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Original Article

Muscle Function in Moderate to Severe Asthma: Association With Clinical Outcomes and Inflammatory Markers

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What is already known about this topic? Many patients with severe asthma report limitations in daily activities, possibly due to muscle dysfunction. Indeed, these patients have been shown to have lower muscle mass than patients with mild to moderate asthma, but the clinical consequences remain unclear.

What does this article add to our knowledge? We showed that lower muscle mass was associated with more airway obstruction and lower functional exercise capacity, whereas lower muscle strength was related to poorer asthma control and quality of life, and a greater likelihood of emergency visits.

How does this study impact current management guidelines? If further longitudinal research confirms that changes in muscle mass and strength affect clinical asthma outcomes, muscle function may become a target for asthma treatment.

BACKGROUND: Patients with severe asthma have been shown to have low muscle mass, but the clinical consequences are unknown.

OBJECTIVE: In a clinical cohort of patients with moderate to severe asthma, we aimed to assess muscle mass and strength and their relation with functional and clinical outcomes, as well as with systemic inflammatory markers.

METHODS: Muscle mass and strength were assessed by the fat-free mass index (FFMI), creatinine excretion in a 24-hour urine sample, and handgrip strength test. Functional outcomes included pulmonary function tests and the 6-minute walking distance, whereas clinical outcomes were assessed with questionnaires on asthma control, quality of life, and health care use. Associations of muscle mass and strength with asthma outcomes were assessed with multivariable regression analyses.

RESULTS: A total of 114 patients participated (36% male; mean age, 51.9 ± 14.4 years; body mass index, 27.7 ± 5.7 kg/m^2). According to predefined criteria, 16% had a low FFMI and 8% a low urinary creatinine excretion, which did not differ between categories of asthma severity. Both lower FFMI and urinary creatinine excretion were associated with lower values of FEV_1 and 6-minute walking distance, whereas a lower handgrip strength was related to worse asthma control, poorer quality of life, and a higher probability of emergency visits (all $P < .05$). Except for higher leukocytes in relation to lower FFMI, we did not find associations between systemic inflammatory markers and muscle function.

CONCLUSIONS: This study demonstrates that low muscle mass is prevalent in patients with moderate to severe asthma and, along with low muscle strength, is associated with poorer clinical and functional outcomes. Our results encourage longitudinal studies into muscle function as a potential target for treatment to improve asthma outcomes. © 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of

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Abbreviations used
6MWD- 6-minute walking distance
ACQ- Asthma Control Questionnaire
BMI- body mass index
CER- creatinine excretion rate
COPD- chronic obstructive pulmonary disease
FFMI- fat-free mass index
FVC- forced vital capacity
GINA- Global Initiative for Asthma
HGS- hand grip strength
OCS- oral corticosteroid

Key words: *Severe asthma; Muscle function; Exercise capacity; Asthma control; Quality of life; Health care use; Airway obstruction; Systemic inflammation*

INTRODUCTION

Asthma is a heterogeneous airway disease characterized by airflow limitation and a variability in respiratory symptoms, and has a significant impact on patients' lives. As with chronic obstructive pulmonary disease (COPD), the disease is not limited to the lungs, but comorbidities and extrapulmonary traits such as deconditioning and systemic inflammation contribute to the burden of asthma.[1] Indeed, many patients with asthma, especially those with severe disease, report exercise intolerance and limitations in daily activities, severely affecting their quality of life.[2,3] Among the many factors that contribute to this activity limitation, low muscle mass and strength could be important.[3]

In COPD, limb muscle dysfunction—characterized by low muscle mass and decreased muscle strength—is considered an important systemic consequence of the disease.[4] Muscle dysfunction in patients with COPD has been associated with worse clinical outcomes, such as exercise intolerance, poor quality of life, high exacerbation risk, and even lower survival rates.[4,5] Exercise training is nowadays considered the most potent intervention to improve muscle function in COPD—whether or not combined with a rehabilitation program or nutritional supplements—and leads to higher exercise tolerance and lower symptom burden.[4,5]

In asthma, data on muscle mass and strength are scarce, although some studies suggest that muscle dysfunction may play a role. It was shown that patients with severe asthma have lower muscle mass than do patients with mild to moderate asthma, even though they more often had obesity.[6] In fact, the level of fat-free mass— a surrogate marker of muscle mass—in these patients with severe asthma was comparable to that of patients with stage IV COPD.[6] Interestingly, in a German longitudinal cohort study, significant loss of muscle mass after 2 years of follow-up was seen in patients with uncontrolled compared with controlled asthma, despite having stable body mass index (BMI).[7] In addition, decreased muscle strength could be of importance because patients with mild and severe asthma were found to have lower handgrip strength (HGS) than healthy controls.[8] However, the clinical consequences of low muscle mass and strength in asthma are still unclear.

Several factors contribute to the etiology of muscle dysfunction. In COPD, factors such as oral corticosteroid (OCS) use, malnutrition, and physical inactivity have been implicated, but systemic inflammation may also play a role.[9,10] Indeed, as a meta-analysis of 132 studies indicates, there is consistent evidence supporting a link between a systemic inflammatory state and the development of muscle dysfunction in various acute and chronic conditions, with C-reactive protein, TNF-α, and IL-6 emerging as most important inflammatory markers.[11] In asthma, which is associated with chronic airway inflammation but often also exhibits systemic inflammatory responses,[12] the role of systemic inflammation in muscle dysfunction has not been studied before.

More insight into the clinical consequences of low muscle mass and strength in asthma and the possible role of underlying systemic inflammation could make muscle function a potential target for treatment to improve asthma outcomes.[1] Therefore, in the current study, we assessed the level of muscle mass and strength in patients with varying asthma severity. Second, we examined whether muscle mass and strength are related to functional and clinical asthma outcomes. Finally, we explored whether systemic inflammatory markers are associated with low muscle mass and strength.

METHODS

Study design and population

This cross-sectional study was conducted in a tertiary teaching hospital in Leeuwarden, The Netherlands, and included patients with asthma from the regular pulmonary outpatient clinic and the severe asthma center.[13] Patients (aged ≥18 years) with a diagnosis of moderate to severe asthma—according to Global Initiative for Asthma (GINA) 2019 step 3 to 5 treatment—were consecutively recruited between June 2019 and October 2022.[14] The diagnosis of asthma was confirmed by a history of either a positive bronchodilator reversibility test result or a positive methacholine challenge test result. Exclusion criteria were pregnancy, concurrent respiratory disease including COPD, or an acute respiratory tract infection or asthma exacerbation in the previous month. All patients underwent an extensive clinical, functional, and laboratory assessment during 1 or 2 regular care visits within 2 weeks. The study was approved by the local medical ethics committee (RTPO 1067; April 29, 2019), and all patients gave their written informed consent.

Data collection

Data on demographic characteristics, medical history, and medication use were obtained from electronic patient records. All patients completed the Asthma Quality-of-Life Questionnaire,[15] the 6-item Asthma Control Questionnaire (ACQ-6),[16] a questionnaire on health care use,[17] and the "short questionnaire to assess health-enhancing physical activity" (SQUASH).[18] Anthropometric measurements were performed including height and weight to calculate BMI.

Lung function testing included spirometry before and after 400 μg inhaled salbutamol,[19] and measurement of fractional exhaled nitric oxide.[20] Functional exercise capacity was determined by the 6-minute walking distance (6MWD), performed according to European Respiratory Society/American Thoracic Society guidelines and expressed as percentage of predicted.[21,22] Venous blood was taken to measure peripheral blood differential cell counts, albumin,

TABLE I. Patient characteristics of total study population

Patient characteristics			
Demographic characteristics	**Value**	**Clinical outcomes**	**Value**
Sample size	114	ACQ-6 score (0-6)	1.7 ± 1.1
Sex: male	41 (36)	AQLQ score (1-7)	5.3 ± 1.0
Age (y)	51.9 ± 14.4	≥1 exacerbations in preceding year	62 (54)
BMI (kg/m^2)	27.7 ± 5.7	≥1 emergency visits in preceding year	55 (48)
BMI ≥25 kg/m^2	80 (70)	Adult-onset asthma	62 (54)
Smoking (pack years)	0 [0-7]	Biological asthma therapy	21 (18)
MVPA (h/wk)	9 [3-16]	OCS-dependent	6 (5)
Inflammatory markers		**Functional outcomes**	
FENO (ppb)	24 [13-36]	pb FEV_1 (%pred)	95.8 ± 16.6
Blood eosinophils ≥0.3 × 10^9/L	27 (24)	pb FEV_1/FVC (%)	73.1 ± 11.9
Sputum eosinophils ≥2% (N = 18)	8 (44)	6MWD (%pred)	82.3 ± 15.8

AQLQ, Asthma Quality-of-Life Questionnaire; *FENO*, fractional exhaled nitric oxide; *IQR*, interquartile range; *MVPA*, moderate-to-vigorous physical activity; *pb*, post-bronchodilator; *ppb*, parts per billion.
Data are presented as mean ± SD, median [IQR], or n (%).

C-reactive protein, TNF-α, and IL-6. Sputum induction was performed in a subset of patients who visited the severe asthma center, using a standardized protocol.[23] Sputum cell counts were calculated as a percentage of nonsquamous cells.

Muscle mass and strength

Muscle mass was estimated by 2 parameters, including the fat-free mass index (FFMI) and urinary creatinine excretion rate (CER) in 24-hour urine. A whole-body bioelectrical impedance analysis was performed to assess the FFMI, using the single-frequency analyzer Bodystat 1500 (Bodystat Ltd, Douglas, Isle of Man, UK). FFMI was calculated as fat-free mass (kg) divided by height squared (m^2). According to the European Respiratory Society statement on nutritional management of COPD, low FFMI was defined as less than 17 kg/m^2 for males and less than 15 kg/m^2 for females.[24] This is in line with age- and sex-adjusted FFMI values below the 10th percentile for normal-weight Whites.[24]

Assessment of creatinine excretion in a 24-hour urine sample is a widely accepted marker of total muscle mass, with higher values indicating higher total muscle mass.[25] CER was calculated by multiplying the volume of a single 24-hour urine collection with the creatinine concentration of an aliquot using the Jaffé method on a Roche Modular P chemistry analyzer (Roche, Basel, Switzerland). Low CER values were defined as a value below the sex-specific 10th percentile of CER in a general population from the Northern Netherlands.[26]

Finally, we assessed HGS as a simple and noninvasive marker of muscle strength. HGS was measured using the Jamar+ Digital Dynamometer (Performance Health, Chicago, Ill) and performed in a seated position, elbows flexed at 90 degrees and forearm in neutral position.[27] Three attempts were performed per side, and the maximum value was used for analysis. A value below the 10th percentile of age- and sex-specific reference norms of a general population was considered a low HGS.[28]

Statistical analysis

Multiple imputation was performed to account for missing data (9.8% of all data points), using chained equations and predictive mean matching modeling on the assumption that data were missing at random. Twenty sets of imputed data were generated, and the results of all analyses below were pooled to obtain a single final estimate. More information about the model specifications and the number of missing data can be found in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

Patient characteristics are presented for the total study population. To assess the level of muscle mass and strength in patients with varying asthma severity, between-group differences were tested with independent-sample *t* tests for the continuous muscle parameters (FFMI, CER, and HGS), and with χ^2 tests for the proportion of subjects with a value below the threshold to define low muscle mass or strength.

Multivariable regression analyses were used to assess the association between muscle parameters (independent variables) and asthma outcomes (dependent variables). The independent variables FFMI, CER, and HGS were categorized according to their sex-specific tertiles (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Linear regression models were used for continuous outcomes (FEV_1, FEV_1/forced vital capacity [FVC], 6MWD, ACQ, asthma-related quality of life) and predicted means were reported for each tertile of the muscle parameters. For categorical outcomes (health care use), a binary logistic regression was performed and predicted probabilities were reported for each tertile of the muscle parameters. The models were additionally adjusted for the potential confounders age, level of moderate-to-vigorous physical activity, and weight (the latter only for FFMI and CER). These confounders were preselected on the basis of what is generally known from the literature and differences between tertiles of muscle parameters.

To evaluate the association of systemic inflammatory markers with muscle mass and strength, a 2-step approach was used. First, multivariable linear regression analyses were performed for each inflammatory marker individually, with FFMI, CER, and HGS as dependent variable. Second, a backward selection process was run, starting with a full model of all inflammatory markers and manually removing terms with the highest *P* value until the remaining inflammatory markers had a *P* value less than .2. All models included the potential confounders sex, age, moderate-to-vigorous physical activity, and weight (for FFMI and CER), which were not removed by backward elimination.

The analyses were performed using IBM SPSS Statistics, version 24 (IBM, Armonk, NY).

TABLE II. Muscle mass and strength by sex and asthma severity

Muscle function parameters	Total (N = 114)	Males (N = 41)	Females (N = 73)	GINA 3 (N = 18)	GINA 4 (N = 34)	GINA 5 (N = 62)
Sex: male	41 (36)			4 (22)	13 (38)	24 (39)
BMI (kg/m^2)	27.7 ± 5.7	27.0 ± 4.2	28.0 ± 6.4	28.2 ± 5.5	26.9 ± 5.0	28.0 ± 6.2
FFMI (kg/m^2)	18.3 ± 2.6	20.1 ± 2.4	17.3 ± 2.0*	18.2 ± 2.4	18.3 ± 2.5	18.3 ± 2.7
Low FFMI, <17 (M) / <15 (F)	18 (16)	5 (12)	13 (18)	2 (11)	4 (12)	12 (19)
CER (mmol/d)	12.5 ± 4.6	15.3 ± 6.0	10.8 ± 2.7*	12.2 ± 3.3	12.4 ± 3.0	12.6 ± 5.6
Low CER, <10th pct†	9 (8)	4 (10)	5 (7)	0 (0)	3 (9)	6 (10)
HGS (kg)	36.3 ± 12.4	48.8 ± 9.6	29.3 ± 7.2*	36.2 ± 14.8	37.5 ± 11.3	35.6 ± 12.5
Low HGS, <10th pct†	6 (5)	2 (5)	4 (5)	1 (6)	0 (0)	5 (8)

F, Female; *M*, male.
Data are presented as mean ± SD or n (%).
*Statistically significant difference ($P < .01$) between males and females.
†Below the sex-specific 10th percentile based on a general population.

RESULTS

Patient characteristics

A total of 114 patients with moderate (GINA 3, 16%), moderate to severe (GINA 4, 30%), and severe (GINA 5, 54%) asthma participated in this study, of whom 34 (30%) were recruited from the severe asthma center. The mean age was 51.9 ± 14.4 years, approximately a third were male, and the majority had never smoked (Table I). The mean BMI was 27.7 ± 5.7 kg/m^2, and 70% had overweight or obesity. Our study population had relatively poor asthma control as the mean ACQ score was 1.7 ± 1.1, and 54% experienced 1 or more exacerbations in the past year. Although 21 patients received biological therapy, only 6 patients required daily OCS use. Long-acting beta-agonists, long-acting muscarinic antagonists, and leukotriene-receptor antagonists were used by 107, 41, and 26 patients, respectively.

Patient characteristics by tertiles of the 3 muscle parameters are presented in Table E2. The mean age was as expected higher in patients of the lowest tertile of muscle mass and strength, whereas a higher BMI was linearly related to higher muscle mass.

Level of muscle mass and strength

The mean FFMI, CER, and HGS for males were 20.1 ± 2.4 kg/m^2, 15.3 ± 6.0 mmol/d, and 48.8 ± 9.6 kg, respectively (Table II). The measures of muscle mass and strength were as expected lower in females, who had an FFMI of 17.3 ± 2.0 kg/m^2, CER of 10.8 ± 2.7 mmol/d, and HGS of 29.3 ± 7.2 kg. According to the predefined criteria for low muscle mass and strength, 18 patients (16%; 95% CI, 9%-22%) had a low FFMI, 9 patients (8%; 95% CI, 3%-13%) had a low CER, and 6 patients (5%; 95% CI, 1%-9%) had a low HGS. These values of muscle mass and strength were irrespective of GINA classification.

Muscle mass and strength in relation to asthma outcomes

The associations of sex-specific tertiles of FFMI, CER, and HGS with functional and clinical asthma outcomes adjusted for potential confounders are shown in Figures 1 and 2 and Table E3 (in this article's Online Repository at www.jaci-inpractice.org). When first considering the functional asthma parameters, we found that patients in the lowest tertile (T1) of FFMI had statistically significantly lower values of post-bronchodilator FEV_1 and FEV_1/FVC and poorer functional exercise capacity as measured by the 6MWD than those in the highest tertile (T3) (Figure 1). A similar association with these functional parameters was shown for tertiles of CER, though significant only for FEV_1 and 6MWD. Muscle strength was not related to any of the functional outcomes.

With respect to the clinical asthma outcomes, we found no significant associations of FFMI or CER with asthma control, asthma-related quality of life, emergency visits, or exacerbations (Figure 2). We did, however, find a relationship with muscle strength, with patients in the lowest tertile of HGS having worse asthma control, poorer quality of life, and a higher probability of requiring 1 or more emergency visits than patients in the highest HGS tertile.

Inflammatory markers associated with muscle mass and strength

The associations of systemic inflammatory markers with muscle mass and strength are summarized in Table III, using a backward selection process with *P* less than .2 as the upper limit for a factor to remain in the model. Higher leukocyte levels were significantly associated with a lower FFMI (β, −0.13; 95% CI, −0.26 to −0.01), after adjusting for sex, age, physical activity, and weight. None of the other inflammatory markers were associated with FFMI. Furthermore, higher blood eosinophils (β, −3.11; 95% CI, −7.46 to 1.25), higher IL-6 levels (β, −0.29; 95% CI, −0.70 to 0.13), and lower albumin levels (β, 0.24; 95% CI, −0.07 to 0.56) had some association with lower CER, although not statistically significantly so. Finally, higher leukocyte levels (β, −0.62; 95% CI, −1.42 to 0.19), lower fractional exhaled nitric oxide (β, 0.05; 95% CI, −0.01 to 0.10), and lower C-reactive protein levels (β, 0.21; 95% CI, −0.05 to 0.47) also had some association with lower muscle strength, although again not statistically significant.

DISCUSSION

To our knowledge, this is the first study to investigate the relationship between lower muscle mass and strength and a broad range of functional and clinical outcomes in a population of patients with moderate to severe asthma, including an analysis of potentially associated markers of chronic systemic inflammation. Our findings show that 8% to 16% of the patients had low muscle mass, dependent on the parameter used, which was irrespective of asthma severity as expressed by GINA class. However, lower muscle mass was associated with more airway

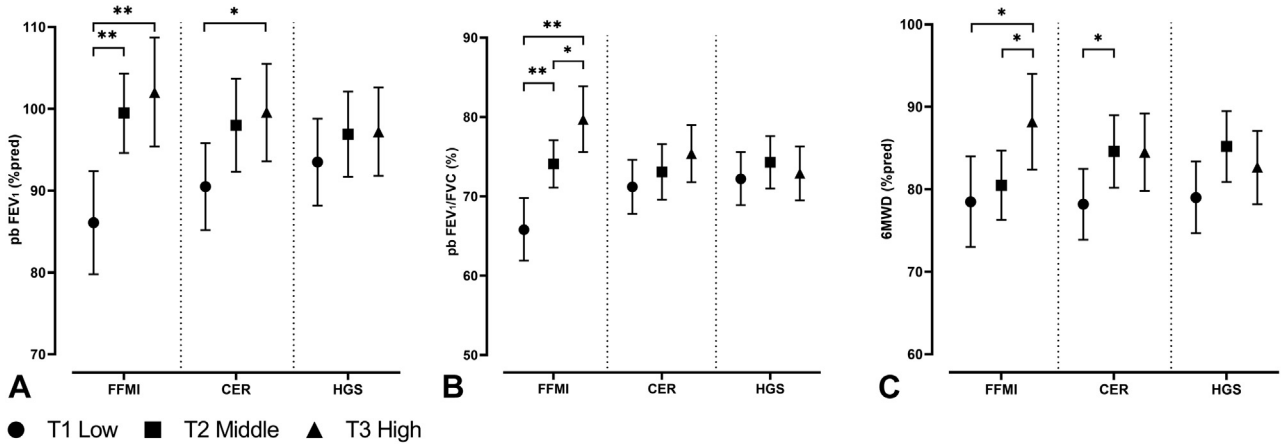

FIGURE 1. Predicted means of functional asthma outcomes by sex-specific tertiles of muscle mass and strength. (**A**) FEV_1 (%pred) postbronchodilator. (**B**) FEV_1/FVC (%) postbronchodilator. (**C**) 6-minute walking distance (%pred). *6MWD*, 6-minute walking distance; *pb*, postbronchodilator; *T1-T3*, tertiles. Covariates: age, physical activity, and weight (latter not for HGS). $*P < .05$. $**P < .01$.

obstruction and lower functional exercise capacity, whereas lower muscle strength was related to poorer asthma control and quality of life, and a greater likelihood of emergency visits. Higher leukocyte counts were significantly associated with lower FFMI, but not with CER and HGS, nor were other systemic inflammatory markers related. If further longitudinal research confirms that changes in muscle mass and strength affect clinical outcomes, muscle function may become a target for asthma treatment.

Although little data on muscle mass in asthma are available to date, we found FFMI levels comparable to previous findings in patients with severe asthma from Greece.[6] However, we could not confirm their findings that patients with severe asthma had lower muscle mass than patients with mild to moderate disease, possibly because of the predominance of patients with very high BMI ($\geq$35 kg/m^2) in the Greek group of severe asthma, and no patients with GINA 1-2 in our cohort. According to international criteria, 16% of our study population had low FFMI values. This prevalence is considerably lower than the 30% to 32% reported in COPD,[29,30] and more in line with the prevalence in European healthy individuals,[31] questioning whether the number of patients with low muscle mass we observed is specific to asthma or rather reflective of the general population.

We also showed that lower muscle mass was related to poorer exercise capacity and airway obstruction, the latter relationship yielding inconsistent results in previous studies. In a small Australian cohort of overweight and obese adults with asthma, total lean body mass was correlated only with static lung function measures, but not with FEV_1 or FEV_1/FVC.[32] Studies in the general population also show associations between muscle mass and pulmonary function. In a British population of older men, low fat-free mass was correlated with lower FEV_1 and FEV_1/FVC,[33] but exclusion of men with possible COPD (FEV_1/FVC $< 70\%$) attenuated these associations, indicating that the results may have been driven by the presence of COPD. In a community-based study among British adults, higher CER was linearly related to higher FEV_1,[34] again questioning whether the observed association between muscle mass and airway obstruction was specific to asthma.

Furthermore, we found associations between lower muscle strength and poorer asthma control, quality of life, and a greater likelihood of emergency visits. In line with our findings, an Australian study of patients with severe asthma showed that lower muscle strength—measured as isometric leg strength—was related to poorer health-related quality of life.[35] In COPD, low HGS has also been related to poorer quality of life and increased COPD morbidity according to a meta-analysis of 18 studies, but no significant effects were found for the occurrence of exacerbations and hospitalizations.[36] Our study is the first to show a link between low muscle mass and strength and asthma control, functional exercise capacity, and the risk of emergency visits among patients with moderate to severe asthma. These results suggest that muscle function may be an important factor to consider in asthma management.

Several mechanisms have been suggested that may be involved in the loss of muscle and strength in asthma. First, uncontrolled asthma is often accompanied by physical inactivity, which has been linked to loss of muscle mass over time.[7] In addition, daily OCS use appears to be an independent predictor of low FFMI in patients with asthma,[6] either as a result of a direct adverse effect of OCS on muscle metabolism[4,37] or as a possible manifestation of the underlying asthma type, most likely severe eosinophilic asthma. The eosinophilic subtype of asthma was well represented in our study, and higher blood eosinophils also emerged as possibly related to lower muscle mass, although significance was lacking, which could be partly attributed to the anti-inflammatory effect of the biologics or OCS used. Furthermore, it has been shown that a high proportion of patients with moderate to severe asthma exhibit dynamic hyperinflation,[38] which is associated with increased work of breathing and higher energy expenditure, leading to weight loss and muscle wasting.[39] This is supported by recent evidence showing that adults with asthma indeed have a higher resting energy expenditure compared with healthy individuals.[40] The researchers also reported a positive correlation between resting energy expenditure and leukocytes, indicating that the higher energy expenditure may be due to proliferation and/or differentiation of immune cells that drive inflammation in asthma.[40] Although this

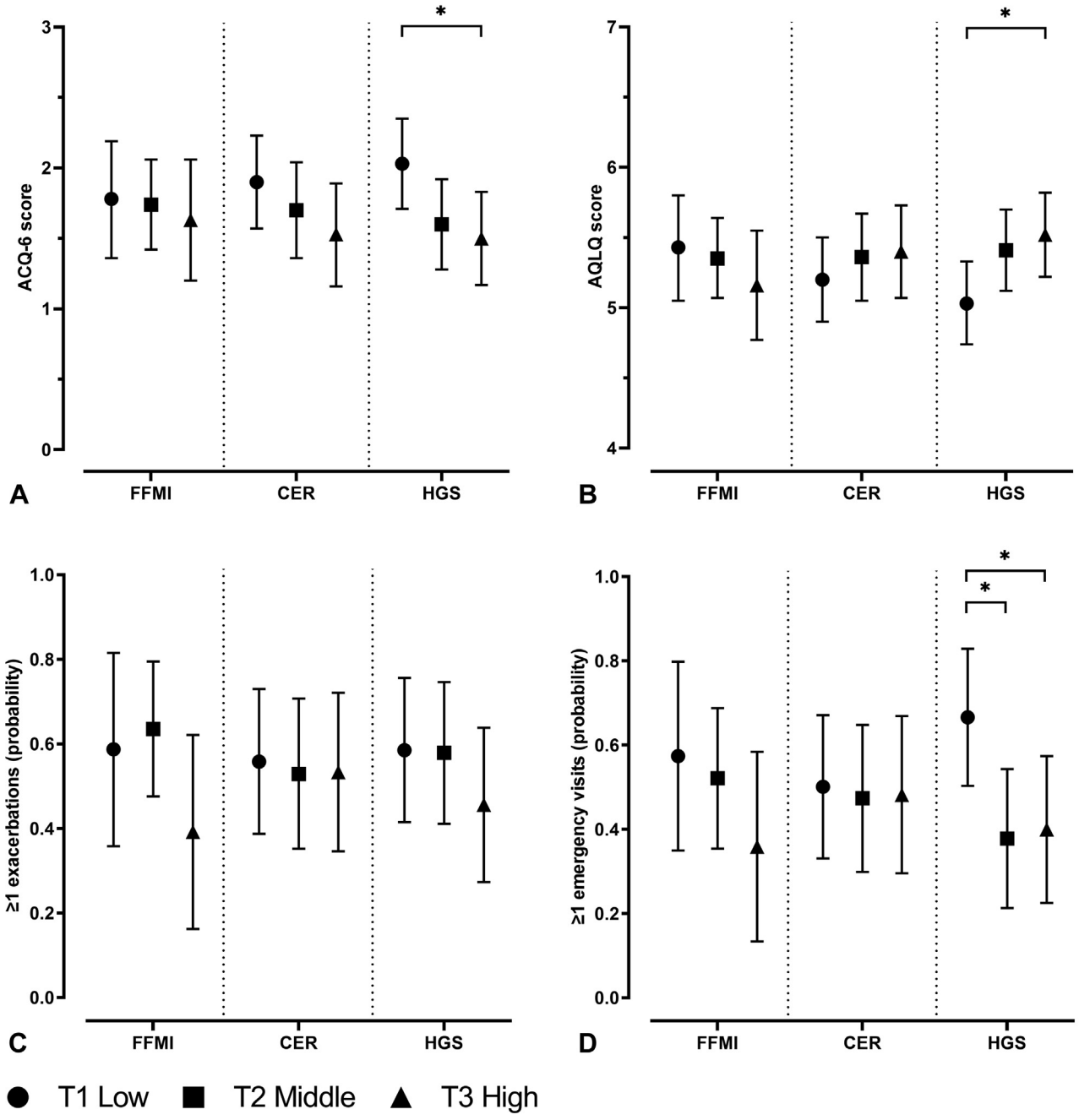

FIGURE 2. Predicted means and probabilities of clinical asthma outcomes by sex-specific tertiles of muscle mass and strength. (**A**) Asthma control score. (**B**) Asthma quality-of-life score. (**C**) One or more exacerbations in preceding year. (**D**) One or more emergency visits in preceding year. *AQLQ*, Asthma Quality-of-Life Questionnaire; T1-3, tertiles. Covariates: age, physical activity, and weight (latter not for HGS). $*P < .05$.

fits our initial hypothesis, our results gave no clear indication that chronic systemic inflammation is involved in the process of muscle dysfunction in asthma. We used only a limited set of markers for systemic inflammation, which could have hampered the ability to find associations. It is also possible that local inflammation, in the airways, is the more important parameter although we found no association with fractional exhaled nitric oxide. Overall, these mechanisms are subject of further research.

Our findings have clinical implications. Although the prevalence of low muscle mass was comparable to that in the general population, we provide evidence that low muscle mass and strength are associated with worse clinical outcomes in patients with moderate to severe asthma. So far, the focus regarding body composition in asthma management has been on obesity and fat mass, but our data suggest that maintaining muscle mass and strength may be of importance as well. It may even be

TABLE III. Association of FENO and blood inflammatory markers with measures of muscle mass and strength

		FFMI		CER		HGS	
	Median [IQR]	Individually*	Backward†	Individually*	Backward†	Individually*	Backward†
FENO (ppb)	24 [13-36]	0.01 (−0.01 to 0.02)	—	0.01 (−0.02 to 0.05)	—	0.04 (−0.02 to 0.10)	0.05 (−0.01 to 0.10)
		.26	—	.39	—	.14	.13
Eosinophils ($\times 10^9$/L)	0.1 [0.1-0.2]	−0.24 (−1.55 to 1.06)	—	−2.96 (−7.42 to 1.49)	−3.11 (−7.46 to 1.25)	1.59 (−6.68 to 9.86)	—
		.72	—	.19	.16	.71	—
Leukocytes ($\times 10^9$/L)	6.9 [5.9-8.0]	−0.13 (−0.26 to −0.01)	−0.13 (−0.26 to −0.01)	−0.27 (−0.70 to 0.16)	—	−0.50 (−1.29 to 0.28)	−0.62 (−1.42 to 0.19)
		.04	.04	.21	—	.21	.13
CRP (mg/L)	2.0 [0.5-4.4]	−0.01 (−0.06 to 0.03)	—	−0.02 (−0.12 to 0.16)	—	0.14 (−0.11 to 0.39)	0.21 (−0.05 to 0.47)
		.54	—	.76	—	.27	.11
IL-6 (pg/mL)	1.5 [1.0-2.4]	−0.08 (−0.21 to 0.05)	—	−0.33 (−0.74 to 0.08)	−0.29 (−0.70 to 0.13)	−0.38 (−1.13 to 0.38)	—
		.22	—	.11	.17	.33	—
TNF-α (pg/mL)	0.7 [0.6-0.9]	0.21 (−0.81 to 1.23)	—	−1.78 (−4.95 to 1.38)	—	−2.80 (−8.93 to 3.33)	—
		.69	—	.27	—	.37	—
Albumin (g/L)	38 [36-39]	0.02 (−0.07 to 0.12)	—	0.29 (−0.02 to 0.59)	0.24 (−0.07 to 0.56)	0.13 (−0.45 to 0.72)	—
		.66	—	.07	.13	.66	—

CRP, C-reactive protein; *FENO*, fractional exhaled nitric oxide; *IQR*, interquartile range; *ppb*, parts per billion.
Data are presented as regression coefficient β (95% CI) and P value.
Covariates: sex, age, physical activity, and weight (latter not for HGS). Covariates were not eliminated from the model.
*Association between each inflammatory marker and muscle parameter individually, adjusted for covariates.
†Backward approach until only inflammatory markers with $P < .2$ remained, including covariates in model.

hypothesized that improvements in muscle mass and strength could yield improvements in asthma outcomes, as has been shown with exercise training in COPD.[4] In asthma, exercise-based pulmonary rehabilitation did indeed improve quality of life and exercise tolerance, as shown by a systematic review of 10 experimental studies,[41] but whether this can be attributed to an improvement in muscle function is unclear. Furthermore, we observed different associations with asthma outcomes for both muscle mass and muscle strength, implying that future research should also look at multiple parameters of muscle function—especially muscle strength—to understand more about the mechanisms of muscle dysfunction in asthma.

Our study has several strengths. We included a relatively large sample of patients with moderate to severe asthma, who were consecutively recruited and without applying strict selection criteria, thereby increasing the generalizability of our results to other populations with clinical asthma. Furthermore, we used 3 measures of muscle function and assessed various clinical parameters to gain a clear picture of the role of muscle mass and strength in relation to asthma outcomes. Because sex is the main determinant of body composition, we used sex-specific cutoff values for the muscle parameters to eliminate confounding by this variable. Although we had some missing data, we performed multiple imputation to use all available data and to obtain unbiased estimates, further improving generalizability of our findings. Reassuringly, complete case analysis yielded similar results for the associations of muscle mass and strength with asthma outcomes. The only difference compared with imputed data was seen for tertiles of FFMI in relation to 6MWD, because complete case analysis showed no significant differences in 6MWD between tertiles of FFMI.

This study has some limitations as well. First, because of the cross-sectional design, we cannot establish cause and effect. Although we hypothesize that lower muscle mass and strength provoke poorer asthma outcomes, the reverse is also possible. Worse lung function and asthma control may lead to activity limitation and as a consequence loss of muscle mass and strength, which may lead to a negative vicious circle. In addition, low daily physical activity has been associated with a faster decline in lung function, further illustrating the complex relation between physical activity, muscle mass, and asthma outcomes.[42] However, the associations we showed were independent of physical activity. Second, we used bioelectrical impedance analysis to assess FFMI, a simple and noninvasive tool to measure body composition. Given the device, we were dependent on the manufacturer's prediction equation to estimate fat-free mass, which was representative of a healthy, normal-weight population. However, these equations tend to overestimate fat-free mass when used in individuals with obesity, because of differences in hydration levels.[43] In our study population, 70% of patients had overweight or obesity and therefore the proportion of patients with low FFMI could have been even higher. Next, although we observed a clinically meaningful greater likelihood of emergency visits and exacerbations for patients in the lowest tertile of FFMI compared with the highest tertile, these observations were not statistically significant, probably due to lack of statistical power. Last, because of restrictions related to the outbreak of the coronavirus disease, we could obtain only a limited number of sputum samples and therefore we were unable to examine the association between airway inflammation and low muscle mass and strength.

CONCLUSIONS

This study demonstrates that low muscle mass is prevalent in patients with moderate to severe asthma and, along with low muscle strength, is associated with poorer asthma outcomes, including airway obstruction, decreased exercise capacity, worse asthma control and quality of life, and a higher probability of emergency visits. We could not find an association of systemic inflammation as possible determinant of muscle dysfunction. Nevertheless, our findings encourage longitudinal studies into muscle function as a potential target for treatment to improve asthma outcomes.

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ONLINE REPOSITORY

MODEL SPECIFICATIONS MULTIPLE IMPUTATION

Overall, 9.8% of all data points were missing, with the highest number of missing data being imputed for the variable CER (Table E1). We assumed that the missing data were missing at random because the percentage of missing data was higher in patients from the regular pulmonary outpatient clinic (10.7% of all data points missing) than in those recruited from the severe asthma center (7.8% of all data points missing). Patients of the severe asthma center were systematically evaluated during a 1-day visit at the center as part of regular care, and therefore had less missing data. In patients of the regular pulmonary outpatient clinic, some study assessments were not always embedded in regular care and were therefore more often missing. Multiple imputation was performed by fully conditional specification and predictive mean matching. The number of imputations was 20, and the maximum number of iterations also 20.

TABLE E1. Missing data before multiple imputation

Variable	N (%) missing
Sex	—
Age	—
Medication use	—
Smoking status	—
Weight	1 (1)
HGS	1 (1)
FFMI	4 (4)
AQLQ score	5 (4)
TNF-α	5 (4)
Albumin	5 (4)
IL-6	6 (5)
Pack years	7 (6)
ACQ-6 score	7 (6)
Leukocytes	7 (6)
F_{ENO}	8 (7)
Exacerbations	9 (8)
Blood eosinophils	9 (8)
CRP	9 (8)
Physical activity	10 (9)
6MWD	10 (9)
Emergency visits	10 (9)
FEV_1, postbronchodilator	17 (15)
FEV_1/FVC, postbronchodilator	17 (15)
CER	19 (17)

AQLQ, Asthma Quality-of-Life Questionnaire; CRP, C-reactive protein; *F_{ENO}*, fractional exhaled nitric oxide; *MVPA*, moderate-to-vigorous physical activity.

TABLE E2. Patient characteristics by sex-specific tertiles of muscle mass and strength

	FFMI (kg/m^2)			CER (mmol/24 h)			HGS (kg)		
Patient characteristics	**T1 | Low**	**T2 | Medium**	**T3 | High**	**T1 | Low**	**T2 | Medium**	**T3 | High**	**T1 | Low**	**T2 | Medium**	**T3 | High**
Cutoff values tertiles									
Males	<19.2	19.2-21.1	≥21.2	<13.3	13.30-15.8	≥15.9	<44.3	44.3-53.3	≥53.4
Females	<16.5	16.5-18.2	≥18.3	<9.8	9.8-12.1	≥12.2	<26.4	26.4-32.3	≥32.4
Demographic characteristics									
Sample size	38	39	37	41	38	35	39	38	37
Males	14 (37)	14 (36)	13 (35)	14 (34)	14 (37)	13 (37)	14 (36)	14 (37)	13 (35)
Age (y)	56.8 ± 14.2*	51.2 ± 12.8*	47.6 ± 15.0*	56.6 ± 12.9*	51.0 ± 13.9*	47.5 ± 15.2*	58.2 ± 12.2*	51.3 ± 15.6*	46.0 ± 12.7*
BMI (kg/m^2)	23.1 ± 2.8*	27.1 ± 3.0*	33.1 ± 5.7*	26.4 ± 5.2*	27.3 ± 5.6*	29.6 ± 6.0*	27.9 ± 5.4	27.3 ± 5.4	27.8 ± 6.4
BMI ≥25 kg/m^2	10 (26)*	34 (87)*	36 (97)*	23 (56)*	27 (71)*	30 (86)*	28 (72)	26 (68)	26 (70)
Smoking (pack years)	0 [0-4]	1 [0-8]	0 [0-6]	0 [0-9]	0 [0-5]	0 [0-6]	0 [0-8]	0 [0-6]	0 [0-7]
MVPA (h/wk)	10 [4-20]	8 [2-13]	10 [4-19]	9 [4-18]	9 [4-19]	9 [2-13]	9 [4-15]	12 [5-24]	6 [2-12]
Clinical outcomes									
ACQ-6 score (0-6)	1.6 ± 1.0	1.8 ± 1.1	1.8 ± 1.1	1.7 ± 1.0	1.7 ± 1.1	1.7 ± 1.2	1.8 ± 1.1	1.6 ± 1.0	1.7 ± 1.1
AQLQ score (1-7)	5.4 ± 0.9	5.3 ± 1.0	5.2 ± 1.0	5.3 ± 1.0	5.3 ± 0.9	5.3 ± 1.0	5.2 ± 1.0	5.4 ± 0.9	5.4 ± 1.0
≥1 exacerbations in preceding year	19 (50)	25 (64)	18 (40)	22 (54)	20 (53)	20 (57)	21 (54)	22 (58)	19 (51)
≥1 emergency visits in preceding year	17 (45)	21 (54)	17 (46)	19 (46)	18 (47)	18 (51)	23 (59)	15 (39)	17 (46)
Adult-onset asthma	23 (61)	19 (49)	20 (54)	27 (66)	18 (47)	17 (49)	26 (67)	19 (50)	17 (46)
Biological asthma therapy	9 (24)	5 (13)	7 (19)	10 (24)	7 (18)	4 (11)	11 (28)	5 (13)	5 (14)
OCS-dependent	1 (3)	3 (8)	2 (5)	3 (7)	1 (3)	2 (6)	4 (10)	0 (0)	2 (5)
Functional outcomes									
pb FEV_1 (%pred)	90.3 ± 21.0*	100.0 ± 14.6*	97.1 ± 11.4*	90.5 ± 18.3*	98.1 ± 16.2*	99.5 ± 13.3*	92.6 ± 18.8	96.5 ± 14.8	98.5 ± 15.7
pb FEV_1/FVC (%)	67.7 ± 14.8*	74.7 ± 9.3*	77.1 ± 9.0*	69.6 ± 13.4*	73.4 ± 12.1*	76.9 ± 8.5*	69.9 ± 11.9	74.2 ± 12.5	75.5 ± 11.0
6MWD (%pred)	85.0 ± 15.5	80.3 ± 16.1	81.7 ± 15.7	81.6 ± 17.7	84.1 ± 15.7	81.1 ± 13.6	82.9 ± 20.1	84.7 ± 11.3	79.2 ± 14.4
Inflammatory markers									
FENO (ppb)	25 [14-36]	25 [12-41]	21 [12-33]	20 [11-36]	24 [14-35]	25 [12-38]	20 [12-36]	20 [12-31]	26 [14-43]
Blood eosinophils ≥0.3 $\times 10^9$/L	12 (32)	11 (28)	5 (14)	14 (34)*	11 (29)*	3 (9)*	9 (23)	9 (24)	10 (27)
Sputum eosinophils ≥2% (N = 18)	3 (50)	3 (50)	2 (33)	4 (57)	2 (33)	2 (33)	4 (44)	2 (33)	2 (67)

AQLQ, Asthma Quality-of-Life Questionnaire; FENO, fractional exhaled nitric oxide; *IQR*, interquartile range; *MVPA*, moderate-to-vigorous physical activity; *pb*, postbronchodilator; *ppb*, parts per billion.
After imputation, data are presented as mean ± SD, median [IQR], or n (%).
*$P < .05$, significant difference between tertiles.

TABLE E3. Predicted means and probabilities of functional and clinical asthma outcomes by sex-specific tertiles of muscle mass and strength

	FFMI (kg/m^2)			CER (mmol/24 h)			HGS (kg)		
Asthma outcomes	**T1 | Low**	**T2 | Medium**	**T3 | High**	**T1 | Low**	**T2 | Medium**	**T3 | High**	**T1 | Low**	**T2 | Medium**	**T3 | High**
pb FEV_1 (%pred)									
PM	86.1	99.5	102.0	90.5	98.0	99.6	93.5	96.9	97.2
95%CI	(79.8-92.4)	(94.6-104.3)	(95.4-108.7)	(85.2-95.8)	(92.3-103.7)	(93.6-105.5)	(88.2-98.8)	(91.7-102.1)	(91.8-102.6)
*P**	**<.01**†	.55‡	**<.01**§	.07†	.73‡	**.03**§	.37†	.94‡	.35§
pb FEV_1/FVC (%)									
PM	65.8	74.1	79.7	71.2	73.1	75.4	72.2	74.3	72.9
95%CI	(61.9-69.8)	(71.1-77.1)	(75.6-83.9)	(67.8-74.6)	(69.5-76.6)	(71.8-79.0)	(68.9-75.6)	(71.0-77.6)	(69.5-76.3)
*P**	**<.01**†	**.03**‡	**<.01**§	.47†	.38‡	.12§	.40†	.56‡	.80§
6MWD (%pred)									
PM	78.5	80.5	88.2	78.2	84.6	84.5	79.0	85.2	82.7
95%CI	(73.0-84.0)	(76.3-84.7)	(82.4-94.0)	(73.9-82.5)	(80.2-89.0)	(79.8-89.2)	(74.7-83.4)	(80.9-89.5)	(78.2-87.1)
*P**	.57†	**0.04**‡	**.046**§	**.04**†	.98‡	.06§	.053†	.43‡	.27§
ACQ-6 score (0-6)									
PM	1.78	1.74	1.63	1.90	1.70	1.55	2.03	1.60	1.50
95%CI	(1.36-2.19)	(1.42-2.06)	(1.20-2.06)	(1.57-2.23)	(1.36-2.04)	(1.16-1.89)	(1.71-2.35)	(1.28-1.92)	(1.17-1.83)
*P**	.89†	.69‡	.69§	.41†	.52‡	.15§	.07†	.67‡	**.03**§
AQLQ score (1-7)									
PM	5.43	5.35	5.16	5.20	5.36	5.40	5.03	5.41	5.52
95%CI	(5.05-5.80)	(5.07-5.64)	(4.77-5.55)	(4.90-5.50)	(5.05-5.67)	(5.07-5.73)	(4.74-5.33)	(5.12-5.70)	(5.22-5.82)
*P**	.78†	.44‡	.41§	.47†	.87‡	.40§	.08†	.61‡	**.03**§
≥1 exacerbations in preceding year									
PP	0.59	0.64	0.39	0.56	0.53	0.53	0.59	0.58	0.46
95%CI	(0.36-0.82)	(0.48-0.80)	(0.16-0.62)	(0.39-0.73)	(0.35-0.71)	(0.35-0.72)	(0.42-0.76)	(0.41-0.75)	(0.27-0.64)
*P**	.73†	.11‡	.35§	.82†	.98‡	.85§	.96†	.35‡	.33§
≥1 emergency visits in preceding year									
PP	0.57	0.52	0.36	0.50	0.47	0.48	0.67	0.38	0.40
95%CI	(0.35-0.80)	(0.35-0.69)	(0.13-0.58)	(0.33-0.67)	(0.30-0.65)	(0.30-0.67)	(0.50-0.83)	(0.21-0.54)	(0.23-0.57)
*P**	.71†	.28‡	.29§	.83†	.95‡	.89§	**.03**†	.86‡	**.047**§

AQLQ, Asthma Quality-of-Life Questionnaire; *pb*, postbronchodilator; *PM*, predicted mean; *PP*, predicted probability.
Covariates: FFMI and CER adjusted by age, MVPA, and weight; HGS adjusted by age and MVPA.
Values in bold indicate statistically significant differences between tertiles ($P < .05$).
*Pairwise comparison between tertiles.
†T1 vs T2.
‡T2 vs T3.
§T3 vs T1.