Obstructive Sleep Apnea and Subclinical Interstitial Lung Disease in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Rationale: Obstructive sleep apnea (OSA) has been postulated to contribute to idiopathic pulmonary fibrosis by promoting alveolar epithelial injury via tractional forces and intermittent hypoxia.

Objectives: To determine whether OSA is associated with subclinical interstitial lung disease (ILD) and with biomarkers of alveolar epithelial injury and remodeling.

Methods: We performed cross-sectional analyses of 1,690 community-dwelling adults who underwent 15-channel in-home polysomnography and thoracic computed tomographic imaging in the Multi-Ethnic Study of Atherosclerosis. We measured the obstructive apnea-hypopnea index (oAHI) by polysomnography and high-attenuation areas (HAAs) and interstitial lung abnormalities (ILAs) by computed tomography. Serum matrix metalloproteinase-7 (MMP-7) and surfactant protein-A (SP-A) were measured by ELISA in 99 participants. We used generalized linear models to adjust for potential confounders.

Results: The mean age was 68 years, and the mean forced vital capacity was 97% predicted. The median oAHI was 8.4 events/h, and 32% had an oAHI greater than 15. After adjusting for demographics,

smoking, and center, an oAHI greater than 15 was associated with a 4.0% HAA increment (95% confidence interval [CI], 1.4–6.8%; $P = 0.003$) and 35% increased odds of ILA (95% CI, 13–61%; $P = 0.001$). However, there was evidence that these associations varied by body mass index (BMI) (P for interaction = 0.08 and 0.04, respectively). Among those with a BMI less than 25 kg/m², an oAHI greater than 15 was associated with a 6.1% HAA increment (95% CI, 0.5–12%; $P = 0.03$) and 2.3-fold increased odds of ILA (95% CI, 1.3–4.1; $P = 0.005$). Among those with a BMI greater than 30 kg/m², an oAHI greater than 15 was associated with 1.8-fold greater odds of ILA (95% CI, 1.1–2.9; $P = 0.01$) but was not associated with HAA. There were no meaningful associations detected among those with a BMI of 25–30 kg/m². Greater oAHI was associated higher serum SP-A and MMP-7 levels, particularly among those with a BMI less than 25 kg/m².

Conclusions: Moderate to severe OSA is associated with subclinical ILD and with evidence of alveolar epithelial injury and extracellular matrix remodeling in community-dwelling adults, an association that is strongest among normal-weight individuals. These findings support the hypothesis that OSA might contribute to early ILD.

Keywords: lung injury; sleep apnea; interstitial lung disease; epidemiologic studies; biomarkers

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Recurrent “microinjuries” of the alveolar epithelium have been postulated to be the antecedent event that leads to aberrant extracellular matrix (ECM) remodeling that precedes idiopathic pulmonary fibrosis (IPF) (1). To date, however, neither pathological evidence of their existence nor the causes of these alveolar microinjuries have been identified.

We and others have attempted to garner evidence of these alveolar microinjuries, using computed tomography (CT)-derived measures of subclinical interstitial lung disease (ILD) in community-dwelling adults. High-attenuation areas (HAAs), the percentage of lung voxels that have CT attenuation values between −600 and −250 Hounsfield units (HU), have been shown to be a quantitative biomarker of subclinical lung injury, inflammation, and ECM remodeling and are associated with the presence of interstitial lung abnormalities (ILAs), a qualitative CT-based subclinical interstitial lung disease phenotype, at 10-year follow-up (2). A growing evidence base suggests that ILA and HAA in the lung fields of community-dwelling adults may, in some cases, capture alveolar microinjuries that precede IPF and other fibrotic ILDs.

“Traction” in the periphery of the lung has been postulated to be a cause of alveolar microinjuries leading to IPF (3). One possible cause of tractional injury is obstructive sleep apnea (OSA) (4, 5), which affects up to 88% of adults with IPF (6, 7). OSA is characterized by repetitive forced inspirations against a completely or partially closed upper airway, occurring up to hundreds of times nightly (8). Wide swings in pleural pressure that occur with obstructive events could exert local strain forces at the periphery of the lung, deforming and stretching alveolar epithelial cells (AECs) in a cyclical fashion, even without changes in lung volume (9). In addition, rapid increases in alveolar volume after an obstructive apnea

might stretch the alveolar walls, exerting stress forces on the alveolar epithelium. Such stress and strain forces are established causes of AEC injury and inflammation, which have been hypothesized to lead to lung fibrosis in susceptible individuals (1, 3–5, 10–13). Oxidative stress and inflammation resulting from intermittent hypoxia might also link OSA to AEC injury (14).

In this study, we tested the hypothesis that OSA severity would be associated with two CT-based subclinical ILD phenotypes (HAA and ILA) among community-dwelling adults. We also tested for consistency of this association across categories of body mass index (BMI) and smoking status; and whether serum surfactant protein-A (SP-A) and matrix metalloproteinase-7 (MMP-7) levels, markers of alveolar injury and remodeling, were associated with OSA severity.

Methods

The full text of the methods is available in the online supplement.

Study Design, Data Source, and Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a National Heart, Lung, and Blood Institute-sponsored prospective cohort study designed to investigate subclinical cardiovascular disease. Enrollment criteria have been described previously (15). MESA enrolled 6,814 adults between 45 and 84 years of age, free of clinically evident cardiovascular disease, sampled from six U.S. communities between 2000 and 2002. There were no selection criteria based on respiratory or sleep symptoms, smoking, or lung disease. MESA participants attended follow-up

visits, with the most recent visit between 2010 and 2012 (Exam 5).

We performed cross-sectional analyses of participants who underwent polysomnography and full lung or cardiac CT imaging in conjunction with MESA Exam 5 (n = 1,690). Of these, 1,152 full lung CT scans were assessed for ILA, and 99 underwent measurement of MMP-7 and SP-A in serum collected at the Exam 5 visit.

Interstitial Lung Abnormalities

Exam 5 full lung CT scans were performed in the supine position, using the MESA Lung/SPIROMICS protocol (16). Each CT scan was visually examined by one of five expert radiologists for the presence of ILA, defined as involvement of more than 5% of nondependent lung by reticular abnormalities, ground-glass abnormalities, diffuse centrilobular nodularity, honeycombing, traction bronchiectasis, and/or nonemphysematous cysts (2, 17, 18).

High-Attenuation Areas on CT Scans

HAAs and percent emphysema were measured on Exam 5 full lung and cardiac CT scans, using a standardized protocol that has been described previously (19–21). HAA was defined as the percentage of voxels having attenuation values between −600 and −250 HU (2, 20, 22).

Polysomnography

Sleep metrics and methods have been described previously (23). MESA participants, none using continuous positive airway pressure or other nightly treatment for OSA, underwent in-home full polysomnography with a 15-channel monitor (Compumedics Somte system; Compumedics Ltd., Abbotsville, Australia) a median of 300 days after MESA Exam 5, permitting standardized assessments of

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sleep stages, arousals, and respiratory events.

Our two primary exposures of interest were the obstructive apnea–hypopnea index (oAHI), defined as the average number of all obstructive apneas plus hypopneas with at least 4% oxygen desaturation per hour of sleep, and the nadir oxyhemoglobin saturation during sleep determined by continuous finger pulse oximetry. We also examined the central sleep apnea index (all central apneas per hour of sleep) to determine whether the observed associations were specific for obstructive events.

Statistical Analysis

We used linear regression to examine associations of oAHI categories (<5, 5–15, >15 events/h) and nadir saturation categories (>90, 80–90, <80%) with natural log–transformed HAA with adjustment for age, sex, race/ethnicity, educational attainment, height, smoking status, cigarette pack-years, glomerular filtration rate, and percent emphysema. We tested for effect modification by BMI category: underweight and normal weight (<25 kg/m²), overweight (25–30 kg/m²), and obese (>30 kg/m²), and by smoking status, using likelihood ratio tests. We combined underweight (BMI < 18.5 kg/m²) and normal weight into a single category for our analyses because less than 1% of the cohort were underweight. Because there was evidence of effect modification by BMI, we estimated coefficients from fully adjusted models that included main effects for BMI category and interaction terms for BMI category × oAHI (or nadir saturation). We performed similar analyses for smoking status. We used logistic regression with cluster-robust variance estimation to account for clustering within study sites to examine the associations of both oAHI categories and nadir saturation categories with ILA with and without adjustment for age, sex, race/ethnicity, and smoking. Coefficients were estimated from fully adjusted models, using interaction terms as described above. We used multivariable linear models for analyses of MMP-7 and SP-A, adjusting for age, sex, race/ethnicity, smoking status, and BMI. We tested for effect modification by BMI (dichotomized at 25 kg/m²) as described above. We used multiple imputation with chained equations for missing covariate data in models without interaction terms, as previously described (2). Analyses were

performed with Stata version 14.2 (StataCorp, College Station, TX) and the gam package in R version 3.2.2 (R Foundation for Statistical Computing) (24).

Results

Study Participants

A total of 2,261 MESA participants participated in the MESA Sleep Study, and 2,060 had polysomnography data that met study quality criteria (23). Of these, 1,690 also had available CT scans suitable for HAA measurement, and 1,152 had valid ILA assessments on full lung CT scans at Exam 5 (2). Baseline characteristics of the 1,690 participants with available HAA measurement are shown in Table 1. The mean age was 68.3 years, 54% were women, 53% were current or former smokers, 0.7% were underweight, 26% were normal weight, 38% were overweight, 35% were obese, the mean BMI was 28.7 kg/m², and the mean forced vital capacity was 97% predicted. The median oAHI was 8.4 events/h (interquartile range [IQR], 3.0–18.7; range, 0–103); 32% had moderate or more severe OSA as defined by an oAHI greater than 15. The median nadir saturation was 85% (IQR, 80–89%; range, 40–96%). The median central sleep apnea index was 0 events/h (IQR, 0–0.27; range, 0–8). The median HAA value was 4.4% (IQR, 3.8–5.4%) and the prevalence of ILA was 11.3%. Baseline characteristics of those in the biomarker subset were similar to those of the overall cohort (Table 1).

Obstructive Apnea–Hypopnea Index

In a precision variable-adjusted model, moderate or more severe OSA (oAHI > 15) was associated with a 7.2% HAA increment (95% CI, 4.5–10%; $P < 0.001$) compared with those with an oAHI less than 5 (Table 2). This association was somewhat attenuated but remained significant after adjustment for age, sex, race, educational attainment, height, smoking status, cigarette pack-years, glomerular filtration rate, study site, percent emphysema, radiation dose, and total volume of imaged lung (4.0% HAA increment; 95% CI, 1.4–6.8; $P = 0.003$). In this adjusted model, however, the association between oAHI and HAA appeared to vary by BMI (P for interaction = 0.08), with a stronger association among those with a BMI less than 25 kg/m². Moderate or more severe

OSA was associated with a 6.1% HAA increment (95% CI, 0.5–12.0%; $P = 0.03$) among normal-weight participants, a 0.8% HAA increment (95% CI, –3.2 to 5.1%; $P = 0.40$) among overweight participants, and a 2.7% HAA increment (95% CI, –1.6 to 7.3%; $P = 0.23$) among obese participants; Table 2). Although there was a significant trend across oAHI categories among obese participants ($P = 0.03$), there was no detectable association among obese participants ($P = 0.10$; see Table E1 in the online supplement). In modeling the oAHI as a continuous variable, greater oAHI was associated with greater HAA among normal-weight participants (mean, 1.0% HAA increment per 5-unit increment in oAHI; 95% CI, 0.1–1.9%; $P = 0.03$; Table E1 and Figure 1A), but not among obese participants ($P = 0.10$).

The prevalence of ILA increased across categories of oAHI: 8.9, 11.5, and 13.9% among those with an oAHI less than 5, 5–15, and more than 15, respectively (P for trend < 0.001). After adjustment for age, sex, race, smoking status, and cigarette pack-years, an oAHI greater than 15 was associated with 35% increased odds of ILA (95% CI, 13–61%; $P = 0.001$) compared with those with an oAHI less than 5 (Table 2). In this model, the association between oAHI and ILA appeared to vary by BMI category (P for interaction = 0.04). Moderate or more severe OSA was associated with 2.3-fold increased odds of ILA (95% CI, 1.3–4.1; $P = 0.005$) among normal-weight participants and 1.8-fold increased odds of ILA (95% CI, 1.1–2.9; $P = 0.01$) among obese participants (Table 2). There was no detectable association between OSA and ILA among overweight participants. Among normal-weight participants, each 5-unit increment in oAHI was associated with 29% increased odds of ILA (95% CI, 13–48%; $P < 0.001$; Table E1 and Figure 1B).

There was no evidence that the association between oAHI and either HAA or ILA varied by smoking status (P values for interaction > 0.20), and these associations were qualitatively similar among never-smokers and among ever-smokers (Table 2 and Table E1).

Sleep-related Hypoxemia

There was a strong inverse correlation between oAHI and nadir saturation (Spearman $\rho = -0.75$; $P < 0.001$). More severe sleep-related hypoxemia (measured

Table 1. Baseline characteristics of study participants

	Obstructive AHI Category			Biomarker Subset*
	<5 Events/h	5 to <15 Events/h	≥15 Events/h	
Participants, n	600	547	543	99
Age, yr	67 ± 9	69 ± 9	69 ± 9	69 ± 8
Female	67%	54%	38%	48%
Race/ethnicity				
White	37%	38%	30%	37%
African-American	29%	27%	27%	31%
Hispanic	21%	23%	29%	18%
Asian	13%	12%	14%	14%
Body mass index, kg/m ²	27 ± 5	29 ± 5	31 ± 6	28 ± 4
<25 kg/m ²	41%	23%	15%	21%
25–30 kg/m ²	36%	43%	35%	56%
>30 kg/m ²	23%	34%	50%	22%
Height, cm	164 ± 10	165 ± 10	167 ± 10	166 ± 10
Weight, kg	73 ± 16	78 ± 15	86 ± 18	76 ± 14
Waist circumference, cm	94 ± 14	100 ± 13	104 ± 14	97 ± 10
Hip circumference, cm	103 ± 11	106 ± 11	109 ± 12	103 ± 8
Smoking status				
Never-smokers	51%	45%	45%	49%
Former smokers	41%	47%	49%	49%
Current smokers	8%	8%	6%	3%
Education				
Less than high school	15%	14%	17%	14%
High school	44%	47%	47%	38%
College	41%	39%	36%	48%
Resting SpO ₂ , %	96 ± 1.2	96 ± 1.4	96 ± 1.3	96 ± 1.4
Forced vital capacity, % predicted	97 ± 17	98 ± 19	97 ± 17	100 ± 17

Definition of abbreviations: AHI = apnea-hypopnea index; SpO₂ = oxygen saturation as measured by pulse oximetry.

*Data are presented as means ± SD and as percentages.

by lower nadir saturation during sleep) was associated with greater HAA (Table 3). For example, in a precision variable-adjusted model, a nadir saturation less than 80% was associated with a 6.1% HAA increment (95% CI, 2.6–9.8%; $P = 0.001$; Table 3). In an adjusted model, HAA increased across categories of nadir saturation (P for trend = 0.01; Table 3), and a nadir saturation less than 80% was associated with a 4.6% HAA increment (95% CI, 1.3–8.0%; $P = 0.02$; Table 3). The association between nadir

Table 2. Associations of the obstructive apnea-hypopnea index with subclinical interstitial lung disease on computed tomography in the Multi-Ethnic Study of Atherosclerosis

	Mean Percent HAA Increment Compared with oAHI < 5 Events/h (95% CI)				Odds Ratio for ILA Compared with oAHI < 5 Events/h (95% CI)			
	<5 Events/h	5–15 Events/h	>15 Events/h	P Trend	<5 Events/h	5–15 Events/h	>15 Events/h	P Trend
Precision adjusted	0 (Ref)	1.4 (−1.2 to 3.9)	7.2 (4.5 to 10)	<0.001	1 (Ref)	1.32 (0.87 to 2.00)	1.64 (1.36 to 1.98)	<0.001
Adjusted	0	0.2 (−0.2 to 2.7)	4.0 (1.4 to 6.8)	0.001	1	0.96 (0.62 to 1.51)	1.35 (1.13 to 1.61)	<0.001
Adjusted with BMI interaction terms								
<25 kg/m ²	0	4.7 (0.1 to 9.5)	6.1 (0.5 to 12.0)	0.03	1	2.06 (1.16 to 3.6)	2.31 (1.30 to 4.12)	0.005
25–30 kg/m ²	0	−1.9 (−5.6 to 2.0)	0.8 (−3.2 to 5.1)	0.48		0.71 (0.35 to 1.43)	0.51 (0.23 to 1.12)	0.10
>30 kg/m ²	0	−3.1 (−7.5 to 1.5)	2.7 (−1.6 to 7.3)	0.03		0.77 (0.29 to 2.07)	1.82 (1.13 to 2.93)	<0.001
Adjusted with smoking interaction term								
Never-smokers	0	3.5 (−0.01 to 7.4)	9.6 (5.6 to 13.6)	<0.001	1	0.73 (0.32 to 1.64)	1.38 (0.84 to 2.28)	0.01
Ever-smokers	0	0.3 (−3.0 to 3.8)	5.2 (1.6 to 8.9)	0.002	1	1.33 (0.75 to 2.35)	1.50 (0.99 to 2.27)	0.050

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HAA = high-attenuation area; ILA = interstitial lung abnormality; oAHI = obstructive apnea-hypopnea index; Ref = reference category.

The precision-adjusted HAA model includes milliamperage (mA) dose, imaged lung volume, and study site for HAA. Note that mA dose is BMI-based, and that this model adjusts for BMI greater than 30 and for BMI less than 20. The precision-adjusted ILA model includes only cluster-robust variance estimation to account for study site. The adjusted HAA model includes adjustment for age, sex, race, educational attainment, height, smoking status, cigarette pack-years, glomerular filtration rate, study site, percent emphysema, milliamperage radiation dose, and total volume of imaged lung. The adjusted ILA model includes adjustment for age, sex, race, smoking status, cigarette pack-years, and cluster-robust variance estimation for study site.

For the HAA model: $P = 0.08$ for the interaction between oAHI and BMI, and $P = 0.23$ for the interaction between oAHI and smoking. For the ILA model, $P = 0.04$ for the interaction between nadir oAHI and BMI, and $P = 0.46$ for the interaction between oAHI and smoking.

Figure 1. Continuous associations of the obstructive apnea hypopnea index with (A) high-attenuation areas and (B) interstitial lung abnormalities stratified by body mass index (BMI) category. HAA models are adjusted for age, sex, race/ethnicity, smoking status and pack-years, educational attainment, height, glomerular filtration rate, percent emphysema on CT, milliampere dose, total imaged lung volume, and study site. ILA models are adjusted for age, sex, race/ethnicity, smoking status, and pack-years. The *thick lines* represent the overall adjusted effect estimate; *thin lines* indicate the 95% confidence bands. Each *vertical mark* in the rug plot along the *x-axis* represents one study participant. *P* values are from generalized additive models and differ somewhat from the *P* values in Table E2, which are from generalized linear models. AHI = apnea-hypopnea index; CT = computed tomography; HAA = high-attenuation area; ILA = interstitial lung abnormality.

saturation and HAA, however, varied by BMI category (*P* for interaction = 0.02), with stronger associations among normal-weight (*P* for trend = 0.049) and obese participants (*P* for trend = 0.03) than among overweight participants (*P* for trend = 0.79; Table 3). Similar associations were found when nadir saturation was treated as a continuous variable (Table E1). Each 5% absolute decrement in nadir saturation was associated with a 1.9% HAA increment (95% CI, 0.3–3.5; *P* = 0.02) among normal-weight participants and with a 1.2% HAA increment (95% CI, 0.3–2.2; *P* = 0.01) among obese participants (Table E1).

The prevalence of ILA increased across descending categories of nadir saturation: 9.3, 10.9, and 14.1% among those with a nadir saturation greater than 90, 80–90, and less than 80%, respectively (*P* for trend < 0.001). A nadir saturation less than 80% was strongly associated with 1.6-fold higher odds of ILA (95% CI, 1.2–2.2; *P* = 0.001) in an unadjusted model. This finding was not statistically significant in an adjusted model, and there was no statistically significant evidence that the association varied by BMI category (*P* for

interaction = 0.56) or by smoking (*P* for interaction = 0.42; Table 3 and Table E1). Nevertheless, in an adjusted model treating nadir saturation as a continuous variable, lower nadir saturation was associated with increased odds of ILA overall (odds ratio [OR], 1.19 per 10% relative decrement in saturation; 95% CI, 1.09–1.30; *P* < 0.001) and among obese participants (OR, 1.24; 95% CI, 1.15–1.35; *P* < 0.001; Table E1). A nadir saturation less than 80% was associated with higher odds of ILA among ever-smokers (OR, 2.29; 95% CI, 1.08–4.82; *P* = 0.03) but not among never-smokers (Table 3).

Central Sleep Apnea Index

The central sleep apnea index was not associated with HAA or ILA in adjusted models (Table E2). There was no evidence of effect modification by BMI category or smoking.

Role of Lung Volume

Among those with a BMI less than 25 kg/m², we found weak evidence that variation in lung volume explained a small fraction (~10%) of the association of either HAA or

ILA with oAHI (Table 4) (25). There was somewhat stronger evidence that lower lung volumes explained some of the association between HAA and nadir saturation (25% explained by lung volumes), but no evidence that lung volumes explained the association between ILA and nadir saturation (Table 4).

Serum MMP-7 and SP-A

The median serum SP-A level was 49 ng/ml (IQR, 34–75 ng/ml), and the median serum MMP-7 level was 3.8 ng/ml (IQR, 3.1–4.8 ng/ml). A greater oAHI was associated with higher levels of MMP-7 (mean, 3.4% MMP-7 increment per 5-unit increase in obstructive AHI; 95% CI, 0.8–6.0; *P* = 0.01), and there was a nonsignificant trend toward an association between greater oAHI and higher SP-A levels (mean, 4.1% SP-A increment per 5-unit increase in obstructive AHI; 95% CI, –0.5 to 8.9; *P* = 0.08) in models adjusted for age, sex, race/ethnicity, BMI, and smoking status (Table 5). Notably, however, both of these associations varied by BMI (*P* for interaction < 0.001 for MMP-7, and 0.03 for SP-A), with stronger associations

Table 3. Associations of sleep-related hypoxemia (nadir saturation) with subclinical interstitial lung disease on computed tomography in Multi-Ethnic Study of Atherosclerosis

	Mean Percent HAA Increment Compared with a Saturation $\geq 90\%$ (95% CI)				Odds Ratio for ILA Compared with a Saturation $\geq 90\%$ (95% CI)			
	<80%	80–89%	$\geq 90\%$	P Trend	<80%	80–89%	$\geq 90\%$	P Trend
Precision adjusted	6.1 (2.6 to 9.8)	3.8 (0.9 to 6.8)	0 (Ref)	0.003	1.64 (1.23 to 2.17)	1.21 (0.92 to 1.61)	1 (Ref)	<0.001
Adjusted	4.6 (1.3 to 8.0)	2.4 (−0.4 to 5.2)	0	0.01	1.35 (0.86 to 2.11)	1.09 (0.76 to 1.58)	1	0.08
Adjusted with BMI interaction term								
<25 kg/m ²	6.9 (−0.1 to 14.3)	3.1 (−1.1 to 7.5)	0	0.049	0.71 (0.14 to 3.60)	2.02 (0.93 to 4.41)	1	0.59
25–30 kg/m ²	−0.5 (−5.7 to 4.9)	2.1 (−2.4 to 6.8)	0	0.79	0.86 (0.28 to 2.62)	0.70 (0.28 to 1.76)	1	0.95
>30 kg/m ²	2.6 (−4.1 to 9.8)	−1.8 (−8.0 to 4.8)	0	0.03	1.89 (0.48 to 7.41)	1.31 (0.27 to 6.30)	1	0.003
Adjusted with smoking interaction term								
Never-smokers	8.1 (3.3 to 13.2)	4.4 (0.4 to 8.6)	0	0.002	0.97 (0.50 to 1.89)	0.98 (0.40 to 2.37)	1	0.93
Ever-smokers	9.0 (4.2 to 14.1)	5.1 (1.0 to 9.4)	0	0.001	2.29 (1.08 to 4.82)	1.51 (0.72 to 3.16)	1	0.008

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HAA = high-attenuation area; ILA = interstitial lung abnormality; Ref = reference category; SpO₂ = oxygen saturation as measured by pulse oximetry.

The precision-adjusted HAA model includes milliamperage (mA) dose, imaged lung volume, and study site for HAA. Note that mA dose is BMI based, and that this model adjusts for BMI greater than 30 and for BMI less than 20. The precision-adjusted ILA model includes only cluster-robust variance estimation to account for study site. The adjusted HAA model includes adjustment for age, sex, race, educational attainment, height, smoking status, cigarette pack-years, glomerular filtration rate, study site, percent emphysema, milliamperage radiation dose, and total volume of imaged lung. The adjusted ILA model includes adjustment for age, sex, race, smoking status, cigarette pack-years, and cluster-robust variance estimation for study site.

For the HAA model, $P = 0.02$ for the interaction between nadir SpO₂ and BMI, and $P = 0.96$ for the interaction between nadir SpO₂ and smoking. For the ILA model, $P = 0.56$ for the interaction between nadir SpO₂ and BMI, and $P = 0.42$ for the interaction between nadir SpO₂ and smoking.

among normal-weight participants (Table 5). Lower nadir saturation was associated with higher SP-A levels but was not associated with MMP-7 (Table 5) without evidence of effect modification by BMI. There were no meaningful associations between the central sleep apnea index and either biomarker.

Discussion

In this study of community-dwelling adults without clinical ILD, we found that the frequency of sleep-related upper airway obstruction and the severity of sleep-related hypoxemia were each associated with two

distinct measures of subclinical ILD on CT, particularly among normal-weight adults. OSA measures were also associated with serum biomarker evidence of AEC injury and ECM remodeling among normal-weight adults. Together, our findings provide evidence to support the hypothesis that OSA contributes to subclinical alveolar injury and remodeling, and therefore might be one of the “microinjuries” postulated to contribute to lung fibrosis.

OSA is recognized as a prevalent comorbidity among adults with clinically diagnosed IPF, yet the pathways connecting the two have remained undefined. We and others have previously hypothesized that OSA might cause early AEC injury through

one of a variety of mechanisms. For example, cyclic hypoxia–reoxygenation during the intermittent breathing of OSA (14, 26) could contribute to oxidative injury and inflammation of the alveolar epithelium (27). In addition, obstructive apneas and hypopneas might cause stretch-mediated AEC injury. Indeed, stretch is a widely recognized cause of AEC injury in both animal models and in humans subjected to high-tidal volume ventilation during the acute respiratory distress syndrome (28). It is possible that linear stretch of AECs, even in the absence of alveolar inflation, may lead to strain-induced cellular injury. Each obstructive event is a forced inspiration against a closed

Table 4. Examination of lung volume as an explanatory factor for associations between subclinical interstitial lung disease and obstructive sleep apnea metrics among those with body mass index less than 25 kg/m²*

	Total Effect Coefficient	Direct Effect Coefficient	Indirect Effect Coefficient	Percentage of Total Effect Explained by Lung Volumes	Interpretation
HAA					
oAHI	0.75	0.67	0.08	11%	Partial (weak) mediation
Nadir saturation	0.03	0.02	0.01	25%	Partial (weak) mediation
ILA					
oAHI	0.25	0.23	0.03	10%	Partial (weak) mediation
Nadir saturation	−0.0028	−0.0043	0.0015	N/A	Suppression

Definition of abbreviations: CT = computed tomography; HAA = high-attenuation area; ILA = interstitial lung abnormality; N/A = not applicable; oAHI = obstructive apnea–hypopnea index.

*Lung volumes were measured on full lung CT scans performed at full inspiration. HAA models are adjusted for age, sex, smoking, site, radiation dose, and percent emphysema. ILA models are adjusted for age, sex, and smoking.

Table 5. Associations between measures of sleep-disordered breathing and serum biomarkers

	Mean Percent Biomarker Increment*	95% CI	P Value	P for Interaction with BMI
Obstructive AHI				
MMP-7				<0.001
Overall	3.4	0.8 to 6.0	0.01	
BMI < 25	16.6	9.7 to 24.0	<0.001	
BMI > 25	1.6	−0.9 to 4.1	0.21	
SP-A				0.03
Overall	4.1	−0.5 to 8.9	0.08	
BMI < 25	17.5	4.5 to 32.2	0.008	
BMI > 25	1.7	−3.0 to 6.6	0.48	
Nadir Saturation				
MMP-7				0.19
Overall	4.2	−0.4 to 9.0	0.07	
BMI < 25	15.0	−0.8 to 33.2	0.06	
BMI > 25	3.6	−1.2 to 8.7	0.15	
SP-A				0.15
Overall	9.1	0.8 to 18.1	0.03	
BMI < 25	22.8	−5.3 to 59.1	0.12	
BMI > 25	6.4	−2.2 to 15.7	0.15	
Central Sleep Apnea Index				
MMP-7				0.93
Overall	6.8	−3.8 to 18.5	0.21	
BMI < 25	5.4	−8.1 to 21.0	0.45	
BMI > 25	6.4	−9.0 to 24.4	0.43	
SP-A				0.95
Overall	−2.7	−19.4 to 17.5	0.77	
BMI < 25	0.8	−21.0 to 28.7	0.95	
BMI > 25	−0.4	−24.5 to 31.5	0.98	

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; MMP-7 = metalloproteinase-7; SP-A = surfactant protein-A.

All models adjusted for age, sex, race, and smoking status. “Overall” models include adjustment for BMI.

*Adjusted mean percent increment in each biomarker per 5-unit absolute increase in obstructive AHI, 5% absolute decrement in nadir saturation, or 1-unit increase in central sleep apnea index.

upper airway, a maneuver that can lead to negative esophageal pressures as large as −60 cm H₂O (29, 30). Although simultaneous reductions in pleural and mean alveolar pressure might lead to only small changes in average transpulmonary pressures, large swings in intrathoracic pressure cause regional pressure differences, particularly in peripheral occluded airways (31). The closure of peripheral airways that is thought to occur during obstructive events (32) may therefore facilitate locally large tractional forces at the periphery of the lung even in the absence of overall changes in lung gas volume. This localized alveolar strain may be further exacerbated by the rapid lung inflation with large tidal volumes that occurs at apnea termination. Moreover, cyclic alveolar deformation, as would be expected to occur in OSA, is more injurious than tonic deformation (10). Supporting this hypothesis, inspiratory resistive loading (analogous to an obstructive apnea) causes AEC injury and promotes lung

inflammation in mice (33). AECs produce IL-8 and monocyte chemotactic protein-1 in response to strain and deformation *in vitro* (11–14), providing potential mechanisms linking stretch forces generated by obstructed respiratory events and lung inflammation. Finally, OSA has been postulated to promote gastroesophageal reflux disease (34), which has been implicated as a possible cause of IPF (35). However, data suggest that gastroesophageal reflux disease may not occur during OSA (36–38), making this a less likely mediator of our observed association between OSA and subclinical ILD.

Some have proposed that the lower lung volumes observed in ILD might promote OSA by reducing traction on the trachea and increasing pharyngeal collapsibility or by worsening sleep-related hypoxemia with hypopneic events (increasing the likelihood that those events are identified on the basis of associated desaturation) (39–41). Our data, however,

argue against this hypothesis. Importantly, we did not study patients with clinically evident ILD and reduced lung volumes. Rather, we studied a community-based sample of middle-aged and older adults in whom subclinical ILD on CT is not expected to lead to a clinically relevant reduction in lung volumes. In our study, forced vital capacity and resting oxygen saturation were largely in the normal range. Second, we found that variation in lung volumes explained only 10–25% of the association between subclinical ILD and OSA, indicating that the majority of our findings were not due to the small variation in lung volumes observed in our study sample.

We observed a complex relationship between body weight and the association between OSA and subclinical ILD. Body weight appeared to modify many of the associations we observed across three measures of subclinical ILD—HAA, ILA, and serum MMP-7 levels—and for both the obstructive AHI and nadir saturation. The

strongest associations between OSA measures and subclinical ILD were consistently found among normal-weight participants, a group in whom the impact of adiposity on lung attenuation, lung volumes, inflammation, and sleep-related hypoxemia is likely small, if not eliminated, perhaps yielding a “cleaner” signal. We have previously detected similar findings, namely that impaired glucose tolerance and OSA are more strongly associated among nonobese than obese individuals (42). Alternatively, because normal-weight individuals are generally more fit and may have stronger respiratory muscles than obese individuals (43), they may be able to generate higher inspiratory pressures terminating periods of airway closure, which we postulate may lead to regional transpleural pressure changes. In contrast, we found that OSA measures were associated with subclinical ILD (particularly ILA) among obese participants in some analyses, and we found no associations among overweight participants. The factors underlying these discrepant findings are not immediately clear. Greater nocturnal desaturation among obese participants may have led to identification of a greater number of hypopneas associated with desaturation (44), easing the ability to detect an association between OSA measures and subclinical ILD.

Two prior studies have identified circulating biomarker evidence of AEC injury in adults with OSA who do not have concomitant lung disease. One study of 11 case subjects with OSA and 10 control

subjects, and a second study of 150 case subjects with OSA and 20 control subjects, found higher circulating levels of Krebs von den Lungen-6 (KL-6), a MUC1 glycoprotein found in type 2 AECs, among case subjects with OSA (4, 45). KL-6 is released into the circulation during AEC injury and found at elevated levels in the serum in patients with acute respiratory distress syndrome and in clinically diagnosed ILD (46–48). Similarly, serum levels of SP-A, a glycoprotein produced by type 2 AECs as well as by club cells and airway submucosal gland cells (49), are elevated after lung injury (50, 51) and in IPF (52, 53). Our study provides additional evidence that OSA may contribute to subclinical AEC injury.

Data from animal models and human studies indicate that MMP-7, a mediator of ECM remodeling, plays a key role in IPF, both as a contributor to the disease and as a diagnostic and prognostic serum biomarker (54–56). HAA is associated with elevated serum MMP-7 levels in community-dwelling adults (2). This is the first study, to our knowledge, to show that measures of OSA severity are associated with greater serum MMP-7 levels. Although circulating MMP-7 may arise from extrapulmonary sources, the associations observed between MMP-7 levels and measures of OSA support the hypothesis that OSA may be a contributor to ECM remodeling in the lung even among community-dwelling adults.

Our findings should be interpreted with several caveats. First, the cross-sectional nature of our study limits our ability to determine whether OSA precedes or follows

subclinical ILD, or whether both are due to an antecedent event. Second, our study does not provide evidence for treatment of OSA as a means for preventing ILD. Our findings do, however, support the novel hypothesis that OSA may be a modifiable risk factor for ILD, and provide strong support for future investigations testing whether OSA treatment can attenuate lung injury and disease progression in IPF and other ILDs. Finally, we note that although HAA and ILA have physiological, biomarker, and radiological features of ILD, neither has been validated histopathologically.

In summary, our findings show that OSA is associated with subtle structural changes to the alveolus manifest as increased CT lung attenuation, visually identifiable abnormalities on CT, and elevations in serum biomarkers known to represent AEC injury and ECM remodeling in community-dwelling adults. These results suggest that OSA may contribute to “microinjuries” to the alveolar epithelium, which precede clinically evident ILD in susceptible individuals. In the context of the limited number of existing targets, OSA should be considered a therapeutic target for both prevention and treatment of ILD in clinical trials. ■

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