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Lower skeletal muscle density and airway structure on computed tomography in asthma

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ABSTRACT

Background: Lower skeletal muscle density may reflect muscle adiposity and metabolic dysregulation that potentially impair disease control and lung function independent of high body mass index (BMI) in patients with asthma.
Objective: To investigate whether the lower density of pectoralis muscles (PMs) and erector spinae muscles (ESMs) on chest computed tomography was associated with airway structural changes in patients with asthma.
Methods: Consecutive patients with asthma and healthy controls undergoing chest computed tomography were retrospectively analyzed. The ESM and PM density, areas of subcutaneous adipose tissue near the PM and epicardial adipose tissue, wall area percent of the airways, and airway fractal dimension (AFD) were quantified on computed tomography.
Results: The study included 179 patients with asthma (52% women) and 88 controls (47% women). All the controls were 60 years old or younger. The PM and ESM density in female patients with asthma who were 60 years old or younger were significantly lower than those in controls after adjustment for BMI. In female patients with asthma at all ages, lower PM and ESM density (but not subcutaneous or epicardial adipose tissue area) was associated with greater wall area percent of the airways and lower AFD after adjusting for age, height, BMI, smoking status, blood eosinophil count, and oral corticosteroid use. The only association between ESM density and AFD was found in male patients with asthma.
Conclusion: Lower skeletal muscle density may be associated with airway wall thickening and less complexity of the airway luminal tree in female patients with asthma.

Introduction

Asthma is a heterogeneous disease, and its management is still unsatisfactory for subgroups of patients.[1,2] Obesity is a well-known factor contributing to severe asthma[3,4] and may cause the deposition of adipose tissue to the airways' wall.[5] Moreover, metabolic dysregulation, such as insulin resistance and ectopic fat accumulation, impairs disease control, lung function, and quality of life, and increases the risk of exacerbations irrespective of body mass index (BMI) in patients with asthma.[6-9] However, the morphologic impacts of fat-related metabolic disorders on asthmatic airways have not been fully elucidated.

Adipose tissue exhibits varying physiologic effects depending on its deposition site, such as subcutaneous and visceral adipose tissue.[10] Recently, the clinical relevance of intramuscular fat accumulation has gained recognition in various medical conditions.[11] Computed tomography (CT) can detect increased intramuscular fat as a lower skeletal muscle density.[12] A lower skeletal muscle density on CT is associated with insulin resistance independent of BMI and

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visceral fat.[13] In female patients with asthma, a lower density of paraspinal muscle on CT is predictive of a subsequent decline in respiratory function independent of BMI.[8] On the basis of these findings, we hypothesized that lower skeletal muscle density reflects increased intramuscular fat, potentially contributing to airway wall remodeling independent of BMI in patients with asthma.

Chest CT is widely used for differential diagnosis and morphologic evaluations of airways and parenchyma in patients with asthma. In addition, chest CT allows for the quantification of the density of skeletal muscles, including the pectoralis muscle (PM) and erector spinae muscle (ESM), and the cross-sectional areas of subcutaneous adipose tissue (SAT) near the PM and epicardial adipose tissue (EAT). With the use of these technical advantages, this study retrospectively analyzed archived chest CT data from patients with asthma and controls to evaluate whether the density of PM and ESM was lower in patients with asthma than in controls and to assess whether the lower density of PM and ESM was associated with airway wall thickening and altered airway lumen tree structure (independent of BMI) in patients with asthma and controls.

Methods

Study Design and Population

This was a retrospective, cross-sectional, single-center study including patients with asthma and healthy controls. Patients with asthma undergoing chest CT and spirometry between 2011 and 2020 were consecutively included. Laboratory and spirometry data were obtained within exacerbation-free 3 months of chest CT. No additional systemic corticosteroid treatment was performed between chest CT scan, blood test, and spirometry. The diagnosis and severity of asthma were assessed according to the Global Initiative for Asthma guidelines.[14] Smokers were defined as those with a life-long smoking history of at least 10 pack-years. The details of treatment were confirmed on the basis of medical records in the previous 3 months before the CT scan. The exclusion criteria were as follows: (1) concurrent respiratory disease other than chronic obstructive pulmonary disease; (2) history of lung resection; (3) acute respiratory tract infections or asthma exacerbations within the preceding 3 months; (4) insufficient quality of CT images, such as inappropriate breath holding during scans; and (5) unavailable spirometry data obtained within exacerbation-free 3 months of chest CT. Healthy controls aged between 40 and 60 years without history of lung diseases who were voluntarily registered as candidates for living-donor lung transplantation and who underwent chest CT and spirometry between 2010 and 2022 were also consecutively included. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee (number R1660-5). Written informed consent was waived because of the retrospective nature of this study.

Pulmonary Function Test

Postbronchodilator spirometry was performed in patients with asthma, and prebronchodilator spirometry was performed in healthy controls following the American Thoracic Society/European Respiratory Society guidelines.[15] The predicted forced vital capacity and forced expiratory volume in 1 second were calculated by using Japanese reference values.[16]

Computed Tomography Scan Acquisition

Full inspiratory whole-lung CT images were obtained by using 3 scanners from the same CT manufacturer, including Aquilion One, Aquilion Prime, and Aquilion Precision (Canon Medical Systems, Otawara, Tochigi, Japan), with the same scanning conditions being used, including 120 kVp and autoexposure control. Images with a 1.0 mm slice thickness were reconstructed with a soft (FC13 or FC11) kernel for quantification of muscle density, adipose tissue area, and total lung volume (TLV). Images with a 0.5 mm slice thickness were reconstructed with a sharp (FC51) kernel for airway morphologic analysis.

Computed Tomography Analysis of Skeletal Muscle Density and Fat Area

As illustrated in Figure 1, after manual masking by using ImageJ Fiji software (https://imagej.net/software/fiji), the density of the PM and ESM and the areas of the SAT and EAT were calculated by using custom-made Python scripts, as previously reported.[17] One inspector quantified these CT parameters for all the CT scans without knowledge of clinical information. The left and right ESMs were manually segmented on a single axial slice at the level of the lower margin of the 12th thoracic vertebra with CT values ranging between −50 and +90 Hounsfield units (HUs).[18] The mean attenuation values in HU were calculated as the ESM density. The left and right PMs were manually segmented from regions with CT values ranging between −50 and +90 HU on a single axial slice at the level of the top of the aortic arch.[19] The mean attenuation values in HU were calculated as the PM density. The SAT was automatically identified as regions located between the PM and the skin surface on the same axial slice.[20] The EAT regions at the origin of the left main coronary artery level were localized by manually tracing the pericardium and extracting areas with CT values between −230 and −30 HU.[21]

Computed Tomography Analysis of Airway Parameters

Airway dimensions and TLV were measured by using Synapse Vincent software (Fujifilm Medical, Tokyo, Japan). Lumen areas and diameters were measured at 14 specific airway branches, including the trachea, right and left main bronchus, bronchus intermedius, segmental and subsegmental (third and fourth generations) bronchus of the right apical (RB1), right lateral (RB4), right posterior basal (RB10), left apicoposterior (LB1+2) and left anteromedial basal (LB10) paths. The geometric mean lumen diameter of these 14 locations was divided by the cube root of the TLV to determine the airway-to-lung size ratio.[22] In addition, the wall areas were measured for the third- and fourth-generation bronchus in the 5 paths, and the percentage of wall area to the sum of wall and lumen areas was calculated as the wall area percent (WA%) and averaged for the third and fourth generations.[23]

Moreover, after the automatic segmentation of the entire airway tree, the airway fractal dimension (AFD) was calculated with a custom Python script on the basis of the box-counting method.[22,24,25] The number of boxes that were needed to completely cover the airway tree (N) was determined by 3-dimensionally placing a square grid of size L onto the airway tree. The process was repeated for various L values. AFD was calculated as the absolute slope of the regression line on a log-log plot, with L on the *x*-axis and N on the *y*-axis.

Statistics

Continuous and categorical variables are expressed as the mean (SD) and absolute number (percentage) unless otherwise indicated. Student *t* test and Fisher exact test were used for comparisons. For CT scans from 20 patients with asthma that were randomly selected from the entire study population, the PM and ESM density and the SAT and EAT areas were repeatedly assessed by the same inspector and independently assessed by 2 inspectors to assess the intraobserver variability and interobserver variability, respectively, by using intraclass correlation coefficients. In the first analysis, patients with asthma aged 60 years or younger were compared with controls because the age of controls ranged between 40 and 60 years owing to the age limit for donors for living-donor lung transplantation. Multivariable linear regression models were constructed to evaluate whether category (patients with asthma vs controls) was associated with CT parameters independent of BMI.

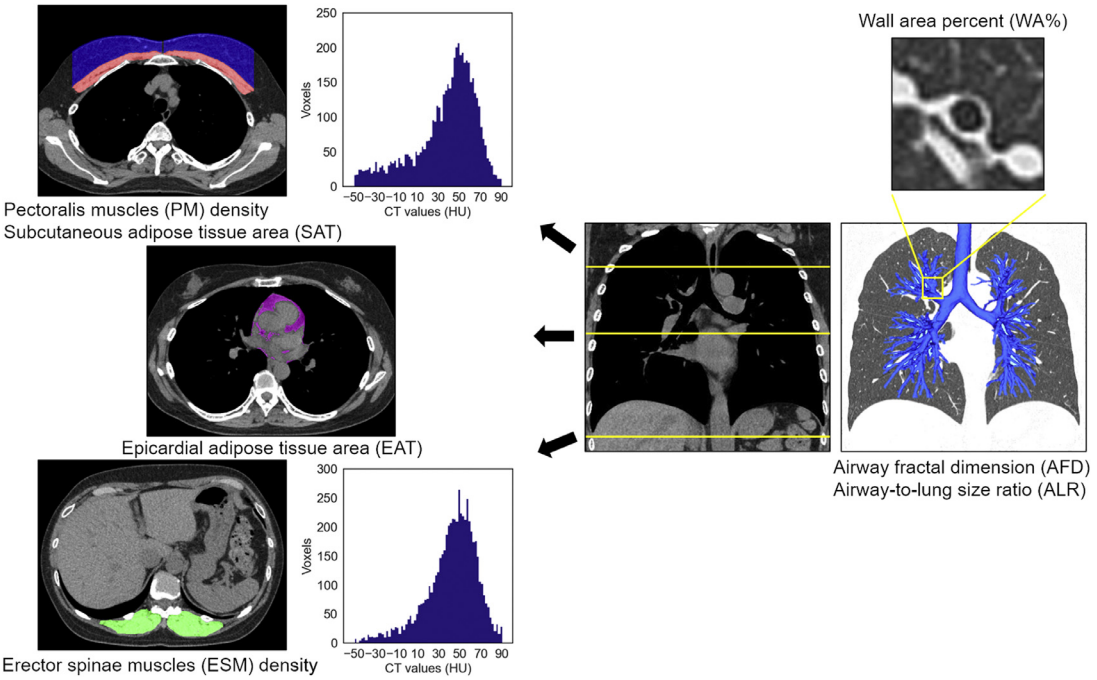

Figure 1. Illustration of extrapulmonary and airway CT structures. Representative extrapulmonary and airway CT images are illustrated. Images reconstructed with a soft kernel are used for quantification of the PM (red) on a single axial slice at the level of the top of the aortic arch, SAT adjacent to the PM (blue), ESM (green) on a single axial slice at the level of the lower margin of the 12th thoracic vertebra, EAT (magenta) at the origin of the left main coronary artery level, and TLV. Frequency distributions of PM and ESM density are also displayed. Images reconstructed with a soft kernel are used for quantification of WA% in the third- and fourth-generation bronchus, ALR, and AFD. AFD, airway fractal dimension; ALR, airway-to-lung size ratio; CT, computed tomography; EAT, epicardial adipose tissue; ESM, erector spinae muscles; PM, pectoralis muscles; SAT, subcutaneous adipose tissue; TLV, total lung volume; WA%, wall area percent.

In the second analysis, the Pearson correlation test was used to evaluate associations of the PM and ESM density and the SAT and EAT areas with WA%, airway-to-lung size ratio, and AFD in all the patients with asthma (irrespective of age) and controls (separately) after visual confirmation of the normality of each parameter on histograms. Multivariable linear regression models for WA% and AFD were constructed for male and female patients with asthma. The models for asthma included each of the CT parameters including the PM and ESM density, SAT and EAT areas, and age, height, BMI, smoking status, blood eosinophil count, and oral corticosteroid use as independent variables.

Finally, the lower limit of normal (LLN) for PM and ESM density in the male and female sexes was calculated as mean $-1.645 \times$ SD using data from male and female controls. Patients with asthma were categorized into 2 groups on the basis of each LLN to evaluate whether PM (or ESM) density below the LLN was associated with higher WA% and lower AFD.

Statistical analysis was performed by using R software version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria), and a *P* value less than .05 was considered statistically significant.

Results

Characteristics of Healthy Controls and Patients 60 Years Old or Younger With Asthma

As illustrated in Figure 2, 88 of 95 healthy controls between 40 and 60 years old and 179 of 208 patients with asthma undergoing chest CT scans and spirometry were included in the analysis. Among them, 49 patients were 60 years old or younger (n = 13 and n = 29 for male and female patients, respectively). Table 1 details the characteristics of the controls and patients with asthma aged 60 years or younger stratified by sex.

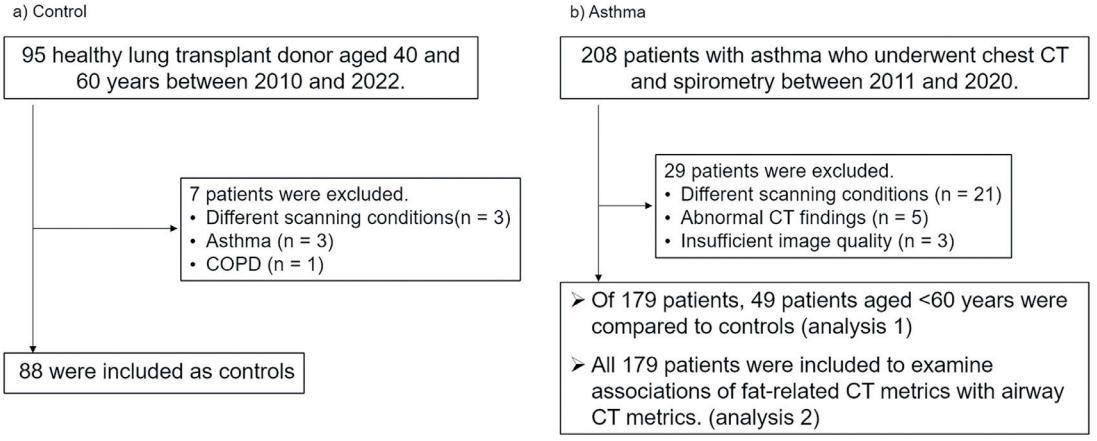

Figure 2. Patient flowchart of this study. COPD, chronic pulmonary obstructive disease; CT, computed tomography.

Table 1
Baseline Characteristics of Controls and Patients Aged 60 Years or Younger With Asthma

Demographics	Male sex		Female sex	
	Control (n = 47)	Asthma, age ≤ 60 y (n = 13)	Control (n = 41)	Asthma, age ≤ 60 y (n = 29)
Age, y	50.4 (5.4)	46.5 (14.9)	48.8 (5.6)	52.1 (6.4)[a]
Height, cm	171.4 (5.8)	169.2 (3.6)	159.1 (5.6)	158.4 (4.3)
BMI, kg/m^2	24.1 (2.8)	26.7 (4.9)[a]	22.5 (3.3)	24.6 (3.30)[b]
Smokers, current/former, n (%)	0 (0)/33 (51.1)	0 (0)/7 (53.8)	0 (0)/4 (9.8)	0 (0)/10 (34.5)[b]
Pack-years	12.1 (12.5)	19.0 (18.4)	2.41 (6.5)	14.2 (21.4)[b]
Diabetes mellitus, n (%)	2 (4.3)	2 (15.4)	1 (2.4)	1 (3.4)
FEV_1, L	3.49 (0.44)	3.01 (0.93)[a]	2.64 (0.38)	2.29 (0.50)[b]
FEV_1/FVC, %	79.9 (6.0)	72.9 (7.4)[b]	82.6 (6.3)	76.1 (8.0)[c]
%predicted FEV_1, %	102.9 (9.8)	88.2 (20.0)[c]	106.7 (13.5)	95.2 (17.7)[b]
FVC, L	4.38 (0.57)	4.30 (1.01)	3.20 (0.45)	2.93 (0.48)[b]
%predicted FVC, %	103.6 (11.2)	102.5 (21.5)	105.7 (13.8)	98.6 (13.3)[a]

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
NOTE. Values indicate the mean (SD) or number (%).
[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$.

Comparison of the Density of Erector Spinae and Pectoralis Muscles and Areas of Subcutaneous and Epicardial Adipose Tissue Between Controls and Patients With Asthma Aged 60 Years or Younger

As illustrated in Figure 3, the PM density (but not the other CT parameters) was significantly lower in male patients with asthma than in male controls. In contrast, the density of the PM and ESM was significantly lower and the areas of the SAT and EAT were significantly greater in female patients with asthma than in female controls. These associations in female patients with asthma remained significant (except for SAT area) after adjustment for BMI (PM density: β = −0.48, P = .02; ESM density: β = −0.61, P = .01; SAT area: β = 0.24, P = .12; EAT area: β = 0.71, $P < .001$) (eTable 1). The intra- and interobserver intraclass correlation coefficients (95% CI) for the PM and ESM density and the SAT and EAT areas were excellent (intraobserver, PM density 0.98 [0.95-0.99], ESM density 0.95 [0.86-0.98], SAT area 1.00 [1.00-1.00], EAT area 0.99 [0.98-1.00]; interobservers, PM density 0.99 [0.95-1.00], ESM density 0.90 [0.71-0.96], SAT area 1.00 [0.99-1.00], EAT area 0.99 [0.96-1.00]).

Associations of the Density of Erector Spinae and Pectoralis Muscles and Areas of Subcutaneous and Epicardial Adipose Tissue With Airway Computed Tomography Parameters in All Patients With Asthma and Controls

The characteristics of all the male and female patients with asthma (of any age) are summarized in Table 2. Age, BMI, and Global Initiative for Asthma severity did not differ between male and female patients. As detailed in Table 3, a lower density of ESM and PM and greater areas of EAT was significantly and weakly associated with greater WA% in the fourth-generation airways and with lower AFD in female patients with asthma. A statistically significant association was found only between lower ESM density and lower AFD in male patients with asthma. In contrast, the PM and ESM density were not associated with the WA% or AFD in male or female controls. Figure 4 illustrates the associations of PM and ESM density with WA% in the fourth generation and AFD in male and female patients with asthma and controls. The associations for the other CT parameters are illustrated in eFigure 1. As illustrated in eFigure 2, the density of the ESM and PM did not significantly correlate with the blood neutrophil or eosinophil count.

Multivariable Models for Airway Computed Tomography Parameters in Patients With Asthma

According to the multivariable models illustrated in Figure 5, a lower ESM density was associated with a lower AFD but not a lower WA% in the fourth-generation airways in male patients with asthma. In contrast, a lower ESM density was associated with both a greater WA% in the fourth-generation airways and a lower AFD in female patients with asthma after adjusting for age, height, BMI, smoking status, blood eosinophil count, and oral corticosteroid use (AFD: estimate [95% CI] = .01 [0.0001-0.02], P = .048; WA%: estimate [95%

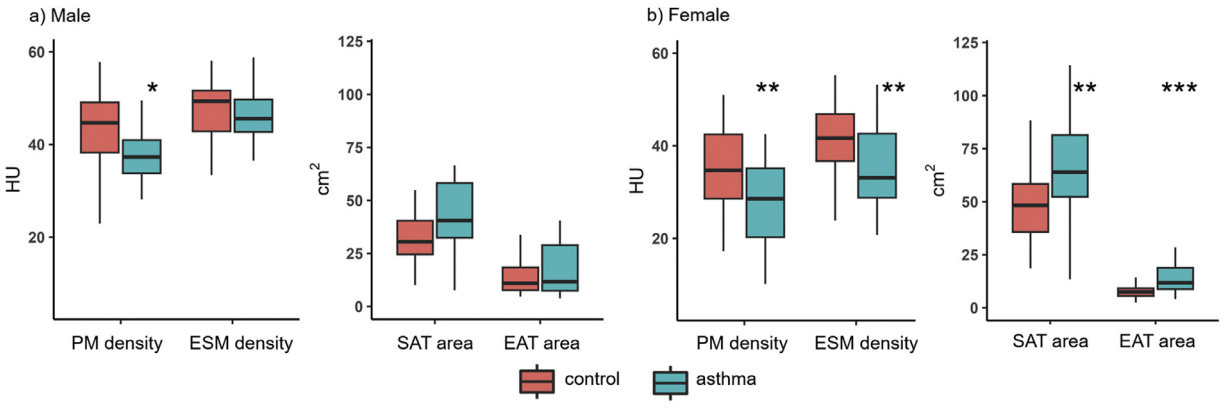

Figure 3. Comparisons of skeletal muscle density and adipose tissue areas between controls and patients with asthma stratified by sex. Distribution of PM and ESM density, SAT, and EAT area in controls and patients with asthma stratified by sex (A, male; B, female). Each parameter was compared between controls and patients with asthma by using the Student t test. *$P < .05$, **$P < .01$, ***$P < .001$. EAT, epicardial adipose tissue; ESM, erector spinae muscle; PM, pectoralis muscle; SAT, subcutaneous adipose tissue.

Table 2
Baseline Characteristics of All Patients With Asthma Stratified by Sex

Characteristics	All N = 179	Male patients n = 86	Female patients n = 93
Age, y	67.7 (12.1)	68.9 (12.4)	66.6 (11.8)
Height, cm	159.8 (8.8)	165.9 (6.3)	154.2 (6.8)
BMI, kg/m^2	24.1 (3.7)	24.3 (3.8)	23.8 (3.6)
Smokers, current/former, n (%)	4 (2.2)/75 (41.9)	4 (4.7)/55 (63.9)	0 (0)/20 (21.5)
Pack-years	20.7 (31.5)	34.7 (37.4)	7.54 (16.1)
Duration of asthma, y	12.8 (12.7)	13.6 (13.9)	12.1 (11.6)
Diabetes mellitus, n (%)	35 (19.6)	24 (27.9)	11 (11.8)
ICS use, n (%)	158 (88.3)	76 (88.4)	82 (88.2)
ICS dose high, %	44 (24.6)	17 (19.8)	27 (29.0)
OCS use, n (%)	15 (8.4)	4 (4.7)	11 (11.8)
Biologic use, n (%)	5 (2.8)	3 (3.2)	2 (2.3)
GINA severe, n (%)	102 (57.0)	47 (54.7)	55 (59.1)
FEV_1, L	2.05 (0.66)	2.25 (0.72)	1.86 (0.54)
FEV_1/FVC, %	69.8 (9.3)	66.1 (9.6)	73.2 (7.7)
%predicted FEV_1, %	86.6 (21.1)	82.6 (20.5)	90.3 (21.1)
FVC, L	2.94 (0.86)	3.45 (0.84)	2.47 (0.56)
%predicted FVC, %	94.9 (19.2)	94.7 (20.6)	95.3 (17.8)
Blood neutrophil count,/μL	4046.9 (1466.9)	4149.2 (1310.5)	3952.3 (1599.5)
Blood eosinophil count,/μL	202.0 (102.6-346.3)	229.1 (160.4-388.6)	152.0 (88.6-337.2)
WA% third, %	58.9 (4.8)	58.4 (5.1)	59.5 (4.5)
WA% fourth, %	61.8 (5.5)	61.7 (5.6)	61.9 (5.3)
AFD	1.75 (0.05)	1.75 (0.05)	1.75 (0.05)
ALR	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)

Abbreviations: AFD, airway fractal dimension; ALR, airway-to-lung size ratio; BMI, body mass index; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; OCS, oral corticosteroid; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; WA%, wall area percent.
NOTE. Values indicate the mean (SD), median (IQR), or n (%);

CI] = −1.54 [−2.87 to −0.21], P = .02). A lower PM density was also associated with a lower AFD and greater WA% in the fourth generation of female patients with asthma (AFD: estimate [95% CI] = 0.01 [0.001- 0.02], P = .03; WA%: estimate [95% CI] = −1.30 [−2.49 to −0.11], P = .03). Furthermore, the associations of ESM density with WA% in the fourth-generation airways and AFD and of PM density with AFD remained significant even in the multivariable models, including only female patients with asthma without oral corticosteroid or biologics treatment (eFigure 3).

Comparison of Airway Computed Tomography Parameters in Patients With Asthma Stratified by the Lower Limit of Normal of Pectoralis or Erector Spinae Muscle Density

As illustrated in eFigure 4, the LLN of PM and ESM density was determined using the data of controls (LLN of PM density, 31.7 HU and 21.0 HU for male and female patients; LLN of ESM density, 35.2 HU and 28.4 HU for male and female patients). In eFigure 5, when patients with asthma were divided into those with low ESM (or PM) density and those with high ESM (or PM) density on the basis of the LLN for ESM (or PM) density, PM and ESM density below the LLN were associated with higher WA% in the fourth generation airway and lower AFD in female patients with asthma but not in male patients with asthma.

Discussion

This study found that the PM and ESM density were lower in female patients with asthma who were 60 years old and younger than in healthy controls who were between 40 and 60 years old, even after adjusting for BMI. Moreover, a lower density of both PM and ESM was associated with a greater WA% in the fourth-generation

Table 3
Correlation Coefficients Between the Skeletal Muscle Density, Adipose Tissue Areas, and Airway Structure on Computed Tomography in All Patients With Asthma and Controls

Variables	WA% (third)		WA% (fourth)		ALR		AFD	
	Control	Asthma	Control	Asthma	Control	Asthma	Control	Asthma
Male sex								
PM density	−0.09	−0.12	−0.18	−0.09	−0.09	−0.01	0.16	0.06
ESM density	−0.12	−0.01	−0.26	−0.17	0.12	−0.02	0.18	0.25[a]
SAT area	0.19	0.01	0.07	−0.01	0.09	0.10	−0.05	−0.08
EAT area	0.06	−0.05	0.22	0.00	0.08	0.11	−0.02	−0.10
Female sex								
PM density	−0.13	−0.21[a]	−0.07	−0.30[b]	0.16	0.16	0.19	0.37[c]
ESM density	−0.07	−0.16	0.15	−0.23[a]	0.01	0.04	−0.13	0.23[a]
SAT area	0.29	0.04	0.37[a]	0.10	−0.27	−0.10	−0.16	−0.24[a]
EAT area	0.35[a]	0.05	0.30	0.22[a]	−0.26	0.01	0.02	−0.34[c]

Abbreviations: AFD, airway fractal dimension; ALR, airway-to-lung size ratio; EAT, epicardial adipose tissue; ESM, erector spinae muscle; PM, pectoralis muscle; SAT, subcutaneous adipose tissue; WA%, wall area percent.
NOTE. The data are expressed as Pearson correlation coefficients, and their significance is indicated as follows:
[a]P < .05.
[b]P < .01
[c]P < .001.

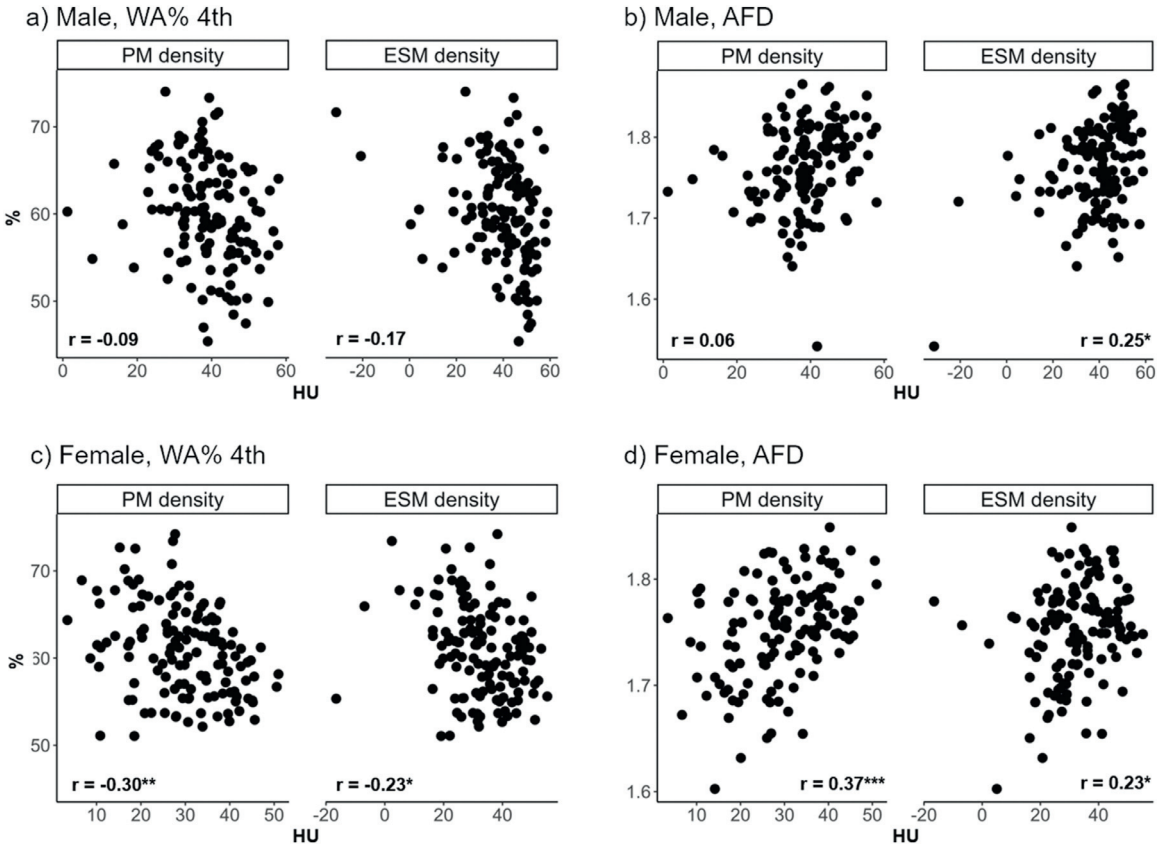

Figure 4. Scatterplots for skeletal muscle density and WA% in the subsegmental airway or AFD in male and female patients with asthma. a) and b) Associations between PM and ESM density and WA% in the fourth generation and AFD in male patients are illustrated as a scatter plot. c) and d) The associations in female patients are illustrated. Pearson's correlation coefficient is depicted in each graph, and its significance is illustrated as follows: $^{*}P < .05$. $^{**}P < .01$, $^{***}P < .001$. AFD, airway fractal dimension; ESM, erector spinae muscle; PM, pectoralis muscle; WA%, wall area percent.

airways and a lower AFD in female patients with asthma after adjustments for BMI and other potential confounding factors, whereas such associations were not found in female controls. To the best of our knowledge, this is the first study to report the associations of skeletal muscle density with wall thickening of the central airways and less complexity of the airway lumen tree in female patients with asthma.

The associations of lower ESM and PM density with a greater WA% in the fourth-generation airways independent of BMI were found in female patients. These data extend the previous finding that a lower density of paraspinal muscles (which was equal to ESM in this study) was associated with a subsequent greater decline in forced expiratory volume in 1 second independent of BMI and worse peripheral airway resistance and reactance measured with airway oscillometry in female patients with asthma.[8,26] A lower CT density of skeletal muscles is associated with intramuscular fat and insulin resistance, which potentially impairs lung function and disease control in patients with asthma.[7,9] Medications that improve insulin resistance, such as metformin, sulfonylureas, and glucagon-like peptide-1

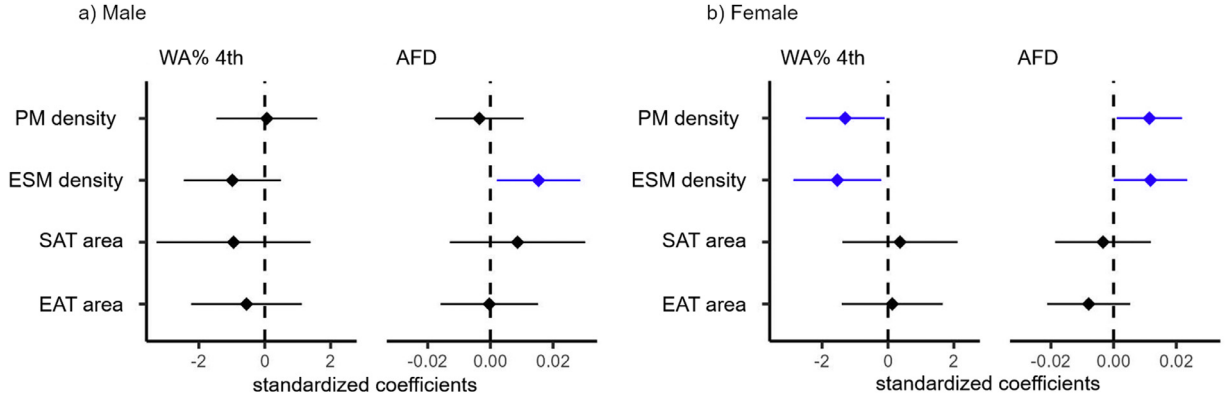

Figure 5. Multivariable models for the relative associations of skeletal muscle density and adipose tissue area with WA% in the subsegmental airways or AFD in patients with asthma. Multivariable models that included each CT parameter, age, height, body mass index, smoking status, blood eosinophil count, and oral corticosteroid use were used as independent variables. a) and b) indicate the models for male and female patients, respectively. The diamonds and lines indicate the standardized coefficients and 95% CIs, respectively, for each CT parameter. AFD, airway fractal dimension; CT, computed tomography; EAT, epicardial adipose tissue; ESM, erector spinae muscle; PM, pectoralis muscle; SAT, subcutaneous adipose tissue; WA%, wall area percent.

receptor agonists, may reduce the symptomatic burden and risk of exacerbations.[6,27,28] Moreover, an increase in serum insulin levels may cause collagen deposition and smooth muscle proliferation in the airways in murine models.[29] Taken together, our data lead to the novel hypothesis that intramuscular fat detected as lower ESM and PM density may induce wall remodeling of the central airways by means of insulin-related pathways in female patients with asthma. Because of the lower prevalence of diabetes in female than male patients with asthma in this study, we further speculate that improvements in intramuscular fat and insulin resistance might be a therapeutic target for female patients with asthma even without a clinical diagnosis of diabetes.

A lower PM and ESM density was associated with a lower AFD in female patients with asthma independent of BMI in this study. A lower AFD can reflect the pruning of airway branches, which is possibly because of mucus plugging and luminal narrowing, in patients with asthma[30] and chronic obstructive pulmonary disease.[24] Moreover, WA% in the segmental airways is associated with peripheral airway resistance and reactance on airway oscillometry in patients with asthma.[31] Together with the observed association between lower ESM density and higher WA%, we speculate that the increase in intramuscular fat may induce greater wall thickening of the relatively peripheral airways that can reduce luminal narrowing and decrease the complexity of the airway tree structure in female patients with asthma. Although WA% in the fifth or more peripheral airways was not measured because of the limited resolution of the conventional CT scanner in this study, whether the low PM and ESM density would be associated with the fifth and sixth generation airways more closely than with the third and fourth generations in female patients with asthma should be investigated in future studies using ultrahigh-resolution CT.[32,33]

The area of EAT, which represents visceral fat, was greater in female patients with asthma than in female controls independent of BMI. However, the EAT area was not associated with the WA% or AFD in female patients with asthma after adjusting for BMI and other confounding factors. The adipose tissue in visceral fat causes low-grade systemic inflammation.[10] In patients with asthma, visceral fat impairs quality of life and lung function[34] and enhances airway hyperresponsiveness through leptin overexpression.[35] Moreover, a previous study reported that visceral fat was associated with WA% on CT in patients with asthma who were infected with HIV; however, it did not assess the relative associations of visceral fat and BMI with WA%.[36] The lack of associations of EAT with WA% or AFD after adjusting for BMI in this study extends those findings, suggesting that visceral fat does not have additional impacts on airway structure over BMI in patients with asthma.

In the multivariable models adjusted for BMI, significant differences in the density of ESM and PM and areas of EAT between controls and patients with asthma were observed in female patients but not in male patients. These findings confirm and extend a previous report on the lower ESM in female patients with asthma.[8] Obesity is more problematic in female patients with severe asthma.[1,2,37] The airway lumen is narrower in female than male individuals, even among healthy ones.[23] Therefore, we speculate that the impact of intramuscular fat on airway morphology may be greater in female than in male patients with asthma.

This study has clinical implications. The ESM and PM density and the SAT and EAT area can be quantified when chest CT is available. Because chest CT is performed in clinical practice for various reasons, including lung cancer screening, consideration of treatment with biologics for severe asthma, and differential diagnosis of cough and dyspnea, the use of these CT parameters may contribute to a more personalized understanding of the underlying pathophysiology and therapeutic management in patients with asthma. However, there were several limitations regarding this study. First, the retrospective nature of the study may have generated selection bias in the choice of patients with asthma who underwent CT imaging. However, we believe that the consecutive enrolment of nearly 200 patients with asthma in comparison with healthy controls should increase the validity of the findings. Second, a causal relationship between intramuscular fat and airway structure cannot be established because of the cross-sectional nature of the study. Third, because of radiation exposure, it is difficult to perform serial CT assessments, especially in younger patients with asthma. There is a need to evaluate the potential of alternative methods such as bioelectrical impedance analysis and airway oscillometry for assessing intramuscular fat and airway remodeling in patients with asthma.

In conclusion, this study revealed that lower skeletal muscle density is a feature of female patients with asthma and is associated with central airway remodeling and less complexity of the airway lumen tree structure (independent of BMI). These findings increase the understanding of airway-extrapulmonary organ interactions in asthma and may contribute to more personalized management of patients with uncontrolled asthma associated with metabolic disorders.

Supplementary Data

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.anai.2024.08.016.

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Disclosures

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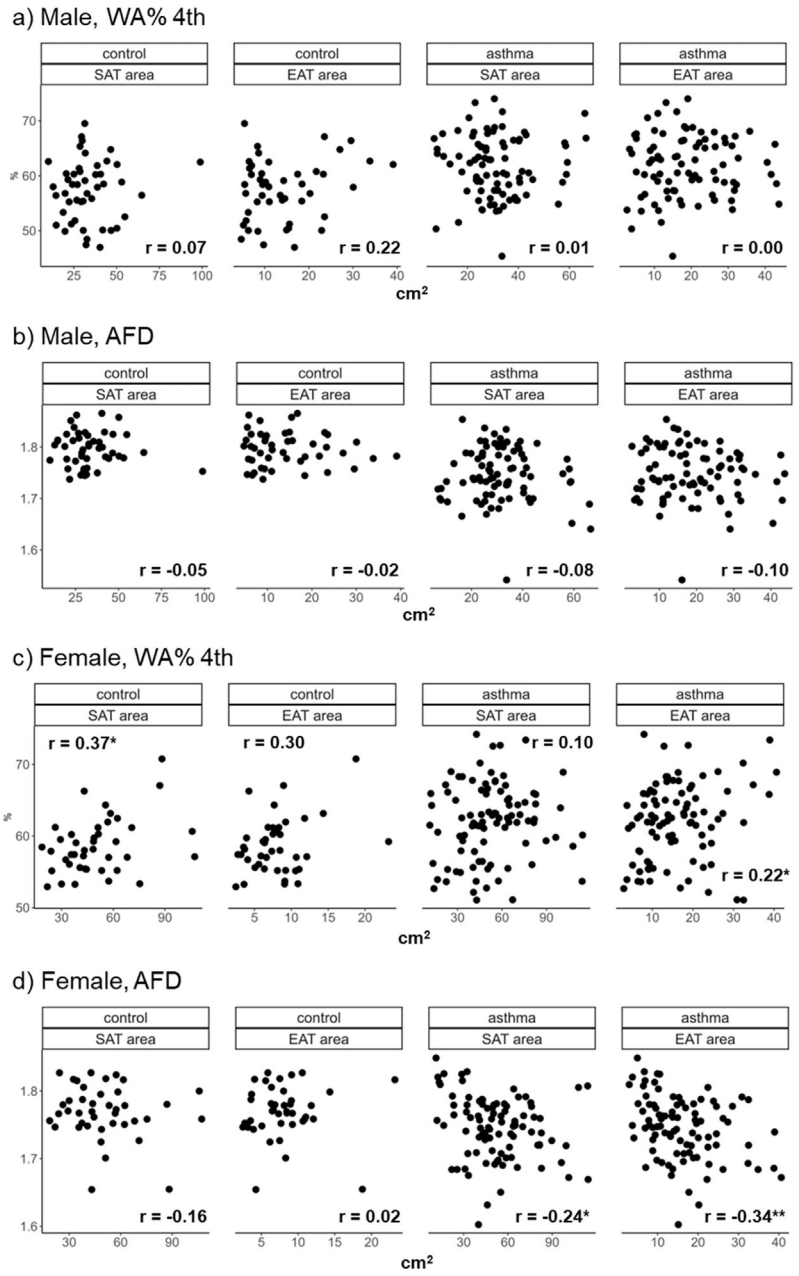
References

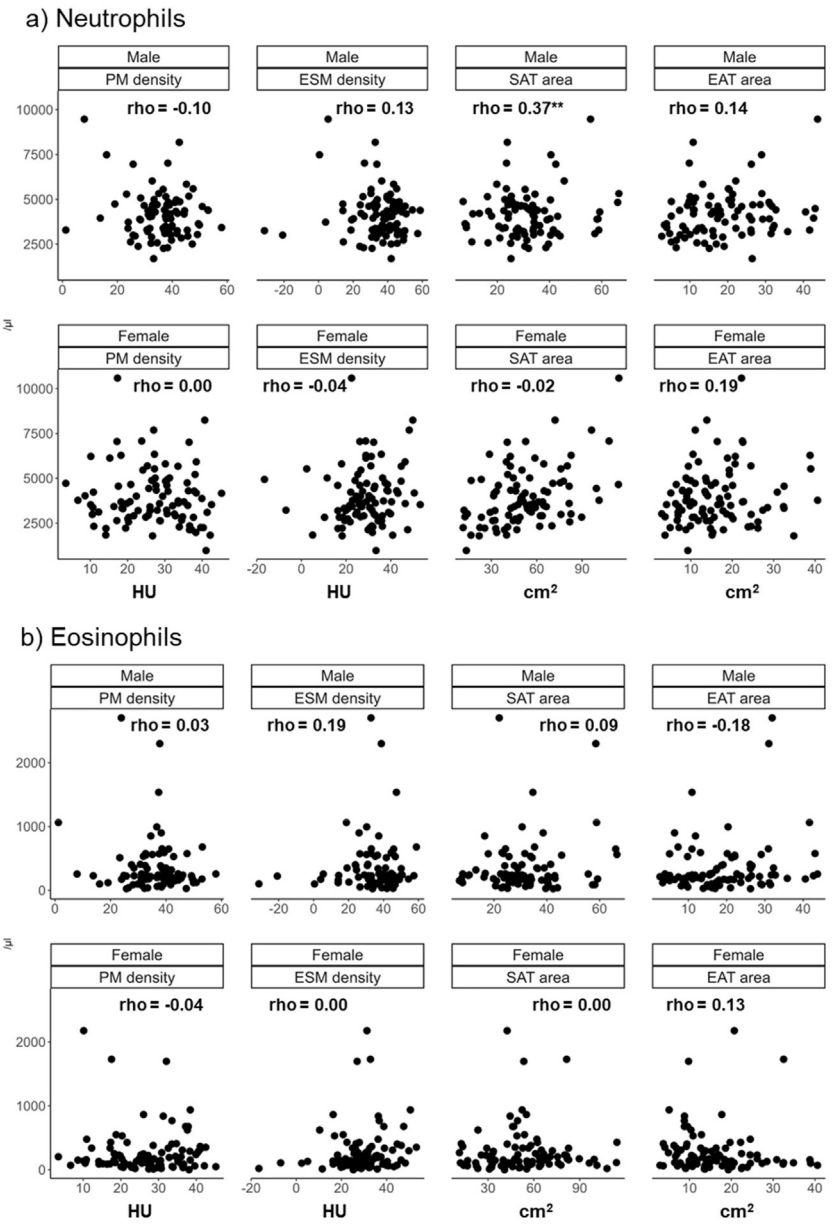
1. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178(3):218–224.
2. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010;181(4):315–323.
3. Barros R, Moreira P, Padrao P, Teixeira VH, Carvalho P, Delgado L, et al. Obesity increases the prevalence and the incidence of asthma and worsens asthma severity. *Clin Nutr*. 2017;36(4):1068–1074.
4. Tay TR, Radhakrishna N, Hore-Lacy F, Smith C, Hoy R, Dabscheck E, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. *Respirology*. 2016;21(8):1384–1390.
5. Elliot JG, Donovan GM, Wang KCW, Green FHY, James AL, Noble PB. Fatty airways: implications for obstructive disease. *Eur Respir J*. 2019;54(6): 1900857.
6. Foer D, Beeler PE, Cui J, Karlson EW, Bates DW, Cahill KN. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like Peptide-1 receptor agonists. *Am J Respir Crit Care Med*. 2021;203(7):831–840.
7. Wu TD, Brigham EP, Keet CA, Brown TT, Hansel NN, McCormack MC. Association between prediabetes/diabetes and asthma exacerbations in a claims-based obese asthma cohort. *J Allergy Clin Immunol Pract*. 2019;7(6):1868–1873.e5.
8. Tattersall MC, Lee KE, Tsuchiya N, Osman F, Korcarz CE, Hansen KM, et al. Skeletal muscle adiposity and lung function trajectory in the severe asthma research program. *Am J Respir Crit Care Med*. 2023;207(4):475–484.

9. Peters MC, Schiebler ML, Cardet JC, Johansson MW, Sorkness R, DeBoer MD, et al. The impact of insulin resistance on loss of lung function and response to treatment in asthma. *Am J Respir Crit Care Med*. 2022;206(9):1096–1106.
10. González-Muniesa P, Mártinez-González MA, Hu FB, Després JP, Matsuzawa Y, Loos RJF, et al. Obesity. *Nat Rev Dis Primers*. 2017;3:17034.
11. Correa-de-Araujo R, Addison O, Miljkovic I, Goodpaster BH, Bergman BC, Clark RV, et al. Myosteatosis in the context of skeletal muscle function deficit: an interdisciplinary workshop at the National Institute on Aging. *Front Physiol*. 2020;11:963.
12. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *J Appl Physiol (1985)*. 2000;89(1):104–110.
13. Miljkovic I, Vella CA, Allison M. Computed tomography-derived Myosteatosis and metabolic disorders. *Diabetes Metab J*. 2021;45(4):482–491.
14. Global Initiative for Asthma. Global strategy for asthma management and prevention. Accessed May 13, 2024. Available at: https://ginasthma.org/.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338.
16. Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. *Respir Investig*. 2014;52(4):242–250.
17. Maetani T, Tanabe N, Shiraishi Y, Shimada T, Terada S, Shima H, et al. Centrilobular emphysema is associated with pectoralis muscle reduction in current smokers without airflow limitation. *Respiration*. 2023;102(3):194–202.
18. Tanimura K, Sato S, Fuseya Y, Hasegawa K, Uemasu K, Sato A, et al. Quantitative assessment of erector spinae muscles in patients with chronic obstructive pulmonary disease. Novel chest computed tomography-derived index for prognosis. *Ann Am Thorac Soc*.. 2016;13(3):334–341.
19. McDonald ML, Diaz AA, Ross JC, Estepar RSJ, Zhou L, Regan EA, et al. Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. A cross-sectional study. *Ann Am Thorac Soc*. 2014;11(3):326–334.
20. Pishgar F, Shabani M, Quinaglia ACST, Bluemke DA, Budoff M, Barr RG, et al. Quantitative analysis of adipose depots by using chest CT and associations with all-cause mortality in chronic obstructive pulmonary disease: longitudinal analysis from MESArthritis ancillary study. *Radiology*. 2021;299(3):703–711.
21. Oyama N, Goto D, Ito YM, Ishimori N, Mimura R, Furumoto T, et al. Single-slice epicardial fat area measurement: do we need to measure the total epicardial fat volume? *Jpn J Radiol*. 2011;29(2):104–109.
22. Maetani T, Tanabe N, Terada S, Shiraishi Y, Shima H, Kaji S, et al. Physiological impacts of computed tomography airway dysanapsis, fractal dimension, and branch count in asymptomatic never smokers. *J Appl Physiol (1985)*. 2023;134(1):20–27.
23. Terada S, Tanabe N, Maetani T, Shiraishi Y, Sakamoto R, Shima H, et al. Association of age with computed tomography airway tree morphology in male and female never smokers without lung disease history. *Respir Med*. 2023;214: 107278.
24. Bodduluri S, Puliyakote ASK, Gerard SE, Reinhardt JM, Hoffman EA, Newell Jr JD, et al. Airway fractal dimension predicts respiratory morbidity and mortality in COPD. *J Clin Invest*. 2018;128(12):5374–5382.
25. Tanabe N, Sato S, Suki B, Hirai T. Fractal analysis of lung structure in chronic obstructive pulmonary disease. *Front Physiol*. 2020;11: 603197.
26. Chan R, Duraikannu C, Thouseef MJ, Lipworth B. Lower paraspinal muscle density is associated with small airway dysfunction in women with persistent asthma. *Ann Allergy Asthma Immunol*. 2024;132(6):767–768.
27. Li CY, Erickson SR, Wu CH. Metformin use and asthma outcomes among patients with concurrent asthma and diabetes. *Respirology*. 2016;21(7):1210–1218.
28. Wu TD, Keet CA, Fawzy A, Segal JB, Brigham EP, McCormack MC. Association of metformin initiation and risk of asthma exacerbation. A claims-based cohort study. *Ann Am Thorac Soc*. 16. 201920192019:1527–1533.
29. Singh S, Bodas M, Bhatraju NK, Pattnaik B, Gheware A, Parameswaran PK, et al. Hyperinsulinemia adversely affects lung structure and function. *Am J Physiol Lung Cell Mol Physiol*. 2016;310(9):L837–L845.
30. Boser SR, Park H, Perry SF, Ménache MG, Green FH. Fractal geometry of airway remodeling in human asthma. *Am J Respir Crit Care Med*. 2005;172(7):817–823.
31. Chan R, Duraikannu C, Thouseef MJ, Lipworth B. Impaired respiratory system resistance and reactance are associated with bronchial wall thickening in persistent asthma. *J Allergy Clin Immunol Pract*. 2023;11(5):1459–1462.e3.
32. Tanabe N, Oguma T, Sato S, Kubo T, Kozawa S, Shima H, et al. Quantitative measurement of airway dimensions using ultra-high resolution computed tomography. *Respir Investig*. 2018;56(6):489–496.
33. Hayashi Y, Tanabe N, Matsumoto H, Shimizu K, Sakamoto R, Oguma T, et al. Associations of fractional exhaled nitric oxide with airway dimension and mucus plugs on ultra-high-resolution computed tomography in former smokers and non-smokers with asthma. *Allergol Int*. 2024;73(3):397–405.
34. Goudarzi H, Konno S, Kimura H, Makita H, Matsumoto M, Takei N, et al. Impact of abdominal visceral adiposity on adult asthma symptoms. *J Allergy Clin Immunol Pract*. 2019;7(4):1222–1229.e5.
35. Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, et al. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med*. 2012;186(7):598–605.
36. Barton JH, Ireland A, Fitzpatrick M, Kessinger C, Camp D, Weinman R, et al. Adiposity influences airway wall thickness and the asthma phenotype of HIV-associated obstructive lung disease: a cross-sectional study. *BMC Pulm Med*. 2016;16(1):111.
37. Loewenthal L, Busby J, McDowell R, Brown T, Burhan H, Chaudhuri R, et al. Impact of sex on severe asthma: a cross-sectional retrospective analysis of UK primary and specialist care. *Thorax*. 2024;79(5):403–411.

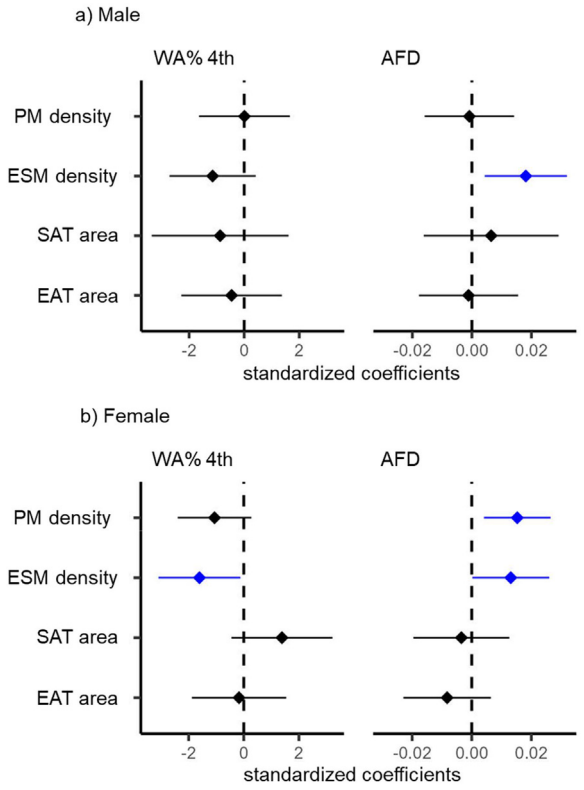
Supplementary Data



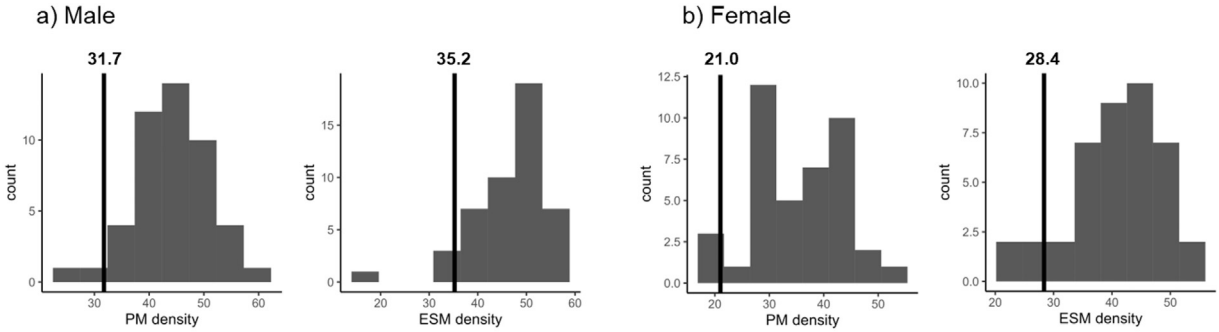
eFigure 1. Scatterplots for SAT and EAT area and WA% in the subsegmental airway or AFD stratified by sex in control subjects and patients with asthma. a) and b) The associations between the SAT and EAT area and WA% in the fourth generation and AFD in male patients are illustrated as a scatterplot. c) and d) The associations in female patients are illustrated. Pearson's correlation coefficient is depicted in each graph, and its significance is illustrated as follows: $^{*}P < .05$, $^{**}P < .01$. AFD, airway fractal dimension; EAT, epicardial adipose tissue; SAT, subcutaneous adipose tissue; WA%, wall area percent.



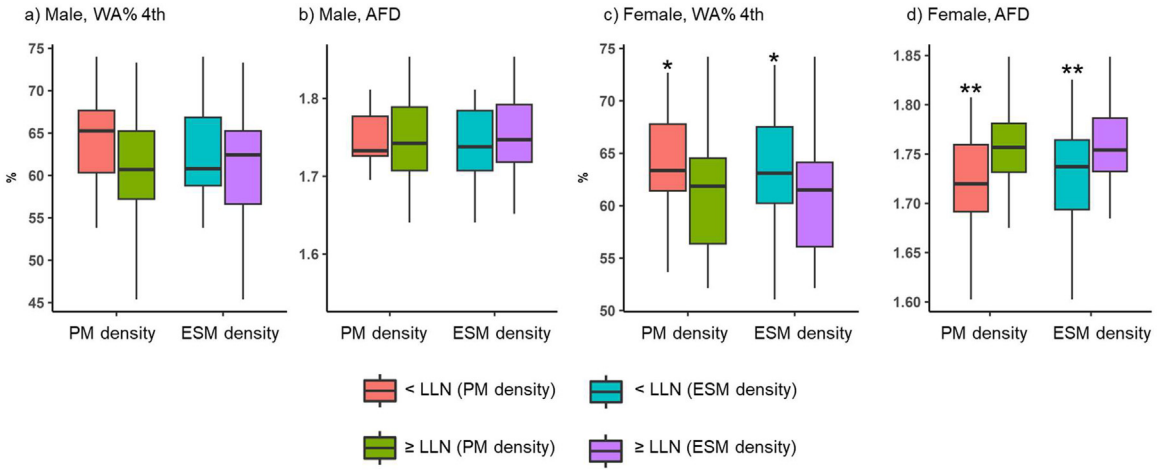
eFigure 2. Scatterplots for PM and ESM density, SAT and EAT area, and blood neutrophil count and eosinophil count stratified by sex in patients with asthma. a) The associations of PM and ESM density, SAT and EAT area with blood neutrophil count are illustrated as a scatterplot. b) The associations with blood eosinophil count are illustrated. Spearman's correlation coefficient is depicted in each graph, and its significance is illustrated as follows: $^{**}P < .01$. EAT, epicardial adipose tissue; ESM, erector spinae muscle; PM, pectoralis muscle; SAT, subcutaneous adipose tissue.



eFigure 3. Sensitivity analysis: multivariable models for the relative associations of fat-related CT metrics with WA% in the subsegmental airways or AFD in patients with asthma without oral corticosteroid and biologic use. Multivariate models that included each CT parameter, age, height, body mass index, smoking status, and blood eosinophil count were used as independent variables. a) and b) indicate the models for male and female patients, respectively. The diamonds and lines indicate the standardized coefficients and 95% CIs, respectively, for each CT parameter. AFD, airway fractal dimension; CT, computed tomography; EAT, epicardial adipose tissue; ESM, erector spinae muscle; PM, pectoralis muscle; SAT, subcutaneous adipose tissue; WA%, wall area percent.



eFigure 4. Histograms of PM and ESM density in male and female controls. a) and b) indicate data for male and female patients, respectively. The vertical lines on the *x*-axis indicate the lower limit of normal calculated as the mean −1.645 SD. ESM, erector spinae muscle; PM, pectoralis muscle.



eFigure 5. Comparisons of PM and ESM density and WA% in the fourth generation or AFD between below and above LLN in patients with asthma stratified by sex. Using the LLN values calculated from male and female controls, respectively, we divided the patients with asthma into 2 groups for each sex. a) WA% for the fourth generation airways and b) AFD were compared in male patients. c) WA% for the fourth generation airways and d) AFD were compared in female patients. $^{*}P < .05$, $^{**}P < .01$. AFD, airway fractal dimension; ESM, erector spinae muscle; LLN, lower limit of normal; PM, pectoralis muscle; WA%, wall area percent.

eTable 1
Multivariable Models Adjusted by BMI for Associations of PM and ESM Density and SAT and EAT Area in Controls and Patients With Asthma Stratified by Sex

Variables	PM density	ESM density	SAT area	EAT area
Male				
Asthma	−0.51 (−1.12 to 0.11)	−0.49 (−1.14 to 0.17)	0.06 (−0.47 to 0.59)	−0.16 (−0.69 to 0.36)
BMI	−0.26 (−0.52 to −0.003)[a]	−0.02 (−0.29 to 0.25)	0.59 (0.37-0.82)[b]	0.64 (0.42-0.86)[b]
Female				
Asthma	−0.48 (−0.89 to −0.07)[a]	−0.61 (−1.09 to −0.13)[a]	0.24 (−0.06 to 0.55)	0.71 (0.29-1.11)[b]
BMI	−0.49 (−0.69 to −0.29)[b]	−0.16 (−0.39 to 0.08)	0.76 (0.61-0.91)[b]	0.41 (0.21-0.61)[b]

Abbreviations: BMI, body mass index; EAT, epicardial adipose tissue; ESM, erector spinae muscle; PM, pectoralis muscle; SAT, subcutaneous adipose tissue.
NOTE. Each model included disease (asthma vs control) and BMI as independent variables. Values indicate the standardized estimate (95% CI).
[a] $P < .05$.
[b] $P < .001$.