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Adiposity and Interstitial Lung Abnormalities in Community-Dwelling Adults

The MESA Cohort Study



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BACKGROUND: Obesity is associated with restrictive ventilatory defects and a faster rate of decline in FVC. This association is not exclusively mediated by mechanical factors and may reflect direct pulmonary injury by adipose-derived mediators.

RESEARCH QUESTION: Is adipose tissue involved in the pathogenesis of interstitial lung disease (ILD)?

STUDY DESIGN AND METHODS: We evaluated the association of CT measures of pericardial, abdominal visceral, and abdominal subcutaneous adipose tissue with high-attenuation areas (HAAs) and interstitial lung abnormalities (ILAs) in a large multicenter cohort study of community-dwelling adults, using multivariable-adjusted models. We secondarily evaluated the association of adipose depot size with FVC and biomarkers of obesity and inflammation.

RESULTS: In fully adjusted models, every doubling in pericardial adipose tissue volume was associated with a 63.4-unit increase in HAA (95% CI, 55.5-71.3), 20% increased odds of ILA (95% CI, -2% to 50%), and a 5.5% decrease in percent predicted FVC (95% CI, -6.8% to -4.3%). IL-6 levels accounted for 8% of the association between pericardial adipose tissue and HAA. Every doubling in visceral adipose tissue area was associated with a 41.5-unit increase in HAA (95% CI, 28.3-54.7), 30% increased odds of ILA (95% CI, -10% to 80%), and a 5.4% decrease in percent predicted FVC (95% CI, -6.6% to -4.3%). IL-6 and leptin accounted for 17% and 18%, respectively, of the association between visceral adipose tissue and HAA.

INTERPRETATION: Greater amounts of pericardial and abdominal visceral adipose tissue were associated with CT measures of early lung injury and lower FVC in a cohort of community-dwelling adults. Adipose tissue may represent a modifiable risk factor for ILD.

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KEY WORDS: high-attenuation areas; IL-6; interstitial lung abnormalities; interstitial lung disease; leptin; obesity

FOR EDITORIAL COMMENT, SEE PAGE 400

ABBREVIATIONS: CRP = C-reactive protein; HAA = high-attenuation area; HU = Hounsfield unit; ILA = interstitial lung abnormalities; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IQR = interquartile range; MCP-1 = monocyte chemoattractant protein-1; MESA = Multi-Ethnic Study of Atherosclerosis; PAT = pericardial adipose tissue volume; SAT = subcutaneous adipose tissue area; TNF- α = tumor necrosis factor α ; VAT = visceral adipose tissue area

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Take-home Points

Study Question: Is adipose tissue involved in the pathogenesis of interstitial lung disease?

Results: Greater amounts of pericardial and abdominal visceral adipose tissue were associated with increased high-attenuation areas and interstitial lung abnormalities, and decreased forced vital capacity in a large multi-center cohort of community-dwelling adults.

Interpretation: Adipose tissue may represent a modifiable risk factor for interstitial lung disease.

The prevalence of obesity is rapidly increasing in the United States and is expected to affect 40% of the population by 2030.¹ Obesity, particularly visceral obesity, is associated with restrictive ventilatory defects in older adults^{2,3} and a greater rate of decline in lung function in the general population.⁴ This does not appear to be exclusively mediated by mechanical factors⁵ and may reflect direct injury by circulating inflammatory cytokines or adipokines.⁶⁻⁹ A better understanding of the role of obesity in lung injury and early fibrosis may identify a novel target for the prevention and treatment of interstitial lung disease (ILD).

In states of obesity, adipocytes undergo hypertrophy to store excess fatty acids. Adipocyte hypertrophy results in recruitment of proinflammatory macrophages, and increased production of IL-6, leptin, and resistin.¹⁰⁻¹² All of these mediators have been shown to contribute to lung injury in animal models of pulmonary fibrosis.^{7,13-15} However, a direct link between adiposity and lung injury, remodeling, and

early fibrosis in humans has not been previously established.

Prior work evaluating the association between BMI and early parenchymal lung injury is inconsistent. Greater BMI may be associated with increased high-attenuation areas,¹⁶ but there is no consistent association between BMI and interstitial lung abnormalities.¹⁷ BMI is a poor measure of adiposity.¹⁸ It varies significantly by sex and race/ethnicity¹⁹ and provides no insight into mechanistic links between obesity and early parenchymal lung injury. In contrast, CT scanning can measure adipose tissue depot size and has been used to establish mechanistic links between adiposity and other forms of lung injury.²⁰

We sought to determine whether adipose tissue depot size was associated with two CT measures of early lung injury and fibrosis, and FVC, in a large cohort of community-dwelling adults. We and others have previously used and validated both an automated, quantitative measure termed high-attenuation areas (HAAs) and a qualitative measure termed interstitial lung abnormalities (ILAs).^{16,21,22} Both measures have been used to identify novel risk factors for early ILD.^{14,16,17,21,22} Here, we hypothesized that greater amounts of pericardial, abdominal visceral, and abdominal subcutaneous adipose tissue would be associated with increased HAAs, greater odds of ILAs, and reduced FVC. We secondarily hypothesized that the association between adipose depots and both HAAs and ILAs would be partially mediated through circulating markers of obesity (leptin, adiponectin, resistin) and inflammation (IL-6, C-reactive protein [CRP], tumor necrosis factor [TNF]- α).

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Methods

Study Participants

The National Heart, Lung, and Blood Institute-funded Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing multicenter prospective cohort study that enrolled 6,814 adults between the ages of 45 and 84 years without clinically evident cardiovascular disease. Enrollment occurred between 2000 and 2002, with six subsequent follow-up examinations (e-Table 1). MESA and its ancillary studies were approved by individual site institutional review boards (e-Appendix 1). All participants provided informed consent.

Pericardial Adipose Tissue Volume

Our primary exposure was pericardial adipose tissue (PAT) volume measured by cardiac CT imaging performed at MESA examination 1 (e-Table 1) on electron beam tomography scanners at three sites (Imatron C-150; Imatron, Inc.) and multidetector CT imaging at three sites (Volume Zoom [Siemens] or GE LightSpeed [GE Healthcare]), using previously published techniques.^{16,23} PAT was defined as all tissue

with the density of adipose (−190 to −30 Hounsfield units [HU]), located between 15 mm above and 30 mm below the superior extent of the left coronary artery, bordered anteriorly by the chest wall, and posteriorly by the aorta and bronchus using volume analysis software (GE Healthcare). This limited region of PAT highly correlates with total volume of PAT ($r = 0.93$) with high intra- and interobserver reliability ($\kappa = 0.999$ and 0.997 , respectively).²³

Abdominal Adipose Tissue Area

Our secondary exposures were visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) cross-sectional areas. At examinations 2 and 3 (2002–2005; e-Table 1), a random subset of 1,947 participants underwent abdominal imaging for measures of aortic calcium, using the scanners noted above. Using previously described techniques to interrogate these scans,²⁴ abdominal adipose tissue cross-sectional area was measured at five locations between L2/L3 and L4/L5. Primary analyses were performed using areas at L4/L5, with sensitivity analyses performed at L3/L4.^{20,25} All tissue within the peritoneal cavity with the density of adipose tissue was identified as VAT. All tissue with the density of adipose and located outside of the peritoneal cavity but not within the muscle was identified as SAT. Using previously described methods, imputation was used to estimate missing SAT area on scans in which the subcutaneous tissue was incompletely imaged.²⁶ These imputed SAT measures were used in primary analyses. Sensitivity analyses were performed, including only subjects with completely imaged SAT.

Biomarkers

All biomarkers were measured in serum samples collected between 2004 and 2005 (examination 3, e-Table 1) and stored in a −80°C freezer. Inflammatory biomarkers (IL-6, TNF- α , CRP) were measured in fasting samples, using an ultrasensitive enzyme-linked immunosorbent assay for IL-6 (Quantikine HS human IL-6 immunoassay; R&D Systems), Bio-Rad Luminex flow cytometry for TNF- α (Millipore), and a particle-enhanced immune photometric assay (BNII nephelometer for CRP; Dade-Behring, Inc). Adipokines (adiponectin, leptin, resistin) were measured by Bio-Rad Luminex flow cytometry (Millipore) at the University of Vermont (Burlington, VT).

Measures of Parenchymal Lung Injury

We examined two validated CT phenotypes of early parenchymal lung injury and fibrosis: a quantitative phenotype (HAAs), and a qualitative phenotype (ILAs).^{16,22,27} HAA was measured as all voxels of lung tissue with attenuation values between −600 and −250 HU on examination 1 (cardiac CT imaging). This range captures ground-glass and reticular changes while excluding denser areas of consolidation, nodules, and vasculature.¹⁶ ILA was visually assessed on examination 5 (full lung CT imaging) by one of five trained radiologists and defined according to Fleischner Society guidelines as the presence of ground glass, reticular changes, emphysematous cysts, honeycombing, or traction bronchiectasis affecting > 5% of any lung zone in a nondependent fashion.^{16,27,28} Radiologists were blinded to measures of adiposity.

Results

Study Participants

A total of 6,814 subjects were enrolled in MESA and underwent cardiac CT imaging performed at examination 1. For 6,784 subjects, measures of both HAA and PAT were available (e-Fig 1). Forty-seven percent of the subjects were male, the median

Spirometry

At examinations 3 and 4 (2004–2007; e-Table 1), spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society guidelines.²⁹

Statistical Analysis

The distributions of adipose depot measures and serum biomarkers were right-skewed, and therefore they were \log_2 transformed. Changes in the outcome are reported per doubling of the predictor. The distribution of HAA was right-skewed; transformation to $-1/\text{HAA}^2$ for regression modeling purposes has been validated and is reported here as HAA.³⁰

We performed Spearman correlations between adipose tissue depot size and height, weight, and BMI to confirm validity. Given that nonlinear associations are often identified in studies of obesity,^{31,32} we tested for nonlinear relationships between predictors and outcomes using generalized additive models with the “gam” function in R with a *loess* smoothing function. Associations appeared to be linear, and therefore we used linear regression to examine the cross-sectional associations of adipose tissue depots with HAA and FVC. We used logistic regression to examine the associations of adipose depots with ILA. HAA models were adjusted for factors known to influence HAA measurement, including the following: study site, imaged lung volume, and radiation dose (milliamperes). We adjusted for potential confounders including age, sex, race/ethnicity, height, smoking status, cigarette pack-years, and percent emphysema (percent voxels with density less than 950 HU) in fully adjusted models.¹⁶ A priori subgroup analyses were performed by sex, age (< 65 or ≥ 65 years), BMI, race, and smoking status using Wald and likelihood ratio tests.

To account for mechanical effects of adiposity (ie, atelectasis), we performed sensitivity analyses that (1) included BMI in models of PAT, and (2) included both VAT and SAT in the same model for assessments of abdominal adipose depots. Given high correlations between these measures, their inclusion in the same model may result in bias, and these estimates should be interpreted with caution.

We assessed the association between biomarkers of obesity (leptin, resistin, adiponectin) and inflammation (IL-6, CRP, TNF- α) with PAT volume and VAT area using Spearman correlations. For biomarkers that were significantly associated with adipose measures, we estimated the proportion of the total association explained by each biomarker, using multilevel mediation analyses with the *ml_mediation* package in STATA (StataCorp) with covariates noted above clustered by study site.

All analyses were performed with STATA/IC version 15.1 (StataCorp), and R version 3.3.1 (R Foundation for Statistical Computing).

(interquartile range [IQR]) age was 62 (53–70) years, 39% were white, 22% were Hispanic, the median BMI was 27.6 kg/m² (IQR, 24.5–31.2), 50% were never smokers, 36% were former smokers, and median pack-years was 15 (IQR, 5–32) (e-Table 2). A total of 1,923 subjects underwent abdominal CT imaging at examination 2 or 3, with available measures of HAA (e-Fig 1). VAT measurement was available on all

TABLE 1] Baseline Characteristics by Tertile of Pericardial Adipose Tissue Volume^a

Characteristic	Lowest Tertile of PAT (n = 2,262)	Middle Tertile of PAT (n = 2,261)	Highest Tertile of PAT (n = 2,261)
Age, y	57 (51-67)	63 (54-70)	65 (57-72)
Sex (male)	762 (34)	986 (44)	1,444 (64)
Race			
White	794 (35)	803 (36)	1,018 (45)
Asian	268 (12)	320 (14)	209 (9)
Black	833 (37)	628 (28)	423 (19)
Hispanic	367 (16)	510 (23)	611 (27)
Weight, kg	60 (69-79)	76 (67-88)	87 (77-99)
Height, cm	164 (158-171)	165 (158-173)	169 (161-176)
BMI, kg/m ²	24.8 (22.5-28.0)	27.5 (25.5-30.8)	30.2 (27.4-34.0)
BMI category			
< 18.5	53 (2)	5 (0)	0 (0)
18.5-25.0	1,105 (49)	601 (27)	180 (8)
25.0-30.0	778 (34)	966 (43)	910 (40)
30-35	233 (10)	468 (21)	723 (32)
> 35	93 (4)	221 (10)	448 (20)
Smoking status			
Never smoker	1,239 (55)	1,181 (52)	981 (43)
Former smoker	700 (31)	780 (35)	995 (44)
Current smoker	316 (14)	292 (13)	278 (12)
Pack-years	12 (3-25)	15 (5-31)	20 (6-38)
PAT volume, cm ³	42 (34-49)	71 (64-79)	115 (100-142)
VAT area, cm ²	91 (65-117)	133 (105-172)	198 (154-245)
SAT area, cm ²	217 (145-283)	239 (172-320)	253 (200-336)

Continuous variables are reported as median (interquartile range); categorical variables are reported as No. (%). PAT = pericardial adipose tissue; SAT = abdominal subcutaneous adipose tissue; VAT = abdominal visceral adipose tissue.

^aMissing values: Smoking status on 22 subjects, and cigarette pack-years on 94 subjects.

abdominal scans, and SAT was completely imaged on 1,388 (86%) scans and imputed on 234 scans (14%). Subjects in the lowest tertile of PAT were less likely to be male or white, had lower weight and BMI, and lower rates of smoking (Table 1). Median PAT, VAT, and SAT values for the PAT cohort were 71 cm³ (IQR, 49-100), 137 cm² (IQR, 97-193), and 236 cm² (IQR, 170-310), respectively, and were similar among subjects with available ILA and FVC (e-Table 2). Subjects with available measures of abdominal VAT, ILA, and FVC appeared similar to the full cohort on baseline characteristics (e-Table 2).

PAT was strongly correlated with abdominal VAT ($\rho = 0.67$), moderately correlated with BMI ($\rho = 0.51$) and weight ($\rho = 0.49$), and weakly correlated with abdominal SAT ($\rho = 0.20$) and height ($\rho = 0.17$) (e-Table 3). Abdominal VAT was moderately correlated with BMI ($\rho = 0.61$) and weight ($\rho =$

0.54), and weakly correlated with abdominal SAT ($\rho = 0.33$). Abdominal SAT was strongly correlated with BMI ($\rho = 0.73$) and moderately correlated with height ($\rho = 0.46$).

High-Attenuation Areas

Every doubling in PAT volume was associated with 63.4-unit higher HAA (fully adjusted 95% CI, 55.5-71.3; $P < .001$) (Table 2, Fig 1A), and every doubling in abdominal VAT area was associated with 41.5-unit higher HAA (fully adjusted 95% CI, 28.3-54.7; $P < .001$) (Fig 1D). Abdominal SAT area was not associated with HAA in base models (9.3 units; 95% CI, -9.4 to 28.1; $P = .33$) (e-Fig 2A) but was associated with HAA in fully adjusted models (56.1 units; 95% CI, 38.8-73.5; $P < .001$).

Results were similar in sensitivity analyses adjusting for BMI and total adiposity (Table 2), among subjects with completely imaged abdominal SAT (e-Table 4), and

TABLE 2] Associations of Adipose Tissue Depots With High-Attenuation Areas, Interstitial Lung Abnormalities, and FVC

Model	No.	Change in HAA per Doubling PAT Volume	95% CI	<i>P</i> Value	No.	Odds of ILA per Doubling PAT Volume	95% CI	<i>P</i> Value	No.	Change in FVC per Doubling PAT Volume	95% CI	<i>P</i> Value
PAT												
Model 1 ^a	6,784	82.0	73.4 to 90.5	< .001	2,423	1.4	1.2 to 1.6	< .001	1,415	-4.1	-5.2 to -2.9	< .001
Model 2 ^b	6,690	63.4	55.5 to 71.3	< .001	2,394	1.2	0.98 to 1.5	.07	1,400	-5.5	-6.8 to -4.3	< .001
Model 3 ^c	6,690	19.6	10.6 to 28.7	< .001	2,394	1.3	1.01 to 1.6	.04	1,400	-4.3	-5.8 to -2.7	< .001
	No.	Change in HAA per Doubling VAT Area	95% CI	<i>P</i> Value	No.	Odds of ILA per Doubling VAT Area	95% CI	<i>P</i> Value	No.	Change in FVC per Doubling VAT Area	95% CI	<i>P</i> Value
VAT												
Model 1 ^a	1,923	57.4	42.6 to 77.1	< .001	861	1.4	1.03 to 1.9	.03	1,419	-4.1	-5.2 to -3.0	< .001
Model 2 ^b	1,838	41.5	28.3 to 54.7	< .001	844	1.3	0.9 to 1.8	.21	1,404	-5.4	-6.6 to -4.3	< .001
Model 3 ^c	1,562	22.1	5.2 to 38.9	.01	726	1.4	0.9 to 2.1	.16	1,229	-4.0	-5.5 to -2.6	< .001
	No.	Change in HAA per Doubling SAT Area	95% CI	<i>P</i> Value	No.	Odds of ILA per Doubling SAT Area	95% CI	<i>P</i> Value	No.	Change in FVC per Doubling SAT Area	95% CI	<i>P</i> Value
SAT												
Model 1 ^a	1,622	9.3	-9.4 to 28.1	.33	740	1.1	0.8 to 1.5	.73	1,241	-5.0	-6.3 to -3.8	< .001
Model 2 ^b	1,605	56.1	38.8 to 73.5	< .001	726	1.0	0.7 to 1.5	.96	1,229	-5.3	-6.7 to -3.9	< .001
Model 3 ^c	1,562	41.2	21.5 to 61.0	< .001	726	0.8	0.5 to 1.4	.49	1,229	-2.6	-4.3 to -0.9	.002

HAA = high-attenuation areas operationalized as (-1/percent HAA²); ILA = interstitial lung abnormalities; PAT = pericardial adipose tissue; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.

^aModel 1: HAA analyses adjusted for study site, imaged lung volume, and radiation dose; ILA and FVC analyses are unadjusted.

^bModel 2: Model 1 + age at examination 1, sex, race, height, smoking status, percent emphysema, cigarette pack-years, and study site.

^cModel 3: Model 2 + BMI (in PAT models), SAT (in VAT models), or VAT (in SAT models).

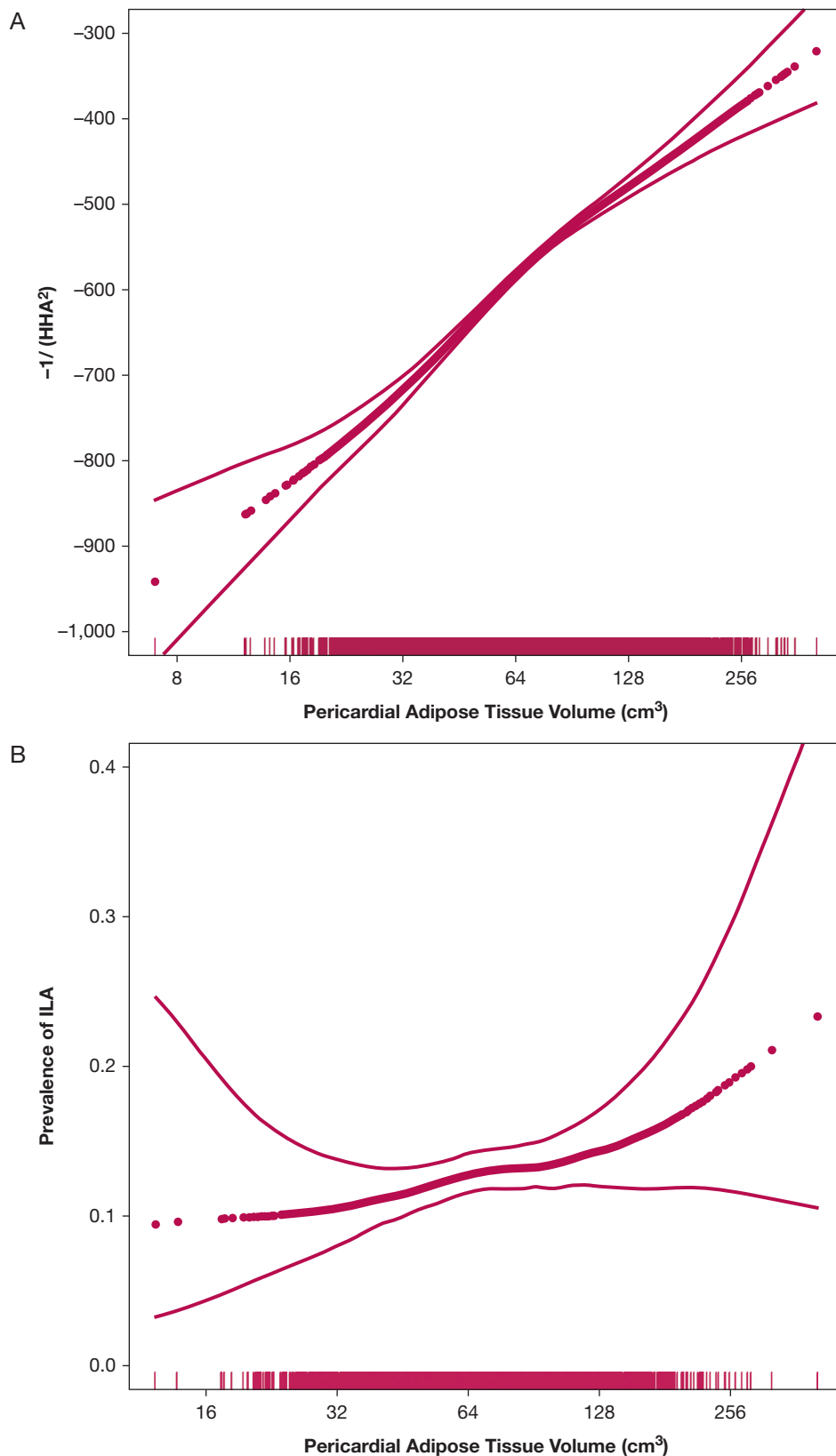


Figure 1 – Associations between pericardial adipose tissue volume and (A) high-attenuation areas (P for association, $<.001$; P for nonlinearity, $.02$), (B) interstitial lung abnormalities (P for association, $<.001$; P for nonlinearity, $.43$), and (C) FVC (P for association, $<.001$; P for nonlinearity, $.02$). Association between abdominal visceral adipose tissue area and (D) high-attenuation areas (P for association, $.002$; P for nonlinearity, $.13$), (E) interstitial lung abnormalities (P for association, $.04$; P for nonlinearity, $.15$), and (F) FVC (P for association, $.001$; P for nonlinearity, $.001$). Models are adjusted for age, sex, and smoking status. Thick dotted black line represents the effect estimates. Surrounding thin lines represent 95% CIs. Vertical lines along the x axis each represent a single study subject.

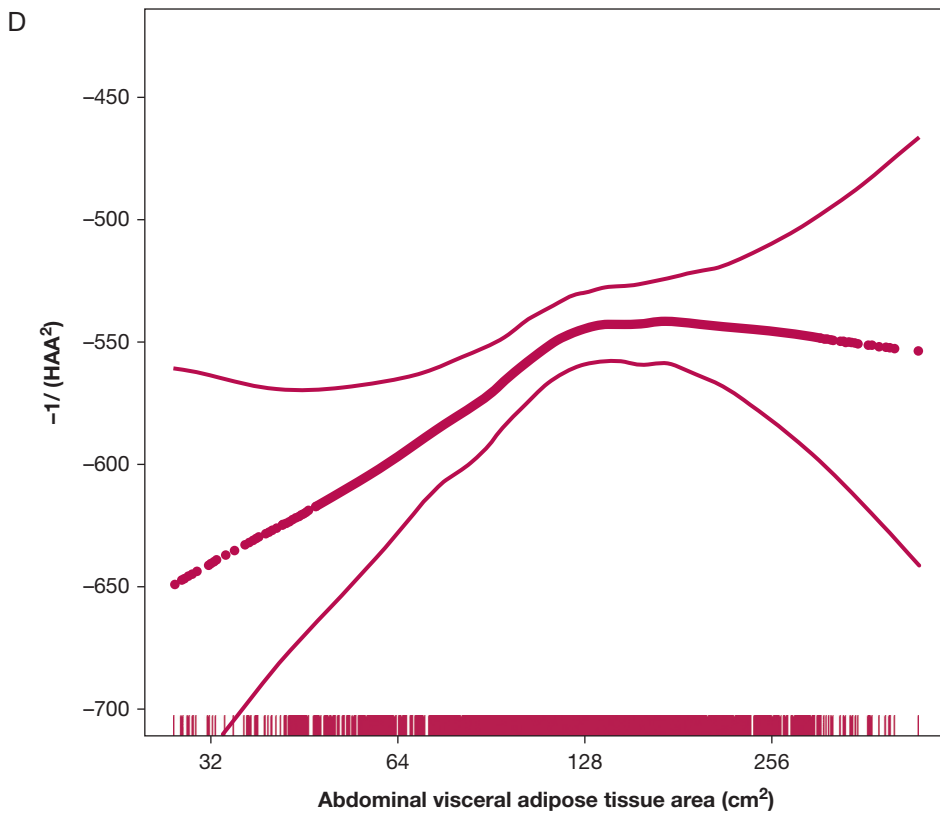
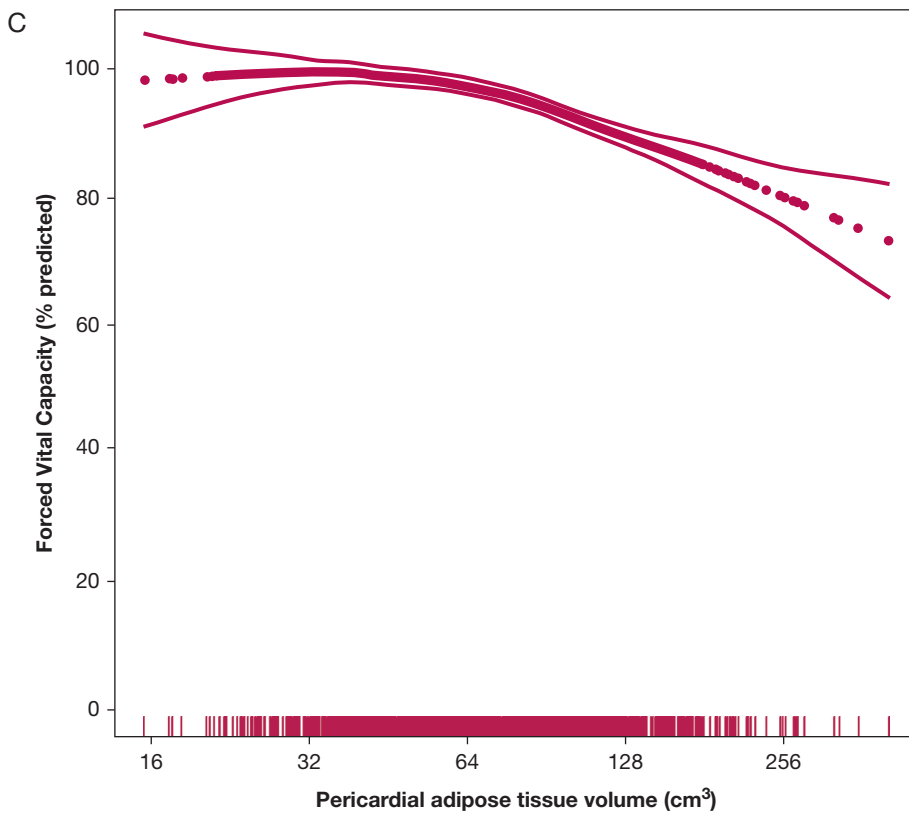
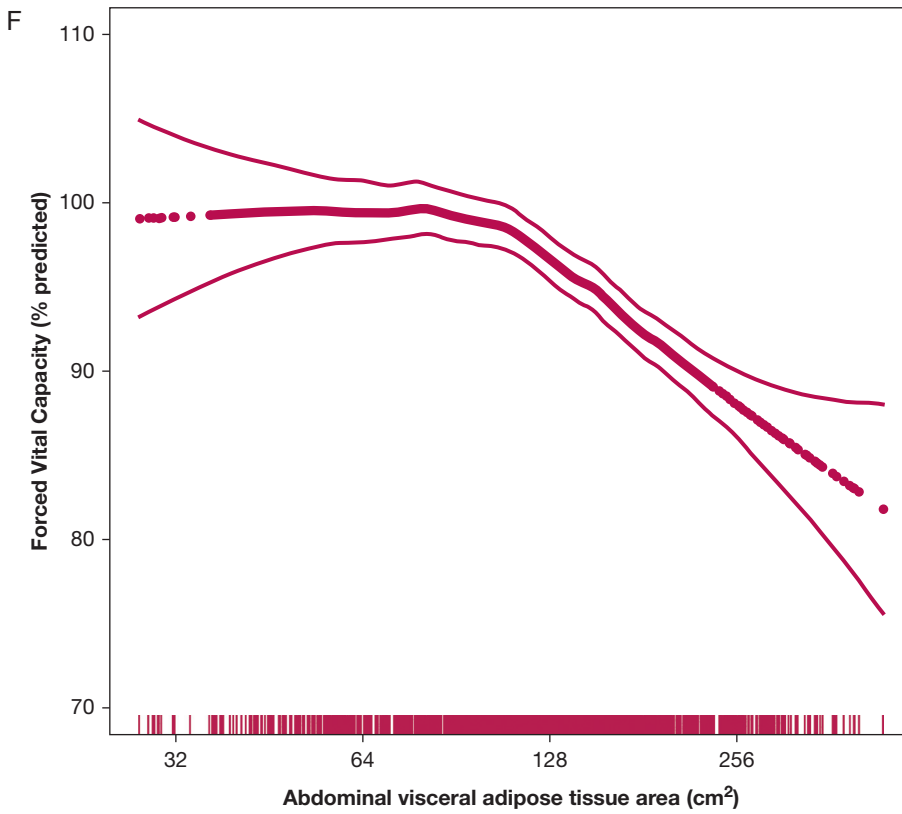
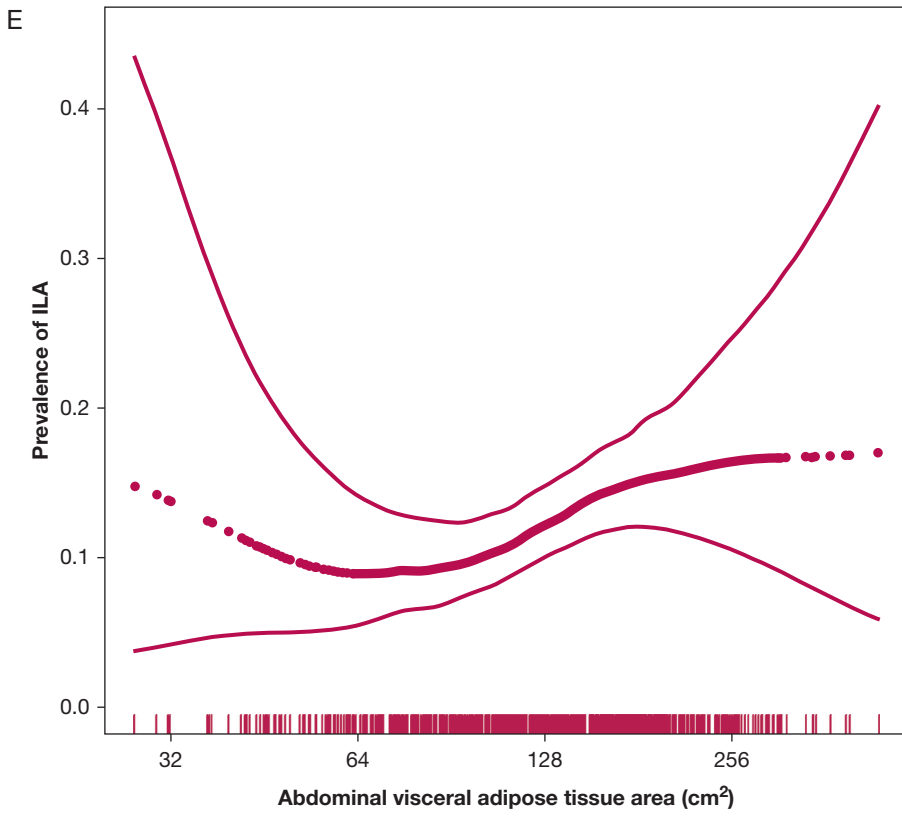


Figure 1 - (Continued)

Figure 1 - (Continued)



using measures from the L3/L4 vertebral level (e-Table 5).

Interstitial Lung Abnormalities

Interstitial lung abnormalities were present in 294 participants (12%) after excluding those with scans indeterminate for ILA. Those with and without ILA had a mean (SD) BMI of 28.1 (4.8) kg/m² and 28.1 (5.1) kg/m², respectively. In fully adjusted models, every doubling in PAT volume was associated with 20% increased odds of ILA (OR, 1.2; 95% CI, 0.98-1.5; $P = .07$) (Table 2, Fig 1B). Similarly, every doubling in abdominal VAT area was associated with increased odds of ILA, although this was not statistically significant in fully adjusted models (OR, 1.3; 95% CI, 0.9-1.8; $P = .21$) (Fig 1E). There was no association between abdominal SAT and ILA (Table 2, e-Fig 2B). Similar associations were present in sensitivity analyses (Table 2, e-Tables 4 and 5).

Spirometry

Every doubling in PAT volume was associated with a 5.5% lower percent predicted FVC in fully adjusted models (95% CI, -6.8 to -4.3; $P < .001$) (Fig 1C). Similarly, greater abdominal VAT area and greater abdominal SAT area were associated with significantly lower FVC in unadjusted and fully adjusted models (Table 2, Fig 1F, e-Fig 2C). Associations were similar in sensitivity analyses (Table 2, e-Tables 4 and 5).

Subgroup Analyses

Sex modified the associations between PAT (P for interaction, $< .001$), abdominal VAT (P for interaction, .15), and HAA (Table 3). Associations were stronger in women, in whom every doubling in PAT volume was associated with 76.7-unit higher HAA (95% CI, 65.5-87.9) and every doubling in VAT area was associated with 52.5-unit higher HAA (95% CI, 33.9-71.2). Among men, every doubling in PAT volume was associated with 47.6-unit higher HAA (95% CI, 36.8-58.5), and every doubling in VAT was associated with 25.9-unit higher HAA (95% CI, 7.1-44.8). The association between PAT and ILA also appeared to be modified by sex (P for interaction, .01). In contrast to HAA, PAT seemed to be associated with a greater risk of ILA among men (OR, 1.5; 95% CI, 1.1-2.0) than among women (OR, 1.0; 95% CI, 0.8-1.3).

There did not appear to be effect modification by age (e-Tables 6-8). Smoking status may modify the association between PAT (P for interaction, .03), abdominal VAT (P for interaction, $< .001$), abdominal SAT (P

interaction, .005), and FVC with a stronger association between adiposity and FVC among ever smokers compared with never smokers (e-Tables 6-8). BMI may modify the association between abdominal SAT and HAA (P for interaction, $< .001$) with a strong effect among a small group of underweight subjects (e-Table 6).

Biomarkers

Biomarker measures were available for 1,468 subjects. As previously reported, there was a moderate correlation between PAT volume and IL-6 (e-Fig 3A).^{33,34} There was no correlation between PAT volume and CRP, adiponectin, or leptin (e-Figs 3B-3D). Abdominal VAT was moderately correlated with IL-6 ($\rho = 0.32$, $P < .001$) (e-Fig 4A) and leptin ($\rho = 0.28$, $P < .001$) (e-Fig 4B), weakly correlated with CRP ($\rho = 0.25$, $P < .001$) (e-Fig 4D), and moderately inversely correlated with adiponectin ($\rho = -0.31$, $P < .001$) (e-Fig 4C). Neither PAT volume nor abdominal VAT area was significantly associated with resistin or TNF- α (e-Figs 2D and 2F, e-Figs 3E and 3F).

In mediation analyses, IL-6 accounted for 8% of the total association between PAT and HAA and 17% of the total association between VAT and HAA (e-Table 9). Leptin accounted for 18% of the total association between VAT area and HAA, and CRP and adiponectin accounted for 11% and 4% of the total association, respectively.

Discussion

Greater amounts of pericardial and abdominal visceral adipose tissue were associated with greater high-attenuation areas on chest CT imaging, higher prevalence of interstitial lung abnormalities, and lower FVC among community-dwelling adults. These associations may vary by sex, and may be partially mediated by plasma IL-6 and leptin. The strength of our study lies in the consistency of our associations across three separate measures of early parenchymal lung injury and fibrosis in a large, multiethnic cohort of community-dwelling adults.

Our findings are consistent with epidemiologic studies demonstrating an association between diabetes, high-fat diet, and idiopathic pulmonary fibrosis (IPF), as well as known associations between greater pericardial adipose tissue volume or greater abdominal obesity with decreased FVC in the general population.^{2-4,35-37} Prior work has been limited to measures of pulmonary function, which are strongly influenced by the mechanical effects of obesity. We demonstrate that these

TABLE 3] Associations of Pericardial Adipose Tissue Volume and Abdominal Visceral Adipose Tissue Area With High-Attenuation Areas, Interstitial Lung Abnormalities, and FVC Within Prespecified Subgroups by Sex

Subgroup	No.	Change in HAA per Doubling in PAT Volume	95% CI	<i>P</i> for Interaction	No.	Change in ILA per Doubling in PAT Volume	95% CI	<i>P</i> for Interaction	No.	Change in Percent Predicted FVC per Doubling in PAT Volume	95% CI	<i>P</i> for Interaction
Sex				< .001				.01				.18
Male	3,144	47.6	36.8 to 58.5		1,125	1.5	1.1 to 2.0		722	-6.7	-8.3 to -5.0	
Female	3,546	76.7	65.5 to 87.9		1,269	1.0	0.8 to 1.3		678	-4.8	-6.7 to -2.9	

Subgroup	No.	Change in HAA per Doubling in VAT Area	95% CI	<i>P</i> for Interaction	No.	Change in ILA per Doubling in VAT Area	95% CI	<i>P</i> for Interaction	No.	Change in Percent Predicted FVC per Doubling in VAT Area	95% CI	<i>P</i> for Interaction
Sex				.15				.11				.10
Male	921	25.9	7.1 to 44.8		424	1.6	0.8 to 2.7		725	-6.6	-8.3 to -4.9	
Female	917	52.5	33.9 to 71.2		420	1.1	0.7 to 1.8		679	-4.9	-6.6 to -3.3	

Models adjusted for study site, age, height, race, smoking status, cigarette pack-years, study site, percent emphysema (FVC and HAA models), imaged lung volume (HAA models), and radiation dose (HAA model). HAA = high-attenuation area; ILA = interstitial lung abnormalities; PAT = pericardial adipose tissue; VAT = visceral adipose tissue.

restrictive ventilatory defects may not exclusively reflect the mechanical effects of obesity, but may also reflect parenchymal changes caused by systemic inflammation and circulating adipokines. BMI is a poor measure of adiposity and varies significantly by sex and race/ethnicity.^{18,19} The use of adipose depot size, rather than BMI,¹⁷ allowed us to identify a novel association between pericardial and visceral adiposity and subclinical ILD. Although mechanical factors may partially explain our findings, they are unlikely to represent the only mechanism linking adiposity and ILD. First, the strength of the association between adiposity and early parenchymal injury was greatest for PAT, which does not exert mechanical effects on the lung. Second, ILAs were qualitatively assessed and less prone to mismeasurement by body habitus. Third, significant associations between adiposity and early lung injury remain after controlling for measures of total adiposity and BMI. Fourth, we demonstrated a significant association with circulating measures of inflammation, suggesting alternate mechanisms.

Multiple nonmechanical mechanisms may link adiposity and ILD. Obese adipose tissue is characterized by adipocyte hypertrophy, resulting in recruitment of proinflammatory adipose tissue macrophages,¹⁰ and production of IL-6 and monocyte chemoattractant protein-1 (MCP-1).⁸ Direct drainage of pericardial adipose into the pulmonary circulation may increase the potential for lung injury by adipose-derived inflammatory cytokines and adipokines.

IL-6 has been implicated in the pathogenesis of IPF. IL-6 and MCP-1 are increased in serum and BAL during acute exacerbations of IPF.^{6,9} IL-6 blockade attenuates fibrosis in mouse models of bleomycin-induced lung injury.¹³ MCP-1 is an important stimulus for recruitment of profibrotic macrophages and fibroblasts to the lung and has been targeted in the treatment of IPF.^{9,38} We found that IL-6 partially mediated the association between adipose depots and HAA, suggesting that inflammation may be an important link between adiposity and lung injury.

The adipokines leptin and resistin are produced by adipocytes in high-energy states^{11,12} and have been linked to lung injury. Leptin, which partially mediates the association between abdominal VAT and HAA in our analyses, is increased in the BAL fluid of patients with acute lung injury and may increase macrophage-mediated inflammatory cytokine production.^{39,40} In bleomycin-induced models of acute lung injury in mice,

leptin resistance decreases fibrosis and inflammation.^{15,41} Notably, we failed to identify a significant association between adipose depots and serum resistin despite having previously demonstrated a significant association between resistin and HAA.¹⁴ This suggests that resistin may play an independent role in lung injury that does not simply reflect greater adiposity.⁴²

This study has significant strengths. We used a large population-based multicenter multiethnic prospective cohort, making our findings generalizable to the greater population. We demonstrated consistent associations across two separate adipose depots and two separate measures of early parenchymal lung injury, as well as reduced FVC, suggesting reproducibility. Extensive sensitivity analyses demonstrated consistent effects.

There are also limitations to this study. First, ILA was measured at examination 5 whereas adipose tissue and lung function measures were from earlier examinations. Reassuringly, weight was highly correlated across study visits, suggesting that there were no significant changes in body composition over time. Second, although we identified a significant association between SAT and HAA in adjusted models, the absence of an association in unadjusted models suggests effect modification. This appears to be driven by a small number of subjects with BMI less than 18.5 kg/m². Weight loss is associated with disease progression in IPF.⁴³ Although our analyses suggest that greater SAT may be associated with greater HAA among underweight subjects, greater SAT may actually be associated with a higher FVC in this subgroup. Given the very small sample size, these results should be interpreted with caution. Further work should evaluate changes in adipose depot size in patients with IPF with weight loss. Third, we identified a significant association between abdominal SAT and FVC despite no clear association between SAT and subclinical ILD, suggesting that factors other than parenchymal changes may explain the association between adiposity and FVC. Fourth, although we replicated these findings across three measures of lung injury, we have not confirmed these findings in other cohorts. Fifth, ILAs were assessed by only one of five radiologists, introducing potential misclassification.

Interpretation

Greater amounts of pericardial and abdominal visceral adipose tissue were associated with interstitial lung abnormalities, increased high-attenuation areas, and

decreased FVC in a large, diverse multicenter study. This association may be partially mediated by leptin and IL-6. Quantification of adipose tissue on CT imaging identified adiposity as a novel target for prevention of

ILD and highlights the importance of the nonmechanical effects of adipose tissue on the lung. Further work should investigate potential roles for IL-6, MCP-1, and leptin in lung injury and fibrosis.

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