Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Uncontrolled asthma is Associated with Increased Visceral Adipose Tissue, Decreased Bone Mineral Content, and Reduced Exercise Capacity

Florence Schleich[1], Stéphanie Ziant[2], Sébastien Louis[2], Catherine Moermans[1], Rita Deroisy[3], Renaud Louis[1], Jean-François Kaux[3], Thierry Bury[2]

[1]Respiratory Medicine, Exercise Physiology Lab, GIGA I3, University and University Hospital of Liège, Liège, Belgium; [2]Respiratory Medicine, University Hospital of Liège, Liège, Belgium; [3]Physical Medicine, Rehabilitation and Sports Traumatology Department, FIFA Medical Centre of Excellence, University and University Hospital of Liège, Liège, Belgium

Correspondence: Florence Schleich, Exercise Physiology Lab, University of Liège, CHU Sart-Tilman B35, Liège, 4000, Belgium, Email fschleich@uliege.be

Introduction: Physical inactivity due to shortness of breath is common among patients with uncontrolled asthma. We evaluated the body mass composition and exercise capacity of patients with poorly controlled asthma, despite maximal inhalation therapy.

Methods: We recruited 56 patients from the Asthma Clinic of the University Hospital of Liège between September 2020 and December 2023, and 14 healthy subjects. Patients with asthma underwent detailed investigations, including induced sputum, exercise testing, and Dual-Energy X-ray Absorptiometry (DXA), to determine overall body fat mass and fat-free mass, while healthy subjects only underwent DXA. This study was approved by the Ethics Committee (2019/362).

Results: The mean age of patients with asthma was 45 years ± 12; 58% were female, 10% were active smokers, and mean post-BD Forced Expiratory Volume in one second was 85.7% predicted. Compared to healthy subjects, asthmatics had a higher BMI (28.5±5.1 kg/m2 vs 22.5 ±2.8 kg/m2, p<0.0001) and fat mass index (FMI; 10.3 ± 3.7 vs 5.9 ± 2.8 kg/m2, p=0.0005), lower lean and bone mass (62% vs 71%, p=0.0012), and greater android fat distribution (1.00 ± 0.22 vs 0.80 ± 0.13, p<0.0001). Eosinophilic asthma (sputum eosinophil count of ≥3%) was characterized by a better VO_2 max compared to non-eosinophilic asthma (20.7 [17.8–24.3] vs 17.3 [14.0–18.9], p=0.04). Higher lean mass was correlated with better asthma control and lower depression scores. Lean mass and bone mineral content correlated with maximal expiratory, inspiratory, and maximal aerobic power.

Conclusion: Our study confirmed that patients with uncontrolled asthma were overweight and had decreased exercise capacity.

Plain language summary: Schleich et al conducted a study on a population of 56 patients with asthma and compared their body composition (fat and lean mass proportion, distribution, and bone mineral content) to that of 14 healthy subjects. Patients with uncontrolled asthma have symptoms of dyspnea that may induce a vicious circle in which shortness of breath limits physical activity. Physical inactivity and treatment with corticosteroids may induce changes in body composition. Therefore, the team evaluated the body mass composition and exercise capacity of patients with poorly controlled asthma, despite maximal inhalation therapy. Patients with asthma also underwent detailed investigations, including lung function testing, exhaled nitric oxide, and induced sputum, to establish the inflammatory phenotype. Compared to healthy subjects, asthmatics had higher body mass index and fat mass index levels, lower lean and bone mass, and more android fat distribution. Eosinophilic asthma was characterized by better exercise tolerance than that of non-eosinophilic asthma. Moreover, higher lean mass was associated with better asthma control and lower depression scores.

In conclusion, this study confirmed that patients with uncontrolled asthma are overweight and have decreased exercise capacity.

Keywords: uncontrolled asthma, phenotype, eosinophils, body composition, fat mass, lean mass, VO_2 max, PROMs

Introduction

Asthma is a serious global health problem that affects all age groups. Its prevalence is increasing in many countries, and this disease places a high burden on healthcare systems and society through the loss of productivity in the workplace.[1]

Received: 5 July 2024
Accepted: 13 December 2024
Published: 31 December 2024

Many different underlying mechanisms have been identified, and the disease tends to be considered a syndrome containing several inflammatory phenotypes, sharing similarities but also displaying differences caused by various etiologies.

Physical inactivity due to shortness of breath is common among patients with uncontrolled asthma. Insufficient training and recurrent exposure to systemic corticosteroids may lead to changes in body composition. In previous studies, we found that 20% of the general population of patients with asthma followed up at the Asthma Clinic of the University Hospital of Liège[2] were obese, and this rate increased to 25% in patients with severe asthma included in the Belgian Severe Asthma Registry.[3]

Being overweight or obese is associated with poor asthma control and quality of life. Poor diet quality, physical inactivity, and consequent excess adipose tissue independently activate inflammatory pathways.[4] In a previous study, we found higher levels of blood leukocytes, C-Reactive Protein (CRP), and fibrinogen, and an increased number of sputum neutrophils in an obese asthmatic population.[2]

Therefore, we aimed to perform a detailed investigation of the body mass composition of patients with uncontrolled moderate-to-severe asthma compared to healthy subjects, with a specific focus on the underlying asthma inflammatory phenotype. In this study, we described body composition as a three-tissue component: fat mass, lean mass, and bone mineral content. We used Dual-energy X-ray absorptiometry (DXA), which is the gold standard for assessing body composition, with precise analysis of bone mineral content and soft tissue of the whole body and specific anatomical regions.[5]

Methods

Study Population and Study Design

Between September 2020 and December 2023, 56 patients with uncontrolled asthma were recruited from the Asthma Clinic of the University Hospital of Liège prior to the commencement of a 12-week aerobic training program (SAMBA trial: Towards a paradigm shift in Severe Asthma Management: Deep analysis of the effect of suBmaximal Aerobic training).

Entry criteria were any patients with moderate-to-severe uncontrolled asthma, aged between 18 and 65 years, who agreed to undergo detailed investigation at the asthma clinic and participate in an aerobic training program. Patients with morbid obesity (a body mass index [BMI] of >35), severe osteoarthritis of the knees and hips, unstable angina, or severe uncontrolled hypertension were excluded.

The control group included data on the body composition of 14 healthy, non-smoking subjects.

Asthma Diagnosis and Phenotyping

Asthma was diagnosed based on the presence of chronic respiratory symptoms such as cough, breathlessness, or dyspnea, together with demonstration of airflow variability. The latter was defined by airway hyper-responsiveness shown by one or more of the following: an increase in forced expiratory volume in 1 s (FEV_1) of more than 12% and 200 mL following inhalation of 400µg salbutamol or inhaled concentration of methacholine, provoking a 20% decrease in FEV_1 of less than 16 mg/mL. Methacholine challenges were performed according to a standardized methodology, as previously described.[6]

Investigations

Patients underwent fractional exhaled nitric oxide (FeNO) measurement at a flow rate of 50 mL/s according to the European Respiratory Society/American Thoracic Society recommendations (NIOX, Aerocrine, Sweden). FeNO was measured first, followed by spirometry with bronchodilation, sputum induction, and blood sampling. All tests were performed on the same day.

Sputum was induced and processed as previously reported.[7] Cell counts were estimated for samples centrifuged (Cytospin) and stained with Hemacolor (Merck) after counting 500 cells (Dade, Brussels, Belgium) in all patients with successful induced sputum. Patients were considered to have eosinophilic asthma if their sputum eosinophil count was ≥3% of their total cell count.

Blood samples were obtained from all patients for measurement of blood leukocytes, total and specific IgE levels, and inflammatory biomarkers (CRP and fibrinogen).

Quality of life was assessed using a self-administered Asthma Quality of Life Questionnaire (AQLQ),[8] and asthma control was assessed using the Asthma Control Test (ACT).[9] Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale.[10]

Anthropometric Measurements

Body height and weight were measured using a stadiometer and high-precision scale, respectively. BMI was calculated as weight (kg) divided by height (m^2). Dual X-ray absorptiometry (DXA), a validated tool to investigate body composition, was used to precisely analyze amounts of bone mineral content and soft tissue in the whole body and in specific body segments, such as the arms, trunk, waist, hips, and legs. Whole-body scans were performed and main body composition parameters, including visceral adipose tissue (VAT) mass and volume, were subsequently analyzed. DXA provides bone density and regional estimates of body composition (ie, parts of the body) by measuring the body's absorbance of X-rays at two different energies, using the fact that fat, bone mineral, and fat-free soft tissue have different absorption properties. Visceral adipose tissue is defined by DXA as a region starting at the iliac crest and ending at a height of 20% of the distance between the iliac crest and the skull base. Quality control and calibration were performed daily. Fat mass index (FMI) and lean mass index (LMI) levels were derived from fat mass and lean mass, respectively, and corrected for height. The subjects were positioned for whole-body scans according to the manufacturer's protocol. The subjects were placed in the supine position on a scanner table with straight legs and arms close to the body. The participants were instructed to remain as still as possible during the scan. Whole-body composition analysis provided data for different regions of interest, including the trunk, arms, and legs.[11] The DXA machine was calibrated daily against a phantom spine containing composites of bone, fat, and lean tissue supplied by the manufacturer before testing. This procedure has been validated for general use of DXA.

Exercise Testing

VO_2 max is classically measured during progressive exercise testing using a bicycle ergometer.[12] The criteria used to assess VO_2 max were a respiratory exchange ratio of >1.10, a heart rate in excess of 90% of the age-predicted maximum, and identification of a VO_2 max plateau. In all tests, two of the three criteria were satisfied.

This study was registered on the ClinicalTrials.gov website (NCT 04395937) and received ethical approval from the Liege Ethics Committee (2019/362). The research study has been performed in accordance with the principles stated in the Declaration of Helsinki. Prior to starting the study, ethical approval has been obtained for the protocol from the Liege Ethics Committee (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège, Route 562, Porte 166, Avenue de l'Hôpital, 14000 Liège, Belgium) confirming the study meets national and international guidelines for research on humans. All participants gave written informed consent prior to study commencement.

Statistical Analyses

Data were expressed as counts and percentages for categorical variables and as mean (SD) or median (interquartile range) for quantitative variables according to the distribution of the data. Comparisons were performed using Pearson's $\chi 2$ test or Fisher's exact test for categorical variables, an ANOVA test for parametric variables, and the Kruskal–Wallis test for nonparametric variables. A p-value of less than 0.05 was considered significant. Pearson's correlation coefficient was used to measure linear relationships between normally distributed variables while spearman's rank correlation coefficient was used for non-parametric variables. Correlation was represented by correlation coefficient r. Statistical analyses were performed using SAS software (version 9.4).

Results

Characteristics of the Study Population

Characteristics of the 56 subjects with uncontrolled asthma are presented in Table 1.

The mean age of the patients with asthma was 45 ±12 years old; 58.2% were female. The median disease duration was 9 years (3–21). Active smoking was observed in 10% of the patients with uncontrolled asthma, while 70% were non-

Table 1 Clinical, Functional and Inflammatory Characteristics of Subjects with Uncontrolled Asthma

Variable	Asthma
N	56
Age, yrs	45 ±12
Gender (F,%)	58
Disease duration, yrs	9 (3–21)
Smoking status Non smoker, % Ex-smoker, % Current smoker, %	 70 20 10
LAMA, %	18
Biologicals, %	14
FeNO, ppb	19 (13–39)
Pre-BD FEV_1, % pred	82.5 ± 18.6
Post-BD FEV_1, % pred	85.7 ± 17.2
Pre-BD FVC, % pred	87.4 ±15.3
Post-BD FVC, % pred	88.6 ± 14.5
Post-BD FEV_1/FVC, %	78.2 ± 9.9
TLC, % pred	99.6 ± 16
DLCO, % pred	99.8 ± 21
KCO, % pred	102 ± 16
FRC, % pred	90.5 ± 22.5
RV, % pred	111 ± 27
Sputum eosinophils, %	0.4 (0.0–3.0)
Blood eosinophils, /mm^3	130 (80–190)
IgE, kU/l	68 (35–241)
DHEA sulfate, μmol/l	4.45 ± 2.94
Cortisol, nmol/l	225.5 ± 95.0
CRP, mg/dL	1.9 (1.0–3.9)
ACQ	2.43 ± 0.76
ACT	13.70 ± 4.12
VO_2 max, mL/min/kg	19.39 ± 6.24
PC20M, mg/mL	0.49 (0.25–3.07)

Abbreviations: LAMA, long-acting muscarinic antagonists; FeNO, exhaled nitric oxide; BD, bronchodilation; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; KCO, carbon monoxide transfer coefficient; FRC, functional residual capacity; RV, residual volume; IgE, immunoglobulin E; DHEA, Dehydroepiandrosterone; CRP, C-reactive protein; ACQ, asthma control questionnaire; ACT, asthma control test; VO_2max, maximal oxygen uptake; PC20M, concentration of methacholine provoking a 20% fall in FEV_1.

smokers. Lung function revealed a post-BD FEV_1 of 85.7% of the predicted value, whereas the post-BD FEV_1/Functional Vital Capacity (FVC) was 78%. Lung volumes were preserved, and there was no alteration in diffusion capacity of the lungs for carbon monoxide (DLCO) (99.8 ±21.0% predicted) and carbon monoxide transfer coefficient (KCO) (99.6 ±16.0 of predicted values).

All patients were treated with long-acting B2 agonists (LABA); however, 18% received long-acting muscarinic antagonists (LAMA). Sixty-eight percent received moderate doses of inhaled corticosteroids (ICS), 32% were treated with high doses of ICS, and 14% were treated with targeted treatments (omalizumab (N=4) and mepolizumab (N=4)).

The median FeNO was 19ppb (13–39) and the blood eosinophil count was 130/mm^3 (80–190).

Compared to healthy subjects, uncontrolled asthmatics had a higher BMI (28.5 ± 5.1 kg/m^2 vs 22.5 ±2.8 kg/m^2, p<0.0001) and FMI (10.3 ± 3.7 vs 5.9 ± 2.8 kg/m^2, p=0.0005), lower lean mass (62% vs 71%, p=0.0012), greater android fat distribution (1.00 ± 0.22 vs 0.80 ± 0.13, p<0.0001), and a higher visceral adipose tissue area (118.9 ± 63.9 vs 50.5 ± 29.0, p<0.0001) (Table 2). There was no significant difference in bone mineral content.

Body Composition According to Type-2 Inflammation

Eosinophilic asthma (a sputum eosinophils of ≥3%, n=9) was characterized by a higher proportion of males and, compared to non-eosinophilic asthma (n=26), the following trends: lower BMI (25.7 [22.6–29.8] vs 31.2 [26.4–32.7]

Table 2 Body Composition Indices for Patients with Asthma and Healthy Subjects

Variable	Patients with asthma	Healthy	p-value
N	56	14	
Age (yrs)	45 ±12	47 ±14	0.57
Female, %	58	64	0.75
Smoking status Non smoker, % Ex-smoker, % Current smoker, %	 70 20 10	 100 0 0	<0.0001
Height, cm	167.6 ± 8.9	168.4 ±12.8	0.94
Weight, kg	80.0 ± 15.7	65.0 ± 10.8	0.0002
BMI, kg/m^2	28.5 ±5.1	22.5 ±2.8	<0.0001
FMI, kg/m^2	10.3 ± 3.7	5.9 ± 2.8	0.0005
BMC, g	2266 ± 408	2318 ± 148	0.57
BMC, %	2.7 ± 0.5	3.6 ±0.5	<0.0001
Lean mass, g	50,219 ± 11,419	46,614 ± 11,527	0.21
Lean mass, %	61.8 ± 8.4	71.3 ± 9.0	0.001
Fat mass, g	28,517 ± 9188	16,039 ± 6360	<0.0001
Fat mass, %	35 ± 8	25 ± 9	0.0006
Android/gynoid ratio	1.00 ± 0.22	0.80 ± 0.13	<0.0001
VAT area	118.9 ± 63.9	50.5 ± 29.0	<0.0001
LMI, kg/m^2	17.5 ± 3.0	16.2 ± 2.3	0.059

Abbreviations: BMI: body mass index. FMI: fat mass index. BMC: bone mineral content. VAT: visceral adipose tissue. LMI: Lean/$height^2$.

https://doi.org/10.2147/JAA.S474667

kg/m^2, p=0.06), lower FMI (8.7 [5.7–9.9] vs 11.0 [8.7–12.9] kg/m^2, p=0.053), a lower percentage of fat mass (28.5 [14.5–66.0] vs 35.9 [25.6–48.8], p=0.07), and significantly better VO_2 max (20.7 mL/min/kg [17.8–24.3] vs 17.3 [14.0–18.9], p=0.04) (Table 3 and Figure 1). There was no difference in bone mineral content.

In the second analysis, we considered patients with type-2 high asthma if they had at least one of the following: sputum eosinophils of ≥3%; a blood eosinophil count of ≥150/mm^3; a FeNO of ≥25ppb, atopy). We then compared their body composition to patients with type-2 low asthma. Patients with type-2 asthma did not exhibit body compositions different to those with non-type 2 asthma.

We classified patients according to the presence or absence of sensitization to common aeroallergens. We did not find any differences in body composition between sensitized and non-sensitized patients.

Body Composition According to Smoking Status and Airway Obstruction

Regarding smoking status, there was a trend for a lower android/gynoid ratio in smokers (0.66 [0.62–0.90] versus non-smokers (0.96 [0.87–1.19]) and ex-smokers (1.10 [1.00–1.27], p=0.089).

Table 3 Body Composition Indices for Eosinophilic and Non Eosinophilic Asthma

	Non Eosinophilic Asthma	Eosinophilic Asthma	p-value
N	26	9	
Age (years)	44 ± 14	46.1 ± 11	0.70
Female (%)	67	29	0.049
Smoking status CS (%) ES (%) NS (%)	 10 19 71	 0 29 71	0.64
BMI, kg/m^2	31.2 (26.4–32.7)	25.7 (22.6–29.8)	0.06
FMI, kg/m^2	11.0 (8.7–12.9)	8.7 (5.7–9.9)	0.053
FMI, %	63.5 (48.0–78.0)	24.5 (13.0–65.5)	0.053
BMC, g	2262 ± 393	2394 ± 423	0.45
BMC, %	2.7 ± 0.5	3 ± 0.6	0.34
Lean mass, g	51,012 ± 10,582	53,167 ± 12,066	0.69
Lean mass, %	60.5 ± 7.7	64.9 ± 9.6	0.23
Fat mass, g	31,475 ± 9469	27,075 ± 10,300	0.057
Fat mass, %	35.9 (25.6–48.8)	28.5 (14.5–66.0)	0.07
Android/gynoid ratio	1.02 ± 0.19	1.11 ± 0.23	0.24
VAT area	124.8 ± 63.6	134.3 ± 73.2	0.84
LMI, kg/m^2	17.88 ± 2.96	18.01 ± 2.92	0.68
VO_2 max, mL/min/kg	17.3 (14.0–18.9)	20.7 (17.8–24.3)	0.04

Abbreviations: BMI, body mass index; FMI, fat mass index; BMC, bone mineral content; VAT, visceral adipose tissue; LMI, Lean/height^2; VO_2max, maximal oxygen uptake.

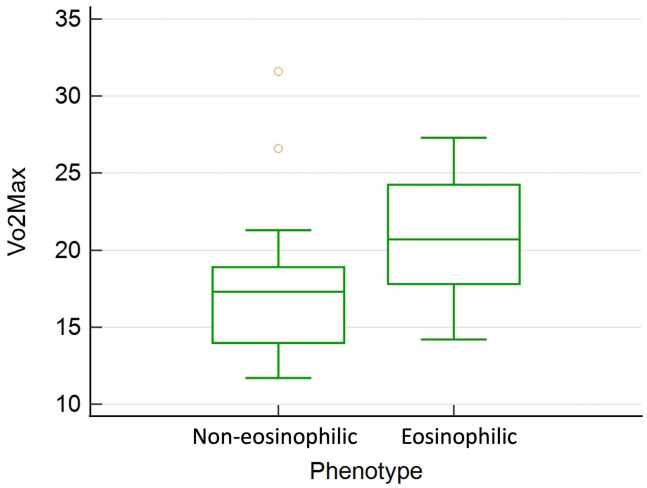

Figure 1 Maximal oxygen uptake according to inflammatory phenotype in asthma. Box-and-whisker. Eosinophilic asthma (sputum eosinophils ≥3%, n=9), non eosinophilic asthma (sputum eosinophils <3%, n=26).

We classified patients according to whether their post-BD FEV_1% predicted was higher or lower than 80% and found no significant differences in body composition between patients with irreversible airflow obstruction and non-obstructive patients.

Body Composition and Lung Function

Spirometry

The percentage of fat mass was inversely correlated with pre-BD FEV_1, post-BD FEV_1, pre-BD FVC, and post-BD FVC (Table 4). We found significant inverse correlations between FMI and pre-BD FEV_1, post-BD FEV_1, pre-BD FVC, and post-BD FVC (Table 4). VAT was correlated with methacholine concentration, provoking a 20% decrease in FEV_1 (PC20) (Table 4).

Lean/height^2 was correlated with pre-BD and post-BD FVC (Table 4). Lean mass was correlated with pre-BD FEV_1, post-BD FEV_1, pre-BD FVC, and post-BD FVC (Table 4).

Bone mineral content (BMC) was correlated with pre-BD FEV_1, post-BD FEV_1, pre-BD FVC, and post-BD FVC (Table 4).

Table 4 Correlation Coefficient (r) Between Body Mass Composition Indices and Lung Function Testing in Asthma Patients

	Pre-BD FEV_1	Post-BD FEV_1	Pre-BD FVC	Post-BD FVC	PC20	FRC	RV	TLC	DLCO
Percentage of fat	−0.43	−0.43	−0.54	−0.53		−0.47	−0.47	−0.60	
FMI	−0.34	−0.34	−0.43	−0.41		−0.31	−0.36	−0.38	−0.39
VAT					0.36	−0.43	−0.35		
Lean/height^2			0.32	0.34		−0.46		0.47	0.44
Lean mass	0.33	0.34	0.44	0.45		−0.35		0.57	0.57
Android/gynoid						−0.57			
BMI						−0.58	−0.47		
BMC	0.46	0.47	0.52	0.54		0.34	0.33	0.52	0.56

Notes: Significant correlation p<0.05. Significant correlation p<0.01. Significant correlation p<0.001.

https://doi.org/10.2147/JAA.S474667

Lung Volumes

Fat mass percentage was inversely correlated with functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC) (Table 4). The android/gynoid ratio was inversely correlated with FRC. BMI was inversely correlated with FRC and RV (Table 4). FMI was inversely correlated with TLC, FRC, and RV (Table 4). Visceral adipose tissue was inversely correlated with FRC and RV (Table 4).

Lean/height^2 and lean mass were inversely correlated with FRC and positively correlated with TLC (Table 4). BMC correlated with FRC, RV, and TLC (Table 4).

Diffusion Capacity

We found a significant inverse correlation between FMI and DLCO (Table 4). Lean/height^2 ratio, lean mass, and bone mineral content were correlated with DLCO (Table 4).

Body Composition and Patients' Related Outcome Measures (PROMs)

A higher lean mass was correlated with better asthma control (ACT; Table 5), and there was a trend toward a better quality of life (AQLQ [p=0.074, r=0.27]) (Figure 2, Table 5).

Regarding anxiety and depression, higher lean mass and lean mass/height^2 were correlated with lower anxiety and depression scores (Table 5). We found a significant inverse correlation between anxiety (HAD A) and the android/gynoid ratio and lean mass (Figure 3 and Table 5). Lean mass/height^2 and lean mass were inversely correlated with depression (HAD D; Figure 3 and Table 5).

Body Composition and Blood Biomarkers

We found a significant correlation between percentage of fat and CRP, cortisol, and hemoglobin levels (Table 5). The android/gynoid ratio was associated with hemoglobin level. BMI was significantly correlated with CRP and fibrinogen levels, whereas FMI was inversely correlated with hemoglobin (Table 5). VAT was correlated with CRP level. Lean/height^2 and lean mass were correlated with hemoglobin levels, whereas BMC correlated with cortisol, DHEA sulfate, and hemoglobin levels (Table 5).

Table 5 Correlation Coefficient (r) Between Body Mass Composition Indices and Patients Related Outcomes Measures and Blood Inflammatory Biomarkers in Asthma Patients

	ACT	HAD	HAD A	HAD D	CRP	Hb	Fibrinogen	cortisol	DHEA
Percentage of fat					0.32	−0.55		−0.32	
VAT					0.45				
Lean/height^2		−0.33		−0.31		0.39			
Lean mass	0.34	−0.38	−0.32	−0.33		0.49			
Android/gynoid			−0.31			0.56			
BMI		−0.35			0.42		0.31		
FMI						−0.41			
BMC						0.42		0.43	0.34

Notes: Significant correlation p<0.05. Significant correlation p<0.01. Significant correlation p<0.001.

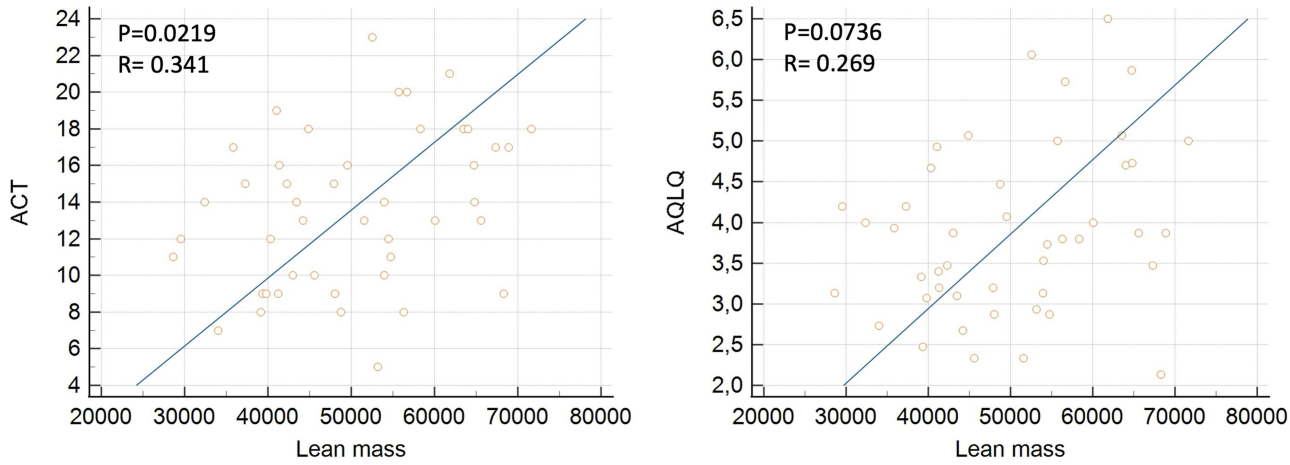

Figure 2 Body composition and asthma Patients Related Outcomes Measures (PROMs). Lean mass expressed in grams.
Abbreviations: ACT, asthma control test; AQLQ, asthma quality of life questionnaire.

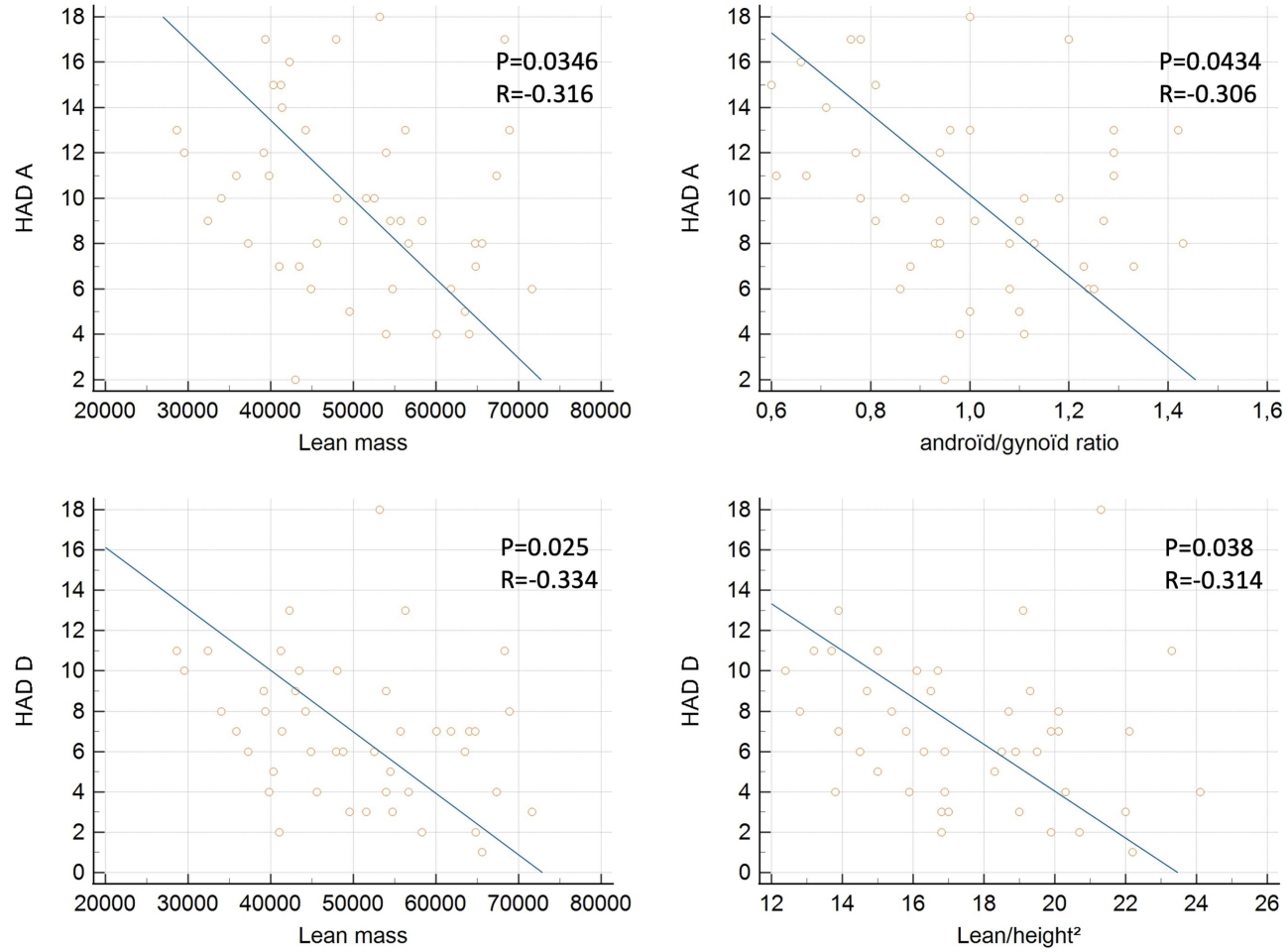

Figure 3 Body composition and asthma patients anxiety and depression scores. HAD A anxiety score. HAD D depression score. Lean mass expressed in grams. Lean/height^2 (LMI) expressed in kg/m^2.

https://doi.org/10.2147/JAA.S474667

Table 6 Correlation Coefficient (r) Between Body Mass Composition Indices and Maximal Inspiratory and Expiratory Pressure, Maximal Aerobic Power and Maximal Oxygen Uptake in Asthma Patients

	MIP	MEP	MAP	VO_2max
Percentage of fat		−0.38	−0.45	−0.56
VAT			0.31	
Lean/height^2	0.35	0.32	0.56	
Lean mass		0.32	0.69	
Android/gynoid	0.31		0.45	
BMI		0.33		−0.56
FMI				−0.59
BMC		0.39	0.63	0.43

Notes: Significant correlation p<0.05. Significant correlation p<0.01. Significant correlation p<0.001.

Body Composition and Maximal Expiratory Pressure, Maximal Inspiratory Pressure, and Maximal Aerobic Power

We found a significant inverse correlation between fat percentage and maximal expiratory pressure (MEP), maximal inspiratory pressure (MIP), and maximal aerobic power (MAP; Table 6). The android/gynoid ratio correlated with MIP and MAP (Table 6). BMI was correlated with MEP, whereas MIP showed a trend (p=0.053, r=0.29). The VAT area was correlated with MAP. Lean/height^2 and lean mass were associated with MEP, MIP, and MAP, whereas BMC was significantly correlated with MEP and MAP (Table 6).

Body Composition and Exercise Testing

We found a significant inverse correlation between VO_2 max and the percentage of fat, BMI, and FMI, whereas BMC was correlated with VO_2 max (Table 6).

Discussion

In this prospective study, we found that patients with uncontrolled moderate-to-severe asthma had higher BMI, fat mass index level, more android fat distribution, higher visceral adipose tissue area, and lower lean mass than healthy subjects, but had the same mineral bone content despite being treated with chronic inhaled corticosteroids. Patients with eosinophilic asthma had better exercise tolerance and tended to have a lower fat mass. Unsurprisingly, fat mass was associated with a restrictive pattern, whereas lean mass and bone mineral content were associated with better lung volume and diffusion capacity. Higher lean mass was correlated with better asthma control and lower depression scores. We confirmed a significant correlation between BMI and systemic inflammatory biomarkers, whereas lean mass and bone mineral content were associated with higher hemoglobin levels. Lean mass and bone mineral content were correlated with maximal expiratory, inspiratory, and maximal aerobic pressures, and we found a significant inverse correlation between exercise tolerance and fat mass.

Patients with uncontrolled moderate-to-severe asthma had higher BMI and fat mass index levels, more android fat distribution, higher visceral adipose tissue areas, and lower lean mass than healthy subjects. According to recently published reference values for DXA from the LEAD study,[13] patients with uncontrolled asthma in our study had a higher fat mass than a random sample of Caucasian Austrian participants. Schiffers et al[14] also reported that asthma patients had

higher indices of obesity, including BMI, central obesity, and visceral fat mass, than the general population. It is important to assess fat mass distribution because the distribution of fat mass negatively influences cardio-metabolic risk.[15] Excessive amounts of visceral adipose tissue are associated with insulin resistance, a higher risk of type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and increased mortality. However, fat gynoid distribution is associated with a lower cardiovascular risk.[16] BMI is the only crude marker of obesity and does not account for either the quantity or distribution of fat and lean tissue, whereas DXA has been shown to be a useful tool to evaluate fat mass distribution and fat-free mass, composed of bone mineral content and lean mass, which are markers of skeletal muscle mass.

In our prospective study, patients with eosinophilic asthma, defined as the presence of sputum eosinophil counts of >3%,[17] had better exercise tolerance and tended to have a lower fat mass. In a previous study, we found that patients with eosinophilic asthma were more often male.[18] In this study, more males had the eosinophilic phenotype, which could partly explain the differences in exercise tolerance. In a study by Schiffers et al,[14] eosinophilic asthma, defined only by blood eosinophils counts of >150/mm^3, was also characterized by a higher proportion of males. Previous studies have also found higher percentages of sputum neutrophils in obese and overweight females with asthma.[2] To the best of our knowledge, this is the first study to demonstrate improved exercise tolerance in patients with eosinophilic asthma.

In contrast to Schiffers et al,[14] who found that allergic asthma was characterized by a lower fat mass index level and visceral adipose tissue area, we did not find any difference in body composition between allergic and non-allergic asthma patients in our study. Moreover, there were no significant differences in body composition with respect to smoking status or fixed airway obstruction patterns.

Unsurprisingly, fat mass was associated with a restrictive pattern.[19] The fat present in the android (abdominal) region reduces the capacity of the diaphragm to shift downward, thereby limiting lung inflation.[20] In a study looking at a population of 44 overweight and obese patients with asthma, Scott et al[21] found an inverse correlation between android fat mass and FRC. Our results confirm these findings and further highlight that not only android fat distribution but also percentage of fat mass, BMI, FMI, and visceral adipose tissue area are inversely correlated with FRC, representing the volume remaining in the lungs after a normal passive exhalation. Moreover, an increase in percentage of fat and FMI was associated with a decrease in total lung capacity, whereas fat percentage, BMI, FMI, and VAT were associated with reduced residual volume. An increase in abdominal fat is associated with reduced FRC, RV, and TLC, reflecting overweight-associated restriction.[22] Lean mass and lean mass/height^2 ratio were also inversely correlated with FRC but positively correlated with TLC, reflecting an improvement in lung volume and reduction in air trapping. Our results also showed that bone mineral content was positively correlated with FRC and TLC.

In our study, the percentage of fat mass and FMI were inversely correlated with pre- and post-BD FEV_1 and FVC, whereas lean mass and bone mineral content were positively associated with these spirometry measures. Scott et al[21] found that, of all body composition measurements, only the percentage of fat and total fat mass of the arms correlated with FEV_1 in overweight and obese female patients with asthma. However, this study did not include patients with a normal weight.

Regarding diffusion capacity, increases in lean mass and bone mineral content were associated with higher DLCO values, whereas FMI was inversely correlated with DLCO. This could be explained, at least in part, by the higher levels of hemoglobin found in patients with higher lean mass and bone mineral content, while there was an inverse correlation between hemoglobin and percentage of fat and FMI.

In our study, we found that increased visceral adipose tissue was associated with decreased bronchial hyper-responsiveness to methacholine challenge, suggesting lower bronchial hyper-responsiveness. It seems clear that the respiratory symptoms reported by patients with increased fat mass are at least partly explained by restrictive patterns, which could overestimate poor asthma symptom control. To our knowledge, this is the first study to demonstrate a relationship between visceral adipose tissue and bronchial hyper-responsiveness to methacholine. In a previous study,[21] gynoid fat mass was associated with lower provocation fall after a hypertonic saline challenge.

Our study also showed that higher lean mass was correlated with better asthma symptom control, lower depression scores, and a trend for better quality of life. Studies have shown that aerobic training is associated with improved asthma symptom control[23] and quality of life,[24] and that patients with a higher lean mass are more likely to engage in regular physical activity. Our study is the first to report lower depression scores in patients with asthma who have higher lean mass, and higher anxiety scores in patients with lower lean mass. Previous studies conducted in the general population

that did not focus on asthma found that physical activity, mental health, and well-being were positively related.[25] Gynoid fat distribution is associated with increased anxiety. This probably reflects the fact that females are twice as likely to develop anxiety disorders as males.[26]

We confirmed a significant correlation between fat mass and systemic inflammatory biomarker levels. Our study showed that the percentage of fat, BMI, and VAT were correlated with increased CRP levels, while BMI was also associated with fibrinogen. In a previous study performed at the Asthma Clinic of the University Hospital of Liege,[2] we found that obese females had higher CRP and fibrinogen levels. Scott et al[21] also found that overweight and obese females with asthma have higher CRP levels.

Lean mass and bone mineral content were positively correlated with maximal expiratory and inspiratory pressures, and maximal aerobic power. Maximal inspiratory pressure and maximal expiratory pressure are global measures of the maximal strength of the respiratory muscles, and are the greater pressures that may be generated during maximal inspiration and expiration against an occluded airway, respectively. Maximal aerobic power is the maximum power developed through maximum heart rate aerobic metabolism, which is reached when the subject uses their maximal oxygen uptake (VO_2 max). Thus, it is not surprising that MIP, MEP, and MAP were correlated with lean mass.

The percentage of fat mass was inversely associated with MEP, MIP, and MAP. The higher the percentage of fat, the lower the percentage of lean mass. However, higher android/gynoid ratios were associated with better MIP and MAP, whereas BMI and VAT area were positively correlated with MEP and MAP. MIP and MEP combine the strength of the chest muscles and the contraction or relaxation of the chest wall. The influence of fat mass remains unclear but could be partly due to the corresponding increase in muscle mass in relation to body weight. We found a correlation between android distribution and BMI (but not fat percentage) and lean mass indices. In a previous study conducted with healthy subjects, BMI was positively correlated with MIP and MEP values.[27]

We found a significant inverse correlation between maximal oxygen uptake (VO_2 max) and fat mass (BMI and FMI), whereas this was found to be positively correlated with bone mineral content. A previous study demonstrated that normal-weight asthmatics with well-controlled disease preserved cardiorespiratory responses to exercise relative to non-asthmatic controls matched for BMI and physical activity levels.[28] However, these similarities do not hold true in patients with combined obesity and asthma. Reduced cardiorespiratory fitness and exercise performance in overweight compared to normal-weight asthmatics is most likely driven by their more sedentary lifestyle and resultant deconditioning,[29] reflected by the low VO_2 max value. The positive association between exercise capacity and bone mineral content likely reflects the higher bone mineral content in more active patients.

A limitation of this study is its small sample size and cross-sectional nature. However, we collected longitudinal data from the SAMBA to evaluate the effectiveness of a three-month sub-maximal aerobic training program on body composition in the training and control groups. These data will be analyzed upon completion. This first analysis, however, generated novel findings, looking at the asthma inflammatory phenotype using the gold standard induced sputum collection method, and showed that patients with eosinophilic asthma had a lower fat mass and better exercise tolerance. Furthermore, all subjects studied had a BMI below 35 kg/m^2 and, as such, our results cannot be generalized to obese patients with asthma.

Conclusion

Our study confirms that patients with uncontrolled asthma despite good adherence to inhaled therapies, have higher BMI and fat mass index level and reduced exercise capacity as compared to healthy subjects. Patients with eosinophilic asthma show better exercise tolerance and tend to have lower fat mass. Interestingly, we found that higher lean mass was associated with better asthma control and lower depression scores. The results of our study supports the importance of nutritional advices and rehabilitation in the management of uncontrolled asthma.

Abbreviations

ACT, Asthma control test; AQLQ, Asthma quality of life questionnaire; BMC, Bone mineral content; BMI, Body Mass Index; CRP, C-Reactive Protein; DLCO, diffusing capacity of the lungs for carbon monoxide; DXA, Dual-Energy X-ray Absorptiometry; FeNO, fractional exhaled nitric oxide; FMI, Fat Mass Index; FRC, Functional Residual Capacity; FVC, Functional Vital Capacity; HAD, Hospital Anxiety and Depression Scale (A: Anxiety score, D: depression score); ICS,

inhaled corticosteroids; KCO, carbon monoxide transfer coefficient; LABA, Long-Acting B2 Agonists; LAMA, Long-Acting Muscarinic antagonist; LMI, lean mass index; MAP, Maximal Aerobic Power; MEP, Maximal Expiratory Pressure; MIP, Maximal Inspiratory Pressure; Post-BD FEV_1, Post-Bronchodilation Forced Expiratory Volume in one second; Pre-BD FEV_1, Pre-Bronchodilation Forced Expiratory Volume in one second; RV, residual volume; SAMBA trial, Towards a paradigm shift in Severe Asthma Management: Deep analysis of the effect of suBmaximal Aerobic training); SD, standard deviation; TLC, Total Lung Capacity; VAT, visceral adipose tissue; VO_2 max, maximal oxygen uptake.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

Prof. Dr. Florence Schleich reports grants from Gsk, grants from Chiesi, grants from AstraZeneca, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Global Initiative for Asthma. Global initiative for asthma: global strategy for asthma management and prevention. Available from: https://ginasthma.org. Accessed December 24, 2024.
2. Peerboom S, Graff S, Seidel L, et al. Predictors of a good response to inhaled corticosteroids in obesity-associated asthma. *Biochem Pharmacol*. 2020;179:113994. doi:10.1016/j.bcp.2020.113994
3. Schleich F, Brusselle G, Louis R, et al. Heterogeneity of phenotypes in severe asthmatics. the Belgian severe asthma registry (BSAR). *Respir Med*. 2014;108(12):1723–1732. doi:10.1016/j.rmed.2014.10.007
4. Scott HA, Wood LG, Gibson PG. Role of obesity in asthma: mechanisms and management strategies. *Curr Allergy Asthma Rep*. 2017;17(8):53. doi:10.1007/s11882-017-0719-9
5. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. *Am J Physiol*. 1996;271(6 Pt 1):E941–51. doi:10.1152/ajpendo.1996.271.6.E941
6. Louis R, Sele J, Henket M, et al. Sputum eosinophil count in a large population of patients with mild to moderate steroid-naive asthma: distribution and relationship with methacholine bronchial hyperresponsiveness 2. *Allergy*. 2002;57(0105–4538):907–912. doi:10.1034/j.1398-9995.2002.23608.x
7. Guiot J, Demarche S, Henket M, et al.Methodology for sputum induction and laboratory processing. *J Vis Exp*. 2017;(130):56612. doi:10.3791/56612
8. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials 1. *Thorax*. 1992;47(0040–6376):76–83. doi:10.1136/thx.47.2.76
9. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65. doi:10.1016/j.jaci.2003.09.008
10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370. doi:10.1111/j.1600-0447.1983.tb09716.x
11. Tarantini F, Baiardini I, Passalacqua G, Braido F, Canonica GW. Asthma treatment: "magic bullets which seek their own targets" 1. *Allergy*. 2007;62(0105–4538):605–610. doi:10.1111/j.1398-9995.2007.01390.x
12. McDonough JRBRA. Maximal exercise testing in assessing cardiovascular function. *J S C Med Assoc* 1969;65(12):Supl1:25–33.
13. Ofenheimer A, Breyer-Kohansal R, Hartl S, et al. Reference values of body composition parameters and visceral adipose tissue (VAT) by DXA in adults aged 18-81 years-results from the LEAD cohort. *Eur J Clin Nutr*. 2020;74(8):1181–1191. doi:10.1038/s41430-020-0596-5
14. Schiffers C, Wouters EFM, Breyer-Kohansal R, et al. Asthma prevalence and phenotyping in the general population: the LEAD (Lung, hEart, sociAl, boDy) study. *J Asthma Allergy*. 2023;16:367–382. doi:10.2147/JAA.S402326
15. Karlsson T, Rask-Andersen M, Pan G, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nat Med*. 2019;25(9):1390–1395. doi:10.1038/s41591-019-0563-7
16. Vasan SK, Osmond C, Canoy D, et al. Comparison of regional fat measurements by dual-energy X-ray absorptiometry and conventional anthropometry and their association with markers of diabetes and cardiovascular disease risk. *Int J Obes Lond*. 2018;42(4):850–857. doi:10.1038/ijo.2017.289
17. Schleich FN, Zanella D, Stefanuto P-H, et al. Exhaled volatile organic compounds are able to discriminate between neutrophilic and eosinophilic asthma. *Am J Respir Crit Care Med*. 2019;200(4):444–453. doi:10.1164/rccm.201811-2210OC
18. Schleich FN, Chevremont A, Paulus V, et al. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *Eur Respir J*. 2014;44(1):97–108. doi:10.1183/09031936.00201813

19. Dharmage SC, Bui DS, Walters EH, et al. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. *Lancet Respir Med*. 2023;11(3):273–282. doi:10.1016/S2213-2600(22)00364-2
20. Salome CMKGGBN. Physiology of obesity and effects on lung function. *J Appl Physiol*. 1985;1:206–211.
21. Scott HA, Gibson PG, Garg ML, et al. Relationship between body composition, inflammation and lung function in overweight and obese asthma. *Respir Res*. 13(1):10. doi:10.1186/1465-9921-13-10
22. Jones RL, Nzekwu -M-MU. The effects of body mass index on lung volumes. *Chest*. 2006;130(3):827–833. doi:10.1378/chest.130.3.827
23. Hansen ESH, Pitzner-Fabricius A, Toennesen LL, et al. Effect of aerobic exercise training on asthma in adults: a systematic review and meta-analysis. *Eur Respir J*. 2020;56(1):2000146. doi:10.1183/13993003.00146-2020
24. McLoughlin RF, Clark VL, Urroz PD, Gibson PG, McDonald VM. Increasing physical activity in severe asthma: a systematic review and meta-analysis. *Eur Respir J*. 2022;60(6):2200546. doi:10.1183/13993003.00546-2022
25. Herbert C. Enhancing mental health, well-being and active lifestyles of university students by means of physical activity and exercise research programs. *Front Public Health*. 2022;10:849093. doi:10.3389/fpubh.2022.849093
26. Catuzzi JE, Beck KD. Anxiety vulnerability in women: a two-hit hypothesis. *Exp Neurol*. 2014;259:75–80. doi:10.1016/j.expneurol.2014.01.023
27. Gil Obando LM, López López A, Avila CL. Normal values of the maximal respiratory pressures in healthy people older than 20 years old in the City of Manizales - Colombia. *Colomb medica*. 2012;43(2):119–125. doi:10.25100/cm.v43i2.1141
28. Cortés-Télles A, Torre-Bouscoulet L, Mejía-Alfaro R, Silva-Cerón M, Wilkie SS, Guenette JA. Cardiorespiratory and sensory responses to exercise in well-controlled asthmatics. *J Asthma*. 2015;52(6):576–582. doi:10.3109/02770903.2014.988223
29. Cortés-Télles A, Torre-Bouscoulet L, Silva-Cerón M, et al. Combined effects of mild-to-moderate obesity and asthma on physiological and sensory responses to exercise. *Respir Med*. 2015;109(11):1397–1403. doi:10.1016/j.rmed.2015.09.010