing two 6MWTs in clinical settings as well as in clinical studies. To date, it remains unclear whether the learning effect extends beyond a second 6MWT. Current knowledge regarding the potential use of a third 6MWT is based on small studies in patients with COPD, showing inconsistent results (41, 42).

Strong associations with oxygen uptake during CPET and dyspnea during daily life demonstrate a good convergent validity of the 6MWT in patients with asthma, supporting the general conceptualization of the 6MWT to be a test of functional exercise performance (12). In addition, 6MWD and measures of constructs that theoretically should not be highly related to it (e.g. body composition, pulmonary function, symptoms of anxiety and depression) were, in fact, not found to be highly correlated, strengthening the discriminant validity of the 6MWT in this patient population. For example, FEV_1 was very weakly associated with the distance covered in the 6MWT, which is in line with prior studies (7, 10), which only increases the added value of a field exercise test, such as the 6MWT. Indeed, based on the lung function attributes a healthcare professional cannot adequately estimate the exercise performance of the individual patient (13). So, a field exercise test needs to be conducted to better understand the exercise capacity of an individual patient with asthma.

A considerable number of independent determinants of 6MWD in patients with asthma were identified, explaining about half of its variance, suggesting that there are other contributors to 6MWD that are not yet completely understood. For instance, dynamic hyperinflation, which has been proven to play a major role in exercise limitation in COPD (43), has also been reported in patients with asthma, with studies showing a direct association with worse overall health, lower wellbeing and impaired activities of daily life (44). Interestingly, severe asthmatic patients seem to develop dynamic hyperinflation during a 6MWT to the same extent as individuals with COPD, without leading to changes in dyspnea perception (45).

Methodological strengths and limitations

The current in-depth analyses of the measurement properties of the 6MWT in patients with asthma are novel and of clinical importance, potentially enhancing the standard operating procedures for the 6MWT in this patient population. Methodological factors that could potentially affect test performance were kept constant when conducting the tests. 6MWTs were conducted by trained and certified personnel using standardized phrases of instruction and encouragement throughout the tests. Additionally, both 6MWTs were performed with the same provision of supplemental oxygen and walking aids used in the first test were also used in the second test.

We acknowledge the fact that the asthma patients included in the current study were referred for pulmonary rehabilitation, resulting in a selected group of patients. Regardless of the fact that our sample showed a broad age range (20-84 years) and a fairly even distribution of males and females, only a minority of patients was aged below 40 years. Of course, this limits the interpretation of the 6MWT measurement properties in patients with asthma to a more narrow age range population. It is worth noting that narrow age-ranges could be identified in most studies conducted in healthy adults to provide reference values for the 6MWT. This also holds true for the reference values(19) used in the current study, which are currently the best option available when assessing a Dutch population. Future research is needed in a large sample from the general population, representing all age groups and well balanced in terms of sex, to formulate new reference values for use in daily clinical practice.

Unfortunately, information regarding comorbidities and functional balance, which have been shown to be variables that can influence the improvement of the second 6MWT in patients with COPD (14, 46), have not been systematically assessed during the baseline pulmonary rehabilitation assessment. Furthermore, the evaluation of known-groups validity in our study is limited, since asthma severity according to GINA guidelines (1) was not determined. Generally, asthma disease severity is assessed retrospectively by a physician after the patient has been on controller treatment for several months (6, 47). However, upon first referral to a pulmonary rehabilitation program, patients may often present a suboptimal disease control due to ineffective or inappropriate treatment or asthma that remains uncontrolled despite sufficient treatment (1), making an adequate examination of disease severity difficult. As a result, the present study aimed to classify patients based on the type of drug (OCS) that they were prescribed, without inferring severity, other than the fact that a referral to a tertiary center was made. Lastly, we cannot completely rule out the fact that some patients present with clinical features of both asthma and

COPD. Asthma patients entering pulmonary rehabilitation are complex in terms of symptoms, frequency of asthma attacks, oral corticosteroid dependency, current smoking, high prevalence of obesity and other comorbidities (48), which might (at least in part) result in clinical features overlapping with patients with COPD (49).

Conclusion

The current study demonstrated excellent test-retest reliability and construct validity of the 6MWT in a large cohort of asthmatics of which the majority was older than 40 years, supporting the use of the 6MWT as a primary end-point in future clinical trials. Nevertheless, our data suggest a considerable learning effect when two tests are conducted. In about 40% of the patients, this learning effect is large enough to be clinically important (≥ 27 m) when the 6MWT is used to assess functional exercise performance and evaluate patient progress. The exact predictive factors of this improvement in walking distance could not be determined. Therefore, it is highly recommended to perform at least two 6MWTs in each patient, after which the best 6MWD should be reported.

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Supplementary material

Table 1. Overview of the medication use.

Type of medication (with specified combinations)	Number of patients (% of total sample)
Monotherapy	4 (2.0)
SABA	2 (1.0)
SAMA	0 (0.0)
LABA	0 (0.0)
LAMA	0 (0.0)
ICS	2 (1.0)
Bronchodilator combinations*	11 (5.5)
SABA/SAMA	1 (0.5)
LABA/SABA	1 (0.5)
LAMA/SABA	1 (0.5)
LABA/LAMA	4 (2.0)
LABA/SAMA/SABA	0 (0.0)
LAMA/SABA/SAMA	1 (0.5)
LABA/LAMA/SABA	2 (1.0)
LABA/LAMA/SABA/SAMA	1 (0.5)
ICS containing combinations*	178 (88.6)
ICS/SABA	3 (1.5)
ICS/SAMA	0 (0.0)
ICS/LABA	24 (11.9)
ICS/LAMA	3 (1.5)
ICS/SABA/SAMA	2 (1.0)
ICS/LABA/SABA	25 (12.4)
ICS/LAMA/SABA	4 (2.0)
ICS/LABA/SAMA	8 (4.0)
ICS/LAMA/SAMA	1 (0.5)
ICS/LABA/LAMA	19 (9.5)
ICS/LABA/SABA/SAMA	13 (6.5)
ICS/LAMA/SABA/SAMA	1 (0.5)
ICS/LABA/LAMA/SABA	41 (20.4)
ICS/LABA/LAMA/SAMA	3 (1.5)
ICS/LABA/LAMA/SABA/SAMA	31 (15.4)
Maintenance OCS	39 (19.4)
Missing	8 (4.0)

Values are presented as frequencies (percentages).

Abbreviations. SABA: short acting beta agonist; SAMA: short acting muscarinic antagonist; ICS: inhalation corticosteroids; LAMA: long acting muscarinic antagonist; LABA: long acting beta agonist; OCS: oral corticosteroids. *the presented combinations include both single-inhaler combination therapies as well as multi-inhaler combination therapies

Table 2. Differences in amount of improvement ($\Delta 6\text{MWD}$) after stratifying for different age groups and smoking status.

Stratification variable	Grouping	N = 201		
		$\Delta 6\text{MWD}$ (m)	N	p-value
Sex	Male	19.9 ± 41.0	84	0.551
	Female	15.9 ± 51.3	117	
Age	18-40 years	6.6 ± 28.0	11	0.732
	40-65 years	18.1 ± 39.9	116	
	65+ years	18.4 ± 58.9	74	
Smoking status	Current	9.8 ± 42.1	17	0.481
	Former	14.7 ± 47.1	92	
	Never	21.9 ± 49.7	86	

Data are expressed as mean $\pm$ SD.

Table 3. Odds ratios for a clinically important improvement of ≥ 27 m in the second 6MWT in comparison with the first 6MWT in patients with asthma.

Variable	Reference	OR	LL	UL	p-value
Age ≥ 65 years	Age < 65 years	1.21	0.67	2.19	0.534
Male gender	Female gender	0.97	0.54	1.74	0.908
BMI ≥ 30	BMI < 30	0.77	0.44	1.36	0.369
Blood eosinophils ≥ 150 cells/ μL	Blood eosinophils < 150 cells/ μL	0.90	0.48	1.70	0.751
OCS use	no OCS use	0.76	0.36	1.59	0.465
mMRC ≥ 2	mMRC < 2	1.35	0.64	2.83	0.432
Rollator yes	Rollator no	0.99	0.44	2.26	0.989
6MWD1 $< 350\text{m}$	6MWD1 $\geq 350\text{m}$	0.82	0.43	1.58	0.557
6MWT1 desat.	6MWT1 no desat.	1.01	0.39	2.61	0.985
FEV ₁ /FVC < 70	FEV ₁ /FVC ≥ 70	0.68	0.36	1.28	0.234
RV/TLC ≥ 40	RV/TLC < 40	0.78	0.42	1.46	0.443
HADS-A ≥ 10	HADS-A < 10	0.84	0.43	1.62	0.592
HADS-D ≥ 10	HADS-D < 10	0.85	0.42	1.71	0.643

Models adjusted for age, sex, and BMI (in analyses considering any of these variables as independent variable, only the two other variables were used for adjustment).

Abbreviations. OR: Odds Ratio; LL: lower limit of the 95% confidence interval for the OR; UL: upper limit of the 95% confidence interval for the OR; BMI: body mass index; OCS: oral corticosteroid; mMRC: modified Medical Research Council; 6MWD1: six-minute walking distance of the first test; 6MWT1: first six-minute walking test; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; HADS-A: Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale, Depression subscale.

Table 4. Test-retest reliability analysis of the 6-minute walking test (6MWT): Distance, oxygen saturation, heart rate and Borg symptom scores.

	6MWT1	6MWT2	Delta	ICC*
Six minute walking distance (6MWD)				
6MWD, meters	392 (376-408)	410 (393-427)	18 (11-24)*	0.91 (0.86-0.94)
6MWD, %predicted	63.2 (60.8-65.5)	66.0 (63.5-68.6)	2.9 (1.7-4.0)*	0.87 (0.82-0.91)
Arterial oxygen saturation (SpO₂)				
SpO ₂ pre-test (at rest), %	94.8 (94.4-95.1)	94.7 (94.4-95.0)	-0.1 (-0.4-0.2)	0.64 (0.55-0.71)
SpO ₂ end-test (peak exertion), %	92.9 (92.2-93.5)	92.6 (92.0-93.3)	-0.2 (-0.6-0.1)	0.82 (0.77-0.86)
Δ SpO ₂ , %	-1.9 (-2.4 - -1.4)	-2.0 (-2.6 - -1.5)	-0.1 (-0.5-0.3)	0.68 (0.60-0.75)
Borg dyspnea and fatigue scores				
Borg dyspnea pre-test (at rest)	2.1 (1.8-2.3)	2.0 (1.8-2.2)	-0.1 (-0.3-0.2)	0.50 (0.38-0.59)
Borg dyspnea end-test (peak exertion)	5.0 (4.7-5.3)	5.3 (4.9-5.6)	0.2 (0.0-0.5)	0.64 (0.55-0.71)
Δ Borg dyspnea	3.0 (2.7-3.2)	3.3 (3.0-3.6)	0.3 (0.0-0.6)*	0.44 (0.32-0.54)
Borg fatigue pre-test (at rest)	1.9 (1.7-2.1)	1.7 (1.5-2.0)	-0.1 (-0.3-0.0)	0.62 (0.52-0.70)
Borg fatigue end-test (peak exertion)	4.2 (3.9-4.5)	4.5 (4.1-4.8)	0.3 (0.0-0.5)*	0.69 (0.61-0.76)
Δ Borg fatigue	2.3 (2.1-2.6)	2.7 (2.4-3.0)	0.4 (0.1-0.7)*	0.47 (0.35-0.57)
Heart rate (HR)				
HR pre-test (at rest), beats/min	81 (80-83)	84 (82-85)	2 (1-4)*	0.74 (0.66-0.80)
HR end-test (peak exertion), beats/min	105 (103-107)	109 (107-112)	4 (3-6)*	0.71 (0.59-0.78)
Δ HR, beats/min	24 (22-26)	26 (24-28)	2 (0-4)*	0.57 (0.47-0.65)

Data are expressed as mean and 95% Confidence Interval. * The two-way random ICC with single measures (ICC2,1) was calculated. * $p < 0.05$

Abbreviations. 6MWT: 6-minute walking test; ICC: intraclass correlation coefficient; 6MWD: Six minute walking distance; SpO₂: Arterial oxygen saturation; HR: Heart rate; min: minute.

Table 5. Comparison of patient characteristics and 6MWD in patients with vs. without rollator use during the 6MWT.

	<i>No rollator use</i>	<i>Rollator use</i>
Number of patients (%)	164 (81.6)	37 (18.4)
Age, years	60 ± 12	67 ± 10*
BMI, kg/m ²	30.1 ± 6.2	35.2 ± 9.1*
FFMI, kg/m ²	18.0 ± 2.6	18.8 ± 3.6
FEV ₁ , % pred	79 ± 27	73 ± 28
FEV ₁ /FVC ratio, %	60 ± 16	58 ± 18
RV, % pred	114 ± 31	123 ± 45
RV/TLC ratio, %	40 ± 9	47 ± 11*
TLC, % pred	104 ± 16	104 ± 21
MIP, % pred	93 ± 28	85 ± 23
MEP, % pred	74 ± 25	69 ± 24
6MWD1, m	426 (411-440)	244 (217-271)*
6MWD1, %pred	67 (65-69)	45 (40-50)*
6MWD2, m	444 (428-459)	258 (227-289)*
6MWD2, %pred	70 (68-72)	48 (43-54)*
Δ6MWD, m	18 (11-26)	14 (3-25)

Data are expressed as mean ± SD or mean and 95% Confidence Interval, as appropriate. * no rollator use vs. rollator use: p<0.05

Abbreviations. BMI: body mass index; FFMI: fat-free mass index; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure; 6MWD1: six-minute walking distance of the first test.

3

CHAPTER 3

Frequency and functional consequences of low appendicular lean mass and sarcopenic obesity in patients with asthma referred for pulmonary rehabilitation

Meys R*, Machado FVC*, Spruit MA, Stoffels AAF, van Hees HWH, van den Borst B, Klijn PH, Burtin C, Pitta F, Franssen FME.

Obes Facts. 2023;16(5):435-446.

Doi: **10.1159/000531196**.

*shared first author

Abstract

Introduction: one of the most prominent extra-pulmonary manifestations in patients with chronic respiratory disease are changes in body weight and composition. However, the frequency and functional consequences of low appendicular lean mass (ALM) or sarcopenic obesity (SO) in patients with asthma is largely unknown. Therefore, the aims of the current study were to assess the frequency and functional consequences of low appendicular lean mass index (ALMI) and SO in patients with asthma.

Methods: a retrospectively analyzed cross-sectional study was conducted in 687 patients with asthma (60% female, 58 ± 13 years, FEV_1 $76 \pm 25\%$ pred) referred for comprehensive pulmonary rehabilitation (PR). Body composition, pulmonary function, exercise capacity, quadriceps muscle function, and quality of life were assessed. Patients were classified as presenting low ALMI according to the 10th percentiles of age-sex-body mass index (BMI)-specific reference values and as having SO according to the diagnostic procedure proposed by the 2022 ESPEN/EASO consensus. In addition, clinical outcomes between patients with normal and low ALMI or with and without SO were compared.

Results: the frequency of patients classified as low ALMI was 19%, whereas 45% of the patients were obese. Among the obese patients, 29% had SO. In patients with normal weight, those with low ALMI were younger and had worse pulmonary function, exercise capacity and quadriceps muscle function than those with normal ALMI (all $p < 0.05$). Overweight patients with low ALMI presented poorer pulmonary function and quadriceps muscle function (both strength and total work capacity). In obese class I patients, those with low ALMI showed lower quadriceps strength and maximal oxygen uptake acquired during cardiopulmonary exercise testing. Both male and female patients with SO showed lower quadriceps muscle function and reduced maximal exercise capacity compared to non-SO asthma patients.

Conclusion/discussion: Approximately one in five asthma patients presented low ALM when age-sex-BMI-specific ALMI cut-offs were applied. Obesity is common among patients with asthma referred for PR. Among the obese patients a significant proportion presented SO. Low ASM and SO were associated with worse functional outcomes.

Introduction

It is well-recognized that extra-pulmonary features contribute to disease burden and functional impairment in patients with chronic respiratory diseases (CRDs) (1, 2). Abnormalities in body weight and body composition are among the most prominent extra-pulmonary manifestations occurring in this population, with both low muscle mass and obesity being frequently reported in patients with chronic obstructive pulmonary disease (COPD) (3, 4). Whereas obesity has been identified as a complicating comorbidity in asthma (5, 6) and an "obese asthma" phenotype has been established (7), most studies have characterized asthma patients affected by obesity based on traditional anthropometric measures such as body mass index (BMI) and/or waist circumference (5). However, a more detailed understanding of body composition in asthma by characterizing skeletal lean mass (LM), supplementary to BMI, is lacking, and may be clinically relevant.

With a high obesity rate among adults with asthma (5), detailed measurements of body composition seem especially important in these subjects, since a high amount of adipose tissue can have a masking effect in terms of sarcopenia (8, 9). The concurrent presence of low muscle mass and obesity has been associated with greater functional impairment, morbidity and mortality, in both the general population (10) and CRDs (3, 11, 12). Recently, a study investigating the prevalence of sarcopenic obesity (SO) in patients seeking weight loss treatment demonstrated a higher prevalence of asthma diagnosis in the SO compared with the non-SO group (13). In addition, the recent consensus on the definition and diagnostic criteria for SO published by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) listed CRDs as one of the suspicion factors for the screening of SO (14, 15). To date, however, the frequency and functional consequences of low LM and SO in overweight and obese adult patients with asthma referred for pulmonary rehabilitation (PR) remain unclear.

Dual-energy X-ray absorptiometry (DEXA) is a validated non-invasive technique enabling precise assessment of the amount of fat mass (FM) and LM of the whole body and of specific anatomical regions (16). Lean soft tissue mass measured at the limbs, also known as appendicular lean mass (ALM), normalized by height squared (ALMI; appendicular lean mass index), is associated with muscle strength and exercise capacity in patients with COPD (11). Since obese people are supposed to have a higher muscle mass than normal-weight subjects, it has been emphasized to take the amount of FM into account when interpreting muscle mass, since both tissue components are interrelated (17, 18). In fact, the contribution of

skeletal muscle to LM is lower at a higher degree of adiposity, due to an increase in connective tissue (19). Hence, it can be hypothesized that applying fixed cutoff values results in underdiagnoses of low ALMI in overweight or obese patients, providing rationale for the use of age-sex-BMI cut-offs. Recently, Ofenheimer et al. (20) published European age- and sex-specific reference values for ALMI with regard to BMI categories.

To date, the frequency of low ALMI according to high-standard age-sex-BMI-specific reference values in patients with asthma remains unknown, as well as the proportion of patients with obesity that present SO according to the 2022 ESPEN/EASO diagnostic procedure. Furthermore, it is relevant to investigate whether and to what extent low ALMI and SO are associated with functional impairment in these patients. Therefore, the aims of the current study were: (1) to quantify the frequency of low ALMI according to European age-sex-BMI specific reference values and SO according to the diagnostic procedure proposed by the ESPEN/EASO consensus in adults with asthma; and (2) to investigate the functional consequences of low ALMI and SO in this population referred for PR.

Methods

Study design and subjects

In the current observational study, 752 adult patients with asthma referred for a pre PR assessment at Ciro (Horn, the Netherlands) between January 2005 and January 2019, were retrospectively analyzed. Inclusion criteria were: (1) respiratory physician-based diagnosis of asthma, based on an initial identification of both a characteristic pattern of symptoms and variable expiratory airflow limitation according to international guidelines (7), (2) clinical stability at the time of the assessment (absence of current exacerbation). Patients who did not complete the assessment of body composition were excluded from the analyses. The medical ethics committee of Maastricht University informed the authors that the Medical Research Involving Human Subjects Act (WMO) does not apply for this study and approved the use of retrospective data for the purpose of this study (METC azM/UM 2020-2379). All procedures were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Anthropometric and body composition measurements

Body weight and height were assessed using a calibrated scale, after which BMI was calculated as weight divided by height squared (kg/m^2). Body composition

measurements were conducted with the GE-Lunar Prodigy (January 2005 - July 2014)/GE-Lunar iDXA (August 2014 - January 2019; GE Healthcare, Madison, WI, USA) DEXA scanner. For the current study, the body composition variables of interest derived from the DEXA output were: LM (kg) and FM (total body weight minus total LM; in kg) of the whole body, trunk and of the limbs. From these measures the following derivative values were calculated: Fat mass index (FMI; fat mass/height²), ALMI (ALM/height²) and trunk lean mass index (TLMI), in which ALM was defined as the sum of the LM of the four limbs and TLM as LM of the trunk (17). In addition, ratios between trunk and appendicular LM (TM/ALM ratio) and between appendicular LM and fat mass (ALM/FM ratio) were calculated. To explore the frequency of osteopenia and osteoporosis in the current population, bone mineral density was measured in the lumbar spine and hips, after which concurrent T-scores were calculated (osteopenia: T score -1 to -2.5 x standard deviation (SD); osteoporosis: T score <-2.5 x SD).

Patients were divided according to World Health Organization (WHO) BMI categories (normal weight: 18.5 to <25 kg/m²; overweight: 25 to <30 kg/m²; low-risk obese class I: 30 to <35 kg/m²; moderate-risk obese class II: 35 to <40 kg/m²; high-risk obese class III: ≥40 kg/m²). Within each of these categories, patients were sub-classified into low or normal ALMI, using the 10th percentiles of age-, sex- and BMI-specific reference values of Ofenheimer et al (20). For the SO classification, the diagnostic criteria proposed by the ESPEN/EASO consensus statement were adopted (14, 15). The first level of the diagnostic procedure (screening) is based on the concomitant presence of an elevated BMI and surrogate indicators of sarcopenia (e.g., risk factors, such as CRDs). Thus, all asthma patients with BMI ≥30 kg/m² were considered for the second level (diagnosis), which can be used to either confirm or reject SO. The first step of the diagnosis level is based on altered skeletal muscle functional parameters considering strength. Patients with less than 80% of the predicted quadriceps peak torque as assessed by using a computerized dynamometer (Biodex System 4 Pro) were classified as presenting altered skeletal muscle function (21). The next step, which is based on altered body composition, was confirmed in patients with increased FM and reduced muscle mass. The reference values given by Gallagher et al. (22) for FM and by Poggiogalle et al. (23) for ALM were applied, as suggested by the ESPEN/EASO consensus. Patients with a positive screening and altered skeletal muscle functional parameters and body composition were classified as SO. Since the proposed staging step by ESPEN/EASO has not been properly investigated yet and is based on clinical expert opinion (14, 15), this step was not taken into account in the current study.

Other assessments

Demographical data (age, sex, smoking status), medication use, and exacerbation/hospitalization history were assessed as part of standard care. Pulmonary function was determined with standardized spirometry equipment (Masterlab®, Jaeger, Würzburg, Germany) following international guidelines (24), with forced expiratory volume in the first second (FEV₁) and FEV₁/forced vital capacity (FVC) ratio as primary outcomes. Lung volumes including residual volume (RV) and total lung capacity (TLC) were determined by body plethysmography (25). The 6-minute walking test assesses the distance walked over 6 minutes (6MWD) as a measure of functional status. The test is performed twice, after which the best 6MWD was reported (26). A symptom limited incremental cardiopulmonary exercise test (CPET) was performed using a cycle ergometer to assess maximal exercise performance. Both the maximum load (W_{max} ; in Watts) as well as peak oxygen uptake (VO_{2peak}) were measured as main outcomes (27). Endurance exercise capacity was measured by a sub-maximal constant work rate cycle test (CWRT) at 75% of the pre-identified W_{max} (28). Isokinetic quadriceps muscle function was determined using a Biodex System 4 Pro (Biodex Medical Systems, Inc., New York, USA) (21). Quadriceps muscle strength was defined as the highest peak torque (Nm), whereas isokinetic quadriceps muscle endurance was defined as the total amount of delivered work (Joules) during a set of 30 repetitions. Health related quality of life (HRQL) was assessed with the St. George's Respiratory Questionnaire (SGRQ; range 0-100) (29) and functional impairment due to dyspnea with the modified Medical Research Council (mMRC; range 0-4; clinical cut-off ≥ 2) dyspnea scale (30). In both of these questionnaires, higher scores indicate more limitations.

Statistics

Results are presented as mean and SD, median and interquartile range (IQR), and/or proportions, as appropriate. Continuous variables were tested for normality. To analyze characteristics and functional outcomes between patients with normal or low ALMI within each BMI category, the independent samples t-test, Mann-Whitney U-test or chi-square test was used, as appropriate. The previously mentioned tests were also used to compare characteristics and functional outcomes between patients with and without SO. In addition, to assess differences in functional outcomes (6MWD, CPET maximal workload, quadriceps strength and SGRQ total score) between normal ALMI and low ALMI groups, while controlling for age and sex, analysis of covariance (ANCOVA) with least significant difference (LSD) multiple comparison test as post-hoc was performed. All statistical analyses were performed using IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, USA) and GraphPad Prism 9.0 (GraphPad Software Inc., California, USA). *A priori*, the level of significance was set at $p < 0.05$.

Results

Out of 752 patients with asthma who completed the assessment, 65 patients were excluded due to missing body composition analysis, resulting in 687 patients for final analyses. On average, these patients were 58 ± 13 years old, presenting with a mean FEV_1 of $76 \pm 25\%$ predicted. Four-hundred-and-fourteen subjects were female (60%). The proportion of patients using (a combination of) medication containing inhaled corticosteroids was 85%, whereas 22% was using maintenance therapy with oral corticosteroids (OCS; Supplementary Material, Table E1). Regarding BMI, 2% of the patients were classified as underweight, 23% as normal weight, 29% as overweight, 26% as obese class I, 14% as obese class II and 6% as obese class III. The general characteristics of the patients after stratification into BMI groups are presented in Table 1.

Frequency of low ALMI and SO

In Figure 1, the frequency of low ALMI and SO is presented. The overall proportion of patients classified as low ALMI was 18.9%. The frequency of patients with low ALMI in underweight, normal weight, overweight and obese groups I, II and III was 29%, 21%, 22%, 23%, 8% and 3%, respectively. Because of the low frequency of patients with low ALMI in obese classes II ($n = 8$) and III ($n = 1$) as well as in underweight patients ($n = 4$), these classes were excluded in further analyses regarding the functional consequences of low ALMI. Figure 2 displays a flowchart with the number of patients in each level and step of the ESPEN/EASO diagnostic criteria (14, 15). Three-hundred-and-ten patients (46%) of the current study population were obese ($BMI \geq 30 \text{ kg/m}^2$). Of these, ninety-one (29.4%) were classified as having SO. The frequency of SO in obese class I, II and III was 30%, 26% and 36%.

Table 1. Characteristics of asthma patients after stratification into BMI groups.

	Underweight n = 14 (2.0%)	Normal weight n = 161 (23.4%)	Overweight n = 202 (29.4%)	Obese Class I n = 175 (25.5%)	Obese Class II n = 96 (14.0%)	Obese Class III n = 39 (5.7%)	p-value between-group difference
Male sex, n (%)	4 (28.6)	68 (42.2)	94 (46.5)	72 (41.1)	25 (26.0)	10 (25.6)	<0.01
Age, years	52 ± 13	57 ± 12	59 ± 13	60 ± 13	57 ± 12	57 ± 13	0.098
Exacerbations ≥ 2 (<12 months), %	58	68	66	70	69	61	0.867
Hospitalizations ≥ 2 (<12 months), %	50	20	19	26	31	18	<0.05
Pack years ≥ 10, %	58	50	50	55	56	44	0.774
ICS use, %	79	87	88	84	80	74	0.177
OCS use, %	29	21	20	25	26	15	0.655
BMI, kg/m ²	17.3 ± 1.1*	22.5 ± 1.8	27.4 ± 1.5*	32.4 ± 1.5*	37.3 ± 1.4*	44.7 ± 4.7*	<0.001
ALMI, kg/m ²	5.2 ± 0.9*	6.4 ± 0.9	7.1 ± 1.0*	8.0 ± 1.1*	8.4 ± 1.1*	9.6 ± 1.7*	<0.001
TLMI, kg/m ^{2~}	6.9 ± 0.9	7.6 ± 0.9	8.3 ± 0.8*	9.1 ± 1.1*	9.9 ± 1.2*	11.3 ± 1.7*	<0.001
TLM/ALM ratio ~	1.25 ± 0.10	1.18 ± 0.14	1.18 ± 0.15	1.18 ± 0.15	1.25 ± 0.20	1.33 ± 0.32*	<0.01
FMI, kg/m ²	3.4 ± 1.3*	6.5 ± 2.0	10.1 ± 2.1*	13.5 ± 2.2*	17.3 ± 2.0*	22.1 ± 3.5*	<0.001
ALM/FM ratio	1.82 ± 0.91*	1.16 ± 0.66	0.75 ± 0.26*	0.62 ± 0.19*	0.50 ± 0.11*	0.44 ± 0.10*	<0.001
FEV ₁ , % predicted	56 ± 30	69 ± 26	76 ± 26*	78 ± 22*	80 ± 20*	87 ± 20*	<0.001
FEV ₁ /FVC ratio	0.52 ± 0.23	0.55 ± 0.17	0.59 ± 0.16	0.63 ± 0.14*	0.68 ± 0.12*	0.70 ± 0.13*	<0.001
RV/TLC ratio	0.54 ± 0.15*	0.45 ± 0.11	0.42 ± 0.11	0.41 ± 0.10*	0.40 ± 0.10*	0.39 ± 0.11	<0.001
RV/TLC ratio ≥ 0.40, %	71	64	51	52	53	44	0.079
mMRC grade ≥ 2, %	71	63	74	84	90	92	<0.01
6MWD, m	438 ± 175	488 ± 130	465 ± 132	431 ± 125*	383 ± 139*	380 ± 102*	<0.001
6MWD, % predicted	62 ± 26	71 ± 18	72 ± 20	70 ± 19	64 ± 21	69 ± 15	<0.05

Table 1. Continued

	Underweight n = 14 (2.0%)	Normal weight n = 161 (23.4%)	Overweight n = 202 (29.4%)	Obese Class I n = 175 (25.5%)	Obese Class II n = 96 (14.0%)	Obese Class III n = 39 (5.7%)	p-value between-group difference
CPET Wmax, Watts	65 ± 34	94 ± 38	104 ± 48	100 ± 45	91 ± 39	97 ± 39	<0.01
CPET Wmax %predicted	52 ± 31	70 ± 27	84 ± 36*	80 ± 35	78 ± 35	83 ± 31	<0.001
CPET VO ₂ peak, ml/min	1046 ± 362	1247 ± 419	1426 ± 500*	1461 ± 482*	1411 ± 457	1620 ± 482*	<0.001
CPET VO ₂ peak, % predicted	59 ± 30	69 ± 34	88 ± 45*	88 ± 41*	91 ± 39*	101 ± 38*	<0.001
CWRT time, s	247 [105-427]	306 [219-455]	318 [226-501]	313 [223-442]	278 [214-421]	333 [228-590]	0.754
PT _{quadriceps} , Nm	61 ± 21*	94 ± 32	101 ± 37	115 ± 42*	108 ± 48	109 ± 48	<0.001
PT _{quadriceps} , % predicted	46 ± 19*	65 ± 18	68 ± 18	81 ± 21*	78 ± 26*	77 ± 24*	<0.001
Total Work quadriceps, J	1135 ± 410*	1694 ± 694	1850 ± 793	2003 ± 802*	1845 ± 950	1900 ± 975	<0.001
SGRQ total score, points	57 [51-74]	57 [42-69]	55 [43-68]	60 [50-68]	57 [49-71]	63 [51-67]	0.238
Osteopenia, n (%)	50	49	51	40	35	44	0.114
Osteoporosis, n (%)	29	21	10	9	5	5	<0.001

*p<0.05 versus normal weight group. ~ n = 316. *Abbreviations.* ICS: inhalation corticosteroids; OCS: oral corticosteroids; BMI: body mass index; ALMI: appendicular lean mass index; TLMi: trunk lean mass index; FMI: fat mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; mMRC: modified Medical Research Council; 6MWD: six-minute walking distance; CPET: cardiopulmonary exercise test; Wmax: maximal achieved workload; VO₂ peak: peak oxygen consumption; CWRT: constant work-rate cycle test; PT_{quadriceps}: isokinetic peak torque of the quadriceps muscle; SGRQ: St. George's Respiratory Questionnaire.

Table 2. Characteristics of asthma patients with normal and low ALMI according to age-sex BMI-specific cut-offs, after stratification into BMI categories.

	Normal weight (n = 161)		Overweight (n = 202)		Obese Class I (n = 175)	
	Normal ALMI (n = 128)	Low ALMI (n = 33)	Normal ALMI (n = 158)	Low ALMI (n = 44)	Normal ALMI (n = 135)	Low ALMI (n = 40)
Male sex, n (%)	49 (38)	19 (58)*	76 (48)	18 (41)	62 (46)	10 (25)*
Age, years	58 ± 12	53 ± 13*	60 ± 14	58 ± 11	60 ± 14	58 ± 10
Exacerbations ≥ 2 (<12 months), %	68	71	63	79	69	74
Hospitalizations ≥ 2 (<12 months), %	21	19	19	21	25	29
Pack years ≥ 10, %	51	45	46	67*	53	61
ICS use, %	86	91	87	93	81	88
OCS use, %	22	18	19	25	25	20
BMI, kg/m ²	22.8 ± 1.7	21.3 ± 1.8*	27.5 ± 1.4	27.0 ± 1.5	32.5 ± 1.5	32.2 ± 1.5
ALMI, kg/m ²	6.6 ± 0.9	5.8 ± 0.7*	7.4 ± 0.8	6.1 ± 0.7*	8.3 ± 1.0	6.9 ± 0.7*
TLMi, kg/m ² ~	7.7 ± 0.9	7.3 ± 0.7	8.4 ± 0.8	7.9 ± 0.6*	9.2 ± 1.1	8.8 ± 1.1
TLM/ALM ratio ~	1.17 ± 0.14	1.26 ± 0.13*	1.14 ± 0.12	1.31 ± 0.14*	1.14 ± 0.13	1.29 ± 0.13*
FMI, kg/m ²	6.5 ± 2.0	6.3 ± 2.1	9.8 ± 2.1	11.0 ± 1.9*	13.1 ± 2.2	14.7 ± 1.8*
ALM/FM ratio	1.19 ± 0.69	1.05 ± 0.51	0.80 ± 0.26	0.58 ± 0.16*	0.66 ± 0.19	0.48 ± 0.11*
FEV ₁ , % predicted	71 ± 26	59 ± 28*	79 ± 25	65 ± 24*	79 ± 23	75 ± 20
FEV ₁ /FVC ratio	0.57 ± 0.16	0.50 ± 0.18*	0.60 ± 0.15	0.54 ± 0.16*	0.62 ± 0.13	0.63 ± 0.15
RV/TLC ratio	0.44 ± 0.11	0.46 ± 0.12	0.40 ± 0.11	0.47 ± 0.11*	0.41 ± 0.10	0.41 ± 0.08
RV/TLC ratio ≥ 0.40, %	61	72	47	67*	53	49
mMRC grade ≥ 2, %	62	67	71	84	84	86
6MWD, m	492 ± 131	469 ± 122	471 ± 135	443 ± 116	432 ± 125	430 ± 123
6MWD, % predicted	73 ± 18	65 ± 15*	73 ± 20	69 ± 17	70 ± 18	71 ± 19

Table 2. Continued

	Normal weight (n = 161)		Overweight (n = 202)		Obese Class I (n = 175)	
	Normal ALMI (n = 128)	Low ALMI (n = 33)	Normal ALMI (n = 158)	Low ALMI (n = 44)	Normal ALMI (n = 135)	Low ALMI (n = 40)
CPET Wmax, Watts	98 ± 38	77 ± 33*	108 ± 50	93 ± 40	103 ± 46	90 ± 40
CPET Wmax %predicted	74 ± 28	56 ± 21*	86 ± 38	75 ± 26	79 ± 35	80 ± 36
CPET VO ₂ peak, ml/min	1305 ± 423	1021 ± 321*	1458 ± 511	1296 ± 440	1512 ± 500	1292 ± 377*
CPET VO ₂ peak, % predicted	76 ± 31	55 ± 21*	92 ± 45	85 ± 32	91 ± 39	93 ± 32
CWRT time, s	329 [227-455]	242 [150-518]	319 [228-510]	292 [189-414]	317 [224-445]	303 [211-420]
PT _{quadriceps} ^f Nm	97 ± 33	80 ± 21*	105 ± 38	88 ± 33*	121 ± 42	95 ± 33*
PT _{quadriceps} ^f % predicted	68 ± 18	50 ± 11*	71 ± 18	60 ± 15*	83 ± 21	70 ± 18*
Total Work quadriceps, J	1764 ± 714	1394 ± 515*	1927 ± 814	1578 ± 651*	2074 ± 834	1763 ± 635
SGRQ total score, points	56 [42-69]	62 [42-70]	54 [42-66]	58 [46-74]	61 [50-69]	55 [49-63]
Osteopenia, n (%)	61 (48)	18 (55)	76 (48)	26 (59)	55 (41)	10 (38)
Osteoporosis, n (%)	25 (20)	9 (27)	18 (11)	2 (5)	12 (9)	4 (10)

* p<0.05 versus normal ALMI from the same BMI group. ~ n = 259. Abbreviations. ALMI: appendicular lean mass index; ICS: inhalation corticosteroids; OCS: oral corticosteroids; BMI: body mass index; TLMI: trunk lean mass index; FMI: fat mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; mMRC: modified Medical Research Council; 6MWD: six-minute walking distance; CPET: cardiopulmonary exercise test; Wmax: maximal achieved workload; VO₂peak: peak oxygen consumption; CWRT: constant work-rate cycle test; PTquadriceps: isokinetic peak torque of the quadriceps muscle; SGRQ: St. George's Respiratory Questionnaire.

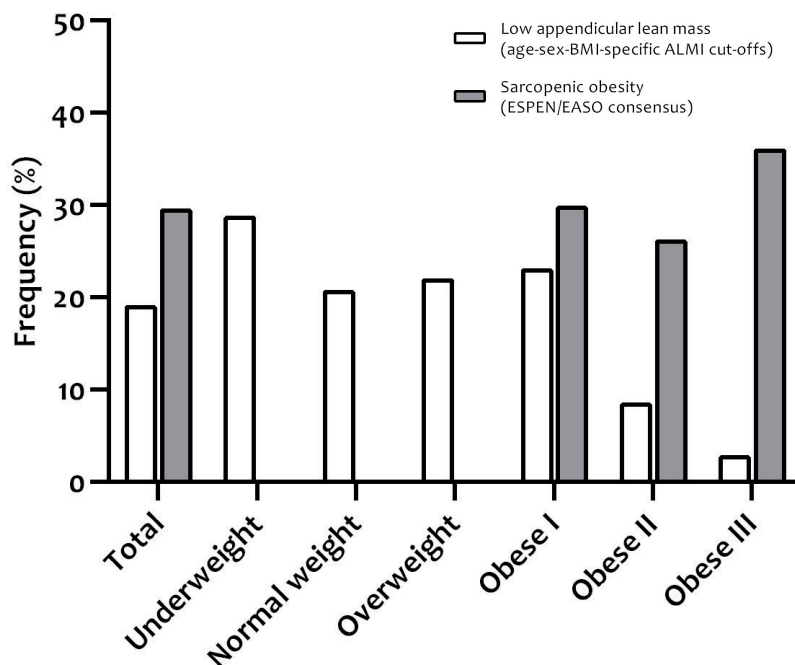


Figure 1. Frequency of low appendicular lean mass index (ALMI) and sarcopenic obesity (SO; only in patients with BMI ≥ 30 kg/m²), in patients with asthma stratified by BMI category. The total frequency of SO is relative to the total of patients in the obese classes.

Functional consequences of low ALMI and SO

In Table 2 comparisons of outcomes are presented between patients with normal and low ALMI after stratification into three BMI categories (normal weight, overweight, obese class I). A higher proportion of males with low ALMI was found in patients with normal weight (58% vs 38%, $p < 0.05$), whereas a lower proportion of males with low ALMI was found in obese class I patients (25% vs 46%, $p < 0.05$). In normal weight patients, those with low ALMI were younger and presented a lower FEV₁ and FEV₁/FVC ratio (all $p < 0.05$). FEV₁ and FEV₁/FVC ratio were also lower in overweight patients presenting with low ALMI as compared to overweight patients with normal ALMI (both $p < 0.05$). The proportion of patients with ≥ 10 pack years was significantly higher in overweight patients with low ALMI values as compared to overweight patients with normal ALMI values ($p < 0.05$; Table 2).

In patients with normal weight, those with low ALMI presented lower 6MWD (% predicted), maximal load during the CPET (W_{max}), peak oxygen consumption during CPET (VO_{2peak}), quadriceps peak torque and quadriceps total work compared

with patients with normal ALMI ($p < 0.05$, for all). Overweight patients with low ALMI demonstrated lower TMI, quadriceps peak torque and total work as compared to overweight patients with normal ALMI. Considering the obese class I patients, those with low ALMI showed lower quadriceps peak torque values and lower $\text{VO}_{2\text{peak}}$ (in milliliters per minute). The ALM/FM ratio was the highest in the normal weight and normal ALMI group (mean of 1.19 ± 0.69 kg of ALM for each kg of FM) and the lowest in the obese class I patients with low ALMI (mean of 0.48 ± 0.11 kg of ALM for each kg of FM).

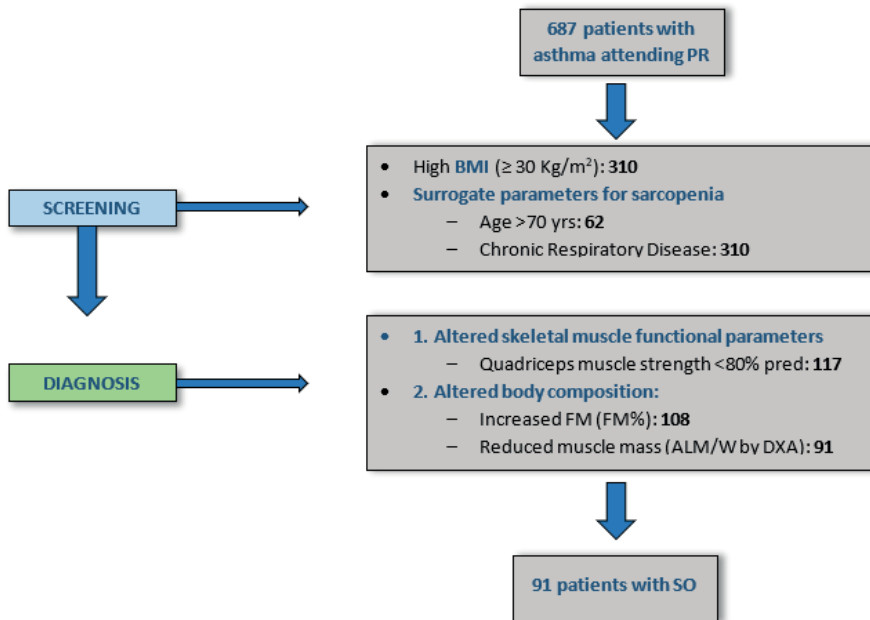


Figure. 2. Diagnostic procedure for the assessment of sarcopenic obesity (SO) based on the ESPEN and EASO consensus statement. Abbreviations: ALM/W: appendicular lean mass adjusted to body weight; BMI: body mass index; DXA: dual x-ray absorptiometry; FM: fat mass; SO: sarcopenic obesity.

In the comparisons of functional outcomes among the six groups (i.e., three BMI groups stratified into normal or low ALMI), whilst controlling for age and sex, it was shown that patients with low ALMI independent of their BMI categories and patients with obesity independent of their ALMI classification presented a significantly lower 6MWD compared with patients with normal weight and normal ALMI (all $p < 0.05$; Figure 3). While normal weight and overweight patients with low ALMI showed reduced maximal load during the CPET compared to their respective BMI groups with normal ALMI, obese class I patients with normal or low ALMI showed similar maximal load during the CPET. Additionally, quadriceps peak torque

was lower in patients with low ALMI compared to patients with normal ALMI across all BMI groups, whereas obese class I patients with normal ALMI showed higher quadriceps peak torque than normal weight patients with normal ALMI. Finally, obese class I patients with normal ALMI presented higher SGRQ total scores than normal weight patients with normal ALMI. Notably, within the obese class I group, patients with low ALMI presented lower SGRQ total scores, indicating less impaired quality of life (Figure 3).

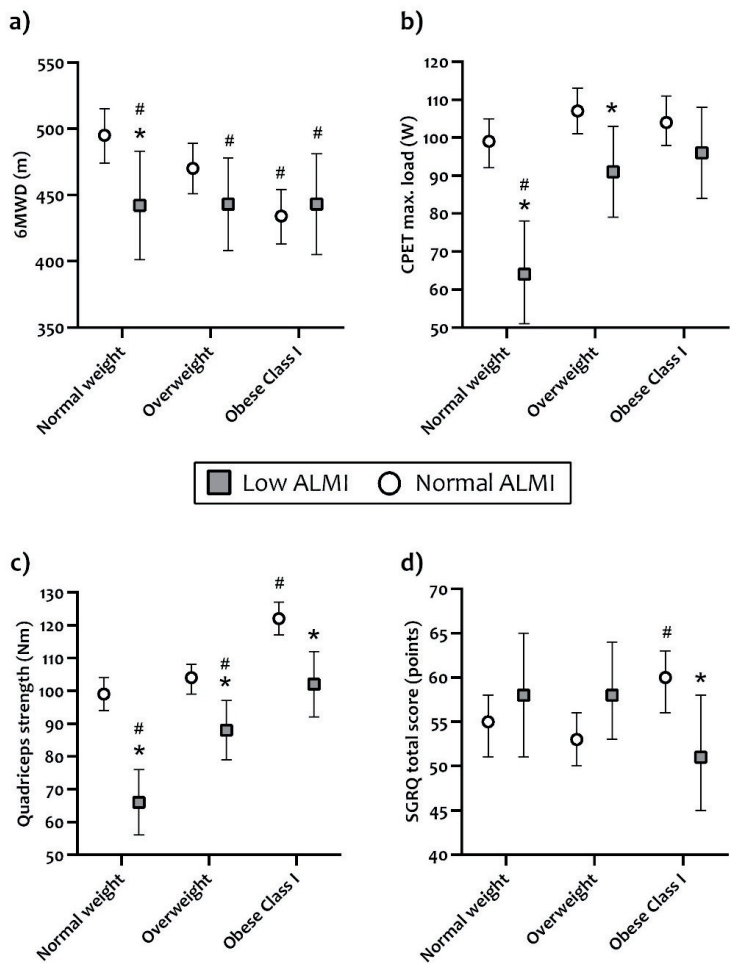


Figure 3. Age-sex adjusted means (and 95% Confidence Intervals) for a) 6-minute walk distance, b) maximal workload in CPET, c) peak quadriceps strength and d) quality of life (SGRQ total score) across BMI groups, displaying normal ALMI (in white) vs low ALMI (in grey). Analysis of covariance (ANCOVA) with LSD post-hoc was performed. * $p < 0.05$ versus normal ALMI from the same BMI group. # $p < 0.05$ versus normal weight and normal ALMI group. *Abbreviations.* ALMI: appendicular lean mass index; 6MWD: six-minute walking distance; CPET: cardiopulmonary exercise test; SGRQ: St. George's Respiratory Questionnaire

In Table 3 comparisons of outcomes are presented between patients with and without SO after stratification for sex. As expected, SO patients presented a significantly lower ALMI and quadriceps muscle function compared with non-SO patients. In addition, SO patients showed a reduced maximal exercise capacity and a higher proportion of patients with osteopenia/osteoporosis compared with the non-SO group (all $p < 0.05$; Table 3).

Table 3. Characteristics of asthma patients with sarcopenic obesity (SO) and non-sarcopenic obesity (NSO) according to the diagnostic procedure proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO).

	Males (n = 107)		Females (n = 203)	
	NSO (n = 80)	SO (n = 27)	NSO (n = 139)	SO (n = 64)
Age, years	61 ± 11	63 ± 10	56 ± 14	59 ± 11
Exacerbations ≥ 2 (<12 months), %	57	79	72	71
Hospitalizations ≥ 2 (<12 months), %	19	13	31	32
Pack years ≥ 10, %	69	57	47	47
ICS use, %	71	89	87	83
OCS use, %	26	26	27	14*
BMI, kg/m ²	34.9 ± 4.7	33.9 ± 3.5	35.6 ± 4.5	36.7 ± 5.1
ALMI, kg/m ²	9.5 ± 1.1	8.7 ± 0.8*	7.9 ± 1.0	7.4 ± 1.0*
TLMI, kg/m ² ~	10.2 ± 0.9	10.3 ± 0.9	9.2 ± 1.3	9.6 ± 1.8
TLM/ALM ratio ~	1.09 ± 0.11	1.23 ± 0.13*	1.21 ± 0.16	1.33 ± 0.27*
FMI, kg/m ²	13.3 ± 3.6	13.2 ± 2.9	16.6 ± 3.2	18.1 ± 3.4*
ALM/FM ratio	0.75 ± 0.18	0.68 ± 0.11*	0.49 ± 0.08	0.42 ± 0.06*
FEV ₁ , % predicted	75 ± 21	73 ± 22	85 ± 22	78 ± 19*
FEV ₁ /FVC ratio	0.61 ± 0.14	0.59 ± 0.13	0.69 ± 0.12	0.66 ± 0.12
RV/TLC ratio	0.39 ± 0.08	0.40 ± 0.08	0.39 ± 0.11	0.44 ± 0.09*
RV/TLC ratio ≥ 0.40, %	48	44	48	67*
mMRC grade ≥ 2, %	83.6	93.3	85.2	94.4
6MWD, m	454 ± 120	426 ± 115	396 ± 134	376 ± 119
6MWD, % predicted	69 ± 17	66 ± 16	68 ± 21	67 ± 19
CPET Wmax, Watts	119 ± 51	100 ± 31*	93 ± 39	76 ± 27*
CPET Wmax %predicted	65 ± 28	58 ± 16	91 ± 37	82 ± 30
CPET VO ₂ peak, ml/min	1825 ± 577	1525 ± 397*	1363 ± 387	1227 ± 258*
CPET VO ₂ peak, % predicted	73 ± 21	65 ± 15	106 ± 40	105 ± 31
CWRT time, s	360 (226-566)	335 (227-422)	305 (235-462)	250 (190-348)*

Table 3. Continued

	Males (n = 107)		Females (n = 203)	
	NSO (n = 80)	SO (n = 27)	NSO (n = 139)	SO (n = 64)
PT _{quadriceps} , Nm	165 ± 38	114 ± 29*	112 ± 27	69 ± 21*
PT _{quadriceps} , % predicted	92 ± 17	65 ± 13*	91 ± 18	59 ± 16*
Total Work quadriceps, J	2750 ± 861	2046 ± 625*	1998 ± 629	1173 ± 540*
SGRQ total score, points	55 (43-69)	60 (50-68)	59 (51-69)	62 (52-72)
Osteopenia, n (%)	27 (33.8)	15 (55.6)*	50 (36.0)	29 (46.0)
Osteoporosis, n (%)	7 (8.8)	4 (14.8)	5 (3.6)	7 (11.1)*

* p<0.05 versus non-sarcopenic obese (NSO) group from the same sex. *Abbreviations.* ALMI: appendicular lean mass index; ICS: inhalation corticosteroids; OCS: oral corticosteroids; BMI: body mass index; TLMI: trunk lean mass index; FMI: fat mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; mMRC: modified Medical Research Council; 6MWD: six-minute walking distance; CPET: cardiopulmonary exercise test; Wmax: maximal achieved workload; VO₂peak: peak oxygen consumption; CWRT: constant work-rate cycle test; PT_{quadriceps}: isokinetic peak torque of the quadriceps muscle; SGRQ: St. George's Respiratory Questionnaire.

Discussion

This study showed that 18.9% of adult patients with asthma referred for PR have low ALM (according to age-sex-BMI-specific ALMI cut-offs) and 29.4% have SO, which in both cases is associated with worse functional outcomes. There is growing evidence to indicate that obesity has detrimental effects on the contractile function of skeletal muscle, thereby reducing mobility and promoting obesity-associated health issues (31). The high prevalence of obesity in patients with asthma highlights the importance of taking into account physiological determinants (age, sex, ethnicity and BMI) when assessing low muscle mass and/or sarcopenia in this population (5, 18). As a matter of fact, the most recent EWGSOP2 consensus on the definition and diagnosis of sarcopenia state that muscle mass is indeed correlated with body size, but the authors make no recommendation to adjust for body size (17). Our results have important consequences for the assessment of overweight and obese patients with asthma, as not taking into account important physiological determinants when assessing low muscle mass may lead to an underestimation of the frequency of low muscle mass in overweight and obese asthmatics.

A recent study by Benz et al. (32), evaluating sarcopenia prevalence and association with CRDs (asthma, COPD or combination of both) in an older population stated that 67% of the patients with CRDs were overweight (44.1%) or obese (22.9%) and

3% were classified as having sarcopenia (asthma: 2.3%; COPD: 3.3%). However, 80.6% of these sarcopenic patients presented a normal weight BMI, whereas 19.4% was overweight and none were obese (32). These results imply that SO is absent in older patients with asthma, which is inconsistent with the frequency of SO that was recently observed in community-dwelling older adults (4-11%) (33), in patients with COPD (10-27%) (3, 12) and in the current study. These differences may be due to the use of BMI-adjusted reference values and the diagnostic procedure proposed by ESPEN/EASO (14, 15) which enhance the diagnosis of low muscle mass/sarcopenia in overweight/obese subjects.

In addition to identifying asthma patients with low ALM and SO, the current study demonstrates the functional consequences of these features in this population. Differences in outcomes were less evident between overweight/obese patients with normal vs. low ALMI in comparison with the differences observed in normal weight patients, indicating a lower impact of presenting low ALMI in patients with higher BMI. In COPD, the volume-reducing effects of obesity have been considered to convey mechanical and respiratory muscle function advantages, leading to a relatively preserved functional status when directly compared to normal weight subjects (34). In the current study, the number of patients presenting with resting pulmonary hyperinflation (RV/TLC ratio ≥ 0.40) was highest in the normal weight patients with low ALMI (Table 2). Thus, the results of the present study clearly show a relatively preserved exercise capacity in overweight/obese subjects when comparing CPET and CWRT results with normal weight subjects, whereas 6MWT results display a diminishing effect of increasing body weight (Figure 3). The choice of exercise modality seems to play an essential role, since previous studies have shown that mild to moderate obesity does not alter exercise performance measured by weight-supported exercise testing (i.e. on a cycle-ergometer, such as the CPET), while this potential advantage of obesity to perform exercise from a mechanical standpoint seems less evident during weight-bearing exercises such as walking (35, 36). This long-lasting mechanical overload during activities of daily living in patients with excess body weight seems to provide some level of preservation in terms of muscle strength, muscle mass and maximal load during the CPET in patients with asthma. This can be hypothesized since the group with obesity with low ALMI shows similar quadriceps muscle strength, maximal load during the CPET (Figure 3) and ALMI (Table 2) compared to normal weight subjects with normal ALMI.

The present study aimed to assess different outcomes which could potentially interact with decreased ALM, such as medication use and osteopenia/osteoporosis.

The Global Initiative For Asthma (GINA) indicates that long-term treatment with OCS (periods >2 weeks) may present with systemic side effects such as obesity, osteoporosis and muscle weakness (7). Overall, the proportion of patients on maintenance OCS in the current study was 22%, which might (partly) explain the high proportion (45%) of obese individuals in the current study population. However, no statistical differences in OCS use were found between patients with low ALMI vs normal ALMI, irrespective of their BMI group. This is in line with a systematic review by Berthon et al. (2014) (37) which concluded that in four out of five studies, mainly conducted in healthy populations with durations of 4 days to 12 months of prednisone/prednisolone use, no change in body composition was reported. This included a 12-month experimental trial in asthma patients which reported no changes in FM% or muscle mass after 5-10 milligrams per day of OCS (38). The majority of the studies assessing obesity and osteoporosis suggest that obesity has a favorable effect on bone density, yet it remains unclear what the effect of obesity is on skeletal microarchitecture (39). The frequency of osteoporosis in the current study was significantly lower in the overweight and obese groups in comparison with the normal weight group, which underlines the potential positive effect of mechanical overload on bone health (40). Taking this in consideration, it is important to emphasize that among the obese asthma patients, those with SO showed a higher proportion of osteopenia/osteoporosis compared to those with no SO, suggesting that preserved skeletal muscle functional parameters are also beneficial in terms of bone health.

Strengths and limitations

To the best of our knowledge, the current study is the first to report the frequency of low ALM measured with DEXA in patients with asthma, based on age-sex-BMI specific reference values. As the ratio of connective tissue to skeletal muscle mass increases with advancing age or obesity (19) and considering the positive association between body size and muscle mass, there is a clear rationale for applying the recently published Ofenheimer reference values (20) which were specifically designed for Lunar Prodigy systems and were based on a well-sampled European general-population cohort aged 18–81 years, which makes them highly applicable to the current study population.

Evidently, some limitations of the current study need to be considered. Variables that can influence body composition, such as physical activity and nutritional status, were not studied. Furthermore, as the studied patient sample consisted of asthma patients referred for PR, the current results cannot be generalized to the whole asthma population. It seems reasonable to assume that the frequency of low

ALMI and SO is probably higher compared to the general asthma population. In fact, severe refractory asthma has been related to the presence of low fat-free mass that is comparable to that of GOLD stage IV COPD (41). Hence, patients attending PR represent an interesting population because of their complexity in terms of symptoms and comorbidities, while demonstrating a high prevalence of obesity and functional impairment (42). Lastly, it is not clear why obese subjects (especially those with low ALMI) demonstrate less impaired quality of life in the present study, since it has been shown that obese asthmatics experience poorer asthma-related quality of life, compared to asthmatics of a healthy weight (6, 43).

Conclusion

In conclusion, the present study showed that one in every five asthma patients referred for PR demonstrates low appendicular lean mass and that obesity is very common. Among the obese patients a significant proportion (29%) presented SO. Moreover, our findings provide important insights into the functional consequences of low ALM and SO in asthma patients referred for PR. Even though differences in functional outcomes between overweight and obese patients with normal and low ALM were less pronounced than in normal weight asthma patients, more emphasis should be put on nonpharmacological interventions such as exercise training programs and nutritional support (as part of PR) that not only target the deleterious effects of obesity in asthmatic patients, but also focus on maintaining or increasing muscle mass, skeletal muscle functional parameters and exercise tolerance in these patients. Future studies should focus on the prognostic impact of low muscle mass and SO in the asthma population and assess the effects of exercise- and nutrition-based interventions in addition to pharmacotherapy.

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4

CHAPTER 4

Effects of asthma on the performance of activities of daily living: a retrospective study

Meys R, Franssen FME, Nakken N, Vaes AW, Janssen DJA, Stoffels AAF, van Hees HWH, van den Borst B, Burtin C, Spruit MA.

Occup Ther Health Care. 2025 Jul;39(3):541-557.

Doi: **10.1080/07380577.2024.2346899.**

Abstract

The study aim was to identify the most problematic self-reported activities of daily living (ADLs). In a retrospective study, 1935 problematic ADLs were reported by 538 clients with 95% experiencing two or more problematic ADLs. Problematic ADLs were assessed by occupational therapists using the Canadian Occupational Performance Measure with walking (67%), household activities (41%), and climbing the stairs (41%) identified as the most prevalent problematic ADLs. Significant but weak associations were found between clinical determinants (e.g. physical, psychosocial) and problematic ADLs. The wide variety of problematic ADLs and the absence of a strong association with clinical determinants emphasizes the need for using individualized interview-based performance measures in clients with asthma.

Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airflow inflammation. It is defined by a 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 (1). Exercise performance as well as the ability to perform activities of daily living (ADLs) may be negatively impacted by the effects of the disease. As occupational therapy aims to support participation in daily life by increasing self-management and optimizing activities in the domains of self-care, leisure, and productivity (2), integrating asthma management strategies into occupational therapy interventions (e.g. patient education, energy conservation) may add value to current adult asthma care. However, asthma may be overlooked by occupational therapy practitioners as a contributing factor affecting a client's ability to engage in ADLs, which may originate from a lack of awareness of asthma's direct impact on functional abilities and participation restrictions (2). Indeed, studies have demonstrated that asthma leads to a limitation in performance of ADLs (3-5) which has also been shown to be a stronger predictor of impaired quality of life than general physical function (6). In addition, clients with partially controlled or uncontrolled asthma were more likely to report ADL limitations and interference in normal physical exertion, compared to those with a good control over their disease (7, 8).

Self-perceived performance and satisfaction of ADLs have been measured using patient-reported questionnaires or scales focusing on general and prespecified ADLs (i.e. Barthel Index (9), and *London Chest Activity of Daily Living* scale (10), providing limited information on the activities that are most important to the individual patient. An alternative approach is offered by administering an individualized outcome measure, such as the *Canadian Occupational Performance Measure* (COPM) (11). The COPM is designed to identify and evaluate self-perceived problematic ADLs (11). It has been shown to be a valid and reliable measure in patients with Chronic Obstructive Pulmonary Disease (COPD) (12). Studies using the COPM have shown that the daily functioning of clients with COPD is greatly impaired (13-16), though, little is known about clients with other chronic lung diseases, such as asthma. It seems reasonable to hypothesize that clients with asthma also report a wide variety of problematic ADLs which are not fully captured in standard questionnaires assessing predetermined ADLs. In addition, the identification of potential determinants of problematic ADLs in clients with asthma may be valuable for occupational therapists to identify clients who are more

likely to experience ADL problems, which can enhance patient-centered care and optimize outcomes (2).

Occupational therapy aims to support participation in daily life by increasing self-management, enabling the patient to engage in social roles that are meaningful to him/her, and to optimize activities in the domains of self-care, leisure, and productivity (2). Therefore, the objectives of the current study were to identify the most prevalent self-reported problematic ADLs, to determine performance and satisfaction scores for these ADLs, and to assess the association between clinical determinants and problematic ADLs in a large sample of adult clients with asthma.

Methods

Design

This observational study is a retrospective analysis of adults with asthma who were referred by a pulmonologist to an inpatient pre-pulmonary rehabilitation assessment at Ciro (a specialty institute for chronic organ failure in Horn, the Netherlands) between January 2005 and April 2019.

The medical ethics committee of the University Hospital Maastricht and Maastricht University approved the use of retrospective data (METC azM/UM 2019-1078), stating that the Medical Research Involving Human Subjects Act (WMO) was not applicable to the current study. Patient records were included if 1) diagnosed with asthma by a physician with initial identification of a characteristic pattern of symptoms and a variable expiratory airflow limitation (1), and 2] clinically stable at the time of assessment (i.e., not experiencing an asthma exacerbation).

Outcomes

Canadian Occupational Performance Measure.

The COPM was assessed by qualified occupational therapists using a protocol-based semi-structured interview (Dutch version) which measures individual, patient-identified problems in the areas of self-care, productivity and leisure (17). As part of the interview, clients were asked to identify any ADLs that were difficult to complete because of their respiratory condition. As mobility-related problems such as walking and cycling are highly prevalent in clients with chronic respiratory disease (14), these problems were categorized as a separate “mobility” domain, instead of including them in the self-care domain (14). After identification of all

problematic ADLs, the patient rated the perceived level of performance and their level of satisfaction with this current level of performance for each of the maximal five most important activities. The performance and satisfaction scores are based on a 10-point scale, ranging from 1 (not at all able to perform/not at all satisfied) to 10 (able to perform extremely well/extremely satisfied).

Characteristics.

As part of routine assessment, age, sex, body mass index (BMI), fat-free mass index (FFMI) and living status (living alone or together) were assessed. The *modified Medical Research Council* (mMRC) dyspnea scale was used to establish functional impairment due to dyspnea (18) with a range of 0 (I only get breathless with strenuous exercise) to 4 points (I am too breathless to leave the house or I am breathless when dressing/undressing).

Pulmonary function.

Forced expiratory volume in the first second (FEV_1), FEV_1 /forced vital capacity (FVC) ratio and residual volume/total lung capacity ratio (RV/TLC) were determined as key pulmonary function indices using standardized equipment following international guidelines (19). Maximal strength of the respiratory muscles was assessed using maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) measurements (20).

Physical status.

Exercise performance was assessed with an incremental cardiopulmonary exercise test (CPET) (21, 22) and the 6-minute walking test (6MWT; performed twice) (23).

Emotional status.

To evaluate quality of life, the *St. George's Respiratory Questionnaire* (SGRQ) (24) was assessed with a range of 0 to 100 points with higher scores indicating decreased quality of life. Mood status was measured with the *Hospital Anxiety and Depression Scale* (HADS) (25). With a range of 0 to 21, higher scores are equivalent to an increase in symptoms of anxiety or depression, respectively.

Data Analysis.

Descriptive data were presented as mean $\pm$ SD, median (interquartile range 25-75%) or proportions (percentage), as appropriate. The most prevalent problematic ADLs were described for the whole sample and after stratification for sex. Logistic regression analyses were conducted to test whether reporting (yes/no) any of the four identified problematic COPM domains (mobility, self-care, productivity and leisure) was associated with the following clinical determinants: age (years), sex (male/

female), living status (alone/together), FEV₁ (% predicted), FFMI (kg/m²), 6-minute walk distance (% predicted), mMRC dyspnea grade (points), maximum oxygen uptake during CPET (VO_{2max}; % predicted), SGRQ total score (points), symptoms of anxiety and depression (HADS; points). Logistic models were fitted for each of the 4 COPM domains separately, after which the area under the curve (AUC) of the receiver operating characteristic (ROC) curve was calculated as a measure of the final models' predictive values. This same set of predictors was tested in their association with performance and satisfaction scores for each of the 4 COPM domains via multiple linear regression models. Performance scores as well as satisfaction scores were averaged over repeated measures per patient within each COPM domain separately. These mean scores were used as outcome variables in regression models. For both linear and logistic regression analyses, multicollinearity tests were carried out in advance and the variables were retained in the models, if the variance inflation factor (VIF) was below 3.0. A stepwise procedure was followed for the selection of the final model variables. Statistical analyses were performed using SPSS statistical software program, version 25.0. *A priori*, p-values of <0.05 were considered statistically significant.

Results

Of the 712 clients with asthma included in the current study, 538 (76%) were eligible for final analyses. Clients who did not complete the full COPM assessment (i.e. missing performance/satisfaction scores; n = 174) were excluded. Demographics and clinical characteristics of the included clients are presented in Table 1. Mean FEV1/FVC ratio of the 538 included clients was $58.7 \pm 15.5\%$, whereas mean 6-minute walk distance was $70.6 \pm 19.1\%$ of predicted.

Problematic ADLs

In total, 1935 problematic ADLs were reported by 538 clients with asthma, of which 513 clients (95%) reported that they experienced two or more problematic ADLs. Overall, the three most prevalent problematic ADLs were walking (67.3%), household activities such as doing the dishes, vacuum cleaning, making up the bed (41.3%), and climbing the stairs (40.9%). The 10 most problematic ADLs are presented in Table 2. After stratification for sex, walking remained the most prevalent problematic ADL. However, the distribution of other problematic ADLs within the top 10 differed between male and female clients. Household activities and self-care were more frequently reported by female clients, whereas cycling and gardening were more frequently reported by male clients (see Table 3 and 4).

Table 1. Patient characteristics

	All records	Females	Males
N	538	306 (56.9%)	232 (43.1%)
Age (years)	58.3 ± 12.7	57.2 ± 13.5	59.8 ± 11.6*
Age range (years)	19.4 - 87.0	19.4 - 84.2	24.0 - 87.0
Body mass index: BMI (kg/m ²)	30.7 ± 7.2	30.9 ± 7.4	30.4 ± 7.0
Fat free mass index: FFMI (kg/m ²)	17.6 ± 2.7	16.7 ± 2.5	19.0 ± 2.4*
Forced Expiratory Vol 1 st sec: FEV ₁ (%pred)	74.4 ± 24.1	77.0 ± 23.3	71.1 ± 24.7*
FEV ₁ ratio (%)	58.7 ± 15.5	61.1 ± 15.4	55.4 ± 15.1*
Residual volume (RV) to Total Lung Capacity (TLC) ratio (%)	42.5 ± 10.7	43.7 ± 11.1	40.9 ± 9.8*
Max inspiratory pressure: MIP (%pred)	87.2 ± 29.4	92.7 ± 31.1	79.7 ± 25.2*
Max expiratory pressure: MEP (%pred)	63.9 ± 25.1	68.8 ± 26.8	56.5 ± 20.1*
Dyspnea: mMRC (points)	2.2 ± 1.0	2.3 ± 1.0	2.1 ± 1.0
Six-minute walk distance: 6MWD (%pred)	70.6 ± 19.1	69.7 ± 19.8	71.7 ± 18.0
VO _{2max} (%pred)	88.8 ± 40.6	106.5 ± 44.0	66.2 ± 19.1*
Quality of life: SGRQ total score (points)	57.1 ± 16.1	58.9 ± 15.2	54.7 ± 17.9*
Anxiety: HADS-A (points)	7.5 ± 4.5	7.9 ± 4.5	7.1 ± 4.4*
Depression: HADS-D (points)	7.1 ± 4.3	7.2 ± 4.3	7.1 ± 4.4

*p<0.05 males vs females

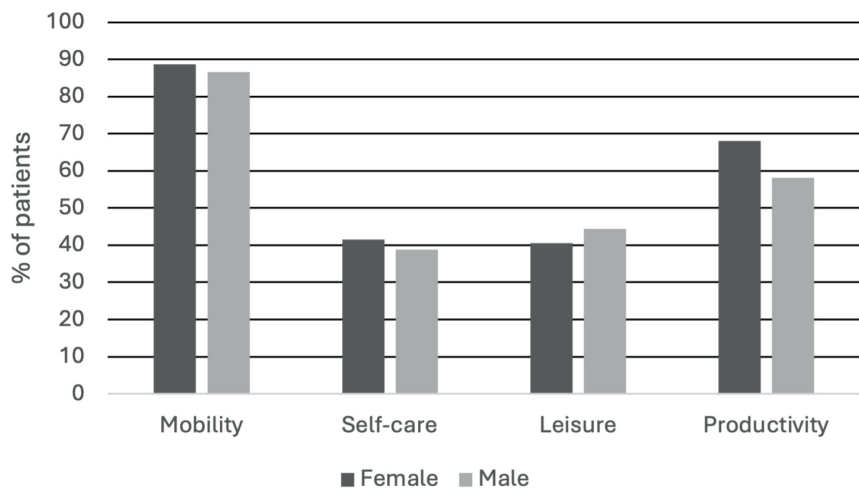


Figure 1. Percentage of clients with asthma who scored within a specific COPM domain stratified for sex. *p<0.05 female vs. male

Table 2. Top 10 Problematic ADLs for all clients (n = 538) with performance and satisfaction scores displayed as mean $\pm$ standard deviation

Nr	Activity	n (%)	Performance	Satisfaction
1	Walking - mobility	362 (67.3%)	4.00 $\pm$ 1.74	3.40 $\pm$ 2.07
2	Household activities - performance	222 (41.3%)	4.18 $\pm$ 1.65	3.69 $\pm$ 1.90
3	Stair climbing - mobility	220 (40.9%)	3.99 $\pm$ 1.58	3.40 $\pm$ 1.87
4	Cycling - mobility	172 (32.0%)	3.70 $\pm$ 2.01	3.40 $\pm$ 2.13
5	Showering and bathing – self care	125 (23.2%)	4.17 $\pm$ 1.63	3.07 $\pm$ 1.71
6	Gardening - performance	89 (16.5%)	3.83 $\pm$ 1.90	3.42 $\pm$ 1.89
7	Dressing/undressing – self care	87 (16.2%)	4.53 $\pm$ 1.61	3.66 $\pm$ 1.87
8	Self-care – self care	76 (14.1%)	4.39 $\pm$ 1.63	3.72 $\pm$ 2.07
9	Sports - leisure	74 (13.8%)	3.35 $\pm$ 2.25	3.12 $\pm$ 2.29
10	Social activities – self care	68 (12.6%)	3.22 $\pm$ 1.86	2.49 $\pm$ 1.72

Table 3. Top 10 Problematic ADLs for male clients (n = 232) with performance and satisfaction scores displayed as mean $\pm$ standard deviation

Nr	Activity	n (%)	Performance	Satisfaction
1	Walking - mobility	140 (60.3%)	4.07 $\pm$ 1.75	3.55 $\pm$ 2.06
2	Stair climbing - mobility	96 (41.4%)	4.30 $\pm$ 1.65	3.70 $\pm$ 1.94
3	Cycling - mobility	87 (37.5%)	3.80 $\pm$ 2.12	3.55 $\pm$ 2.19
4	Household activities - performance	62 (26.7%)	4.02 $\pm$ 1.75	3.44 $\pm$ 1.76
5	Showering and bathing – self care	53 (22.8%)	4.13 $\pm$ 1.57	3.06 $\pm$ 1.67
6	Gardening - performance	51 (22.0%)	3.61 $\pm$ 1.96	3.16 $\pm$ 1.79
7	Dressing/undressing – self care	42 (18.1%)	4.57 $\pm$ 1.68	3.62 $\pm$ 1.92
8	Sports - leisure	34 (14.7%)	3.62 $\pm$ 2.36	3.53 $\pm$ 2.36
9	Social activities - leisure	29 (12.5%)	3.66 $\pm$ 2.04	2.93 $\pm$ 1.75
10	Self-care – self care	28 (12.1%)	4.32 $\pm$ 1.12	3.86 $\pm$ 2.12

COPM Domains

All four COPM domains were represented in the top 10 of problematic activities, showing the diversity of the problematic ADLs that appear in clients with asthma. The most frequently scored COPM domain was the “mobility” domain (88%) (mean performance score: 3.9 $\pm$ 1.5 points, mean satisfaction score: 3.3 $\pm$ 1.8 points) followed by “productivity” (64%) (mean performance score: 4.0 $\pm$ 1.7 points, mean satisfaction score: 3.4 $\pm$ 1.9 points), “leisure” (42%) (mean performance score: 3.6 $\pm$ 2.0 points, mean satisfaction score: 2.9 $\pm$ 2.0 points), and “self-care” (40%) (mean performance score: 4.3 $\pm$ 1.5 points, mean satisfaction score: 3.4 $\pm$ 1.8 points). In Figure 1, the percentage of clients with asthma who scored within a specific COPM domain are presented, after stratification for sex. The proportion of female

clients reporting a problematic ADL within the “productivity” domain (68.0%) was significantly higher than the proportion of male clients (58.2%; $p < 0.05$).

Table 4. Top 10 Problematic ADLs for female clients ($n = 306$) with performance and satisfaction scores displayed as mean $\pm$ standard deviation

Nr	Activity	n (%)	Performance	Satisfaction
1	Walking - mobility	222 (72.5%)	3.95 ± 1.74	3.31 ± 2.07
2	Household activities - performance	160 (52.3%)	4.24 ± 1.62	3.79 ± 1.94
3	Stair climbing - mobility	124 (40.5%)	3.76 ± 1.48	3.17 ± 1.77
4	Cycling - mobility	85 (27.8%)	3.60 ± 1.89	3.24 ± 2.07
5	Showering and bathing - self care	72 (23.5%)	4.19 ± 1.68	3.08 ± 1.74
6	Self-care - self care	48 (15.7%)	4.44 ± 1.87	3.65 ± 2.06
7	Dressing/undressing - self care	45 (14.7%)	4.49 ± 1.56	3.69 ± 1.84
8	Sports - leisure	40 (13.1%)	3.13 ± 1.63	2.78 ± 2.19
9	Social activities - leisure	39 (12.7%)	2.90 ± 1.67	2.15 ± 1.63
10	Gardening - performance	38 (12.4%)	4.13 ± 1.79	3.76 ± 1.99

Clinical determinants of ADL performance and satisfaction

Six clinical determinants significantly affected the odds of reporting problematic ADLs in one of the 4 COPM domains (Table 5). Clients with a higher SGRQ total score or a lower HADS-Depression score had higher odds to score 1 or more problematic ADLs within the COPM domain “mobility”. Clients who were older, who had a higher FFMI, with a higher SGRQ score or a lower MIP had higher odds to score 1 or more problematic ADLs within the COPM domain “self-care”. Clients who were living alone had higher odds of scoring 1 or more problematic ADLs within the COPM domain “productivity”, whereas younger clients had higher odds of scoring 1 or more problematic ADLs within the COPM domain “leisure” (Table 3). No uniform pattern of association was found across the COPM domains. The identified predictors were poor to moderate in discriminating between clients with asthma with and without one or more problematic ADLs in the four COPM domains, with AUCs of the ROC analysis ranging from 0.530 – 0.683 (Table 5). The same models of predictors were used to test for associations between clinical determinants and the mean scores for performance and satisfaction for each COPM domain (Table 6). Similar to the logistic regression analyses, the multiple linear regression analysis showed that performance and satisfaction scores among different COPM domains could not be adequately predicted using these clinical determinants. No unique predicting variable was found to influence all domain scores simultaneously and the goodness-of-fit for all models was poor (R^2 0.114 -0.227; Table 6).

Table 5. Odds Ratios (OR) of clinical determinants significantly affecting reporting (Yes, No) any of the 4 Canadian Occupational Performance Measure Domains (Logistic Regression)

	Mobility		Self-care		Productivity		Leisure	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value
Depression:HADS-D (points)	0.773 (0.600 - 0.997)	0.048						
Quality of Life:SGRQ total score (points)	1.084 (1.017 - 1.157)	0.014	1.078 (1.034 - 1.123)	<0.001				
Age (years)			1.049 (1.006 - 1.094)	0.027			0.964 (0.930 - 1.000)	0.049
Fat-free mass index: FFMI (kg/m2)			1.377 (1.049 - 1.809)	0.021				
Max inspiratory pressure: MIP (kPa)			0.987 (0.958 - 0.999)	0.044				
Living together (ref: living alone)					0.287 (0.095 - 0.869)	0.027		
<i>Model fit</i>								
AUC	0.618		0.683		0.548		0.530	
95% CI; LL	0.523		0.622		0.493		0.481	
95% CI; UL	0.712		0.744		0.602		0.579	

ORs are presented per unit increase of the independent variable together with the lower limit and upper limit of the 95% CI. Effects of the following variables were also tested, but no statistical significance was observed: sex, FEV1 (% predicted), 6-minute walk distance (% predicted), mMRC dyspnea grade, maximum oxygen uptake during CPET (VO2max; % predicted), symptoms of anxiety (HADS-A).

Abbreviations: AUC, area under the curve; CI, confidence interval; FFMI, fat-free mass index; HADS, Hospital Anxiety and Depression scale; LL: lower limit; MIP, maximal inspiratory pressure; ref, reference value; SGRQ, St. George's Respiratory Questionnaire; UL, upper limit.

Table 6. Betas (β) of clinical determinants significantly affecting Performance (P) and Satisfaction (S) of any of the 4 Canadian Occupational Performance Measure domains (Linear Regression)

	Mobility β		Self-care β		Productivity β		Leisure β	
	P	S	P	S	P	S	P	S
Quality of Life:SGRQ total score (points)	-0.025 (-0.043 – -0.006)							
Age (years)				0.056 (0.009 – 0.103)				
Max inspiratory pressure:MIP (kPa)	-0.011 (-0.023 – 0.000)							
Male sex			-1.150 (-2.159 – -0.142)					1.526 (0.327 – 2.724)
RV/TLC ratio	-4.829 (-8.258 – -1.401)					6.460 (2.512 – 10.409)		
Dyspnea: mMRC (points)		-0.594 (-0.973 – -0.216)			-0.700 (-1.209 – -0.190)	-0.408 (-0.809 – -0.006)	-0.651 (-1.266 – -0.036)	
<i>Model fit</i>								
R²	0.190	0.114	0.149	0.160	0.134	0.227	0.114	0.156

β s (and 95% CI) represent an average increase in the scores per unit increase in the independent variable. Effects of the following variables were also tested, but no statistical significance was observed: living status, FEV1 (% predicted), 6-minute walk distance (% predicted maximum oxygen uptake during CPET (VO2max; % predicted), symptoms of anxiety and depression (HADS-A and HADS-D).

Abbreviations: CI, confidence interval; MIP, maximal inspiratory pressure; mMRC, modified Medical Research Council; RV/TLC ratio, residual volume to total lung capacity ratio; SGRQ, St. George's Respiratory Questionnaire.

Discussion

This study is the first to describe that adult clients with asthma have a variety of self-perceived problematic ADLs, with 1935 different problematic ADLs being reported by 538 clients. Literature focusing on individuals with chronic respiratory disease has been stating for years that ADLs are important for quality of life (26). However, only a limited number of studies have actually concentrated on the performance or satisfaction of ADLs in this population (13, 14, 27). Instead, studies (28, 29) focus on underlying mechanisms, such as persisting respiratory and non-respiratory symptoms (e.g. fatigue). The current study did not find clinical determinants of problematic ADLs. Therefore, more knowledge regarding the performance of ADLs is required to design appropriate interventions within asthma management.

Factors potentially contributing to ADL limitations in adult clients with asthma, include psychological factors, respiratory load and dynamic hyperinflation (i.e., exercise-induced air trapping) (30). Indeed, dynamic hyperinflation has been associated with impaired ADLs in clients with asthma, independent of asthma severity (31). As clients with severe asthma display a comparable degree of dynamic hyperinflation during walking as clients with COPD (32), it seems reasonable to hypothesize that these clients may also experience a relatively high respiratory load and dyspnea perception during the performance of ADLs, as seen in COPD (33). It seems likely that these physical restrictions can negatively affect the performance of ADLs, such as getting dressed, doing household activities, and walking up and down the stairs. However, in the present study, clinical characteristics such as the degree of airflow limitation and physical functioning were not associated with performance or satisfaction scores. Similar findings were reported in clients with COPD (14). So, pulmonary function tests and exercise tests cannot be used to obtain and understand which ADLs are limited. In addition, depressive symptoms, co-occurring with insomnia, may also impede one's ability or require changes in methods used to perform ADLs in clients with asthma (34). Nevertheless, the current study reported that symptoms of anxiety and depression were not significant predictors of self-perceived ADL limitations. Perhaps adult clients with asthma who are depressed experience less ADL limitations as they are more passive.

Although asthma symptoms, reduced quality of life and limitation in performance of ADLs are all important patient-reported outcomes, not all are considered equally important in current asthma management. Commonly administered questionnaires such as the *Asthma Control Questionnaire* (ACQ) (35) and *Asthma Control Test* (ACT) (36) focus on classical symptoms (e.g. shortness of breath, wheezing), with little to no emphasis being put on ADL limitations. Since clients reporting

poor asthma control were more likely to have ADL limitations than those with controlled asthma (7), it seems valuable to evaluate constructs relevant to performance of ADLs as seen from the perspective of the patient within the context of his or her everyday life. Moreover, basic characteristics such as age and marital status should not be overlooked, since the current study showed that younger clients experienced more problems in terms of leisure activities and people who live alone experience more problems regarding productivity.

Implications for Occupational Therapy Practice

The role of occupational therapy is overlooked in current clinical asthma guidelines. Even though occupational therapy, either provided as a monodisciplinary home-based program (27, 37) or as part of a multidisciplinary pulmonary rehabilitation program (13, 38, 39), appears to be effective in improving both performance and satisfaction of problematic ADLs in clients with moderate to severe COPD, occupational therapy remains rarely integrated in clinical practice and asthma trials. Based on the findings of the current study, some practice implications should be considered.

First, occupational therapists should develop strategies to incorporate energy conservation and activity modification techniques into daily activities to cope with physical demands and respiratory symptoms associated with asthma. Therapists should start with prioritizing the problematic ADLs based on their importance, dissatisfaction and/or which ADL is easiest to adapt. Using activity analysis using observation or reviewing the process, intervention can be initiated. Two examples of methods often used in occupational therapy treatment for asthma clients include: Simplification of the activity and the “4-Ps” method. Simplification or energy conservation strategies includes 1) Eliminating parts of the activity such as using a bathrobe instead of drying off; 2) Changing the order in order to conserve energy such as preparing the vegetables for dinner in the morning; 3) Simplify the method of performing the task such as using the bed’s electrical adjustments to change the bed linen; and 4) Combining tasks such as cooking more than one meal and freeze others. The 4Ps method is also a method to conserve energy by 1) Prioritizing activities needed to get done daily by the client recognizing their personal abilities and work within them by asking what should be done now; 2) Planning the day ahead so that there is enough energy for the most important activities, such as social, alternating the easy/passive/mental activities with the ones that are more difficult/active/physical; 3) Pace activities by taking regular rest breaks before getting tired or out of breath, for example taking a rest every 3 stair steps; and 4) Position the body in the most comfortable position such as sitting when gardening and avoid extensive bending or reaching.

Limitations

To our knowledge, this study is the most comprehensive evaluation of problematic ADLs in clients with asthma. Self-perceived problematic ADLs were assessed in a large sample of clients with asthma using the COPM as a semi-structured interview measure which can be regarded as superior to standardized questionnaires that focus on specific ADLs that may not be meaningful to these clients. Nevertheless, limitations must be addressed. First, it should be considered that clients were solely recruited in a specialized pulmonary rehabilitation setting, limiting the external validity of the current study because symptom burden of the study population is probably increased compared to asthma patients in the general population. Secondly, clients variably reported problematic ADLs differently. For instance, some clients reported their ADLs in a more generic way (e.g. household activities), whereas others mentioned their ADLs in a very specific way (e.g. doing the dishes). This might have led to an underestimation of various ADLs.

Recommendations

The current data clearly provide a rationale to assess the additional effects of occupational therapy on the functional performance of clients with asthma, either as individualized therapy or as part of a comprehensive pulmonary rehabilitation program. Future studies should include methods to address occupational therapy interventions such as educating clients to use techniques such as energy conservation, activity or environmental modification, fatigue and pain management, use of adapted equipment, time management, coping strategies and lifestyle adaptations. Furthermore, future studies should incorporate details on employment status, since it can be hypothesized that the lack of productivity statements among male clients could be attributed to the fact that 38% of them were at or beyond retirement age. Asthmatic symptoms could have contributed to the decision to retire prematurely, after which the productivity domain might no longer be prioritized by clients.

Conclusions

To conclude, self-perceived performance and satisfaction in ADLs are affected in clients with asthma referred for pulmonary rehabilitation, with 95% of the current sample experiencing at least two problematic activities. The wide variety of problematic ADLs and the absence of a strong association with clinical determinants such as pulmonary function and exercise capacity emphasizes the need for using individualized interview-based performance measures to allow patient-tailored interventions to support clients with asthma in their participation in relevant everyday life activities.

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5

CHAPTER 5

Clinical importance of patient-reported outcome measures in severe asthma: results from U-BIOPRED

Meys R, Franssen FME, Van 't Hul AJ, Bakke PS, Caruso M, Dahlén B, Fowler SJ, Geiser T, Howarth PH, Horváth I, Krug N, Behndig AF, Singer F, Musial J, Shaw DE, Montuschi P, Zee AHM, Sterk PJ, Roberts G, Kermani NZ, Incalzi RA, Louis R, Andersson LI, Wagers SS, Dahlén SE, Chung KF, Adcock IM, Spruit MA.

U-BIOPRED Study Group.

Health Qual Life Outcomes. 2024 Dec 20;22(1):109.

Doi: **10.1186/s12955-024-02321-3.**

Abstract

Rationale: Knowledge about the clinical importance of patient-reported outcome measures (PROMs) in severe asthma is limited.

Objectives: To assess whether and to what extent asthma exacerbations affect changes in PROMS over time and asthma-specific PROMs can predict exacerbations in adult patients with severe asthma in usual care.

Methods: Data of 421 patients with severe asthma (62% female; mean age 51.9 ± 13.4 years; mean FEV_1 $67.5 \pm 21.3\%$ pred) from the U-BIOPRED cohort were analyzed. The included PROMs were: Asthma Control Questionnaire (ACQ5); Asthma Quality of Life Questionnaire (AQLQ); Hospital Anxiety and Depression scale (HADS); Epworth Sleepiness Scale (ESS); Medication Adherence Report Scale (MARS); Sino-Nasal Outcomes Test (SNOT20). Participants were assessed at baseline and after 12–18 months of usual care.

Results: PROMs showed very weak to weak correlations with clinical characteristics such as age, body mass index, FEV_1 , FeNO and eosinophilic cell count. Patients presenting no exacerbations during follow-up showed a statistically significant improvement in all PROMs (except for MARS), whereas individuals experiencing >2 exacerbations showed a deterioration. Baseline ACQ5 was a predictor of exacerbations with an AUC of 0.590 (95%CI 0.514–0.666).

Conclusions: The association of PROMs with clinical measures was poor in severe asthmatics. Moreover, PROMs were prone to changes in usual care, with exacerbations playing a key role. PROMs need to be systematically evaluated in severe asthma to improve clinical care based on specific patient's needs.

Introduction

Severe asthma is a prevalent and heterogeneous condition that is defined by frequent asthma exacerbations and comorbidities, such as rhinosinusitis, allergies, obesity and psychopathologies (1). In addition to its defining symptoms and impact on lung function, asthma may have extra-pulmonary manifestations, which also have a considerable impact on patient's health and quality of life (2). Initially, severe asthma treatment was focused on physiological indices of health, such as improving pulmonary function. However, the forced expiratory volume in the first second (FEV₁) correlates weakly with patients' quality of life (3). Therefore, a true patient-centered approach needs to take the patient's perspective into account, as some consequences of the disease can only be reported by patients (2). Patient-reported outcome measures (PROMs) can be used to assess daily symptoms and understand the impact of severe asthma and the burden of its treatment (4).

PROMs show promise as being useful to support clinical decision-making (5). However, asthma-related PROMs have mostly been evaluated in research contexts, for example with the aim of evaluating the effects of interventions on quality of life (6-8). Knowledge about changes in PROMs in standard clinical asthma care, in which asthma exacerbations play a major role and outcomes cannot be directly attributed to specific experimental interventions, is scarce and mostly limited to respiratory-specific outcomes (9, 10). It seems reasonable to hypothesize that asthma patients who experience exacerbations are prone to changes over time in both asthma-specific as well as more generic PROMs. Accordingly, the aims of the current study were to assess whether and to what extent: (1) asthma exacerbations affect changes in PROMs over time in usual asthma care and, (2) asthma-specific PROMs can predict asthma exacerbations in adult patients with severe asthma.

Methods

This is an analysis of the data from the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes project (U-BIOPRED; NCT01982162, registered October 30, 2013), a multicenter prospective longitudinal cohort study in which 610 adults (18+ years) from 16 clinical institutions across Europe were recruited between May 2011 and April 2013 (11). The current study included the 421 adult patients with *severe asthma* from the cohort, which was defined as having uncontrolled symptoms and/or frequent (≥ 2 per year) exacerbations despite high intensity asthma treatment (≥ 1000 $\mu\text{g/day}$ fluticasone equivalent and/or daily oral

corticosteroids combined with long-acting β_2 agonists or any other controller medication) (12). Asthma diagnosis was confirmed by a history of wheeze (either spontaneously or on exertion), as well as variable airflow limitation by one of the following: airflow reversibility (increase in forced expiratory volume in 1s (FEV_1) $>12\%$ predicted and 200 mL following inhalation of 400 μg salbutamol), airway hyperresponsiveness (methacholine provocative concentration causing a 20% fall in FEV_1 $<8 \text{ mg}\cdot\text{mL}^{-1}$, a diurnal peak expiratory flow amplitude $>8\%$ of mean), or a decrease in FEV_1 of 12% predicted and 200 mL within 4 weeks after tapering maintenance treatment (12). Participants with severe asthma were reviewed at baseline and 12–18 months after enrolment. The medical ethics committee of each participating center approved this study and all patients gave written informed consent. Baseline data, details of the participating centers and standard operating procedures of the U-BIOPRED project have been published (11). Moreover, studies focusing on self-reported medication adherence, using the Medication Adherence Report Scale (MARS) (13), and treatable traits in the adult U-BIOPRED cohort (14) have been performed.

PROMs

Asthma symptom control was measured with the Asthma Control Questionnaire (ACQ5), a self-administered 5-item questionnaire with scores ranging from 0 (totally controlled) to 6 (severely uncontrolled) points (15). A cut-off score of >1.5 points was used to identify patients with uncontrolled asthma (16). To evaluate quality of life, the Asthma Quality of Life Questionnaire (AQLQ) was administered (17). The AQLQ consists of 32 questions (7-point Likert scale), covering 4 domains (symptoms, activity limitation, emotional function and environmental exposure), with higher scores indicating better quality of life. An AQLQ score <4.7 points was used as a cut-off value for impaired quality of life (18).

Mood status was measured with the 14-item Hospital Anxiety and Depression scale (HADS; range 0–21 points per domain) (19). Cut-off scores of ≥ 8 points were used to identify patients with elevated levels of anxiety or depression (20). Sleep propensity in daily life or ‘daytime sleepiness’ was determined with the Epworth Sleepiness Scale (ESS) (21), a self-administered questionnaire containing 8 questions with a 4-point scale (0–3). A higher score represents more daytime sleepiness and a cut-off of ≥ 11 points was used to indicate a high risk on excessive daytime sleepiness (ESS) (21). The MARS is a 5-item measure of self-reported adherence, in which a cut-off of <23 points was applied to indicate poor adherence (13, 22). Upper airway symptoms were assessed with the Sino-Nasal Outcomes Test (SNOT20) (23),

a 20-question survey in which a higher score indicates greater impairment. A score of ≥ 2 points was considered abnormal (24).

Other assessments

Demographics, body mass index (BMI, body weight in kilograms divided by the height in squared meters), smoking history and medication use were recorded. Both at the baseline and the follow up visit, participants were asked to report the number of exacerbations that needed systemic corticosteroid therapy in the previous 12 months.. In addition, the presence of the following comorbidities were captured: allergic rhinitis, non-allergic rhinitis, nasal polyps, laryngeal dysfunction, chronic sinusitis, hay fever, emphysema, psychopathologies, atopic dermatitis, obesity (BMI ≥ 30), gastroesophageal reflux disease (GERD), congestive heart failure, coronary heart disease, hypertension, diabetes, osteoporosis. To measure pulmonary function, participants underwent fractional exhaled nitric oxide (FeNO) testing at 50 mL/s and spirometric measurements (FEV₁) (25, 26). Allergic sensitization was obtained by measuring specific immunoglobulin (IgE) to six common aeroallergens or skin prick testing (27). Blood samples were obtained for measurement of hematological indices, such as eosinophilic and neutrophilic cell count as well as for total IgE. Procedures are detailed further in previous work (11).

Statistics

The data of the current study was downloaded in February 2022 from tranSMART, an open-source knowledge management platform, after which analyses were performed using IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, USA) and GraphPad Prism 9.0 (GraphPad Software Inc., California, USA). Results are presented as mean and standard deviation (SD), median and interquartile range (IQR), and/or frequencies, as appropriate. Continuous variables were tested for normality. The interrelationship between PROMs and the relationship between PROMs and clinical characteristics were analyzed using Spearman's correlations. The strength of correlations has been classified according to British Medical Journal (BMJ) guidelines, which classify significant correlation coefficients of 0–0.19 as very weak, 0.2–0.39 as weak, 0.4–0.59 as moderate, 0.6–0.79 as strong, and 0.8–1 as very strong (28). Differences between the baseline and longitudinal assessment were analyzed using paired T-tests or Wilcoxon signed rank test, as appropriate. To assess the effect of asthma exacerbations, differences in PROM scores at baseline and changes in PROMs were compared after stratification into three groups based on the number of exacerbations in the preceding 12 months (0 exacerbations; 1-2 exacerbations; >2 exacerbations) recorded at the longitudinal follow-up. Between-group differences were analyzed using Analysis of Variance (ANOVA) with Bonferroni post-

hoc correction. Finally, to assess the diagnostic value of asthma-specific PROMs in terms of predicting an asthma exacerbation, the AUC (Area Under The Curve) ROC (Receiver Operating Characteristics) curve was calculated. The ROC analysis results were interpreted as follows: AUC <0.70, low diagnostic accuracy; AUC 0.70–0.90, moderate diagnostic accuracy; and AUC $\geq$ 0.90, high diagnostic accuracy (29). *A priori*, the level of significance was set at $\leq$ 0.05.

Results

Patient characteristics and baseline PROM scores of the 421 included patients are presented in Table 1. The majority of patients were female (62%), with a mean age of 51.9 ± 13.4 years. One-hundred-and-sixty-four patients (39%) were obese and the mean FEV₁ was 67.5 ± 21.3 % of predicted. The median number of experienced asthma exacerbations in the 12 preceding months was 2 (IQR 1-3), whereas the median number of comorbidities at baseline was 4 (2 – 5). The mean ACQ5 score at baseline was 2.28 ± 1.17 points and 74% of the patients were classified as having uncontrolled asthma. The mean baseline AQLQ score was 4.45 ± 1.21 points and in 57% of the patients an impaired asthma-related quality of life was observed. Mean HADS-A and HADS-D scores were 7.1 ± 4.5 points and 5.6 ± 4.6 points, with 44% and 30% of patients presenting increased levels of anxiety and depression (values above the ≥ 8 points cut-off), respectively.

Correlations PROMs and clinical characteristics

All PROMs showed very weak or non-significant correlations with clinical characteristics (age, BMI, FEV₁%pred, FeNO, eosinophilic and neutrophilic cell count and number of exacerbations in the preceding 12 months) at baseline (Table 2). Weak correlations were only found between asthma control (ACQ5) and FEV₁%pred or the number of exacerbations in the past 12 months, and between quality of life (AQLQ) and FEV₁%pred (p : 0.23-0.25; all $p < 0.001$). The interrelationship of the PROMs is shown in Table E1. In brief, the correlation between the asthma control (ACQ5) and quality of life (AQLQ) and the correlation between depression and anxiety (HADS-D and HADS-A) were the strongest (p : -0.77 and 0.75, respectively; $p < 0.001$).

Table 1. Baseline characteristics and PROM scores.

Clinical characteristics	Age, years	51.9 ± 13.4
	Age at diagnosis, years	26.0 (9.0 – 42.0)
	Females, n (%)	261 (62.0)
	BMI, kg/m²	29.2 ± 6.3
	BMI >30 kg/m ² , n (%)	164 (39.0)
	Smoking: current/former/never, n (%)	42 (10) /115 (27) /264 (63)
	Serum IgE, IU/mL	122 (51 – 350)
	Atopy test positive, n (%)	275 (64.3)
	FEV₁, %predicted	67.5 ± 21.3
	FVC, %predicted	87.9 ± 19.3
	FEV₁/FVC ratio	0.63 ± 0.14
	FeNO, ppb	26 (15 – 47)
	Blood neutrophils, cells/μL	4810 (3700 – 6778)
	Blood eosinophils, cells/μL	200 (100 – 400)
	Asthma exacerbations <12 months, n	2 (1 – 3)
	0 exacerbations, n (%)	79 (18.8)
	1-2 exacerbations, n (%)	177 (42.1)
	≥3 exacerbations, n (%)	164 (39.0)
	Comorbidities, n	4 (2 – 5)
	≥2 comorbidities, n (%)	362 (86.0)
PROMs	ACQ5, points	2.28 ± 1.17
	ACQ5 >1.5 points, n (%)	285/388 (73.5)
	AQLQ, points	4.45 ± 1.21
	AQLQ <4.7 points, n (%)	237/414 (57.2)
	ESS, points	7.52 ± 4.47
	ESS ≥11 points, n (%)	99/386 (25.6)
	HADS-A, points	7.14 ± 4.52
	HADS-A ≥8 points, n (%)	173/391 (44.2)
	HADS-D, points	5.63 ± 4.56
	HADS-D ≥8 points, n (%)	118/391 (30.2)
	MARS, points	22.37 ± 2.47
	MARS <23 points, n (%)	158/404 (39.1)
	SNOT20, points	1.59 ± 0.88
	SNOT20 >2 points, n (%)	102/347 (29.4)

Summary variables are presented as n (%) for discrete variables, mean ± standard deviation for quantitative variables or median (Interquartile range) for skewed variables.

Abbreviations: PROMs, patient-reported outcomes; BMI, body mass index; kg/m², kilogram per square meter; IgE, Immunoglobuline E; IU/mL, international units per milliliter; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; cells/μL, cells per microliter; ACQ5, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ESS, Epworth Sleepiness Scale; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; MARS, Medication Adherence Report Scale; SNOT20, Sino-Nasal Outcomes Test.

Table 2. Correlations PROMs and clinical characteristics

	Age, years	BMI, kg/m ²	FEV ₁ , %pred	FeNO, ppb	Eos, cells/μL	Neutros, cells/μL	Exacerb. <12m, n
ACQ5	-0.14** (388)	0.10 (388)	-0.23*** (385)	-0.04 (362)	-0.06 (376)	0.04 (376)	0.25*** (387)
AQLQ	0.03 (414)	-0.08 (414)	0.24*** (411)	0.06 (388)	0.01 (401)	0.05 (401)	-0.17*** (413)
ESS	-0.08 (386)	0.04 (386)	-0.01 (383)	-0.02 (363)	-0.08 (373)	0.05 (373)	0.05 (385)
HADS-A	0.06 (391)	0.08 (391)	-0.07 (389)	-0.10 (364)	-0.11* (379)	0.03 (379)	0.12* (390)
HADS-D	0.05 (391)	0.12* (391)	-0.10 (389)	-0.06 (364)	-0.09 (379)	0.06 (379)	0.11* (390)
MARS	0.17** (404)	0.06 (404)	0.01 (402)	0.00 (378)	0.00 (393)	0.05 (393)	-0.02 (403)
SNOT20	-0.10 (347)	-0.06 (347)	0.02 (345)	-0.04 (327)	0.00 (336)	-0.03 (336)	0.10 (346)
0.00 - 0.19		0.20 - 0.39	0.40 - 0.59	0.60 - 0.79	0.80 - 1.00		
very weak		weak	moderate	strong	very strong		

Spearman's rho was used to calculate correlations between variables. (n) represents the total number of sample values per analysis. * p<0.05; ** p<0.01; *** p<0.001

Abbreviations: ACQ5, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ESS, Epworth Sleepiness Scale; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; MARS, Medication Adherence Report Scale; SNOT20, Sino-Nasal Outcomes Test; BMI, body mass index; kg·m⁻², kilogram per square meter; FEV₁, forced expiratory volume in the first second; %pred, percentage of the predicted value; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; Eos, eosinophilic cell count; cells/μL, cells per microliter; Neutros, neutrophilic cell count; exacerb. <12m, number of exacerbations in the preceding 12 months (assessed at baseline).

Changes in PROMs

The median time between the baseline and follow-up visit was 444 (IQR 400-514) days. Patients who did not consent to participate in the longitudinal assessment (n = 104) and patients who attended the follow-up visit less than 365 days after the baseline visit (n = 17) were excluded, resulting in 300 patients (71.3%) for the longitudinal analyses. Patients who attended the longitudinal visit (n = 300) and excluded patients (n = 121) were comparable regarding baseline characteristics (Table E2).

Changes in PROMs after stratification for exacerbations

After stratification for the number of asthma exacerbations during follow-up (0 versus 1-2 versus >2), multiple differences were observed at follow-up (Table 3). The group of patients who did not experience any asthma exacerbation during follow-up showed a statistically significant improvement in all PROMs (except for

MARS score), while FEV₁, FeNO and blood eosinophils did not change significantly over this time-frame. The groups of individuals experiencing >2 asthma exacerbations during the follow-up period deteriorated in terms of PROM scores, even though this group already presented the worse PROM scores at baseline and showed no changes in any of the clinical characteristics (Table 3).

Prediction of asthma exacerbations using asthma-specific PROMs

ROC curve analysis revealed that baseline asthma control (ACQ5) was a significant discriminant factor in predicting at least one asthma exacerbation between baseline and the follow-up visit (Figure E1) with an AUC of 0.590 (95%CI 0.514 – 0.666), indicating low diagnostic accuracy. The ACQ5 cut-off value of >1.5 points (16) represented 78.8% sensitivity and 62.8% specificity. The number of asthma exacerbations in the 12 months preceding the baseline assessment was the strongest predictor for an asthma exacerbation during follow-up, with an AUC 0.684 (95%CI 0.615 – 0.753; $p < 0.001$). Baseline quality of life (AQLQ score), FEV₁%pred, age and BMI were no significant predictive factors regarding asthma exacerbations during the follow-up period (all $p > 0.05$; Figure E1).

Table 3. Differences in PROM scores at baseline and changes in PROMs after stratification based on the number of exacerbations in the preceding 12 months (recorded at the longitudinal follow-up).

Clinical characteristics	0 exacerbations (n = 84)	1-2 exacerbations (n = 100)	>2 exacerbations (n = 116)	Between group difference <i>p</i> -value
Age, baseline, years	52.6 ± 14.7	54.4 ± 12.6	51.0 ± 12.5	0.178
Age at diagnosis, years	29 (11-44)	26 (7-44)	25 (7-37)	0.574
Female sex, n (%)	43 (51.2)	60 (60.0)	76 (65.5)	0.125
Follow-up, days	455 (393-520)	446 (404-510)	441 (402-511)	0.600
BMI, baseline, kg/m²	28.3 ± 5.0	29.2 ± 6.3	29.4 ± 6.3	0.429
Comorbidities (baseline), n	4 (2-5)	4 (2-5)	4 (2-6)	0.324
≥2 comorbidities	76 (90.5)	84 (84.0)	98 (84.5)	0.377
Exacerbations <12 months (baseline), n	1 (0-2)	2 (1-3)	3 (2-4) ^{NS}	<0.001
Blood eosinophils, cells/μL	220 (100 – 460)	230 (120 – 500)	200 (100 – 400)	0.449
ΔBlood eosinophils, cells/μL	-0.3 (-100 – 64)	-1.18 (-170 – 100)	0 (-99 – 152)	0.678
FEV1, %pred (baseline)	64.1 ± 18.8	67.5 ± 21.6	66.5 ± 21.9	0.526
ΔFEV1, %pred	0.7 ± 12.7	1.8 ± 14.3	-0.9 ± 14.8	0.386
FeNO, ppb	27 (15 – 39)	29 (16 – 58)	24 (15 – 45)	0.460
ΔFeNO, ppb	-1 (-15 – 8)	2 (-13 – 9)	0 (-9 – 6)	0.540
Tapering of ICS, n (%)	8 (9.5)	12 (12.1)	20 (17.2)	0.258
Tapering of OCS, n (%)	3 (3.6)	12 (12.0)	20 (17.2)	<0.05

Table 3. Continued

PROMs	0 exacerbations (n = 84)	1-2 exacerbations (n = 100)	>2 exacerbations (n = 116)	Between group difference p-value
ACQ5, baseline score, points	2.03 ± 1.17	2.12 ± 1.18	2.62 ± 1.13 [#]	<0.001
ΔACQ5, points	-0.44 ± 1.08*	-0.09 ± 1.03	0.28 ± 1.02 [#]	<0.001
ΔACQ5 ≤ -0.5, n (%)	33 (39.3)	30 (30.0)	18 (15.5)	<0.001
AQLQ, baseline score, points	4.60 ± 1.26	4.65 ± 1.23	4.21 ± 1.08	<0.05
ΔAQLQ, points	0.30 ± 0.96*	0.18 ± 0.71*	-0.13 ± 0.74 [#]	<0.01
Δ AQLQ ≤ + 0.5, n (%)	34 (40.5)	26 (26.0)	14 (12.1)	<0.001
ESS, baseline score, points	8.00 ± 4.33	7.92 ± 4.52	8.13 ± 4.56	0.949
ΔESS, points	-1.03 ± 4.29*	0.09 ± 3.33	0.49 ± 3.15*	<0.05
HADS-A, baseline score, points	6.99 ± 4.53	6.32 ± 4.42	7.74 ± 4.63	0.113
ΔHADS-A, points	-0.89 ± 3.52*	0.27 ± 3.06	0.47 ± 3.35*	<0.05
HADS-D, baseline score, points	5.81 ± 4.27	5.23 ± 4.62	5.90 ± 4.60	0.568
ΔHADS-D, points	-1.01 ± 3.22*	-0.14 ± 3.17	0.12 ± 3.21	0.066
MARS, baseline score, points	22.07 ± 2.75	22.79 ± 2.10	22.00 ± 2.41	<0.05
ΔMARS, points	-0.27 ± 3.01	0.16 ± 1.90	0.10 ± 1.95	0.410
SNOT20, baseline score, points	1.55 ± 0.82	1.46 ± 0.86	1.86 ± 0.95*	<0.05
ΔSNOT20, points	-0.21 ± 0.76*	0.04 ± 0.58	0.10 ± 0.77*	<0.05

Summary variables are presented as n (%) for discrete variables, mean ± standard deviation for quantitative variables or median (interquartile range) for skewed variables. * p<0.05 pre vs post (paired samples T-test); # p<0.05 0 exacerbations vs >2 exacerbations vs >2 exacerbations group; & p<0.05 1-2 exacerbations vs >2 exacerbations group.

Abbreviations: PROMs, patient-reported outcomes; BMI, body mass index; kg/m², kilogram per square meter; cells/μL, cells per microliter; FEV₁, forced expiratory volume in the first second; %pred, percentage of the predicted value; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; ICS, inhaled corticosteroids; OCS, oral corticosteroids; ACQ5, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ESS, Epworth Sleepiness Scale; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; MARS, Medication Adherence Report Scale; SNOT20, Sino-Nasal Outcomes Test

Discussion

This study demonstrates that all PROM scores improved significantly over time in patients with severe asthma who did not experience an asthma exacerbation in the 12 months preceding the follow-up measurement, while no changes were observed in clinical characteristics such as FEV₁, FeNO or blood eosinophils. Contrastingly, patients who experienced more than two asthma exacerbations showed a deterioration in PROM scores, despite the fact that baseline scores were already significantly worse in these patients at baseline compared to those with fewer exacerbations during follow up. Furthermore, PROMs, which are generally impaired in patients with severe asthma, show a very weak or non-significant association with clinical characteristics, which highlights the importance of considering patient-reported outcomes to better understand the true impact of the disease on patients' lives, and in turn, as one of the key outcomes. This well established decoupling between biological and patient-related measures in obstructive pulmonary disease (30, 31) testifies to the fact that the transition from the biological to the clinical/health status dimension is complex (i.e. explaining the mediating mechanisms) and should be considered when designing future trials on asthma, mainly for the selection of outcome variables.

The aim of the U-BIOPRED project was to comprehensively assess the impact of asthma on all domains relevant to patients in addition to measuring traditional and relatively new biomedical markers (11). Therefore, multiple asthma-specific as well as more generic instruments such as the ESS (daytime sleepiness) and the HADS (anxiety and depression) were included. The most convincing interrelationship between PROMs was found between quality of life and asthma control, which has been shown before and seems to be the result of the fact that both questionnaires (AQLQ and ACQ5) are measuring strongly related concepts related to symptoms and impacts directly of asthma (3). The weak-to-moderate interrelationship between the other PROMs in the current study clearly indicates that these questionnaires are not interchangeable, as they assess different aspects of the disease and therefore provide information on different dimensions or attributes other than asthma. However, this also raises uncertainty about which PRO data to use and underlines the fact that there is no "one-size-fits-all" approach for integrating PROs into clinical practice. In light of this, the PROTEUS- Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders) was formed to specifically address the use of PROs in clinical practice (32). The PROTEUS-Practice Guide identifies general barriers for using PROs in clinical care and highlights potential solutions to help overcome these challenges (32). Despite substantial improvements in this area in recent years, PROMs remain rarely integrated in general asthma care, with specialized centers

being the only exempt. By incorporating PROMs, these centers are able to tailor patient treatment plans to individual patient needs, monitor disease progression and assess the impact of interventions (33, 34). For instance, patients enrolled to the UK Severe Asthma Registry (UKSAR) after referral to Specialist UK Severe Asthma Centres are regularly assessed using PROMs to evaluate the impact of biologic therapies on patient-reported asthma control and quality of life (35). The current study provides important insights in the impact of severe asthma as seen from the patient's perspective, which shows a tendency to significantly change over a relatively short period of time, supporting the growing evidence to collect PROMs on a routinely basis (1, 34, 36) , thereby enabling better and more patient-centered care.

The fact that baseline PROMs in the current cohort were already impaired in a considerable number of patients, which has not resulted in specific non-pharmacological treatments during follow-up, confirms the lack of clear guidance regarding the use of PROMs in clinical practice. In fact, poor self-reported adherence to medication was measured in 40% of the patients at baseline using the MARS questionnaire. However, no significant improvements in adherence were observed during follow-up across all three exacerbation groups. This underlines the fact that low adherence, whether measured directly or self-reported, is a common problem in severe asthma (13). By combining several strategies such as patient education and fixed-dose regimens, healthcare providers are able to help patients with asthma improve their medication adherence, leading to better asthma control and overall health outcomes (37).

Prior to enrolment in the U-BIOPRED study, participants with severe asthma were required to have been under follow-up by a respiratory physician for at least 6 months, guided by assessments to optimize both asthma control and medication adherence (11). Furthermore, patients in the included cohort were, on average, diagnosed with asthma for more than 25 years. Nevertheless, the current study was able to show that, when taking into account the prospective number of asthma exacerbations, asthma control and asthma-related quality of life were prone to clinically significant changes over the course of a little more than one year. This is highly relevant to the use of PROMs in clinical settings, as experiencing an asthma exacerbation during follow up seemed to affect almost every PROM in a negative way, whereas the group of patients who did not experience an exacerbation showed significant improvements over time in every PROM. These results underline the importance of “zero tolerance for asthma exacerbations”, as advocated by the Lancet Asthma Commission in 2017 (2), who urged the need

to identify and advertise high-risk periods and to provide targeted and effective patient advice, seeking value in the development of a risk score (38), which could be incorporated into an annual examination, and might aid the primary prevention of asthma exacerbations.

Based on the current study it can be concluded that the accuracy of asthma-specific PROMs and clinical variables such as age and FEV_1 in terms of predicting an asthma exacerbation is low. Only the amount of previous asthma exacerbations tended to be able to predict a future exacerbation, which is in line with a large population-based study (39). In fact, it seems that in the general population not only those with more severe disease or higher levels of treatment present with asthma exacerbations, suggesting risk may reflect individual susceptibility, rather than simply being associated with severe asthma (40).

To date, little is known about the possibilities of improving PROMs in patients with severe asthma. Existing knowledge is mostly based on robust literature regarding indications and components of pulmonary rehabilitation (PR) in patients affected by COPD (41). PR has been shown to be a successful intervention for these patients with clinically meaningful improvements in terms of symptoms, depression and health-related quality of life, irrespective of pulmonary function (42). Although several studies also suggest an important role of non-pharmacological treatment in addition to pharmacological therapy in patients with asthma (43-45), future research is needed to improve clinical care based on specific patient's needs while integrating the inherent information of PROMs into a comprehensive view of the patient.

To the best of our knowledge, the current study is the first to assess the course of multiple asthma-specific as well as more generic PROMs over time in patients with severe asthma, who are being treated based on routine asthma care, without receiving any experimental type of intervention. Another strength of the current study assessing PROMs is the fact that patients were actively involved in the development of the U-BIOPRED research protocol, as patient and public involvement (PPI) is becoming increasingly important when conducting research. Nevertheless, some limitations need to be acknowledged. Data collection was limited to only two time points. This limits the ability to identify fluctuations in symptom presentation and other contributors to changes in PROMs, with no direct linkage between the timing of exacerbations and the time of assessment. Future research should focus on measuring intermediate time-points with possibly, a longer follow-up period. The current study sample consisted of young adults on average and, thus, a different PROMs-asthma severity relationship might characterize subjects with late onset

asthma, who also have a different pattern of comorbidity. Since comorbidities can exacerbate asthma symptoms and complicate its management, leading to worse health outcomes and lower quality of life for patients, treating comorbidities in patients with severe asthma is likely to improve PROMs for both asthma and the comorbid conditions. Lastly, severe asthma is increasingly recognized to be different from mild-to-moderate asthma, in particular regarding the impact of hospitalizations and the frequent use of OCS (1). The PROMs used in the current study have not been developed specifically for severe asthma and have not been assessed regarding their discriminative, classificatory and prognostic properties in this population. These PROMs might therefore fail to assess factors that are unique to severe asthma. Nonetheless, all of the included PROMs have been shown to differ between patients with severe asthma and patients with mild/moderate asthma, with all outcomes being far worse in the former group (11). Future methodological studies assessing the clinimetric properties of both existing and new PROMS such as the Severe Asthma Questionnaire (SAQ) (46) are needed to select the ones most suitable to patients with severe asthma.

In conclusion, PROMs are significantly impaired in patients with severe asthma, with asthma-specific outcomes (e.g. asthma control and asthma-related quality of life) being impacted the most. Asthma exacerbations seem to be the main drivers of changes (either an improvement or a deterioration) in ACQ5 and AQLQ scores during follow up while receiving standard care. The very weak or non-existent correlation with clinical measures in this sample, emphasizes the need to systematically evaluate PROMs in the clinical care of patients with severe asthma and to take into account the perception of disease impact. Once more, it has been proven that patients with similar clinical characteristics can present different responses to the impact of symptoms on their lives, supporting the evolution to more personalized, patient-focused disease management. Profound phenotyping using high-dimensional molecular biomarkers is necessary to identify associations that are not displayed in this first PROMs analysis in severe asthmatics.

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Supplementary material

Table E1. Interrelationship PROMS

	ACQ5	AQLQ	ESS	HADS-A	HADS-D	MARS	SNOT20
ACQ5							
AQLQ	-0.77*** (383)						
ESS	0.19*** (357)	-0.24*** (381)					
HADS-A	0.38*** (361)	-0.48*** (386)	0.26*** (365)				
HADS-D	0.37*** (361)	-0.46*** (386)	0.32*** (365)	0.75*** (391)			
MARS	-0.20*** (374)	0.14** (399)	-0.05 (373)	-0.11* (380)	-0.09 (380)		
SNOT20	0.44*** (326)	-0.50*** (342)	0.34*** (327)	0.51*** (328)	0.50*** (328)	-0.15** (335)	
0.00 - 0.19	0.20 - 0.39	0.40 - 0.59	0.60 - 0.79	0.80 - 1.00			
very weak	weak	moderate	strong	very strong			

Spearman's rho was used to calculate correlations between variables. (n) represents the total number of sample values per analysis. * p<0.05; ** p<0.01; *** p<0.001

Abbreviations: ACQ5, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ESS, Epworth Sleepiness Scale; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; MARS, Medication Adherence Report Scale; SNOT20, Sino-Nasal Outcomes Test.

Table E2. Baseline characteristics of patients who attended the longitudinal visit (n = 300) vs. excluded patients (n = 121)

	Patients who attended longitudinal visit (n=300)	Excluded patients (n=121)
Age, years	52.6 ± 13.2	50.3 ± 14.0
Age at diagnosis, years	26.0 (7.0 – 42.0)	25.0 (10.0 – 43.0)
Females, n (%)	179 (59.7)	82 (67.8)
BMI, kg/m²	29.0 ± 6.0	29.8 ± 7.0
BMI >30 kg/m², n (%)	119 (39.7)	45 (37.2)
Smoking: current/former/never, n (%)	33 (11) /76 (25) /191 (64)	9 (7)/ 39 (32)/ 73 (60)
Serum IgE, IU/mL	130 (52 – 342)	113 (45 – 374)
Atopy test positive, n (%)	197 (65.7)	78 (64.5)
FEV₁, %pred	66.2 ± 20.9	70.7 ± 22.0
FVC, %pred	87.5 ± 19.1	88.7 ± 19.9
FEV₁/FVC ratio	0.62 ± 0.14	0.66 ± 0.14*
FeNO, ppb	26 (15 – 47)	25 (15 – 48)
Blood neutrophils, cells/μL	4695 (3623 – 6760)	5250 (4000 – 6995)
Blood eosinophils, cells/μL	200 (100 – 400)	225 (100 – 438)
Asthma exacerbations <12 months	2 (1 – 3)	2 (1 – 4)

Summary variables are presented as n (%) for discrete variables, mean ± standard deviation for quantitative variables or median (Interquartile range) for skewed variables. * p<0.05, assessed with Independent Samples T-test

Abbreviations: BMI, body mass index; kg/m², kilogram per square metre; IgE, Immunoglobuline E; IU/mL, international units per millilitre; FEV₁, forced expiratory volume in the first second; %pred, percentage of the predicted value; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; cells/μL, cells per microliter.

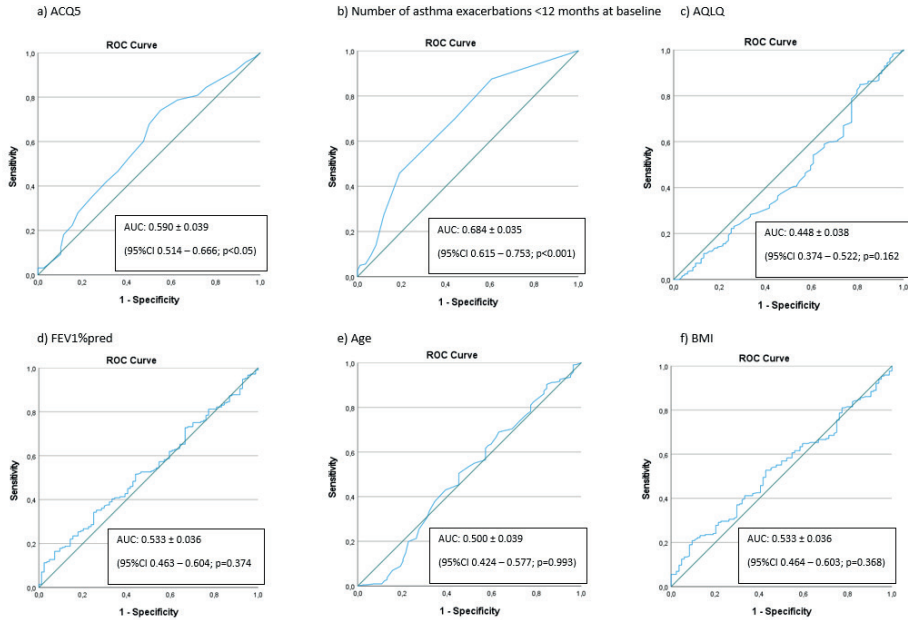


Figure E1. ROC (Receiver Operating Characteristics) analysis with AUC (Area Under The Curve) calculations for different PROMs and clinical variables in terms of predicting an asthma exacerbation. *Abbreviations: PROMs*, patient-reported outcomes; ACQ5, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV₁, forced expiratory volume in the first second; BMI, body mass index.



CHAPTER 6

Baseline dependent minimally important differences for clinical outcomes of pulmonary rehabilitation in patients with asthma

Meys R, Conemans LH, Franssen FME, Groenen MTJ, Vaes AW, Brauwers B, Stoffels AAF, van Hees HWH, van den Borst B, Agterhuis D, Wouters EFM, Vanfleteren LEGW, Burtin C, Spruit MA.

Submitted

Abstract

Background and objective: Pulmonary rehabilitation (PR) has shown promise as a non-pharmacological treatment in improving asthma-related outcomes, though minimal important differences (MIDs) for clinical PR outcomes in asthma patients remain undefined. This study aimed to develop MIDs for clinical outcomes of PR in patients with asthma and examine their variation based on baseline characteristics.

Methods: A retrospective analysis of 722 patients with asthma who completed PR at Ciro (Netherlands) was conducted. Data included demographics, lung function, history of exacerbations, quality of life (SGRQ), dyspnea (mMRC), symptoms of anxiety and depression (HADS), and exercise capacity (6MWT, CWRT). MIDs were calculated using distribution-based methods, for the whole sample and stratified by baseline values.

Results: Significant improvements were observed in exercise capacity, quality of life, and psychological symptoms after PR. MIDs were established as follows: 6MWD (33.8 m), CWRT (180.3 s), SGRQ total score (8.3 points), HADS Anxiety (1.9 points), and HADS Depression (1.9 points). Stratification for baseline values revealed that MIDs varied for the 6MWD, SGRQ impact domain, and HADS scores, with larger MIDs in patients with lower baseline values.

Conclusion: This study is the first to establish MIDs for PR outcomes in patients with asthma, highlighting that MIDs can differ based on baseline characteristics. These findings provide important insights into evaluating PR efficacy in asthma care, emphasizing the use of the established MIDs as a benchmark for meaningful changes, and supporting tailored intervention approaches.

Introduction

Asthma is a chronic respiratory disease defined by variable expiratory airflow limitation in combination with recurring respiratory symptoms such as cough, wheezing and dyspnea (1). For the majority of patients with asthma, current pharmacological treatment options offer good control of these symptoms. Nevertheless, some patients still experience high burden of disease and/or persistent airway obstruction, which puts them at increased risk of disease-related morbidity and mortality (2). It has been shown that patients with asthma frequently exhibit extrapulmonary traits such as an impaired physical functioning (3) and fatigue (4, 5). This justifies the implementation of non-pharmacological treatment modalities, especially in those with uncontrolled asthma (6, 7). Pulmonary rehabilitation (PR) is an interdisciplinary intervention based on a thorough patient assessment, that seeks to combine non-pharmacological treatments such as exercise training, education, nutritional and psychosocial support into a comprehensive patient-tailored program (8). In patients with chronic obstructive pulmonary disease (COPD), PR is beneficial in improving health-related quality of life and exercise capacity and therefore serves as an important component of disease-management (9).

Only in recent years, PR has been proven to be a safe and effective treatment strategy in patients with uncontrolled asthma (10). Indeed, several studies have presented significant improvements in exercise capacity (11, 12), asthma control (11, 13, 14), perceived dyspnea (11-14), quality of life (11, 13, 14) and symptoms of anxiety and depression (11) following PR. From a clinical perspective however, a statistically significant change may not indicate a true improvement or decline. The minimally important difference (MID) approach has therefore been developed to detect the smallest change in an outcome measure that can be interpreted as a meaningful effect of an intervention (15). Multiple MIDs have been established in patients with COPD, but these MIDs seem to be context and patient specific (16-18). This means that the type of intervention and the patients' baseline characteristics determine, at least in part, the MIDs.

To date, no MIDs for common outcomes of PR have been established in patients with asthma. Therefore, the objectives of the current study were to develop MIDs for clinical outcomes of PR in patients with asthma for the whole sample and after stratification for baseline characteristics.

Methods

This was a retrospective study of 722 patients with a clinical diagnosis of asthma who were evaluated during the initial assessment of a comprehensive PR program at Ciro, a center for patients with complex chronic lung diseases in Horn (The Netherlands), which they completed between January 2005 and June 2022. Data of patients who had not objected to the use of routine clinical data for research purposes were extracted from the electronic patient files. Patients were included if they met the following inclusion criteria: a primary diagnosis of asthma by a chest physician (initial identification of a characteristic pattern of symptoms and a variable expiratory airflow limitation (1)), clinically stable at the time of assessment and completion of PR. The medical ethics committee of the University Hospital Maastricht and Maastricht University (METC azM/UM) informed the authors that the Medical Research Involving Human Subject Act (WMO) did not apply to this study (2019-1081).

Data collection and intervention

Patients were evaluated at baseline and at the end of PR. Each evaluation included demographics, anthropometric measurements (body-mass index; BMI), body composition assessment (fat-free mass index using DXA-scan; FFMI) and assessment of exacerbation and hospitalization frequency in the last 12 months (self-reported). The St George's Respiratory Questionnaire (SGRQ) was used to measure impaired health and quality of life of patients. This respiratory-specific questionnaire has three domains (symptom, activity, and impact) and a total score (range 0-100 points), with higher scores indicating a worse quality of life (19). Additionally, the mMRC Dyspnea Scale (range 0-4 points (20)) and the Hospital Anxiety and Depression Scale (HADS; range 0-21 points with a cutoff value of ≥ 10 points (21)) were used to quantify disability attributable to breathlessness and to assess symptoms of anxiety and depression, respectively. Functional exercise capacity was assessed using the 6-minute walk test (6MWT) and a constant work-rate cycle test (CWRT), set at 75% of the determined peak work rate achieved during a maximal incremental cycle test (22). The 6MWT was performed twice (23) in accordance with American Thoracic Society (ATS) & European Respiratory Society (ERS) standards (24), after which the best baseline 6-minute walking distance (6MWD) was used for further analyses.

All patients underwent a comprehensive interdisciplinary PR program consisting of 40 sessions, in line with the 2013 ATS/ERS Statement on PR (25). In brief, patients were allocated to an outpatient (8 weeks, 3 half days/week, followed by 8 weeks 2 half days/week) or inpatient (8 weeks, 5 days/week) setting based on an

interdisciplinary evaluation after the baseline assessment. During this assessment, a careful characterization of the extra-pulmonary features of patients with asthma was performed, based on which various treatments were applied: physical exercise training, occupational therapy, nutritional counselling, psychosocial counselling, educational strategies and exacerbation management. The cornerstone of the patient-tailored PR program was physical exercise training, mainly consisting of exercises to strengthen muscles of upper and lower extremities, treadmill walking, stationary cycling, flexibility exercises and daily supervised 30-minute outdoor walks. All exercises were performed at moderate-to-high intensity to obtain an overload stimulus, with training intensity increasing over the course of the rehabilitation period.

Statistical analyses

Analyses were performed using IBM SPSS Statistics for Windows, Version 28.0. Results are presented as mean $\pm$ standard deviation (SD) or median (interquartile range; IQR), based on the symmetry of the distribution. Symmetry was evaluated by assessing skewness scores with values lower than -0.5 or above 0.5 being considered as non-symmetrically distributed. MIDs can be calculated using distribution- and anchor-based methods. In the current analyses, the anchor-based method could not be used as a suitable patient-based method as a clinical 'anchor' was not available (26). Therefore, a distribution-based method was used to calculate the MIDs by using either 0.5 x SD of the change from pre- to post-PR for symmetrically distributed outcomes or 0.5 x IQR for non-symmetrically distributed outcomes (27). MIDs were determined for 6MWD, CWRT cycle endurance time, FFMI, SGRQ total, symptom, activity and impact scores, and HADS anxiety and depression scores. To calculate MIDs stratified for baseline outcome scores, data were split into tertiles for each outcome (T1 = low, T2 = moderate, T3 = high). If one MID was not symmetrically distributed, all MIDs for the specific outcome were assessed using 0.5 x IQR. To assess differences in the MIDs between tertiles, Levene's test was used to test the homogeneity of variances between groups. The level of statistical significance was set at $p < 0.05$. Whenever the assumption of homogeneity was violated, post-hoc Levene's independent t-tests were applied to explore differences between subgroups. An adjustment for multiple testing was made with a Bonferroni correction, after which statistical significance was accepted at $p < 0.0167$.

Results

Table 1 summarizes the baseline characteristics of 722 patients with asthma (60% women) with a moderate degree of airflow limitation. Of all patients, 80.8% had

moderate to severe dyspnea (mMRC score of ≥ 2), whereas 64.0% of the study sample experienced ≥ 2 exacerbations in the previous 12 months. 20.1% of patients reported no exacerbations in the previous 12 months.

Table 1. Patient characteristics (n = 722)

Age, years	58.6 $\pm$ 13.1
Male, n (%)	292 (40.4)
FEV ₁ , % predicted	75.6 $\pm$ 24.4
mMRC	
0	10 (2.5)
1	68 (16.7)
2	184 (45.3)
3	94 (23.2)
4	50 (12.3)
Exacerbations <12 months	
0	132 (20.1)
≥ 2	420 (64.0)
Hospitalizations <12 months	
0	386 (58.7)
≥ 2	148 (22.5)
6MWD, m	443 $\pm$ 130
CWRT cycle endurance time, s	318 (230-475)
FFMI, kg/m ²	18.1 $\pm$ 2.6
FFMI below clinical cut-off (<15 F; <17 M), n (%)	89 (15.3)
SGRQ total score, points	57 $\pm$ 17
SGRQ symptom, points	65 $\pm$ 17
SGRQ activity, points	70 $\pm$ 21
SGRQ impact, points	46 $\pm$ 20
HADS Anxiety, points	7.7 $\pm$ 4.5
HADS Anxiety score ≥ 10 points, n (%)	228 (33.2)
HADS Depression, points	7.3 $\pm$ 4.3
HADS Anxiety score ≥ 10 points, n (%)	224 (32.6)

Summary variables are presented as n (%) for discrete variables, mean $\pm$ standard deviation for quantitative variables or median (Interquartile range) for skewed variables. Abbreviations. FEV₁: forced expiratory volume in one second; mMRC: modified Medical Research Council; 6MWD: six-minute walk distance; CWRT: constant work-rate cycle test; FFMI: fat-free mass index; SGRQ: St. George's Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale.

Mean changes following PR

Generally, patients showed improvements on the 6MWD (35.8 ± 67.6 m), cycle endurance time (339.2 ± 360.7 s) and FFMI (0.20 ± 0.61 kg/m²) after completion of the PR program. Moreover, patient-reported outcomes, such as SGRQ total score (-8.0 ± 14.2 points) and its domains (symptom: 8.8 ± 19.9 points; activity: -6.5 ± 21.1 points and impact: -11.0 ± 16.5 points, respectively) and symptoms of anxiety (-1.7 ± 3.9 points) and depression (-2.2 ± 3.8 points) improved statistically significantly compared to baseline (Table 2).

MIDs for the whole sample

The MIDs for outcomes after PR are presented in Table 2.

Table 2. Distribution-based MIDs for outcomes following PR: whole sample

Variable	Mean change	MID
6MWD, m	35.8 + 67.6	33.8
CWRT cycle endurance time, s	339.2 ± 360.7	180.3
FFMI, kg/m ²	0.20 ± 0.61	0.37*
SGRQ total score, points	-8.0 ± 14.2	8.3*
SGRQ symptom, points	-8.8 ± 19.9	10.0
SGRQ activity, points	-6.5 ± 21.1	11.3*
SGRQ impact, points	-11.0 ± 16.5	8.2
HADS Anxiety, points	-1.7 ± 3.9	1.9
HADS Depression, points	-2.2 ± 3.8	1.9

*MIDs presented as $0.5 \times \text{IQR}$ (due to non-symmetrical distribution). Abbreviations. 6MWD: six-minute walk distance; CWRT: constant work-rate cycle test; FFMI: fat-free mass index; SGRQ: St. George's Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale.

MIDs after stratification for baseline values

Table 3 summarizes the main findings of the distribution-based method to obtain MIDs after stratification for baseline values. In brief, the MIDs differed between strata for 6MWD, SGRQ impact domain, and symptoms of anxiety and depression (HADS). All other MIDs did not differ after stratification for various baseline values.

Discussion

The current study is the first to provide distribution-based MIDs for outcomes relevant for PR in patients with asthma. Moreover, some of the MIDs seem to differ

after stratification for baseline values. As stated by *Bonini et al.*, the interpretation of MIDs and its direct relevance in disease management should consider differences within the study population, providing a rationale to establish different MIDs to target specific subgroups of patients (28). A diversified set of MID cut-offs is currently available and validated among various populations of patients with asthma (28). However, most of the evidence focuses on either lung function variables or asthma-specific patient-reported outcomes (ASUI, ACQ, ACT), and comes from pharmacotherapy studies. Therefore, the current study was unable to corroborate previously reported MIDs on outcomes of PR in patients with asthma. The constant work-rate exercise test, for instance, can be considered the gold standard to assess changes in exercise tolerance following interventions, with cycle or tolerance time being the primary outcome (29). Since the CWRT is rarely assessed in clinical asthma care and is mainly performed to measure the direct effect of an intervention or training program, there is limited information on MID estimates for cycle endurance time, especially in patients with asthma. In COPD, MIDs of 100-200s after pulmonary rehabilitation have been reported (16, 30), which is in line with the MID of 180s established for individuals with asthma in the current study.

Table 3. Distribution-based MIDs for outcomes following PR: stratification for baseline values

Variable	Low (T1)	Moderate (T2)	High (T3)	p
6MWD, m	39.5	29.8	27.8	<0.001
<i>Tertile cut-offs</i>	≤394,00	394,01 - 504,99	≥505,00	
CWRT cycle endurance time, s	188.6	175.2	172.7	0.149
<i>Tertile cut-offs</i>	≤254,00	254,01 - 409,00	≥409,01	
FFMI, kg/m2	0.34*	0.35*	0.37*	0.053
<i>Tertile cut-offs</i>	≤16,86	16,87 - 19,01	≥19,02	
SGRQ total score, points	8.5*	9.2*	9.5*	0.750
<i>Tertile cut-offs</i>	≤50,50	50,51 - 64,8	≥64,81	
SGRQ symptom, points	9.5	8.8	9.9	0.830
<i>Tertile cut-offs</i>	≤57.85	57,86 - 73,58	≥73.59	
SGRQ activity, points	12.8*	11.1*	10.0*	0.373
<i>Tertile cut-offs</i>	≤65,60	65,61 - 83,30	≥83,31	
SGRQ impact, points	6.3	7.8	8.5	<0.01
<i>Tertile cut-offs</i>	≤36,90	36,91 - 54,50	≥54,51	
HADS Anxiety, points	1.4	1.7	2.2	<0.001
<i>Tertile cut-offs</i>	≤5,00	6,00 - 9,00	≥10,00	
HADS Depression, points	1.3	1.5	2.1	<0.001
<i>Tertile cut-offs</i>	≤4,00	5,00 - 8,00	≥9,00	

*MIDs presented as 0.5 x IQR (due to non-symmetrical distribution). Abbreviations. 6MWD: six-minute walk distance; CWRT: constant work-rate cycle test; FFMI: fat-free mass index; SGRQ: St. George's Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale.

For the 6MWT, there is no clear evidence to suggest that the MID range for 6MWD, which has previously been established at 25 to 33m, would vary across different chronic respiratory diseases (31). Hence, it has always been assumed that this MID spectrum would also be applicable to patients with asthma, particularly in those with fixed airway obstruction (28). While the calculated MID of 33.8m in the current sample settles at the upper range of this spectrum, thereby confirming prior estimates, this is the first study in patients with asthma undergoing pulmonary rehabilitation to show that the MID for 6MWD can vary depending on the baseline disease burden (i.e. patients with lower baseline 6MWD had a higher MID). It is known that individuals with greater baseline exercise capacity reach a point where further improvement becomes inherently limited, regardless of the efficacy of the intervention, also known as the "ceiling effect" (3). This phenomenon not only reduces the variation in responses observed within this subgroup but also lowers the apparent MID because smaller changes may be statistically significant but not clinically meaningful. Stratified MIDs, adjusted to account for baseline characteristics, facilitate a more precise interpretation of outcomes by calibrating thresholds for improvement relative to the specific baseline performance of each subgroup. This approach captures what constitutes a minimal important change for each subgroup, while mitigating the limitations of a uniform benchmark that may underestimate improvements in certain groups and overestimate them in others.

For patient-reported outcome measures, MID estimates were fairly comparable to MIDs previously established in the COPD population. For instance, the MID for HADS Anxiety and HADS Depression was 1.9 points in the current study, whereas Smid et al. (2017) described an MID of 1.8 points (also calculated with $0.5 \times \text{SD}$) in patients with COPD (32). Jenkins et al. observed a lack of concordance within the SGRQ when assessing MIDs for patients with COPD on a domain basis, which was also the case in the current sample of patients with asthma (16). The MIDs for HADS Depression, HADS Anxiety and the SGRQ impact domain were susceptible to change based upon baseline values. However, this was not the case for the SGRQ total score and the symptom and activity domains. The SGRQ impact domain covers a wide range of disturbances of psycho-social function and therefore it is the broadest component of the questionnaire, covering the whole range of disturbances that respiratory patients experience in their lives. This might explain the more heterogeneous response in this domain in patients impacted the most at baseline. This is supported by previous research showing that MID values of patient-reported outcomes may differ by patient features and clinical context. For instance, it has been shown that women have unique symptom profiles on detailed item analyses of three currently available asthma questionnaires (ASUI, ACQ and

Mini Asthma Quality of Life Questionnaire), proving that using solely the overall score of certain patient-reported outcome measures might not detect sex-specific differences in asthma symptoms (33). In COPD, the widely used MID for the SGRQ score represents a decrease of ≥ 4 points (34). However, this MID was not thoroughly validated for patients with severe disease. As a result, a different MID of 8.3 points was estimated for patients with severe COPD, showing that disease severity can also impact MID values (35). The fact that the MID for the SGRQ score is 8.3 points in the current study as well, proves that this is an elderly population with severe and complicated, frequently exacerbating asthma that is typically referred for tertiary specialized pulmonary rehabilitation.

Limitations

There was no data available regarding inflammatory biomarkers or asthma-specific patient reported outcome measures (e.g. ACQ, ACT) in the current dataset. While these clearly represent an interesting scope for future clinical studies on PR in patients with asthma, the retrospective nature of the current study limited the ability to include these outcomes and calculate MIDs. Knowledge regarding a comprehensive integrated treatment such as PR has mostly been gathered with extensive research in COPD populations. With growing evidence on the effectiveness of PR in patients with asthma and, therefore, increasing referral rates, a true shift towards a asthma specific outcome assessment and PR program has only been observed very recently.

No independent measure that is understandable and relevant to patients (i.e. an external criterion or anchor) was found whilst calculating the MIDs. Despite the fact that the calculated MIDs solely rely on the statistical characteristics of our study sample, we believe these results are novel and useful for measuring intervention efficacy with PR in the asthma population, based upon which different MID approaches and sample size calculations can be implemented in prospective studies as well. Lastly, a non-symmetrical distribution was observed in some outcomes, which presented difficulties in determining the MID based on the standard deviation of data. To counteract this, we used a non-parametric equivalent (i.e. IQR) and after visual inspection of the data, MIDs showed strong similarity between both approaches.

Conclusion

This study is the first to provide MIDs for patients with asthma who completed a pulmonary rehabilitation program. Moreover, we found that MIDs can differ based on patients' baseline characteristics. In light of this, the current study aims to bridge

the gap between statistical and clinical significance in asthma practice in order to properly measure intervention efficacy of pulmonary rehabilitation and suggests a potential need to move away from generalized MIDs for measuring intervention efficacy in pulmonary rehabilitation and shift towards individually tailored MIDs.

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CHAPTER 7

Summary & General Discussion

Summary

Asthma is a chronic respiratory disease characterized by airway inflammation and narrowing, resulting in symptoms such as wheezing, shortness of breath, and coughing. It affected an estimated 262 million people worldwide in 2019 (1) and imposes considerable costs on healthcare systems. The disease burden is high, impacting both physical and psychosocial health. Standard treatment includes pharmacological therapy and self-management strategies, while pulmonary rehabilitation (PR) offers a complementary approach aimed at improving physical capacity, psychological wellbeing, and daily functioning. Increasing evidence indicates that the impact of asthma extends beyond the airways, with extrapulmonary factors contributing significantly to symptom burden, functional limitations, and overall quality of life.

Building on this perspective, the overarching aim of this thesis was to expand current knowledge on extrapulmonary features of asthma, with particular focus on their assessment and the impact of PR. Across the preceding chapters, different aspects of extrapulmonary involvement were examined, ranging from functional capacity and body composition to patient-reported limitations in daily activities and health status. This work has provided new insights into the heterogeneity of asthma and the potential of PR to target extrapulmonary traits.

In **Chapter 2**, the measurement properties of the six-minute walk test (6MWT) were examined in a large cohort of patients with asthma. The 6MWT proved to be a reliable and valid tool for assessing functional exercise capacity in this population. Determinants of walking distance extended beyond lung function and included factors such as body mass index (BMI), underscoring the multifactorial nature of exercise limitation in patients with asthma.

Chapter 3 focused on abnormalities in body composition. Low appendicular lean mass index (ALMI) and sarcopenic obesity (SO) were shown to be prevalent among patients with asthma attending PR. Importantly, these traits were associated with impaired exercise performance and poorer quality of life, highlighting body composition as an extrapulmonary target that may influence outcomes of PR.

Chapter 4 investigated limitations in activities of daily living (ADLs) from the patient perspective. Using the Canadian Occupational Performance Measure (COPM), patients with asthma reported a wide range of problematic ADLs, with the most frequent difficulties involving physical exertion and household tasks. These self-reported limitations correlated weakly with clinical characteristics such as

airflow limitation, age, and body composition, confirming the value of integrating problematic ADLs in the assessment of the impact of asthma.

In **Chapter 5**, the focus shifted to patient-reported outcome measures (PROMs) in severe asthma. Exacerbations were found to significantly impair health status across multiple domains, and PROMs demonstrated limited predictive potential for future exacerbation risk. These findings emphasize the role of PROMs as sensitive markers of disease burden and as valuable tools for monitoring patient trajectories in clinical practice.

Finally, **Chapter 6** presented the first study to define minimal important differences (MIDs) for PR outcomes in patients with asthma. In a large cohort of individuals with asthma completing PR, significant improvements were observed in exercise capacity, quality of life, and psychological symptoms. MIDs were established for the six-minute walk distance, cycle endurance time, quality of life, fat-free mass index (FFMI) and symptoms of anxiety and depression. Subgroup analyses revealed that some of these MIDs varied according to baseline status, with larger MIDs in patients starting from lower baseline values. These results provide a benchmark for interpreting clinically meaningful changes in asthma PR and support a tailored approach to intervention.

Taken together, the findings of this thesis confirm that asthma is not only a disease of the airways but also characterized by a range of extrapulmonary features that significantly contribute to patient burden. Functional exercise capacity, body composition, limitations in daily activities, psychological symptoms, and quality of life are all important aspects of disease expression. Moreover, PR emerges as a promising intervention to address these dimensions, although structural barriers in implementation remain. In this **Chapter 7**, the results will be placed in the context of existing literature, clinical and policy implications will be explored, and directions for future research will be outlined.

Extrapulmonary features of asthma in perspective

Functional capacity

Chapter 2 demonstrated that the 6MWT is a reliable tool in adults with asthma, though a modest but clinically relevant learning effect was observed. On average, patients improved by 18 meters on repeated testing, corresponding to about 5% of baseline distance. This parallels findings in COPD. For example, Hernandez et

al. reported a mean increase of 27 m with 82% of patients walking further on the second 6MWT (2), and Delbressine et al. advised that a third test may be needed in patients with low baseline distance to adequately capture functional capacity (3). Predictors of improvement, however, appear to differ between diseases. In COPD, a poor performance in the first 6MWT, combined with few comorbidities and non-obesity, was identified as the most relevant determinant of a change between the first and second tests that exceeds clinical importance (2). Moreover, patients with a six-minute walk distance (6MWD) below 350 meters and GOLD stage I or II are more likely to improve by 42 meters or more on a third 6MWT (3). In asthma, no clear predictors of the learning effect were reported (**Chapter 2**). Together, these observations suggest that repeated baseline testing should be standard practice not only in COPD but also in asthma, especially when functional outcomes guide clinical or research decisions. In clinical practice, this can guide choices such as referral to PR, tailoring exercise or therapy plans, or monitoring patients at risk of functional decline. In research, repeated testing improves the reliability of measurements and strengthens the validity of conclusions when the 6MWT outcomes serve as primary endpoints.

Chapter 2 identified independent determinants of 6MWD in asthma that partly differ from those reported in previous multivariate analyses. For example, the study by Pitzner-Fabircius et al., found BMI and asthma control to be significant predictors of 6MWD (4). In contrast, our analysis in **Chapter 2** additionally highlighted maximal workload (W_{max}), maximal expiratory pressure (MEP), and rollator use as independent determinants, alongside BMI and forced expiratory volume in one second (FEV₁), explaining 58% of the variability. These differences likely reflect variations in study populations and the specific functional and physiological variables included. Notably, as discussed in **Chapter 3**, body composition, including low muscle mass or sarcopenic obesity, has direct functional consequences and may indeed help explain reductions in 6MWD.

The 6MWT is a widely used, safe, and pragmatic measure of functional capacity in adults with asthma, including those with severe disease, with no serious adverse events reported (5). While it provides valid information about functional status, evidence on its ability to reflect maximal aerobic capacity in adult asthma is limited. Externally paced field tests, such as the incremental shuttle walk test (ISWT), have been developed to provide a closer approximation of maximal cardiopulmonary responses, as demonstrated in COPD, where ISWT distance strongly correlates with VO₂peak and work rate measured by cardiopulmonary exercise tests ($r = 0.75\text{--}0.88$) and elicits a linear cardiopulmonary response throughout the test (6, 7). In adults with

severe asthma, however, performance during the ISWT shows a distinct pattern. Majd et al. (2019) found that although the ISWT is reproducible, a significant learning effect exists, with most participants achieving their best performance in the third test (8). Even at peak performance, patients did not reach maximal effort compared to incremental cycle ergometer or treadmill tests, indicating that the ISWT elicits a submaximal response in this population (8). Despite the potential of externally paced tests to provide additional insight into exercise limitation, current evidence in severe asthma indicates that their exact role and limitations are not yet well defined. Accordingly, the optimal use of field walking tests in adults with asthma, their sensitivity to interventions, and their ability to capture meaningful changes in functional capacity, remain to be established. In **Chapter 6**, one of these gaps is addressed by establishing MIDs for 6MWD in a PR context, providing a practical benchmark for interpreting changes in functional capacity in adults with asthma.

Body composition

Chapter 3 showed that patients with asthma referred for PR frequently present with abnormalities in body composition, notably low appendicular lean mass index (ALMI) and sarcopenic obesity (SO). Both were associated with impaired exercise capacity and poorer health status, confirming their clinical relevance. These results indicate that asthma, like COPD, involves systemic changes that contribute to disease burden.

The broader literature supports this perspective. Uncontrolled asthma has been linked to increased visceral adipose tissue, reduced bone mineral content, and decreased exercise capacity (8), while persistent uncontrolled disease is associated with adverse long-term changes in body composition (9). Physical activity was shown to be an independent predictor of body composition and a reliable long-term marker of symptom control in patients with asthma (9). More recently, biologic therapies have been reported to favorably affect body composition, with improvements in lean mass and reductions in fat mass during treatment (10). Data from the LEAD study further confirm the heterogeneity of asthma phenotypes, identifying subgroups with obesity-related and low muscle mass profiles (11). These findings parallel well-established evidence in COPD. Low fat-free mass and sarcopenia are recognized treatable traits in COPD, strongly associated with poor prognosis and functional decline (12). Evidence in COPD also shows that these traits are reversible. Nutritional support combined with resistance or endurance training can restore muscle mass and function, which translates into improvements in exercise capacity, symptoms and even survival (13-15). This

underscores that abnormalities in body composition are not only prognostically relevant but also treatable. Importantly, such abnormalities often remain hidden when BMI alone is considered, as low muscle mass is prevalent even in overweight or obese patients (16-18).

The current thesis demonstrates that a similar phenomenon exists in asthma: muscle dysfunction and sarcopenic obesity occur despite normal or elevated BMI and contribute significantly to impaired functioning. Early interventional studies in asthma suggest that body composition may also be amenable to change. In obese adults with asthma, the addition of structured exercise to a weight-loss program resulted in greater reductions in fat mass, improved asthma control, and reductions in airway and systemic inflammation (14). Comparable benefits have been observed in postmenopausal women with asthma, where targeted lifestyle interventions reduced fat mass and modestly increased lean mass (19). However, it remains uncertain whether sarcopenia itself is reversible in asthma and whether restoring muscle mass translates into better long-term outcomes such as reduced exacerbations, functional improvement, or survival. Addressing this gap should be a priority for future research.

Activities of daily living

The work presented in **Chapter 4** revealed that patients with asthma often experience substantial limitations in activities of daily living (ADLs). Using the Canadian Occupational Performance Measure (COPM), nearly all patients identified at least two problematic ADLs, most often related to walking, stair climbing, and household tasks. These limitations could not be reliably predicted based on clinical characteristics such as lung function, exercise capacity, or psychological scores, which suggests that the impact of asthma on daily life is complex and cannot be captured fully by traditional physiological assessments alone.

These observations are consistent with evidence from COPD, where problematic ADLs are common yet only weakly associated with clinical determinants such as spirometry (20). Studies have shown that daily activity performance is often more limited than physiological measures would suggest, and that such limitations occur early in the disease course (21). In comparison, Sánchez Castillo et al. have documented that restrictions in ADLs affect not only older adults with COPD but also those with asthma and asthma-COPD overlap (ACO) (22).

Taken together, these findings demonstrate that asthma imposes meaningful restrictions on everyday functioning, much like COPD. Importantly, these restrictions

are not fully explained by pulmonary function tests, emphasizing the need for patient-centered assessments. In COPD, rehabilitation programs have been shown to improve both performance and satisfaction with daily activities (23), and it seems likely that patients with asthma derive similar benefit. Routine evaluation of ADLs could therefore enrich clinical assessment in asthma and provide an additional rationale for referral to PR.

PROMs and MIDs in asthma

Patient-reported outcome measures (PROMs) are increasingly recognized as essential tools in asthma research and care because they capture domains of disease burden not reflected in lung function or biomarkers. In **Chapter 5**, the U-BIOPRED cohort analysis confirmed this dissociation: PROMs such as the Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), Hospital Anxiety and Depression Scale (HADS), Epworth Sleepiness Scale (ESS), Medication Adherence Report Scale (MARS), and the 20-item Sinonasal Outcome Test (SNOT-20) correlated only weakly with forced expiratory volume in one second (FEV₁) and fractional exhaled nitric oxide (FeNO). By contrast, they were strongly responsive to exacerbation status, with patients free from exacerbations reporting improvements across nearly all PROMs, whereas those with recurrent attacks deteriorated despite stable lung function. These findings underline exacerbations as a key driver of patient-perceived burden and demonstrate the sensitivity of PROMs to changes that matter in daily life.

The relevance of PROMs in severe asthma is increasingly recognized in the literature. A recent Delphi consensus identified the Asthma Control Test (ACT), mini-AQLQ, modified Medical Research Council dyspnea scale (mMRC), and treatment adherence tools such as the Test of Adherence to Inhalers (TAI) as feasible for routine follow-up (24). While feasibility ratings for the mini-AQLQ and MMAS were somewhat lower than for ACT, mMRC and TAI, consensus was nonetheless reached that these PROMs are relevant to patient follow-up in severe asthma (24). Newer instruments such as the Asthma Impairment and Risk Questionnaire (AIRQ), which integrates symptom impairment with prior exacerbation risk, and CompEx, a composite endpoint combining diary-based events with exacerbations, aim to provide earlier and more accurate detection of deterioration (25). Real-world evidence also shows that moderate exacerbations, often underrepresented in clinical trials, significantly affect symptom control and health-care utilization (26). Moreover, PROMs are increasingly considered relevant clinical trial endpoints. Crossnohere et al. recently argued that incorporating PROMs as endpoints can influence trial outcomes, regulatory decisions,

and clinical practice, offering insights into the benefits and burdens of interventions beyond physiological measures alone (27).

The next step is not only to measure PROMs, but also to interpret their changes in a clinically meaningful way. The concept of minimally important difference (MID) provides an anchor to judge whether observed changes are perceptible and relevant to patients. MIDs are well established for some PROMs in asthma, such as the ACQ and AQLQ (~0.5-point change (28, 29), and for physiological endpoints reported in pharmacotherapy trials. For example, pre-bronchodilator FEV₁ changes of approximately 100 mL are commonly used as a meaningful benchmark (30). However, robust estimates of MIDs for functional outcomes in asthma have been largely lacking to date. The current thesis extends this knowledge by determining MIDs for pulmonary rehabilitation outcomes in asthma, including exercise capacity, quality of life, and psychological symptoms in **Chapter 6**. Importantly, these MIDs were not fixed values but varied with baseline severity for several outcomes: patients with more severe impairment required larger changes to perceive benefit. This baseline dependence has also been observed in COPD (31) and challenges the common use of universal MID thresholds.

Taken together, PROMs and MIDs provide complementary perspectives. PROMs reveal what matters to patients, taking the impact of exacerbations and extra-pulmonary traits into account, while MIDs help determine whether changes in PROMs or clinical outcomes are large enough to be meaningful. This combined framework supports more personalized asthma management, better trial design, and ultimately a more patient-centered approach to severe asthma care.

Rethinking diagnostic boundaries in asthma and COPD

Across **Chapters 2, 3, 4 and 6**, the findings of this thesis show that patients with asthma admitted to PR at Ciro closely resemble those enrolled in international severe asthma cohorts such as U-BIOPRED, as described in **Chapter 5**. This similarity is evident in demographic and clinical profiles, confirming that referral to rehabilitation is limited to a highly selected group with severe disease. This selection reflects the Dutch guideline on severe asthma (32), which recommends rehabilitation only in patients with uncontrolled asthma despite maximal pharmacological treatment, frequent exacerbations (≥ 2 per year or ≥ 1 hospitalization), and the presence of multiple treatable traits (>2) that sustain high disease burden. The indication is established in a multidisciplinary consultation, ensuring that patients referred for rehabilitation

represent the most complex and a highly selected group with uncontrolled severe asthma despite guideline-based pharmacological management.

Beyond this comparison, the outcomes observed in patients with asthma analyzed in the current thesis were strikingly similar to those reported in COPD cohorts. The reproducibility of the 6MWT, the self-reported problematic ADLs, and the MIDs established for rehabilitation outcomes were all of comparable magnitude to findings in COPD, as discussed before. These parallels underscore that once patients are referred to PR, the functional and extrapulmonary burden is largely shared between asthma and COPD.

This convergence is supported by large real-world evidence. The NOVELTY study demonstrated substantial heterogeneity both within and between physician-assigned labels of asthma, COPD, and ACO, with symptoms, airflow limitation, and exacerbation patterns distributed across diagnostic groups rather than confined to a single disease (33, 34). The ERS *Breathe* review on asthma in the elderly further emphasized that ageing and comorbidities modify the clinical picture of asthma, reducing reversibility and increasing fixed airflow limitation, thereby blurring the distinction from COPD (35). Together, these findings highlight that variability in age, comorbidity, and phenotype diminishes the utility of rigid diagnostic categories for functional management, supporting an approach that organizes care around treatable traits rather than diagnostic labels.

Nevertheless, diagnostic boundaries retain importance in pharmacological management, particularly in the era of biologics where precise phenotyping determines eligibility and treatment response. For biologic therapies, accurate classification of asthma phenotypes remains crucial (36). For non-pharmacological interventions, however, the overlap between asthma and COPD suggests that lessons from COPD rehabilitation can, to a certain extent, be applied to asthma, provided reimbursement and organizational barriers are addressed. Moving forward, a pragmatic approach that combines precise phenotyping for pharmacology with trait-based strategies for paramedical care offers the best route to personalized and equitable care of patients with asthma.

Referral and reimbursements differences in asthma versus COPD

Despite growing recognition of its benefits, patients with severe asthma are referred to PR far less often than patients with COPD. This imbalance is observed in the Netherlands, across Europe, and worldwide (37). PR has historically been developed and validated in COPD, resulting in well-established referral pathways, reimbursement structures, and clinical routines that, to date, strongly favor COPD. Consequently, patients with COPD dominate most PR programs, while asthma remains underrepresented (37, 38).

Several factors contribute to this discrepancy. International guidelines have positioned PR differently across the two diseases. In COPD, PR is described as a cornerstone of treatment, supported by a large body of randomized controlled trials showing consistent improvements in exercise capacity, symptoms, and quality of life (39). In asthma, by contrast, guidelines have traditionally emphasized pharmacological therapy, with PR recommended only for patients with severe or difficult-to-treat disease (40, 41). Strikingly, the most recent ATS guideline on PR for adults with chronic respiratory disease (42) excluded asthma from its scope, highlighting a persistent imbalance in PR access and recognition between COPD and asthma, despite growing evidence of PR benefits in asthma.

The strength of the evidence base further reinforces this difference. In COPD, high-certainty evidence from numerous randomized trials has driven systematic inclusion of PR in both guidelines and health policy (43). In asthma, although several studies demonstrate meaningful improvements in exercise capacity and quality of life following PR (44-48), the total number of high-quality studies is small, and certainty of evidence remains low to moderate. This weaker evidence base has slowed adoption into guidelines and reimbursement frameworks. Nevertheless, in contrast to COPD, asthma rehabilitation studies also indicate potential disease-modifying effects. França-Pinto et al. showed that aerobic training reduced bronchial hyperresponsiveness, lowered systemic inflammatory cytokines, and improved quality of life in patients with moderate to severe asthma (49). In obese patients with asthma, Freitas et al. found that adding structured exercise to a weight-loss program led to greater weight reduction, improved asthma control, and reductions in both airway and systemic inflammation (50). These findings highlight unique opportunities for PR in asthma that go beyond functional outcomes and point toward meaningful improvements in underlying disease processes.

Empirical data confirm the consequences. In a recent German severe asthma cohort, only 20% of patients attended PR, despite high symptom burden and frequent exacerbations (51). Although COPD referral can still be considered suboptimal in many settings (52), patients with COPD nonetheless form the majority of PR participants, as described before. Practical, organizational, and financial barriers amplify these differences. PR programs often operate at constrained capacity and are configured around COPD care pathways. Overall, limited awareness of PR among healthcare professionals is commonly cited as the main reason for patients with COPD not being referred to PR (53). In asthma, clinicians may even be less familiar with referral criteria, and patients may face challenges related to time, transport, and perceived benefit.

In the Netherlands, reimbursement policies exacerbate these disparities. Since 2010, bundled payment models have been introduced for selected chronic diseases, explicitly including COPD but not asthma (54, 55). Coverage for physiotherapy and exercise therapy in COPD has been expanded in recent years, with broader basic insurance coverage available from GOLD stage II onward since 2025 (56). By contrast, adult patients with asthma typically receive no routine reimbursement for physiotherapy from the basic package and rely on supplementary insurance or out-of-pocket payments (57). Patient organizations and allied health professional bodies have repeatedly called for improved first-line paramedical access for asthma, arguing that structured physiotherapy and allied health involvement can reduce symptom burden and improve functioning, but translation into a coherent national reimbursement framework for asthma has been limited to date. The Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT) guideline on severe asthma (32) recommends considering first-line physiotherapy for patients with severe or difficult-to-treat asthma who experience exercise intolerance or functional limitations, and as a continuation after PR to maintain or enhance outcomes. Despite these recommendations, physiotherapy for severe asthma is not routinely reimbursed, highlighting a persistent gap in access and recognition compared with COPD.

Taken together, the lower referral of patients with severe asthma to PR reflects a combination of guideline positioning, disease conceptualization, a smaller evidence base, organizational constraints, and reimbursement policies that have historically favored COPD. Addressing this inequity requires further high quality research to define the asthma phenotypes most likely to benefit, clearer guideline referral criteria for asthma subgroups with persistent functional impairment, routine collection of relevant outcomes, and policy measures to expand reimbursement

for paramedical and multidisciplinary care in asthma. Through detailed assessment of functional capacity, body composition, daily activities, and PROMs in severe asthma, this thesis offers tools to refine referral criteria and to support broader implementation of PR in asthma care.

Strengths, limitations, and interpretative considerations

A major strength of this PhD thesis is the comprehensive and systematic evaluation of extrapulmonary traits in a large cohort of patients with asthma undergoing PR. Functional capacity, body composition, ADLs, and PROMs were all assessed, allowing for an integrated view of the extrapulmonary burden in asthma. The large sample size in several chapters, particularly for the derivation of MIDs, provides robust estimates that can inform both research and clinical practice. Together, these aspects offer novel and clinically relevant insights in an area where high-quality data is scarce.

Some limitations warrant consideration. First, the analyses in **Chapters 2, 3, 4, and 6** were based on patients referred to Ciro, a single specialized center, which may limit generalizability. The referral of only patients with severe and uncontrolled asthma introduces selection bias and means that the findings cannot be directly extrapolated to those with milder disease. Second, asthma-specific PROMs such as ACT and AQLQ were not included in these chapters because systematic collection at Ciro only began in recent years, while the data analyzed in this thesis span back to 2005. Third, the MIDs established in **Chapter 6** were derived using distribution-based methods, and no anchor-based estimates could be calculated because suitable anchors were unavailable. Fourth, the analyses were observational and retrospective, which may have led to incomplete recording of relevant variables and inconsistencies in measurement over time. Finally, most data were collected before the widespread introduction of biologics in asthma care, which may affect the applicability of findings to present-day clinical practice.

These limitations underline the need to interpret the results in context, but also highlight the unique contribution of this thesis. As noted in recent reviews and guidelines, randomized controlled trials of PR in severe asthma are difficult to conduct for ethical and logistical reasons, given the severity and heterogeneity of the disease (32). Large, carefully analyzed observational cohorts therefore provide essential real-world evidence to guide clinical practice and policy.

Future directions

The work presented in this thesis sets the stage for future research in several directions. First, there is a clear need to investigate how PR interacts with modern pharmacological treatments, particularly biologics. With the advent of targeted therapies, many patients with severe asthma experience reductions in symptoms and exacerbations, but the extent to which PR adds value on top of biologic treatment remains largely unexplored. Combined approaches could potentially yield additive or even synergistic effects by addressing both airway inflammation and extrapulmonary traits such as muscle dysfunction, obesity, and psychological burden.

Second, the impact of PR on exacerbations in asthma requires clarification. While reductions in exacerbation frequency and severity are well documented in COPD, evidence in asthma is sparse. Observational data suggest that improvements in functional capacity and self-management skills may indirectly reduce exacerbation risk, but prospective studies are needed to establish this relationship more firmly. Given that exacerbations emerged as a key driver of patient-perceived burden in **Chapter 5**, understanding whether PR can modify this outcome is of high clinical relevance.

Third, future research should broaden the scope of treatable traits studied in asthma rehabilitation. This thesis focused on functional capacity, body composition, ADLs, and psychological symptoms, but other extrapulmonary traits may also be highly relevant. Osteoporosis, for example, is a recognized comorbidity in severe asthma, driven by systemic corticosteroid exposure, physical inactivity, and coexisting conditions (58, 59). Its prevalence and impact on functional capacity are well documented, but direct evidence on responsiveness to PR is lacking. Future studies should therefore include bone health outcomes alongside established measures of exercise capacity and quality of life.

Taken together, this thesis contributes to a growing recognition that severe asthma is characterised by extrapulmonary features that substantially shape disease burden. By systematically evaluating functional capacity, body composition, activities of daily living, and PROMs, and by establishing clinically meaningful benchmarks for PR outcomes, the work presented here provides tools to better characterise patients and to refine referral and treatment strategies. While important gaps remain, these findings underline the potential of PR as an integral component of severe asthma care and provide a foundation for future research and policy development.

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ADDENDA

SAMENVATTING

IMPACT PARAGRAPH

DANKWOORD

CURRICULUM VITAE

LIST OF PUBLICATIONS

SAMENVATTING

Astma is een chronische luchtwegaandoening die wordt gekenmerkt door ontsteking en vernauwing van de luchtwegen, wat resulteert in symptomen zoals een piepende ademhaling, kortademigheid en hoesten. In 2019 trof de ziekte naar schatting 262 miljoen mensen wereldwijd en de aandoening brengt aanzienlijke kosten voor de gezondheidszorg met zich mee. De ziektelast is hoog en de aandoening beïnvloedt zowel de fysieke als de psychosociale gezondheid. De standaardbehandeling bestaat uit farmacologische therapie en zelfmanagementstrategieën, terwijl longrevalidatie een complementaire aanpak biedt gericht op het verbeteren van de fysieke capaciteit, het psychologisch welzijn en het dagelijks functioneren. Er is steeds meer bewijs dat de impact van astma verder reikt dan de luchtwegen alleen, waarbij extrapulmonale kenmerken aanzienlijk bijdragen aan de symptomlast, functionele beperkingen en de algehele kwaliteit van leven.

Voortbouwend op dit perspectief was het overkoepelende doel van dit proefschrift om de huidige kennis over extrapulmonale kenmerken van astma uit te breiden, met specifieke aandacht voor het in kaart brengen hiervan en de impact van longrevalidatie. In dit proefschrift werden verschillende aspecten van extrapulmonale betrokkenheid onderzocht, variërend van functionele capaciteit en lichaamssamenstelling tot patiënt-gerapporteerde beperkingen in dagelijkse activiteiten en gezondheidstoestand. Dit werk biedt nieuwe inzichten in de heterogeniteit van astma en het potentieel van longrevalidatie om zich te richten op deze kenmerken.

In **Hoofdstuk 2** werd de waarde en bruikbaarheid van de zes-minuten wandeltest (6MWT) onderzocht in een groot cohort patiënten met astma. De 6MWT bleek een betrouwbaar en valide instrument voor het in kaart brengen van de functionele inspanningscapaciteit in deze populatie. De factoren die de loopafstand bij patiënten met astma beïnvloedden reikten verder dan de longfunctie alleen en omvatten onder andere de Body Mass Index (BMI). Dit onderstreept het multifactoriële karakter van inspanningsbeperking en bevestigt dat functionele capaciteit niet uitsluitend wordt bepaald door luchtwegobstructie. Tevens werd bij deze patiënten een leereffect geobserveerd. Dit impliceert dat herhaald testen essentieel is voor een betrouwbare nulmeting bij astma, zoals dit binnen de longrevalidatie voor andere chronische longaandoeningen, waaronder COPD, reeds de norm is.

In **Hoofdstuk 3** werd de lichaamssamenstelling van patiënten met astma die werden verwezen voor longrevalidatie gedetailleerd in kaart gebracht middels DEXA-scans. Hieruit bleek dat een lage spiermassa in de ledematen, eventueel

in combinatie met een te hoog vetpercentage (sarcopene obesitas), frequent voorkomt in deze populatie. Deze afwijkingen hangen duidelijk samen met een verminderd inspanningsvermogen en een lagere kwaliteit van leven. De bevindingen benadrukken dat de BMI alleen onvoldoende inzicht biedt en identificeren de lichaamssamenstelling als een relevant extrapulmonaal kenmerk dat de uitkomsten van longrevalidatie kan beïnvloeden.

In **Hoofdstuk 4** werden beperkingen in activiteiten van het dagelijks leven (ADL) onderzocht vanuit het perspectief van de patiënt. Middels de Canadian Occupational Performance Measure (COPM) rapporteerden patiënten met astma een breed scala aan problematische ADL's, waarbij de meest voorkomende problemen betrekking hadden op fysieke inspanning en huishoudelijke taken. Deze zelfgerapporteerde beperkingen correleerden slechts zwak met klinische kenmerken zoals de mate van luchtwegobstructie, leeftijd en lichaamssamenstelling. Dit bevestigt de meerwaarde van het integreren van problematische ADL's in de beoordeling van de impact van astma. In **Hoofdstuk 5** verschoof de focus naar patiëntgerapporteerde uitkomstmaten (PROMs) bij ernstig astma binnen het U-BIOPRED cohort. Longaanvallen bleken een sterke negatieve invloed te hebben op de zelfgerapporteerde gezondheidstoestand en kwaliteit van leven, terwijl de longfunctie relatief stabiel bleef. Dit onderstreept dat PROMs informatie verschaffen die niet wordt gevangen door fysiologische metingen. Hoewel hun vermogen om toekomstige longaanvallen te voorspellen beperkt was, bevestigden deze bevindingen dat PROMs onmisbaar zijn voor het systematisch monitoren van de ervaren ziektelast en het evalueren van het klachtenverloop van de individuele patiënt in de dagelijkse praktijk.

In **Hoofdstuk 6** werd een studie gepresenteerd waarin minimale belangrijke verschillen (MIDs) voor uitkomsten van longrevalidatie bij patiënten met astma werden vastgesteld. In een groot cohort patiënten werden significante verbeteringen waargenomen in het inspanningsvermogen, de kwaliteit van leven en psychologische symptomen. Er werden MIDs vastgesteld voor de zes-minuten wandelafstand, de fietstijd tijdens de submaximale fietstest, kwaliteit van leven, de vetvrije massa-index en symptomen van angst en depressie. Subgroep analyses toonden aan dat sommige van deze MIDs varieerden op basis van de Ausgangssituatie: patiënten die met een slechtere conditie startten, hadden grotere veranderingen nodig om een verbetering als betekenisvol te ervaren. Deze resultaten bieden een concreet referentiekader voor het interpreteren van klinisch betekenisvolle veranderingen bij astma en ondersteunen een behandeling op maat.

In **Hoofdstuk 7** werden de bevindingen in een breder perspectief geplaatst en werden de klinische implicaties, methodologische overwegingen en mogelijkheden voor toekomstig onderzoek besproken. De resultaten lieten zien dat patiënten met ernstig astma die verwezen worden voor longrevalidatie, in hun functionele en extrapulmonale profiel sterk lijken op patiënten met COPD. De ziektelast bij opname voor revalidatie is grotendeels vergelijkbaar, wat een aanpak ondersteunt waarbij de zorg wordt georganiseerd rondom 'behandelbare kenmerken' (treatable traits) in plaats van uitsluitend op basis van diagnostische labels.

Ondanks deze overeenkomsten worden patiënten met ernstig astma aanzienlijk minder vaak verwezen naar longrevalidatie dan patiënten met COPD. Dit verschil wordt deels verklaard door de beperktere (maar groeiende) bewijslast voor revalidatie bij astma, de positionering in internationale richtlijnen en structurele barrières in de Nederlandse zorgvergoeding. Waar fysiotherapie bij COPD routinematig uit het basispakket wordt vergoed, zijn patiënten met astma vaak afhankelijk van aanvullende verzekeringen. Deze ongelijkheid in toegang tot zorg staat in schril contrast met de aanbevelingen in de NVALT-richtlijn voor ernstig astma en de in dit proefschrift aangetoonde ziektelast.

Een kracht van dit proefschrift is de systematische evaluatie van een groot cohort patiënten met ernstig astma. Hoewel de retrospectieve aard en de focus op één gespecialiseerd centrum (Ciro) beperkingen met zich meebrengen, biedt dit werk essentiële "real-world evidence" in een populatie waar gerandomiseerd onderzoek ethisch en logistiek complex is. De meeste data zijn verzameld vóór de brede introductie van biologicals, doelgerichte medicijnen die specifieke ontstekingsreacties in de luchtwegen remmen, en die een belangrijke rol spelen in de huidige praktijk van ernstig astma. Toekomstig onderzoek moet uitwijzen hoe longrevalidatie interacteert met moderne biologicals en of revalidatie de frequentie van longaanvallen kan verlagen. Ook andere kenmerken, zoals osteoporose door corticosteroïdgebruik, verdienen meer aandacht binnen de revalidatiecontext.

Gezamenlijk bevestigen de bevindingen in dit proefschrift dat astma niet louter een aandoening van de luchtwegen is, maar wordt gekenmerkt door een scala aan extrapulmonale kenmerken die in belangrijke mate bijdragen aan de ziektelast. Het functionele inspanningsvermogen, de lichaamssamenstelling, beperkingen in het dagelijks leven en psychologische symptomen zijn stuk voor stuk essentiële aspecten van de ziekte. Bovendien komt longrevalidatie naar voren als een veelbelovende interventie om deze dimensies aan te pakken, al blijven er structurele barrières voor de implementatie bestaan. Door deze kenmerken en de bijbehorende referentiekaders

zoals MIDs systematisch in kaart te brengen, biedt dit werk het fundament voor meer gepersonaliseerde zorg en een bredere inzet van longrevalidatie binnen de astmazorg.



IMPACT PARAGRAPH

This thesis has deepened the understanding of the functional and extrapulmonary consequences of severe asthma and the role of pulmonary rehabilitation (PR) in its management. The following section reflects on the scientific and societal impact of the findings by elaborating on four questions: (1) What was the main objective of the research described in this thesis, and what are the most important results and conclusions? (2) What is the potential contribution of these results to science and society? (3) For whom are the research findings most relevant, and why? (4) How can these groups be engaged and informed so that the knowledge gained can be applied in the future?

Main objectives, findings and conclusions

The central aim of this thesis was to improve understanding of extrapulmonary features in adults with asthma and to explore how PR can address these traits to improve functioning and quality of life. Although asthma is traditionally viewed as a disease of the airways, this work showed that its impact reaches far beyond the lungs. Physical deconditioning, changes in body composition, limitations in daily activities, and psychological distress all contribute substantially to the overall burden of severe asthma.

The studies presented in this thesis provide an integrated view of these aspects. **Chapters 2, 3, 4 and 6** were based on data from patients with asthma who underwent PR at Ciro. **Chapter 2** demonstrated that the six-minute walk test (6MWT) is a reliable measure of functional capacity in asthma and that exercise limitation is influenced by factors beyond lung function, such as body composition and muscle strength. **Chapter 3** showed that low appendicular lean mass and sarcopenic obesity are common in severe asthma and are strongly associated with lower exercise performance and poorer health status. **Chapter 4** revealed that many patients experience substantial limitations in daily activities, often unrelated to lung function. Finally, **Chapter 6** established minimal important differences (MIDs) for key PR outcomes, providing practical benchmarks for interpreting meaningful change in exercise capacity, psychological wellbeing, and quality of life.

Together, these findings show that PR can address multiple dimensions of asthma burden that are not captured by traditional physiological measures alone. The extrapulmonary features in patients with asthma reported in this thesis show much resemblance with our understanding of patients with COPD who are referred for PR, suggesting that principles of multidisciplinary rehabilitation can be applied to

both diseases. This thesis therefore reframes asthma as a condition that requires not only optimal pharmacological management but also a broader, trait-based approach focused on restoring functioning and wellbeing.

Potential contribution to science and society

This thesis contributes to the growing recognition that asthma should be viewed as a multidimensional disease. Scientifically, it expands understanding of the interplay between respiratory and extrapulmonary features and highlights how PR can address traits such as reduced muscle strength, physical deconditioning, and psychological distress. By systematically characterizing these traits, this work broadens asthma research beyond airway inflammation and lung function to include functional capacity, body composition, and daily functioning.

The studies based on Ciro data provide unique real-world insight into severe asthma. Demonstrating that 6MWT is reliable and clinically meaningful, that sarcopenic obesity is frequent, and that MIDs can be established for PR outcomes represents an important methodological and clinical contribution. These findings create a foundation for future research on extrapulmonary treatable traits and for integrating such assessments into daily clinical practice.

From a societal perspective, this work supports a more comprehensive approach to asthma care. By identifying and treating extrapulmonary limitations, PR can help patients regain independence and improve participation in daily life, thereby enhancing quality of life and potentially reducing healthcare use. This thesis shows that patients with severe asthma referred for PR experience a burden comparable to that of COPD, yet current care pathways in asthma do not always reflect this level of complexity. These findings strengthen the case for rethinking how paramedical care for asthma is organized, and for clarifying which patients can be treated in primary care and which require more intensive rehabilitation.

Overall, by framing asthma as a heterogeneous condition shaped by both pulmonary and extrapulmonary traits, this thesis contributes to a broader scientific and societal goal: personalizing care around the traits that limit asthma patients most.

Target groups

First and foremost, the results of this thesis are relevant for *patients with severe asthma and their families*. The findings show that asthma affects much more than the lungs alone and that problems such as muscle weakness, fatigue, and inactivity can strongly influence daily life. By showing that PR can enhance both physical



and psychological wellbeing, this work offers patients new perspectives on disease management. It also empowers them to discuss rehabilitation options more confidently with their care teams.

For *healthcare professionals*, including pulmonologists, physiotherapists, occupational therapists, psychologists, and nurses, the findings encourage a more holistic approach to asthma management. They emphasize the value of assessing functional capacity, body composition, and daily activity limitations in addition to lung function and biomarkers. The MIDs established in this thesis provide practical reference points to interpret outcomes during PR.

For *researchers*, this thesis provides methodological tools and MIDs for evaluating functional and psychosocial outcomes in asthma. It also highlights knowledge gaps, such as the need to study interactions between PR and pharmacological treatments and to identify other extrapulmonary traits that might respond to rehabilitation.

Finally, for *policymakers and healthcare insurers*, the results demonstrate that patients with severe asthma referred to PR experience a burden comparable to that reported in studies of COPD, and they support reflection on whether current asthma care pathways and access to PR sufficiently match this level of impairment. Aligning care pathways and reimbursement policies could help ensure that all patients with chronic respiratory disease receive equitable, evidence-based support.

Activities

Several initiatives have been undertaken to disseminate the findings of this thesis among healthcare professionals and researchers. The results of **Chapters 2, 3, 4, 5 and 6** were presented at international congresses including the European Respiratory Society (ERS) Congress in 2022 (Barcelona, Spain), 2023 (Milan, Italy), and 2025 (Amsterdam, the Netherlands), as well as at local meetings such as the annual NUTRIM symposium at Maastricht University and various Ciro research events.

The results of **Chapter 2** were presented at the Specialists in Training Access to Relevant Research Overseas and Worldwide (SPARROW) meeting in Amersfoort (the Netherlands), organized by GlaxoSmithKline (GSK) in 2021, where the presentation was awarded Best Scientific Presentation.

Findings from this thesis have been or will be published in international, peer-reviewed journals, ensuring broad dissemination within the scientific community. Beyond academia, the results of **Chapter 5** were summarized in a Dutch-language

article, *'Levenskwaliteit en patiëntgerapporteerde uitkomsten bij ernstig astma: er is meer dan longfunctiemetingen'*, published in *Medi-Sfeer* in 2025, a Belgian journal distributed to all active general practitioners. This outreach aims to raise awareness of patient-reported outcomes and to encourage a more holistic view of asthma care in general practice.

Together, these activities ensure that the insights from this thesis contribute to advancing research, improving patient care, and strengthening the role of PR in asthma management.



DANKWOORD

Men zegt wel eens dat een PhD een marathon is, geen sprint. Na ruim zeven jaar kan ik dit volmondig bevestigen. Hoewel de finishlijn voor mijn gevoel telkens een paar kilometer werd verplaatst, heeft de steun van een grote groep mensen ervoor gezorgd dat ik de eindstreep nu toch echt heb gehaald. Een aantal van hen wil ik hieronder persoonlijk bedanken.

In de eerste plaats mijn promotoren. **Frits**, om in marathontermen te blijven: zonder jou was ik hoogstwaarschijnlijk niet eens aan de start verschenen. Jij gaf het vertrouwen aan een longfunctieanalist met wetenschappelijke achtergrond om dit traject aan te gaan, iets waar ik je nog altijd zeer dankbaar voor ben. Ondanks je overvolle agenda heb ik je persoonlijke aandacht en jouw oprechte betrokkenheid bij de patiënt altijd enorm gewaardeerd; je herinnerde me er voortdurend aan waarom het onderwerp van dit proefschrift zo relevant is voor onze patiënten. Ik hoop dat we elkaar nog regelmatig treffen in **Ciro** om te sparren over de longfunctie of om simpelweg even bij te praten.

Martijn, jij hebt er hoofdzakelijk voor gezorgd dat ik na zeven jaar ook daadwerkelijk de finish heb bereikt. Jouw innovatieve blik was cruciaal, zeker toen we midden in de pandemie besloten van onderwerp te veranderen. Ik waardeer de manier waarop je me weet te motiveren om door te zetten en het beste uit mezelf te halen. Daarnaast ben ik je dankbaar voor de kansen die je me binnen **Ciro** hebt geboden. Ik ben erg blij dat we in mijn huidige rol nog steeds veel contact hebben; ik leer veel van je en hoop dat we nog vele jaren mogen samenwerken.

Hartelijk dank aan de leden van de beoordelingscommissie, bestaande uit **prof. dr. G.H. Goossens, prof. dr. A. Marques, prof. dr. K. Meijer, dr. E.J. Weersink en em. prof. dr. G. Wesseling**, voor de tijd die jullie hebben geïnvesteerd in het beoordelen van mijn proefschrift. Ik kijk uit naar de wetenschappelijke discussie tijdens de verdediging. A special thank you to **prof. dr. A. Marques** for travelling all the way to Maastricht to attend the defense in person. Tevens gaat mijn dank uit naar **prof. dr. H. Demeyer** voor het plaatsnemen in de oppositiecommissie.

Mijn oprechte dank gaat uit naar alle **patiënten met astma** die hun data beschikbaar hebben gesteld, zowel binnen **Ciro** als via de U-BIOPRED studie. Zonder jullie medewerking waren alle studies in het kader van dit proefschrift simpelweg niet mogelijk geweest. In mijn dagelijkse werk zie ik van dichtbij hoe intensief de testen en gesprekken binnen een assessment kunnen zijn; ik ervaar

jullie bereidheid dan ook absoluut niet als vanzelfsprekend en dank jullie voor alle inzet. De persoonlijke verhalen die jullie op een kwetsbaar moment durven te delen, blijven voor mij de belangrijkste herinnering aan de mens achter de cijfers en de noodzaak van dit proefschrift.

De totstandkoming van dit proefschrift werd mede mogelijk gemaakt door de financiële en academische steun van het **Longfonds, Universiteit Maastricht** en **Ciro**. Ik ben hen zeer dankbaar voor de kans en de middelen om mijn PhD uit te voeren. Daarnaast gaat mijn dank uit naar alle leden van het **BASES consortium**. In het bijzonder natuurlijk **Jana**. De hele BASES-studie was namelijk nooit mogelijk geweest zonder al jouw harde werk in de jaren daarvoor. Vanaf het begin waren Anouk en ik van harte welkom bij jou in Hasselt om de opzet van onze studie uit te werken. Er werd serieus gewerkt, maar ook veel gelachen. Bedankt dat je zo gastvrij was en dat je regelmatig even checkte hoe het met mijn 'boekje' ging. **Chris**, ook jij was altijd even vriendelijk en in voor een praatje; die Belgische hartelijkheid heb ik enorm gewaardeerd. **Jeroen en Bram**, bedankt voor jullie betrokkenheid vanuit het Radboud. Jullie toonden altijd oprechte interesse in de voortgang van mijn PhD-traject en gaven zeer waardevolle feedback op mijn artikelen. Wat jullie allemaal betreft: ik hoop dat we elkaar nog vaak treffen om op professioneel vlak van gedachten te wisselen of gewoon voor een gezellig babbeltje.

Een speciaal woord voor mijn directe **Ciro**-collega's van team Diagnostiek: **Danja, Denys, Ellis, Ellen, Heidi, Jeannet, Jos, Jules, Marianne, Mariëtte, Petra, Sarine en Tess**. Ik ben iedere dag heel trots dat ik coördinator van dit geweldige team mag zijn. Bedankt voor de fijne samenwerking, jullie inzet voor onze patiënten en de gezelligheid en gezonde dosis humor op de werkvloer. Jullie zorgen ervoor dat ik elke dag met heel veel plezier naar mijn werk kom vanuit het altijd zonnige Heerlen. Ook mijn voormalige teamleden, **Annelies, Britt, Kitty, Lars, Nina, Robin, Thea, Vera, Vera** en stagiaires **Puck en Bo**, wil ik hierin absoluut niet vergeten; bedankt voor de fijne tijd samen.

Als je ruim zeven jaar over je promotieonderzoek doet, is het grote voordeel dat je enorm veel leuke collega-onderzoekers leert kennen. Een speciale vermelding voor de 'COVID-OG's' is hier echter wel op zijn plek: **Anouk, Felipe, Jeannet, Kiki, Maarten, Sarah en Yvonne**. Waar we in 2019 nog dagelijks een groot kantoor (het 'Gezelligheidshok') deelden en ieder aan onze eigen studies werkten, kwam daar in maart 2020 abrupt een einde aan. Van de ene op de andere dag werkten we allemaal noodgedwongen vanuit thuis. Het bijzondere is dat we, ondanks die afstand, juist in die periode een megahecht team werden. Samenwerken aan



onderzoek, koffiemomentjes via Teams en digitale spelletjesavonden: achteraf gezien was het een unieke tijd. Ik ben ontzettend blij dat ik jullie toen als collega's had. Inmiddels zijn de meesten van jullie me voorgegaan. Ik heb enorm veel van jullie geleerd, heb veel respect voor jullie onderzoeksvaardigheden en heb jullie met grote trots zien promoveren. Daarnaast zijn er nog vele andere (oud-) onderzoekers met wie ik in meer of mindere mate heb samengewerkt tijdens mijn PhD-traject: **Anouk M, Banchia, Bente, Britt, Carmen, Cindy, Daphne, Gui, Joana, Miranda, Nienke, Qichen, Sara Miranda, Spencer en Yuqin**. Bedankt voor de fijne tijd en de leuke teamuitjes.

Ook een heel groot dankjewel aan het kernteam van **Ciro: Gwen, Jérôme, Kristel, Mara, Maurice, Paula, Rein, Sandra, Sarah en Vera**. Vanaf het allereerste moment voelde ik me bij jullie welkom. Ik heb door de jaren heen enorm veel van jullie geleerd over de behandeling van onze patiënten. Hoewel we een groep zijn met veel verschillende persoonlijkheden, pakt het op de een of andere manier toch heel mooi samen. Ik bewonder stuk voor stuk jullie enorme hart voor de patiënt en geniet van de discussies die we voeren, maar waardeer met name het luisterend oor dat we voor elkaar zijn. Laten we dit vooral samen zo voortzetten in de toekomst! Ook voormalig teamleden **Nicole en Stéphanie**: bedankt voor de leuke momenten die we samen hadden.

Ingrid, jou wil ik persoonlijk bedanken voor alle kansen die je mij hebt geboden. De longfunctie is wat ons vanaf het begin verbond; als we het daarover hadden, zag ik altijd weer die sprankeling in je ogen. Ik heb heel veel respect voor de weg die je hebt bewandeld: van de longfunctieafdeling naar bestuurder van **Ciro** en uiteindelijk ook zelf gepromoveerd. Ik durf best te stellen dat ik zonder jou niet op de plek was geweest waar ik nu ben. Bedankt voor je vertrouwen en ik wens je alle geluk toe.

Een speciaal bedankje aan **Bente** en **Tess** voor jullie hulp bij het ontwerpen van mijn cover. Zelfs wanneer ik zelf niet precies wist wat ik in gedachten had, zorgden jullie creatieve ideeën voor een eindresultaat waar ik ontzettend blij mee ben.

Afsluitend wil ik graag alle andere **Ciro-collega's** bedanken die ik niet persoonlijk bij naam heb genoemd. Bedankt voor de fijne tijd en het dagelijkse werkplezier dat ik hier ervaar. Het is de gezamenlijke, tomeloze inzet voor onze patiënten die **Ciro** tot zo'n bijzondere plek maakt om te werken. Of het nu gaat om een kort praatje bij het koffieautomaat, een padeltoernooi, een wandeling door de prachtige natuur of de samenwerking tussen de afdelingen: bedankt voor de fijne sfeer!

Anouk, mijn «BASES-buddy» en paranimf. We begonnen tegelijkertijd aan onze PhD en de klik was er meteen. Samen hebben we met veel enthousiasme de BASES-studie opgezet, en hoewel we die uiteindelijk helaas niet zelf hebben kunnen uitvoeren, heb ik enorm genoten van onze tijd samen. Zowel op je hardloopschoenen als in het promotietraject was je me echter ver voor: ik heb dan ook met veel trots als paranimf naast je mogen staan tijdens jouw eigen verdediging. Ik kon me simpelweg niemand anders bedenken om op 28 mei naast mij te hebben staan. Bedankt voor al het lachen, je eeuwige positiviteit en de manier waarop je in het leven staat. Je bent een echte powervrouw, blijf vooral wie je bent!

Felipe, meu outro paranimfo. Muito obrigado por estar ao meu lado no dia 28 de maio e por toda a sua amizade e apoio durante estes anos. É uma honra ter você aqui! De rest kan gewoon in het Nederlands, want na die paar jaar in Nederland en België heb je je dat inmiddels al helemaal eigen gemaakt. Ik heb enorm veel respect voor het feit dat je samen met **Bruna** de stap vanuit Brazilië hiernaartoe hebt gewaagd. Vanaf het eerste moment bij **Ciro** hadden we goede gesprekken over fitness, voeding en natuurlijk onderzoek. Naast het werken aan onze eigen spiermassa tijdens de gezamenlijke sportsessies buiten werktijd, ben ik vooral heel blij dat ik met jou als specialist kon sparren over spiermassa bij patiënten met astma en daarmee over de inhoud van hoofdstuk 3. Inmiddels ben je zelf gepromoveerd én papa van **Matteo**: hier mag je echt zo enorm trots op zijn. Ik ben blij dat ik je mijn vriend kan noemen en hoop nog vaak op bezoek te komen bij jou en je mooie gezinnetje.

Oud-collega's van Zuyderland: **Armand, Bob, Dewi, Jacqueline, Jelle, Nadine en Sanne**: fijn dat jullie nog steeds werkzaam zijn binnen ons mooie vak en dat we nog altijd contact hebben. Ik vind het leuk om te horen hoe het er op de verschillende longfunctieafdelingen in Limburg aan toe gaat. **Francine**, als we elkaar weer eens tegenkwamen bij carnaval vroeg je altijd hoe het met mij en mijn onderzoek ging; bedankt voor je oprechte interesse. **Henk**, ik heb in al die jaren niemand leren kennen die zoveel passie voor het longfunctievak had als jij. Jij hebt me de fijne kneepjes geleerd en je enthousiasme werkte aanstekelijk. Bedankt dat je aan me dacht toen het stokje voor de spirometrie-scholingen moest worden overgedragen; dat vertrouwen heeft veel voor me betekend. Inmiddels ben je met welverdiend pensioen; geniet vooral van de tijd die komen gaat.

Daniël, van oud-collega naar goede vriend. Hoewel je het jammer vond dat ik vertrok, heb je mijn overstap naar **Ciro** altijd gesteund. Sindsdien is ons contact niet verwaterd, maar is onze band juist sterker geworden. Als iemand weet dat het

leven soms te kort is om kansen níét te grijpen, dan ben jij het wel. Ik heb er dan ook veel bewondering voor dat je je dromen bent gaan najagen als professioneel fotograaf. Ik ben blij dat ik je mijn vriend kan noemen. En wat onze sportsessies betreft: bereid je maar voor, want ik heb binnenkort weer wat meer tijd om onze PR's flink aan te scherpen.

Dan een aantal mensen die, net als ik, bezig waren met een promotietraject maar niet tot de onderzoeksgroep van **Ciro** behoorden. **Tim**, op het voetbalveld is het ons nooit gelukt om te promoveren, maar het is mooi om te zien dat het ons op deze manier wel lukt. Ik heb veel respect voor je betekenisvolle werk als kinderarts-neonatoloog en de manier waarop je dit hebt weten te combineren met een PhD. **Steffi**, jij bent de enige die ik ken die ook druk bezig is met een "astma-boekje"; het was fijn om hier af en toe over te kunnen sparren. Bedankt voor je oprechte interesse en succes met de laatste loodjes. **Rein**, binnen **Ciro** kregen we de afgelopen jaren steeds meer inhoudelijk contact. Mooi om te zien dat we ongeveer tegelijk ons promotietraject afronden. Jij hebt, ondanks je drukke bestaan, een sterke eindsprint gemaakt en promoveert al in april. Fijn dat het erop zit, ik kijk ernaar uit om ons werk binnen **Ciro** samen voort te zetten.

Hanneke, Jeroen, Lotte en Marieke: bedankt voor alles wat jullie me hebben geleerd over het longfunctievak, onderzoek en het begeleiden van studenten. Al jarenlang vormen we de kern van de afstudeerdocenten longfunctie bij de LOI. Ik heb jullie betrokkenheid altijd zeer gewaardeerd en hoop dat we ons nog lang samen kunnen blijven inzetten voor deze mooie opleiding.

Enrique, Kelly en Pedro, oftewel de 'uni-matties'. Van **Trein-Limbo's** tijdens onze studie Gezondheidswetenschappen tot nog steeds goede vrienden. Ik had toen niet verwacht dat juist ik een PhD zou doen. Ik geniet van onze bijpraatmomenten en etentjes, laten we die traditie vooral voortzetten!

Bart, Bram, Damian, Joep, Joy, Martijn, Nick, Roel en Tom: 'de boys'. Er wordt wel eens beweerd dat vriendschappen die de grens van zeven jaar passeren, voor het leven zijn. Of dit echt wetenschappelijk bewezen is, durf ik niet met zekerheid te zeggen, maar ik weet wel zeker dat ik me geen leven zonder jullie kan voorstellen. We kennen elkaar door en door, maar ik durf vrij zeker te stellen dat jullie oprecht geen idee hebben waar ik de afgelopen jaren mee bezig ben geweest, maar juist dat is wat onze vriendschap zo bijzonder maakt. Voetbal is wat ons jaren geleden samenbracht. Het voelt als de dag van gisteren dat we ieder weekend de kantine uitrolden om op stap te gaan in Heerlen. Tegenwoordig lijken we wel wat

verstandiger te zijn geworden en betreft het vooral padelavondjes, F1 kijken of een hapje eten samen. Want hoewel de festivals uiteraard niet mogen ontbreken, zijn we de laatste jaren toch echt in een andere fase terechtgekomen. Om sommige van jullie nu in de rol van papa te zien, maakt me als vriend zijnde mega trots. Ik geniet enorm van de tijd die ik mag doorbrengen met jullie en jullie gezinnetjes; simpelweg genieten van alles wat het leven brengt, met de mensen die je graag om je heen hebt.

Sanne, ik ken je al langer dan dat ik Deem ken. Bedankt dat je de afgelopen jaren af en toe polste hoe het met m'n onderzoek ging. Ik geniet van de momenten samen met **Deem, Lotte en Jarne**, en natuurlijk van het oppassen op onze "leenhond" **Noof**.

Natuurlijk mag ook mijn schoonfamilie niet ontbreken. **Ron en Monique**, bij jullie voel ik me altijd welkom en op mijn gemak, niet in de laatste plaats door de aanwezigheid van **Puk**. Dat is me veel waard. Ik waardeer het enorm dat jullie me hebben gesteund in de beslissing om mijn vaste contract bij Zuyderland op te zeggen en toentertijd de sprong naar **Ciro** te wagen. Jullie vertrouwen deed me goed. **Saskia en Rick**, bedankt voor jullie oprechte interesse in mijn PhD. Maar bovenal geniet ik ervan om bij jullie over de vloer te komen als 'Ome Roy'. De glimlach van **Noah en Daan** tovert ook bij mij altijd direct een lach op mijn gezicht.

Een speciaal woord voor **Anjes, Edwin, Chelsea en Lorenzo**. We zijn een kleine familie, wat onze band en de gezelligheid tijdens de momenten die we de afgelopen jaren hebben gevierd juist zo bijzonder maakt. Deze momenten zorgden voor een fijne afleiding; het was soms heerlijk om het even helemaal niet over werk te hoeven hebben.

Lieve **oma**, «het jungske» heeft «de studie» eindelijk af. Altijd als ik bij je op bezoek kwam, vroeg je ernaar, en ik vind het ontzettend bijzonder dat je erbij bent als ik daadwerkelijk ga afronden. Ik heb er veel bewondering voor hoe je de draad hebt opgepakt na het overlijden van **opa**. Wat hadden we allebei graag gewild dat hij er bij had kunnen zijn, maar ik weet zeker dat hij met een enorme glimlach en vol trots zou hebben meegekeken. Ik koester de leuke momenten die we samen hebben.

Dan **Mandy**, mijn kleine zusje. Ik ben ontzettend trots op hoe jij samen met **Stan** de wereld aan het veroveren bent. Ik vind het waanzinnig knap dat jullie op zo'n jonge leeftijd allebei de stap hebben gezet om een eigen zaak te starten. Met FBLS Weddings doe je iets totaal anders dan ik, maar juist dat contrast vind ik fijn als



we samen zijn. Weet dat ik mega trots ben op wie je bent. Bij dezen dan ook een stukje schaamteloze promotie: mocht je na het lezen van dit proefschrift nog gaan trouwen of een goede bedrijfsfotograaf zoeken, spreek me na de verdediging gerust even aan!

Pap en Mam, ik zeg het niet vaak genoeg, maar bedankt voor alles. Jullie hebben mij altijd de vrijheid gegeven om mijn eigen keuzes te maken en mij daar onvoorwaardelijk in gesteund. Jullie hebben mij gevormd tot de persoon die ik nu ben; de normen en waarden die ik van huis uit heb meegekregen, pas ik nog dagelijks toe in mijn werk. Ik kom nog altijd graag naar huis, niet in de laatste plaats voor de enthousiaste begroeting van m'n maatje **Rayko**. Bedankt dat jullie er altijd voor me zijn.

Als laatste, **Jessica**, de belangrijkste persoon in mijn leven en degene die alles echt de moeite waard maakt. Zeven jaar geleden begonnen we samen aan deze marathon. Inmiddels weten we dat écht samen hardlopen voor ons geen goed idee is, maar jij was wel de allerbeste supporter die ik me kon wensen. Dit proefschrift mag dan wel op mijn naam staan, maar zonder jouw steun, geduld en vertrouwen was de weg ernaartoe een stuk minder mooi geweest. Je maakt mijn leven al jarenlang een heel stuk mooier en brengt precies de balans die ik nodig heb. Bedankt dat je me altijd mijn eigen gang laat gaan, ook al kan ik soms behoorlijk eigenwijs zijn. Juist de etentjes, festivals en reizen samen zijn de momenten waarop ik weer beseft wat er echt toe doet in het leven. Ik kijk er enorm naar uit om nu samen te genieten van de tijd die vrijkomt en nog veel meer herinneringen te maken op alle plekken die we nog samen gaan ontdekken.



CURRICULUM VITAE

Roy Meys was born on March 17th, 1990 in Heerlen, the Netherlands. After completing his secondary education (VWO) at Grotius College in Heerlen, he began his Bachelor of Health Sciences at Maastricht University, focusing on Human Movement Sciences and Bioregulation. He subsequently earned a Master's degree in Human Movement Sciences in 2012 at Maastricht University, specializing in the Biology of Human Performance and Health.



Following these academic years, he pursued a professional Bachelor's degree to become a pulmonary function technician (longfunctieanalist). He completed this qualification through remote learning at the Leidse Onderwijs Instellingen (LOI) while simultaneously working and gaining extensive clinical experience in respiratory diagnostics at Zuyderland Medical Center (Heerlen and Sittard) from 2013 to 2018.

In 2019, he started his PhD at Ciro, Horn, in collaboration with the School of Nutrition and Translational Research in Metabolism (NUTRIM) of Maastricht University. His research initially focused on beta-alanine supplementation combined with neuromuscular electrostimulation in patients with COPD. Due to the impact of the COVID-19 pandemic, the scope of his PhD project shifted toward the study of extrapulmonary features in patients with asthma.

Throughout his PhD, he has had the opportunity to supervise students for the LOI pulmonary function technician program, the same program he once completed himself. In this capacity, he is responsible for supervising and assessing Bachelor's theses and has contributed to the development of course materials. In recent years, he has also provided clinical lessons on spirometry for primary care nurse practitioners in the Limburg region (the Netherlands).

Since 2023, Roy has been appointed as the coordinator of the diagnostics ward at Ciro. In this role, he aims to bridge the gap between research and clinical practice to optimize patient assessment in Ciro alongside his colleagues of the diagnostic team.



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