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## SUPPLEMENTAL METHODS

*Study participants:* The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited cases of COPD and controls predominantly from MESA, a population-based prospective cohort study of subclinical atherosclerosis,[20] a non-overlapping lung cancer screening study,[21] and the outpatient community at Columbia University Medical Center. Participants were 50–79 years of age with  $\geq 10$  pack-year smoking history. Exclusion criteria were clinical cardiovascular disease, stage IIIb-V chronic kidney disease, asthma prior to age 45 years, prior lung resection, contraindication to magnetic resonance imaging, and pregnancy.

The Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS) is recruiting participants 40–80 years of age with  $>20$  pack-year smoking history with COPD and controls with  $>20$  pack-year smoking history, as well as never smokers.[22] Exclusion criteria include other chronic lung diseases except asthma (e.g., sarcoidosis, interstitial lung disease), body mass index (BMI)  $>40$  kg/m<sup>2</sup>, prior lung resection, metal in the chest (e.g., pacemaker) and pregnancy. The present analysis was performed on the first 1278 current or former smokers completing the baseline evaluation.

Study protocols were approved by the institutional review board of participating institutions and by the National Heart, Lung, and Blood Institute. Written informed consent was obtained from all participants.

*Chest computed tomography (CT) acquisition and analysis:* All participants in both studies underwent full-lung thoracic CT on 64 or 128-slice helical scanners (120 kVp, 0.625–0.75 mm slice thickness, 0.5 sec. rotation time). Scans were acquired with milliamperes (mA) set by body mass index (BMI) (80–145 mA for  $<20$  kg/m<sup>2</sup>, 100–180 mA for 20–30 kg/m<sup>2</sup> and 145–270

mA for >30 kg/m<sup>2</sup>) to maintain a consistent volume CT dose index (6.1, 7.6, 11.4 mGy respectively) across scanner types in SPIROMICS and in MESA COPD participants recruited from MESA; mA was set at 200 mA for MESA COPD participants recruited outside of MESA.[1 2] Images were obtained at suspended full inspiration. Airway dimensions were assessed at a single reading center for both studies blinded to other participant information.

The central airway tree was identified using Apollo Software (VIDA Diagnostics, Coralville, Iowa).[3] Airways were labeled anatomically[4] from trachea to subsegmental bronchi along five pre-specified paths: RB1 (apical segment of right upper lobe); RB4 (lateral segment of right middle lobe); RB10 (posterior basal segment of right lower lobe); LB1 (apical segment of left upper lobe); and LB10 (posterior basal of left lower lobe). Segmentation and labeling were visually verified by a dedicated image analyst and all labeled airways were assigned a generation number based on the number of branch points from the trachea, which was assigned generation 0. Cross-sectional airway wall area and wall thickness, as well as lumen area, diameter, and perimeter were measured perpendicular to the local airway segment's long axis using a subvoxel resolution algorithm in the Apollo Software, within an image plane, and measurements were averaged along the middle third of each labeled airway segment. Apollo uses the optimal surface algorithm[5] to simultaneously locate the inner (lumen) and outer airway border. Both borders are segmented simultaneously in three-dimensions and the lumen border guides the outer border in cases where the outer border is hard to identify (e.g., due to adjacent vessels and dense tissue). Other airway measurement algorithms tend to overestimate the size of small airways due to partial volume effect.[6] Apollo automatically corrects for this

and provides sub-voxel accuracy for all airway sizes. Airway segment length was measured as the distance between the proximal and distal branch points of each airway.

Percent wall area was calculated for each airway as the ratio of wall area to the sum of wall and lumen area, multiplied by 100. Pi10 was calculated by regressing the square-root wall area on internal perimeter of included airways to predict the square-root wall area of a single hypothetical airway with internal perimeter of 10 mm ( $\approx 3.2$  mm diameter).[7] A Pi10 was calculated for each participant using all measured airways, as well as using airways from each generation with five or more airways. Airway counts were determined by software summing all visually-confirmed airway segments detected along the five pre-specified paths and stratified by lumen diameter. Reliability of airway analyses were evaluated using 117 randomly selected MESA COPD CT scans assessed by two independent image analysts. Intra-class correlation coefficients with one-way random effects were computed.[8] Intra-class correlation coefficients for reproducibility of airway measures in the MESA COPD Study were 0.79-0.99, 0.74-0.99 and 0.78-0.96 for wall area, lumen area, and airway count, respectively (Web Supplement Tables E1-E2).

Lung volumes were quantified from segmented lung images. Percent emphysema-like lung was defined as the percentage of total voxels within the lung field  $< -950$  Hounsfield units (percent emphysema<sub>-950HU</sub>).[9]

*Spirometry:* Post-bronchodilator spirometry was performed following American Thoracic Society (ATS) recommendations[10] on a dry-rolling-sealed spirometer (Occupational Marketing, Inc., Houston, TX) in MESA COPD and a pneumotachograph spirometer (nSpire Health, Longmont, CO) in SPIROMICS.[10 11] Predicted spirometry values were calculated using

Hankinson reference equations.[12] COPD was defined as post-bronchodilator ratio of forced expired volume in one second to forced vital capacity ( $FEV_1/FVC$ ) less than 0.7 and spirometric severity as mild ( $FEV_1 \geq 80\%$  predicted), moderate ( $50\% \leq FEV_1 < 80\%$  predicted), severe ( $30\% \leq FEV_1 < 50\%$  predicted), and very severe ( $FEV_1 < 30\%$  predicted).[13] Controls had a post-bronchodilator  $FEV_1/FVC > 0.7$  and an FVC above the lower limit of normal.[12]

## TABLES

Table E1. Reproducibility of Airway Analysis in 117 Randomly Selected MESA COPD CT Scans Assessed by Two Independent Image Analysts.

Generation number (anatomic name)	ICC wall area	ICC lumen area
0 (trachea)	0.99	0.99
1 (RMB, LMB)	0.95	0.99
2 (RUL, BI, LUL, LLL proximal to LB6)	0.85	0.87
3 (RB1, RML, RLL proximal to RB7, LB1+2, LLL distal to LB6)	0.95	0.97
4 (RB1 subsegments, RB4, RLL distal to RB7, LB1, LB10)	0.83	0.86
5 (RB1 subsubsegments, RB4 subsegments, RB10, LB1 subsegments, LB10 subsegments)	0.82	0.81
6 (RB4 subsubsegments, RB10 subsegments, LB1 subsubsegments, LB10 subsubsegments)	0.79	0.74

Abbreviations: MESA denotes Multi-Ethnic Study of Atherosclerosis, COPD chronic obstructive pulmonary disease, CT computed tomography, ICC intra-class correlation coefficient, RMB right mainstem bronchus, LMB left mainstem bronchus, RUL right upper lobe bronchus, BI bronchus intermedius, LUL left upper lobe bronchus, LLL left lower lobe bronchus, LB6 left superior segmental bronchus, RB1 right apical segmental bronchus, RML right middle lobe bronchus, RLL right lower lobe bronchus, RB7 right medial basal bronchus, LB1+2 left apical-posterior bronchus, RB4 right lateral segmental bronchus, LB1 left apical segmental bronchus, LB10 left posterior basal segmental bronchus, RB10 right posterior segmental bronchus.

Table E2. Reproducibility of Airway Counting in 117 Randomly Selected MESA COPD CT Scans Assessed by Two Independent Image Analysts.

Airway lumen diameter strata	ICC airway count
Lumen diameter > 11.5 mm	0.96
10.0 mm < lumen diameter ≤ 11.5 mm	0.78
8.5 mm < lumen diameter ≤ 10.0 mm	0.91
7.0 mm < lumen diameter ≤ 8.5 mm	0.87
5.5 mm < lumen diameter ≤ 7.0 mm	0.84
4.0 mm < lumen diameter ≤ 5.5 mm	0.80
2.5 mm < lumen diameter ≤ 4.0 mm	0.92

Abbreviations: MESA denotes Multi-Ethnic Study of Atherosclerosis, COPD chronic obstructive pulmonary disease, CT computed tomography, and ICC intra-class correlation coefficient.

Table E3. Characteristics of Participants with Complete and Incomplete Airway Data.

	MESA COPD		SPIROMICS	
	Complete airway data N=311	Incomplete airway data N=18	Complete airway data N=1248	Incomplete airway data N=30
Age – year	68±7	67±8	65±9	64±8
Male – %	60	72	54	63
Race-ethnicity – %				
White	53	61	79	83
Black	27	28	17	17
Other	20	11	5	0
Height – cm	169±9	170±10	171±10	172±9
Weight – kg	80±18	82±15	81±18	79±22
Smoking status – %				
Former	72	72	63	63
Current	28	28	37	37
Pack-years	37±24	51±33	50±24	51±28
Percent predicted FEV <sub>1</sub>	88±22	76±23	74±26	60±31
FEV <sub>1</sub> /FVC	0.69±0.13	0.61±0.16	0.61±0.17	0.51±0.17
COPD GOLD severity – %				
No COPD (FEV <sub>1</sub> /FVC ≥ 0.70)	53	28	35	20
Mild (FEV <sub>1</sub> ≥80% predicted)	18	33	16	3
Moderate (50% ≥ FEV <sub>1</sub> < 80% predicted)	22	22	29	27
Severe (30% ≥ FEV <sub>1</sub> < 50% predicted)	6	11	15	40
Very severe (FEV <sub>1</sub> <30% predicted)	1	6	6	10
CT performed after spirometry, on same day – %	46	-	86	-
Time interval – minutes	138±62	-	58±45	-

Plus-minus values are means±SD.

Abbreviations: MESA denotes Multi-Ethnic Study of Atherosclerosis, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, COPD chronic obstructive pulmonary disease, FEV<sub>1</sub> forced expired volume in the first second, FVC forced vital capacity, CT computed tomography, and SD standard deviation.



Table E4: Airway Lumen Area According to COPD Status Stratified by Generation Number in the MESA COPD Study and SPIROMICS.

MESA COPD	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway lumen area in mm <sup>2</sup>							
COPD	264.0	143.1	81.1	32.0	16.6	9.0	6.6
No COPD	244.6	139.8	82.0	35.9	18.8	10.2	7.3
Difference (95% CI) P-value	19.4 (3.7 to 36.2) 0.02	3.4 (-4.4 to 11.6) 0.41	-1.0 (-5.4 to 3.8) 0.68	-3.9 (-5.7 to -2.0) <0.001	-2.2 (-3.2 to -1.2) <0.001	-1.2 (-1.7 to -0.6) <0.001	-0.7 (-1.0 to -1.0) 0.002
Mean airway lumen area in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>-950HU</sub> , BMI-determined CT dose, and lung volume at CT							
COPD	253.0	135.9	77.7	30.8	16.2	8.6	6.4
No COPD	256.9	145.5	84.5	36.9	19.4	10.6	7.7
Difference (95% CI) P-value	-3.9 (-16.6 to 9.5) p=0.56	-9.6 (-15.6 to -3.4) p=0.003	-6.8 (-10.6 to -2.8) p<0.001	-6.1 (-8.0 to -4.0) p<0.001	-3.2 (-4.2 to -2.1) p<0.001	-2.1 (-2.6 to -1.5) p<0.001	-1.3 (-1.7 to -0.9) p<0.001
SPIROMICS	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway lumen area in mm <sup>2</sup>							
COPD	268.5	150.0	84.7	34.9	18.2	9.4	6.5
No COPD	260.1	148.6	86.8	38.9	21.1	11.4	7.5
Difference (95% CI) P-value	8.4 (0.2 to 16.9) 0.04	1.4 (-3.1 to 6.0) 0.54	-2.1 (-4.7 to 0.6) 0.12	-4.1 (-5.1 to -3.0) <0.001	-2.9 (-3.5 to -2.3) <0.001	-2.0 (-2.3 to -1.7) <0.001	-1.0 (-1.2 to -0.8) <0.001
Mean airway lumen area in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>-950HU</sub> , BMI-determined CT dose, and lung volume at CT							
COPD	259.6	123.8	77.1	29.9	15.0	8.0	6.4
No COPD	278.8	132.6	84.7	34.8	18.0	9.8	7.8
Difference (95% CI) P-value	-19.2 (-26.8 to -11.3) p<0.001	-8.8 (-12.1 to -5.5) p<0.001	-7.6 (-10.0 to -5.1) p<0.001	-4.9 (-5.9 to -3.9) p<0.001	-3.0 (-3.6 to -2.5) p<0.001	-1.8 (-2.1 to -1.5) p<0.001	-1.3 (-1.5 to -1.2) p<0.001

Mean values and differences, along with 95% CI and p-values were estimated using linear regression with generalized estimating equations.

Abbreviations: COPD denotes chronic obstructive pulmonary disease, MESA Multi-Ethnic Study of Atherosclerosis, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, HU Hounsfield units, BMI body mass index, CT computed tomography, and CI confidence interval.

Table E5: Airway Lumen Area Associations with Percent Predicted FEV<sub>1</sub> and FVC Stratified by Generation Number in the MESA COPD Study and SPIROMICS.

MESA COPD	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway lumen area difference in mm <sup>2</sup>							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	3.8 (0.3 to 7.5) 0.03	-0.3 (-2.1 to 1.4) 0.73	-0.5 (-1.6 to 0.7) 0.38	-0.9 (-1.4 to -0.5) <0.001	-0.6 (-0.8 to -0.3) <0.001	-0.3 (-0.5 to -0.2) <0.001	-0.1 (-0.2 to 0.0) 0.006
Per 10% decrement in FVC (95% CI) P-value	4.9 (0.5 to 9.3) 0.03	0.3 (-2.0 to 2.4) 0.84	-0.2 (-1.5 to 1.1) 0.79	-0.5 (-1.1 to 0.1) 0.11	-0.1 (-0.5 to 0.2) 0.41	-0.1 (-0.3 to 0.1) 0.30	0.0 (-0.2 to 0.1) 0.61
Mean airway lumen area difference in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, airway length, smoking status, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	0.2 (-2.8 to 3.1) p=0.92	-1.7 (-2.9 to -0.6) p=0.003	-1.0 (-1.9 to -0.1) p=0.03	-0.9 (-1.2 to -0.6) p<0.001	-0.5 (-0.7 to -0.3) p<0.001	-0.3 (-0.4 to -0.2) p<0.001	-0.2 (-0.3 to -0.1) p<0.001
Per 10% decrement in FVC (95% CI) P-value	3.3 (-0.8 to 7.5) p=0.12	-0.2 (-1.8 to 1.3) p=0.77	-0.3 (-1.5 to 0.9) p=0.60	-0.5 (-1.0 to 0.0) p=0.07	-0.1 (-0.4 to 0.2) p=0.34	-0.1 (-0.3 to 0.1) p=0.26	0.0 (-0.1 to 0.1) p=0.68
SPIROMICS	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway lumen area difference in mm <sup>2</sup>							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	-1.3 (-2.9 to 0.0) 0.06	-2.1 (-3.0 to -1.3) <0.001	-1.7 (-2.2 to -1.3) <0.001	-1.4 (-1.6 to -1.2) <0.001	-0.9 (-1.0 to -0.8) <0.001	-0.5 (-0.6 to -0.4) <0.001	-0.3 (-0.3 to -0.2) <0.001
Per 10% decrement in FVC (95% CI) P-value	-4.5 (-6.6 to -2.1) <0.001	-4.0 (-5.1 to -3.0) <0.001	-2.4 (-3.2 to -1.8) <0.001	-1.7 (-2.0 to -1.4) <0.001	-0.9 (-1.1 to -0.8) <0.001	-0.4 (-0.5 to -0.3) <0.001	-0.2 (-0.3 to -0.2) <0.001
Mean airway area difference in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, airway length, smoking status, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	-4.5 (-5.7 to -3.3) p<0.001	-3.1 (-3.7 to -2.6) p<0.001	-2.4 (-2.8 to -2.0) p<0.001	-1.5 (-1.6 to -1.3) p<0.001	-0.8 (-0.8 to -0.7) p<0.001	-0.4 (-0.4 to -0.4) p<0.001	-0.3 (-0.3 to -0.2) p<0.001
Per 10% decrement in FVC (95% CI) P-value	-3.5 (-5.0 to -2.0) p<0.001	-2.7 (-3.4 to -2.1) p<0.001	-1.8 (-2.3 to -1.4) p<0.001	-1.1 (-1.3 to -0.9) p<0.001	-0.5 (-0.6 to -0.4) p<0.001	-0.3 (-0.3 to -0.2) p<0.001	-0.2 (-0.2 to -0.1) p<0.001

Mean values and differences, along with 95% CI and p-values were estimated using linear regression with generalized estimating equations.

Abbreviations: FEV<sub>1</sub> denotes forced expired volume in one second, FVC forced vital capacity, MESA Multi-Ethnic Study of Atherosclerosis, COPD chronic obstructive pulmonary disease, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, HU Hounsfield units, BMI body mass index, CT computed tomography, and CI confidence interval.

Table E6: Airway Wall Area According to COPD Status Stratified by Anatomic Name in the MESA COPD Study and SPIROMICS.

MESA COPD	Anatomic name				
	Trachea	Mainstem bronchi	Lobar bronchi	Segmental bronchi	Subsegmental bronchi
Unadjusted mean airway wall area in mm <sup>2</sup>					
COPD	179.1	109.3	57.5	29.9	19.0
No COPD	168.0	106.9	56.9	31.4	20.7
Difference	11.1	2.4	0.6	-1.5	-1.7
(95% CI)	(2.3 to 20.3)	(-3.2 to 8.4)	(-1.7 to 2.9)	(-2.6 to -0.3)	(-2.5 to -0.8)
P-value	0.01	0.41	0.62	<0.001	<0.001
Mean airway wall area in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT					
COPD	161.0	93.4	50.5	28.0	17.5
No COPD	164.1	99.2	53.0	31.0	20.2
Difference	-3.0	-5.8	-2.5	-3.0	-2.7
(95% CI)	(-9.2 to 3.4)	(-9.6 to -1.8)	(-4.3 to -0.7)	(-4.0 to -1.9)	(-3.4 to -1.9)
P-value	p=0.36	p=0.005	p=0.006	p<0.001	p<0.001
SPIROMICS	Anatomic name				
	Trachea	Mainstem bronchi	Lobar bronchi	Segmental bronchi	Subsegmental bronchi
Unadjusted mean airway wall area in mm <sup>2</sup>					
COPD	181.3	113.5	57.5	31.0	19.3
No COPD	173.5	112.0	59.1	33.2	21.9
Difference	7.8	1.5	-1.7	-2.2	-2.6
(95% CI)	(3.5 to 12.2)	(-1.9 to 5.0)	(-2.9 to -0.4)	(-2.9 to -1.5)	(-3.0 to -2.2)
P-value	<0.001	0.40	0.01	<0.001	<0.001
Mean airway wall area in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT					
COPD	177.0	96.3	48.8	27.9	17.7
No COPD	180.6	101.3	52.2	30.6	20.0
Difference	-3.6	-5.0	-3.4	-2.7	-2.3
(95% CI)	(-7.2 to 0.0)	(-7.7 to -2.2)	(-4.4 to -2.4)	(-3.3 to -2.0)	(-2.7 to -1.9)
P-value	p=0.049	p<0.001	p<0.001	p<0.001	p<0.001

Mean values and differences, along with 95% CI and p-values were estimated using linear regression with generalized estimating equations.

Abbreviations: COPD denotes chronic obstructive pulmonary disease, MESA Multi-Ethnic Study of Atherosclerosis, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, HU Hounsfield units, BMI body mass index, CT computed tomography, and CI confidence interval.

Table E7: Airway Wall Thickness According to COPD Status Stratified by Generation Number in the MESA COPD Study and SPIROMICS.

MESA COPD	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway wall thickness in mm							
COPD	2.61	2.18	1.95	1.73	1.42	1.16	1.07
No COPD	2.55	2.16	1.90	1.69	1.43	1.21	1.10
Difference	0.05	0.02	0.05	0.04	-0.01	-0.05	-0.04
(95% CI)	(-0.00 to 0.11)	(-0.04 to 0.08)	(0.01 to 0.10)	(0.01 to 0.07)	(-0.04 to 0.01)	(-0.07 to -0.03)	(-0.06 to -0.05)
P-value	0.07	0.53	0.01	0.008	0.29	<0.001	<0.001
Mean airway wall thickness in mm adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
COPD	13.1	8.4	6.8	5.5	4.1	3.2	2.9
No COPD	13.4	8.9	6.8	5.5	4.2	3.4	3.0
Difference	-0.3	-0.5	0.0	0.0	-0.2	-0.2	-0.2
(95% CI)	(-0.9 to 0.4)	(-0.9 to -0.1)	(-0.3 to 0.2)	(-0.1 to 0.1)	(-0.2 to -0.1)	(-0.3 to -0.2)	(-0.2 to -0.1)
P-value	p=0.38	p=0.02	p=0.82	p=0.96	p=0.001	p<0.001	p<0.001
SPIROMICS	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway wall thickness in mm							
COPD	2.63	2.20	1.92	1.69	1.43	1.17	1.05
No COPD	2.57	2.20	1.93	1.69	1.45	1.22	1.09
Difference	0.05	0.01	-0.01	-0.00	-0.02	-0.05	-0.05
(95% CI)	(0.02 to 0.08)	(-0.03 to 0.04)	(-0.04 to 0.01)	(-0.02 to 0.02)	(-0.04 to -0.01)	(-0.06 to -0.04)	(-0.06 to -0.04)
P-value	<0.001	0.64	0.34	0.90	0.001	<0.001	<0.001
Mean airway wall thickness in mm adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
COPD	13.6	7.7	6.1	5.1	4.1	3.2	3.1
No COPD	13.3	8.0	6.4	5.1	4.1	3.4	3.2
Difference	0.3	-0.2	-0.3	-0.1	-0.1	-0.1	-0.2
(95% CI)	(0.0 to 0.7)	(-0.5 to 0.0)	(-0.5 to -0.2)	(-0.2 to 0.0)	(-0.1 to 0.0)	(-0.2 to -0.1)	(-0.2 to -0.1)
P-value	p=0.07	p=0.08	p<0.001	p=0.02	p=0.002	p<0.001	p<0.001

Mean values and differences, along with 95% CI and p-values were estimated using linear regression with generalized estimating equations.

Abbreviations: COPD denotes chronic obstructive pulmonary disease, MESA Multi-Ethnic Study of Atherosclerosis, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, HU Hounsfield units, BMI body mass index, CT computed tomography, and CI confidence interval.

Table E8: Airway Wall Area Associations with Percent Predicted FEV<sub>1</sub> and FVC Stratified by Generation Number in the MESA COPD Study and SPIROMICS.

MESA COPD	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway wall area difference in mm <sup>2</sup>							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	2.4 (0.3 to 4.6) 0.02	-0.1 (-1.3 to 1.2) 0.93	0.1 (-0.7 to 0.8) 0.88	-0.2 (-0.6 to 0.2) 0.30	-0.4 (-0.7 to -0.1) 0.006	-0.4 (-0.6 to -0.2) <0.001	-0.2 (-0.4 to -0.1) 0.002
Per 10% decrement in FVC (95% CI) P-value	2.8 (0.3 to 5.5) 0.02	0.5 (-1.1 to 2.2) 0.52	0.1 (-0.9 to 1.0) 0.89	0.0 (-0.5 to 0.5) 0.92	0.1 (-0.3 to 0.4) 0.73	0.0 (-0.3 to 0.2) 0.80	0.0 (-0.1 to 0.2) 0.75
Mean airway wall area difference in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>-950HU</sub> , BMI-determined CT dose, and lung volume at CT							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	0.0 (-1.6 to 1.5) p=0.97	-1.1 (-2.0 to -0.3) p=0.01	-0.7 (-1.3 to -0.1) p=0.02	-0.6 (-0.9 to -0.3) p<0.001	-0.5 (-0.7 to -0.3) p<0.001	-0.4 (-0.6 to -0.3) p<0.001	-0.3 (-0.4 to -0.1) p<0.001
Per 10% decrement in FVC (95% CI) P-value	1.1 (-0.8 to 3.1) p=0.25	0.0 (-1.2 to 1.3) p=0.94	-0.4 (-1.2 to 0.3) p=0.25	-0.4 (-0.7 to 0.0) p=0.06	-0.1 (-0.4 to 0.2) p=0.50	-0.1 (-0.3 to 0.1) p=0.36	0.0 (-0.2 to 0.2) p=0.96
SPIROMICS	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway wall area difference in mm <sup>2</sup>							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	-0.2 (-0.9 to 0.7) 0.77	-1.7 (-2.2 to -1.1) <0.001	-1.1 (-1.4 to -0.8) <0.001	-0.9 (-1.0 to -0.7) <0.001	-0.8 (-0.9 to -0.6) <0.001	-0.6 (-0.7 to -0.5) <0.001	-0.4 (-0.4 to -0.3) <0.001
Per 10% decrement in FVC (95% CI) P-value	-1.8 (-2.8 to -0.7) 0.001	-3.1 (-3.9 to -2.2) <0.001	-1.7 (-2.2 to -1.1) <0.001	-1.0 (-1.3 to -0.8) <0.001	-0.8 (-1.0 to -0.6) <0.001	-0.5 (-0.6 to -0.4) <0.001	-0.3 (-0.3 to -0.2) <0.001
Mean airway wall area difference in mm <sup>2</sup> adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>-950HU</sub> , BMI-determined CT dose, and lung volume at CT							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	-1.5 (-2.1 to -0.9) p<0.001	-2.4 (-2.8 to -1.9) p<0.001	-1.6 (-1.9 to -1.3) p<0.001	-1.0 (-1.2 to -0.9) p<0.001	-0.8 (-0.9 to -0.7) p<0.001	-0.5 (-0.6 to -0.5) p<0.001	-0.4 (-0.5 to -0.4) p<0.001
Per 10% decrement in FVC (95% CI) P-value	-1.5 (-2.2 to -0.8) p<0.001	-2.2 (-2.7 to -1.6) p<0.001	-1.3 (-1.6 to -1.0) p<0.001	-0.9 (-1.0 to -0.7) p<0.001	-0.6 (-0.7 to -0.5) p<0.001	-0.4 (-0.5 to -0.3) p<0.001	-0.3 (-0.3 to -0.2) p<0.001

Mean values and differences, along with 95% CI and p-values were estimated using linear regression with generalized estimating equations.

Abbreviations: FEV<sub>1</sub> denotes forced expired volume in one second, FVC forced vital capacity, MESA Multi-Ethnic Study of Atherosclerosis, COPD chronic obstructive pulmonary disease, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, HU Hounsfield units, BMI body mass index, CT computed tomography, and CI confidence interval.

Table E9: Percent Wall Area According to COPD Status Stratified by Generation Number in the MESA COPD Study and SPIROMICS.

MESA COPD	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway percent wall area							
COPD	40.5	43.4	48.4	58.4	62.6	65.6	67.3
No COPD	40.8	43.4	47.3	55.8	60.9	64.9	67.0
Difference	-0.3	-0.0	1.1	2.6	1.7	0.6	0.3
(95% CI)	(-0.9 to 0.4)	(-0.5 to 0.5)	(0.5 to 1.6)	(1.8 to 3.3)	(1.1 to 2.3)	(0.1 to 1.1)	(-0.2 to 0.7)
P-value	0.38	0.90	<0.001	<0.001	<0.001	0.02	0.26
Mean airway percent wall area adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
COPD	40.6	43.2	47.9	58.1	62.5	66.3	67.9
No COPD	40.7	43.0	46.8	55.3	60.5	64.9	66.9
Difference	-0.1	0.2	1.1	2.7	1.9	1.4	0.9
(95% CI)	(-0.8 to 0.7)	(-0.4 to 0.8)	(0.5 to 1.8)	(1.8 to 3.6)	(1.2 to 2.7)	(0.8 to 2.0)	(0.4 to 1.5)
P-value	p=0.87	p=0.50	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
SPIROMICS	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean airway percent wall area							
COPD	40.4	43.1	47.3	56.2	61.4	65.1	67.1
No COPD	40.1	43.0	47.0	54.5	59.6	63.7	66.4
Difference	0.3	0.1	0.3	1.7	1.7	1.5	0.7
(95% CI)	(-0.1 to 0.7)	(-0.2 to 0.3)	(0.0 to 0.6)	(1.3 to 2.1)	(1.4 to 2.0)	(1.2 to 1.7)	(0.5 to 0.9)
P-value	0.12	0.48	0.04	<0.001	<0.001	<0.001	<0.001
Mean airway percent wall area adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
COPD	40.4	43.9	46.9	56.7	62.6	67.3	68.6
No COPD	39.2	43.5	46.4	54.8	60.4	65.5	67.4
Difference	1.2	0.4	0.5	1.9	2.2	1.9	1.2
(95% CI)	(0.8 to 1.7)	(0.2 to 0.7)	(0.2 to 0.9)	(1.5 to 2.4)	(1.8 to 2.6)	(1.5 to 2.2)	(1.0 to 1.5)
P-value	p<0.001	p=0.003	p=0.005	p<0.001	p<0.001	p<0.001	p<0.001

Percent wall area was calculated as the ratio of airway wall area to the sum of wall and lumen area multiplied by 100. Mean values and differences, along with 95% CI and p-values were estimated using linear regression with generalized estimating equations.

Abbreviations: COPD denotes chronic obstructive pulmonary disease, MESA Multi-Ethnic Study of Atherosclerosis, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, HU Hounsfield units, BMI body mass index, CT computed tomography, and CI confidence interval.

Table E10: Percent Wall Area Associations with Percent Predicted FEV<sub>1</sub> and FVC Stratified by Generation Number in the MESA COPD Study and SPIROMICS.

MESA COPD	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean percent wall area difference							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	0.0 (-0.2 to 0.1) 0.74	0.0 (-0.1 to 0.2) 0.48	0.1 (0.0 to 0.2) 0.04	0.6 (0.3 to 0.7) <0.001	0.4 (0.3 to 0.6) <0.001	0.2 (0.1 to 0.3) 0.003	0.1 (-0.1 to 0.2) 0.18
Per 10% decrement in FVC (95% CI) P-value	0.0 (-0.2 to 0.1) 0.57	0.1 (0.0 to 0.2) 0.21	0.1 (-0.1 to 0.2) 0.40	0.3 (0.1 to 0.6) 0.01	0.2 (0.0 to 0.6) 0.07	0.2 (0.0 to 0.4) 0.07	0.1 (0.0 to 0.3) 0.08
Mean percent wall area difference adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	0.0 (-0.2 to 0.1) p=0.87	0.1 (-0.1 to 0.2) p=0.38	0.1 (-0.1 to 0.3) p=0.35	0.5 (0.3 to 0.8) p<0.001	0.5 (0.3 to 0.7) p<0.001	0.3 (0.1 to 0.5) p<0.001	0.1 (0.0 to 0.3) p=0.07
Per 10% decrement in FVC (95% CI) P-value	-0.1 (-0.3 to 0.1) p=0.25	0.1 (-0.1 to 0.2) p=0.50	-0.1 (-0.2 to 0.1) p=0.60	0.2 (-0.1 to 0.4) p=0.22	0.1 (-0.1 to 0.4) p=0.40	0.1 (-0.1 to 0.4) p=0.27	0.1 (-0.1 to 0.2) p=0.29
SPIROMICS	Airway generation number						
	0	1	2	3	4	5	6
Unadjusted mean percent wall area difference							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	0.1 (0.0 to 0.2) 0.002	0.0 (0.0 to 0.0) 0.68	0.1 (0.1 to 0.2) <0.001	0.6 (0.4 to 0.6) <0.001	0.5 (0.4 to 0.5) <0.001	0.4 (0.4 to 0.5) <0.001	0.3 (0.2 to 0.3) <0.001
Per 10% decrement in FVC (95% CI) P-value	0.2 (0.0 to 0.2) 0.003	0.0 (-0.1 to 0.0) 0.80	0.2 (0.1 to 0.3) <0.001	0.6 (0.5 to 0.7) <0.001	0.5 (0.4 to 0.6) <0.001	0.4 (0.3 to 0.5) <0.001	0.3 (0.2 to 0.3) <0.001
Mean percent wall area difference adjusted for age, gender, height, race-ethnicity, smoking status, airway length, percent emphysema <sub>.950HU</sub> , BMI-determined CT dose, and lung volume at CT							
Per 10% decrement in FEV <sub>1</sub> (95% CI) P-value	0.3 (0.2 to 0.4) p<0.001	0.0 (0.0 to 0.1) p=0.29	0.20 (0.1 to 0.3) p<0.001	0.8 (0.7 to 0.8) p<0.001	0.7 (0.7 to 0.8) p<0.001	0.5 (0.5 to 0.6) p<0.001	0.4 (0.3 to 0.4) p<0.001
Per 10% decrement in FVC (95% CI) P-value	0.2 (0.0 to 0.3) p=0.007	0.0 (-0.1 to 0.1) p=0.65	0.2 (0.1 to 0.2) p<0.001	0.6 (0.5 to 0.8) p<0.001	0.6 (0.4 to 0.7) p<0.001	0.4 (0.3 to 0.5) p<0.001	0.3 (0.2 to 0.3) p<0.001

Percent wall area was calculated as the ratio of airway wall area to the sum of wall and lumen area multiplied by 100. Mean values and differences, along with 95% CI and p-values were estimated using linear regression with generalized estimating equations.

Abbreviations: FEV<sub>1</sub> denotes forced expired volume in one second, FVC forced vital capacity, MESA Multi-Ethnic Study of Atherosclerosis, COPD chronic obstructive pulmonary disease, SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study, HU Hounsfield units, BMI body mass index, CT computed tomography, and CI confidence interval.

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