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Frequency and Functional Consequences of Low Appendicular Lean Mass and Sarcopenic Obesity in Patients with Asthma Referred for Pulmonary Rehabilitation

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Keywords
Body composition · Sarcopenia · Obesity · Low muscle mass · Asthma

Abstract

Introduction: One of the most prominent extrapulmonary manifestations in patients with chronic respiratory disease is changes in body weight and composition. However, the frequency and functional consequences of low appendicular lean mass (ALM) or sarcopenic obesity (SO) in patients with asthma are largely unknown. Therefore, the aim of the current study was to assess the frequency and functional consequences of low appendicular lean mass index (ALMI) and SO in patients with asthma. ***Methods:*** A retrospectively analyzed cross-sectional study was conducted in 687 patients with asthma (60% female, 58 ± 13 years, FEV_1 76 ± 25% pred) referred for comprehensive pulmonary rehabilitation (PR). Body composition, pulmonary function, exercise capacity, quadriceps muscle function, and quality of life were assessed. Patients were classified as presenting low ALMI according to the 10th percentiles of age-sex-body mass index (BMI)-specific reference values and as having SO according to the diagnostic procedure proposed by the 2022 ESPEN/EASO consensus. In addition, clinical outcomes between patients with normal and low ALMI or with and without SO were compared. ***Results:*** The frequency of patients classified as low ALMI was 19%, whereas 45% of the patients were obese. Among the obese patients, 29% had SO. In

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patients with normal weight, those with low ALMI were younger and had worse pulmonary function, exercise capacity and quadriceps muscle function than those with normal ALMI (all $p < 0.05$). Overweight patients with low ALMI presented poorer pulmonary function and quadriceps muscle function (both strength and total work capacity). In obese class I patients, those with low ALMI showed lower quadriceps strength and maximal oxygen uptake acquired during cardiopulmonary exercise testing. Both male and female patients with SO showed lower quadriceps muscle function and reduced maximal exercise capacity compared to non-SO asthma patients. ***Conclusion:*** Approximately one in five asthma patients presented low ALM when age-sex-BMI-specific ALMI cut-offs were applied. Obesity is common among patients with asthma referred for PR. Among the obese patients, a significant proportion presented SO. Low ALM and SO were associated with worse functional outcomes.

Introduction

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

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

Dual-energy X-ray absorptiometry (DEXA) is a validated noninvasive technique enabling precise assessment of the amount of fat mass (FM) and LM of the whole body and of specific anatomical regions [16]. Lean soft tissue mass measured at the limbs, also known as appendicular lean mass (ALM), normalized by height squared (ALMI; appendicular lean mass index), is associated with muscle strength and exercise capacity in patients with COPD [11]. Since obese people are supposed to have a higher muscle mass than normal-weight subjects, it has been emphasized to take the amount of FM into account when interpreting muscle mass since both tissue components are interrelated [17, 18]. In fact, the contribution of skeletal muscle to LM is lower at a higher degree of adiposity, due to an increase in connective tissue [19]. Hence, it can be hypothesized that applying fixed cutoff values results in underdiagnoses of low ALMI in overweight or obese patients, providing rationale for the use of age-sex-BMI cut-offs. Recently, Ofenheimer et al. [20] published European age- and sex-specific reference values for ALMI with regard to BMI categories.

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

Methods

Study Design and Subjects

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

Anthropometric and Body Composition Measurements

Body weight and height were assessed using a calibrated scale, after which BMI was calculated as weight divided by height squared (kg/m^2). Body composition measurements were conducted with the GE-Lunar Prodigy (January 2005-July 2014)/ GE-Lunar iDXA (August 2014-January 2019; GE Healthcare, Madison, WI, USA) DEXA scanner. For the current study, the body composition variables of interest derived from the DEXA output were LM (kg) and FM (total body weight minus total LM; in kg) of the whole body, trunk, and of the limbs. From these measures, the following derivative values were calculated: fat mass index (FMI; FM/height^2), ALMI (ALM/height^2), and trunk lean mass index (TLMI), in which ALM was defined as the sum of the LM of the four limbs and TLM as LM of the trunk [17]. In addition, ratios between trunk and appendicular LM (TM/ALM ratio) and between appendicular LM and FM (ALM/FM ratio) were calculated. To explore the frequency of osteopenia and osteoporosis in the current population, bone mineral density was measured in the lumbar spine and hips, after which concurrent T scores were calculated (osteopenia: T score −1 to −2.5 × standard deviation (SD); osteoporosis: T score <−2.5 × 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 subclassified into low or normal ALMI, using the 10th percentiles of age-, sex- and BMI-specific reference values of Ofenheimer et al. [20]. For the SO classification, the diagnostic criteria proposed by the ESPEN/EASO consensus statement were adopted [14, 15]. The first level of the diagnostic procedure (screening) is based on the concomitant presence of an elevated BMI and surrogate indicators of sarcopenia (e.g., risk factors, such as CRDs). Thus, all asthma patients with BMI ≥30 kg/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 ALM were applied, as suggested by the ESPEN/EASO consensus. Patients with a positive screening and altered skeletal muscle functional parameters and body composition were classified as SO. Since the proposed staging step by ESPEN/EASO has not been properly investigated yet and is based on clinical expert opinion [14, 15], this step was not taken into account in the current study.

Other Assessments

Demographical data (age, sex, smoking status), medication use, and exacerbation/hospitalization history were assessed as part of standard care. Pulmonary function was determined with standardized spirometry equipment (Masterlab®, Jaeger, Würzburg, Germany) following international guidelines [24], with forced expiratory volume in the first second (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-min walking test assesses the distance walked over 6 min (6WMD) as a measure of functional status. The test is performed twice, after which the best 6MWD was reported) [26]. A symptom limited incremental cardiopulmonary exercise test (CPET) was performed using a cycle-ergometer to assess maximal exercise performance. Both the maximum load (W_{max}; in Watts) as well as peak oxygen uptake ($VO2_{peak}$) were measured as main outcomes [27]. Endurance exercise capacity was measured by a submaximal constant work-rate cycle test (CWRT) at 75% of the pre-identified W_{max} [28]. Isokinetic quadriceps muscle function was determined using a Biodex System 4 Pro (Biodex Medical Systems, Inc., NY, USA) [21]. Quadriceps muscle strength was defined as the highest peak torque (Nm), whereas isokinetic quadriceps muscle endurance was be defined as the total amount of delivered work (Joules) during a set of 30 repetitions. Health-related quality of life (HRQL) was assessed with the St. George's Respiratory Questionnaire (SGRQ; range 0–100) [29] and functional impairment due to dyspnea with the modified Medical Research Council (mMRC; range 0–4; clinical cut-off ≥2) dyspnea scale [30]. In both of these questionnaires, higher scores indicate more limitations.

Statistics

Results are presented as mean and SD, median and interquartile range, and/or proportions, as appropriate. Continuous variables were tested for normality. To analyze characteristics and functional outcomes between patients with normal or low ALMI within each BMI category, the independent samples *t* test, Mann-Whitney U test or χ^2 test was used, as appropriate. The previously mentioned tests were also used to compare characteristics and functional outcomes between patients with and without SO. In addition, to assess differences in functional outcomes (6MWD, CPET maximal workload, quadriceps strength, and SGRQ total score) between normal ALMI and low ALMI groups, while controlling for age and sex, analysis of covariance with least significant difference 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., CA, 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; online suppl. material Table E1; for all online suppl. material, see https://doi.org/10.1159/000531196), regarding BMI, 2% of the patients were classified as underweight, 23% as normal weight, 29% as overweight, 26% as obese class I, 14% as obese class II, and 6% as obese class III. The general characteristics of the patients after stratification into BMI groups are presented in Table 1.

Frequency of Low ALMI and SO

In Figure 1, the frequency of low ALMI and SO is presented. The overall proportion of patients classified as low ALMI was 18.9%. The frequency of patients with low ALMI in underweight, normal weight, overweight, and obese groups I, II, and III was 29%, 21%, 22%, 23%, 8%, and 3%, respectively. Because of the low frequency of patients with low ALMI in obese classes II ($n = 8$) and III ($n = 1$) as well as in underweight patients ($n = 4$), these classes were excluded in further analyses regarding the functional consequences of low ALMI. Figure 2 displays a flowchart with the number of patients in each level and step of the ESPEN/EASO diagnostic criteria [14, 15]. Three hundred and ten patients (46%) of the current study population were obese (BMI ≥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%.

Functional Consequences of Low ALMI and SO

In Table 2, comparisons of outcomes are presented between patients with normal and low ALMI after stratification into three BMI categories (normal weight, overweight, obese class I). A higher proportion of males with low ALMI was found in patients with normal weight (58% vs. 38%, $p < 0.05$), whereas a lower proportion of males with low ALMI was found in obese class I patients (25% vs. 46%, $p < 0.05$). In normal weight patients, those with low ALMI were younger and presented a lower FEV_1 and FEV_1/FVC ratio (all $p < 0.05$). FEV_1 and FEV_1/FVC ratios were also lower in overweight patients presenting with low ALMI as compared to overweight patients with normal ALMI (both $p < 0.05$). The proportion of patients with ≥10 pack years was significantly higher in overweight patients with low ALMI values as compared to overweight patients with normal ALMI values ($p < 0.05$; Table 2).

In patients with normal weight, those with low ALMI presented lower 6MWD (% predicted), maximal load during the CPET (W_{max}), peak oxygen consumption during CPET ($VO2_{peak}$), quadriceps peak torque, and quadriceps total work compared with patients with normal ALMI ($p < 0.05$, for all). Overweight patients with low ALMI demonstrated lower TMI, quadriceps peak torque and total work as compared to overweight patients with normal ALMI. Considering the obese class I patients, those with low ALMI showed lower quadriceps peak torque values and lower $VO2_{peak}$ (in milliliters per minute). The ALM/FM ratio was the highest in the normal weight and normal ALMI group (mean of 1.19 ± 0.69 kg of ALM for each kg of FM) and the lowest in the obese class I patients with low ALMI (mean of 0.48 ± 0.11 kg of ALM for each kg of FM).

In the comparisons of functional outcomes among the six groups (i.e., three BMI groups stratified into normal or low ALMI), whilst controlling for age and sex, it was shown that patients with low ALMI independent of their BMI categories and patients with obesity independent of their ALMI classification presented a significantly lower 6MWD compared with patients with normal weight and normal ALMI (all $p < 0.05$; Fig. 3). While normal weight and overweight patients with low ALMI showed reduced maximal load during the CPET compared to their respective BMI groups with normal ALMI, obese class I patients with normal or low ALMI showed similar maximal load during the CPET. Additionally, quadriceps peak torque was lower in patients with low ALMI compared to patients with normal ALMI across all BMI groups, whereas obese class I patients with normal ALMI showed higher quadriceps peak torque than normal weight patients with normal ALMI. Finally, obese class I patients with normal ALMI presented higher SGRQ total scores than normal weight patients with normal ALMI (Fig. 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 ALMI and quadriceps muscle function compared with non-SO patients. In addition, SO patients showed a reduced maximal exercise capacity and a higher proportion of patients with osteopenia/osteoporosis compared with the non-SO group (all $p < 0.05$; Table 3).

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

	Underweight *n* = 14 (2.0%)	Normal weight *n* = 161 (23.4%)	Overweight *n* = 202 (29.4%)	Obese class I *n* = 175 (25.5%)	Obese class II *n* = 96 (14.0%)	Obese class III *n* = 39 (5.7%)	*p* value Between-group difference
Male sex, *n* (%)	4 (28.6)	68 (42.2)	94 (46.5)	72 (41.1)	25 (26.0)	10 (25.6)	<0.01
Age, years	52±13	57±12	59±13	60±13	57±12	57±13	0.098
Exacerbations ≥2 (<12 months), %	58	68	66	70	69	61	0.867
Hospitalizations ≥2 (<12 months), %	50	20	19	26	31	18	<0.05
Pack years ≥10, %	58	50	50	55	56	44	0.774
ICS use, %	79	87	88	84	80	74	0.177
OCS use, %	29	21	20	25	26	15	0.655
BMI, kg/m^2	17.3±1.1*	22.5±1.8	27.4±1.5*	32.4±1.5*	37.3±1.4*	44.7±4.7*	<0.001
ALMI, kg/m^2	5.2±0.9*	6.4±0.9	7.1±1.0*	8.0±1.1*	8.4±1.1*	9.6±1.7*	<0.001
TLMI,[a] kg/m^2	6.9±0.9	7.6±0.9	8.3±0.8*	9.1±1.1*	9.9±1.2*	11.3±1.7*	<0.001
TLM/ALM ratio[a]	1.25±0.10	1.18±0.14	1.18±0.15	1.18±0.15	1.25±0.20	1.33±0.32*	<0.01
FMI, kg/m^2	3.4±1.3*	6.5±2.0	10.1±2.1*	13.5±2.2*	17.3±2.0*	22.1±3.5*	<0.001
ALM/FM ratio	1.82±0.91*	1.16±0.66	0.75±0.26*	0.62±0.19*	0.50±0.11*	0.44±0.10*	<0.001
FEV_1, % predicted	56±30	69±26	76±26*	78±22*	80±20*	87±20*	<0.001
FEV_1/FVC ratio	0.52±0.23	0.55±0.17	0.59±0.16	0.63±0.14*	0.68±0.12*	0.70±0.13*	<0.001
RV/TLC ratio	0.54±0.15*	0.45±0.11	0.42±0.11	0.41±0.10*	0.40±0.10*	0.39±0.11	<0.001
RV/TLC ratio ≥0.40, %	71	64	51	52	53	44	0.079
mMRC grade ≥2, %	71	63	74	84	90	92	<0.01
6MWD, m	438±175	488±130	465±132	431±125*	383±139*	380±102*	<0.001
6MWD, % predicted	62±26	71±18	72±20	70±19	64±21	69±15	<0.05
CPET Wmax, Watts	65±34	94±38	104±48	100±45	91±39	97±39	<0.01
CPET Wmax, % predicted	52±31	70±27	84±36*	80±35	78±35	83±31	<0.001
CPET VO_2peak, mL/min	1,046±362	1,247±419	1,426±500*	1,461±482*	1,411±457	1,620±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	1,135±410*	1,694±694	1,850±793	2,003±802*	1,845±950	1,900±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

ICS, inhalation corticosteroids; OCS, oral corticosteroids; BMI, body mass index; ALMI, appendicular lean mass index; TLMI, trunk lean mass index; FMI, fat mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; mMRC, modified Medical Research Council; 6MWD, 6-min walking distance; CPET, cardiopulmonary exercise test; Wmax, 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. *$p < 0.05$ versus normal weight group. [a]$n = 316$.

Discussion

This study showed that 18.9% of adult patients with asthma referred for PR have low ALM (according to age-sex-BMI-specific ALMI cut-offs) and 29.4% have SO, which in both cases is associated with worse functional outcomes. There is growing evidence to indicate that obesity has detrimental effects on the contractile function of skeletal muscle, thereby reducing mobility and promoting obesity-associated health issues [31]. The high prevalence of obesity in patients with asthma highlights the importance of taking into account physiological determinants (age, sex, ethnicity and BMI) when assessing low muscle mass and/or sarcopenia in this population [5, 18]. As a matter of fact, the most recent EWGSOP2 consensus on the definition and diagnosis of sarcopenia state that muscle mass is indeed correlated with body size, but the authors make no recommendation to adjust for

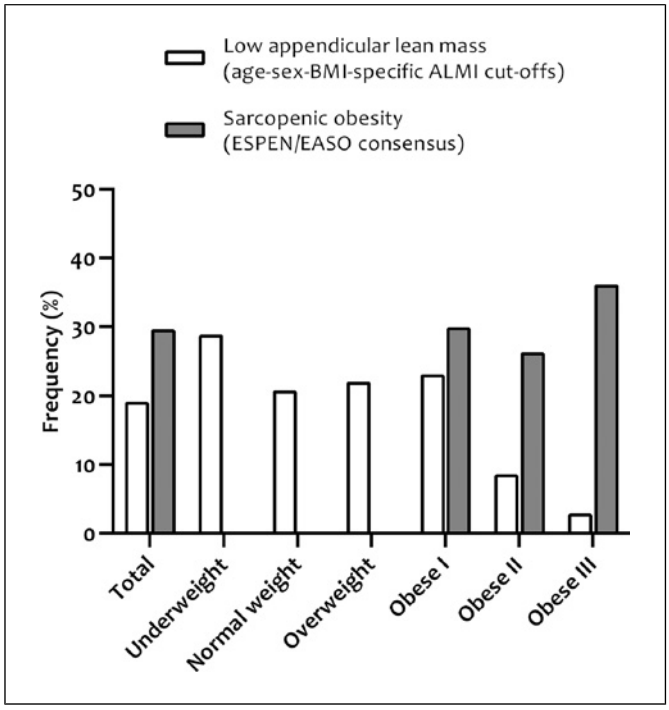

Fig. 1. Frequency of low appendicular lean mass index (ALMI) and sarcopenic obesity (SO; only in patients with BMI ≥30 kg/m^2) in patients with asthma stratified by BMI category. The total frequency of SO is relative to the total of patients in the obese classes.

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 enhances the diagnosis of low muscle mass/sarcopenia in overweight/obese subjects.

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

The present study aimed to assess different outcomes which could potentially interact with decreased ALM, such as medication use and osteopenia/osteoporosis. The Global Initiative for Asthma (GINA) indicates that long-term treatment with OCS (periods >2 weeks) may present with systemic side effects such as obesity, osteoporosis and muscle weakness [7]. Overall, the proportion of patients on maintenance OCS in the current study was 22%, which might (partly) explain the high proportion (45%) of obese individuals in the current study population. However, no statistical differences in OCS use were

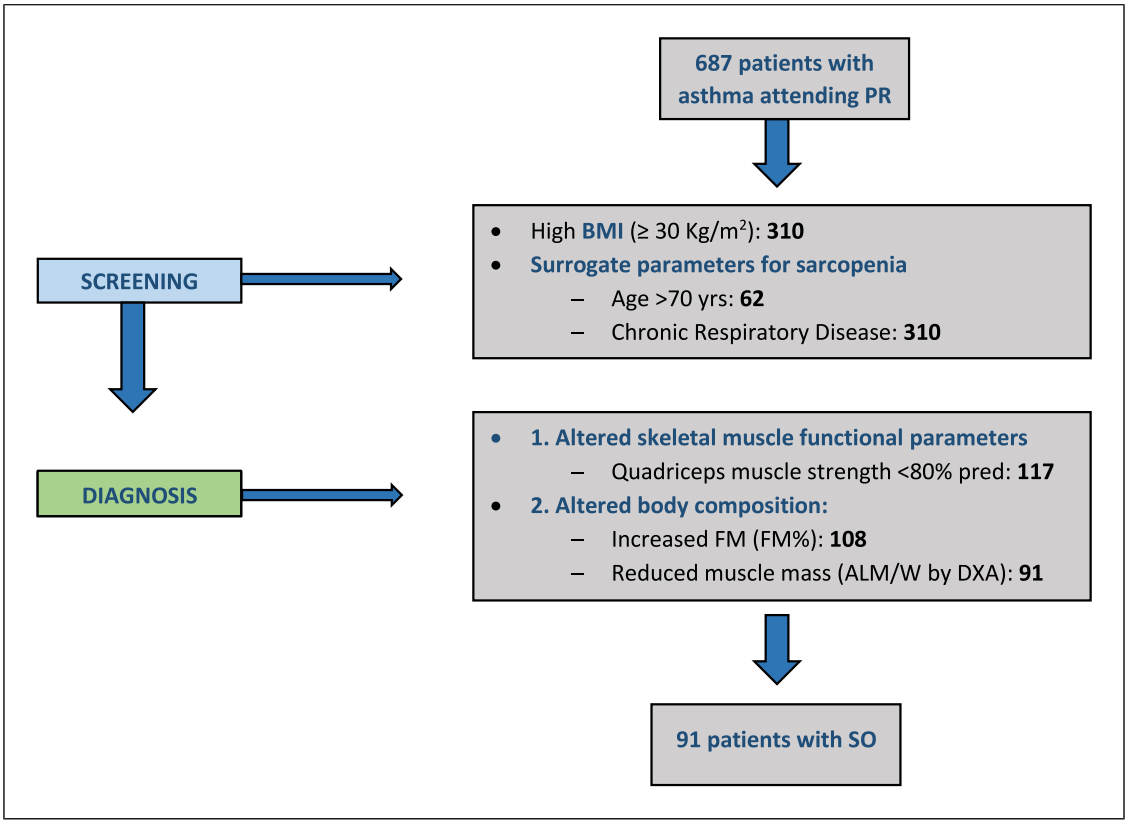

Fig. 2. Diagnostic procedure for the assessment of sarcopenic obesity (SO) based on the ESPEN and EASO consensus statement. ALM/W, appendicular lean mass adjusted to body weight; BMI, body mass index; DXA, dual X-ray absorptiometry; FM, fat mass; SO, sarcopenic obesity.

found between patients with low ALMI versus normal ALMI, irrespective of their BMI group. This is in line with a systematic review by Berthon et al. [37] which concluded that in four out of five studies, mainly conducted in healthy populations with durations of 4 days–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 mg per day of OCS [38]. The majority of the studies assessing obesity and osteoporosis suggest that obesity has a favorable effect on bone density, yet it remains unclear what the effect of obesity is on skeletal microarchitecture [39]. The frequency of osteoporosis in the current study was significantly lower in the overweight and obese groups in comparison with the normal weight group, which underlines the potential positive effect of mechanical overload on bone health [40]. Taking this in consideration, it is important to emphasize that among the obese asthma patients, those with SO showed a higher proportion of osteopenia/osteoporosis compared to those with no SO, suggesting that preserved skeletal muscle functional parameters are also beneficial in terms of bone health.

Strengths and Limitations

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

Evidently, some limitations of the current study need to be considered. Variables that can influence body

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

	Normal weight (n = 161)		Overweight (n = 202)		Obese class I (n = 175)	
	normal ALMI (n = 128)	low ALMI (n = 33)	normal ALMI (n = 158)	low ALMI (n = 44)	normal ALMI (n = 135)	low ALMI (n = 40)
Male sex, n (%)	49 (38)	19 (58)*	76 (48)	18 (41)	62 (46)	10 (25)*
Age, years	58±12	53±13*	60±14	58±11	60±14	58±10
Exacerbations ≥2 (<12 months), %	68	71	63	79	69	74
Hospitalizations ≥2 (<12 months), %	21	19	19	21	25	29
Pack years ≥10, %	51	45	46	67*	53	61
ICS use, %	86	91	87	93	81	88
OCS use, %	22	18	19	25	25	20
BMI, kg/m^2	22.8±1.7	21.3±1.8*	27.5±1.4	27.0±1.5	32.5±1.5	32.2±1.5
ALMI, kg/m^2	6.6±0.9	5.8±0.7*	7.4±0.8	6.1±0.7*	8.3±1.0	6.9±0.7*
TLMI[a], kg/m^2	7.7±0.9	7.3±0.7	8.4±0.8	7.9±0.6*	9.2±1.1	8.8±1.1
TLM/ALM ratio[a]	1.17±0.14	1.26±0.13*	1.14±0.12	1.31±0.14*	1.14±0.13	1.29±0.13*
FMI, kg/m^2	6.5±2.0	6.3±2.1	9.8±2.1	11.0±1.9*	13.1±2.2	14.7±1.8*
ALM/FM ratio	1.19±0.69	1.05±0.51	0.80±0.26	0.58±0.16*	0.66±0.19	0.48±0.11*
FEV_1, % predicted	71±26	59±28*	79±25	65±24*	79±23	75±20
FEV_1/FVC ratio	0.57±0.16	0.50±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 Wmax, Watts	98±38	77±33*	108±50	93±40	103±46	90±40
CPET Wmax, % predicted	74±28	56±21*	86±38	75±26	79±35	80±36
CPET VO_2peak, mL/min	1,305±423	1,021±321*	1,458±511	1,296±440	1,512±500	1,292±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	1,764±714	1,394±515*	1,927±814	1,578±651*	2,074±834	1,763±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)

ALMI, appendicular lean mass index; ICS, inhalation corticosteroids; OCS, oral corticosteroids; BMI, body mass index; TLMI, trunk lean mass index; FMI, fat mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; mMRC, modified Medical Research Council; 6MWD, 6-min walking distance; CPET, cardiopulmonary exercise test; Wmax, 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. *$p < 0.05$ versus normal ALMI from the same BMI group. [a]n = 259.

composition, such as physical activity and nutritional status, were not studied. Furthermore, as the studied patient sample consisted of asthma patients referred for PR, the current results cannot be generalized to the whole asthma population. It seems reasonable to assume that the frequency of low ALMI and SO is probably higher compared to the general asthma population. In fact, severe refractory asthma has been related to the presence of low fat-free mass that is comparable to that of GOLD stage IV COPD [41]. Hence, patients attending PR represent an interesting population because of their complexity in terms of symptoms and comorbidities, while demonstrating a high prevalence of obesity and functional impairment [42]. Lastly, it is not clear why obese subjects (especially those with low ALMI) demonstrate less impaired quality of life in the present study

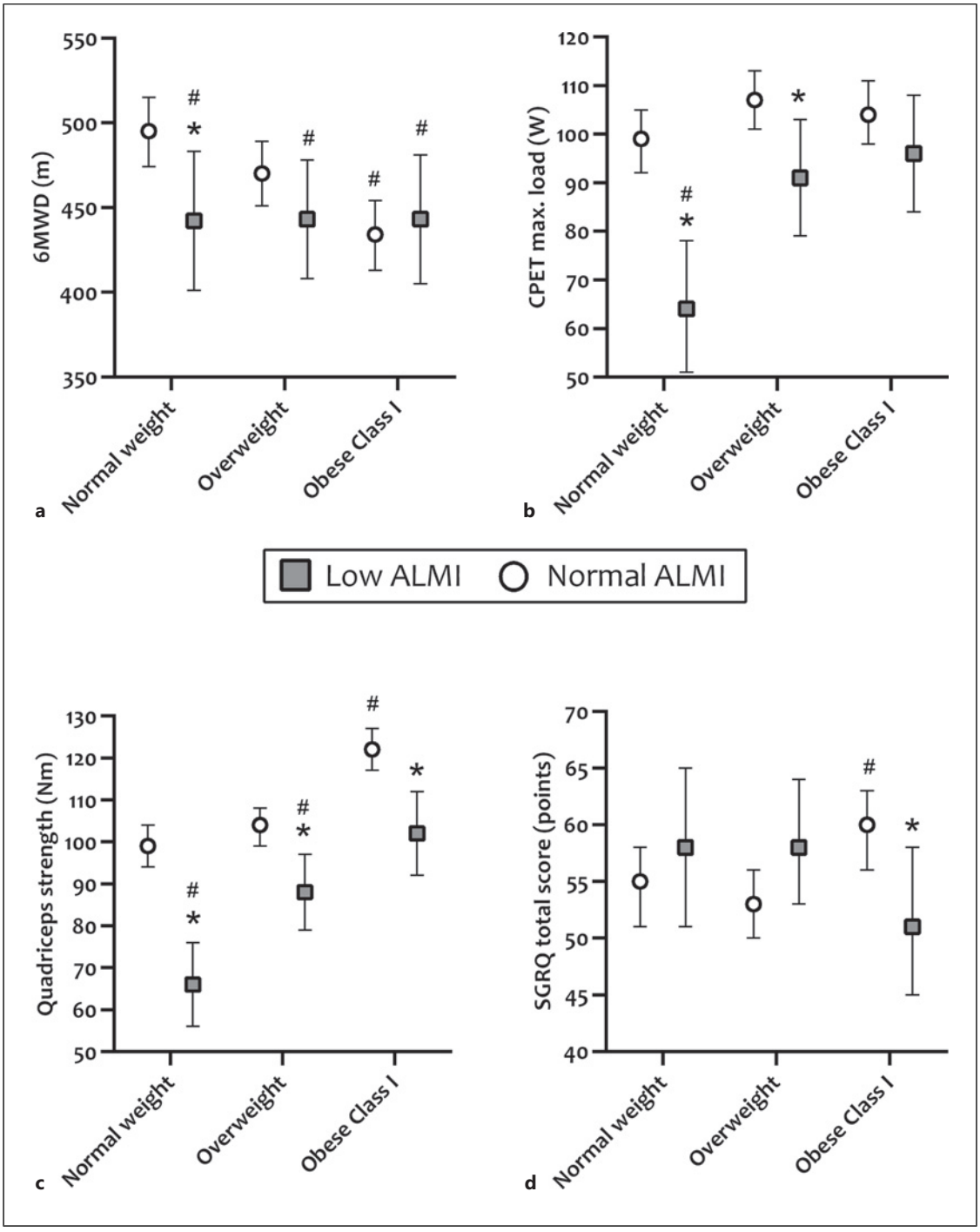

Fig. 3. Age-sex adjusted means (and 95% confidence intervals) for (**a**) 6-min walk distance, (**b**) maximal workload in CPET, (**c**) peak quadriceps strength, and (**d**) quality of life (SGRQ total score) across BMI groups, displaying normal ALMI (in white) versus low ALMI (in grey). Analysis of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

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

	Males (n = 107)		Females (n = 203)	
	NSO (n = 80)	SO (n = 27)	NSO (n = 139)	SO (n = 64)
Age, years	61±11	63±10	56±14	59±11
Exacerbations ≥2 (<12 months), %	57	79	72	71
Hospitalizations ≥2 (<12 months), %	19	13	31	32
Pack years ≥10, %	69	57	47	47
ICS use, %	71	89	87	83
OCS use, %	26	26	27	14*
BMI, kg/m^2	34.9±4.7	33.9±3.5	35.6±4.5	36.7±5.1
ALMI, kg/m^2	9.5±1.1	8.7±0.8*	7.9±1.0	7.4±1.0*
TLMI,[a] kg/m^2	10.2±0.9	10.3±0.9	9.2±1.3	9.6±1.8
TLM/ALM ratio[a]	1.09±0.11	1.23±0.13*	1.21±0.16	1.33±0.27*
FMI, kg/m^2	13.3±3.6	13.2±2.9	16.6±3.2	18.1±3.4*
ALM/FM ratio	0.75±0.18	0.68±0.11*	0.49±0.08	0.42±0.06*
FEV_1, % predicted	75±21	73±22	85±22	78±19*
FEV_1/FVC ratio	0.61±0.14	0.59±0.13	0.69±0.12	0.66±0.12
RV/TLC ratio	0.39±0.08	0.40±0.08	0.39±0.11	0.44±0.09*
RV/TLC ratio ≥0.40, %	48	44	48	67*
mMRC grade ≥2, %	83.6	93.3	85.2	94.4
6MWD, m	454±120	426±115	396±134	376±119
6MWD, % predicted	69±17	66±16	68±21	67±19
CPET Wmax, Watts	119±51	100±31*	93±39	76±27*
CPET Wmax, % predicted	65±28	58±16	91±37	82±30
CPET VO_2peak, mL/min	1,825±577	1,525±397*	1,363±387	1,227±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	2,750±861	2,046±625*	1,998±629	1,173±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)*

ALMI, appendicular lean mass index; ICS, inhalation corticosteroids; OCS, oral corticosteroids; BMI, body mass index; TLMI, trunk lean mass index; FMI, fat mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; mMRC, modified Medical Research Council; 6MWD, 6-min walking distance; CPET, cardiopulmonary exercise test; Wmax, 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. *$p < 0.05$ versus non-sarcopenic obese (NSO) group from the same sex. [a]n = 122.

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 ALM and that obesity is very common. Among the obese patients, a significant proportion (29%) presented SO. Moreover, our findings provide important insights into the functional consequences of low ALM and SO in asthma patients referred for PR. Even though differences in functional outcomes between overweight and obese patients with normal and low ALM were less pronounced than in normal weight asthma patients, more emphasis should be put on nonpharmacological interventions such as exercise training programs and nutritional support (as part of PR) that not only target

the deleterious effects of obesity in asthmatic patients but also focus on maintaining or increasing muscle mass, skeletal muscle functional parameters, and exercise tolerance in these patients. Future studies should focus on the prognostic impact of low muscle mass and SO in the asthma population and assess the effects of exercise- and nutrition-based interventions in addition to pharmacotherapy.

Statement of Ethics

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. At the start of the PR program, all patients included in the current study did not formally object to the use of their data for research purposes, in agreement with Ciro's research data policy. Therefore, written informed consent was not required, which was approved by the Medical Ethics Committee of Maastricht University.

Conflict of Interest Statement

Frits M.E. Franssen reports grants and personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from GlaxoSmithKline, grants and personal fees from Novartis, personal fees from TEVA, and outside the submitted work. Bram van den Borst reports personal fees from Genzyme Europe B.V. and Boehringer Ingelheim, consulting fees from Boehringer Ingelheim and support for attending meetings and/or travel from Chiesi Pharmaceuticals B.V., all outside the submitted work. Martijn A. Spruit reports research grants from Netherlands Lung Foundation, AstraZeneca, Boehringer Ingelheim, TEVA, Chiesi, and Stichting Astma Bestrijding, and all outside the submitted work. Roy Meys, Felipe V.C. Machado, Anouk A.F. Stoffels, Hieronymus W.H. van Hees, Peter H. Klijn, Chris Burtin, and Fabio Pitta have nothing to declare.

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Author Contributions

Roy Meys and Felipe V.C. Machado: conceptualization, methodology, formal analysis, writing – original draft, and visualization. Martijn A. Spruit: conceptualization, writing – review and editing, supervision, and funding acquisition. Anouk A.F. Stoffels, Bram van den Borst, Peter H. Klijn, Chris Burtin, Fabio Pitta, and Hieronymus W.H. van Hees: writing – review and editing. Frits M.E. Franssen: conceptualization, writing – review and editing, and supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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