Body composition abnormalities in chronic respiratory disease

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BODY COMPOSITION ABNORMALITIES IN CHRONIC RESPIRATORY DISEASE

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Cover design Rodrigo Macedo Rizzi
Layout Renate Siebes | Proefschrift.nu
Printing ProefschriftMaken | www.proefschriftmaken.nl
ISBN 978-94-6423-943-0

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DISSERTATION

to obtain the degree of Doctor at the Maastricht University,
on the authority of the Rector Magnificus, Prof. dr. Pamela Habibović
in accordance with the decision of the Board of Deans,
to be defended in public
on Tuesday 27 September 2022, at 16:00 hours

by

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Chapter I

General introduction

Chronic respiratory diseases

Chronic respiratory diseases (CRDs) are long-lasting and/or progressive conditions of the airways and other structures of the lung.[1] The main risk factors are preventable and include smoking, second-hand smoke exposure, ambient pollution, allergens, and occupational agents.[1] In addition, associations between a history of severe respiratory infections during childhood and increased risk of chronic respiratory health problems have been shown.[2] Although environmental factors contribute significantly to the onset and progression of CRDs, it has been demonstrated that also genetic components play an important role. Genome-wide association studies have identified reproducible associations between common single nucleotide polymorphisms and the susceptibility of CRDs.[3,4,5] Estimates indicate that 544.9 million individuals (including children, adolescents, adults and elderly people) had a CRD in 2017, which corresponds to a global prevalence of approximately 7.1%.[6] In the last decades, important advances in preventing, identifying and treating CRDs resulted in a drop in their prevalence and mortality rates when estimates were adjusted for population growth and ageing.[6] Nevertheless, CRDs are still a major cause of morbidity, social-economic burden and mortality. Globally, deaths due to CRDs accounted for 7.0% (6·8–7·2%) of total all-cause deaths in 2017, which places CRDs as the third leading cause of death, just behind cardiovascular diseases, and neoplasms.[6] The most prevalent CRDs are chronic obstructive pulmonary disease (COPD), asthma and interstitial lung diseases (ILDs); these diseases accounted for approximately 81.7%, 12.6% and 3.7% of the deaths due to CRDs in 2017.[6]

Chronic obstructive pulmonary disease

COPD is defined as '*a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development*'.[7] COPD is the most prevalent CRD in individuals older than 40 years, overcoming a higher prevalence of asthma among the CRDs in younger individuals.[6] The diagnosis of COPD is considered in individuals over 40 years who present symptoms, recurrent lower respiratory tract infections, a history of risk factors and/or family history of COPD.[7,8] Spirometry is required to confirm the diagnosis of COPD. The presence of a post-bronchodilator forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) < 0.70 confirms the presence of persistent airflow limitation and thus of COPD in this group of individuals at risk.[7,8] A study conducted in a large cohort of patients with COPD showed that the most frequently reported symptoms are dyspnea (72.5%),

sputum production (63.6%), and chronic cough (58.7%).[9] These symptoms vary over the day and the week, and impact on daily activities and physical functioning.[9] Usually, the sequence of events following the occurrence and progression of persistent airflow limitation and dyspnea are a further decrease in physical activity and a deterioration of exercise capacity.[10] In all stages of the disease, individuals are at risk of exacerbations, which are periods of acute worsening of respiratory symptoms requiring additional medications.[7] Data from the multicentre study SPIROMICS demonstrated that among 1,105 patients with COPD followed during 3 years, 538 (49%) had at least one acute exacerbation.[11] Exacerbations contribute to reduced health status and progressive lung function decline,[12] may lead to hospitalizations and account for the greatest proportion of the total COPD burden on the healthcare system.[7]

Asthma

Asthma is '*a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation*'.[13] Asthma is the second most prevalent CRD and the second leading cause of death among CRDs.[6] When asthma is suspected, appropriate lung function testing including pre- and postbronchodilator spirometry should be performed.[14] Once the diagnosis is confirmed, the goal of asthma treatment is to achieve good asthma control, to reduce symptom burden and the risk of exacerbations. The level of treatment required to control symptoms and exacerbations is used to determine asthma severity.[13] In a large cohort of patients with severe asthma, Luskin et al.[15] showed that exacerbation frequency and severity as well as the number of asthma triggers at baseline were strongly associated with asthma-related quality of life. Individuals with asthma and similar demographic, clinical and/or pathophysiological characteristics are usually grouped into "asthma phenotypes".[13] According to the 2021 Global Initiative for Asthma (GINA) report, the most common asthma phenotypes are: allergic asthma, non-allergic asthma, late-onset asthma, asthma with obesity and asthma with persistent airflow limitation.[13] Asthma and COPD may co-exist in some patients since emphysema, hyperinflation, and the loss of lung elastic recoil may also be present in the later stages of severe asthma.[16]

Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis (IPF) is one of the major ILDs. IPF is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown

cause that occurs primarily in older adults, is limited to the lungs, and is defined by the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).[17] In addition to genetic factors,[18] environmental exposures are risk factors and are related with the onset and progression of IPF. These risk factors include smoking, metal, wood, vegetable, and silica dust exposure.[17] Recently, a meta-analysis including 20 case-control studies found that specific viral infections, such as the Epstein-Barr virus, cytomegalovirus, human herpesvirus 7 and 8, are also associated with higher risk of IPF.[19] IPF is characterized by progressive lung fibrosis, worsening of dyspnea and poor prognosis. Zappala et al.[20] showed that a FVC decline of 5 to 10% in 6 months is linked to increased mortality in IPF in comparison with patients with stable disease. In the mentioned study, only 16 (19%) from the 84 initially recruited IPF patients were alive after 5 years of the study inclusion.[20] However, significant progress has been made in the management of these patients, since two agents (nintedanib and pirfenidone) consistently proved to reduce the rate of progression of the fibrotic process.[21] IPF should be considered in adult individuals with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and/or digital clubbing that occur without symptoms that suggest a multisystemic disease.[17] The diagnosis requires a combination of clinical, pathophysiological, immunological and imaging (especially high-resolution computed tomography) features after exclusion of other known causes of ILDs such as domestic and occupational environmental exposures, connective tissue disease, or drug toxicity.[17] The incidence of IPF is more common in men and increases with older age.[17] Based on conservative estimates from Europe and North America presented in a recent systematic review the current incidence of IPF ranges from 3 to 9 per 100,000 per year.[22]

Body composition

Body composition refers to the relative amounts of the various components of the body in relation to total body weight. Three specific tissues are particularly important in body composition research: bone, adipose tissue, and skeletal muscle mass.[23] Assessment of bone density is crucial for diagnosing osteopenia and osteoporosis, which predispose individuals to an increased risk of fractures and associated morbidity.[24] Adipose tissue is the most varying compartment—between individuals, but also within an individual over time.[25] Initially, adipose tissue was described mainly as being an efficient source of energy. However, advances of the past decades showed that adipose tissue is an endocrine organ in view of the production of adipokines and its role in metabolism

regulation.[26] Meanwhile a deeper understanding of the properties of skeletal muscle mass is motivating a shift from the traditional perspective that this tissue is simply important for generating movement via contraction to a view which places skeletal muscle mass as one of the largest organs in the human body, also with an important role in metabolism regulation.[27]

The balance between the amount of adipose tissue and skeletal muscle mass is crucial since they represent energy-storing and energy-consuming components in the body, but also because of their interrelated function in the maintenance of homeostasis and prevention of metabolic and cardiovascular diseases.[27] In addition to disease prevention, appropriate levels of adipose tissue and muscle mass are also fundamental for a good physical and mental condition. This was demonstrated by Villareal et al.[28] who showed that frail elderly presented lower skeletal muscle mass compared to non-frail elderly. In the cited study, both frail elderly and obese elderly presented significantly lower exercise capacity, muscle strength and health-related quality of life (HRQL) compared to sex- and age-matched controls with normal body composition.[28] Maintenance of a normal body composition is associated with health benefits and this fits perfectly with the definition of health from the World Health Organization (WHO), that considers health not merely the absence of disease, but also a state of complete physical and mental well-being.[29] Thus, studying body composition is highly relevant for clinical practice. In particular, topics of major interest include the understanding of how body composition: (1) is influenced by aging, nutrition, exercise, and disease, (2) should be measured, (3) is considered normal or abnormal, and (4) impacts on prognosis and disease-related outcomes.

Why measure body composition in individuals with CRDs?

There are reasonable arguments to include body composition in the routine initial assessment of patients with CRDs. Firstly, smoking is not only the main risk factor for the development of CRDs but has also been associated with abnormalities in the amount of muscle mass and fat distribution. A study including 1,700 community-dwelling older adults identified that male (Odds Ratio (OR): 2.27; 95% CI, 1.23–4.17) and female (OR: 2.01; 95% CI, 1.28–3.17) current smokers were more likely to be at the lowest tertile of muscle mass than their non-smokers peers.[30] Additionally, Clair et al.[31] analysed the baseline data from the CoLaus study, a cross-sectional, population-based study of 6,123 participants to assess the association between the number of cigarettes smoked per day and waist circumference, body fat and body mass index (BMI). Logistic regression models with adjustment for age, education and alcohol

consumption showed that men and women classified as heavy smokers (≥20 cigarettes/day) were 1.94 (95% CI, 1.11-3.27) and 2.15 (95% CI, 1.26-3.64) more likely to present abdominal obesity (defined as waist circumference ≥102 cm for men and ≥88 cm for women) compared with light smokers.[31] Associations between heavy smoking and a higher waist circumference or an excessive amount of body fat were identified even though there were no associations between number of cigarettes smoked per day and BMI.[31] Moreover, smokers are frequently encountered with low levels of physical activity and unhealthy diet, which contribute to changes in body composition.[32]

Additionally, although CRDs affect mainly the lungs and the airways, they are also associated with significant systemic manifestations. One of the most evident clinical features is exercise intolerance. This is a well-recognized feature in adults with COPD,[33] asthma[34] and IPF.[35] Thus, in these patient populations, exercise intolerance is an additional barrier for being physically active, considering the individual's inability to achieve the desired physical activity level - assuming a positive intrinsic motivation. After controlling for sedentary time and socio-demographic covariates, van Dyck et al.[36] found a curvilinear relationship between accelerometer assessed moderate-to-vigorous intensity physical activity (MVPA) and the probability of being overweight/obese in 5,712 adults (18–65 years). This relationship was almost linearly negative when MVPA levels ranged between 0 and 50 min per day and were attenuated at higher levels of MVPA.[36] On the other hand, older adults with higher levels of MVPA had a significantly lower likelihood of presenting low skeletal muscle mass.[37,38]

Methods for assessing body composition

Among the options of techniques to assess body composition there are relatively simple methods, such as bioelectrical impedance analysis (BIA), and more sophisticated direct volumetric measurements based on three-dimensional imaging techniques. These require the use of relatively expensive equipment such as whole-body Magnetic Resonance Imaging (MRI). The following methods have been used to assess body composition in research in individuals with CRDs: BIA, dual-energy X-ray absorptiometry (DXA), ultrasound measurement, stable isotope dilution techniques, computed tomography (CT), and MRI. When testing their population with these techniques and instruments, researchers and clinicians should note that each method will provide different variables which are based on different physical principles, models, and assumptions. Therefore, they can be more (or less) appropriate to assess the amount and distribution of muscle mass or fat mass. The choice of the method may depend on the outcome of interest and on available resources.

The use of BIA is convenient since the equipment is portable and safe and the procedure is simple and non-invasive. BIA uses the electrical properties of the tissues in the body to estimate fat-free mass (FFM) and total body water (TBW).[39] FFM is the sum of all tissues, excluding fat, which includes visceral protein, intracellular water, extracellular water, and bone mineral tissue.[39] Consequently, fat mass can be calculated simply by subtracting FFM from the total body weight. These electrical properties of the body can be measured over a range of frequencies. Therefore, there are single-frequency (which usually operate at 50 kHz) and multi-frequency (uses different frequencies such as 0, 1, 5, 50, 100, 200 to 500 kHz) BIA analysers. Multi-frequency BIA allows the evaluation of intracellular and extracellular water while this stratification is not possible by using single-frequency BIA.[39] Body composition can be determined using BIA provided that hydration status of the subject is normal. Also, the equations used to estimate the variables should be validated against reference methods and applicable to the study population, with regard to gender, age, and ethnic group.[39]

DXA is another commonly used method to assess body composition. It allows the quantification of skeletal muscle mass, fat mass and bone mineral content by using X-rays with two different energies.[25] DXA is mainly used for bone mineral density measurements, where it is considered as the gold standard. However, it can also be used to estimate total and regional body fat and muscle mass.[25] The possibility of determining regional body composition is a major step forward for investigating individual differences in the distribution of fat and muscle mass, which can vary among trunk, upper and lower limbs. Thus, an interesting variable that can be obtained by using DXA is the appendicular skeletal muscle mass (ASM),[40] the non-bone, non-fat component of the limbs that includes muscle, fibrotic and connective tissue, and water. A disadvantage is that the DXA instrument is not yet portable for use in the community and that measurements can also be influenced by the hydration status of the patient.[40]

An alternative to assess local body composition is by using ultrasound measurements. Ultrasound measurement has the advantage over DXA and BIA to give both quantitative and qualitative information on muscle.[41] A systematic review showed that ultrasound is a valid and reliable to estimate muscle mass in older adults with comorbid conditions, including individuals with COPD.[42] A recent review aiming to provide a standardization of ultrasound measurements for assessing muscle mass proposed that five components can be measure: muscle thickness (distance between deep and superficial aponeurosis), pennation angle (angle of insertion of muscle fiber fascicles into the deep aponeurosis), fascicle length (length of the fascicular path),

echo intensity (the brightness of the image acquired through ultrasound) and cross-sectional area (area of cross-section of a muscle perpendicular to its longitudinal axis).[41] In addition, ultrasound measurement showed to be accurate to measure body fat mass in adults with a high level of accuracy in accordance with DXA.[43] Limitations of the method include lack of standardization and validated prediction equations for those with different health conditions and functional status.[41]

Stable isotope dilution techniques allow the evaluation of FFM by assuming that the hydration of FFM is stable (i.e., TBW/FFM=0.73).[44] Deuterated (^{2}H), tritated (^{3}H), or oxygen-labeled (^{18}O) water are examples of tracers that can be used to determine TBW by dilution. The administration of the tracer is made usually at night before bedtime and the equilibration takes place overnight. After this period, a sample of urine, saliva or blood is collected and isotope enrichment is measured, compared to a background sample (collected before the administration of the tracer) and then used to estimate TBW.[44] The main limitation of this method is the error introduced when hydration is affected by diseases and with other states such as growth and aging. Also, the technique is too complex for clinical application. Recently, a new method of estimating muscle mass by using the dilution of a stable isotope-labeled creatine was validated against MRI in adults, postmenopausal women and older adults.[45] Similarly to the previous mentioned dilution techniques, total muscle mass can be calculated from the isotope-labeled creatine enrichment in urine.[45]

MRI and CT are considered to be gold standards for non-invasive assessment of muscle quantity/mass.[40] Both methods have been validated and showed to provide accurate estimates of appendicular FFM and subcutaneous fat compared with cadaver sections, which supports the use of these methods in vivo.[46] However, these tools are not commonly used in primary care because of high equipment costs, lack of portability, and the requirement for highly trained personnel to use the equipment.[47] Full body MRI or CT is even more expensive and only used in specific research settings. Consequently, these techniques are usually used to measure individual muscle groups. A detailed description of non-invasive imaging modalities, including ultrasound, CT and MRI, and acquisition techniques that have been used to evaluate skeletal muscle size and composition in individuals with CRDs is available in a recent systematic review.[48]

In addition, there are anthropometry methods (i.e., BMI, waist circumference, calf circumference and mid-upper arm circumference) that can be used to study nutritional status in older adults. These methods are less expensive and usually require less training.

However, their validity is limited when applied to individuals due to significant prediction errors. As an example, two systematic reviews showed that BMI and waist circumference presented high specificity, but low sensitivity to identify excess body fat according to other methods of body composition.[49,50] Similarly, calf circumference and mid-upper arm circumference showed high specificity, but low sensitivity to detect low muscle mass among older adults as compared to DXA (used as reference method).[51] Thus, anthropometry may be used for screening or as diagnostic proxy for body composition abnormalities in settings where no other methods are available[40,51] rather than for assessing and determining whether body composition is normal.

How should we define abnormal body composition?

The next step following the assessment of body composition is the interpretation of the results according to the variables that can be obtained by the various methods. It is of great interest to identify whether the individual presents low muscle mass. This is a fundamental requirement for confirming the diagnosis of sarcopenia, a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality.[40] Moreover, it is also important to identify if the individual has an abnormal or excessive accumulation of fat that may impair health, which is the definition of overweight and obesity according to the WHO.[52]

Body composition parameters and distribution may vary considerably depending on sex, age and body size.[53-57] Thus, the normal range of expected values should be individualized or take these determinants into account. In order to have a comparative basis to answer the key question concerning the normality of the amount of skeletal muscle and fat mass, reference values or prediction equations are necessary. A list of the currently available reference values for parameters of body composition in adults and older adults is presented in **Supplementary Table S1**. Reference values should be obtained from individuals whose characteristics are similar to those of the patient population. This includes not only anthropometric data, but also demographic, social, racial, and physical activity characteristics. It is necessary to include a sufficiently large sample size to allow a uniform distribution of individuals for sex and age and to avoid potential bias due to selected samples.

In individuals with CRDs, the use of prediction equations and reference values for lung function variables provide a clear and quick measure of how much the values obtained for that individual deviate from the mean of the expected normal range of values.[58] The

same principles can be used when assessing body composition. Consequently, cutoff values based on statistical or clinical criteria can be applied. As an example, the latest recommendations from the European Working Group on Sarcopenia in Older People concerning the definition of low muscle quantity are the use of normative references from healthy young adults with cutoff values usually set at -2 standard deviations (or -2.5 for more conservative diagnosis) compared to the mean reference value.[40] On the other hand, the definition of an optimal cutoff value for diagnosing an excessive accumulation of fat is still controversial and may vary from a body fat percentage >20% to >45% in men and 25% to 43% in women.[50,59] Recently, Woolcott et al.[60] found that men and women with body fat percentages higher than 30% and 40%, respectively, have around 50% higher risk of death compared to men and women with body fat percentage < 25% and 35% after adjustment for age, BMI category, ethnicity, education level, and smoking status. Percentile distributions are useful in determining whether or not an individual falls within the population range. Percentile ranks, such as the 10th and 90th percentiles can be used to define low muscle mass and obesity, assuming that the average in the population is desirable.[61] When defining normal or abnormal body composition, researchers and clinicians should select appropriate reference and cutoff values, consistent with the method used and the population studied. Options for cutoff values include the numerical value of the lower or upper limit of normality, a percentile or a z-score and should be well described to facilitate comparisons among different studies and populations.

Aim and outline of the thesis

This thesis aims to expand the existing knowledge on the frequency and impact of body composition abnormalities in individuals with CRDs, especially COPD, asthma and IPF. Thus, the focus of the thesis is on investigating which pulmonary and extrapulmonary characteristics can be observed in groups of patients after stratification into normal or abnormal body composition according to different methods, variables, and cutoff values. Moreover, specific research questions related to the onset and progression of body composition abnormalities and the differential impact of body composition in subgroups of patients with COPD are investigated.

The **Chapters 2-5** focused on the description of the frequency of low muscle mass and obesity in patients with CRDs. In **Chapter 2**, patients with COPD recruited during the initial evaluation for admission in a physical training program of two study centers in Brazil were classified into four body composition phenotypes: normal

body composition, obese, sarcopenic and sarcopenic obese (SO). This classification was based on values of FFM and fat mass divided by height squared (FFMI and FMI) rather than on BMI cutoff values. The results of this chapter not only provide the first estimates of the frequency of patients with COPD that can be classified into these body composition phenotypes in Brazil, but also demonstrate the poor ability of BMI to reflect body composition abnormalities in patients with COPD. However, there is a positive association between BMI and FFMI. This means that the application of cutoff values developed in samples with lower BMI (fixed cutoff values) may be less sensitive when applied to individuals with higher BMI. For this reason, the frequency of low muscle mass in patients with COPD after application of fixed and BMI-adjusted cutoff values was investigated in **Chapter 3**. In this chapter a specific attention was given to the clinical impact of low muscle mass in overweight and obese COPD patients. A similar approach was applied in **Chapter 4**, in which the frequency of low appendicular skeletal muscle mass index (ASMI) according to BMI-adjusted cutoff values was investigated in patients with asthma referred for pulmonary rehabilitation. Also, in **Chapter 4**, the frequency of asthma patients with sarcopenic obesity 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) was investigated. In **Chapter 5**, two methods of interpretation of BIA by using two different variables - FFMI and phase angle (PhA) - were compared in a sample of patients with IPF referred to a specialised rehabilitation centre in Germany.

The two next chapters explored more specific research questions. To date, there is no convincing evidence to determine whether the higher prevalence of low FFM in patients with COPD results from a different trajectory characterized by an accelerated loss of FFM with aging or if these patients present lower FFM early in their life. In **Chapter 6**, insights related to this topic could be obtained, since longitudinal changes after two years of follow-up in total and regional body composition were investigated in patients with COPD and compared with the changes of smoking and non-smoking controls. Finally, **Chapter 7** was designed based on findings from some of the previous chapters of this thesis, which suggests that the clinical impact of low muscle mass could be lower in overweight and obese patients. In this chapter a large cohort of patients with COPD was used to investigate whether the impact of presenting low FFMI on exercise capacity, physical activity, HRQL and systemic inflammation is similar among patients with COPD stratified into different weight classifications.

The results of all chapters, lessons learned, and future perspectives based on the research studies that compose this thesis are discussed in **Chapter 8**.

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Supplementary Material

Table S1. Studies providing normal reference values for body composition parameters in male and female adults and older adults

First author (Year of publication)	Study location	Sample size (Male/Female)	Age	Sample characteristics	Methodology	Primary variables
Woo et al. (1998) [S1]	China	160 M/ 407 F	20-88 years	Patients with predominantly psychosomatic complaints who were not on regular medication and volunteers.	DXA	FFM, FM
Pichard et al. (2000) [S2]	Switzerland	1,838 M/ 1,555 F	15-64 years	Individuals recruited by offering free BIA on an exhibition stand at trade fairs and fun runs and among public administration staff.	BIA	FFM, FM
Dey et al. (2001) [S3]	Sweden	344 M/ 479 F	70-75 years	Individuals belonging to two birth cohorts representative of the community-dwelling elderly in Sweden.	BIA	FFM, FM, %FM
Kyle et al. (2001) [S4]	Switzerland	2,735 M/ 2,490 F	15-98 years	Individuals recruited by offering free BIA on an exhibition stand at trade fairs and fun runs, among public administration staff and members of leisure clubs for the elderly.	BIA	FFM, FM, %FM
Dittmar et al. (2003) [S5]	Germany	244 M/ 409 F	20-90 years	Individuals recruited by the author through advertisements in local newspapers, flyers, and community centers.	BIA	PhA
Barbosa-Silva et al. (2005) [S6]	United States	832 M/ 1135 F	18-94 years	Healthy adults recruited from hospital staff and the local area.	BIA	PhA
Bosy-Westphal et al. (2006) [S7]	Germany	30,750 M/ 183,982 F	18-102 years	Adult subjects were recruited from commercial weight-management facilities.	BIA	PhA
Coin et al. (2008) [S8]	Italy	431 M/ 1,435 F	20-80 years	Individuals visiting centers for the diagnosis and treatment of osteoporosis in Italy.	DXA	FFM, FM

Table S1. *Continued*

First author (Year of publication)	Study location	Sample size (Male/Female)	Age	Sample characteristics	Methodology	Primary variables
Tengvall et al. (2009) [S9]	Sweden	229 M/ 345 F	75 years	Participants in the Geriatric and Gerontologic Population Study and the Population Study of Women in Goteborg, Sweden.	BIA	FFM
Kim et al. (2011) [S10]	Korea	504 M/ 771 F	18-89 years	Community-dwelling older adults in Korea.	DXA	FFM, FM, %FM
Hong et al. (2011) [S11]	Korea	4,476 M/ 5,980 F	20-85 years	Participants of the KNHANES IV, a nationwide cross-sectional sample representative of the non-institutionalized civilian Korean population.	DXA	ASM, FM
Coin et al. (2012) [S12]	Italy	331 M/ 1240 F	20-80 years	Individuals visiting centers for the diagnosis and treatment of osteoporosis in Italy.	DXA	Limb FFM and FM
Coin et al. (2012) [S13]	Italy	329 M/ 1241 F	20-80 years	Individuals visiting centers for the diagnosis and treatment of osteoporosis in Italy.	DXA	Leg FM, Trunk FM
Lu et al. (2012) [S14]	China	39,855 M/ 21,527	18-92 years	Individuals recruited at the health examination center of Chinese PLA general hospital.	BIA	FFM, FM, %FM
Souza et al. (2013) [S15]	Brazil	500 F	20-84 years	Women selected by convenience among caregivers and relatives of patients seen at the Outpatient Clinics in the Federal University of São Paulo/Escola Paulista de Medicina.	DXA	FFM, ASM, FM
Fan et al. (2014) [S16]	United States	10,858 M/ 9,568	8-85 years	Individuals recruited in the 2008 NHANES – a probability sample representative of the civilian, noninstitutionalized population with oversampling of persons older than 60 yr.	DXA	FFM, FM, %FM, ASM

Table S1 continues on next page.

Table S1. *Continued*

First author (Year of publication)	Study location	Sample size (Male/Female)	Age	Sample characteristics	Methodology	Primary variables
Franssen et al. (2014) [S17]	United Kingdom	85,822 M/ 101,153 F	45-69 years	Individuals recruited from the UK Biobank - a prospective population-based cohort study.	BIA	FFM, FM
Prado et al. (2014) [S18]	United States	6,656 M/ 6,580 F	20-85 years	Individuals from the NHANES reference database from 1999–2004.	DXA	ASM, FM,
Saragat et al. (2014) [S19]	Italy	265 M/ 295 F	65-100 years	Older adults recruited on a voluntary basis in the Veneto region and Sardinia.	BIA	PhA
Seino et al. (2015) [S20]	Japan	2,145 M/ 2,333 F	65-94 years	Individuals recruited for four cohort studies in Japan.	BIA	FFM, FM, ASM
Ibáñez et al. (2015) [S21]	Italy-Spain	213 M/ 297 F	18-30 years	Individuals were recruited from the population of Italy and from a large database of 967 individuals from all the regions of Spain.	BIA	PhA
Clark et al. (2016) [S22]	Mexico	2,829 M/ 6,694 F	7-89 years	Employees and their relatives from three health and academic institutions in Mexico.	DXA	FFM, FM, ASM
Imboden et al. (2017) [S23]	United States	1,251 M/ 2,076 F	20-80 years	Individuals were either self-referred, residents of the surrounding communities, or research subjects or participants in a variety of health-related programs.	DXA	FM, %FM, Limb FM
Hinton et al. (2017) [S24]	United States	8,825 M/ 7,083 F	8-85 years	Individuals from the NHANES reference database from 1999–2004.	DXA	Limbs FFM, limbs FM
Miazgowski et al. (2017) [S25]	Poland	208 M/ 214 F	20-30 years	Participants of a national program evaluating the prevalence of obesity among the young population, university students recruited by local announcements and self-referrals to the Densitometry Unit of the Medical University.	DXA	VAT

Table S1. *Continued*

First author (Year of publication)	Study location	Sample size (Male/Female)	Age	Sample characteristics	Methodology	Primary variables
Xiao et al. (2018) [S26]	United States	3,006 M/ 3,366 F	18-90 years	Individuals from the NHANES reference database from 1988–1994.	BIA	FM/FFM ratio
Bai et al. (2018) [S27]	China	1,595 M/ 1,824 F	18-82 years	Chinese Han adults from Shaanxi Province recruited by a health management center.	BIA	Limbs FFM, limbs FM
Leite et al. (2018) [S28]	Italy	1,384 M/ 2,328 F	18-88 years	Adults and older adults from the Italy recruited between 2002 and 2009.	DXA	FFM
Pasco et al. (2019) [S29]	Australia	1,411 M/ 960 F	20-93 years	Adults and older adults from a population-based cohort study in Australia.	DXA	ASM/BMI
Bastawrous et al. (2019) [S30]	Kenya	950 M/ 1,045 F	50-98 years	Participants from the longitudinal Nakuru Eye Disease Cohort Study.	BIA	FFM, FM
Jin et al. (2019) [S31]	China	3,627 M/ 5,332 F	18-80 years	Individuals recruited in the China National Health Survey, a cross-sectional population-based survey.	BIA	FFM, FM
Spadaccini et al. (2020) [S32]	Italy	226 M/ 569 F	65-100 years	Patients admitted to the post-acute geriatric care unit for functional loss secondary to a nondisabling medical disease.	DXA	VAT
Lee at al. (2020) [S33]	United Kingdom	180,719 M/ 209,846 F	40-69 years	Individuals recruited from the UK Biobank - a prospective population-based cohort study.	BIA	ASM, FM
Ofenheimer et al. (2020) [S34]	Austria	5,147 M/ 5,747 F	18-81 years	Adults and older adults included in the LEAD Study – a random sample from the general population of Austria.	DXA	VAT, ASM, FFM, FM

Table S1 continues on next page.

Table S1. *Continued*

First author (Year of publication)	Study location	Sample size (Male/Female)	Age	Sample characteristics	Methodology	Primary variables
Nguyen et al. (2021) [S35]	Vietnam	1,459 M/ 2,700 F	20-90 years	Participants were recruited via television, internet, flyers in universities and from list of members of organizations.	DXA	FFM, FM, limb FFM, limb FM
Yoon et al. (2021) [S36]	Korea	408 M/ 251 F	20-60 years	Individuals who had undergone abdominal CT examinations as part of an evaluation for liver donation.	CT	SMA, SMI
Zhang et al. (2021) [S37]	China	5.584 M/ 8,206 F	35-74 years	Individuals included in the Ningxia cohort study - a prospective study on rural areas.	BIA	ASM, FM
Lundblad et al. (2021) [S38]	Norway	1,523 M/ 2,152 F	40-84 years	Adults and older adults included in the Tromsø Study – a population based study.	DXA	VAT
Kong et al. (2022) [S39]	China	902 M/ 885 F	20-88 years	Individuals recruited in four cities in northern China who performed an abdominal CT examination.	CT	SMI

The studies were identified in an electronic database (Pubmed) using the following search strategy: ((Body composition[Title/Abstract]) AND (Reference values[Title/Abstract])) NOT (children[Title/Abstract]). From the 237 records identified, 203 were excluded after screening the title and abstract. In addition, 5 studies were identified by hand search resulting in 39 studies. **DXA:** dual-energy X-ray absorptiometry, **FFM:** fat-free mass, **FM:** fat mass, **BIA:** bioelectrical impedance analysis, **%FM:** body fat percentage, **PhA:** phase angle, **ASM:** appendicular skeletal muscle mass, **BMI:** body mass index, **VAT:** visceral adipose tissue, **CT:** computed tomography, **SMA:** skeletal muscle area, **SMI:** skeletal muscle index.

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Chapter 2

Clinical impact of body composition phenotypes in patients with COPD: a retrospective analysis

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European Journal of Clinical Nutrition, 2019 Nov;73(11):1512–19
doi: 10.1038/s41430-019-0390-4.

Abstract

Background/Objectives: Abnormal body composition is an independent determinant of COPD outcomes. To date, it is already known that patient stratification into body composition phenotypes is associated with important outcomes, such as exercise capacity and inflammation, but there are no data comparing physical activity and muscle strength among these phenotypes. Thus, the aim of this study was to compare clinical characteristics and physical function in patients with COPD stratified into body composition phenotypes.

Subjects/Methods: 270 stable COPD patients were classified according to the 10th and 90th percentiles of sex-age-BMI-specific reference values for fat-free and fat mass indexes into four groups: Normal Body Composition (NBC), Obese, Sarcopenic, and Sarcopenic-obese (SO). Patients underwent assessment of exercise capacity, peripheral and respiratory muscle strength, physical activity, dyspnea severity, functional status and symptoms of anxiety and depression.

Results: The prevalence of patients classified as NBC, Obese, Sarcopenic and SO was 39%, 13%, 21%, or 27%, respectively. SO presented lower 6MWT compared with NBC (P<0.05). Sarcopenic and SO groups presented worse muscle strength compared with NBC (P<0.05). Sarcopenic group presented more time in moderate-to-vigorous physical activity compared to all other groups (P<0.05) and less sedentary time when compared with NBC and Obese groups (P<0.05). There were no differences regarding dyspnea severity, functional status and symptoms of anxiety and depression (P>0.16). Sarcopenic and SO groups had, respectively, 7.8 [95% CI: 1.6-37.7] and 9.5 [2.2-41.7] times higher odds to have a 6MWT equal or lower to 350 meters.

Conclusions: Body composition phenotypes are associated with physical function in patients with COPD. Sarcopenic-obese patients were the most impaired.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airway and/or alveolar abnormalities and significant extrapulmonary (systemic) effects.[1] One of these systemic effects of COPD includes an abnormal body composition, which is highly prevalent in these patients, affects prognosis[2] and is an important independent determinant of COPD outcomes,[3] including exercise capacity and inflammation.[4] Body composition abnormalities in this population may include an increase in fat mass (FM), a decrease in fat-free mass (FFM) or even, a shift from FFM toward FM.[2]

Therefore, it is recommended to stratify these patients, in specific body composition phenotypes.[3] Considering the previous described abnormalities of body composition the common existent body composition phenotypes in patients with COPD are characterized by low FFM[5] (sarcopenia), high FM[6] (obesity) or a combination thereof (i.e., Sarcopenic-obesity).[4] A recent study showed that patients with COPD were 3 times more likely to present Sarcopenic-obesity compared to a non-COPD control group.[4] Additionally, Sarcopenic-obesity was independently associated with reduced six-minute walking test (6MWT) and a higher risk of presenting with elevated systemic inflammatory biomarkers.[4]

To date, it remains unknown whether and to what extent peripheral and respiratory muscle strength, physical activity in daily life (PADL), symptoms of anxiety and depression, and functional status are different after patient stratification into body composition phenotypes. Our hypothesis is that there are differences in these outcomes in patients with COPD stratified into body composition phenotypes. This could be supported in part to the already described impact of body composition phenotypes in exercise capacity and inflammation in patients with COPD[4] and due to the already described relationship between body composition and physical function in the general population.[7,8] Thus, the aim of this study was to compare clinical characteristics and physical function in patients with COPD stratified body composition phenotypes.

Methods

Participants and study design

A retrospective study with a cross-sectional analysis was conducted with patients with COPD recruited during the initial evaluation for admission in a physical training program of two already published studies[9,10] and an ongoing study (ClinicalTrials.gov

number, NCT03127878). The data collection occurred at the University Hospital of Londrina, Brazil and at the Pitágoras Unopar University, Londrina, Brazil, from 2006 until 2018. The initial evaluations performed in all studies were similar.

Patients from both centers were assessed for eligibility and according to the assessment of body composition classified into four different groups. The results of the assessments of clinical characteristics and physical function were compared between these groups. The inclusion criteria were diagnosis of COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria;[1] clinical stability defined as the absence of exacerbations within at least one month prior the study; absence of any regular physical training in the preceding year, absence of any important comorbidities (orthopaedic, rheumatological, neurological or cardiovascular) which could interfere in the research protocol. Patients were excluded if they did not complete the assessment of body composition. All studies were approved by the Research Ethics Committee of the two institutions (number 123/09 and 377/10) and all participants signed an informed consent term.

Body composition

Body weight and height were measured on a calibrated scale (Filizola model 21; Filizola, Brazil), to the nearest 0.5 kg and 0.5 cm, respectively. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Body composition was assessed by bioelectrical impedance analysis (BIA) using a single-frequency analyser (Biodynamics 310TM; Biodynamics Corp, USA, in both centers) according to the protocol of Lukaski et al.[11] and manufacturer's recommendations. Participants were instructed to avoid exercising for at least 12 h before the test and refrain from the ingestion of coffee, tea, chocolate or alcoholic beverages. Body composition assessment was performed in a single measurement with patients lying in the supine position during the morning at the same room. In addition, patients fasted for at least 4 h before the test and emptied their bladder immediately before the evaluation.

FFM was calculated from the impedance using a specific formula derived for patients with COPD (Male: 8.383 + 0.465 * height^2/Resistance + 0.213 * weight; Female: 7.610 + 0.474 * height^2/Resistance + 0.184 * weight).[12] FM was calculated by subtracting FFM from body weight. FFM and FM were adjusted for differences in body surface by dividing by height squared, consequently FFM and FM indexes (FFMI and FMI, respectively) were calculated.

The FFMI and FMI values were compared with previously published age-sex-BMI specific reference values obtained from the general population.[13] Values of FFMI lower than the 10th percentile and values of FMI equal or higher than the 90th percentile of the reference values were considered as abnormal.[4] Therefore, patients were classified into four groups: Normal Body Composition (NBC, patients with FFMI≥10th percentile and FMI<90th percentile), Obese (FMI≥90th percentile and FFMI≥10th percentile), Sarcopenic (FFMI<10th percentile and FMI<90th percentile), or Sarcopenic-obese (SO, FFMI<10th percentile and FMI≥90th percentile).

Clinical characteristics

Demographic data (sex and age) and history of self-reported comorbidities (diabetes, hypertension, cardiopathy and others) were collected using a specific questionnaire, developed by the authors. The level of functional limitation due to breathlessness in activities of daily living was assessed using the Medical Research Council (MRC) dyspnea scale.[14] The London Chest Activity of Daily Living (LCADL) scale[15] was used in order to assess functional status. Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).[16]

Physical function

The functional exercise capacity was assessed by the 6-minute walk test (6MWT). It was performed according to international standardization.[17] The predicted 6-minute walking distance (6MWD) was calculated according to reference values proposed by Britto et al.[18] for the Brazilian population. Peripheral muscle strength was assessed using the one-repetition maximum test (1RM), following international standardization,[19] for each of three exercises performed on gymnasium equipment (CRW 1000; Embreex, Brazil): leg extension, arm extension and arm flexion. Respiratory muscle strength was assessed by digital manovacuometer (MVD 300®; Globalmed, Brazil) according to international standardization.[20] Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were determined, and reference values used were proposed by Neder et al.[21] for the Brazilian population.

PADL was assessed during two consecutive weekdays with a validated[22,23] multisensory PA monitor (SenseWear Pro Armband, BodyMedia, Pittsburgh, USA). Patients were instructed to wear the monitor during awake time for 12 hours, starting from the time that the patient wake up.[24,25] A valid assessment day was considered if the patient wore the monitor for at least 10 hours.[26,27] The mean of the variables assessed from both days were used for the analysis. The variables used were: steps per day; average

metabolic equivalents (METs) per day; sedentary time (time spent in activities below 1.5 METs [ST<1.5 METs]),[28] light activities (time spent in activities within 1.5 and 3 METs)[28] moderate-to-vigorous physical activity (time spent in activities above 3 METs [MVPA]).[28]

Statistical analysis

Normality in data distribution was evaluated using the Shapiro-Wilk test. The results were described as mean ± standard deviation or median [interquartile range 25%-75%]. Firstly, the comparisons of continuous variables between patients from the two centers were performed with Student's *t* test for independent samples or Mann-Whitney U test. One-way ANOVA or Kruskal-Wallis test were performed for the comparisons between body composition phenotypes groups. Categorical variables were compared using the Chi-square test. A one-way ANCOVA was performed for comparisons among the body composition phenotypes groups considering adjustments for potential cofounders. All the tests with comparisons between more than two groups were followed by Bonferroni post-hoc test for pairwise comparisons. A binomial logistic regression was performed to ascertain factors associated with the likelihood of patients present a 6MWT equal or lower than 350 meters.[29] The software used was SPSS 22.0 (IBM, Armonk, NY, USA). Significance level was set at $P<0.05$.

Results

In this study a total of 279 participants were enrolled. Of these, 9 patients were excluded because they did not perform the body composition assessment. From the 270 remaining patients, 201 were recruited at the University Hospital of Londrina and 69 at the Pitágoras Unopar University. There were no differences regarding demographic, anthropometric, clinical and physical function data between patients from the two different centres ($P>0.10$ for all).

Demographic and pulmonary function characteristics of the patients are presented in **Table 1**. From the 270 patients considered in the analysis, 106 (39%) were classified as NBC, 34 (13%) were classified as Obese, 56 (21%) were classified as Sarcopenic, and 74 (27%) were classified as SO. There were no differences in the proportion of patients classified as NBC, Obese, Sarcopenic and SO between the two centers ($P>0.42$). Sarcopenic and SO groups presented lower forced expiratory volume in the first second (FEV_1) and higher proportion of patients classified as GOLD III (severe) and

Table 1. Anthropometrics, demographics, lung function and body composition of COPD patients stratified into body composition phenotypes

Variables	NBC (n=106)	Obese (n=34)	Sarcopenic (n=56)	SO (n=74)	*P* value
Sex (Male/Female)	(33/73)	(25/9)*	(35/21)*	(59/15)*	<0.01
Age (years)	67±7	67±8	67±8	68±9	0.81
Height (cm)	157±9	161±8	160±7*	164±8*	<0.01
Weight (Kg)	68±14	83±16*	57±11*†	67±13†#	<0.01
FVC (%predicted)	72±16	70±18	79±19	65±16	0.40
FEV_1 (%predicted)	50±14	47±16	43±16*	42±16*	<0.01
FEV_1/FVC	58±13	59±17	50±12*†	54±14	<0.01
GOLD (I/II/III/IV)	(2/53/46/5)	(0/14/15/5)	(1/19/23/13)*	(1/21/31/21)*	<0.01
Comorbidities/patient	2[1-2]	2[1-3]	1[1-2]†	1[1-2]	0.02
Male					
BMI (kg/m^2)	29.8[26.8-32.4]	29.6[24.7-34.9]	20.6[19.6-26.0]*†	25.0[22.6-28.3]*†	<0.01
FFMI (kg/m^2)	20.9±1.7	20.3±2.4	16.5±1.7*†	16.5±2.2*†	<0.01
FMI (kg/m^2)	7.4±2.6	10.4±3.9*	5.9±2.2†	8.6±2.5#	<0.01
Female					
BMI (kg/m^2)	27.3±4.6	35.7±6.4*	21.8±4.7*†	24.3±4.9.†	<0.01
FFMI (kg/m^2)	17.1±1.8	18.8±2.4*	14.0±1.3*†	13.9±1.7*†	<0.01
FMI (kg/m^2)	10.5[7.7-12.8]	16.3[14.2-20.6]*	6.9[4.8-11.2]*†	12.7[8.6-14.1]#	<0.01

Data expressed as absolute frequency, mean±SD or median [IQR 25-75%]. **NBC:** Normal body composition; **SO:** Sarcopenic-obese; **FVC:** forced vital capacity; **FEV_1:** forced expiratory volume in the first second; **GOLD:** Global Initiative for Chronic Lung Disease; **BMI:** body mass index; **FFMI:** fat-free mass index; **FMI:** fat-mass index;
*P<0.05 compared with NBC.
†P<0.05 compared with Obese.
#P<0.05 compared with Sarcopenic.

Table 2. Clinical characteristics and physical function of COPD patients stratified into body composition phenotypes

Variables	NBC	Obese	Sarcopenic	SO	*P* value
6MWD (m)	465[414-505]	480[365-541]	473[416-524]	472[390-506]	0.81
6MWD (% predicted)	88[81-99]	90[73-98]	85[71-95]	83[72-90]*	<0.01
1RM Quadriceps (Kg)	17[12-21]	19[13-24]	16[13-19]	15[11-21]	0.39
1RMBiceps (Kg)	11[9-14]	12[8-15]	10[8-12]	12[9-14]	0.35
1RM Triceps (Kg)	14±5	14±5	12±4	12±5	0.09
MIP (%predicted)	78±23	74±28	69±27	70±25	0.10
MEP (%predicted)	103[89-135]	118[102-145]	83[66-111]*†	88[75-113]*†	<0.01
Steps/day	4441[2830-6894]	5515[2663-8552]	5520[2839-8742]	3789[2210-5355]	0.05
MVPA > 3 METs (min/day)	22[9-44]	20[7-45]	36[7-89]	16[3-31]#	<0.04
Light Activities (min/day)	211±97	206±113	224±89	214±117	0.91
ST < 1.5 METs (min/day)	465±118	470±144	418±109	482±135	0.15
Average METs/day	1.45[1.25-1.71]	1.35[1.15-1.85]	1.75[1.48-2.0]*†	1.40[1.15-1.65]#	<0.01
MRC	4[2-4]	3[2-4]	4[2-4]	4[2-4]	0.44
HADS Anxiety (pts)	5[3-10]	4[3-9]	5[3-7]	6[3-8]	0.68
HADS Depression (pts)	4[2-8]	4[1-6]	4[1-7]	4[1-8]	0.74
LCADL (pts)	22[16-28]	18[13-24]	22[17-29]	24[15-30]	0.16

Data expressed as mean±SD or median [IQR 25-75%]. **NBC:** Normal body composition; **SO:** Sarcopenic-obese; **6MWD:** six-minute walk distance; **1RM:** one-maximum repetition; **MIP:** maximum inspiratory pressure; **MEP:** maximum expiratory pressure; **MVPA:** time in moderate-to-vigorous physical activity (above 3METs); **ST:** time in sedentary activities (bellow 1.5METs); **METs:** metabolic equivalents of task; **MRC:** Medical Research Council dyspnea scale; **HADS:** Hospital Anxiety and Depression scale; **LCADL:** London Chest Activity Daily Living scale. For 6MWD: (n=259), 1RM: (n=251); MIP and MEP: (n=267); MVPA, light activities, ST, Average METs, Steps: (n=160); MRC: (n=230); HADS: (n=159); LCADL: (n=230).

*P<0.05 compared with NBC.

†P<0.05 compared with Obese.

#P<0.05 compared with Sarcopenic.

GOLD IV (very severe) (P<0.01). The proportion of female patients were higher in NBC group compared with all the other groups (P<0.01). The Obese group presented higher numbers of comorbidities compared with Sarcopenic group. In general, Obese patients presented a higher prevalence of diabetes and hypertension (data not shown).

Table 2 presents the comparisons of clinical characteristics and physical function data among patients with COPD stratified into body composition phenotypes. There were no differences regarding symptoms of anxiety and depression, dyspnea severity and functional status between the groups. Sarcopenic and SO groups presented, in

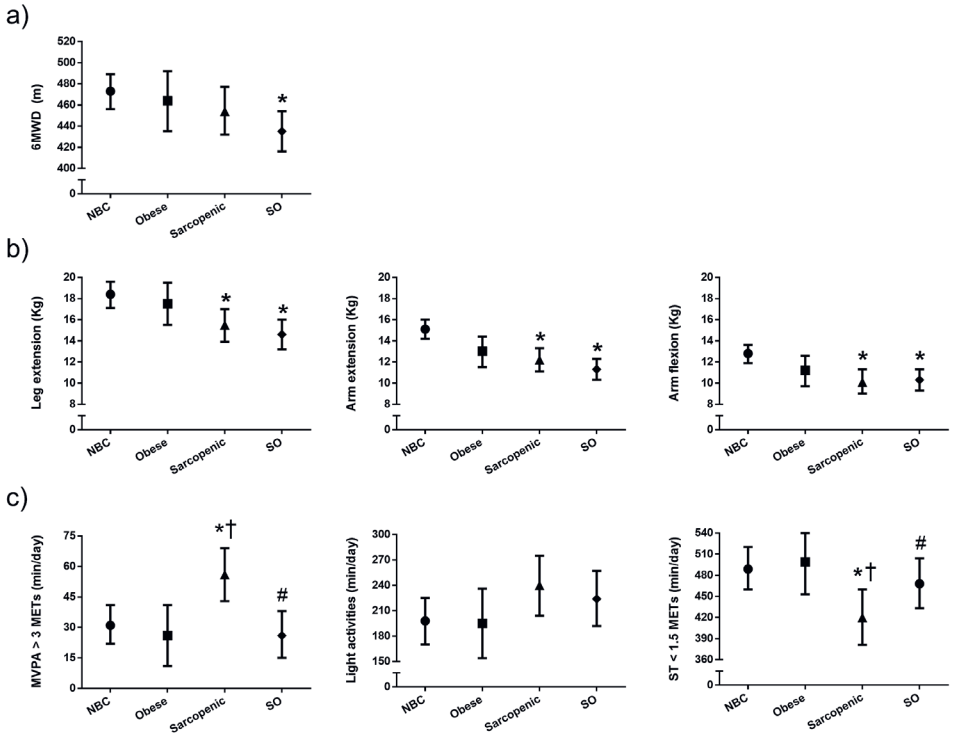

Figure 1. Comparisons of exercise capacity, peripheral muscle strength and PADL between COPD patients stratified into body composition phenotypes.

6MWD: six-minute walk distance; **NBC:** Normal body composition; **SO:** Sarcopenic-obese; **MVPA:** time in moderate-to-vigorous physical activity, **ST:** sedentary activities;

a) Adjusted for: Sex, body mass index and forced expiratory volume in the first second (%predicted). NBC (n=100), Obese: (n=33); Sarcopenic: (n=53); SO: (n=73).

b) Adjusted for: Sex. NBC (n=95), Obese: (n=32); Sarcopenic: (n=52); SO: (n=72).

c) Adjusted for: Sex, forced expiratory volume in the first second (%predicted) and 6MWD (%predicted). For NBC (n=62), Obese: (n=21); Sarcopenic: (n=32); SO: (n=42).

*P<0.05 compared with NBC.

†P<0.05 compared with Obese.

#P<0.05 compared with Sarcopenic.

comparison with NBC and Obese groups, lower 6MWD and MEP in percentage of predicted (P<0.01, for all). In addition, SO group presented lower time in MVPA compared to Sarcopenic (P<0.01). Sarcopenic group presented higher average METs per day compared to all other groups (P<0.01).

Figure 1 presents the one-way ANCOVA for the comparison of absolute values of the 6MWD, peripheral muscle strength and PADL, after adjustments for confounders. Patients with SO still presented significant reductions in 6MWD after adjustments for sex, BMI and lung function. After adjustment for sex the Sarcopenic and SO groups presented lower peripheral muscle strength regarding leg extension, arm extension, and arm flexion compared with NBC. Sarcopenic group presented more time in MVPA compared to all other groups and less sedentary time when compared with NBC and Obese groups, when adjusting for sex, exercise capacity and lung function.

The logistic regression model was statistically significant (P<0.01). From the predictor variables inserted on the model, an increasing BMI and age was associated with increased likelihood, whereas increasing FEV_1 and being male were associated with a reduction in the likelihood of presenting a distance equal or lower than 350 meters at the 6MWT (**Table 3**). Sarcopenic and SO groups had, respectively, 7.8 and 9.5 times higher odds to have a 6MWT equal or lower to 350 meters.

Table 3. Binomial logistic regression to ascertain factors associated with the likelihood of patients present a 6MWT equal or lower than 350 meters in relation to normal body composition

Variables	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
6MWD (≤350m)				
Sex (male)	0.14	0.04	0.44	<0.01
BMI (kg/m²)	1.17	1.05	1.31	<0.01
Age (years)	1.18	1.10	1.28	<0.01
FEV_1 (%predicted)	0.97	0.94	1.00	0.03
Obese	2.80	0.50	15.68	0.24
Sarcopenic	7.85	1.63	37.70	0.01
SO	9.51	2.17	41.66	<0.01

CI: Confidence interval; 6MWD: six-minute walk distance; BMI: body mass index; FEV_1: forced expiratory volume in the first second; SO: sarcopenic-obesity.
The Odds Ratio presented for Obese, Sarcopenic and SO patients are relative to Normal body composition group.

Discussion

The present study compared clinical characteristics and physical function after stratification into body composition phenotypes in patients with COPD. The relative prevalence of patients classified as Obese, Sarcopenic and SO were 13%, 21% or 27%, respectively, and there were a higher proportion of male in these groups. Patients with SO presented significant worse exercise capacity, peripheral and respiratory muscle strength and were less physically active compared with the other groups. On the other hand, Obese patients were the less impaired and presented no differences for any of the outcomes when compared with NBC patients. Patients stratified as Sarcopenic and SO presented a higher disease severity; this finding is in accordance with the study from Joppa et al.[4] Both groups presented lower exercise capacity, peripheral and respiratory muscle strength compared with the other patients; the main differences between these two groups were that Sarcopenic group presented more time in MVPA and less sedentary time per day.

Considering exercise capacity, peripheral and respiratory muscle strength both groups with normal FFMI (NBC and Obese) presented similar results, whereas the groups with abnormally low FFMI (Sarcopenic and SO) presented significant reductions. These findings are in accordance with previous studies that show a close relationship between FFM and exercise capacity,[4,30,31] skeletal muscle weakness,[30,32] and respiratory muscle strength.[33,34] According to our results body compositions are less associated with clinical characteristics, since there were no differences in dyspnea severity, functional status and symptoms of anxiety and depression between the groups, all these outcomes frequently are impaired in patients with COPD[2] and could be considered major characteristics of the disease.

Notwithstanding, that Sarcopenic patients presented a higher average METs, time spent in MVPA and less sedentary time, whereas the number of steps were similar and muscle strength was reduced compared with NBC and Obese groups, suggesting that these last groups of patients perform the same amount of PADL, but in a lower intensity and that being Sarcopenic has a stronger association with muscle strength than the difference in time spent in MVPA between the groups. In addition, Sarcopenic patients also presented FM reduction (lower FMI compared with the other groups [except with NBC in male patients]) (**Table 1**). It is well known that weight loss (i.e., fat and muscle loss) occurs if energy requirements are not fully met.[3] These findings raise the hypothesis that a negative energy balance in these patients could be associated with the development of these abnormalities. Although reduction of energy expenditure or

PADL is not desirable in patients with COPD, their energy balance could be restored by increasing the energy intake.[3]

In contrast, patients stratified as Obese presented no differences in any of the assessments when compared with NBC group. Our hypothesis is that this could be partially explained by a not yet fully understood phenomenon called "obesity paradox" – associated with better survival and functional outcomes but, on the other hand, associated with increased risk of cardiovascular and metabolic disease.[30] The obesity paradox could be related to the direct effect of adipose tissue on lung mechanics[35] or an epiphenomenon of other, yet unknown disease characteristics that confers both a reduced mortality risk and preserved fat mass and/or FFM[3] (e.g. patients in a positive energy balance or reduced protein turnover). In the present study, male Obese patients presented preserved FFM and female Obese patients presented higher FFM compared with NBC. It was not surprising since there is a positive correlation between BMI and FFMI.[36]

In the One-way ANCOVA we adjusted the absolute values of the 6MWD for sex proportion and BMI because these are important determinants of the 6MWD in healthy Brazilians and are factors included in the reference equation for the prediction of the 6MWD.[18] Peripheral muscle strength was adjusted for sex proportion due to difference in absolute values of strength between male and female.[37] PADL were adjusted for sex, lung function and exercise capacity because these factors are associated with physical activity.[38] We inserted a between-center variable as a confounder, but it did not have a statistically significant effect on the dependent variables (P>0.10, for all).

To our knowledge this is the first study with the aim of comparing, peripheral and respiratory muscle strength, PADL, symptoms of anxiety and depression, and functional status in patients with COPD stratified into body composition phenotypes. The findings of the present study confirm the increasing evidence that body composition phenotypes are independently associated with outcomes in patients with COPD. And that in patients with COPD the BMI is limited to identify body composition abnormalities since, according to a widely accepted cut-off point in the classification of obesity (BMI≥30kg/m^2),[8] most of patients from SO group would be classified as normal weight/overweight, whereas most of patients from NBC group would be classified as overweight/obese (**Table 1**).

Some limitations of the present study include: (1) the cross-sectional analysis, that does not allow direct cause-consequence understanding, (2) reference values for FFMI and FMI as well as the formula for estimating FFM used were not developed

specifically for Brazilian population, since they are not yet available, (3) the assessment of PADL was performed in two consecutive weekdays that despite being sufficient for reliable measurement in more severe patients may not be enough for less impaired patients,[38] (4) the lack of some important information, such as, socioeconomic status and weather conditions during PADL assessment. In addition, the use of BIA present limitations related to fluid and electrolyte abnormalities and the choice of an appropriate population, age or pathology-specific BIA equations.[39]

Future studies should investigate the associations of body composition phenotypes and other outcomes such as, mortality and hospital admissions as well as, confirm our results preferably, in a multi-center study including patients from different regions and with a prospective design to better explore cause-consequence understanding. Investigate whether patients stratified in body composition phenotypes have benefits of changing to other groups. Also, investigate whether patients stratified in these phenotypes present different response to the same pulmonary rehabilitation program and develop targeted interventions specifically for the different phenotypes in order to compare it with the effects of traditional pulmonary rehabilitation.

Conclusion

Body composition phenotypes are associated with physical function in patients with COPD. Obese patients present preserved characteristics and were similar to NBC patients. SO patients were the most impaired, considering their reductions in exercise capacity, PADL, peripheral and respiratory muscle strength. Sarcopenic patients present the same impairments in physical function compared with SO, although higher time spent in MVPA and less sedentary time per day. Clinical characteristics were similar across the different body composition phenotypes.

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Chapter 3

Frequency and functional translation of low muscle mass in overweight and obese patients with COPD

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Respiratory Research, 2021 Mar;22(1):93
doi: 10.1186/s12931-021-01689-w.

Abstract

Background: Cut offs for fat-free mass index (FFMI) and appendicular skeletal muscle mass index (ASMI) are available for diagnosing low muscle mass in patients with COPD. This study aimed to investigate: (1) the frequency of low muscle mass (FFMI and ASMI) applying different cut-offs and (2) the functional translation (clinical impact) of low muscle mass, in patients with COPD stratified into BMI categories.

Methods: Patients with COPD were assessed regarding body composition, exercise capacity, quadriceps muscle strength, symptoms of anxiety and depression, dyspnea and quality of life upon referral to pulmonary rehabilitation. The proportion of patients with low muscle mass was compared among BMI categories. Clinical outcomes between patients with normal and low muscle mass within each BMI category were compared.

Results: 469 patients with COPD were included for analyses. The frequency of patients classified as low FFMI varied significantly according to the choice of cut-off (32% to 54%; $P<0.05$), whereas the frequency of patients with low ASMI was 64%. When applying age-gender-BMI-specific cut-offs, 254 patients (54%) were classified as low FFMI. The choice of the cut-off affected the frequency of patients with low muscle mass in all BMI categories. Overweight and obese patients with low muscle mass were more frequently males and presented worse pulmonary function, exercise capacity and muscle strength compared with overweight and obese patients with normal muscle mass.

Conclusions: Approximately half of the overweight and obese patients with COPD have low muscle mass when applying age-gender-BMI-specific cut-offs. Low muscle mass is associated with worse functional outcomes in overweight and obese COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is defined by the presence of chronic respiratory symptoms and airflow limitation.[1] Extra-pulmonary features and comorbidities contribute to the burden of this disease[2] and are recognized as treatable traits in the integrated management of the disease.[3] Low fat-free mass (FFM), as a whole-body marker of muscle mass, is commonly found in COPD[4,5] and strongly associated with muscle weakness,[6,7] exercise intolerance[8] and poor health status.[9] Obesity is another condition frequently coinciding with COPD[10] related to increased respiratory symptoms,[11] reduced health status[12] and low functional performance.[13]

For the measurement of body composition in COPD, one of the most appropriate methods is dual-energy X-ray absorptiometry (DEXA), which allows a combined assessment of FFM, fat-mass and bone mineral density.[14] In addition, DEXA provides an assessment of FFM and fat-mass at regional level and can provide the measurement of appendicular skeletal muscle mass index (ASMI), which is used to define sarcopenia according to fixed cut-offs <7.23 $kg \cdot m^{-2}$ for men and <5.67 $kg \cdot m^{-2}$ for women.[15] However, DEXA is relatively expensive and not widely available. As an alternative, bioelectrical impedance analysis (BIA) is an easy, non-invasive and relatively less expensive method to assess whole-body FFM, widely used in many clinical settings.[16,17] Despite not enabling assessment of ASMI, BIA can provide an estimate of the whole-body FFM that is usually normalized for body size (dividing FFM for height squared) and expressed as FFM index (FFMI). Irrespective of the methodology of assessment, the European Respiratory Society statement on nutritional management of COPD, proposed a cut-off of 17 $kg.m^{-2}$ for males and 15 $kg.m^{-2}$ for females to identify patients with low FFMI.[14] These values correspond to the 10th percentile of most normal to underweight patients with COPD.[14] However, it is important to consider that body composition is positively related to body mass index (BMI) and that FFMI declines with aging.[18,19] Hence, the use of fixed cut-off values may result in underdiagnoses of low FFMI in overweight or obese patients[20,21] and overdiagnoses in underweight patients and those with advanced age. For underweight (BMI lower than 18.5 $kg.m^{-2}$) patients with COPD, the clinical impact of the choice of the cut-off value might be less relevant, since low BMI by itself, provides useful prognostic information;[22] however, this issue is relevant in COPD patients with BMI corresponding to normal weight, overweight and obesity, since BMI is not reliable to determine (ab)normal fat mass and FFM values in these groups.[23,24]

In 2014, Franssen et al.[25] published age-sex-BMI-specific reference values for FFMI based on a sample of 186,975 healthy subjects. The frequency of low FFMI in

overweight and obese patients with COPD diagnosed according to age-sex-BMI-specific cut-offs in comparison with fixed cut-off for FFMI and ASMI is currently unknown, as well as whether and to what extent low FFMI is translated in functional impairment in patients in different BMI categories. We hypothesize that the use of age-sex-BMI-specific cut-offs may improve the diagnosis of body composition abnormalities in patients with higher BMI and discriminate groups of patients with more impairment in physical function and clinical characteristics within the category of high BMI patients. Therefore, the aims of the present study were to investigate: (1) the frequency of low muscle mass (FFMI and ASMI) applying different cut-offs and (2) the functional translation (clinical impact) of low muscle mass, in patients with COPD stratified into BMI categories.

Material and methods

Study population

The current analysis used data from the Chance Study: an observational, prospective, single-center study focused on COPD, health status and comorbidities.[26] The study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre+ (METC 11-3-070) and is registered at http://www.trialregister.nl (NTR 3416). Inclusion criteria were: 1) diagnosis of COPD according to GOLD strategy,[1] 2) referral for a comprehensive pulmonary rehabilitation program at CIRO (Horn, the Netherlands) and 3) no exacerbation at least 4 weeks prior to the study. Patients were excluded if they had a history of other lung diseases, had undergone lung surgery or had malignancy within the last five years and/or presented BMI lower than 18.5 $kg.m^{-2}$. All patients gave written informed consent, and the study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Procedures

In addition to medical history, anthropometric and demographic variables, DEXA (Lunar Expert-XL Bone Densitometer; Lunar Radiation Corporation, Madison, WI, USA) was performed to assess body composition. FFMI was calculated by dividing FFM (lean mass plus bone mineral content (BMC) by $height^2$. ASMI was calculated as the sum of lean mass of the four extremities divided by $height^2$. The following measurements were also performed: symptoms of dyspnoea using the modified Medical Research Council (mMRC) dyspnoea scale; exercise capacity using

a symptom-limited cardiopulmonary incremental cycle test, the six-minute walking test (6MWT) and a constant work rate exercise test (CWRT); quadriceps peak muscle strength using a isokinetic dynamometer (Biodex System 4 Pro, Biodex Medical Systems, Inc., New York, USA); health related quality of life (HRQL) using St. George's Respiratory Questionnaire (SGRQ); and symptoms of anxiety and depression using Hospital Anxiety and Depression Scale (HADS).

Statistical analysis

Patients were classified into BMI categories according to World Health Organization criteria:[27] normal weight (18.5–24.9 $kg{\cdot}m^{-2}$), overweight (25–29.9 $kg{\cdot}m^{-2}$) or obese (≥ 30 $kg{\cdot}m^{-2}$). Afterwards, patients were sub-classified within each BMI category into low or normal FFMI and low or normal ASMI. For FFMI, two cut-offs were applied: the European Respiratory Society statement sex-specific values[14] (17 $kg.m^{-2}$ for males and 15 $kg.m^{-2}$ for females) and the 10th percentiles of the reference values from the UK Biobank general population (age-sex-BMI-specific cut-offs).[25] For ASMI classification, the cut-offs applied (<7.23 $kg{\cdot}m^{-2}$ for men; <5.67 $kg{\cdot}m^{-2}$ for women) were in accordance with the Health Aging and Body Composition (Health ABC) Study.[15]

Continuous variables are presented as mean and standard deviation (SD) or median [interquartile range 25%-75%], according to normality in data distribution. Categorical variables are presented as absolute and relative frequency. A chi-square test of independence was conducted to investigate whether there is association between the choice of different cut-offs and the proportion of patients diagnosed with low FFMI and ASMI. The comparisons of continuous variables between patients with normal or low FFMI and normal or low ASMI within each BMI category were performed with Student's t-test for independent samples or Mann-Whitney U-test, whereas the comparisons of categorical variables were performed with a Chi-square test. Statistics were performed using SPSS (version 24.0, IBM Corporation, Armonk, NY, USA). A priori, the level of significance was set at $P<0.05$.

Results

The Chance study enrolled 518 patients with COPD. Nineteen patients were excluded from the analysis because of missing body composition analysis and 30 patients were excluded due to BMI < 18.5 $kg{\cdot}m^{-2}$. The general characteristics of the included patients are presented in **Table 1**. Patients were on average 64 years and presented severe airflow

Table 1. Characteristics of COPD patients with normal and low FFMI according to age-sex BMI-specific cut-offs, after stratification into BMI categories

BMI group	**Normal weight (n=206)**		**Overweight (n=157)**		**Obese (n=106)**	
FFMI group	**Normal (n=88)**	**Low (n=118)**	**Normal (n=66)**	**Low (n=91)**	**Normal (n=61)**	**Low (n=45)**
Subjects, % males	49.0	52.5	50.0	67.0*	44.3	66.7*
Age, y	64 ± 10	64 ± 8	65 ± 9	65 ± 10	64 ± 8	64 ± 9
BMI, $kg{\cdot}m^{-2}$	22.3 ± 1.8	21.6 ± 1.7†	27.7 ± 1.5	27.0 ± 1.2†	34.4 ± 2.9	31.7 ± 1.8#
FFMI, $kg{\cdot}m^{-2}$	17.2[15.2-18.0]	14.5[13.8-16.3]#	19.0[16.4-19.6]	17.1[15.5-18.2]#	20.4[18.6-21.8]	19.1[16.5-20.1]#
FEV_1, l	1.10[0.83-1.44]	0.92[0.68-1.41]	1.33[0.96-1.90]	1.13[0.77-1.72]	1.32[0.99-1.74]	1.45[1.04-1.92]
FEV_1, %pred	44.5[34-55.6]	37.3[27.4-51.1]†	55.6[41.9-69.4]	41.0[32.0-65.7]*	56.0[41.4-70.3]	53.5[42.6-63.2]
FEV_1/FVC, %	32.6[27.8-41.3]	30.8[25.2-41.2]	40.3[32.0-48.2]	33.0[25.6-44.7]*	44[34.7-53.4]	41.6[33.5-49.2]
TLCO, %pred	45.5[37-57.8]	40.3[32.0-48.5]†	46.6[38.0-63.0]	48.1[40.9-61.1]	57.3[49.5-68.8]	50.8[42.0-60.1]*
mMRC, % grade ≥ 2	70.4	87.3†	81.8	75.8	86.7	82.2
6MWD, m	458 ± 121	410 ± 122†	434 ± 118	414 ± 126	402 ± 108	430 ± 118
6MWD, %pred	70 ±17	62 ± 18#	70 ± 17	67 ±17	70 ± 17	69 ± 16
W_{max}, W	63[49-87]	53[41-68]†	69[54-97]	64[48-83]	66[55-86]	75[54-97]
W_{max}, %pred	52[38-73]	42[31-61]†	55[44-76]	48[37-64]*	59[41-91]	53[43-65]
VO_2max, $ml{\cdot}m^{-1}$	998[805-1234]	811[661-978]#	1108[872- 1349]	1088[900-1291]	1126[892-1368]	1267[974-1542]
VO_2max, %pred	57[47-78]	50[36-73]*	67[51-86]	58[48-77]	81[55-112]	64[54-75]*
CWRT, s	267[184-351]	190[149-269]#	250[173-343]	218[176-302]	243[172-445]	254[171-410]
Quadriceps PT, Nm	87 ± 26	77 ± 29†	105 ± 37	95 ± 32	107 ± 38	108 ± 42
Quadriceps PT, %pred	64 ± 17	55 ± 14#	75 ± 17	65 ± 18†	79 ± 15	72 ± 21*
SGRQ Total score, pts	59[39-75]	63[50-75]	62[49-73]	63[49-73]	68[57-75]	63[52-73]
HADS Anxiety score, pts	7[4-11]	6[4-11]	8[5-13]	6[4-10]	7[5-12]	8[4-12]
HADS Depression score, pts	7[3-11]	6[3-10]	7[4-11]	7[4-10]	8[5-10]	6[4-11]
ASMI, $kg{\cdot}m^{-2}$	6.58 ± 0.80	5.73 ± 0.77*	7.18 ± 1.06	6.67 ± 0.91*	7.98 ± 1.13	7.50 ± 1.10*
Lumbar spine, T-score	-1.29 ± 1.38	-1.09 ± 1.69	-0.74 ± 1.37	-0.99 ± 1.66	-0.68 ± 1.27	-0.87 ± 1.64
Hip, T-score	-1.56 ± 1.00	-1.86 ± 0.95*	-1.69 ±0.90	-1.67 ± 1.00	-1.15 ± 1.06	-1.19 ± 0.91

Mean ± standard deviation, median [interquartile range 25%-75%] or frequency reported. **ASMI:** appendicular skeletal muscle mass index; **BMI:** body mass index; **FFMI:** fat-free mass index; **FEV_1:** forced expiratory volume in the first second; **FVC:** forced vital capacity; **TLCO:** transfer factor for carbon monoxide; **mMRC:** modified Medical Research Council; **6MWD:** six-minute walking distance; **W_{max}:** peak load during cycle ergometry; **VO_{2max}:** peak oxygen uptake during cycle ergometry; **CWRT:** time during constant work rate test; **PT:** peak torque; **SGRQ:** St George's Respiratory Questionnaire; **HADS:** hospital anxiety and depression questionnaire. *: $P<0.05$ versus normal FFMI from the same BMI group. †: $P<0.01$ versus normal FFMI from the same BMI group. #: $P<0.001$ versus normal FFMI from the same BMI group.

limitation, reduced exercise capacity and quadriceps muscle strength and impaired HRQL. More than half of patients were overweight or obese.

Frequency of low FFMI

Figure 1 shows the frequency of low FFMI according to the different cut-offs. The overall frequency of patients classified as low FFMI was lower when applying the fixed cut-off in comparison with the age-sex-BMI-specific cut-off (32% and 54%, respectively; $P<0.05$).

Considering the fixed cut-off, the frequency of low FFMI decreased with an increase in BMI; the frequency of patients with low FFMI in normal weight, overweight and obese categories was 58%, 17% and 1%, respectively. Considering the age-sex-BMI-specific cut-offs, the frequency of patients with low FFMI, in normal weight, overweight and obese groups was 57%, 58% and 42%, respectively. The frequency of low FFMI as identified by the fixed cut-off was comparable to the frequency identified by the age-sex-BMI-specific cut-off for patients with a normal weight BMI, but lower for patients with an overweight or obese BMI ($P<0.05$, for all) (**Figure 1**).

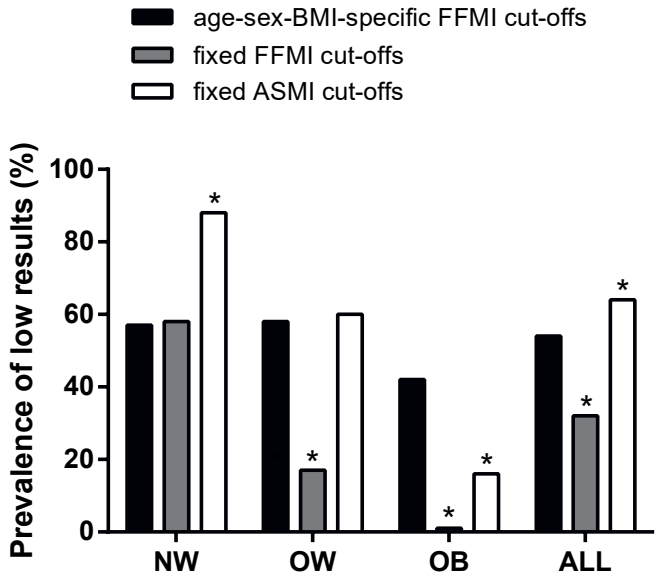

Figure 1. Proportion of patients with low muscle mass, using different cut-offs, after stratification for body mass index. **NW:** normal weight; **OW:** overweight; **OB:** obese; **ALL:** all patients; *Chi-square test $P<0.05$ vs age-sex-BMI-specific cut-offs.

Clinical impact of low FFMI

Table 1 presents the comparisons of outcomes between patients with normal and low FFMI, according to the age-sex-BMI specific cut-offs, after stratification into BMI categories. A higher frequency of males with low FFMI were found in patients with an overweight or obese BMI. In patients with normal weight, those with low FFMI presented lower forced expiratory volume in the first second (FEV_1), transfer factor for carbon monoxide (TL_{CO}), six-minute walking distance (6MWD), peak load during cycle ergometry (W_{max}), peak oxygen consumption during cycle ergometry (VO_{2max}), quadriceps peak torque (PT) and hip bone mineral density (BMD) compared with normal weight patients with normal FFMI. Overweight patients with low FFMI presented lower FEV_1, W_{max} and PT, compared with overweight patients with normal FFMI. Finally, obese patients with low FFMI presented lower TL_{CO}, VO_{2max} and PT compared to patients with normal FFMI from the same BMI category.

Frequency of low ASMI

The overall frequency of patients classified as low ASMI was 62% (**Figure 1**). The frequency of patients with low ASMI in normal weight, overweight and obese groups was 88%, 60% and 16%, respectively. The frequency of low ASMI was significantly higher than the frequency of low FFMI (according to the age-sex-BMI adjusted cut-offs) in normal weight patients, comparable in overweight patients, and lower for patients stratified into the obese category ($P<0.05$, for all) (**Figure 1**).

Clinical impact of low ASMI

Comparisons of outcomes between patients with normal and low ASMI after stratification into BMI categories are presented in **Table 2**. In patients with normal weight, those with low ASMI presented lower FEV_1, TL_{CO}, 6MWD, W_{max}, VO_{2max}, CWRT, quadriceps PT, lumbar BMD, and a higher proportion of this group were males and patients with symptoms of dyspnea (mMRC ≥2) ($P<0.05$, for all). Considering the overweight patients, those with low ASMI presented lower FEV_1, 6MWD, W_{max}, VO_{2max}, quadriceps PT. For the group of obese patients, those with low ASMI presented lower FEV_1, TL_{CO}, 6MWD, W_{max}, VO_{2max}, quadriceps PT, and higher symptoms of dyspnea.

Table 2. Characteristics of COPD patients referred for pulmonary rehabilitation with normal and low ASMI, after stratification into BMI categories

BMI group	**Normal weight (n=205)**		**Overweight (n=156)**		**Obese (n=103)**	
ASMI group	**Normal (n=25)**	**Low (n=180)**	**Normal (n=62)**	**Low (n=94)**	**Normal (n=87)**	**Low (n=16)**
Subjects, % males	28.0	54.4*	53.2	63.8	55.1	56.2
Age, y	62 ± 9	64 ± 9	65 ± 10	66 ± 9	64 ± 9	63 ± 7
BMI, $kg{\cdot}m^{-2}$	21.9 ± 1.9	21.9 ± 1.8	27.8 ± 1.5	27.0 ± 1.2#	33.5 ± 2.9	31.7 ± 2.1#
FFMI, $kg{\cdot}m^{-2}$	16.3[15.3-18.0]	15.3[14.2-17.0]†	18.5[16.5-19.6]	17.1[15.7-18.3]#	20.1[18.4-21.4]	18.0[15.6-19.2]#
FEV_1, l	1.34[0.91-1.84]	0.98[0.74-1.37]†	1.47[0.96-2.01]	1.09[0.77-1.57]†	1.49[1.09-1.83	1.01[0.66-1.60]†
FEV_1, %pred	53.2[43.4-67.1]	37.8[29.1-52.1]#	59.8[41.9-74.4]	42.4[30.9-59.4]#	57.0[44.6-68.8]	41.3[27.3-54.5]†
FEV_1/FVC, %	38.3[32.1-43.3]	31.0[25.4-40.8]#	43.4[32.5-50.7]	32.6[25.5-43.0]†	44.0[36.6-52.7]	33.5[28.1-41.3]†
TLCO, %pred	52.0[41.5-69.7]	42.1[33.4-50.0]†	52.0[40.8-63.1]	47.0[36.7-61.0]	57.1[49.2-68.5]	42.0[34.3-49.0]#
mMRC, % grade ≥ 2	56.0	83.8†	75.8	82.4	82.6	93.7
6MWD, m	523 ± 92	417 ± 123#	471 ± 110	391 ± 122#	426 ± 114	356 ± 97*
6MWD, %pred	81 ± 12	63 ± 18#	76 ± 15	64 ± 17#	71 ± 16	59 ± 15†
W_{max}, W	84[61-98]	55[44-74]#	74[58-100]	64[46-78]†	74[61-95]	54[37-72]*
W_{max}, %pred	69[46-96]	45[32-65]#	58[48-84]	47[37-64]#	58[43-86]	45[36-55]*
VO_2max, $ml{\cdot}m^{-1}$	1244[880-1438]	888[691-1034]#	1156[900-1402]	1060[873-1303]	1230[995-1501]	958[818-1147]*
VO_2max, %pred	75[51-102]	52[37-72]#	67[53-88]	56[46-76]†	67[55-97]	55[46-70]
CWRT, s	285[219-491]	206[154-298]†	255[187-360]	214[175-314]	258[172-461]	230[172-304]
Quadriceps PT, Nm	90 ± 23	81 ± 29	139 ± 35	144 ± 29	113 ± 42	93 ± 29
Quadriceps PT, %pred	72 ± 18	58 ± 15#	76 ± 16	65 ± 17#	79 ± 18	64 ± 13*
SGRQ Total score, pts	55[38-68]	63[49-75]	58[46-70]	65[52-74]	65[52-75]	66[61-79]
HADS Anxiety score, pts	9[3-11]	6[4-11]	6[5-12]	7[5-11]	7[5-11]	11[5-13]*
HADS Depression score, pts	7[4-11]	6[3-10]	7[4-10]	8[4-11]	8[4-10]	6[4-14]
ASMI, $kg{\cdot}m^{-2}$	6.39 ± 0.80	5.55 ± 0.79#	6.93 ± 0.86	6.07 ± 0.87#	7.53 ± 1.00	6.20 ± 0.76
Lumbar spine T-score	-2.04 ± 1.60	-1.05 ± 1.53†	-0.88 ± 1.35	-0.90 ± 1.67	-0.74 ± 1.46	-0.98 ± 1.41
Hip T-score	-1.66 ± 0.99	-1.75 ± 0.98	-1.66 ± 0.89	-1.70 ± 0.98	-1.11 ± 1.03	-1.41 ± 0.80

Mean ± standard deviation, median [interquartile range 25%-75%] or frequency reported. **ASMI:** appendicular skeletal muscle mass index; **BMI:** body mass index; **FFMI:** fat-free mass index; **FEV_1:** forced expiratory volume in the first second; **FVC:** forced vital capacity; **TLCO:** transfer factor for carbon monoxide; **mMRC:** modified Medical Research Council; **6MWD:** six-minute walking distance; **W_{max}:** peak load during cycle ergometry; **VO_{2max}:** peak oxygen uptake during cycle ergometry; **CWRT:** time during constant work rate test; **PT:** peak torque; **SGRQ:** St George's Respiratory Questionnaire; **HADS:** hospital anxiety and depression questionnaire; *: $P<0.05$ versus normal FFMI from the same BMI group. †: $P<0.01$ versus normal FFMI from the same BMI group. #: $P<0.001$ versus normal FFMI from the same BMI group.

Discussion

This study compared the frequency of abnormal body composition diagnosed according to fixed whole-body (FFMI) and regional (ASMI) cut-offs versus age-sex-BMI-specific cut-offs for FFMI in patients with COPD, after stratification into BMI categories. The study has three main findings. First, low FFMI is more commonly diagnosed in overweight and obese patients with COPD using age-sex-BMI-specific cut-offs, in contrast to when fixed cut-offs are applied. Second, the effects of low FFMI are less pronounced in higher categories of BMI, but patients with low FFMI in overweight/obese categories are characterized by worse lung function, muscle strength and exercise tolerance compared to patients with comparable BMI and normal FFMI. Finally, the frequency of males with low FFMI in overweight/obese was higher, despite the use of a sex-specific cut-off, suggesting that sex-dependent FFMI disturbances in these groups of patients.

The first study to apply age-sex-BMI-specific cut-offs for FFMI[23] found that patients with COPD were 3 times more likely to present sarcopenic obesity compared with a control group and that the presence of sarcopenic obesity was associated with worse physical performance and higher systemic inflammation. Despite identifying participants with relative imbalance in fat and FFM across a wide range of BMI,[23] this study did not compare the frequency of low FFMI and ASMI according to different cut-offs or the impact of presenting low FFMI after stratification into BMI categories. Another study found that the frequency of patients with low FFMI according to a fixed cut-off was 34.5%. However, from the total sample with low FFMI, 36%, 53% and 11% were underweight, normal weight and overweight, respectively, whereas no obese patient presented low FFMI.[21] Similarly, a previous study which aimed to identified distinct clusters based on the comorbidity profiles in a cohort of moderate to very severe patients with COPD, found that the frequency of low FFMI was 28%, but the metabolic cluster, characterized by a higher frequency of obesity (61%), presented no patients classified as low FFMI (according to fixed cut-offs values).[20] The study of van de Bool et al.[21] applied the fixed cut-offs for ASMI and found a high frequency of low ASMI across all BMI categories (100%, 97%, 88% and 54% in underweight, normal weight, overweight and obese, respectively). The explanation for the higher frequency of low ASMI in overweight and obese patients in that study compared to the current is unclear as age, sex distribution, disease severity, study center and methodology to assess body composition were comparable.

In addition to further identification of patients with low FFMI, this study also demonstrates the functional translation of low FFMI in patients with higher BMI. We found that the differences in outcomes between overweight/obese patients with normal and low FFMI were less pronounced when compared with the differences observed in normal weight patients, suggesting a lower influence of presenting low FFMI in patients with higher BMI. Our hypothesis is that the direct effects of increased BMI on respiratory mechanics at rest and during exercise could be related with relatively preserved lung function and functional outcomes.[28] In addition, despite FFMI being strongly related with muscle strength, other determinants of strength (e.g., muscle activation, specific force of the muscle fibers)[29] could be enhanced in lower limbs of patients with higher BMI, due to training effect for being constantly submitted to overload during activities of daily living (e.g. walking, climbing stairs). This is supported by findings from the study of van de Bool et al.[21] whose results show that muscle strength increases linearly with an increasing BMI and that patients with low FFMI and abdominally obese (i.e. higher BMI) present higher efficiency of the lower limbs muscles (expressed as the ratio between muscle strength and ASMI).

Exercise and nutrition-based interventions as part of comprehensive pulmonary rehabilitation program should focus not only on treating the deleterious effects of obesity, but also on maintaining or increasing FFM, lower-limb muscle function and exercise tolerance in these patients. In obese patients with COPD, a previous study showed that caloric restriction with maintained protein intake associated with resistance exercise training is effective to promote weight loss, without the loss of muscle mass and with improvement in functional outcomes.[30] These benefits have also been demonstrated in obese older adults, however with additional effects of including aerobic training to calorie restriction and resistance training.[31]

In the present study there were no differences in HRQL between patients with normal and low FFMI according to the age-sex-BMI-specific cut-offs. This finding is in contrast with previous studies which showed that patients with low FFMI present worse HRQL, as assessed by using the SGRQ.[32,33] However, it is not yet clear if the fact of presenting low FFMI is independently associated with reduction of quality of life, since in both studies, other variables, such as dyspnea[32] and exercise capacity[33] were deemed to be mediators of the effect of low FFMI on HRQL. In the present study quality of life was, in general, impaired in patients with COPD, independently of body weight and FFMI categories. Pulmonary rehabilitation is strongly recommended to improve HRQL in patients with COPD and evidence support that patients with low FFMI can improve HRQL to the same extent as patients with normal FFMI.[33]

The present study included patients with COPD referred for pulmonary rehabilitation. Therefore, the observed frequency of low FFMI is probably higher compared to the general COPD population. However, rather than establishing the exact frequency of low FFMI in patients with COPD or compare the agreement of different cut-offs, the focus of this study was on the comparison of applying age-sex-BMI-specific and fixed cut-offs to the same cohort of patients for diagnosing low FFMI and ASMI and to provide a better understanding on the effects of low FFMI in different BMI categories. Moreover, in the present study DEXA was used to calculate FFMI, while normative values for FFMI were based on BIA.[25] BIA may lead to a slight underestimation of FFM when compared with DEXA in patients with COPD.[34] Although the 10th percentile values for FFMI based on BIA may represent an even lower percentile of FFMI based on DEXA, this would result in a slightly underestimation of the proportion of patients with low FFMI and the frequency of low FFMI would be actually higher than presented. In addition, the ERS statement on nutritional management in COPD does not mention or recommend the use of method-specific reference values.[14] Thus, the use of age-sex-BMI-specific reference values has shown potential to improve the diagnosis of body composition abnormalities in patients with higher BMI, mainly in clinical practice, considering that BIA is more commonly available than DEXA.

While this study showed that large proportion of overweight and obese COPD patients suffer from low FFMI and its functional consequences, it is not fully understood whether and to what extent these patients benefit from non-pharmacological treatment. Studying the effects of exercise training in combination with nutritional support in overweight and obese patients with low FFMI is an interesting topic for future investigation. Furthermore, the prognostic value and impact of low FFMI on long-term outcomes in overweight and obese patients should be investigated. Finally, longitudinal changes in body composition in these sub-group of patients with COPD and their impact on outcomes can also be part of future research projects.

Conclusion

This study showed that the application of age-sex-BMI-specific cut-offs resulted in a high proportion of overweight and obese patients with COPD presenting low FFMI and these patients are characterized by worse lung function, muscle strength and exercise tolerance. While it was previously reported that low FFMI is absent in overweight and obese patients with COPD, the present study encourages the application of age-sex-BMI-specific cut-offs in order to identify these patients. The results of the present

study have important consequences for the assessment of overweight and obese patients with COPD.

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Chapter 4

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

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Submitted

Abstract

Background & Aims: 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 muscle mass 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 skeletal muscle mass index (ASMI) 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, FEV1 76±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 ASMI 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 ASMI or with and without SO were compared.

Results: The frequency of patients classified as low ASMI was 19%, whereas 45% of the patients were obese. Among the obese patients, 29% had SO. In patients with normal weight, those with low ASMI were younger and had worse pulmonary function, exercise capacity and quadriceps muscle function than those with normal ASMI (all $P<0.05$). Overweight patients with low ASMI presented poorer pulmonary function and quadriceps muscle function (both strength and total work capacity). In obese class I patients, those with low ASMI 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.

Conclusions: Approximately one in five asthma patients presented low muscle mass when age-sex-BMI-specific ASMI cut-offs were applied. Obesity is common among patients with asthma referred for PR. Among the obese patients a significant proportion presented SO. Low muscle mass 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 muscle mass, 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 muscle mass 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 muscle mass of the whole body and of specific anatomical regions.[16] Muscle mass measured at the limbs, also known as appendicular skeletal muscle mass (ASM), normalized by height squared (ASMI; appendicular skeletal muscle 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 lean mass

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 ASMI 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 ASMI with regard to BMI categories.

To date, the frequency of low ASMI 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 ASMI 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 ASMI 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 ASMI 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: muscle mass (kg) and FM (total body weight minus total lean mass; in kg) of the whole body and of defined anatomical regions. From these measures the following derivative values were calculated: Fat mass index (FMI; fat mass/height^2), and ASMI (ASM/height^2), in which ASM was defined as the sum of the lean mass of the four limbs.[17] 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/m^2; overweight: 25 to <30 kg/m^2; low-risk obese class I: 30 to <35 kg/m^2; moderate-risk obese class II: 35 to <40 kg/m^2; high-risk obese class III: ≥40 kg/m^2). Within each of these categories, patients were sub-classified into low or normal ASMI, 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/m^2 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 Gallangher et al.[22] for FM and by Poggiogalle et al.[23] for ASM 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 (FEV_1) and FEV_1/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 (6MWT; performed twice, after which the best six-minute walk distance (6WMD) was reported),[26] symptom limited incremental cardiopulmonary exercise test (CPET)[27] and constant work-rate cycle test (CWRT)[28] were used to assess exercise performance. Isokinetic quadriceps muscle function (i.e. peak torque and total work) was determined using a Biodex System 4 Pro (Biodex Medical Systems, Inc., New York, USA).[21] 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 ASMI 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 ASMI and low ASMI 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±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 S1**), 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 patients after stratification in BMI groups are presented in **Table 1**.

Frequency of low ASMI and SO

In **Figure 1**, the frequency of low ASMI and SO is presented. The overall proportion of patients classified as low ASMI was 18.9%. The frequency of patients with low ASMI 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 ASMI 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 ASMI. **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 ≥ 30 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%.

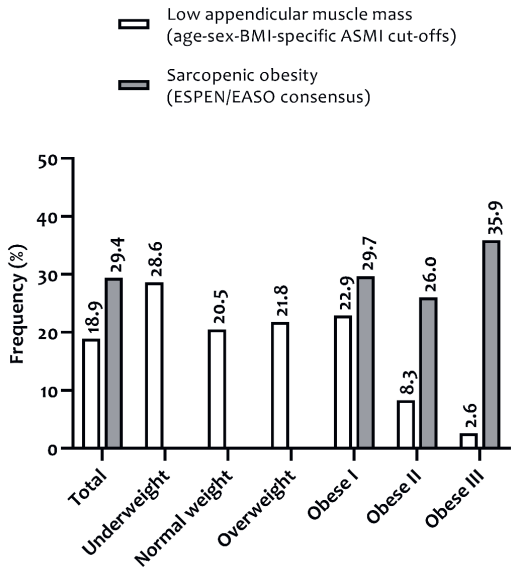

Figure 1. Frequency of low appendicular skeletal muscle mass index (ASMI) and sarcopenic obesity (SO; only in patients with BMI ≥30 kg/m^2), in patients with asthma stratified by BMI category. The total frequency of SO is relative to the total of patients in the obese classes.

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
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
ASMI, 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
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
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
CPET W_{max}, Watts	65 ± 34	94 ± 38	104 ± 48	100 ± 45	91 ± 39	97 ± 39	<0.01
CPET W_{max}, %predicted	52 ± 31	70 ± 27	84 ± 36*	80 ± 35	78 ± 35	83 ± 31	<0.001
CPET VO_2peak, ml/min	1046 ± 362	1247 ± 419	1426 ± 500*	1461 ± 482*	1411 ± 457	1620 ± 482*	<0.001
CPET VO_2peak, % 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. Abbreviations. **ICS:** inhalation corticosteroids; **OCS:** oral corticosteroids; **BMI:** body mass index; **ASMI:** appendicular skeletal muscle mass index; **FMI:** fat mass index; **FEV_1:** 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; **W_{max}:** maximal achieved workload; **VO_{2peak}:** peak oxygen consumption; **CWRT:** constant work-rate cycle test; **$PT_{quadriceps}$:** isokinetic peak torque of the quadriceps muscle; **SGRQ:** St. George's Respiratory Questionnaire.

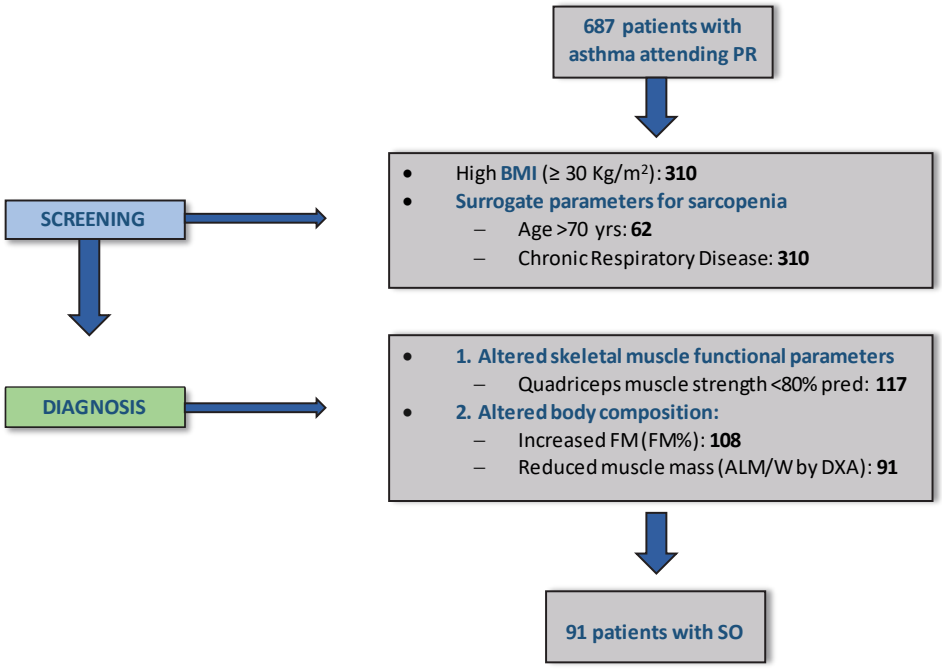

Figure 2. Diagnostic procedure for the assessment of sarcopenic obesity (SO) based on the ESPEN and EASO consensus statement. Abbreviations: **ALM/W:** appendicular lean mass adjusted to body weight; **BMI:** body mass index; **DXA:** dual x-ray absorptiometry; **FM:** fat mass; **SO:** sarcopenic obesity.

Functional consequences of low ASMI and SO

In **Table 2** comparisons of outcomes are presented between patients with normal and low ASMI after stratification into three BMI categories (normal weight, overweight, obese class I). A higher proportion of males with low ASMI was found in patients with normal weight (58% vs 38%, $P<0.05$), whereas a lower proportion of males with low ASMI was found in obese class I patients (25% vs 46%, $P<0.05$). In normal weight patients, those with low ASMI were younger and presented a lower FEV_1 and FEV_1/FVC ratio (all $P<0.05$). FEV_1 and FEV_1/FVC ratio were also lower in overweight patients presenting with low ASMI as compared to overweight patients with normal ASMI (both $P<0.05$). The proportion of patients who experienced 2 or more exacerbations or hospitalizations in the last 12 months did not statistically differ between patients with low ASMI and patients with normal ASMI, across all BMI groups (all $P>0.05$; **Table 2**). The proportion of patients with ≥10 pack years was significantly higher in overweight patients with low ASMI values as compared to overweight patients with normal ASMI values ($P<0.05$; **Table 2**).

Table 2. Characteristics of asthma patients with normal and low ASMI 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 ASMI (n=128)	Low ASMI (n=33)	Normal ASMI (n=158)	Low ASMI (n=44)	Normal ASMI (n=135)	Low ASMI (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
ASMI, 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*
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*
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 ± 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
CPET W_{max}, Watts	98 ± 38	77 ± 33*	108 ± 50	93 ± 40	103 ± 46	90 ± 40
CPET W_{max} %predicted	74 ± 28	56 ± 21*	86 ± 38	75 ± 26	79 ± 35	80 ± 36
CPET VO_{2peak}, ml/min	1305 ± 423	1021 ± 321*	1458 ± 511	1296 ± 440	1512 ± 500	1292 ± 377*
CPET VO_{2peak}, % 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]
$PT_{quadriceps}$, Nm	97 ± 33	80 ± 21*	105 ± 38	88 ± 33*	121 ± 42	95 ± 33*
$PT_{quadriceps}$, % 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 ASMI from the same BMI group. **ASMI:** appendicular skeletal muscle mass index; **ICS:** inhalation corticosteroids; **OCS:** oral corticosteroids; **BMI:** body mass index; **FMI:** fat mass index; **FEV_1:** 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; **W_{max}:** maximal achieved workload; **VO_{2peak}:** peak oxygen consumption; **CWRT:** constant work-rate cycle test; **$PT_{quadriceps}$:** isokinetic peak torque of the quadriceps muscle; **SGRQ:** St. George's Respiratory Questionnaire.

In patients with normal weight, those with low ASMI 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 ASMI (P<0.05, for all). Overweight patients with low ASMI demonstrated lower quadriceps peak torque and total work as compared to overweight patients with normal ASMI. Considering the obese class I patients, those with low ASMI showed lower quadriceps peak torque values and lower VO_{2peak} (in milliliters per minute). Quality of life, as reflected by SGRQ total score, and the proportion of patients with osteopenia, osteoporosis and symptoms of dyspnea did not statistically differ between patients with low ASMI and patients with normal ASMI, across all BMI groups (all P>0.05).

In the comparisons of functional outcomes among the six groups (i.e., three BMI groups stratified into normal or low ASMI), whilst controlling for age and sex, it was shown that patients with low ASMI independent of their BMI categories and patients with obesity independent of their ASMI classification presented a significantly lower 6MWD compared with patients with normal weight and normal ASMI (all P<0.05; **Figure 3**). While normal weight and overweight patients with low ASMI showed reduced maximal load during the CPET compared to their respective BMI groups with normal ASMI, obese class I patients with normal or low ASMI showed similar maximal load during the CPET. Additionally, quadriceps peak torque was lower in patients with low ASMI compared to patients with normal ASMI across all BMI groups, whereas obese class I patients with normal ASMI showed higher quadriceps peak torque than normal weight patients with normal ASMI. Finally, obese class I patients with normal ASMI presented higher SGRQ total scores than normal weight patients with normal ASMI. Notably, within the obese class I group, patients with low ASMI presented lower SGRQ total scores, indicating less impaired quality of life (**Figure 3**).

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 ASMI 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**).

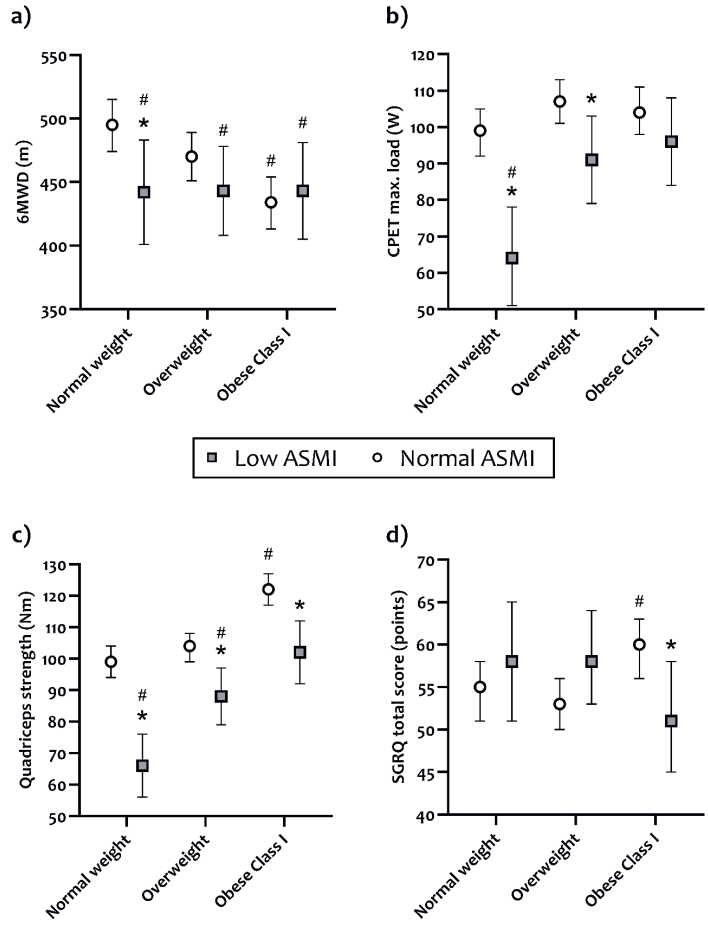

Figure 3. Age-sex adjusted means (and 95% Confidence Intervals) for a) 6-minute walk distance, b) maximal workload in CPET, c) peak quadriceps strength and d) quality of life (SGRQ total score) across BMI groups, displaying normal ASMI (in white) vs low ASMI (in grey). Analysis of covariance (ANCOVA)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

Discussion

This study showed that 18.9% of adult patients with asthma referred for PR have low muscle mass (according to age-sex-BMI-specific ASMI 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

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
ASMI, kg/m^2	9.5 ± 1.1	8.7 ± 0.8*	7.9 ± 1.0	7.4 ± 1.0*
FMI, kg/m^2	13.3 ± 3.6	13.2 ± 2.9	16.6 ± 3.2	18.1 ± 3.4*
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 W_{max}, Watts	119 ± 51	100 ± 31*	93 ± 39	76 ± 27*
CPET W_{max} %predicted	65 ± 28	58 ± 16	91 ± 37	82 ± 30
CPET VO_{2peak}, ml/min	1825 ± 577	1525 ± 397*	1363 ± 387	1227 ± 258*
CPET VO_{2peak}, % predicted	73 ± 21	65 ± 15	106 ± 40	105 ± 31
CWRT time, s	360 (226-566)	335 (227-422)	305 (235-462)	250 (190-348)*
$PT_{quadriceps}$, 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. **ASMI:** appendicular skeletal muscle mass index; **ICS:** inhalation corticosteroids; **OCS:** oral corticosteroids; **BMI:** body mass index; **FMI:** fat mass index; **FEV_1:** 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; **W_{max}:** maximal achieved workload; **VO_{2peak}:** peak oxygen consumption; **CWRT:** constant work-rate cycle test; **$PT_{quadriceps}$:** isokinetic peak torque of the quadriceps muscle; **SGRQ:** St. George's Respiratory Questionnaire.

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 muscle mass 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 ASMI in comparison with the differences observed in normal weight patients, indicating a lower impact of presenting low ASMI 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 amount of patients presenting with resting pulmonary hyperinflation (RV/TLC ratio ≥0.40) was highest in the normal weight patients with low ASMI (**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 ASMI shows similar quadriceps muscle strength, maximal load during the CPET (**Figure 3**) and ASMI (**Table 2**) compared to normal weight subjects with normal ASMI.

The present study aimed to assess different outcomes which could potentially interact with decreased muscle mass, 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 ASMI vs normal ASMI, irrespective of their BMI group. This is in line with a systematic review by Berthon et al.[37] (2014) 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 muscle mass 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 ASMI 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 ASMI) 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 muscle 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 muscle mass and SO in asthma patients referred for PR. Even though differences in functional outcomes between overweight and obese patients with normal and low muscle mass 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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Supplementary Material

Table S1. Overview of the medication use

Type of medication (with specified combinations)	Number of patients (% of total sample)
Monotherapy	14 (2.1)
SABA	7 (1.0)
SAMA	2 (0.3)
LABA	0 (0.0)
LAMA	1 (0.1)
ICS	4 (0.6)
Bronchodilator combinations*	31 (4.6)
SABA/SAMA	12 (1.8)
LABA/SABA	1 (0.1)
LAMA/SABA	1 (0.1)
LABA/LAMA	5 (0.7)
LABA/SAMA	2 (0.3)
LABA/SAMA/SABA	2 (0.3)
LAMA/SABA/SAMA	3 (0.4)
LABA/LAMA/SABA	3 (0.4)
LABA/LAMA/SABA/SAMA	2 (0.3)
ICS containing combinations*	569 (84.5)
ICS/SABA	8 (1.2)
ICS/SAMA	5 (0.7)
ICS/LABA	75 (11.1)
ICS/LAMA	5 (0.7)
ICS/SABA/SAMA	13 (1.9)
ICS/LABA/SABA	69 (10.3)
ICS/LAMA/SABA	6 (0.9)
ICS/LABA/SAMA	24 (3.6)
ICS/LAMA/SAMA	1 (0.1)
ICS/LABA/LAMA	73 (10.8)
ICS/LABA/SABA/SAMA	77 (11.4)
ICS/LAMA/SABA/SAMA	5 (0.7)
ICS/LABA/LAMA/SABA	112 (16.6)
ICS/LABA/LAMA/SAMA	7 (1.0)
ICS/LABA/LAMA/SABA/SAMA	89 (13.2)
Maintenance OCS	149 (22.1)
Missing	59 (8.8)

Values are presented as frequencies (percentages). **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.

Chapter 5

Relationship between body composition, exercise capacity and health related quality of life in Idiopathic Pulmonary Fibrosis

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BMJ Open Respiratory Research, 2021 Oct;8(1):e001039
doi: 10.1136/bmjresp-2021-001039.

Abstract

Introduction: Bioelectrical impedance analysis (BIA) can be used to estimate fat-free mass index (FFMI). However, the use of directly-measured BIA variables, such as phase angle (PhA), has gained attention. The frequency of low FFMI and PhA and its associations with exercise capacity and health-related quality of life (HRQL) in patients with idiopathic pulmonary fibrosis (IPF) have been scarcely studied.

Objectives: To investigate the frequency of low FFMI and PhA and their associations with exercise capacity and HRQL in patients with IPF.

Methods: Patients underwent assessment of lung function, body composition, exercise capacity by the six-minute walk distance (6MWD), and HRQL by the Medical Outcomes Study Short-Form 36-item Questionnaire (SF-36). Patients were classified as presenting normal or low PhA or FFMI, accordingly to the 10^{th} percentiles of age-sex-BMI-specific reference values.

Results: 98 patients (84 males, age: 68±8 years, FVC: 64±18%predicted) were included. 24 patients presented low PhA. They were characterized by worse lung function, exercise capacity and HRQL compared with patients with normal PhA. 10 patients presented low FFMI, but despite differences in body composition, no differences were found between these patients and patients with normal FFMI. In a single regression analysis, age, lung function and body composition variables (except FFMI) were related to 6MWD and SF-36 Physical Summary Score (R^2=0.06-0.36, P<0.05). None of the variables were related to SF-36 Mental Summary Score.

Conclusion: One fourth of the patients with IPF with normal to obese body mass index (BMI) present abnormally low PhA. Patients classified as low PhA presented worse lung function, exercise capacity and HRQL.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause characterized by progressive worsening of dyspnea and lung function.[1] It is a rare disease with an unpredictable clinical course and high mortality. In Europe the annual incidence ranges from 0.22 to 7.4 and the prevalence from 1.25 to 23.4 cases per 100,000 population.[2] Patients with IPF suffer from exercise intolerance, physical inactivity, and impaired health-related quality of life (HRQL).[3-6] Schwebel et al. found nearly 50% of patients with severe IPF with normal body weight had nutritional depletion.[7] A prospective cohort with patients with interstitial lung disease (ILD), including 40 patients with IPF, found a significantly lower muscle mass and higher fat mass in subjects with more impaired lung function.[8] In addition, low erector spine cross-sectional area and low fat-free mass index (FFMI) are related to increased mortality in this population, independent of BMI.[9-11] FFMI is frequently assessed by using bioelectrical impedance analysis (BIA). The estimation of FFMI by this method provides reliable information in subjects without significant fluid and electrolyte abnormalities when using appropriate population, age or pathology-specific BIA equations and established procedures.[12] However, this commonly used method of estimating FFMI using BIA equations has been suggested to present disadvantages.[12] On the other hand, the use of directly measured BIA variables, such as phase angle (PhA), have gained attention since they are not affected by some of these disadvantages, such as equation inherent errors and the necessary assumptions for BIA classification of body compartments (consequently for the estimation of FFMI).[13]

PhA is a measure of the relationship between reactance and resistance, two different electrical properties of tissues, obtained from BIA, that are affected in various ways by disease, nutrition and hydration status.[12] PhA has been suggested to be an indicator of cellular health where higher values reflect higher cellularity, cell membrane integrity and better cell function.[13] This variable has shown to be an independent predictor of muscle strength, more strongly associated to handgrip strength and respiratory muscle strength than BIA-based estimates of FFMI or anthropometric parameters in patients with chronic obstructive pulmonary disease (COPD).[14] In addition, PhA is independently associated with measures of physical function, disease severity and early all-cause mortality in this population.[15,16]

Recently, Rinaldi et al.[17] showed that in fibrotic ILD, low FFMI controlled for age and sex is significantly associated with exercise capacity independent of lung function. This same research group also investigated whether PhA is an appropriate surrogate marker

of nutrition status as assessed using the subjective global assessment,[11] however, a comparison of the frequency of patients with abnormal low FFMI and PhA, and which of these variables are strongly associated with exercise capacity and HRQL was not investigated. Based on previous findings in other populations, such as COPD[14-16] and elderly patients with cancer,[18] it seems reasonable to hypothesize that PhA is related to these outcomes and can offer information beyond BMI and FFMI in patients with IPF. Thus, the aim of the present study was to investigate the frequency of abnormal low PhA and FFMI and their associations with exercise capacity and HRQL in patients with IPF. Preliminary results of this study have been previously reported in the form of abstract in the European Respiratory Society congress 2020.[19]

Materials and methods

Participants and study design

This study assessed for eligibility, all patients with IPF referred to the specialized rehabilitation center (Schoen Klinik Berchtesgadener Land, Schoenau, Germany) from March 2012 - November 2017. The diagnosis of IPF has been previously confirmed according to the criteria of current guidelines.[1] No patient presented clinical conditions that potentially influence fluid balance (e.g., renal failure, cirrhosis, myocardial disease). All patients have signed an informed consent term at time of admission to authorize the use of data from all measures throughout the time of stay for further research. As all data included in this study were already collected an ethic approval was waived. During a pre-rehabilitation assessment demographic data (sex and age), lung function and smoking history, body composition, exercise capacity and HRQL were collected.

Assessments

Lung function was evaluated by body plethysmography (MasterScreen Body; Jaeger, Germany). The test procedures were performed according to ATS/ERS standardization.[20] Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), total lung capacity (TLC), residual volume (RV) and diffusion capacity for carbon monoxide (DLCO) were determined. Arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$) from the hyperemic earlobe and C-reactive protein [CRP]) were also assessed.

Body weight was measured using a calibrated electronic scale to the nearest 0.1 kg and height was measured in an anthropometer to the nearest 0.5 cm. For both measures,

patients were barefoot and in underwear. Body mass index (BMI) was calculated as the ratio between weight and height squared (kg/m^2). Body composition was assessed by BIA using a multi-frequency impedance analyser (Nutriguard-MS; Data Input, Germany). Assessments were performed between 7:00 and 7:45 AM, after an overnight fast and after a time of 10 minutes in the supine position. The procedure was performed according to manufacturer's instructions. Fat-free mass was adjusted for differences in body surface by dividing by squared height, and FFMI was calculated.

FFMI values were compared with previously published age-sex-BMI specific reference values obtained from the general population.[21] PhA was also assessed and compared with previously published age-sex-BMI specific reference values obtained from a German population.[22] Values of FFMI or PhA lower than the 10th percentile of the reference values were considered low. Other variables such as fat mass index (FMI), body cell mass, extracellular mass, body water, intracellular and extracellular water were also assessed.

The six-minute walk test (6MWT) was used to assess exercise capacity and was performed according to the current international guidelines in a 30-meter corridor.[23] The predicted values for the six-minute walk distance (6MWD) were calculated according to the reference values of Troosters et al.[24]

HRQL was assessed using a validated German version of the Medical Outcomes Study Short-Form 36-item Questionnaire (SF-36). The questionnaire consisted of 36 questions covering 8 health concepts: physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These 8 health components were combined in two summary dimensions: the Physical Summary and the Mental Summary Scores. The score ranges from 0 to 100, with higher scores indicating better HRQL.[25]

Statistical analysis

Data are reported as mean ± standard deviation or median [interquartile range 25%-75%]. Variables were examined for normality with histograms and qq-plots. For continuous variables, comparisons between patients with normal and low PhA and normal and low FFMI were performed with Student's t test for independent samples or Mann-Whitney U test, according to normality in data distribution. For categorical variables, between-group comparisons were performed with the Chi-square test. The analysis of covariance (ANCOVA) was used to compare 6MWD between patients with normal and low PhA and FFMI, while adjusting for gender and age. Simple linear

regression analysis was used to assess the relationship between the variables of body composition and lung function with the variables of exercise capacity and HRQL. Multiple linear regression analyses were performed to compare 6MWD between patients with normal and low PhA and FFMI, while adjusting for gender, age and lung function. The Chi-square test was used to compare the proportion of patients with normal and low PhA who present increased risk of mortality, by presenting 6MWD lower than 250 meters.[26] The software used for performing the statistical analyses was SPSS 25.0 (IBM, Armonk, NY, USA). The significance level was set at $P<0.05$.

Patient and public involvement

There is no patient or public involvement (PPI) to report in the design, conduction, or dissemination of this retrospective observational study.

Results

Table 1 displays the main characteristics of the 98 patients with IPF analyzed in the study. Overall, 86% of the patients were male, 56% were on long term oxygen therapy (LTOT), and 22% were never smokers. As a group, patients demonstrated moderate restrictive lung function impairment with severe diffusion abnormality. In addition, patients presented moderate exercise intolerance and impaired HRQL. Finally, accordingly with BMI, most patients were classified as overweight or normal weight (41 and 37%, respectively) whereas 20% of the patients were classified as obese and 2% as underweight. The frequency of patients with low FFMI was 9%, whereas 26% of the patients presented low PhA.

Table 2 displays the comparisons between patients with normal and low FFMI or PhA. Patients with low FFMI presented lower, BMI, FFMI, body cell mass, body water and PhA compared with patients with normal FFMI. On the other hand, patients with low PhA presented lower FVC, FEV_1, PaO_2, 6MWD and SF-36 Physical Summary score, but higher amount of extracellular mass, CRP levels and pack years compared to patients with normal PhA. In addition, the proportion of patients on LTOT where higher in patients with low PhA compared to patients with normal PhA. After controlling for gender and age, the mean difference in 6MWD between patients with normal and low PhA was -106m (95% CI, -154 to -58m; $P\leq0.001$) (**Figure 1**).

In a single regression analysis (**Table 3**), age, body cell mass, PhA, FVC, FEV_1, TLC, and DLCO, but not FFMI, were significantly related to 6MWD, whereas the same

variables, except age and body cell mass were significantly related with SF-36 Physical Summary Score (P<0.05, for all). None of the variables were significantly related with SF-36 Mental Summary Score.

Table 1. Characteristics of the sample

Variables	(n=98)
Sex (male), n (%)	84 (85.7)
Age (years)	68±8
BMI (kg/m^2)	26.6±4.3
Underweight, n (%)	2 (2.0)
Normal weight, n (%)	36 (36.7)
Overweight, n (%)	40 (40.8)
Obese, n (%)	20 (20.4)
FFMI (kg/m^2)	19.8±2.6
FMI (kg/m^2)	6.7±2.7
Low FFMI, n (%)	9 (9.2)
Body cell mass (kg)	29±6
Extracellular mass (kg)	32±6
Body water (L)	44±8
Intracellular water (L)	26±3
Extracellular water (L)	19±4
Phase Angle (°)	5.2±0.9
Low Phase Angle, n (%)	25 (25.5)
Never Smoker, n (%)	22 (22.4)
Pack years	20[10-40]
FVC (%predicted)	64±18
FEV_1 (%predicted)	72±19
TLC (%predicted)	71±14
RV (%predicted)	86±21
DLCO (%predicted)*	31±15
PaO_2 (mmHg)	67±12
$PaCO_2$ (mmHg)	37±4
LTOT, n (%)	55 (56.1)
CRP (mg/dl)	6[3-13]
6MWD (m)	383±114
6MWD (%predicted)	68±20
SF-36 Physical Summary Score	37±10
SF-36 Mental Summary Score	43±14

Data expressed as frequency, mean±SD or median [IQR 25-75%]; *n=78; **BMI:** body mass index; **FFMI:** fat-free mass index; **FMI:** fat mass index; **FVC:** forced vital capacity; **FEV_1:** forced expiratory volume in the first second; **TLC:** total lung capacity; **RV:** residual volume; **DLCO:** diffusion capacity for carbon monoxide; **PaO_2:** arterial oxygen tension; **$PaCO_2$:** arterial carbon dioxide tension; **LTOT:** long term oxygen therapy; **CRP:** plasma C-reactive protein; **6MWD:** six-minute walk distance; **SF-36:** Short-Form 36-item Questionnaire.

Table 2. Comparisons between patients with normal and low phase angle (PhA) or Fat- Free Mass Index (FFMI)

	PhA			FFMI		
Variables	**Normal (n=73)**	**Low (n=25)**	***P*-value**	**Normal (n=89)**	**Low (n=9)**	***P*-value**
Sex (male), n (%)	62 (85)	22 (88)	0.70	76 (85)	8 (89)	0.77
Age (years)	69±4	66±10	0.28	68±8	71±5	0.21
BMI (kg/m²)	26.3±4.3	27.4±4.3	0.31	27.0±4.1	23.3±5.0	0.01
FFMI (kg/m²)	19.8±2.7	19.9±2.5	0.87	20.1±2.5	16.7±2.2	<0.01
FMI (kg/m²)	6.5±2.5	7.4±3.0	0.14	6.8±2.6	5.7±3.1	0.23
Body cell mass (kg)	29±7	27±6	0.10	29±6	23±6	<0.01
Extracellular mass (kg)	30±5	36±6	<0.01	32±6	29±7	0.14
Body water (L)	44±8	46±8	0.27	45±8	38±8	0.01
Intracellular water (L)	26±4	26±3	0.67	26±3	23±10	0.02
Extracellular water (L)	18±4	20±4	0.11	19±4	15±5	0.01
Phase Angle (°)	5.5±0.7	4.4±0.7	<0.01	5.3±0.8	4.7±1.0	0.05
Pack years	13[8-34]	40[15-50]	0.02	20[9-40]	30[10-50]	0.25
FVC (%predicted)	67±19	55±13	<0.01	65±19	58±12	0.25
FEV_1 (%predicted)	75±20	63±14	<0.01	73±20	67±14	0.50
TLC (%predicted)	72±14	66±13	0.05	71±14	66±14	0.45
RV (%predicted)	85±20	89±24	0.44	86±21	86±21	0.97
DLCO (%predicted)	32±16	26±14	0.14	31±15	27±18	0.69
PaO_2 (mmHg)	69±11	60±12	<0.01	67±11	61±13	0.15
$PaCO_2$ (mmHg)	37±4	36±5	0.80	37±4	37±4	0.99
LTOT, n (%)	36 (49)	19 (76)	0.02	49 (55)	6 (67)	0.50
CRP (mg/dl)	5[3-10]	8[5-18]	0.03	6[3-13]	6[3-25]	0.93
6MWD (m)	407±109	312±103	<0.01	387±114	344±117	0.28
6MWD (%predicted)	73±19	54±17	<0.01	69±20	61±21	0.23
SF-36 Physical Summary Score	39±9	33±8	<0.01	37±10	38±7	0.80
SF-36 Mental Summary Score	44±14	41±14	0.47	43±14	44±14	0.95

Data expressed as frequency, mean±SD or median [IQR 25-75%]; **BMI:** body mass index; **FMI:** fat mass index; **FFMI:** fat-free mass index; **FVC:** forced vital capacity; **FEV_1:** forced expiratory volume in the first second; **TLC:** total lung capacity; **RV:** residual volume; **DLCO:** diffusion capacity for carbon monoxide; **PaO_2:** arterial oxygen tension; **$PaCO_2$:** arterial carbon dioxide tension; **LTOT:** long term oxygen therapy; **CRP:** plasma C-reactive protein; **6MWD:** six-minute walk distance; **SF-36:** Short-Form 36-item Questionnaire.

Table 4 displays the impact of low PhA and FFMI, after adjustment for gender, age, DLCO and FVC, the mean difference in 6MWD between patients with normal and low PhA was -76.2m (95% CI, -119.1 to -33.3m; *P*=0.001), whereas the mean difference in 6MWD between patients with normal and low FFMI was -7.4m (95% CI, -75.6 to 60.7m; *P*=0.83). The proportion of patients who presented a 6MWD lower than 250m showed statistically significant difference between patients with normal and low phase angle (7 vs 39%; *P*<0.01).

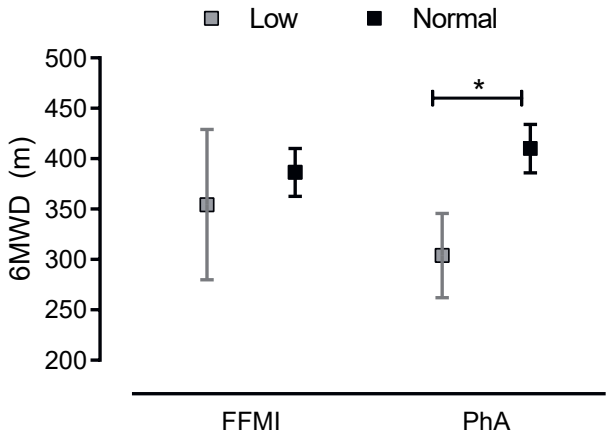

Figure 1. Comparisons of 6 min walk distance (6MWD) between patients with normal and low fat-free mass index (FFMI) and phase angle (PhA). Adjusted means and CIs reported from ANCOVA, after adjusting for gender and age. *P<0.05. ANCOVA, analysis of covariance.

Table 3. Relationship between exercise capacity and health related quality of life with body composition and lung function

Variables	6MWD (m)	SF-36 (Physical Summary)	SF-36 (Mental Summary)
Age (years)	0.07**	NS	NS
FFMI (kg/m^2)	NS	NS	NS
Body cell mass (kg)	0.13*	NS	NS
Phase Angle (°)	0.29*	0.06**	NS
FVC (%predicted)	0.24*	0.21*	NS
FEV_1 (%predicted)	0.17*	0.20*	NS
TLC (%predicted)	0.16*	0.21*	NS
DLCO (%predicted)	0.36*	0.26*	NS

Single regression analysis. R^2 values are shown.
6MWD: six-minute walk distance; **SF-36:** Short-Form 36-item Questionnaire; **NS:** not significant; **FFMI:** fat-free mass index; **FVC:** forced vital capacity; **FEV_1:** forced expiratory volume in the first second; **TLC:** total lung capacity; **DLCO:** diffusion capacity for carbon monoxide.
*P<0.01.
** P<0.05.

Discussion

This is the first study to report (1) the frequency of low FFMI and PhA according to the 10th percentile of age-sex-BMI specific reference values and (2) the clinical impact of presenting low FFMI and PhA in terms of lung function, exercise capacity and HRQL in patients with IPF. It was demonstrated that PhA is associated with exercise capacity and HRQL, whereas FFMI was not related to these outcomes. In addition,

Table 4. Multiple linear regression analyses to compare 6MWD between patients with normal and low PhA and FFMI, while adjusting for gender, age and lung function

Model	Correlates	Beta	95% CI	*P*-value
6MWD (m) Adjusted R^2=0.54 *P*-value<0.001	(Constant)	557.9	388.0/727.8	<0.001
	Sex (male)	-33.6	-17.7/84.8	0.19
	Age (years)	-5.2	-7.5/-2.9	<0.001
	DLCO (%predicted)	3.7	2.2/5.2	<0.001
	FVC (%predicted)	0.9	-0.5/2.2	0.20
	Phase Angle (Low)	-76.2	-119.1/-33.3	0.001
6MWD (m) Adjusted R^2=0.46 *P*-value<0.001	(Constant)	480.4	301.6/659.1	<0.001
	Sex (male)	28.6	-26.9/84.2	0.31
	Age (years)	-4.7	-7.2/-2.2	<0.001
	DLCO (%predicted)	3.6	2.0/5.3	<0.001
	FVC (%predicted)	1.4	-0.02/2.8	0.05
	FFMI (Low)	-7.4	-75.5/60.7	0.83

6MWD: six-minute walk distance; **DLCO:** diffusion capacity for carbon monoxide; **FVC:** forced vital capacity; **FFMI:** fat-free mass index.

stratification of patients in normal and low PhA could better discriminate patients with worse lung function, exercise capacity and HRQL, compared with stratification in normal and low FFMI. After adjustment for gender, age and lung function, the effect of being classified as low PhA on 6MWD was -76.2m. These findings are in accordance with a previous study, that included a large cohort of patients with COPD, and demonstrated that PhA is a valid functional and prognostic biomarker, offering information beyond FFMI, which did not identify patients with the greatest level of impairment or disease severity.[15]

The 6MWT has been demonstrated as a valid, reliable and responsive measure for the assessment of exercise capacity[27,28] and as an independent predictor of mortality in patients with IPF.[26] A previous study identified several determinants of the 6MWD, including cardiac, circulatory, and pulmonary variables, suggesting a multifactorial nature of exercise limitation in this population.[29] The present study demonstrated that body composition is also an important factor associated with exercise capacity in patients with IPF and could be a factor limiting exercise capacity or a consequence of reduced exercise capacity and physical inactivity in this population.

HRQL is a component of the broader concept of quality of life and is defined as satisfaction with health.[30] Many different instruments have been used to assess HRQL in patients with IPF, one of the most used is the SF-36,[3,31] which have been demonstrated as a valid questionnaire.[32] Patients with IPF have significantly impaired

HRQL in both Physical and Mental Summary Scores,[3,32] however, recently Cox et al.[31] showed that domain scores reflecting physical wellness (activity and symptoms) were generally worse than those reflecting emotional wellness (impact), which agrees with the findings of the present study. No factor was associated with the Mental Summary Score of the SF-36. This could be explained due to the fact that the Mental Summary Score includes questions that measure mainly individual's perception, and these measures tend to be more highly correlated with other perception-based measures such as reported dyspnea, in other words, patients with objectively equal physiological parameters can present different self-reported quality of life.[3]

The present study adds to the current literature information regarding the clinical applications of BIA in patients with IPF. We found that stratification of patients with IPF into normal and low PhA or FFMI discriminates patients with clearly different characteristics. While stratification into low FFMI identified patients with significantly lower weight due to tissue depletion, including not only lower FFMI, but also lower body cell mass and body water, the stratification into low PhA performed better to discriminate patients with worse lung function, exercise capacity and HRQL, despite no differences in BMI and other body composition variables (except for higher amount of extracellular). Extracellular mass includes all metabolically inactive tissues of the body, and a higher extracellular mass/body cell mass ratio is an early warning sign of worsening nutritional status.[33,34] These findings support the ability of PhA as a proxy of cellular health (higher number of cells with better membrane integrity and function).[13] A limitation of the study is the use of only a generic instrument to measure HRQL, it could be valuable to compare whether the results would be similar when using a disease-specific instrument, such as the IPF-specific version of the St George's Respiratory Questionnaire (SGRQI) and the King's Brief Interstitial Lung Disease questionnaire (KBILD), which are able to capture unique aspects of the disease.

It is already known that a 12-week supervised exercise training program is clinically beneficial to enhance exercise capacity, quality of life, physical activity and body composition outcomes in patients with IPF;[35,36] however, there are no studies showing if improvement in these outcomes are associated. Thus, future studies should investigate whether PhA is a stronger prognostic factor than FFMI and can be improved after interventions, such as pulmonary rehabilitation and nutritional support/counselling. Finally, it would be interesting to understand the associations between body composition, exercise capacity and HRQL in a prospective study design to better explore cause-consequence understanding.

Conclusion

The findings of the present study indicate that the frequency of abnormal low PhA (26%) is higher than expected, according to the use of the 10th percentile of the reference values for the general population. While the use of BMI and FFMI would identify only 2% and 9% of the patients with low weight and muscle mass, the use of PhA revealed two groups of patients with clearly distinct characteristics, it should be noted that patients with low PhA present worse lung function, exercise capacity and HRQL.

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Chapter 6

Longitudinal changes in total and regional body composition in patients with chronic obstructive pulmonary disease

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Respirology, 2021 Sep;26(9):851–60
doi: 10.1111/resp.14100.

Abstract

Background and objective: Low fat-free mass (FFM) is common in patients with COPD and contributes to morbidity and mortality. Few studies have evaluated longitudinal changes in body composition in patients with COPD compared with non-COPD controls. This study aimed to compare longitudinal changes in total and regional body composition between patients with COPD and non-COPD controls and investigate predictors of changes in body composition in COPD.

Methods: Patients with COPD and non-COPD controls participating in the ICE-Age study, a single-centre, longitudinal, observational study, were included. Subjects were assessed at baseline and after two years of follow-up. Among other procedures, body composition was measured by dual energy x-ray absorptiometry (DEXA) scan. The number of exacerbations/hospitalizations one year before inclusion and during follow-up were assessed in patients with COPD.

Results: 405 subjects were included (205 COPD, 87 smoking and 113 non-smoking controls). Patients with COPD and smoking controls presented a significant decline in total FFM (mean[95% CI]: -1173[-1527/-820]g and -486[-816/-156]g, respectively) while body composition remained stable in non-smoking controls. In patients with COPD, the decline in FFM was more pronounced in legs (-174[-361/14]g) and trunk (-675[-944/406]g) rather than in arms (54[-19/126]g). The predictors of changes in total and regional FFM in patients with COPD were gender, number of previous hospitalizations, baseline values of FFM and body mass index (BMI).

Conclusion: Patients with COPD present a significant decline in FFM after two years of follow up, this decline is more pronounced in their legs and trunk.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease known to be a leading cause of morbidity and mortality worldwide and inducing a substantial economic and social burden.1 Patients with COPD present chronic airflow obstruction and respiratory symptoms, however there is a substantial variation in risk of exacerbations, exercise capacity, level of physical activity and other characteristics among patients.[1] Thus, COPD is considered a complex and heterogeneous disease and studies have identified different patients' clusters based on a comprehensive assessment of lung function,[2] response to pulmonary rehabilitation,[3] comorbidities,[4,5] physical activity[6] and body composition.[7,8]

Body composition abnormalities have been extensively investigated in patients with COPD.[9] Studies have found a higher prevalence of body composition abnormalities in this population compared with non-COPD control groups, affecting surrogate markers of muscle mass and fat mass.[7,10] There is evidence showing a "cachectic" comorbidity cluster that is specifically related with COPD and represents a disease-specific phenotype.[5,11] In addition, a population-based cohort study found that the presence of sarcopenia appears to be independent of chronic diseases apart from COPD.[12] Indeed, changes in body composition are expected with normal aging and are gender dependent.[13] However, patients with COPD present an accelerated aging process,[14] raising the hypothesis that the changes in body composition may also be different in COPD compared with non-COPD controls.

Only few studies investigated longitudinal changes in body composition in patients with COPD.[10,15-17] In these studies, the time of follow up ranged from 1 to 7 years and body composition variables were measures of total body or legs, whereas no specific variables for trunk and arms were available. The studies that included a control group found small changes in body composition in patients with COPD which were comparable with the changes of smoking and non-smoking controls.[10,15,16] In the case of regional assessment of body composition (with stratification in trunk and limbs), only a few cross-sectional studies are available.[18-20] The findings from these studies suggest that limbs are more affected in patients with COPD whereas changes in trunk body composition are more present in patients with worse disease severity and/or presenting emphysema.[18-20] To our knowledge, no previous study has investigated longitudinal changes in regional body composition in patients with COPD compared with non-COPD controls, neither identified a sub-group of patients with a different body composition trajectory.

Therefore, this study aimed: (1) to compare longitudinal changes in total and regional body composition between patient with COPD, smoking and non-smoking controls, (2) to investigate baseline predictors of longitudinal changes in body composition in patients with COPD, and (3) to investigate the associations of longitudinal changes of body composition with longitudinal changes of symptoms, lung function, health-related quality of life (HRQL) and occurrence of exacerbations/hospitalizations in patients with COPD, after two years of follow up.

Methods

Study design and subjects

The Individualized COPD Evaluation in relation to Ageing (ICE-Age) study, was a single-center, prospective, observational study performed in CIRO (Horn, the Netherlands) with two years of follow up. Detailed information regarding inclusion and exclusion criteria as well as the enrollment process were previously described.[14] Patients with COPD were recruited on referral to pulmonary rehabilitation at CIRO during a clinically stable phase (absence of respiratory tract infection or exacerbation of the disease for <4 weeks before study entry). Smoking and non-smoking controls were recruited from the same region (south of the Netherlands) from December 2010 to August 2016.

Assessments

Anthropometric and demographic data were collected. Body weight and height were assessed and used to calculate BMI (weight divided by height squared [kg/m^2]). Subjects were classified into BMI categories according to World Health Organization (WHO) criteria: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) or obese (≥30 kg/m^2).[21] In patients with COPD, the number of exacerbations and hospitalizations due to COPD in the previous year and use of long-term oxygen therapy (LTOT) were recorded. An exacerbation was defined as an acute need to use a course of oral glucocorticosteroids or antibiotics and/or hospitalization due to acute respiratory worsening.

Body composition was assessed by dual energy x-ray absorptiometry (DEXA) scan (Lunar Prodigy system - GE Healthcare, Madison, WI, USA). Total and regional body composition, including lean, fat and bone mass was analyzed. Fat-free mass (FFM) was calculated as the sum of lean mass plus bone mineral content and described

as total FFM, legs FFM, trunk FFM and arms FFM. Fat mass (FM) was calculated as the difference between weight and total FFM. Bone mineral density (BMD) was measured in the lumbar spine and proximal femur (hips) and its respective T-scores calculated. FFM index (FFMI) and FM index (FMI) were calculated by dividing total FFM and FM by height^2, respectively. Patients were classified into low FFMI and high FMI according to the 10th and 90th percentiles of age-gender-BMI-specific cut-offs,[22] respectively.

Post-bronchodilator lung function tests were performed to assess forced expiratory volume in the first second (FEV1), functional vital capacity (FVC) and its ratio (FEV1/FVC), using a standardized spirometer method (Masterlab®, Jaeger, Germany), following ATS/ERS guidelines.[23] Residual volume (RV) and intra thoracic gas volume (ITGV) were determined by body-plethysmography (Masterlab®, Jaeger, Germany) following the quality control guidelines.[24] Transfer factor for carbon monoxide (TLCO) was assessed by using single-breath method (Masterlab®, Jaeger, Germany).[25] All parameters were expressed as percentage of reference values.[26-28] The number of pack-years smoked and smoking status (habitual smokers, ex-smokers [≥10 packyears] and non-smokers [<10 packyears] were recorded.

In patients with COPD, the Medical Research Council (MRC) scale[29] and the COPD-specific version of St. George Respiratory (SGRQ) questionnaire[30] were applied to assess the level of functional limitation due to breathlessness in activities of daily living and disease related quality of life, respectively. All the previously described assessments were performed at baseline and repeated after two years of follow up. In the time between, the occurrence of exacerbations during follow-up was recorded by telephone contact every 3 months.

Statistical analysis

Normality in data distribution was evaluated using the Shapiro-Wilk test. Quantitative variables were described as mean ± standard deviation or median [interquartile range 25-75%] as appropriate. Categorical variables were described as absolute and relative frequency. The longitudinal change in variables were calculated by subtracting the data at year two from baseline data. For the comparisons of the baseline characteristics and the longitudinal change in body composition between patients with COPD, smoking and non-smoking controls, the One-way analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables and the Chi-square test for categorical variables were performed as appropriate. The paired t-test or Wilcoxon signed-rank test was used

to compare differences between paired observations (baseline vs two years of follow up) within each group. In order to evaluate the predictive value of the different baseline factors to explain the variance in the change of total and regional body composition of patients with COPD, a stepwise multiple regression analysis was performed. Since baseline values of FFMI and number of hospitalizations one year before baseline were found to be associated with changes in total and regional body composition (see results), further analysis to examine whether patients with COPD classified as normal (or low) FFMI and with (or without) at least one hospitalization in the previous year present different body composition trajectories were performed using the Two-way analysis of variance (ANOVA) test. All the tests with comparisons between more than two groups were followed by Bonferroni post hoc test for pairwise comparisons.

Correlations between changes in total and regional body composition with changes in lung function and health-related quality of life in patients with COPD were assessed by Pearson's r or Spearman's r as appropriate. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS v 25 for Windows; SPSS Inc, Chicago, IL). Figures were created using GraphPad Prism 9.0 (GraphPad Software Inc., USA). Significance level was set at $P<0.05$.

Results

A total of 205 patients with COPD and 200 subjects without COPD (87 smoking controls and 113 non-smoking controls) were included for these analyses. The baseline characteristics of the sample are presented in **Table 1**. The group of non-smoking controls was younger, presented a higher proportion of female subjects and as expected, reduced smoking history compared with patients with COPD. Per definition, patients with COPD presented impaired lung function compared with smoking and non-smoking controls. Baseline BMI was comparable between groups.

Frequency of peripheral vascular disease, cardiovascular disease and osteoporosis was significantly increased in COPD compared with smoking and non-smoking controls. In general, patients with COPD were classified as overweight, heavy smokers, with moderate to severe airflow obstruction, moderately impaired diffusion capacity and increased static lung volumes. A total of 82 (40%) of the patients with COPD were classified as low FFMI whereas 72 (35%) were classified as high FMI. In addition, patients with COPD presented moderate to severe functional limitation due to breathlessness in activities of daily living and reduced quality of life (**Table 2**).

Table 1. Baseline characteristics of the sample

Variables	COPD (N=205)	Smoking controls (N=87)	Non-smoking controls (N=113)
Male, n(%)	119(58)	51(59)	39(34)*†
Age, (years)	62[57-67]	61[59-65]	60[55-64]*
BMI, (kg/m²)	27.0[22.9-30.4]	27.2[25.4-29.1]	25.8[24.0-28.4]
Underweight, n(%)	10(5)	0(0)	0(0)
Normal weight, n(%)	63(31)	18(21)	42(37)†
Overweight, n(%)	72(35)	56(64)*	52(46)†
Obese, n(%)	60(29)	13(15)*	19(17)*
Body composition			
FFMI (kg/m²)	17.4[15.6-19.4]	18.9[16.4-20.2]*	17.2[15.6-19.4]†
Low FFMI, n(%)	82(40)	19(22)*	23(20)*
FMI (kg/m²)	9.2[6.3-11.4]	8.5[6.8-10.6]	8.7[7.0-10.7]
High FMI, n(%)	72(35)	20(23)	24(21)*
Arms FFM (kg)	4.67[3.67-5.86]	5.84[4.05-6.70]*	4.33[3.66-6.38]†
Legs FFM (kg)	13.99[11.24-17.15]	16.49[12.27-18.70]*	13.07[11.78-17.16]†
Trunk FFM (kg)	23.59[19.30-28.86]	24.80[19.84-27.56]	20.78[18.70-25.35]*†
BMD L2-L4 (g/cm²)	1.10[0.95-1.23]	1.19[1.05-1.36]	1.22[1.08-1.34]*
BMD Hip (g/cm²)	0.84[0.76-0.92]	0.91[0.83-1.06]	0.94[0.87-1.03]*
Lumbar spine T-score	-1.1[-1.8-0.2]	-0.2[-1.3-1.1]*	0.1[-1.1-1.1]*
Hip T-score	-1.5[-2.1--0.9]	-1.0[-1.6-0.1]*	-0.6[-1.3-0.2]*
Osteopenia, n(%)	109(53)	40(46)	37(33)*
Osteoporosis, n(%)	41(20)	6(7)	6(5)*
Smoking status			
Ex-smoker, n(%)	174(85)	65(75)	50(44)*
Habitual smoker, n(%)	28 (14)	22(25)*	4(3)*†
Non-smoker, n(%)	3(1)	0(0)	59(52)*
Pack years	43[31-59]	21[14-31]*	0[0-4]*†
Lung function			
FEV_1 (%predicted)	50[36-62]	116[107-125]*	120[109-130]*
FVC (%predicted)	98[82-111]	122[110-132]*	124[114-135]*
FEV_1/FVC	40[32-49]	77[75-83]*	79[76-83]*
ITGV (%predicted)	144±33	98±17*	101±19*
RV (%predicted)	152[130-184]	95[84-104]*	95[83-106]*
TL_{CO} (%predicted)	52[43-66]	91[81-101]*	92[85-104]*
LTOT use, n(%)	32(16)	0(0)*	0(0)*
Self-reported comorbidities			
Hypertension, n(%)	46(22)	23(26)	19(17)
Peripheral vascular disease, n(%)	40(19)	1(1)*	2(2)*
Joint disease, n(%)	27(13)	17(19)	20(18)
Diabetes Mellitus, n(%)	19(9)	4(5)	2(2)*
Gastrointestinal disease, n(%)	20(10)	3(3)	6(5)
Psychological disorder, n(%)	17(8)	2(2)	4(3)
Hypercholesterolemia, n(%)	15(7)	8(9)	5(4)
Cardiac disease, n(%)	40(19)	6(7)*	4(3)*
Sleep apnea, n(%)	13(6)	3(3)	1(1)
Other, n(%)	34(17)	16(18)	17(15)

BMI: body mass index. **FFMI:** fat-free mass index. **FMI:** fat mass index. **BMD:** bone mineral density. **FEV_1:** forced expiratory volume in the first second. **FVC:** forced vital capacity. **ITGV:** intra-thoracic gas volume. **RV:** residual volume. **TL_{co}:** transfer factor for carbon monoxide. **LTOT:** long term oxygen therapy. * $P<0.05$ compared with COPD; † $P<0.05$ compared with Smoking Control.

Table 2. Level of functional limitation due to breathlessness in activities of daily living, disease related quality of life, number of exacerbations and hospitalizations in patients with COPD

Variables	COPD
Questionnaires	
MRC	3[2-4]
SGRQ symptoms	59.6[42.7-72.1]
SGRQ impact	41.3[28.2-54.3]
SGRQ activity	56.4[42.0-67.0]
SGRQ total	56.4[42.0-67.0]
Number of exacerbations in the previous year	
0, n(%)	44(23)
1, n(%)	57(29)
2 or more, n(%)	93(48)
Number of hospitalizations in the previous year	
0, n(%)	140(69)
1, n(%)	60(30)
2 or more, n(%)	3(1)

MRC: Medical Research Council. **SGRQ:** Saint George Respiratory Questionnaire.

After two years of follow up, 10 patients with COPD, 1 non-smoking control and 3 smoking controls did not return for outcome assessments at the second visit but were followed-up by a phone call. Eleven patients with COPD declined to participate or were not available to perform outcome assessments at the second visit. Ten patients with COPD and 1 non-smoking control died during the study. The remaining 174 (85%) patients with COPD, 84 (96%) smoking controls and 111 (98%) non-smoking controls repeated the measurements. As presented in **Figure 1**, weight remained stable in all groups, however patients with COPD and smoking controls presented a significant decline in FFM and increase in FM, while non-smoking controls presented no significant differences in body composition. Regarding regional body composition, patients with COPD presented a significant decline in legs and trunk FFM. The decline in FFM in smoking controls is mostly explained by a decline in trunk FFM, since an increase in legs and arms FFM were observed. Non-smoking controls presented a significant increase in legs FFM, but no differences in trunk and arms FFM.

Table 3 shows the results of the stepwise multiple regression performed to identify the baseline predictors of longitudinal changes in total and regional body composition in patients with COPD. Baseline values of total and regional FFM were significant predictors of their own change. In addition, the number of hospitalizations one year before baseline was associated with greater decline in FFMI and arms FFM. In contrast, higher baseline values of BMI were associated with lower decline in FFMI,

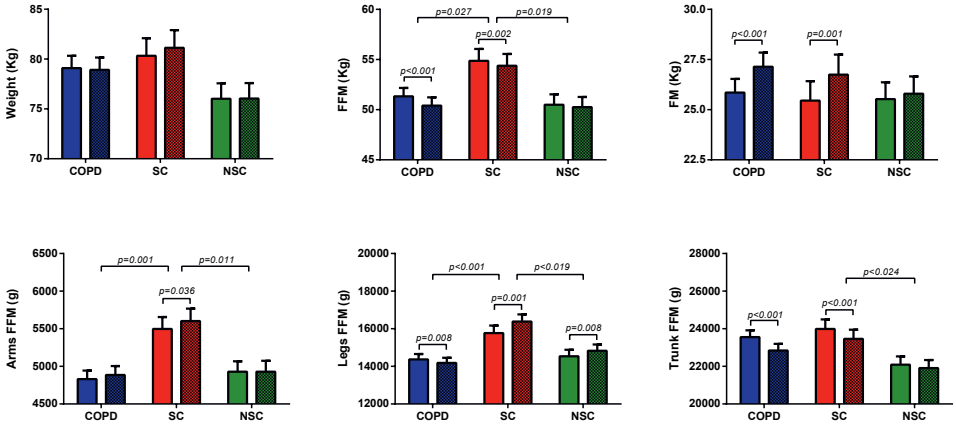

Figure 1. Comparison of changes in total and regional body composition among patients with COPD, smoking and non-smoking controls after 2 years of follow up. Figure displays the mean and standard error. Clean bars: baseline. Hatched bars: two years of follow up. **SC:** Smoking controls. **NSC:** Non-smoking controls.

Table 3. Multiple stepwise regression to identify independent contributors to the variance in the change of total and regional body composition in patients with COPD after 2 years of follow up

Model	Correlates	Beta	95% CI (lower/upper)	*P*-value
Δ FFMI (kg/m²) Adjusted R^2=0.20 *P*-value<0.001	(Constant)	2.01	0.79/3.24	<0.01
	Baseline FFMI (kg/m²)	-0.28	-0.40/-0.16	<0.001
	BMI (kg/m²)	0.09	0.04/0.14	<0.001
	Gender (male)	0.59	0.14/1.04	0.01
	Previous Hospitalization (n)	-0.30	-0.56/-0.04	0.02
Δ Legs FFM (g) Adjusted R^2=0.16 *P*-value<0.001	(Constant)	-860	-1952/231	0.12
	Baseline Leg FFM (g)	-0.13	-0.20/-0.07	<0.001
	BMI (kg/m²)	96	49/142	<0.001
Δ Trunk FFM (g) Adjusted R^2=0.16 *P*-value<0.001	(Constant)	3818	1967/5668	<0.001
	Baseline Trunk FFM (g)	-0.22	-0.31/-0.12	<0.001
	Gender (male)	1145	259/2032	0.04
Δ Arms FFM (g) Adjusted R^2=0.15 *P*-value<0.001	(Constant)	-109	-570/353	0.64
	BMI (kg/m²)	33	15/51	<0.001
	Baseline Arm FFM (g)	-0.2	-0.3/-0.1	<0.001
	Gender (male)	443	176/710	0.001
	Previous Hospitalization (n)	-142	-280/-4	0.04

FFMI: fat-free mass index. **BMI:** body mass index. Excluded variables: age, pack years, lung function in percent of predicted (forced expiratory volume in the first second, forced vital capacity, intra-thoracic gas volume, residual volume, transfer factor for carbon monoxide), number of previous exacerbations, number of exacerbations during the follow-up, number of hospitalizations during the follow-up.

legs and arms FFM. Male gender showed a protective effect for the decline in FFMI, trunk and arms FFM. There were no associations between longitudinal changes in body composition with smoking status, lung function, and number of exacerbations/ hospitalizations during follow-up. Patients classified as normal FFMI and presenting hospitalizations one year before baseline presented a greater decline in total and leg FFM compared with patients with normal FFMI, but no hospitalizations and patients with low FFMI (**Figure 2**).

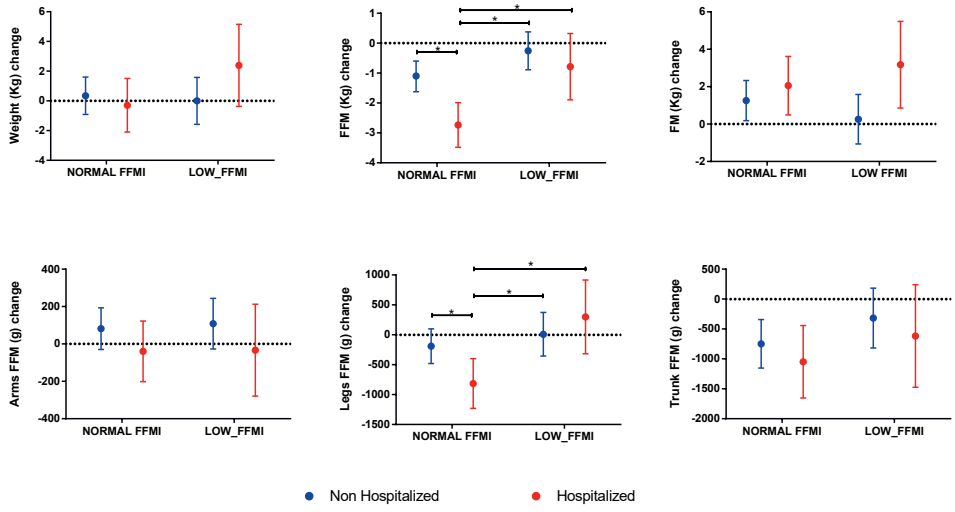

Figure 2. Comparison of changes, after two years of follow up, in total and regional body composition among patients with COPD stratified according to baseline FFMI (normal/low) and occurrence of previous hospitalization (Hospitalized/Non-hospitalized). Means [95% confidence interval] reported. Normal FFMI and Non-Hospitalized (n=69); Normal FFMI and Hospitalized (n=33); Low FFMI and Non-Hospitalized (n=45); Low FFMI and Hospitalized (n=15); * $P<0.05$.

Table 4 presents the single correlations between changes in total and regional body composition with changes in lung function and HRQL in patients with COPD. The change in body weight was negatively associated with the change in ITGV (r=-0.18) and positively associated with the change in MRC (r=0.23). The change in total FFM was negatively associated with change in SGRQ symptoms score (r=-0.22). The changes in FM were positively associated with change in MRC (r=0.29) and SGRQ activity score (r=0.20). Finally, change in trunk FFM was negatively associated with change in FEV1 (r=-0.17) and positively associated with changes in RV (r=0.18) whereas arms FFM was negatively associated with changes in ITGV (r=-0.20) and RV (r=-0.16) and positively associated with changes in TLCO (r=0.21). No additional associations were found between other variables of body composition and lung function or HRQL.

Table 4. Correlations between changes in total and regional body composition with changes in lung function, symptoms of dyspnea and health-related quality of life in patients with COPD

	Change Weight	Change FFM	Change FM	Change Legs FFM	Change Trunk FFM	Change Arms FFM
Change FEV1%pred	r=-0.03 *P*=0.70	r=-0.01 *P*=0.88	r=-0.02 *P*=0.69	r=-0.02 *P*=0.80	**r=-0.17* *P*= 0.04**	r=0.09 *P*=0.25
Change FVC%pred	r=-0.13 *P*=0.09	r=-0.05 *P*=0.54	r=-0.10 *P*=0.19	r=0.01 *P*=0.92	r= -0.13 *P*= 0.10	r=0.05 *P*=0.50
Change ITGV%pred	**r=-0.18* *P*=0.02**	r=-0.14 *P*=0.09	r=-0.14 *P*=0.85	r=-0.07 *P*=0.40	r= 0.05 *P*= 0.58	**r=-0.20* *P*=0.01**
Change RV%pred	r=0.01 *P*=0.89	r=-0.06 *P*=0.50	r=0.04 *P*=0.59	r=-0.10 *P*=0.23	**r= 0.18* *P*= 0.03**	**r=-0.16* *P*=0.04**
Change TL_{CO}%pred	r=0.07 *P*=0.42	r=0.14 *P*=0.09	r=0.03 *P*=0.69	r=0.09 *P*=0.25	r=0.05 *P*=0.56	**r=0.21* *P*=0.01**
Change MRC	**r=0.23* *P*=0.04**	r=-0.14 *P*=0.22	**r=0.29* *P*=0.01**	r=0.05 *P*=0.64	r=-0.18 *P*=0.13	r=0.02 *P*=0.87
Change SGRQ symptoms	r=0.02 *P*=0.82	**r=-0.22* *P*=0.03**	r=0.14 *P*=0.16	r=-0.08 *P*=0.42	r=-0.14 *P*=0.18	r=0.00 *P*=0.93
Change SGRQ impact	r=0.09 *P*=0.38	r=0.00 *P*=0.98	r=0.09 *P*=0.36	r=-0.04 *P*=0.65	r=-0.00 *P*=0.98	r=0.08 *P*=0.41
Change SGRQ activity	r=0.16 *P*=0.11	r=-0.05 *P*=0.65	**r=0.20 *P*=0.04**	r=-0.02 *P*=0.84	r=-0.11 *P*=0.26	r=-0.10 *P*=0.30
Change SGRQ total	r=0.13 *P*=0.18	r=-0.06 *P*=0.56	r=0.17 *P*=0.08	r=-0.08 *P*=0.41	r=-0.08 *P*=0.41	r=-0.04 *P*=0.70

FFM: fat-free mass. **FM:** fat mass. **FEV_1:** forced expiratory volume in the first second. **FVC:** forced vital capacity. **ITGV:** intra-thoracic gas volume. **RV:** residual volume. **TL_{co}:** transfer factor for carbon monoxide. **MRC:** Medical Research Council. **SGRQ:** Saint George Respiratory Questionnaire. * *P*<0.05.

Discussion

This was the first study to compare longitudinal changes in total and regional body composition between patients with COPD, smoking and non-smoking controls, during two years of follow up. The study shows that patients with COPD present a significant decline in total, leg and trunk FFM compared with smoking and/or non-smoking controls, while no changes were observed in arms FFM. In addition, preserved total and regional FFM at baseline and a history of previous hospitalizations were associated with longitudinal changes in FFM in patients with COPD, and these characteristics could discriminate a sub-group of patients presenting greater decline in total and legs FFM. Lastly, changes in lung function, in symptoms of dyspnea and in HRQL were weakly associated with changes in body composition in patients with COPD.

Previous studies found no difference in longitudinal changes of body composition between patients with COPD and non-COPD controls.[10,16] In contrast, the present study found a significant decline of FFM in patients with COPD after two years of follow up whereas no changes in FFM were observed in non-smoking controls. We hypothesize that the difference between these findings is caused by differences in the population included (e.g. older subjects with obstructive lung disease (OLD))[16] and methods of assessment of body composition (bio-electrical impedance analysis vs DEXA scan).[10] The strengths of the present study are the inclusion of a relatively large sample of patients with COPD and smoking and non-smoking controls as well as a comprehensive assessment of body composition by DEXA scan, including total and regional variables.

The study from van den Borst et al.[16] aimed to investigate whether OLD and smoking accelerate aging-related decline in lean mass. Subjects were followed for a period of seven years. While at baseline large differences were observed in body composition between OLD and smoking controls compared with non-smoking controls, the longitudinal changes in body composition were similar between the groups. However, this study included subjects with OLD with ages from 70-79 years old. Therefore, the results may not be generalizable to younger subjects and middle-aged patients with clinical diagnosis of COPD.

Another study by Rutten et al.[10] evaluated changes in body composition over three years in a cohort of patients with COPD in comparison with smoking and non-smoking controls. This study showed that the changes in body composition in patients with COPD were comparable with the change in smoking and nonsmoking controls after three years and were independent of the initial body weight. In this previous study, the changes in FFMI and FMI of patients with COPD were less pronounced (-0.1[-0.6/0.5], -0.1[-1.1/0.8], respectively) than the changes of the present study (-0.4[-0.9/0.1], 0.3[-0.5/1.5], respectively). Later, Rutten et al.[15] showed that the proportion of patients with continuous FFM decline was small, but higher in patients with COPD compared with non-COPD controls. The authors suggested that there may be a subgroup of patients with disease-specific muscle wasting defined by continuous FFM decline, which might be partly explained by higher number of exacerbations.[15]

The present study found that, despite presenting a significant decline in legs FFM, patients with COPD present no changes in arms FFM after two years of follow up. A possible explanation is that most of self-care activities and activities of daily living are done with the arms whereas legs dysfunction is closely related to higher-intensity

physical activity (legs are directly involved in locomotion and exercise capacity), which is usually reduced in this population.[31] Previous studies have found that patients with COPD present relatively preserved characteristics in arms compared with legs regarding muscle strength and endurance,[32-34] mechanical efficiency,[35] oxidative capacity[36] and duration of daily arm activities, despite lower intensity and at cost of higher effort of trapezius compared with healthy control subjects.[32] In addition, previous findings support that patients with severe disease exhibit disproportional leg muscle wasting compared with patients with mild COPD.[18] In relation to the changes in trunk body composition, previous findings suggest that the reduction in trunk FFM is present specifically in patients with worse disease severity and/or presenting emphysema.[19,20] In the present study, we did not find any lung function factor independently associated with the change in trunk FFM.

This is not the first study to find association between higher baselines values of FFM and higher decline in FFM over time. Hopkinson et al.[17] found that baseline values of FFM was retained in a stepwise regression analyses as a predictor of the change in FFM after one year of follow-up. Our results suggest an interaction effect in which the impact of hospitalizations is higher for patients with preserved FFMI, since patients presenting these features were identified as a subgroup with greater decline in total and legs FFM after two years of follow-up. Notably, during hospitalization patients with COPD present very low level of baseline physical activity.[33,34] A similar effect has been reported for the impact of exacerbations on longitudinal changes of FEV_1, which is higher for patients with COPD with mild disease.[37] Our hypothesis is the existence of a floor effect, in which patients with lower FFM values may have experienced a significant decline in FFM before the inclusion in the study and are less susceptible to the negative effects of hospitalizations.

Changes in body composition were weakly associated with changes in lung function, symptoms of dyspnea and HRQL in patients with COPD ($r<0.3$, for all). Our models could explain only 15-20% of the variance in changes in body composition, suggesting that these changes are affected by a great number of different factors, beyond the factors covered by this study (e.g. nutrition, physical activity, use of drugs, systemic inflammation). The knowledge of COPD as a complex, multidimensional, and heterogeneous disease, in which patients may present comparable degrees of airflow obstruction, but considerable differences in their MRC and SGRQ scores[38] or body composition,[8,39] may be extended for a longitudinal perspective. Thus, patients may also present different patterns of longitudinal changes in the aforementioned outcomes which are mildly associated.

Some limitations of the present study include: (1) most of patients with COPD were recruited in a tertiary care pulmonary rehabilitation and results should not be generalized for other stages of the disease or patient profiles, (2) the lack of additional variables that could also be related with longitudinal changes in body composition, such as physical activity and dietary habits, (3) this study could not assess the impact of longitudinal changes in body composition to other outcomes (e.g. mortality, exercise capacity, muscle strength), (4) patients with COPD underwent an eight-week pulmonary rehabilitation program, but the effect of this short-term intervention on body composition was not assessed in this study. Based on a previous study from our center, no substantial changes were anticipated.[40] Future studies should be conducted in order to investigate longitudinal changes in body composition in a broader sample of patients with COPD in comparison with non-COPD controls, during a longer period of time, to confirm the present findings and to provide information regarding the prognostic value of changes in total and regional body composition. Furthermore, studies investigating strategies to slow down (or prevent) the decline in regional FFM in patients with COPD and its benefits are an interest topic.

In conclusion, patients with COPD and smoking controls present a significant decline in FFM after two years of follow up, and this decline is more pronounced in their legs and trunk. Patients with COPD with higher baseline FFMI and occurrence of recent hospitalizations were identified as a subgroup presenting greater decline in total and legs FFM. Longitudinal changes in body composition are weakly associated with longitudinal changes in lung function, symptoms of dyspnea and HRQL.

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Chapter 7

Differential impact of low fat-free mass in COPD patients with different weight classification: results from COSYCONET

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Submitted

Abstract

Background: Alterations in body composition, including a low fat-free mass index (FFMI), are common in patients with chronic obstructive pulmonary disease (COPD) and occur regardless of body weight. While it is well-recognized that low FFMI is associated with increased morbidity and mortality in the overall COPD population, it is yet unknown whether there is a differential impact of low FFMI among COPD patients stratified in different weight classifications.

Methods: We analysed baseline data of COPD patients from the COSYCONET (COPD and Systemic Consequences - Comorbidities Network) cohort. Assessments included lung function, body composition by bioelectrical impedance analysis, six-minute walk distance (6MWD), health-related quality of life (HRQL) and markers of systemic inflammation. Patients were stratified in categories of underweight [UW], normal weight [NW], overweight [OW] and obese [OB]) according to their BMI as well as presenting low, medium and high FFMI using 25th and 75th percentiles of reference values. Comparisons between groups were performed using GLM with adjustment for sex and age. Multiple linear regression was used to investigate the independent associations between body composition and secondary outcomes in each BMI group.

Results: 2137 COPD patients (61% males, age: 65±8 years, FEV_1: 52.5±18.8 %pred) were included. The proportions of patients in UW, NW, OW and OB groups were 12.3%, 31.3%, 39.6%, 16.8%, respectively. The frequency of low FFMI decreased from lower to higher BMI groups (UW: 81%, NW: 53%, OW: 42%, OB: 39%). FFM was associated with the 6MWD in the UW and NW groups, even when adjusting for a broad set of covariates *P*P<0.05). HRQL was not associated with FFM after adjustment for lung function or dyspnea (*P*>0.09). Fat mass was associated with higher systemic inflammation in the NW and OW groups (*P*<0.05).

Conclusion: In patients with COPD with lower weight, such as UW and NW patients, increased FFMI is associated with better 6MWD and HRQL. On the other hand, in OW and OB COPD patients less favourable associations of an increased FFMI were observed.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined by the presence of chronic airflow limitation in patients with persistent respiratory symptoms and significant exposure to noxious stimuli.[1] Patients with COPD often exhibit extra-pulmonary manifestations and comorbidities which contribute to the clinical presentation of the disease.[2-4] Alterations in body composition, including low fat-free mass index (FFMI), are a recognized predictor of mortality and future acute exacerbation risk in these patients[5,6] and may occur regardless of changes in body weight. Thus, patients with a comparable body mass index (BMI) may differ considerably in their body composition.[7-9] Moreover, alterations in body composition are associated with the presence of comorbidities that demand specific management.[3] Therefore, there is growing interest in understanding whether and to what extent alterations in body composition are related to patients' physical condition and health status.

While previous studies demonstrated that low FFMI is associated with reduced exercise capacity in patients with COPD,[10,11] ambiguous results are reported on the independent association between FFMI and health-related quality of life (HRQL).[12-14] On the other hand, increased fat mass has been shown to be associated with higher systemic inflammation,[15,16] and worse exercise capacity[10] in clinically stable patients with COPD. However, these prior studies were conducted in selected and relatively small samples of patients. Associations of FFMI, exercise capacity, HRQL and markers of systemic inflammation were not investigated in a large and well-characterized multicenter COPD cohort, accounting for a broad panel of potential confounders. In particular, it needs to be elucidated whether the impact of low FFMI on these outcomes is similar in groups of patients with COPD with different weight classifications.

The aims of the present study were [1] to investigate whether the stratification of patients with COPD from the same BMI group into different FFMI groups discriminates patients with distinct characteristics and [2] to explore the independent associations between fat-free mass and fat mass with exercise capacity, HRQL and systemic inflammation in each BMI group. We hypothesized that patients with low FFMI present worse exercise capacity and HRQL irrespective of their BMI group. Furthermore, we expect that the contribution of body composition, comorbidities and other characteristics (age, sex, lung function, dyspnea) are differently associated with the impairment on exercise capacity and HRQL and the degree of systemic inflammation depending on the weight classification.

Methods

Participants and study design

We used data from the baseline visit of the prospective, observational, multicenter COSYCONET (German COPD and Systemic Consequences – Comorbidities Network) study, which recruited 2741 participants in 31 study centers across Germany.[2] This study was conducted in accordance with the amended Declaration of Helsinki and is registered on ClinicalTrials.gov (NCT01245933). All participants had given their written informed consent, and the study was approved by the Ethics Committee of the University of Marburg as coordinating center and the ethics committees of all study centers. Detailed information about the inclusion and exclusion criteria and recruitment process are available elsewhere.[2]

From the 2741 patients initially recruited in COSYCONET, we excluded 450 patients with GOLD stage 0 or missing GOLD stage. From the remaining 2291 patients with a diagnosis of COPD (GOLD stage 1-4), we excluded 154 patients in obesity classes II and III (BMI≥35 kg/m^2) because they represent a small proportion of patients with more severe obesity. In addition, BIA results must be interpreted with caution in these individuals since this technique requires further validation in these obesity classes.[17]

Assessments

Age, sex, smoking status, and number of exacerbations within the year before the visit were assessed in standardized interviews. A broad panel of comorbidities (sleep apnea, hypertension, coronary artery disease, cardiac infarction, cardiac dysrhythmia, heart failure, stroke, venous thrombosis, gastritis, GE reflux disease, peptic ulcer, diabetes, elevated cholesterol level, gout, tumor, arthrosis/arthritis, osteoporosis, psychiatric disorders, cognitive impairment, peripheral neuropathy, allergy and chronic bronchitis) were assessed by structured interviews based on patients' reports of physician-based diagnoses and the presence of disease-specific medication. The lung function assessments included measurement of post-bronchodilator forced expiratory volume in 1 s (FEV_1) by spirometry and single breath-maneuver for the measurement of diffusing capacity for carbon monoxide (TLCO). Procedures were performed according to SOPs following international guidelines and recommendations.[18] All parameters were taken as percent of their respective Global Lung Function Initiative (GLI) or European Coal and Steel Community (ECSC) predictive values.[19,20] The modified Medical Research Council (mMRC) scale was used to evaluate the level of functional limitation in activities of daily living due to symptoms of dyspnea.[21]

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2) based on measured height and weight. Overweight (BMI 25-<30 kg/m^2) and obese class I (BMI 30-<35 kg/m^2) were defined as proposed by the World Health Organization (WHO) criteria. We chose a BMI<21 kg/m^2 for the stratification of underweight patients since this value was useful to discriminate patients with COPD with worse prognosis.[22] Normal weight patients were classified as BMI 21-<25 kg/m^2. For the assessment of body composition, the study centers were equipped with identical instruments to perform BIA (Nutribox, Data Input). Fat-free mass (FFM) was estimated and used to calculate FFMI (FFM in kilograms divided by height in meters squared) and fat mass (total body weight minus FFM). Patients were classified with low (FFMI <25th percentile), medium (FFMI 25th-<75th percentile) or high (FFMI ≥75th percentile) FFMI according to the reference values of the UK Biobank general population.[23]

Exercise capacity and functioning was assessed using the 6-min walk distance (6MWD) and the Timed up&go test (TUG), following standard recommendations.[24,25] Self-reported physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), the overall physical activity was reported using a metabolic equivalent task scored in minutes per week.[26] Health-related quality of life was assessed using the disease-specific Saint George's Respiratory Questionnaire for COPD (SGRQ).[27] Several markers in the blood were assessed to evaluate systemic inflammation. White blood cells (WBC) count and C-reactive protein (CRP) were determined in the laboratories of the study centers using quality-controlled procedures. Concentrations of fibrinogen, interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α) were determined in the central biobank following the manufacturers' instructions.

Statistical analysis

Quantitative data are described as mean values and standard deviations (SD) or median and 25-75 interquartile range. Qualitative data are presented as absolute and relative frequencies. Comparisons between BMI groups (and between FFMI groups within each BMI group) were performed using the analysis of variance (ANOVA), Kruskal-Wallis test or Chi-squared test, as appropriate. We determined whether FFM and fat mass were independently associated with exercise capacity, HRQL and systemic inflammation using multiple linear regression models for each BMI group. Since CRP was elevated in overweight and obese patients, we opted to use this marker of systemic inflammation as the dependent variable. Because the distribution of CRP was skewed

the variable was log_{10}-transformed to yield a normal distribution before entering the regression analyses. Associations were adjusted for potential confounders in five models: model 1, crude; model 2, adjusted for demographic confounders (age and sex); model 3, additionally adjusted for lung function (FEV_1 %predicted and TLCO %predicted); model 4, additionally adjusted for limitations due to dyspnea (mMRC) and model 5, additionally adjusted for comorbidities. Model 4 was considered the main model since the addition of comorbidities did not improve the explanatory power (change in R^2) for most of the analyses. A general linear model (GLM univariate regression analysis) was employed to investigate the differences between presenting low, medium or high FFMI in each BMI group, after adjustment for age and sex. In the GLM univariate regression analysis the normal weight and high FFMI group was set as reference. All analyses were carried out using the software package SPSS 25.0 (SPSS Inc; Chicago, Illinois) and GraphPad Prism, version 9.2.0 (GraphPad Software Inc., La Jolla, CA, USA). A 2-tailed *P*-value less than .05 was considered significant.

Results

Overall, data from 2137 (1306 male, 61%) patients of spirometric COPD grades 1-4 (n=197, 887, 812, 241) were available for analysis. Patients' characteristics are given in **Table 1**. According to BMI, most patients were stratified as overweight (39.6%) and normal weight (31.3%), while a small proportion of patients were obese class I (16.8%), and the minority was stratified as underweight (12.3%). Compared to the normal weight group, underweight patients were slightly younger with a greater proportion of females and current smokers and presented worse lung function and lower exercise capacity. On the other hand, overweight and obese groups had a greater proportion of males, presented better lung function and higher levels of CRP compared to the normal weight group. Generally, obese patients had the most impaired exercise capacity, HRQL and limitations in activities of daily living due to symptoms of dyspnea.

As expected, BMI was positively associated with FFMI. The use of BMI-adjusted cutoffs allowed the identification of patients with low, medium and high FFMI in male and female patients from all BMI groups (**Figure S1**). However, as displayed in **Figure 1**, the proportion of patients with low FFMI decreased gradually according to the increase in BMI (from underweight to obese groups: 81%, 53%, 42%, 39%). We compared the characteristics among patients with low, medium or high FFMI within each BMI group (**Table 2**). Patients with normal weight and high FFMI presented the lowest degree of airflow limitation (FEV_1: 59.5±20.7 %predicted), lowest proportion of

Table 1. Baseline characteristics of COPD patients stratified into BMI groups

	Missing (In total)	All patients (n=2137)	Underweight (n=262) <21 kg/m²	Normal weight (n=668) 21-<25 kg/m²	Overweight (n=847) 25-<30 kg/m²	Obesity Class I (n=360) 30-<35 kg/m²
Male sex, n (%)	0	1306 (61)	98 (37)#	395 (59)	568 (67)#	245 (68)#
Age (years)	0	65 ± 8	63 ± 9#	65 ± 8	66 ± 8	65 ± 8
BMI (kg/m²)	0	25.8 ± 4.1	18.9 ± 1.6*	23.2 ± 1.1	27.3 ± 1.4*	32.0 ± 1.4*
FFM (kg)	107	54.0 ± 12.0	41.3 ± 7.8*	49.3 ± 9.0	55.8 ± 9.9*	62.1 ± 11.5*
FFMI (kg/m²)	107	18.0 ± 2.8	14.5 ± 1.7*	16.8 ± 1.9	18.8 ± 2.0*	20.8 ± 2.5*
FEV_1 (%predicted)	0	52.5 ± 18.8	45.7 ± 19.4*	51.4 ± 19.6	54.1 ± 18.0*	55.7 ± 17.5*
TLCO (%predicted)	123	51.9 ± 20.3	39.8 ± 18.3*	49.3 ± 19.5	54.7 ± 20.0*	58.4 ± 19.8*
Current smokers, n (%)	3	532 (25)	93 (36)	179 (27)	170 (20)#	90 (25)
Smoking history (py)	13	40 [19-62]	34 [14-55]	38 [17-60]	42 [19-64]	45 [22-70]#
Exacerbations ≥ 2, n (%)	0	1065 (50)	141 (54)	334 (50)	409 (48)	181 (50)
mMRC ≥ 2, n (%)	0	986 (46)	129 (49)	281 (42)	392 (46)	184 (51)#
IPAQ (MET-min/wk)	80	2718 [815-5706]	2623 [825-5541]	2772 [951-5790]	2778 [824-6030]	2079 [577-5160]
TUG (s)	54	6.6 [5.4-8.0]	6.6 [5.5-7.8]	6.2 [5.3-7.8]	6.6 [5.3-8.0]	7.0 [5.8-8.0]*
6MWD (m)	67	420 ± 106	419 ± 101	429 ± 110	423 ± 105	400 ± 100#
6MWD (%predicted)	67	72 ± 18	67 ± 16*	72 ± 19	74 ± 18	73 ± 18
Fibrinogen (g/L)	216	2.4 [1.8-3.2]	2.3 [1.8-3.2]	2.5 [1.8-3.2]	2.5 [1.8-3.3]	2.3 [1.7-3.1]
CRP (mg/dL)	26	0.4 [0.2-0.7]	0.3 [0.1-0.6]	0.3 [0.1-0.6]	0.5 [0.2-0.8]*	0.5 [0.3-1.0]*
IL-6 (pg/mL)	154	2.9 [0.6-8.7]	2.0 [0.3-11.0]	2.8 [0.4-6.9]	3.0 [0.6-8.8]	3.8 [0.9-9.9]#
IL-8 (pg/mL)	154	8.3 [5.5-12.1]	9.1 [6.0-13.3]	8.1 [5.5-11.8]	8.3 [5.4-11.9]	7.8 [5.6-11.9]
TNF-α (pg/mL)	154	8.0 [4.9-12.4]	6.9 [4.1-11.7]	7.8 [4.9-11.6]	8.6 [5.3-13.3]#	7.8 [4.9-12.7]
WBC count (10^9/mL)	36	7.6 [6.4-9.1]	7.6 [6.3-9.4]	7.5 [6.3-9.0]	7.7 [6.4-9.1]	7.6 [6.5-9.0]
SGRQ symptoms	12	56 ± 21	57 ± 20	55 ± 22	55 ± 22	57 ± 21
SGRQ activity	16	58 ± 26	60 ± 25	56 ± 27	56 ± 25	64 ± 23*
SGRQ impact	10	30 ± 21	32 ± 21	29 ± 21	30 ± 20	33 ± 22*
SGRQ total (pts)	19	43 ± 20	45 ± 20	42 ± 20	42 ± 20	47 ± 20*

Data are presented as mean±SD, median [interquartile range] or number (%). Comparison between groups were performed by One-way ANOVA, Kruskal Wallis H test or Chi-square test with Bonferroni correction. #P<0.05 versus normal weight. *P<0.01 versus normal weight. **BMI:** body mass index; **FFM:** fat-free mass; **FFMI:** fat-free mass index; **FEV_1:** forced expiratory volume in the first second; **TLCO:** lung transfer factor for CO; **mMRC:** modified Medical Research Council dyspnea scale; **IPAQ:** International Physical Activity Questionnaire; **MET-min/wk:** metabolic equivalent task scored in minute per week; **TUG:** Timed-up-and-go test; **6MWD:** six minute walk distance; **CRP:** C-reactive protein; **IL-6:** interleukin 6; **IL-8:** interleukin 8; **TNF- α:** tumor necrosis factor alpha; **WBC:** white blood cells; **SGRQ:** St. George Respiratory Questionnaire.

Table 2. Baseline characteristics of the COPD patients stratified into low, medium and high FFMI within BMI groups

BMI group	**Underweight (n=243) <21 kg/m²**			**Normal weight (n=633) 21-<25 kg/m²**			**Overweight (n=811) 25-<30 kg/m²**			**Obesity Class I (n=343) 30-<35 kg/m²**		
FFMI group	**Low (n=197)**	**Medium (n=32)**	**High (n=14)**	**Low (n=337)**	**Medium (n=194)**	**High (n=102)**	**Low (n=341)**	**Medium (n=328)**	**High (n=142)**	**Low (n=132)**	**Medium (n=119)**	**High (n=92)**
Male sex, n (%)	77 (39)	8 (25)	6 (43)	208 (62)	101 (52)	61 (60)	253 (75)	217 (66)	76 (54)#	102 (77)	75 (63)#	55 (60)#
Age (years)	63 ± 9	62 ± 9	65 ± 8	66 ± 8	65 ± 8	65 ± 9	65 ± 8	66 ± 8	66 ± 8	65 ± 9	65 ± 8	63 ± 8
FFMI (kg/m²)	14.1 ± 1.6	15.7 ± 1.3*	16.8 ± 1.6*	16.0 ± 1.4	17.1 ± 1.6*	19.0 ± 1.9*	17.8 ± 1.6	19.0 ± 1.7*	20.6 ± 2.3*	19.6 ± 1.7	20.6 ± 2.0*	22.9 ± 2.7*
FEV_1 (%predicted)	44.5 ± 19.4	49.0 ± 19.1	53.0 ± 21.3	47.9 ± 18.8	53.5 ± 18.8*	59.5 ± 20.7*	51.5 ± 18.6	56.2 ± 17.8*	56.2 ± 16.5#	52.4 ± 17.2	57.4 ± 16.6	56.6 ± 18.1
TLCO (%predicted)	38.9 ± 18.4	43.3 ± 18.6	41.3 ± 13.5	46.6 ± 18.6	50.2 ± 18.5	58.5 ± 21.7*	51.5 ± 18.1	57.0 ± 21.6*	57.0 ± 18.1#	56.6 ± 19.6	57.5 ± 18.5	62.3 ± 21.7
Current Smokers, n (%)	67 (34)	12 (38)	5 (39)	90 (27)	50 (26)	26 (26)	73 (21)	58 (18)	31 (22)	27 (21)	31 (26)	29(32)
Smoking History (py)	34 [16-56]	38 [16-48]	43 [22-55]	37 [18-59]	40 [16-62]	36 [15-57]	42 [19-64]	42 [19-64]	42 [21-60]	46 [26-72]	46 [29-69]	40 [16-71]
Exacerbations ≥ 2 n(%)	106 (54)	20 (62)	5 (36)	178 (53)	91 (47)	43 (42)	174 (51)	152 (46)	62 (44)	73 (55)	54 (45)	45 (49)
mMRC ≥ 2 n (%)	99 (50)	14 (44)	8 (57)	161 (48)	76 (39)	28 (27)*	179 (53)	135 (41)#	63 (44)	70 (53)	59 (50)	46 (50)
IPAQ (MET-min/wk)	2629 [859-5554]	2688 [815-5379]	1555 [834-3864]	2113 [700-5224]	2833 [1281-6377]	3732* [1386-7391]	2679 [648-5343]	2895 [834-6399]	3399* [1440-8106]	2182 [638-5729]	1746 [495-5490]	1980 [678-4279]
CRP (mg/dL)	0.3 [0.1-0.6]	0.2 [0.1-0.5]	0.3 [0.0-0.5]	0.4 [0.2-0.6]	0.3 [0.1-0.6]	0.3 [0.1-0.6]#	0.5 [0.2-0.8]	0.5 [0.2-0.7]	0.4 [0.2-0.6]	0.5 [0.3-1.0]	0.5 [0.2-0.7]	0.6 [0.3-1.1]
6MWD (m)	409 ± 103	455 ± 80#	464 ± 93	415 ± 113	444 ± 99#	456 ± 104*	413 ± 111	437 ± 101#	416 ± 103	397 ± 101	408 ± 88	400 ± 111
6MWD (%predicted)	65 ± 16	73 ± 14 #	75 ± 18	70 ± 19	74 ± 17#	77 ± 17*	71 ± 18	77 ± 17#	74 ± 19	72 ± 18	74 ± 16	72 ± 20
TUG (s)	6.9 [5.7-8.0]	6.0 [5.2-7.1]	6.4 [5.8-7.7]	6.4 [5.3-8.0]	6.1 [5.2-7.7]	6.0 [5.2-7.3]	6.7 [5.3-8.0]	6.3 [5.3-7.6]	6.7 [5.3-8.3]	7.0 [5.5-8.3]	6.8 [5.8-8.0]	7.0 [5.8-8.0]
SGRQ symptoms (pts)	57 ± 20	56 ± 20	59 ± 18	55 ± 22	55 ± 21	52 ± 23	56 ± 21	55 ± 22	56 ± 22	56 ± 21	57 ± 20	58 ± 21
SGRQ activity (pts)	61 ± 25	55 ± 25	56 ± 24	60 ± 26	53 ± 26#	48 ± 29*	58 ± 25	53 ± 26	56 ± 26	65 ± 23	64 ± 25	62 ± 22
SGRQ impact (pts)	32 ± 21	28 ± 16	30 ± 16	30 ± 21	26 ± 19	25 ± 22	31 ± 20	28 ± 19	30 ± 21	35 ± 23	30 ± 20	34 ± 23
SGRQ total (pts)	46 ± 20	41 ± 17	43 ± 16	44 ± 20	40 ± 19	37 ± 22#	44 ± 19	40 ± 19	43 ± 20	48 ± 20	45 ± 19	47 ± 20

Data are presented as mean±SD, median [interquartile range] or number (%). Comparison between groups were performed by One-way ANOVA, Kruskal Wallis H test or Chi-square test with Bonferroni correction. #P<0.05 versus low FFMI from the same BMI group. *P<0.01 versus low FFMI from the same BMI group. **BMI:** body mass index; **FFMI:** fat-free mass index; **FEV_1:** forced expiratory volume in the first second; **TLCO:** lung transfer factor for CO; **mMRC:** modified Medical Research Council dyspnea scale; **IPAQ:** International Physical Activity Questionnaire; **MET-min/wk:** metabolic equivalent task scored in minute per week; **TUG:** Timed-up-and-go test; **6MWD:** six minute walk distance; **CRP:** C-reactive protein; **IL-6:** interleukin 6; **IL-8:** interleukin 8; **TNF- α:** tumor necrosis factor alpha; **WBC:** white blood cells; **SGRQ:** St. George Respiratory Questionnaire.

patients with moderate to severe limitations in activities of daily living due to dyspnea (27%), highest levels of physical activity (IPAQ: 3732 [1386-7391] MET-min/wk), best exercise capacity (6MWD: 77±17 %predicted) and HRQL (SGRQ total score: 37±22 pts). Underweight patients with medium and high FFMI showed a better exercise capacity compared with underweight patients with low FFMI. Overweight patients with medium and high FFMI presented slightly better lung function, exercise capacity and physical activity compared to overweight patients with low FFMI. There were no significant differences among obese patients after stratification for low, medium or high FFMI (**Table 2**).

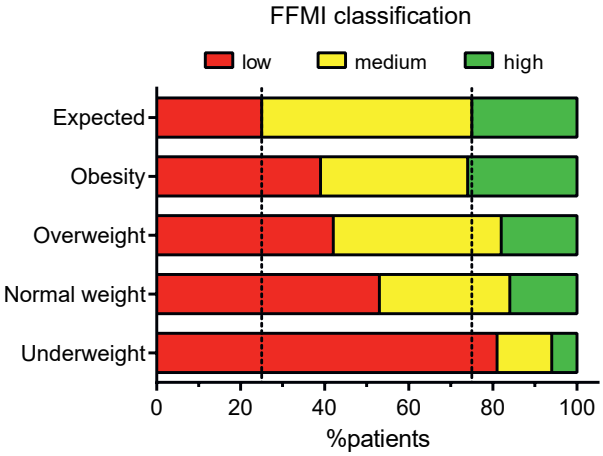

Figure 1. Proportion of COPD patients stratified into low, medium or high fat-free mass index (FFMI) within body mass index (BMI) groups. First row shows the expected proportion according to the reference values.

To enable a direct comparison of exercise capacity and HRQL among patients with low, medium and high FFMI in each BMI group, we performed GLM univariate regression analysis controlling for age and gender (**Figure 2**). We observed a FFMI-dependent linear increase in 6MWD and a decrease in SGRQ total score (better health status) in normal weight patients. In addition, patients with low FFMI irrespective of the BMI classification, and obese patients irrespective of the FFMI classification, showed lower 6MWD and higher SGRQ total scores compared with normal weight patients with high FFMI.

Subsequently, **Table 3** presents the unstandardized regression coefficients and confidence intervals from the different models which were designed to explore the associations between FFM and fat mass with exercise capacity, quality of life and markers of systemic inflammation after adjustment for potential confounders. FFM was associated with the 6MWD in underweight and normal weight groups, even when adjusting for a broad set

of covariates (Model 5 - B [95% CI]: 4.28 [1.78/7.85]m and 2.26 [0.80/3.72]m per Kg of FFM, respectively). In the overweight group, FFM was not associated with the 6MWD after adjustment for FEV_1 and TLCO ($P \geq 0.237$). In the obese group, while FFM was not associated with 6MWD, fat mass was negatively associated with 6MWD even after adjustment for all the covariates (Model 5 - B [95% CI]: -1.69 [-3.07/-0.31]m per Kg of fat mass). Moreover, associations between FFM and SGRQ total score were found in normal weight and underweight patients, which were not statistically significant after adjustment for FEV_1, TLCO and symptoms of dyspnea. Finally, in normal weight and overweight patients, fat mass was independently associated with log-transformed CRP (Model 5 - B [95% CI] 0.016 [0.006/0.026] and 0.008 [0.000/0.016] per Kg of fat mass, respectively).

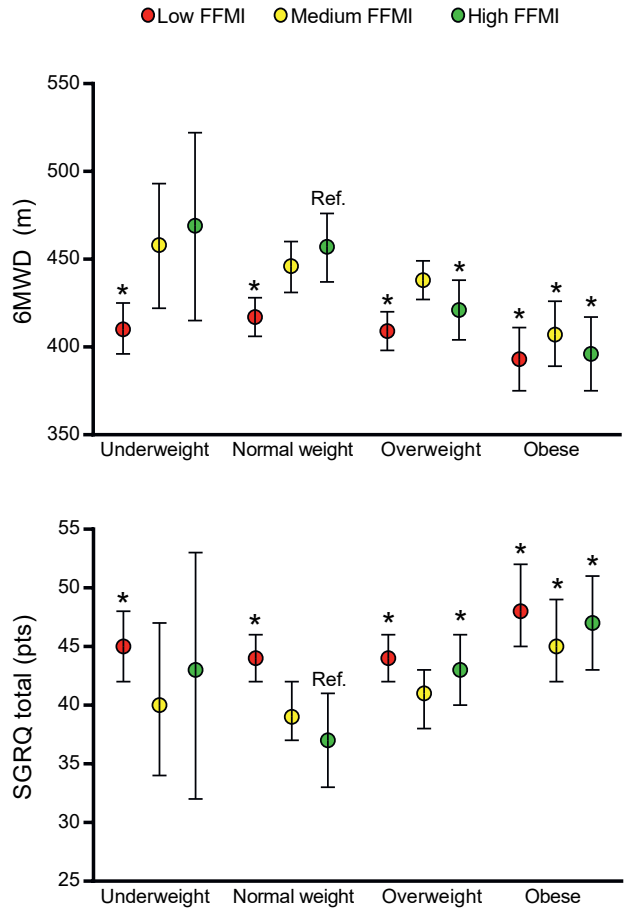

Figure 2. Comparisons of exercise capacity and HRQL between COPD patients with low, medium or high fat-free mass index (FFMI) within body mass index (BMI) groups. Estimate means and confidence interval from GLM Univariate Regression Analysis with adjustment for age and sex.

Table 3. Associations of fat-free mass (FFM) and fat mass (FM) with exercise capacity, quality of life and systemic inflammation in patients with COPD

	Model 1		Model 2		Model 3		Model 4		Model 5	
6MWD (m)	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**
Underweight										
FFM (per 1 kg)	2.57 (0.70/4.45)	0.008	6.89 (4.38/9.40)	<0.001	4.54 (2.29/6.80)	<0.001	4.08 (1.90/6.26)	<0.001	4.28 (1.90/6.65)	<0.001
FM (per 1 kg)	1.94 (-1.42/5.29)	0.256	-0.08 (-3.34/3.19)	0.963	-1.30 (-4.15/1.55)	0.369	-0.98 (-3.73/1.77)	0.483	-0.93 (-3.88/2.02)	0.536
Normal weight										
FFM (per 1 kg)	2.68 (1.61/3.75)	<0.001	5.28 (3.67/6.89)	<0.001	2.10 (0.61/3.59)	0.006	1.95 (0.52/3.38)	0.008	2.26 (0.80/3.72)	0.002
FM (per 1 kg)	-0.66 (-2.66/1.34)	0.518	-1.07 (-3.02/0.89)	0.285	-0.59 (-2.31/1.13)	0.502	-0.25 (-1.90/1.41)	0.772	-0.59 (-2.30/1.12)	0.498
Overweight										
FFM (per 1 kg)	1.98 (1.20/2.77)	<0.001	1.53 (0.30/2.76)	0.014	0.35 (-0.71/1.42)	0.514	0.31 (-0.68/1.30)	0.544	0.23 (-0.77/1.23)	0.651
FM (per 1 kg)	-0.51 (-1.97/0.95)	0.491	-1.12 (-2.57/0.33)	0.131	-1.01 (-2.26/0.24)	0.113	-0.61 (-1.78/0.56)	0.304	-0.57 (-1.76/0.62)	0.346
Obese										
FFM (per 1 kg)	0.77 (-0.24/1.78)	0.136	0.11 (-1.40/1.63)	0.882	-0.26 (-1.53/1.01)	0.689	-0.42 (-1.60/0.76)	0.481	-0.82 (-2.05/0.42)	0.195
FM (per 1 kg)	-1.86 (-3.60/-0.12)	0.036	-2.43(-4.14/-0.73)	0.005	-1.55 (-3.00/-0.10)	0.036	-1.37 (-2.71/-0.03)	0.044	-1.69 (-3.07/-0.31)	0.017
SGRQ Total (pts)	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**
Underweight										
FFM (per 1 kg)	-0.27 (-0.63/0.10)	0.156	-1.00 (-1.50/-0.50)	<0.001	-0.51 (-0.97/-0.06)	0.028	-0.32 (-0.70/0.06)	0.103	-0.29 (-0.69/0.10)	0.146
FM (per 1 kg)	-0.42 (-1.08/0.24)	0.208	-0.12 (-0.78/0.53)	0.711	0.07 (-0.51/0.65)	0.813	-0.07 (-0.55/0.41)	0.788	0.06 (-0.43/0.55)	0.811
Normal weight										
FFM (per 1 kg)	-0.29 (-0.49/-0.09)	0.005	-0.87 (-1.17/-0.56)	<0.001	-0.24 (-0.52/0.04)	0.093	-0.19 (-0.42/0.05)	0.121	-0.18 (-0.42/0.05)	0.127
FM (per 1 kg)	-0.15 (-0.53/0.22)	0.424	-0.04 (-0.41/0.34)	0.851	-0.12 (-0.44/0.21)	0.481	-0.25 (-0.52/0.03)	0.078	-0.18 (-0.45/0.10)	0.204
Overweight										
FFM (per 1 kg)	-0.22 (-0.37/-0.07)	0.003	-0.14 (-0.38/0.09)	0.237	0.06 (-0.16/0.27)	0.592	0.07 (-0.10/0.25)	0.418	0.14 (-0.03/0.32)	0.105
FM (per 1 kg)	0.02 (-0.25/0.30)	0.866	0.03 (-0.25/0.32)	0.816	0.02 (-0.24/0.27)	0.898	-0.11 (-0.31/0.10)	0.322	-0.02 (-0.22/0.19)	0.887
Obese										
FFM (per 1 kg)	0.00 (-0.20/0.21)	0.979	0.03 (-0.28/0.34)	0.845	0.09 (-0.20/0.38)	0.542	0.14 (-0.09/0.38)	0.234	0.15 (-0.09/0.40)	0.208
FM (per 1 kg)	0.24 (-0.11/0.59)	0.175	0.24 (-0.11/0.60)	0.178	0.10 (-0.22/0.43)	0.540	0.04 (-0.23/0.31)	0.750	0.02 (-0.25/0.28)	0.910

Table 3 continues on next page.

Table 3. *Continued*

	Model 1		Model 2		Model 3		Model 4		Model 5	
Log_{10} (CRP)	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**	**B (95% CI)**	***P*-value**
Underweight										
FFM (per 1 kg)	0.006 (-0.005/0.016)	0.297	-0.004 (-0.019/0.011)	0.609	-0.003 (-0.019/0.012)	0.666	-0.003 (-0.019/0.013)	0.706	-0.002 (-0.019/0.015)	0.814
FM (per 1 kg)	-0.004 (-0.023/0.016)	0.712	0.002 (-0.018/0.021)	0.879	0.002 (-0.018/0.022)	0.865	0.001 (-0.018/0.021)	0.887	0.004 (-0.018/0.025)	0.735
Normal weight										
FFM (per 1 kg)	0.001 (-0.004/0.007)	0.604	-0.009 (-0.017/-0.001)	0.036	-0.007 (-0.015/0.002)	0.124	-0.007 (-0.015/0.002)	0.129	-0.008 (-0.017/0.000)	0.064
FM (per 1 kg)	0.014 (0.004/0.024)	0.005	0.016 (0.006/0.025)	0.002	0.015 (0.005/0.025)	0.002	0.015 (0.005/0.025)	0.003	0.016 (0.006/0.026)	0.002
Overweight										
FFM (per 1 kg)	0.002 (-0.002/0.006)	0.252	0.000 (-0.007/0.006)	0.958	0.001 (-0.005/0.008)	0.687	0.001 (-0.005/0.008)	0.685	-0.001 (-0.007/0.006)	0.866
FM (per 1 kg)	0.008 (0.001/0.016)	0.033	0.009 (0.001/0.016)	0.027	0.008 (0.001/0.016)	0.028	0.008 (0.001/0.016)	0.030	0.008 (0.000/0.016)	0.046
Obese										
FFM (per 1 kg)	-0.003 (-0.008/0.002)	0.208	0.000 (-0.008/0.008)	0.983	0.001 (-0.007/0.008)	0.858	0.001 (-0.007/0.008)	0.843	0.000 (-0.008/0.008)	0.972
FM (per 1 kg)	0.002 (-0.006/0.011)	0.611	0.002 (-0.007/0.011)	0.705	-0.001 (-0.010/0.008)	0.812	-0.001 (-0.010/0.008)	0.798	-0.001 (-0.010/0.008)	0.863

B (95% CI): indicates coefficients and 95% confidence interval obtained from the multiple linear regression models. **Model 1:** Crude. **Model 2:** adjusted for age and sex. **Model 3:** additionally adjusted for lung function (FEV_1 and TLCO %predicted). **Model 4:** additionally adjusted for dyspnea (mMRC). **Model 5:** additionally adjusted for comorbidities.

The complete results of the main model (Model 4) are shown in the Online Supplement (**Tables S1**, **S2**, **S3**). The addition of comorbidities in Model 5 did not improve the explanatory power of most of the analyses (Sig. F Change $P>0.05$). In the underweight group, none of the assessed comorbidities was associated with exercise capacity, HRQL or inflammation status. In the normal weight group, the following comorbidities were associated with a higher SGRQ total score: sleep apnea (6.73 [1.22/12.25] pts), chronic bronchitis (4.32 [2.04/6.60] pts), GE reflux disease (3.68 [0.04/17.32] pts) and psychiatric disorders (5.74 [2.94/8.55] pts). In the overweight group, heart failure was negatively (-44.87 [-73.62/-16.12] m), and asthma was positively (16.27 [0.57/31.97] m) associated with the 6MWD, while the presence of asthma (4.68 [1.95/7.41] pts), chronic bronchitis (2.23 [0.15/4.32] pts), psychiatric disorders (6.25 [3.48/9.01] pts), and peripheral neuropathy (5.00 [0.60/9.38] pts) were associated with a higher SGRQ total score. Finally, in the obese group, sleep apnea (4.43 [0.41/8.44] pts), cardiac dysrhythmia (6.79 [0.45/13.14] pts), asthma (7.11 [2.20/12.01] pts) and chronic bronchitis (5.80 [2.41/9.20] pts) were associated with a higher SGRQ total score.

Discussion

The main finding of our study is that patients with COPD with low FFMI, independent of the BMI group, showed a lower exercise capacity and worse HRQL compared with normal weight patients with high FFMI. Moreover, body composition was differently associated with exercise capacity, HRQL and markers of systemic inflammation depending on the BMI group. Our models showed that FFM is a factor strongly associated with exercise capacity in underweight patients, however, the impact of dyspnea, age and reduced lung function increased and overtook the contribution of FFM to exercise capacity in the other BMI groups. In the obese group, the amount of fat mass was independently and negatively associated with exercise capacity. In addition, the present study showed that HRQL is not associated with FFM after adjustment for lung function or dyspnea, and higher amounts of fat mass are associated with higher plasma levels of CRP in normal weight and overweight COPD patients. Interestingly, we identified which specific comorbidities are associated with exercise capacity and HRQL in each BMI group.

Stratification into BMI groups

We found that stratification using BMI allowed the discrimination of groups of patients with COPD who showed slight but significant differences in lung function, exercise

capacity, HRQL and systemic inflammation. As BMI is a simple and inexpensive measure, this variable has been widely studied in patients with COPD. In a recent systematic review, Souto-Miranda et al.[28] demonstrated that from thirty-two studies that reported body composition as an outcome domain to evaluate the impact of pulmonary rehabilitation, twenty-two used BMI as an outcome measure. However, as BMI does not allow differentiation between fat-free and fat mass, a strong association between this variable and patients' physical condition or health status is unexpected. The current evidence shows that being underweight in COPD is usually associated with increased disease severity, more impaired diffusion capacity (suggesting more severe emphysema) and specific comorbidities such as osteoporosis and renal impairment.[3,28,29] In contrast, obese patients with COPD frequently present relatively preserved lung function but chronic bronchitis and increased cardiovascular risk factors.[3,28,29] In addition, in more severe COPD stages, overweight and obese patients present improved survival compared with normal weight patients with COPD.[30,31] Our findings suggest that being normal-to-overweight is associated with better exercise capacity and HRQL in comparison with patients that are on both extremities of BMI (i.e., BMI <21 or ≥30 kg/m^2). Importantly, when interpreting the clinical meaning of BMI values in patients with COPD one should also consider other aspects, such as disease severity, frequency of exacerbations, cardiovascular risk factors and body composition.

Stratification into FFMI groups

Although some information can be obtained by the stratification into BMI groups, FFMI is a more accurate and suitable parameter to express pulmonary and extrapulmonary characteristics, such as disease severity and exercise capacity.[14] Using BIA, we were able to further stratify patients with COPD from this cohort into clinically significant FFMI groups. Previous studies have also shown that the frequency of low FFMI in patients with COPD decreases in higher BMI groups and is more common in male patients.[9,10] The stratification into medium and high FFMI showed subgroups of patients with better lung function, exercise capacity, physical activity, HRQL and symptoms compared with their low FFMI counterparts. These differences were found mainly in the normal weight and overweight groups. In the underweight group, the absence of statistically significant differences may be partially explained by a lack of power in view of the low number of patients in the medium (n=32) and high (n=14) FFMI groups. On the other hand, the absence of differences between patients with low, medium and high FFMI in the obese group occurred despite a relatively

uniform distribution of patients. This suggests that FFMI as assessed by BIA is not an informative variable in obese patients with COPD.

Different association between body composition, exercise capacity, HRQL and systemic inflammation

One of the strengths of our study is the use of a large and well characterized multi-center COPD cohort with data for several potential confounders and other risk factors for worse exercise capacity, HRQL and inflammation status. Our findings regarding the association between body composition and exercise capacity, HRQL and systemic inflammation corroborate and further extend results from previous studies. Regarding exercise capacity, Ischaki et al.[14] found a moderate correlation (r^2=0.42) between FFMI and 6MWD in clinically stable patients with COPD whereas Rodríguez et al.[34] demonstrated that determinants of exercise capacity may differ between obese and non-obese patients with COPD. Interestingly, BMI was inversely associated with 6MWD only in obese patients with COPD[34] and fat mass index has already been shown to be negatively associated with the 6MWD in this population.[10] Also, we were able to demonstrate that dyspnea and lung function, and not body composition, are the main determinants of SGRQ total score. In relation to systemic inflammation, Rutten et al.[15] showed that fat mass was associated with plasma levels of CRP independent of sex and age in a group of moderate to severe patients with COPD. In the current study, the amount of fat mass was independently associated with systemic inflammation exclusively in normal-to-overweight COPD patients. However, the overweight and obese groups showed higher plasma levels of CRP compared to normal weight patients. Finally, Divo et al.[30] found that specific comorbidities that impact independently on mortality are different in the BMI groups. We extend these findings demonstrating that different comorbidities are also associated with exercise capacity and HRQL depending on the BMI group which the patient is allocated.

Limitations of our study

First, the use of BIA to assess body composition may be considered a limitation since it provides a measure of whole body FFM which may be affected by the hydration and fed conditions. The use of other methods that allow quantification of muscle mass at regional levels (i.e., trunk, upper and lower limbs), such as DEXA and magnetic resonance imaging could be more appropriate. However, the use of these methods may be limited by equipment costs and need for highly trained operating personnel which could hamper their use in large cohorts. On the other hand, BIA is a reliable and

more easily accessible method for estimating FFM in chronic diseases if a standardized methodology is used.[17] Second, this study presents cross-sectional analysis and can only report associations, but not causal relationships. We highlight that the findings regarding the BMI related associations between body composition, exercise capacity, HRQL and systemic inflammation are plausible and more than mere correlations - considering that we explored different models with the addition of important potential confounders. However, we acknowledge that the inclusion of longitudinal outcomes such as the incidence of exacerbations and hospitalizations and all-cause mortality would be a major advance. Third, the comparisons between patients with low, medium and high FFMI in the underweight group may have been influenced by low statistical power as revealed by meaningful differences not reaching a significant *P*-value (6MWD: high FFMI [464±93 m] vs low FFMI [409±103 m]). Nevertheless, the size of these groups is a result of the present study, which reveals the proportion or patients with these BMI and FFMI values in the COSYCONET cohort. We were able to demonstrate that one in every five patients with COPD with BMI <21 kg/m^2 present a FFMI higher than the 25th percentile of their sex-age-BMI specific reference values which is associated with better characteristics.

Clinical implications and conclusions

Using a large data set of a COPD cohort we demonstrated that depending on BMI, body composition is differently associated with exercise capacity, HRQL and systemic inflammation. Low FFMI is associated with reduced exercise capacity and HRQL in underweight, normal weight and overweight COPD patients. The group of obese patients was the most impaired in terms of exercise capacity and HRQL irrespective of their FFMI. Taking into account lung function, physical condition and health status, we demonstrated that normal weight with high FFMI is the favourable combination within the broad spectrum of body weight and body composition in patients with COPD. Our findings suggest that in under or normal weight COPD patients, interventions aiming to increase FFMI are more likely to be associated with improvement in exercise capacity and HRQL. On the other hand, in overweight and obese patients the benefits of increasing FFMI are hampered by influences of excessive fat mass. In these patients, weight loss with preservation of FFMI might be the first and most important therapeutic aim. However, we acknowledge that these hypotheses should be further investigated in longitudinal and intervention studies.

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Table S1. Multiple linear regression analysis with 6MWD as dependent variable in COPD patients stratified in BMI groups

Model 4	Covariate	Standardized Coefficients	Unstandardized Coefficients	SE	*P*	95% CI	
						Lower	Upper
6MWD (m) Underweight (n=219) R^2=0.41	FFM (kg)	0.32	4.08	1.11	<0.001	1.90	6.26
	FM (kg)	-0.04	-0.98	1.39	0.483	-3.73	1.77
	Gender (male)	-0.25	-52.93	18.50	0.005	-89.39	-16.47
	Age (years)	-0.07	-0.83	0.62	0.179	-2.05	0.39
	FEV_1 (%predicted)	0.17	0.91	0.36	0.012	0.21	1.61
	TLCO (%predicted)	0.24	1.34	0.35	<0.001	0.65	2.03
	mMRC (pts)	-0.26	-28.84	6.98	<0.001	-42.60	-15.07
6MWD (m) Normal weight (n=595) R^2=0.37	FFM (kg)	0.16	1.95	0.73	0.008	0.52	3.38
	FM (kg)	-0.01	-0.25	0.84	0.772	-1.90	1.41
	Gender (male)	-0.02	-4.87	13.20	0.712	-30.78	21.05
	Age (years)	-0.19	-2.44	0.44	<0.001	-3.31	-1.57
	FEV_1 (%predicted)	0.25	1.43	0.25	<0.001	0.94	1.91
	TLCO (%predicted)	0.12	0.67	0.23	0.004	0.21	1.12
	mMRC (pts)	-0.28	-34.09	4.79	<0.001	-43.49	-24.69
6MWD (m) Overweight (n=772) R^2=0.42	FFM (kg)	0.03	0.31	0.50	0.544	-0.68	1.30
	FM (kg)	-0.03	-0.61	0.59	0.304	-1.78	0.56
	Gender (male)	0.08	18.23	10.65	0.087	-2.67	38.13
	Age (years)	-0.23	-2.88	0.36	<0.001	-3.59	-2.17
	FEV_1 (%predicted)	0.22	1.26	0.20	<0.001	0.87	1.64
	TLCO (%predicted)	0.17	0.89	0.17	<0.001	0.55	1.23
	mMRC (pts)	-0.35	-41.08	3.72	<0.001	-48.37	-33.79
6MWD (m) Obese (n=321) R^2=0.46	FFM (kg)	-0.05	-0.42	0.60	0.481	-1.60	0.76
	FM (kg)	-0.09	-1.37	0.68	0.044	-2.71	-0.30
	Gender (male)	0.08	17.04	14.55	0.242	-11.59	45.68
	Age (years)	-0.30	-3.65	0.54	<0.001	-4.71	-2.59
	FEV_1 (%predicted)	0.21	1.20	0.29	<0.001	0.63	1.78
	TLCO (%predicted)	0.23	1.15	0.25	<0.001	0.66	1.64
	mMRC (pts)	-0.34	-37.59	5.12	<0.001	-47.65	-27.52

6MWD: six-minute walk distance; **FFM:** fat-free mass; **FM:** fat mass; **FEV_1:** forced expiratory volume in the first second; **TLCO:** lung transfer factor for CO; **mMRC:** modified Medical Research Council dyspnea scale.

Table S2. Multiple linear regression analysis with SGRQ as dependent variable in COPD patients stratified in BMI groups

Model 4	Covariate	Standardized Coefficients	Unstandardized Coefficients	SE	*P*	95% CI	
						Lower	Upper
SGRQ total (pts) Underweight (n=219) R^2=0.52	FFM (kg)	-0.13	-0.32	0.19	0.103	-0.70	0.06
	FM (kg)	-0.02	-0.07	0.24	0.778	-0.55	0.41
	Gender (male)	0.11	4.29	3.23	0.186	-2.08	10.65
	Age (years)	-0.07	-0.16	0.11	0.147	-0.37	0.06
	FEV_1 (%predicted)	-0.16	-0.16	0.06	0.011	-0.28	-0.04
	TLCO (%predicted)	-0.08	-0.08	0.06	0.192	-0.20	0.04
	mMRC (pts)	0.57	12.16	1.22	<0.001	9.76	14.56
SGRQ total (pts) Normal weight (n=595) R^2=0.51	FFM (kg)	-0.08	-0.19	0.12	0.121	-0.42	0.05
	FM (kg)	-0.06	-0.25	0.14	0.078	-0.52	0.03
	Gender (male)	0.05	2.22	2.16	0.304	-2.02	6.47
	Age (years)	-0.07	-0.17	0.07	0.019	-0.31	-0.03
	FEV_1 (%predicted)	-0.20	-0.21	0.04	<0.001	-0.29	-0.13
	TLCO (%predicted)	-0.03	-0.03	0.04	0.431	-0.10	0.04
	mMRC (pts)	0.56	12.61	0.78	<0.001	11.07	14.15
SGRQ total (pts) Overweight (n=772) R^2=0.46	FFM (kg)	0.04	0.07	0.09	0.418	-0.10	0.25
	FM (kg)	-0.03	-0.11	0.11	0.322	-0.31	0.10
	Gender (male)	-0.09	-3.68	1.91	0.055	-7.43	0.07
	Age (years)	0.03	0.08	0.07	0.246	-0.05	0.20
	FEV_1 (%predicted)	-0.14	-0.16	0.04	<0.001	-0.23	-0.09
	TLCO (%predicted)	-0.08	-0.07	0.03	0.017	-0.14	-0.01
	mMRC (pts)	0.57	12.54	0.67	<0.001	11.23	13.84
SGRQ total (pts) Obese (n=314) R^2=0.44	FFM (kg)	0.08	0.14	0.12	0.234	-0.09	0.38
	FM (kg)	0.02	0.04	0.14	0.750	-0.23	0.31
	Gender (male)	-0.03	-1.32	2.92	0.651	-7.07	4.43
	Age (years)	0.00	0.02	0.11	0.857	-0.19	0.23
	FEV_1 (%predicted)	-0.05	-0.05	0.06	0.383	-0.17	0.07
	TLCO (%predicted)	-0.15	-0.14	0.05	0.004	-0.24	-0.05
	mMRC (pts)	0.58	12.53	1.03	<0.001	10.51	14.55

6MWD: six-minute walk distance; **FFM:** fat-free mass; **FM:** fat mass; **FEV_1:** forced expiratory volume in the first second; **TLCO:** lung transfer factor for CO; **mMRC:** modified Medical Research Council dyspnea scale.

Table S3. Multiple linear regression analysis with Log10 CRP as dependent variable in COPD patients stratified in BMI groups

Model 4	Covariate	Standardized Coefficients	Unstandardized Coefficients	SE	*P*	95% CI	
						Lower	Upper
Log_{10} (CRP) Underweight (n=219) R^2=0.04	FFM (kg)	-0.04	-0.003	0.008	0.706	-0.019	0.013
	FM (kg)	0.01	0.001	0.010	0.887	-0.018	0.021
	Gender (male)	0.18	0.216	0.134	0.108	-0.048	0.481
	Age (years)	0.09	0.005	0.004	0.222	-0.003	0.014
	FEV_1 (%predicted)	0.00	0.000	0.003	0.968	-0.005	0.005
	TLCO (%predicted)	0.00	0.000	0.003	0.998	-0.005	0.005
	mMRC (pts)	0.04	0.025	0.051	0.618	-0.074	0.125
Log_{10} (CRP) Normal weight (n=595) R^2=0.04	FFM (kg)	-0.11	-0.007	0.004	0.129	-0.015	0.002
	FM (kg)	0.14	0.015	0.005	0.003	0.005	0.025
	Gender (male)	0.19	0.205	0.078	0.009	0.052	0.357
	Age (years)	0.00	0.000	0.003	0.944	-0.005	0.005
	FEV_1 (%predicted)	0.00	0.000	0.001	0.994	-0.003	0.003
	TLCO (%predicted)	-0.06	-0.002	0.001	0.230	-0.004	0.001
	mMRC (pts)	0.03	0.017	0.028	0.550	-0.038	0.072
Log_{10} (CRP) Overweight (n=761) R^2=0.02	FFM (kg)	0.03	0.001	0.003	0.685	-0.005	0.008
	FM (kg)	0.09	0.008	0.004	0.030	0.001	0.016
	Gender (male)	0.04	0.044	0.069	0.529	-0.092	0.180
	Age (years)	0.00	0.000	0.002	0.897	-0.004	0.005
	FEV_1 (%predicted)	-0.09	-0.003	0.001	0.037	-0.005	0.000
	TLCO (%predicted)	-0.05	-0.001	0.001	0.286	-0.003	0.001
	mMRC (pts)	0.01	0.008	0.024	0.750	-0.040	0.055
Log_{10} (CRP) Obese (n=318) R^2=0.08	FFM (kg)	0.02	0.001	0.004	0.843	-0.007	0.008
	FM (kg)	-0.02	-0.001	0.004	0.798	-0.010	0.008
	Gender (male)	-0.09	-0.099	0.094	0.293	-0.283	0.086
	Age (years)	0.00	0.000	0.003	0.974	-0.007	0.007
	FEV_1 (%predicted)	-0.03	-0.001	0.002	0.607	-0.005	0.003
	TLCO (%predicted)	-0.24	-0.006	0.002	<0.001	-0.009	-0.003
	mMRC (pts)	0.03	0.018	0.033	0.591	-0.047	0.083

6MWD: six-minute walk distance; **FFM:** fat-free mass; **FM:** fat mass; **FEV_1:** forced expiratory volume in the first second; **TLCO:** lung transfer factor for CO; **mMRC:** modified Medical Research Council dyspnea scale.

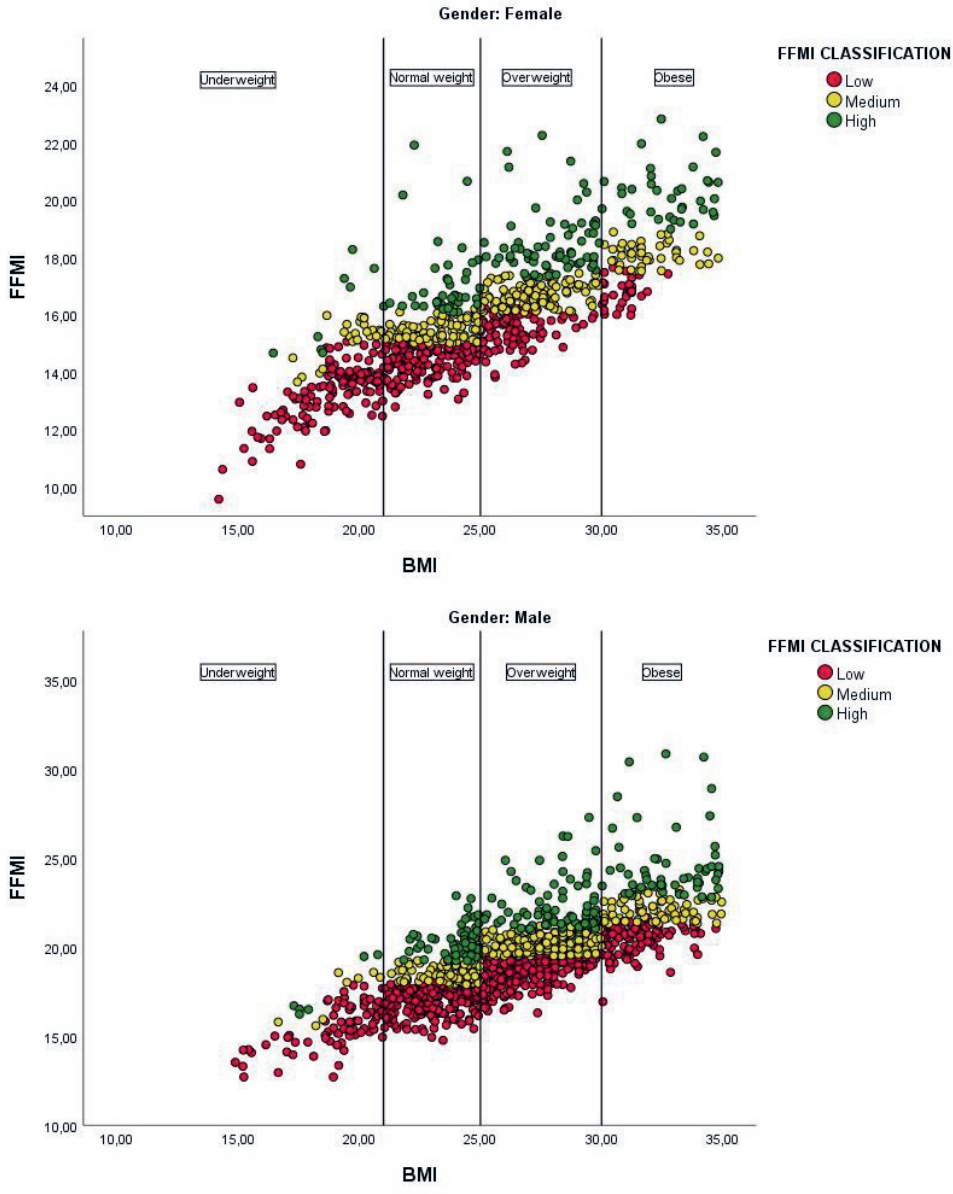

Figure S1. Correlation between BMI and FFMI in female (top) and male (bottom) in COPD patients stratified in low, medium and high FFMI in each BMI group.

Chapter 8

Summary and general discussion

Summary and general discussion

The main objective of this thesis was to investigate the frequency and impact of body composition abnormalities in individuals with chronic respiratory diseases (CRDs), especially chronic obstructive pulmonary disease (COPD), asthma and idiopathic pulmonary fibrosis (IPF). Our data demonstrate that only a minority of patients with CRDs referred for pulmonary rehabilitation exhibit normal body composition in terms of the expected amount of muscle mass, assessed by surrogate markers such as fat-free mass index (FFMI), appendicular skeletal muscle mass index (ASMI) or phase angle (PhA), and fat mass. In **Chapter 2**, we demonstrated that only 39% of the patients with COPD had a normal body composition while all the remaining patients presented a high amount of fat mass, a low amount of FFMI or a combination thereof. In **Chapter 3**, more than half of the patients with COPD enrolled were overweight or obese according to body mass index (BMI). Among the entire sample, the proportion of patients with normal BMI and normal FFMI was 18.8%. Additionally, the results from **Chapter 4**, showed that only one in every four adult patients with asthma referred for pulmonary rehabilitation is classified as having normal weight according to body mass index (BMI) and approximately 20% of these patients present low ASMI. Similar results were found in IPF (**Chapter 5**). We demonstrated that 36% of the patients with IPF were classified as normal body weight according to BMI. In general, the frequency of abnormal low PhA (26%) was higher than expected, according to the use of the 10th percentile of the reference values for the general population. Finally, in **Chapter 7**, body composition abnormalities were investigated in outpatients from a large multicentre COPD cohort. Almost fifteen percent of patients was considered as presenting normal weight and preserved FFMI. In summary, these studies show that body composition abnormalities are common in patients with CRDs referred for pulmonary rehabilitation and possibly in the totality of patients with CRDs. Data from **Chapter 6** reiterate the finding of a higher frequency of body composition abnormalities in COPD since 42% and 35% of the patients presented low FFMI and high fat mass index (FMI), whereas applying the same criteria in smoking and non-smoking controls yielded considerably lower frequencies. Besides, the main results from **Chapter 6** demonstrate that patients with COPD present a significant decline in total, leg- and trunk-FFM after 2 years of follow-up compared with non-smoking controls. Notably, we were able to identify a subgroup of patients with COPD showing a different body composition trajectory characterized by a greater decline in total and legs FFM.

Also, this thesis clearly demonstrated that the more the body composition of an individual with CRDs is deviated from normal (defined as the mean of the general population), the more impairment is observed in pulmonary and extra-pulmonary characteristics. In **Chapter 2**, we found that sarcopenic obese (SO) patients with COPD, which exhibit the largest deviation from their expected body composition, were generally the most impaired concerning the severity of airflow limitation and reductions in physical functioning. The results suggest that this sub-group of patients is at higher risk of mortality since these patients showed 9.5 times higher odds of having a six-minute walk distance (6MWD) ≤350 meters, a well establish cut-off value independently associated with worse survival.[1] In **Chapter 7**, body composition could be explored in detail by the stratification of patients with COPD into twelve groups (four BMI groups stratified into three FFMI groups), patients with the lowest deviation from their expected body composition (normal weight patients with high FFMI) showed the best clinical characteristics. In addition, patients with COPD and asthma with low muscle mass independent of their BMI and patients with obesity independent of their muscle mass presented significantly worse physical functioning compared with patients with normal body composition. A summary description of the sample characteristics, techniques used to assess body composition, frequency of body composition abnormalities and secondary outcomes assessed in each chapter of this thesis is presented in **Table 1**.

Moreover, based on the novel knowledge resulted by this thesis, the following topics about body composition abnormalities in CRDs will be discussed in detail: firstly, the limitations of using BMI and how to appropriately interpret this variable will be presented; secondly, the main findings related to the influence of the chosen variable and cut-off value for the detection of body composition abnormalities will be described; lastly, the associations between body composition abnormalities, physical functioning and patient-reported outcomes (PROs) will be discussed, focusing first on low muscle mass and then on obesity.

Limitations and clinical interpretation of BMI in individuals with CRDs

BMI is still widely used for the quantitative study of body mass in health and illness. However, it is recognized that this variable has several limitations since the normalization of weight for standing height contributes poorly to the understanding of fat distribution or altered body composition. These limitations have already been demonstrated in older adults and includes: (1) many individuals not labeled as obese based on BMI might indeed have excess adiposity[2] and be considered metabolically

Table 1. Summary description of the sample characteristics, techniques used to assess body composition, frequency of body composition abnormalities and secondary outcomes assessed in each chapter of this thesis

Chapter	Sample	Body composition assessment	BMI classification	Body composition classification	Secondary outcomes
2	270 patients with COPD recruited during the initial evaluation for admission in a physical training program of two study centres in Brazil.	BIA	Underweight: 7% Normal weight: 34% Overweight: 35% Obese: 24%	Low FFMI: 48% High FMI: 40%	6MWT, 1RM, MIP, MEP, PADL, MRC, LCADL, HADS, comorbidities.
3	469 patients with COPD referred for a pre-PR assessment at Ciro, the Netherlands.	DXA	Normal weight: 44% Overweight: 33% Obese: 23%	Low FFMI: 32%* Low FFMI: 54% Low ASMI: 62%*	6MWT, CPET, CWRT, PT, mMRC, SGRQ, HADS.
4	687 patients with asthma referred for a pre-PR assessment at Ciro, the Netherlands.	DXA	Underweight: 2% Normal weight: 23% Overweight: 29% Obese: 46%	Low ASMI: 19%	6MWT, CPET, CWRT, PT, mMRC, SGRQ, exacerbations, hospitalizations.
5	98 patients with IPF referred to the specialised rehabilitation centre Schoen Klinik Berchtesgadener Land, Germany.	BIA	Underweight: 2% Normal weight: 37% Overweight: 41% Obese: 20%	Low FFMI: 9% Low PhA: 26%	6MWT, SF-36, CRP.
6	205 patients with COPD referred for a pre-PR assessment at Ciro and 200 controls recruited from the same region (south of the Netherlands).	DXA	Underweight: 5% Normal weight: 31% Overweight: 35% Obese: 29%	Low FFMI: 40% High FMI: 35%	MRC, SGRQ, comorbidities, exacerbations, hospitalizations.
7	2,137 patients with COPD recruited in the COSYCONET cohort, which includes 31 German study centres.	BIA	Underweight: 12% Normal weight: 31% Overweight: 40% Obese: 17%	Low FFMI: 50% Medium FFMI: 33% High FFMI: 17%	6MWT, TUG, PADL, mMRC, SGRQ, CRP, IL-6, IL-8, TNF-α, WBC count, fibrinogen, comorbidities, exacerbations.

*According to fixed cut-offs. **COPD:** chronic obstructive pulmonary disease, **IPF:** idiopathic pulmonary fibrosis, **PR:** pulmonary rehabilitation, **BIA:** bioelectrical impedance analysis, **DXA:** dual-energy X-ray absorptiometry, **BMI:** body mass index, **FFMI:** fat-free mass index, **FMI:** fat mass index; **ASMI:** appendicular skeletal muscle mass index, **PhA:** phase angle, **6MWT:** six-minute walk test, **1RM:** one-maximum repetition, **MIP:** maximum inspiratory pressure, **MEP:** maximum expiratory pressure, **PADL:** physical activity in daily life, **MRC:** Medical Research Council dyspnea scale, **LCADL:** London Chest Activity of Daily Living scale, **HADS:** Hospital Anxiety and Depression Scale, **CPET:** cardiopulmonary exercise test, **CWRT:** constant work rate test, **PT:** peak torque, **mMRC:** modified Medical Research Council dyspnea scale, **SGRQ:** Saint George Respiratory Questionnaire, **SF-36:** Short-Form 36-item Questionnaire, **CRP:** C reactive protein, **TUG:** Timed-Up and Go test, **IL-6:** interleukin 6, **IL-8:** interleukin 8, **TNF-α:** tumor necrosis factor alpha, **WBC:** white blood cells.

obese normal weight;[3] (2) there is a great individual variation in body fat percentages of individuals with the same BMI, even in overweight and obese categories;[4,5] (3) BMI provide limited information regarding the maintenance of a normal amount of muscle mass; approximately one-fourth of adults in normal weight and overweight BMI categories may present low ASMI, which is hidden by high adiposity.[6]

In patients with COPD, we demonstrated that BMI is limited to identifying altered body composition since most of the SO patients with COPD would be classified as normal weight or overweight based on BMI (**Chapter 2**). On the other hand, the BMI classification would sort most of the patients with normal FFMI and FMI in the overweight group. A previous study by Rutten et al.[7] included 175 male and 120 female patients with COPD of which approximately 19% had both low FFMI and abdominal obesity. The mean BMI of male and female patients with COPD with low FFMI and abdominal obesity was 26.1 kg/m^2 and 25.7 kg/m^2, respectively. This suggests that most patients with both abnormalities would be classified as normal weight or overweight. Moreover, 61 (75%) among the 81 COPD patients with low FFMI included in the study of Beijers et al.[8] had abdominal obesity, despite exhibiting normal BMI. Also, the study of Joppa et al.[9] conducted in a large group of patients with COPD who participated in the ECLIPSE study, identified participants with imbalance in FFMI and FMI across a wide range of BMI. Certainly, patients with COPD classified into the same BMI group can be further stratified into different clinically important body composition groups. We have demonstrated this in two different samples of COPD recruited in the CHANCE study (**Chapter 3**) and in the COSYCONET cohort (**Chapter 7**).

An increasing number of studies suggest that individuals with asthma are more likely to be obese and show higher fat mass,[10] while individuals with COPD are more likely to be underweight and having less muscle mass.[11,12] Indeed, results of a population based cross-sectional epidemiologic study indicated that underweight is significantly associated with COPD in men, while being underweight apparently protects from the possibility of being diagnosed with asthma.[13] However, lower values of FFMI were found in patients with severe refractory asthma when compared to mild-to-moderate asthma, despite the presence of higher values of BMI.[12] The levels of FFMI in patients with severe refractory asthma were comparable with the levels of FFMI in severe patients with COPD (GOLD stage IV).[12] Additionally, patients with uncontrolled asthma showed increased fat mass and decreased muscle mass compared to patients with controlled asthma and healthy controls.[14] In **Chapter 4**, patients with asthma referred for pulmonary rehabilitation who were allocated into the same BMI group could be further stratified into different clinically important ASMI groups. Another

example of the limited ability of BMI to capture changes in body composition in asthmatics is demonstrated in the study from Abdo et al.[14] Among 161 patients who attended the follow-up visit, 64 (40%) patients suffered from persistent uncontrolled asthma. Despite having unchanged BMI, this sub-group of patients showed a significant loss of muscle mass with (-1.2%) and fat accumulation (+1.0%) over two years.[14] In contrast, no significant changes in body composition were observed in patients with controlled or temporarily uncontrolled asthma.[14]

In **Chapter 5**, patients with IPF were stratified into normal and low PhA according to the 10th percentile of the reference values. No significant differences were found when comparing BMI between patients with normal and low PhA. This finding suggests that changes in the electrical properties of tissues summarized by PhA might be present in patients with IPF independently of changes in body weight. In a previous study, the prevalence of muscle loss in patients with IPF receiving antifibrotic therapy was investigated by using computed tomography (CT) measures of the cross-sectional area and muscle attenuation of erector spinae muscles.[15] The distributions of both measures of muscle mass were significantly reduced in patients with IPF than in controls despite no difference in BMI.[15] Additionally, Schwebel et al.[16] stratified 78 lung transplantation candidates into four groups (Group 1: low body weight and low lean body mass; Group 2: low body weight and normal lean body mass, Group 3: normal body weight and low lean body mass; Group 4: normal body weight and normal lean mass). The cases of IPF were concentrated in Group 3, suggesting that loss of muscle mass is masked by a relative increase in fat mass in this population.[16]

Therefore, this thesis clearly demonstrates that BMI is a simple variable that is not capable of reflecting the complexity of body composition abnormalities that frequently occur in individuals with CRDs. BMI cut-off values may be used to identify patients with COPD at a higher risk of death.[1,17,18] Furthermore, BMI appears to be useful in screening body composition abnormalities in settings where access to body composition analysis is limited. As an example, in **Chapter 2**, 57% of patients with COPD with low FFMI would unlikely be identified by using BMI alone since they presented with elevated fat mass. However, most of the remaining sarcopenic patients could be identified by using a BMI<21 kg/m^2 as a criterion. This can be explained by the fact that these patients had reductions in both FFMI and FMI. Since underweight is rare in comparison to the prevalence of obesity in asthmatics, it is not surprising that few studies investigated thresholds of low BMI or FFMI in this population. Consequently, screening for low muscle mass based on BMI in asthmatic patients is not realistic. In patients with IPF, a study conducted with a nationwide inpatient database

without assessment of body composition demonstrated that being underweight is associated with higher in-hospital mortality rate than patients with normal weight.[19] However, the results reviewed in this chapter suggest that muscle loss is not generally accompanied by evident BMI reductions in patients with IPF. In all CRDs, as well as in older adults, a BMI ≥30 kg/m^2 can be used as a criterion to confirm elevated fat mass resulting in a minimal proportion of false positives due to the high specificity of this threshold.[2,20] Notably, most of the participants with CRDs included in the studies of this thesis were classified as either normal weight or overweight (**Table 1**). In these cases, BMI will frequently range between 21-30 kg/m^2 and based solely on this variable it is virtually impossible to define whether the body composition can be considered normal in these patients.

Influence of the chosen variable and cut-off value for the detection of body composition abnormalities

A recent systematic review aiming to estimate the prevalence of sarcopenia among COPD patients revealed that the prevalence of low muscle mass varies from 5.3% to 86.5%.[21] Another systematic review with a similar aim found that the prevalence estimates of sarcopenia in COPD varied between 12.4% and 28.1% in clinical settings, 7.9% and 8.4% in population-based settings and 53.8% to 66.7% in nursing home settings.[22] Different settings could partially explain the wide variability in estimates. This great variability could also be due to the use of different variables and the choice of various cut-off values. As an example, Rutten et al.[23] showed that the frequency of low muscle mass is largely dependent upon the used cut-off values, especially in male COPD patients. In accordance with this previous study, results from **Chapter 3** demonstrated that the frequency of patients with COPD classified as low FFMI or low ASMI varied significantly according to the used cut-off values (32% to 64%; $P<0.05$). Remarkably, the use of BMI adjusted cut-off values, increased the proportion of patients with low FFMI in the overweight and obese groups. Jones et al.[24] studied the prevalence and risk factors for sarcopenia in COPD recruited from an outpatient respiratory clinic. Among the 622 patients included in the study, 117 (18.8%) showed low muscle mass. The large difference in BMI between patients with low muscle mass and normal muscle mass (21.1 ± 3.0 vs. 28.8 ± 5.7 kg/m^2, $P<0.01$) indicates that the prevalence of low muscle mass was higher in patients with lower BMI values. In addition, Van de Bool et al.[25] also reported variability among the frequencies of patients with COPD identified as having low FFMI or low ASMI. A conceptual difference between these two variables lies in the fact that FFMI also includes bone, organs and

trunk muscle tissues, whereas ASMI is an estimate of the muscle mass contained in the limbs, which generally represents 75% of the total body skeletal muscle mass.[26] Interestingly, our data support that adjusting ASMI cut-off values for BMI or body weight is also critical for detecting low muscle mass especially in obese asthmatics (**Chapter 4**). A recent study investigated the relationship between asthma and sarcopenia in a community-dwelling geriatric population.[27] In the mentioned study, body composition was measured using dual-energy X-ray absorptiometry (DXA) and the cut-off values applied were an ASMI <7.0kg/m^2 for males and <5.4 kg/m^2 for females. Thirty-six percent of the asthma patients included presented reduced muscle mass and showed significantly lower mean BMI compared with asthma patients with preserved muscle mass (21.6 kg/m^2 vs. 25.6 kg/m^2, P<0.001).[27] Hypothetically, several individuals with asthma with higher BMI and imbalance in the amount of muscle mass were not identified due to the use of cut-off values which are not adjusted by BMI or body weight. Similarly, as revealed by **Chapter 5**, the choice of the variable also influences the frequency of body composition abnormalities in patients with IPF. The frequency of low FFMI, low PhA or low BMI in this sample were 9%, 26% and 2% respectively. Recently, Faverio et al.[28] reported that the majority of IPF patients showed a normal nutritional status (67.8%), while 25.3% were obese, 4.6% showed sarcopenia and the minority (2.3%) were SO. In the mentioned study, the use of BMI to diagnose obesity and fixed cut-offs to determine low muscle mass are reasonable hypotheses to explain a lower prevalence of patients with IPF with body composition abnormalities.

Evidently, the studies included in this thesis demonstrate that the use of different variables and cut-off values affect the frequency of body composition abnormalities that will be detected in patients with CRDs. The influence of the chosen methodology for the detection of abnormalities in body composition is also an unresolved issue in other disease states and in older adults. For this reason, there is still an extensive debate on this topic and several attempts to propose standardized diagnostic procedures and algorithms describing how to define body composition abnormalities. Both, the latest consensus on definition and diagnosis of sarcopenia published by the European Working Group on Sarcopenia in Older People (EWGSOP)[29] and the latest consensus on the definition and diagnostic criteria for sarcopenic obesity published by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO)[30] recommend the use of DXA and BIA for the assessment of body composition. Other methods, including magnetic resonance imaging and CT, are also mentioned, but with the caveat that cut-off values for low muscle mass are not yet well defined for these measurements.[29]

Furthermore, these specific techniques should be considered primarily in patients undergoing investigation for additional diagnostic reasons.[30] The current EWGSOP recommendations regarding cut-off values for low muscle quantity are an ASMI lower than 7.0 kg/m^2 for men and 5.5 kg/m^2 for women.[29] The EWGSOP acknowledges that muscle mass is correlated with body size and, therefore, individuals with a larger body size normally have larger muscle mass. Nonetheless, no clear recommendation to adjust muscle mass for body size is provided. In contrast, the recent ESPEN/EASO consensus recommends preferably the use of variables adjusted for body weight, since they can be more informative about the relative reduction of muscle mass. Hence, these variables should be used in combination with variables that represent increased fat mass.[30] The panel suggests various cut-off values to be used in specific situations; however, the panel encourages researchers to further investigate the validity of the proposed cut-off values and highlights this topic as one of the major areas of uncertainty.

Low muscle mass in individuals with CRDs

This thesis consistently showed that, in patients with COPD, the frequency of low muscle mass is greater in males than in females. In **Chapter 2**, the proportion of males was higher in the groups with body composition abnormalities (obese: 73.5%, sarcopenic: 62.5%, SO: 79.7%) than in the group with normal body composition (31.1%). In **Chapter 3**, the frequency of male COPD patients in the overweight and obese groups with low FFMI was higher compared to the frequency of males in the same BMI group but with normal FFMI. Similarly, **Chapter 7** showed that, within the overweight and obese groups, the proportion of male COPD patients gradually decreases among patients with low, medium, and high FFMI. Joppa et al.[9] also demonstrated a higher frequency of males in sarcopenic and SO COPD patients in comparison with patients with COPD and normal body composition (70.3% and 85.3% vs. 64.0%). In **Chapter 4**, the proportion of male patients with asthma was higher in the normal weight group with low ASMI compared to normal ASMI (58% vs. 38%, $P<0.05$). Indeed, Won et al.[27] found that the risk of sarcopenia in elderly patients with asthma is 3.21 (95% CI: 1.23-8.39) higher in males compared to females. However, the application of the diagnostic procedure proposed by the 2022 ESPEN/EASO consensus yielded a similar frequency of SO between male and female asthma patients (25% vs. 31%). In accordance with previous studies,[15,16,28] the majority of the patients with IPF included in **Chapter 5** were male (86%). On the basis of the great disparity between the proportion of male and female patients with IPF included in the studies, it is challenging to study sex-specific differences in the occurrence of low muscle mass in this population. One

possible explanation for the higher frequency of low muscle mass observed in male patients with COPD is hypogonadism. Hypogonadism is a decrease in the functional activity of the gonads that may lead to a decrease in the production of sex hormones, such as testosterone. It is a common manifestation in elderly men, and it has been identified in approximately half of clinically stable male patients with COPD attending an outpatient clinic.[31] Interestingly, Casaburi et al.[32] investigated changes in body composition and muscle strength before and after a 10-week intervention among male patients with severe COPD and low testosterone levels randomized into four groups: (1) placebo injections and no training, (2) testosterone injections and no training, (3) placebo injections and resistance training, or (4) testosterone injections and resistance training. In the mentioned study, the treatment arm with resistance training combined with testosterone injections tended to show superior muscle mass and strength gains than either intervention alone.[32] In the general population (subjects initially aged 46–80 years), a greater decline in FFM and physical activity were observed in men than in women over an average of 9.4 years of follow up.[33] Indeed, more longitudinal studies are required to compare the sex-specific changes in body composition between patients with CRDs and control groups, as well as to investigate which factors are involved in these changes and whether these factors differ between male and female patients.

In individuals with all the studied CRDs, an association between different histories of smoking and reduced muscle mass were identified. In **Chapter 6**, not only patients with COPD, but also smoking controls presented a significant decline in FFM and an increase in fat mass, while non-smoking controls presented no significant differences in body composition. A recent longitudinal study using data from the Sarcopenia and Physical Impairment with advancing Age cohort investigated the relationship between smoking status and the incidence of sarcopenia over 5 years.[34] Smokers showed a 2.36-fold higher risk of developing sarcopenia than those who did not smoke.[34] In **Chapter 4**, patients with asthma in the overweight group with low ASMI presented a significantly greater proportion of patients with ≥10 pack years compared to patients with comparable BMI but normal ASMI. Furthermore, as demonstrated in **Chapter 5**, patients with IPF with low PhA presented higher amount of pack years compared to their normal PhA peers. Locquet et al.[34] demonstrated the dose-dependent effect of smoking on sarcopenia risk in older individuals aged ≥65 years. Notably, an increase in the consumption of one cigarette per day resulted in a 5% higher risk of developing sarcopenia over 5 years.[34] In accordance, Castillo et al.[35] identified that older individuals that are current smokers and physically inactive are more likely to be classified as having low muscle mass and being sarcopenic.

Two of the six studies included in this thesis included physical activity as an outcome (**Table 1**). In **Chapter 7**, normal weight and overweight COPD patients with high FFMI presented higher levels of self-reported physical activity compared to those with comparable BMI but low FFMI. Waschki et al.[36] found that even though the decline in physical activity was not associated with changes on muscle mass in COPD, a sustained low level of physical activity was associated with an accelerated loss of muscle mass during follow-up independent of airflow limitation. Notably, in **Chapter 2**, stratification of patients with COPD into sarcopenic and SO patients revealed groups with distinct physical activity profiles. Patients with sarcopenia presented a higher average metabolic equivalent of task (METs), time spent in moderate physical activity and less sedentary time compared to SO patients. Jones et al.[24] stratified patients with COPD into four groups according to the presence of low muscle mass, low muscle function or sarcopenia (combination between low muscle mass and function). The sub-group of patients with low muscle mass, but preserved muscle function, showed a higher amount of time in moderate intensity activity compared to the other groups.[24] These findings raise the hypothesis that other factors such as malnutrition (e.g., negative energy balance, low protein intake) could represent an important lifestyle factor associated with low muscle mass in patients with COPD who present relatively preserved physical activity levels. Interestingly, Van de Bool et al.[37] showed that more than 60% of COPD patients with low FFMI had an inadequate protein intake per kg body weight, considering a recommended lower limit of 1.5 g/kg body weight. In addition, results from the double-blind placebo controlled multi-centre NUTRAIN-trial showed that specific nutritional supplementation positively influenced physical activity in COPD patients with low muscle mass.[38] In this thesis, studies which included individuals with asthma and IPF did not measure physical activity. However, higher physical activity levels have been shown to be significantly associated with higher muscle mass and lower fat mass in individuals with asthma.[14,27] To our knowledge, no study investigated the association between physical activity and low muscle mass in patients with IPF, but lower levels of physical activity and FFMI were both associated with higher mortality in this population.[39,40]

In general, our data illustrate that lower muscle mass is associated with worse lung function in individuals with CRDs. Patients with COPD with low FFMI generally demonstrated more severe airflow limitation and reduced oxygen uptake as assessed by forced expiratory volume in one second (FEV_1) and diffusion capacity for carbon monoxide (DLCO) in percent of predicted compared to patients with normal FFMI. Normal weight and overweight asthmatic patients with low ASMI also showed more

severe airflow limitation compared to their normal ASMI peers. Additionally, patients with IPF with low PhA showed more reduced lung volumes as assessed by forced vital capacity (FVC) and total lung capacity (TLC) in percent of predicted compared with IPF patients with normal PhA. Lung function is frequently associated with different outcomes in patients with CRDs. Therefore, it is of great interest to understand the independent impact of a lower muscle mass. In **Chapter 2**, we showed that sarcopenic COPD patients are 7.85 more likely to show a 6MWD ≤350 meters compared to patients with normal body composition even after adjustment for FEV_1. Indeed, great part of the variability of muscle strength and exercise capacity in patients with COPD can be explained by using markers of muscle mass as predictors.[25] A previous study by Bernard et al.[41] showed that muscle strength and muscle mass are proportionally reduced in COPD in comparison with a control group. Our data in patients with IPF, demonstrated that low PhA is a strong predictor of the 6MWD independent of DLCO and FVC. In accordance, Rinaldi et al.[42] showed in a sample of fibrotic interstitial lung disease including 46% of patients with IPF that low FFMI controlled for age and sex is significantly associated with 6MWD independent of lung function. These findings support that low muscle mass is a factor independently associated with exercise intolerance and muscle weakness in CRDs. We add relevant information to this topic in **Chapter 7**, in which we describe that the negative associations between muscle mass and 6MWD are stronger in underweight and normal weight than in overweight and obese patients.

On the other hand, the associations between muscle mass and PROs in this population is much more controversial. Some of the most important PROs measured in studies including patients with CRDs are health-related quality of life (HRQL), functional status, and symptoms. All the chapters of this thesis included at least one of these measures (**Table 1**). Our findings from **Chapter 2** do not support that body composition is associated with differences in functional status, symptoms of anxiety and depression and dyspnea severity. In contrast, in **Chapter 3**, the group of normal weight COPD patients with low FFMI contained a higher proportion of patients with moderate to severe symptoms of dyspnea (modified Medical Research Council dyspnea scale (mMRC) ≥2) compared to patients with normal FFMI. In **Chapter 4**, HRQL and the proportion of asthmatics with moderate to severe symptoms of dyspnea did not significantly differ between patients with low or normal ASMI. Finally, in patients with IPF, our data demonstrate that none of the body composition variables were significantly related with the Short-Form 36-item Questionnaire (SF-36) Mental Summary Score. A previous study by Rutten et al.[18] showed that underweight COPD patients whose

FFMI decreased over 3 years had a significantly increased risk of deterioration in their HRQL (increase ≥4 points in the Saint George Respiratory Questionnaire (SGRQ) total score). Indeed, in **Chapter 7**, we found that associations between muscle mass and SGRQ total score may depend on the BMI classification. Significant associations between FFM and HRQL were found especially in normal weight and underweight COPD patients; however, these associations were not significant after adjustment for lung function or symptoms of dyspnea. It still remains to be elucidated whether presenting low muscle mass is independently associated with PROs in individuals with CRDs. Up to the present moment, the findings reviewed in this chapter indicate that PROs poorly correlate with surrogate markers of muscle mass in this population.

Excess of fat mass in CRDs: what is associated with this extra load?

Global estimates indicate that the age-standardized prevalence of obesity among adults rose from 7% to 12.5% between 1980 and 2015.[43] The prevalence of CRDs is also rising in absolute numbers, especially in high-income nations.[44] In addition, physical inactivity can be considered a risk factor for obesity[45] and is a feature frequently found in patients with CRDs. Therefore, the likelihood of individuals with both conditions being referred to rehabilitation centers is expected to be higher in the coming years. Consequently, it is of fundamental importance to understand the effects of the extra mechanical, metabolic and inflammatory load possibly caused by an excess of fat mass on lung function, physical functioning and PROs in individuals with CRDs. In general, our data indicate that lung function is relatively preserved in overweight and obese patients with COPD and asthma in comparison with patients with normal weight. As demonstrated in **Chapter 2**, obese COPD patients presented no differences in any of the lung function variables when compared with patients with normal body composition, whereas sarcopenic and SO patients showed more severe airflow limitation. In **Chapter 3**, we observed a gradual increase in the severity of airflow limitation and impairment in oxygen uptake, assessed by FEV_1 and DLCO, as BMI classification decreased from obesity to normal weight. Indeed, a preservation of the FEV_1/FVC and normal or increased DLCO are some of the listed changes associated with obesity.[46] In **Chapter 4**, the proportion of asthmatic patients presenting resting pulmonary hyperinflation (residual volume/TLC ratio ≥0.40) was the highest in the normal weight patients with low ASMI (72%) and the lowest in obese patients (50%). Remarkably, O'Donnell et al.[47] studied the relationship between BMI and lung volumes and capacities, as well as spirometric indices of airway function in patients with airflow limitation. In the cited study, residual volume decreased exponentially

with increasing BMI regardless of the severity of airway obstruction.[47] Other sign of a relatively lower hyperinflation in overweight and obese individuals is a negative linear association between expiratory reserve volume with increasing BMI.[48] These findings suggest a mechanical advantage of an increasing BMI in relation to the severity of airflow limitation and hyperinflation in overweight and obese patients with CRDs.

However, this relative advantage in lung function in obese patients does not seem to reflect on enhanced extra-pulmonary characteristics. By contrast, in **Chapter 7**, obese COPD patients were deemed the most impaired group concerning exercise capacity, HRQL and limitations in activities of daily living due to symptoms of dyspnea (mMRC scale), even though presenting the highest values of FEV_1 and DLCO in percentage of predicted. Considering exercise capacity, the exercise modality has been shown to be a key factor. In a sample of 216 patients with COPD (including 50% obese and non-obese patients matched for gender, age and FEV_1), peak cycling capacity has shown to be preserved in obese patients compared with normal weight patients, while 6MWD was significantly reduced.[49] Similarly, our data in **Chapter 4** demonstrated that the group of obese patients with asthma showed a significant lower 6MWD, but comparable, or even higher, quadriceps muscle strength and maximal load during the cardiopulmonary exercise test (CPET), compared to normal weight asthmatics. In summary, our analysis with stratification of patients into normal or low muscle mass within BMI groups contributes to the understanding of why muscle strength and weight-supported exercise capacity may be considered preserved or higher in obese than in non-obese individuals with CRDs. We observe that absolute levels of muscle mass, muscle strength and maximal load during the CPET gradually increase according to the increase in BMI. However, presenting low muscle mass is associated with worse muscle strength and weight-supported exercise capacity as long as the patients is compared with a patient with normal muscle mass who belong to the same BMI group. It is known that the determinants of exercise capacity can be different between obese and non-obese patients with COPD and exercise modality.[50] In obese COPD patients, a higher BMI is associated with a lower 6MWD.[50] Also, in this group, the mMRC scale was a strong predictor of exercise performance, independently of the exercise protocol.[50] Our models from **Chapter 7** demonstrate that the mMRC scale is also one of the main predictors of HRQL in overweight and obese patients with COPD. Since a higher prevalence of patients with moderate to severe symptoms of dyspnea (mMRC ≥2) were observed in the group of obese patients with COPD. It can be assumed that reduced HRQL in this population is mediated by the effects of a higher fat mass and body weight on dyspnea. In accordance, in **Chapter 6**, we found

that the increase in fat mass after two years of follow-up was weakly but significantly associated with worsening in limitations in activities of daily living due to symptoms of dyspnea (r=0.29, *P*=0.01).

Notably, we could also identify components of a higher number of comorbidities and an extra inflammatory load previously observed in patients with COPD with higher body weight and fat mass. In **Chapter 2**, obese patients presented a higher prevalence of diabetes and hypertension. This finding resembles the metabolic cluster described by Vanfleteren et al.[51] which present a higher proportion of patients with a combination of obesity, hypertension and hyperglycaemia. In **Chapter 7**, we confirmed and extended results from previous studies in patients with COPD showing that the plasma levels of C reactive protein (CRP) are positively associated with fat mass and that obese patients are more likely to have highly elevated levels of CRP compared to normal-weight COPD patients.[7,52] Using data from a large cohort of patients with COPD, we could explore the associations between fat mass and plasma levels of CRP in different BMI groups. The overweight and obese groups showed higher plasma levels of CRP compared to normal weight patients. Remarkably, higher fat mass was significantly associated with higher levels of CRP in normal weight and overweight patients with COPD. Importantly, the recent ESPEN/EASO consensus on sarcopenic obesity highlights that obesity can also lead to loss of muscle mass due to inflammation, oxidative stress, sedentary lifestyle, insulin resistance and the high prevalence of chronic non-communicable diseases that negatively impact muscle metabolism.[30] Nevertheless, the expert panel listed CRDs as one of the suspicion factors for the screening of sarcopenic obesity. The studies of the present thesis are in accordance with the concepts and recommendations of the ESPEN/EASO consensus. As an example, the expert panel highlights the need of interpretating muscle changes considering the context of obesity. We provide novel evidence that contributes to the understanding of the factors associated with low muscle mass in overweight and obese individuals with CRDs.

Conclusions and future directions

In summary, this thesis demonstrates that body composition abnormalities are frequently present in individuals with COPD, asthma or IPF. However, identifying these abnormalities requires the use of an appropriate methodology and a comprehensive interpretation of available data. This means that both the absolute and relative amounts of muscle mass and fat mass need to be considered rather than unidimensional indexes. Clearly, it is important that patients with CRDs have a body weight within the normal

weight range, however, it is even more important that this is consistent with body composition variables within the normal limits. Furthermore, this thesis describes the extent to which body composition abnormalities are associated with lifestyle factors, physical functioning and PROs in individuals with CRDs. These associations are complex as they can vary in terms of significance and strength depending on the different weight classifications. Notably, we could identify associations that are more likely to have a causal relationship with the occurrence and accelerated progression of low muscle mass. The most prominent lifestyle factor associated with reduced muscle mass was smoking. Also, our findings demonstrate that male individuals with COPD are at a higher risk of being classified as having low muscle mass, despite the use of sex-specific cut-off values. Nevertheless, the emphasis of the present thesis was on factors that are more likely to be considered as consequences of an abnormal body composition. Low muscle mass has often been associated with poorer lung function and physical functioning in COPD, asthma and IPF. On the other hand, excess of fat mass has shown to be associated with more severe limitations in activities of daily living due to symptoms of dyspnea, which is strongly associated with patient's quality of life. Attention should be draw to the coexistence of low muscle mass and excess of fat mass which should be considered a distinct entity since it may induce a significantly worse impact due to a synergistic combination of deleterious effects.

The present thesis adds novel and relevant knowledge to the literature. We demonstrated how often the body composition is abnormal in patients with CRDs compared to values obtained from people of the same age and BMI. We have shown an underestimation in the detection of low muscle mass when criteria used in normal weight individuals are applied in individuals who have higher body weight. Also, we have revealed sets of characteristics that are usually accompanied with an altered body composition. However, some important topics remain to be elucidated. First of all, future studies should focus on determining the independent role of each different potential risk factor for muscle loss and fat accumulation in individuals with CRDs. A well designed, multicentre, longitudinal study assessing body composition in individuals with CRDs and a control group for a longer period of time (≥10 years) is necessary. Importantly, such study should include reliable measures of various potential risk factors such as smoking, physical activity, nutritional aspects, the number of exacerbations and hospitalisations, medications and comorbidities. In addition, this study should preferably be powered to investigate whether there are differences in the determinants of body composition abnormalities between male and female patients and among a wide range of patterns and severity of the disease. Once the risk factors and their

contributions to the onset and progression of body composition abnormalities are well established, appropriate prevention and treatment strategies can be developed and refined. For example, smoking cessation, exercise training, targeted nutrition, and interventions aiming to increase physical activity and reduce sedentary lifestyle are tools that could potentially contribute to the preservation of muscle mass and/or inhibition of fat accumulation. It would be interesting to know whether and to what degree these interventions are able to modify the trajectory of body composition (e.g., slowdown loss of muscle mass and fat accumulation) in patients with CRDs.

Additionally, the results of this thesis show that the less the body composition of an individual with CRDs is deviated from normal, less evident is the impairment observed in pulmonary and extra-pulmonary characteristics. Nevertheless, more emphasis should be put on the investigation of whether restoring body composition to normal is associated with additional benefits such as better survival, lower incidence of exacerbations and hospitalizations, lower intensity of symptoms and better quality of life. We still need more evidence to define from what moment and to what level of priority improving body composition should be considered an objective of a pulmonary rehabilitation program. Recently, the scientific advances concerning pharmacological and non-pharmacological treatment options primarily targeting sarcopenia in COPD patients were extensively reviewed.[53] In this framework, the European Respiratory Society (ERS) statement on nutritional assessment and therapy in COPD concludes that nutritional intervention is likely to be effective in undernourished patients and is probably most effective if combined with an exercise program.[54] Remarkably, previous studies support that some of the strategies to increase muscle mass without the inclusion of resistance/exercise training are usually not translated into an improved muscle function or physical functioning in patients with COPD. This was observed in a placebo-controlled, double-blind, randomized trial that investigated the effects of activin type II receptor blockade by bimagrumab treatment in underweight and/or sarcopenic patients with COPD.[55] These receptors act as a pathway for multiple negative regulators of muscle mass, such as myostatin. The group that received bimagrumab treatment showed substantial gains in thigh muscle volume.[55] However, the observed hypertrophy of the thigh muscles did not result in a significant improvement in 6MWD, handgrip strength, leg press one-repetition maximum or SGRQ total score.[55] In addition, the administration of testosterone injections in patients with COPD without the addition of resistance training yielded a greater increase in surrogate markers of muscle mass compared to COPD patients that performed resistance training and received placebo injections.[32] Nevertheless, both

groups improved the strength and fatigability of the quadriceps to the same extent.[32] Further studies with administration of anabolic agents in patients with COPD, but without the inclusion of resistance training, demonstrate the superiority of the anabolic agents in increasing surrogate markers of muscle mass, but modest or even absent benefits in physical functioning.[56,57] On the other hand, little is known about the effects of weight loss interventions in overweight and obese patients with COPD. Surprisingly, only one proof of concept clinical trial by McDonald et al.[58] evaluated the feasibility of a weight loss intervention and its effects in obese patients with COPD. This study enrolled twenty-eight obese patients with COPD who underwent dietary counselling and calorie restriction using meal replacements and resistance training. Importantly, patients achieved weight loss, whilst preserving skeletal muscle mass and improving other clinical outcomes. Up to the present time, weight loss interventions and its effects are much more explored in overweight and obese individuals with asthma since several randomized controlled trials investigating how to improve body composition are available in this population.[59-61] These studies can provide an initial guidance for clinicians and researchers aiming to increase muscle mass or reduce fat mass in patients with CRDs. Consequently, novel studies can be designed to further investigate how to effectively improve body composition and whether the path chosen to achieve this goal is important to generate additional improvement in pulmonary rehabilitation outcomes as well as for the long-term maintenance of these benefits.

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Samenvatting

Samenvatting

Het hoofddoel van dit proefschrift was het onderzoeken van de frequentie en impact van afwijkingen in de lichaamssamenstelling bij personen met chronische luchtweg-aandoeningen (CRD's), in het bijzonder chronische obstructieve longziekte (COPD), astma en idiopathische longfibrose (IPF). Onze gegevens tonen aan dat slechts een minderheid van de patiënten met CRD's die zijn verwezen voor longrevalidatie een normale lichaamssamenstelling heeft wat betreft de verwachte hoeveelheid spiermassa, gemeten met behulp van surrogaatmarkers zoals vetvrije massa-index (FFMI), appendiculaire skeletspiermassa-index (ASMI) of fasehoek (PhA) en vetmassa. In **Hoofdstuk 2** hebben we aangetoond dat slechts 39% van de patiënten met COPD een normale lichaamssamenstelling had, terwijl alle overige patiënten een hoge hoeveelheid vetmassa, een lage FFMI of een combinatie daarvan vertoonden. In **Hoofdstuk 3** had meer dan de helft van de patiënten met COPD die deelnamen overgewicht of obesitas op basis van de body mass index (BMI). Van de gehele steekproef was het aandeel patiënten met een normale BMI en een normale FFMI 18,8%. Bovendien lieten de resultaten van **Hoofdstuk 4** zien dat bij slechts één op de vier volwassen patiënten met astma die voor longrevalidatie zijn verwezen, het gewicht geclassificeerd wordt als normaal op basis van BMI en dat ongeveer 20% van deze patiënten een lage ASMI heeft. Vergelijkbare resultaten werden gevonden in patiënten met IPF (**Hoofdstuk 5**). We toonden aan dat bij 36% van de patiënten met IPF het lichaamsgewicht op basis van BMI werd geclassificeerd als normaal. Over het algemeen was de frequentie van abnormaal lage PhA (26%) hoger dan verwacht, op basis van het 10^{e} percentiel van de referentiewaarden voor de algemene bevolking. Tot slot, in **Hoofdstuk 7**, werden afwijkingen in de lichaamssamenstelling onderzocht bij poliklinische patiënten van een groot multicenter COPD-cohort. Bijna vijftien procent van de patiënten bleek een normaal gewicht te hebben en FFMI te behouden. Samengevat laten deze onderzoeken zien dat afwijkingen in de lichaamssamenstelling vaak voorkomen bij patiënten met CRD's die zijn verwezen voor longrevalidatie en mogelijk zelfs voorkomen bij alle patiënten met CRD's. Gegevens uit **Hoofdstuk 6** bevestigen de bevinding van een hogere frequentie van afwijkingen in lichaamssamenstelling bij COPD, aangezien 42% en 35% van de patiënten een lage FFMI en een hoge vetmassa-index (FMI) vertoonden. Het toepassen van dezelfde criteria bij rokende en niet-rokende controle-deelnemers leverde aanzienlijk lagere frequenties op. Bovendien laten de belangrijkste resultaten van **Hoofdstuk 6** zien dat patiënten met COPD een significante afname in totale, been- en romp-FFM vertonen na 2 jaar follow-up in vergelijking met niet-rokende controles. De resultaten van dit studie maakten het mogelijk om een subgroep

van patiënten met COPD te identificeren die een andere lichaamssamenstelling traject vertoonden ten opzichte van de andere patiënten met COPD, die werd gekenmerkt door een grotere afname van de totale en benen FFM.

Ook toonde dit proefschrift aan dat hoe meer de lichaamssamenstelling van een persoon met CRD's afwijkt van de norm (gedefinieerd als het gemiddelde van de algemene populatie), hoe meer afwijkingen worden waargenomen in pulmonale en extra pulmonale kenmerken. In **Hoofdstuk 2** vonden we dat sarcopene zwaarlijvige (SO) patiënten met COPD, die de grootste afwijking van hun verwachte lichaamssamenstelling vertoonden, over het algemeen het meest beperkt waren met betrekking tot de ernst van luchtwegobstructie en het fysiek functioneren. De resultaten suggereren dat deze subgroep van patiënten een hoger risico heeft op overlijden, aangezien deze patiënten een 9,5 keer hogere kans hadden op een loopafstand van zes minuten (6MWD) ≤350 meter, een gevalideerde grenswaarde die onafhankelijk geassocieerd is met slechtere overlevingskans. In **Hoofdstuk 7** kon de lichaamssamenstelling in detail worden onderzocht door de stratificatie van patiënten met COPD in twaalf groepen (vier BMI-groepen, die elk gestratificeerd werden in drie FFMI-groepen). Ptiënten die het minste afweken van hun verwachte lichaamssamenstelling (patiënten met een normaal gewicht met hoge FFMI) vertoonden de beste klinische kenmerken. Bovendien vertoonden patiënten met COPD en astma met een lage spiermassa onafhankelijk van hun BMI en patiënten met obesitas onafhankelijk van hun spiermassa een significant slechter fysiek functioneren in vergelijking met patiënten met een normale lichaamssamenstelling.

Verder worden op basis van de nieuw vergaarde kennis in dit proefschrift, de volgende onderwerpen over afwijkingen in de lichaamssamenstelling bij CRD's in detail behandeld: ten eerst zullen de beperkingen van het gebruik van BMI besproken worden en hoe deze variabele op de juiste manier geïnterpreteerd kan worden; ten tweede worden de belangrijkste bevindingen met betrekking tot de invloed van de gekozen variabele en afkapwaarde voor de detectie van afwijkingen in de lichaamssamenstelling beschreven; ten slotte zullen de associaties tussen afwijkingen in de lichaamssamenstelling, fysiek functioneren en patiëntgerapporteerde uitkomsten (PRO's) worden besproken, waarbij aandacht wordt besteed aan lage spiermassa en obesitas.

Impact section

Impact section

The aim of this section is to provide a reflection on the scientific and social impact of the results of the research described in the thesis for a wide target group. In summary, this can be accomplished by answering four questions: 1. What is the main objective of the research described in the thesis and what are the most important results and conclusions? 2. What is the (potential) contribution of the results from this research to science and social sectors? 3. To whom and why are the research results relevant? 4. How can these target groups be involved in and informed about the research results, so that the knowledge gained can be used in the future?

Main objective, most important results and conclusions

Researchers have been investigating not only how chronic diseases affect life expectancy, but also how it may affect the condition of individuals to perform physical activity. Moreover, the impact of chronic diseases on the deterioration of the quality of life of individuals is a relevant topic among the scientific community. CRDs are examples of chronic diseases that are diagnosed mainly through tests that evaluate the function and the structure of the lungs and airways. Interestingly, people with CRDs frequently present problems in other tissues and organs. The main aim of this thesis was to study the proportion of patients with CRDs who usually present abnormalities in their body composition. In addition, we aimed to explore the associations between body composition, lung and physical function, intensity of symptoms, systemic inflammation and quality of life in this population. Four studies of this thesis included patients with COPD, which is the most prevalent CRD. This thesis demonstrates that worse lung function, exercise limitation and muscle weakness are frequently observed in groups of individuals with COPD characterized by low muscle mass. On the other hand, the COPD groups with higher amount of fat mass showed more severe limitations in activities of daily living due to symptoms of dyspnea, worse health-related quality of life and higher levels of systemic inflammation. The other two studies included patients with asthma and IPF referred for pulmonary rehabilitation. At the time of referral, one in every five asthma patients and one in every four IPF patients demonstrated abnormally low markers of muscle mass. Our main conclusion is that a great proportion of individuals with CRDs do not present adequate amounts of markers of muscle mass and/or fat mass, these irregularities are associated with negative clinical characteristics.

Potential contribution of the results to science and to social sectors

This PhD thesis present novel findings that support the relevance of screening for body composition abnormalities in individuals with CRDs. The social and scientific impact of this thesis is illustrated by our contribution to the understanding of the influence of the chosen cut-off values for the detection of body composition abnormalities. We hope that our results stimulate the scientific community and health care professionals to adapt the methodology when investigating the occurrence of low muscle mass in individuals with CRDs who are overweight or obese. In addition, our explanation about the limitations of using BMI to classify patients with CRDs in different weight groups can be highlighted as another element of the impact of this thesis on science and society. Based on our results, health care professionals and researchers should not rule out the possibility of a patient with CRD with normal BMI having an abnormal body composition. Researchers and clinicians can use the current findings to anticipate what is expected in terms of physical functioning and patient reported outcomes from patients with CRDs according to their body composition.

To whom and why are the research results relevant?

The results of this thesis are relevant for patients with CRDs, healthcare professionals and future researchers. The patients with CRDs will benefit from a better understanding of how and to what extent body composition abnormalities are associated with physical function and patients reported outcomes. Early education towards the need for monitoring and maintaining adequate levels of muscle and fat mass may be beneficial for these patients. Moreover, health care professionals also benefit from our results since they are increasingly required to base their clinical decisions on the available evidence in combination with clinical expertise and patient values. The studies from this thesis might be useful for them as an introductory guidance on how to detect body composition abnormalities in patients with CRDs. Healthcare professionals should pay particular attention to patients with body composition abnormalities since they may present associated negative characteristics. On the other hand, strategies may be used to maintain adequate levels of muscle and fat mass in those patients with normal body composition. Finally, our results are also relevant for other researchers. We contributed by adding information to previous research questions regarding the frequency, potential causes and functional consequences of abnormal body composition in patients with CRDs. In addition, we provided clear directions for future studies in the light of our results.

Using the acquired knowledge in the future

The studies described in the different chapters of this thesis were or will be published in scientific journals and presented in scientific congresses. These are traditional dissemination strategies which can be used to effectively let other researchers and health care professionals know about our novel findings. Consequently, the acquired knowledge can be used in the future in clinical or research settings. Since education is one of the major features of pulmonary rehabilitation, the acquired knowledge will reach patients with CRDs through health professionals who participate in the patient education process. Moreover, the acquired knowledge can be used in the future to help researchers to select sub-groups of patients and to explore the most successful interventions/strategies to treat patients with CRD according to their body composition.

Acknowledgments

Acknowledgments

Many people have contributed to the development of the competences and skills that enabled me to become a PhD student and defend my doctoral thesis. Probably, a lot more people contributed in a certain way to this achievement but will not be mentioned here. Thus, in this first paragraph, I express my gratitude to all those who have contributed to my educational and personal growth.

Next, I would like to acknowledge my supervisors Prof. Dr. Frits Franssen, Prof. Dr. Martijn Spruit and Prof. Dr. Fabio Pitta. Dear Frits and Martijn, since before starting my master's studies in Brazil, I have been greatly inspired by many of your publications. I really appreciate the opportunity and the support to be part of the great team of researchers that you coordinate at Ciro. I have no words to express my appreciation for the knowledge and experience you have shared with me during the time we have worked together over the last years. Dear Fabio, I am very grateful to you, firstly for welcoming me as an undergraduate student in your research group. Also, because you gave me a chance to explain my wishes regarding my professional future. Then, you helped me to turn my expectations and dreams into goals and plans and now you share the joy of all my accomplishments.

I would like to thank Prof. Dr. G. Wesseling, Prof. Dr. D. Jonkers, Prof. Dr. E. Blaak, Prof. Dr. D. Hansen, Prof. Dr. A. Marques, who kindly agreed to be members of my thesis assessment committee and to take a time to review my thesis. Your expertise has been greatly appreciated and I thank you for your contribution to this milestone in my career. I also thank the co-authors of every chapter of this thesis. I am thankful for their valuable insights that led me to the final version of each separate scholarly article. A special thank you to Prof. Dr. K. Kenn and Prof. Dr. P. Alter, and their respective research groups, who trusted me to use some of the data collected in their research centers. To all patients who were volunteers and/or allowed the use of their data for scientific purposes, thank you very much for dedicating time and energy to contribute to our scientific research.

I would like to acknowledge The Netherlands Organisation for Health Research and Development (ZonMw) for the financial support to develop my PhD activities in the Netherlands. I would also like to acknowledge the financial and academic support from CIRO (Horn, The Netherlands) and Maastricht University (Maastricht, The Netherlands) as well as the employees who helped me within these institutions.

Thank you to my colleagues from Ciro. A special thank you to Anouk Vaes, Anouk Stoffels, Anouk Muijsenberg, Cindy, Jeannet, Kiki, Maarten, Qichen, Roy, Sara Miranda, Sarah, Tereza, Yvonne and Yuqin. You have been great friends since I joined Ciro in 2020. I am grateful for all the moments we have had together in Ciro and elsewhere. I would like to highlight that Yvonne and Jeannet (my paranymphs) have always helped me to find/solve everything that I needed in Ciro and for this reason I am really grateful. Furthermore, I am thankful to Roy, since he was an excellent teammate with whom I had the opportunity to work together and who has a special contribution to one of the chapters of this thesis. I have no doubt that everybody has contributed in a different way to my professional and personal growth while making my days a lot more fun. There are also more colleagues from Ciro with whom I have had less contact, but they have made my time in Ciro a really good experience.

I would also like to acknowledge all my colleagues from the Laboratory of Research on Respiratory Physiotherapy (LFIP) and State University of Londrina. Thank you to Andrea, Antenor, Gianna, Igor and Nidia for introducing me to the first concepts in research methodology. Thank you to Ana, Emely, Guto, Humberto, Jéssica, Joice, Karina, Laís, Larissa Castro, Larissa Martinez, Leandro, Letícia, Lorena, Mariana, Raquel, Thais, Wagner and Walter for the moments we spent together. You know how much I miss being in the laboratory working with you and drinking coffee on our breaks. Thank you to many friends in Brazil (from Londrina, Jaguariúna and Campinas) who never ceased to contact me and support me even with the distance and lack of daily contact. Thank you to Rodrigo for your excellent work in designing the cover for this thesis.

Thank you (*dankjewel*) to my language coach, Jo Goffin, for all the time you have devoted to teaching me Dutch. I appreciate all the lessons and the knowledge you have shared with me. Thanks to you I was able to try a couple of conversations in Dutch with the locals and it was easier to explore this "new world" around me. I would also like to thank the Dutch society and people for being respectful, friendly and helpful, which made my life experience in the Netherlands really good.

A special thank you to all my family. Thank you to my sister Marina, who has also been supportive and contributing to my personal growth over the last years. Many thanks to my beloved parents, Antonio and Wilza, who have always supported my decisions. I am and will always be thankful for all that you have done for us. Thank you for all your efforts in providing us with the best. I would never be here if it weren't for your unconditional support. I would also like to acknowledge my beloved wife,

Bruna. Bruna, thank you for all your love and support. Thank you for being here with me during this stage of my career. Thank you for being the most incredible partner that I could have and thank you for inspiring me to be as strong, motivated and energetic as you are.

Curriculum vitae
List of publications

Curriculum vitae

Felipe Machado was born on August 11, 1994, in Campinas, São Paulo – Brazil. He completed his secondary education at Colégio Técnico Bento Quirino in Campinas in 2011. In the next year, he moved to Londrina, Paraná – Brazil, where he started a 4-years graduation course in Physiotherapy at Londrina State University. In 2013, during the second year of the graduation in Physiotherapy, he started to participate at the Laboratory of Research on Respiratory Physiotherapy (LFIP) as undergraduate research student. After his graduation, Felipe continued his activities at LFIP as a master's student. He obtained his master's degree in Rehabilitation Sciences at the Londrina State University in 2018. During these five years, he has assisted, conducted, and supervised several exercise tests in patients with COPD, presented a considerable number of studies at internal and external events or symposia and published his first scientific articles. In 2020, Felipe started his PhD at the Department of Respiratory Medicine of the School of Nutrition and Translational Research in Metabolism (NUTRIM) of the Maastricht University in collaboration with Ciro, Horn. His research focused on the frequency and associations of body composition abnormalities in patients with chronic respiratory diseases. During his PhD, Felipe had the opportunity to contribute to a project conducted in a large sample of patients with confirmed or suspected COVID-19, to follow courses on methodology and statistics and to present his preliminary findings at international congresses. He has recently been appointed as Postdoctoral assistant at the Faculty of Rehabilitation Sciences of the Hasselt University. Thus, he is now preparing to start his new employment and keep working as a researcher in the field of rehabilitation of chronic diseases.

List of publications

1. Paes T., **Machado F.V.C.**, Cavalheri V., Pitta F. and Hernandes N.A. Multitask protocols to evaluate activities of daily living performance in people with COPD: a systematic review. *Expert Rev Respir Med*. 2017 Jul;11(7):581-590. doi: 10.1080/17476348.2017.1335198.

2. **Machado F.V.C.**, Bisca G.W., Morita A.A., Rodrigues A., Probst V.S., Furlanetto K.C., Pitta F. and Hernandes N.A. Agreement of different reference equations to classify patients with COPD as having reduced or preserved 6MWD. *Pulmonology*. 2017 Nov 27:S2173-5115(17)30151-3. doi: 10.1016/j.rppnen.2017.08.007.

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4. Bisca G.W., Fava L.R., Morita A.A., **Machado F.V.C.**, Pitta F. and Hernandes N.A. 4-Meter Gait Speed Test in Chronic Obstructive Pulmonary Disease: INTERRATER RELIABILITY USING A STOPWATCH. *J Cardiopulm Rehabil Prev*. 2018 Jul;38(4):E10-E13. doi: 10.1097/HCR.0000000000000297.

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