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ORIGINAL ARTICLE

A Genetic Risk Score Associated with Chronic Obstructive Pulmonary Disease Susceptibility and Lung Structure on Computed Tomography

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Abstract

Rationale: Chronic obstructive pulmonary disease (COPD) has been associated with numerous genetic variants, yet the extent to which its genetic risk is mediated by variation in lung structure remains unknown.

Objectives: To characterize associations between a genetic risk score (GRS) associated with COPD susceptibility and lung structure on computed tomography (CT).

Methods: We analyzed data from MESA Lung (Multi-Ethnic Study of Atherosclerosis Lung Study), a U.S. general population–based cohort, and SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study). A weighted GRS was calculated from 83 SNPs that were previously associated with lung function. Lung density, spatially matched airway dimensions, and airway counts were assessed on full-lung CT. Generalized linear models were adjusted for age, age squared, sex, height, principal components of genetic ancestry, smoking status, pack-years, CT model, milliamperes, and total lung volume.

Measurements and Main Results: MESA Lung and SPIROMICS contributed 2,517 and 2,339 participants, respectively. Higher GRS was associated with lower lung function and increased COPD risk, as well as lower lung density, smaller airway lumens, and fewer small airways, without effect modification by smoking. Adjustment for CT lung structure, particularly small airway measures, attenuated associations between the GRS and FEV_1/FVC by 100% and 60% in MESA and SPIROMICS, respectively. Lung structure ($P < 0.0001$), but not the GRS ($P > 0.10$), improved discrimination of moderate-to-severe COPD cases relative to clinical factors alone.

Conclusions: A GRS associated with COPD susceptibility was associated with CT lung structure. Lung structure may be an important mediator of heritability and determinant of personalized COPD risk.

Keywords: spirometry; emphysema; airway remodeling

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At a Glance Commentary

Scientific Knowledge on the Subject: Chronic obstructive pulmonary disease (COPD) has been associated with numerous genetic variants, yet the extent to which its genetic risk is mediated by variation in lung structure remains unknown.

What This Study Adds to the Field: This is the first study to demonstrate that a genetic risk score associated with COPD susceptibility was also associated with variation in lung structure on computed tomography. Our findings suggest that elements of lung structure, particularly those relating to the small airways, may be important mediators of COPD heritability and major determinants of personalized risk for COPD.

Chronic obstructive pulmonary disease (COPD), which is defined by airflow limitation that is incompletely reversible (1), is the third leading cause of death worldwide (2, 3). Prediction and prevention of COPD are particularly important given the lack of medical therapies that have been proved to reduce COPD-related mortality (4, 5).

Numerous genetic variants have been associated with low lung function and COPD, providing a promising avenue for estimation of personalized COPD risk. A genome-wide association study (GWAS) of participants at extremes of lung function in the UK Biobank found 43 new signals for lung function (6). Combined with 54 previously reported signals, 97 SNPs were estimated to account for up to 14% of the SNP-based heritability of lung function traits, which is equivalent to one-third of the total estimated heritability (7, 8). Based on 95 of 97 SNPs, a genetic risk score (GRS) was developed and found to be associated with COPD status in several COPD case–control studies, a lung resection cohort, and two community-based studies (6). Furthermore, the GRS was associated with lung function in children (6), suggesting that it may index developmental factors relevant to risk of spirometry-defined COPD in adulthood (9–11).

Variations in lung structure are increasingly recognized as risk determinants for COPD (12–19). We tested the hypothesis that the GRS would be associated with quantitative measures from lung computed tomography (CT) in adults included in a general U.S. population–based cohort and a large case–control study of COPD. Furthermore, to understand the potential importance of genetic testing and CT scanning in COPD risk prediction, we tested the contributions of the GRS and CT lung structure to discrimination of moderate-to-severe COPD. Some of the results have been previously reported in the form of abstracts (20, 21).

Methods

Samples

MESA (Multi-Ethnic Study of Atherosclerosis) enrolled 6,814 participants, 45–84 years old, who self-reported non-Hispanic white, African American, Hispanic/Latino, or Asian American race/ethnicity in 2000–2002. The exclusion criteria were a history of clinical cardiovascular disease, weight $>$ 136 kg, and impediments to long-term participation (22). MESA Lung (23) comprised a random subsample with baseline endothelial function measurement, genetic consent, and spirometry in 2004–2006; participants in MESA Air, which recruited 257 participants in 2006–2007 using MESA inclusion criteria (24); and a random sample of participants undergoing cardiac magnetic resonance imaging in 2010–2012. The present analysis included all MESA Lung participants who underwent chest CT in 2010–2012.

SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) recruited individuals with and without COPD, 40–80 years old, with $\geqslant$20 pack-years of smoking, in 2010–2015 (25). The exclusion criteria included other chronic lung diseases except asthma, body mass index $>$ 40 kg/m^2, prior lung resection, metal in chest, and pregnancy. A small number of SPIROMICS nonsmokers ($<$1 pack-year) were excluded from the current analysis.

Institutional review board approval was obtained at each clinical site for both studies.

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Author Contributions: E.C.O.: study design, data quality control and harmonization, data analysis, and manuscript preparation. V.E.O.: data quality control and harmonization, calculation of genetic risk score, data analysis, and critical review of the manuscript. B.M.S. and E.A.H.: study design, measurement of lung structure, and critical review of the manuscript. J.N.N., A.W.M., X.G., K.D.T., and S.P.: calculation of genetic risk score and critical review of the manuscript. P.G.W., D.J.C., N.N.H., F.J.M., R.P., M.K.H., C.C., M.T.D., G.C., J.A.K., R.B., and R.G.B.: study design, data collection, and critical review of the manuscript. E.R.B. and D.A.M.: data collection, calculation of genetic risk score, and critical review of the manuscript. S.S.R. and J.I.R.: study design, data collection, calculation of genetic risk score, and critical review of the manuscript. E.C.O. had full access to all of the data in the studies and had final responsibility for the decision to submit for publication.

Written informed consent was obtained from all participants.

Genotyping

Genotyping was performed in MESA using the Affymetrix Human SNP array 6.0 (Affymetrix Inc.), and in SPIROMICS via the Illumina HumanOmniExpressExome BeadChip and BeadStudio (Illumina, Inc.). A total of 897,981 SNPs passed study-specific quality control, and an additional ~2 million SNPs were imputed in each racial/ethnic group via 1,000 Genomes imputation (Phase 3, v5) and the Haplotype Reference Consortium.

The GRS was calculated and risk alleles were weighted based on the prior publication (6). SNPs that were not available in the imputation files or had low imputation quality ($R^2 \leqslant 0.5$) were not used (Table E1 in the online supplement). An unweighted GRS was used for sensitivity analyses.

Genotype data were also used to estimate principal components of genetic ancestry (26).

Lung Function

Spirometry was performed in accordance with American Thoracic Society recommendations (27) on a dry-rolling-seal spirometer in MESA Lung and a pneumotachograph in SPIROMICS. Exams with fewer than two acceptable measures repeatable within 200 ml were excluded. Predicted values and limits of normal were calculated using reference equations (28). COPD was defined as a post-bronchodilator $FEV_1/FVC < 0.70$ (1). Moderate-to-severe COPD was defined by an FEV_1% predicted < 80% (1).

Lung Structure

Participants underwent full-lung inspiratory CT on 64-slice or 128-slice helical scanners (120 kVp, 0.625- to 0.75-mm slice thickness, and 0.5-s rotation time) via the same protocol in both studies (29).

Percent emphysema was defined on inspiratory scans as lung voxels with attenuation < -950 Hounsfield units (HU) divided by total imaged lung voxels $\times 100$ (30). The upper limit of normal (ULN) for percent emphysema was defined by reference equations (31).

In SPIROMICS, paired expiratory scans were also obtained, permitting parametric response mapping (PRM) analysis to define functional small airway disease (PRM^{fSAD}) as areas of lung > -950 HU on inspiration and < -856 HU on expiration (32).

Airway dimensions were assessed on inspiratory scans at a single reading center for both studies blinded to other participant information (33). The central airway tree was identified using Apollo Software (VIDA Diagnostics). Airways were labeled anatomically from the trachea to subsegmental bronchi along five prespecified paths (RB1, RB4, RB10, LB1, and LB10). 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 (generation 0). The small airway count was defined as the sum of airway counts for generations 6 or greater (34). All paths were counted in MESA Lung, whereas only five paths were measured in SPIROMICS.

The cross-sectional airway wall area and wall thickness, as well as the lumen area, diameter, and perimeter, were measured perpendicular to the local airway segment's long axis using a subvoxel resolution algorithm, within an image plane, and measurements were averaged along the middle third of each labeled airway segment (33, 35, 36). Percent wall area was defined as (airway wall area/total cross-sectional area) $\times 100$.

Covariates

Age, sex, race/ethnicity, and tobacco use were self-reported. Never-smokers in MESA were defined by lifetime smoking of <100 cigarettes, and current smokers were defined by cigarette use within the past 30 days, with biochemical verification in a subset (24). Pack-years were calculated as (cigarettes per day/20) $\times$ years smoked. Height was measured using standard techniques.

Statistical Analysis

Effect estimates for the GRS were reported per SD and per quintile. All models were stratified by study.

Associations between the GRS and lung function (FEV_1, FVC, and FEV_1/FVC), lung density (log-transformed percent emphysema and PRM^{fSAD}), and small airway count were analyzed in linear regression models. Associations with moderate-to-severe COPD were tested by logistic regression. Generalized estimating equations accounting for repeated measures within subjects were used to test associations with airway dimensions.

As in the study that derived the GRS (6), models were adjusted for age, age squared, sex, height, smoking status, pack-years, principal components of ancestry 1–10, and site. Models for CT lung structure endpoints were additionally adjusted for CT model, milliamperes, and total imaged lung volume. In sensitivity analyses, the impact of additional adjustment for lung function was assessed, and differential associations by age, racial/ethnic group, and smoking status were tested in stratified models and via multiplicative interaction terms.

Based on our hypotheses (Figure E1), we assessed the potential mediation of the association between the GRS and low lung function (37). First, the effect estimate for the GRS with respect to lung function was assessed in models adjusted for the standard covariates mentioned above, yielding $\beta_{GRS,total}$. Next, the effect estimate for the GRS was recalculated after additional adjustment for elements of lung structure, which were treated as mediators, yielding $\beta_{GRS,unmediated}$. Percent mediation was defined as $(\beta_{GRS,total} - \beta_{GRS,unmediated})/\beta_{GRS,total} \times 100$. The Sobel test was used to test the significance of potential mediation effects.

With respect to discrimination of cases of moderate-to-severe COPD, logistic regression models including clinical risk factors only versus those additionally including the GRS and/or lung structure were contrasted using concordance (c) statistics, or rank correlations between predicted probabilities of moderate-to-severe COPD versus the observed disease status (38), and receiver operating characteristic curves, compared using DeLong's test (39).

Analyses were performed in SAS, version 9.4 or R.

Results

Characteristics

The analytic sample included 2,517 MESA Lung participants and 2,339 SPIROMICS participants (Table 1). The average age was 69 years for MESA Lung participants and 64 years for SPIROMICS participants, and the proportion of male participants was 48% and 54%, respectively.

With respect to self-reported race/ethnicity, 40% of MESA Lung participants were non-Hispanic white, 25% were African

Table 1. Baseline Characteristics of the Participants

	MESA Lung (*N* = 2,517)	SPIROMICS (*N* = 2,339)	
		Control Subjects (*n* = 781)	Cases (*n* = 1,558)
Genetic risk score, mean (SD)	87.3 (6.6)	88.0 (6.6)	88.7 (6.5)
Age, mean (SD), yr	69.1 (9.3)	60.5 (9.6)	65.3 (8.0)
Height, mean (SD), cm	165.4 (9.9)	169.5 (9.3)	170.2 (9.6)
Body mass index, mean (SD), kg/m^2	28.4 (5.5)	29.0 (5.1)	27.3 (5.3)
Male, *n* (%)	1,206 (47.9)	374 (47.9)	894 (57.4)
Race/ethnicity, *n* (%)			
Non-Hispanic white	995 (39.5)	557 (71.3)	1,292 (82.9)
African American	617 (24.5)	206 (26.4)	238 (15.3)
Hispanic/Latino	551 (21.9)	0 (0)	0 (0)
Asian American	354 (14.1)	4 (0.5)	19 (1.2)
Smoking status, *n* (%)			
Never	1,228 (48.8)	0 (0)	0 (0)
Former	1,126 (44.7)	382 (48.9)	1,018 (65.3)
Current	163 (6.5)	399 (51.1)	540 (34.7)
Pack-years, median (Q1–Q3)*	12 (2–30)	37.5 (30.0–49.5)	47.0 (35.0–63.0)
Lung function			
FEV_1, mean (SD), percent predicted†	95.5 (23.0)	90.8 (14.3)	53.9 (22.4)
FEV_1/FVC, mean (SD), percent	74.1 (8.8)	74.0 (5.5)	49.7 (12.9)
COPD, *n* (%)			
GOLD 1	89 (4.2)	11 (1.4)	340 (21.9)
GOLD 2	62 (2.9)	9 (1.2)	699 (44.9)
GOLD 3	9 (0.4)	0 (0)	363 (23.3)
GOLD 4	8 (0.4)	0 (0)	148 (9.5)
Lung structure			
Lung density			
Percent emphysema, median (Q1–Q3), percent	1.44 (0.58–3.02)	0.98 (0.47–2.06)	6.70 (2.34–15.46)
Percent emphysema > ULN, *n* (%)	207 (8.2)	59 (7.6)	836 (53.7)
PRM^{fSAD}, median (Q1–Q3), percent		6.0 (2.0–11.0)	27.0 (16.0–37.0)
Airway dimensions			
Inner airway diameter, median (Q1–Q3), mm	4.3 (3.6–5.0)	4.4 (3.1–6.2)	4.1 (2.7–5.9)
Average wall area, median (Q1–Q3), mm^2	30.3 (24.2–37.1)	51.7 (29.1–87.9)	47.3 (25.2–82.6)
Percent wall area, median (Q1–Q3), percent	61.5 (58.2–64.4)	60.2 (53.6–65.0)	61.8 (55.0–66.3)
Small airway count, *n* (SD)	186 (124–250)	18 (17–19)	17 (14–18)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MESA = Multi-Ethnic Study of Atherosclerosis; PRM^{fSAD} = parametric response mapping of functional small airway disease; Q = quartile; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study; ULN = upper limit of normal.
Excludes participants without valid measurement of genetic risk score for COPD susceptibility and/or valid measurements of lung function and structure.
*In ever-smokers.
†Prebronchodilator.

American, 22% were Hispanic/Latino, and 14% were Asian American. In SPIROMICS, 80% were non-Hispanic white and 19% were African American. GRS distributions varied slightly by race/ethnicity: compared with non-Hispanic white participants, African American and Hispanic/Latino participants had higher average GRS, whereas Asian American participants had lower average GRS (Figure E2).

In MESA Lung, 49% of the participants were never-smokers and 7% were current smokers. Among ever-smokers, the median pack-years smoked was 12. By contrast, 40% of the SPIROMICS participants were current smokers, and the median pack-years smoked was 44. Although participants in higher quintiles of the GRS for COPD included a higher proportion of current smokers (Tables E2 and E3), these differences were not statistically significant within racial/ethnic strata.

Moderate-to-severe COPD was present in 4% ($n = 79$) of MESA Lung participants, in contrast to 52% ($n = 1{,}219$) of SPIROMICS participants (Table 1). In both cohorts, lower lung function and more cases of moderate-to-severe COPD were observed in higher GRS quintiles (Tables E2 and E3).

Percent emphysema > ULN was found in 8% and 38% of MESA Lung and SPIROMICS participants, respectively (Table 1). Airway measurements were similar across cohorts, except for the small airway count, which was expected given the differences in the airways measured. Participants in higher GRS quintiles demonstrated more percent emphysema > ULN, fewer small airways, thinner airway lumens, and thinner airway walls (Tables E2 and E3).

Lung Function

In adjusted models, higher GRS was associated with lower FEV_1 and FEV_1/FVC (Table 2). Effect estimates were larger in SPIROMICS than in MESA Lung, yet the results were statistically significant in both cohorts; associations with FVC were nonsignificant. One SD greater GRS was associated with an odds ratio for moderate-to-severe COPD of 1.44 in MESA Lung and 1.28 in SPIROMICS. There was no evidence for effect modification by race/ethnicity ($P_{\text{interaction}} > 0.20$).

Table 2. Associations between the Genetic Risk Score and Lung Function

	Quintile of Genetic Risk Score						
	Q1	Q2	Q3	Q4	Q5	Per SD (95% CI)	*P* Value*
FEV_1, ml							
MESA Lung	Ref	12.3	−19.1	−50.3	−56.2	−22.1 (−40.3 to −3.9)	0.0173
SPIROMICS	Ref	−10.4	−58.4	−48.8	−173.1†	−56.0 (−86.5 to −26.0)	0.0003
FVC, ml							
MESA Lung	Ref	30.3	28.3	10.8	21.8	7.1 (−14.9 to 29.2)	0.53
SPIROMICS	Ref	28.7	0.1	21.0	−70.1	−21.5 (−50.1 to 7.8)	0.15
FEV_1/FVC, percent							
MESA Lung	Ref	−0.52	−1.28‡	−1.83†	−2.21†	−0.80 (−1.13 to −0.46)	<0.0001
SPIROMICS	Ref	−0.73	−1.71	−1.74	−4.32†	−1.37 (−1.95 to −0.78)	<0.0001
Moderate-to-severe COPD							
MESA Lung	Ref	0.90	1.57	2.23	2.14	1.44 (1.12 to 1.86)	0.0051
SPIROMICS	Ref	1.11‡	1.32	1.50	2.01†	1.28 (1.17 to 1.40)	<0.0001

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; MESA = Multi-Ethnic Study of Atherosclerosis; Q = quintile; Ref = reference; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study.
One SD is equivalent to 6.6 in MESA Lung and 6.5 in SPIROMICS. The linear regression models were adjusted for age, age^2, sex, height, smoking status, pack-years, principal components of ancestry 1–10, and site.
*Significance for linear model of continuous genetic risk score.
†Significance for quintiles of genetic risk score: $P < 0.001$.
‡Significance for quintiles of genetic risk score: $P < 0.05$.

Lung Structure

Higher GRS was associated with lower lung density (Table 3). In MESA Lung, per SD, the GRS for COPD was associated with 5% greater percent emphysema. In SPIROMICS, the GRS was not significantly associated with percent emphysema, but was associated with 6% greater PRM^{fSAD} per SD.

Furthermore, higher GRS was associated with lower small airway counts and smaller airway lumens in both cohorts, with similar effect estimates. Higher GRS was associated with thinner airway walls but a greater percent wall area, consistent with a proportionately

Table 3. Associations between the Genetic Risk Score and Lung Structure on Computed Tomography

	Quintile of Genetic Risk Score						
	Q1	Q2	Q3	Q4	Q5	Per SD (95% CI)	*P* Value*
Lung density							
Log-transformed % emphysema							
MESA Lung	Ref	1.14†	1.13†	1.15†	1.14†	1.05 (1.02 to 1.09)	0.0010
SPIROMICS	Ref	1.00	1.03	1.02	1.10	1.03 (0.99 to 1.08)	0.147
Log-transformed % PRM^{fSAD}							
SPIROMICS	Ref	0.98	1.03	1.06	1.15†	1.06 (1.02 to 1.10)	0.0027
Small airway count‡							
MESA Lung	Ref	−9.59	−22.16§	−27.07§	−34.18§	−13.65 (−17.06 to −10.25)	<0.0001
SPIROMICS	Ref	−0.44	−0.49	−0.41	−0.83†	−0.28 (−0.48 to −0.09)	0.0037
Airway dimensions							
Inner airway diameter							
MESA Lung	Ref	0.04	−0.01	−0.04	−0.09§	−0.07 (−0.09 to −0.05)	<0.0001
SPIROMICS	Ref	0.05	0.00	−0.01	−0.09§	−0.06 (−0.08 to −0.03)	<0.0001
Average wall area							
MESA Lung	Ref	0.26	−0.15	−0.25	−0.63†	−0.47 (−0.65 to −0.29)	<0.0001
SPIROMICS	Ref	1.11†	0.07	−0.42	−2.14§	−1.31 (−1.85 to −0.78)	<0.0001
Percent wall area							
MESA Lung	Ref	−0.25†	0.04	0.18	0.42§	0.32 (0.21 to 0.42)	<0.0001
SPIROMICS	Ref	−0.05	−0.06	0.04	0.29§	0.17 (0.09 to 0.26)	<0.0001

Definition of abbreviations: CI = confidence interval; MESA = Multi-Ethnic Study of Atherosclerosis; PRM^{fSAD} = functional small airway disease; Q = quintile; Ref = reference; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study.
One SD is equivalent to 6.6 in MESA and 6.5 in SPIROMICS. Number of participants: 2,517 in MESA analyses and 2,339 in SPIROMICS analyses. The linear regression model was adjusted for age, age^2, sex, height, smoking status, pack-years, principal components of ancestry 1–10, site, computed tomography scanner model, and body mass index high/low; airway count and dimension analyses were additionally adjusted for total lung volume and lobe.
*Significance for linear model of continuous genetic risk score.
†Significance for quintiles of genetic risk score: $P < 0.05$.
‡Count of airway generations 6–9. All paths were counted in MESA, whereas only five paths were measured in SPIROMICS.
§Significance for quintiles of genetic risk score: $P < 0.001$.

greater decrement in lumen size than in wall area.

Results according to GRS quintile showed monotonic associations without strong evidence for nonlinear associations.

Sensitivity Analyses

Among never-smokers in MESA Lung ($n = 1{,}228$), significant associations with the GRS were observed for all lung structural elements, and there was no evidence of effect modification by smoking status in either cohort ($P_{interaction} > 0.20$; Table E4 and Figures E3–E5).

Compared with participants <65 years old, elderly SPIROMICS participants demonstrated a larger effect estimate for small airway count ($P_{interaction} = 0.0066$) and, notably, demonstrated the same effect estimate for percent emphysema as was observed in elderly MESA Lung participants (1.05 per SD of the GRS; Table E4 and Figures E3–E5).

Associations between the GRS and lung structure on CT were similar across strata of race/ethnicity in MESA Lung (Table E4 and Figures E3–E5). In SPIROMICS, African American participants demonstrated weaker GRS–structure associations, but no definite evidence for effect modification was observed ($P_{interaction} = 0.054$–0.91).

Further adjustment for lung function substantially attenuated associations between the GRS and PRM^{fSAD} in SPIROMICS (Table E5). By contrast, associations between the GRS and percent emphysema were independent of lung function in MESA Lung, as were associations with airway dimensions and airway counts in both cohorts.

Similar results were obtained using the unweighted GRS (Tables E6 and E7).

Mediation

Associations between the GRS and FEV_1 and FEV_1/FVC were attenuated by adjustment for lung structure on CT (Figure 1), consistent with substantial mediation of GRS–lung function associations by lung structure. In MESA Lung, the small airway count alone attenuated 93% of the association with FEV_1 and 82% of the association with FEV_1/FVC. In SPIROMICS, the greatest attenuation was observed for PRM^{fSAD}: 68% for FEV_1 and 60% for FEV_1/FVC. Percent emphysema was associated with a significant attenuation in MESA Lung, but not in SPIROMICS. In both cohorts, small airway dimensions were associated with a modest but significant attenuation. Adjustment for all CT lung structure elements in the same model resulted in full attenuation of the associations in MESA Lung, and 60–76% attenuation in SPIROMICS.

Discrimination of Moderate-to-Severe COPD

Despite strong and statistically significant associations with moderate-to-severe COPD, the contribution of the GRS to discrimination of cases was low: the c-statistic increased 0.004 in MESA Lung and 0.006 in SPIROMICS ($P > 0.10$ for both;

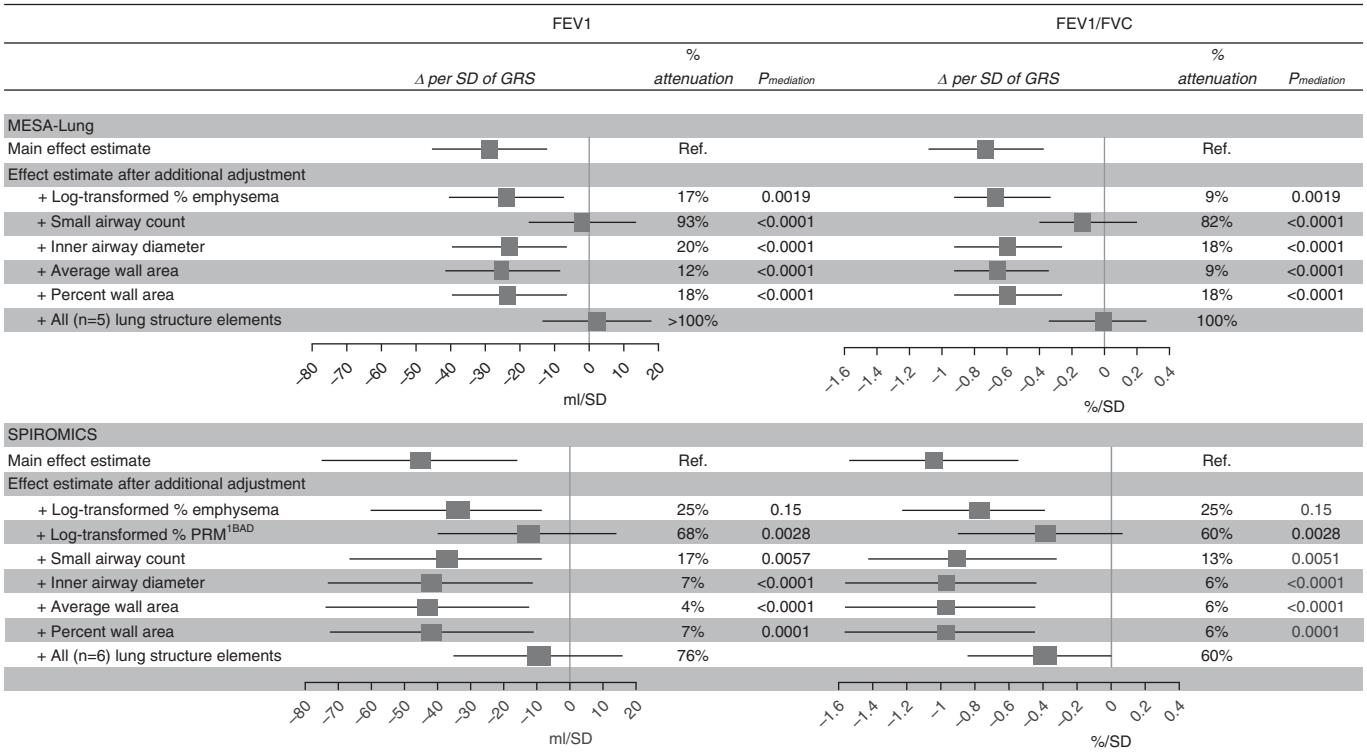
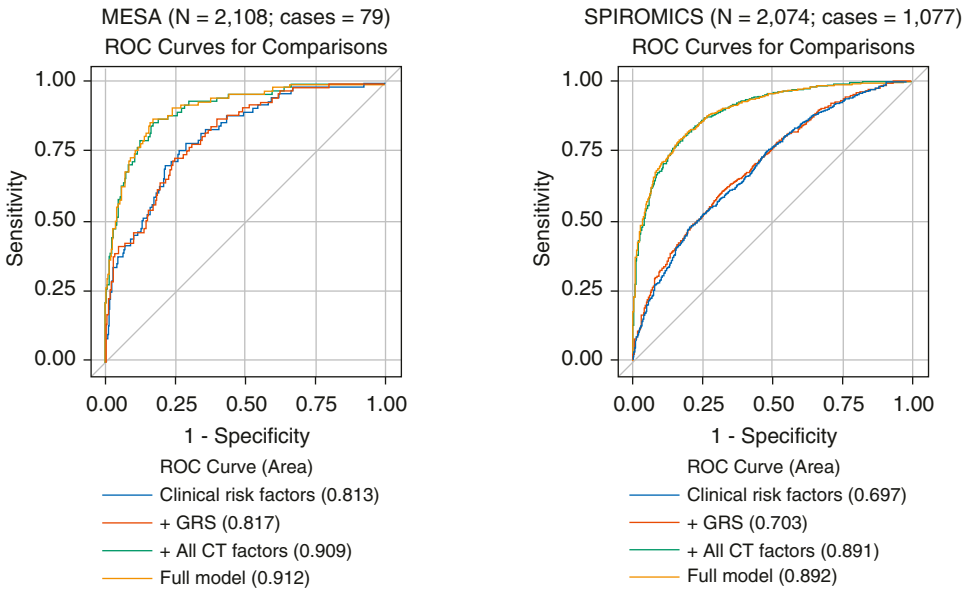


Figure 1. Associations between the genetic risk score (GRS) and lung function, sequentially adjusted by features of lung structure on computed tomography (CT). Number of participants: 2,517 in MESA (Multi-Ethnic Study of Atherosclerosis) analyses and 2,339 in SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) analyses. The linear regression model was adjusted for age, age^2, sex, height, smoking status, pack-years, principal components of ancestry 1–10, site, CT model, body mass index high/low, total imaged lung volume, and lobe. The percent attenuation of the main effect estimate after additional adjustment for CT lung structural element(s) is calculated as [(original effect estimate − adjusted effect estimate)/original effect estimate] × 100. The statistical significance of potential mediational effects was evaluated by the Sobel (cross-product) method. COPD = chronic obstructive pulmonary disease; PRM^{fSAD} = parametric response mapping of functional small airway disease; Ref. = reference.



	MESA			SPIROMICS		
	AUC (95% CI)	*Δ c*	*P-value*	*AUC (95% CI)*	*Δ c*	*P-value*
Clinical risk factors	.81 (.77, .86)	Ref		.70 (.67, .72)	Ref	
+ GRS	.82 (.77, .86)	.004	.59	.70 (.68, .72)	.006	.13
+ % emphysema	.86 (.82, .90)	.048	.0001	.85 (.83, .86)	.151	<.0001
+ % fSAD				.88 (.86, .89)	.181	<.0001
+ small airway count	.88 (.84, .92)	.066	<.0001	.73 (.71, .75)	.030	<.0001
+ all CT	.91 (.88, .94)	.096	<.0001	.89 (.88, .90)	.195	<.0001
+ GRS and all CT	.91 (.88, .94)	.098	<.0001	.89 (.88, .91)	.196	<.0001

Figure 2. Receiver operating characteristic (ROC) curves for moderate-to-severe chronic obstructive pulmonary disease according to clinical risk factors, lung structure, and genetic risk score (GRS). Clinical risk factors included in the referent model were age, age^2, sex, height, smoking status, pack-years, site, and principal components of ancestry 1–10. To this model, the following factors were added individually: the GRS for COPD, percent emphysema, percent functional small airway disease (fSAD, where available), and small airway count. Then, all CT factors (percent emphysema, percent fSAD, and small airway count) were added as a group. Lastly, a full model including clinical risk factors, the GRS, and CT factors was compared. Participants with missing post-bronchodilator spirometry data in MESA (Multi-Ethnic Study of Atherosclerosis) Lung or missing parametric response mapping of fSAD data in SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) were excluded. AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CT = computed tomography; Ref = reference.

Figure 2). By contrast, percent emphysema, percent PRM^{fSAD}, and small airway count all significantly improved discrimination of cases. The combination of these lung structure features increased the c-statistic by 0.096 in MESA Lung and 0.195 in SPIROMICS, for a total area under the curve of 0.91 in MESA Lung and 0.89 in SPIROMICS.

Discussion

In a general U.S. population–based sample, as well as in a case–control study of COPD, we found that a GRS associated with COPD susceptibility was significantly associated with greater percent emphysema and PRM^{fSAD}, fewer small airways, smaller airway lumens, and thinner airway walls. Elements of lung structure on CT, particularly the small airway count and PRM^{fSAD}, strongly attenuated the associations between the GRS and lower lung function, consistent with substantial mediation. We also observed that lung structure on CT provided greater discrimination of moderate-to-severe COPD cases than the GRS. Our results suggest that variation in lung structure on CT may be an important mediator of COPD heritability and may be suitable for personalized prediction of COPD.

Risk of COPD has been associated with impairments in peak lung function and accelerated lung function decline (9). Peak lung function is determined by developmental and early life factors (40), whereas the most well-established cause of accelerated lung function decline is smoking (41, 42). Current evidence suggests that genetic variants associated with low lung function are more likely to be

associated with peak lung function than with accelerated decline (43). For example, previous genetic studies of lung function have implicated pathways (e.g., Hedgehog signaling) critical to early development (6, 12), and demonstrated a shared genetic architecture for lung function among never- and heavy smokers (44). To date, strong gene–environment interactions with respect to smoking and lung function decline have remained elusive, although this may be due to inadequate statistical power (45). Consistent with the hypothesis that a GRS derived from a GWAS of lung function traits, not clinical COPD, would predominantly index developmental rather than acquired risk factors, we found similar GRS performance in never- and ever-smokers.

Peak lung function is contingent on adequate lung structural development (46, 47). Impairments in lung growth have been linked to early life infections and environmental exposures, such as parental smoking and air pollution (10, 48–51). Although lung CT has not been used extensively in healthy children and young adults, it has demonstrated marked differences among adults with respect to lung density and airway dimensions, which have been validated against pathological samples and associated with COPD incidence and progression (16–19, 52–54). By correlating adult structural variation with variation in genetic risk, this work provides evidence that variation in lung structure may be a biologically plausible mechanism for increased genetic susceptibility to COPD, and suggests that CT lung structure in middle and old age may be informative with respect to developmental differences and peak lung development.

In particular, our work suggests that small airway development and dysfunction may be important mediators of lung function heritability. The small airway count was found to be a potentially major mediator of genetic risk in the population-based MESA sample, although less so in SPIROMICS. This may be due to methodological differences or selection biases, particularly relating to the "healthy smokers" recruited in SPIROMICS (55). Nonetheless, it is interesting to consider that prior work that associated the total airway count with accelerated lung function decline and COPD severity was performed in another population-based sample with a low burden of smoking and clinical disease (56). This suggests that a low number of small airways may precede other structural abnormalities. The possibility that a deficit in small airway development reflects a heritable, high-risk phenotype warrants further investigation. Meanwhile, among smokers in SPIROMICS, an index of small airway dysfunction, PRM^{fSAD}, was the strongest potential mediator of genetic risk. In addition to correlating with small airway disease, PRM^{fSAD} has been hypothesized to precede percent emphysema (57), which was associated with the GRS in MESA and among elderly SPIROMICS participants. Hence, in addition to the emphasis on variation in small airways, our results suggest that genetic risk may be associated with, and partially mediated by, the development of emphysematous lung deterioration, consistent with the enrichment of elastic fiber pathways identified among the variants in the GRS (6).

Our findings suggest that lung-structure measures enhance discrimination of COPD cases to a greater extent than the GRS. This is not unexpected, as lung structural variation is not fully explained by genetic variation and strongly associates with smoking intensity and accelerated lung function decline (16–18, 36, 56), both of which are major COPD risk factors that are not associated with variation in this GRS (6, 43, 58). An updated GRS based on a larger BioBank general population that includes 184 additional variants could add to the GRS's discriminative performance, but this is unlikely to alter our main conclusions; in fact, relative to clinical factors, the updated GRS was reported to increase the c-statistic for moderate-to-severe COPD by only 0.02 (58). This increment is approximately five times what we observed in our study, but only 10–20% of the increment provided by CT measures.

The strengths of the present work include the application of a rigorously defined GRS, quantitative measurement of lung structure elements using full-lung CT, and the comparison of results from two large, highly characterized studies that are informative regarding COPD risk in both the general population and in heavy smokers. Nonetheless, certain limitations must be considered.

Our results are consistent with the hypothesis that variation in lung structure substantially mediates the genetic risk of low lung function; however, alternative hypotheses must be considered. Our hypothesis is predicated on the assumption that changes in lung structure precede and predict loss of lung function and COPD, which is supported by recent studies (16–18, 56) and the robustness of our findings in a population-based sample of individuals with relatively preserved lung function. Nonetheless, spirometric obstruction can also influence lung structure. Indeed, the extent of potential mediation we observed, particularly in MESA, was greater than would be expected based on the number of genetic variants in the GRS without clear linkages to lung structural development (6). With respect to potential bidirectional relationships between structure and function, we found that lung function attenuated the GRS–structure associations to a lesser extent than lung structure attenuated the GRS–function associations. Interestingly, the observation that GRS–structure associations were independent of lung function could be consistent with lung structure indexing "preobstructive" disease (16, 17) and/or nonobstructive emphysema or the "symptomatic smoking" phenotype (14, 35, 59). Future studies should examine causal pathways more precisely by leveraging structure-specific GWAS signals, subclassified COPD endotypes, and longitudinal measurements of disease incidence and progression (60, 61).

Both the original GRS (6) and updated GRS (58) were developed in persons of European ancestry. In the current report, we did not find any definite evidence for effect modification of the GRS–structure associations by race/ethnicity. However, we found that the average GRS was higher in African American and Hispanic/Latino participants, among whom some GRS–structure associations were of lower magnitude. This is consistent with some previous work (58) and reflects, at least in part, varying allele frequencies of lung function loci across individuals from different racial/ethnic groups with varying ancestral backgrounds (62). Other considerations that could not be definitively resolved include selection bias, imprecision, or differential associations. We anticipate that incorporating genetic risk determinants in non-European ancestries (31, 63) may be important to optimize the performance of the GRS in ethnically diverse populations.

CT measures may be differentially misclassified in the context of current

smoking, which increases lung inflammation and thereby artifactually decreases estimates of percent emphysema and gas trapping (64). Nonetheless, the models were adjusted for smoking status and pack-years history, no significant effect modification by smoking status was observed, and results were similar in both the general population–based and heavy-smoking samples.

Lastly, MESA Lung and SPIROMICS measured lung function and lung structure later in life; hence our inferences regarding associations between genetic risk and peak lung function attainment in early adulthood are based on indirect evidence. This highlights the need to develop additional cohorts of young adults with measurements of lung structure.

In conclusion, a GRS associated with COPD susceptibility was significantly associated with lower lung density, fewer smaller airways, and altered airway dimensions on CT, independently of smoking history. Lung structure substantially mediated associations between the GRS and lung function, and also, unlike the GRS, improved discrimination of COPD cases. This is the first study to use imaging to demonstrate that a GRS obtained by a general-population GWAS of lung function may partially exert its effects through mechanisms resulting in lung structure abnormalities. The findings suggest that lung structure may be an important mediator of heritability and determinant of personalized risk for COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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