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Early View

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Radiographic Pulmonary Vessel Volume, Lung Function, and Airways Disease in the Framingham Heart Study

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TITLE PAGE

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Take home summary:
Lower total and peripheral pulmonary blood vessel volumes on CT are associated with worse lung health in a generally healthy population. CT imaging may be useful in detecting early changes in the pulmonary vessels, even before lung disease develops.

ABSTRACT

Radiographic abnormalities of the pulmonary vessels, such as vascular pruning, are common in advanced airways disease, but it is unknown if pulmonary vascular volumes are related to measures of lung health and airways disease in healthier populations.

In 2,388 participants of the Framingham Heart Study CT sub-study, we calculated total vessel volumes and the small vessel fraction using automated CT image analysis and evaluated associations with measures of lung function, airflow obstruction on spirometry, and emphysema on CT. We further tested if associations of vascular volumes with lung function were present among those with normal FEV_1 and FVC.

In fully adjusted linear and logistic models, we found that lower total and small vessel volumes were consistently associated with worse measures of lung health, including lower spirometric volumes, lower diffusing capacity, and/or higher odds of airflow obstruction. For example, each standard deviation lower small vessel fraction (indicating more severe pruning) was associated with a 37% greater odds of obstruction (OR 1.37, 95% CI: 1.11-1.71, p=0.004). A similar pattern was observed in the subset of participants with normal spirometry.

Lower total and small vessel pulmonary vascular volumes were associated with poorer measures of lung health and/or greater odds of airflow obstruction in this cohort of generally healthy adults without high burdens of smoking or airways disease. Our findings suggest that quantitative CT assessment may detect subtle pulmonary vasculopathy that occurs in the setting of subclinical and early pulmonary and airways pathology.

MAIN TEXT

Introduction

Abnormalities of the pulmonary vessels are commonly seen across a number of pulmonary diseases, including chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, bronchiectasis, and others [1–4]. For individuals with these conditions, the development of overt pulmonary vascular disease (known as Group 3 pulmonary hypertension in the World Health Organization classification scheme [5]) is a major clinical inflection point that predicts future morbidity and mortality [6–10]. It is likely that mild perturbations in the pulmonary vascular system, even below traditional thresholds of disease, are associated with poor outcomes [11,12].

Assessment of the pulmonary vessels has historically required invasive angiography or tissue specimens [13]. As a result, the ability to study how pulmonary vascular abnormalities develop and progress in the setting of lung disease has been limited. Using computer-based image analysis of computed tomography (CT) scans, the total volume of the pulmonary blood vessels of varying sizes can now be assessed noninvasively [14]. By quantifying relative reductions in volume of the smallest, most peripheral pulmonary vessels, this method can generate a CT surrogate of vascular pruning, which is known to occur angiographically in COPD [15–17]. In cohorts of individuals selected on the basis of airways disease, including COPD and asthma, radiographic pruning has been associated with severity of lung disease, including poorer lung function, right ventricular dysfunction, and higher pulmonary artery pressures [1,2,14,18,19].

These results have generated new insights into the “vascular substance” of pulmonary disease, and raised the possibility that quantifying vascular abnormalities may play a role in phenotyping and

stratifying populations with lung disease [20]. However, this work has primarily focused on cohorts specifically selected on the basis of clinically manifested airways disease and/or smoking. For the much larger number of individuals who have subclinical or early pulmonary pathology, it is unknown whether abnormalities of the pulmonary vessels are detectable by CT, and whether these vascular abnormalities are associated with poorer baseline lung function or more severe decline in lung function over time.

To address this knowledge gap, we investigated associations of absolute and relative pulmonary blood vessel volumes and measures of pulmonary function and airways disease in the Framingham Heart Study, a large, community-dwelling cohort without high burdens of smoking or lung disease. We hypothesized that more severe vascular pruning as shown by CT would be associated with poorer lung function and greater odds of airflow obstruction on spirometry or emphysema on CT.

Materials and Methods

Study Population

The study population consists of participants of the Framingham Heart Study Offspring and Third Generation cohorts, described previously [21,22]. From 2008-2011, 2,764 participants underwent volumetric chest CT scans as part of the Multi-Detector Computed Tomography 2 sub-study, with the primary goal of assessing coronary artery calcification [23–25]. Of these, 2,484 participants had image data satisfactory for measuring vascular morphology; those without demographic data or information on smoking history were excluded, leaving 2,388 participants in the analysis. Most participants attended Framingham Offspring examination 8 (2005-2008) and Third Generation examination 2 (2008-2011), except 9 participants (8 from Offspring) who attended Offspring examination 7 (1998-2001) or Third Generation examination 1 (2002-2005). Our sample included a sub-population of 842 Offspring

participants who had repeated measures of spirometry data from examination 9 (2011-2014), which were compared to prior results to assess the trajectory of lung function. This study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Boards of the Beth Israel Deaconess Medical Center and Boston University Medical Center approved this study. All participants provided written informed consent.

Radiographic Pulmonary Vascular Assessment

Inspiratory, non-contrast, CT examinations covering the entire thorax were performed in supine body position using a 64-detector-row scanner (Discovery, GE Healthcare, Waukesha, WI, USA), with uniform acquisition and reconstruction protocols. Acquisition parameters were 120kVp, 300–350mA (based on body weight), 350ms rotation time, and 0.625mm section thickness. Image analysis was performed in the Applied Chest Imaging Laboratory at Brigham and Women's Hospital utilizing software based on the Chest Imaging Platform (www.chestimagingplatform.org) as previously described [1]. An automated algorithm generated three-dimensional reconstructions of the pulmonary vasculature from which the volume of vessels of varying cross-sectional area were calculated (**Figure 1**), including the total volume of all intraparenchymal vessels (TBV) and of the small vessels (defined by cross-sectional area $<5mm^2$, BV5). The measures generated by this algorithm reflect the volume of the entire vessel, including the vascular wall and lumen, and both arterial and venous vessels are included. The small vessel fraction (BV5/TBV), representing the relative distribution of blood vessel volume in the smallest, most peripheral blood vessels detectable by CT, was calculated as a radiographic measure reflective of pulmonary vascular pruning [1,2,26].

Measures of Pulmonary Function and Airways Disease

Lung function testing was performed at each Framingham Heart Study examination. In our sample of 2,388 participants, 2,255 (94.4%) had spirometry results from a visit at the time of, or before, their respective CT scan. For Offspring examination 7, spirometric data were obtained using a Collins Survey II Water-Seal Spirometer (Warren Collins, Inc., Braintree, MA, USA) and acquisition and quality control software (S&M Instruments, Doylestown, PA, USA), calibrated daily. For Offspring examinations 8 and 9, and Third Generation examinations 1 and 2, spirometric data were obtained using a Collins Comprehensive Pulmonary Laboratory system (nSpire Health, Inc., Longmont, CO, USA), calibrated daily. Spirometric maneuvers were performed according to American Thoracic Society standards [27]. Measures of pulmonary function included forced expiratory volume in 1-second (FEV_1), forced vital capacity (FVC), ratio of FEV_1/FVC, and diffusing capacity of carbon monoxide (DLCO). In a subset of the Offspring cohort who underwent follow-up lung function testing after their CT scan, we calculated the annualized change in FEV_1, FVC, and DLCO to assess trajectory of lung function.

Measures of airways disease included airflow obstruction on spirometry and visual appearance of emphysema on CT. Obstruction was defined as moderate-to-severe airflow limitation based on FEV_1/FVC ratio <0.70 with a percent-predicted FEV_1 <80% [28]. Emphysema was determined based on visual evaluation by three board-certified radiologists using a modified sequential reading method as previously described [23,29,30], and was available for 2,291 participants (95.9%). This assessment was performed on the same CT scan that was used to generate the pulmonary vascular volumes.

Statistical Methods

Multivariable linear regression models were used to examine associations of CT vascular measures (TBV, BV5 and BV5/TBV) with continuous pulmonary outcomes (FEV_1, FVC, DLCO, and annualized change in these measures), and multivariable logistic regression models were used for binary

outcomes (airflow obstruction on spirometry and visual emphysema on CT). We evaluated departures from linearity for the association of CT vascular measures and lung function by plotting penalised splines with generalised additive models with a Gaussian distribution, and used the likelihood ratio test to compare the nested models. All models included covariates which were selected *a priori* based on known or suspected associations with airways disease, thoracic size, and/or abnormalities of pulmonary vessels. These included age at time of CT, sex, height, weight, smoking status (current, former, or never), total cumulative pack-years of cigarette exposure, personal educational attainment [30], occupation (laborer, sales/clerical, professional/technical, executive/supervisory, or other) [31], census tract median neighborhood income (using home address at visit date and year 2005-2009 census data) [31], and cohort identifier. We did not adjust for race/ethnicity because nearly all participants are of European ancestry [32].

In secondary analyses, we added interactions terms to our primary models to test for evidence of differential associations of radiographic pulmonary blood vessel volumes with measures of pulmonary function and airways disease based on ever-smoking status. For continuous measures of lung function, we performed a sensitivity analysis assessing the association of radiographic pulmonary vascular volumes and FEV_1, FVC, and DLCO in the 1,984 participants (83.1%) who had normal spirometric volumes (i.e. percent-predicted FEV_1 and FVC both ≥80%). Regression coefficients and odds ratios are reported with 95% confidence intervals and expressed per standard deviation difference in the vascular parameter. For interaction terms, a two-sided p-value of <0.10 for the Wald test was considered statistically significant effect modification. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA), and penalised spline plots were produced using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1: Characteristics of Study Participants (n=2,388)

Age (years, mean ± SD)	59.0 ± 11.7
Female (n, %)	1,219 (51.1)
Body-Mass Index (kg/m^2, mean ± SD)	28.4 ± 5.4
Occupation Category (n, %)	
Laborer	191 (8.0)
Sales/Clerical	609 (25.5)
Prof./Exec./Supervisory/Technical	989 (41.4)
Other	599 (25.1)
Educational attainment (n, %)	
High School or Less	504 (21.1)
Some College	758 (31.7)
College/Grad School	1126 (47.2)
Census tract income ($, median, IQR)	83,065 (36,801)
Offspring Cohort (n, %)	1093 (45.8)
Smoking Status (n, %)	
Never	1,168 (48.9)
Former	1,043 (43.7)
Current	177 (7.4)
Pack-years of smoking (mean ± SD)	
Entire sample	9.8 ± 15.7
Former smokers	16.9 ± 16.7
Current smokers	32.7 ± 15.5
Percent-predicted FEV_1 (mean ± SD)	97.9 ± 15.2
Percent-predicted FVC (mean ± SD)	101.8 ± 13.3
Percent-predicted DLCO (mean ± SD)	96.6 ± 15.7
Airflow Obstruction on Spirometry (n, %)	167 (7.4)
Emphysema on CT (n, %)	297 (13.0)
CT Pulmonary Vascular Measures	
TBV (mL, mean ± SD)	143.1 ± 30.8
BV5 (mL, mean ± SD)	55.9 ± 11.5
BV5/TBV (%, mean ± SD)	39.3 ± 4.1

Study Participant Characteristics

Details of the study cohort are provided in **Table 1**. The mean age of the cohort was 59.0±11.7 years and 51.1% were female. Nearly half the participants (48.9%) were never-smokers, while 43.7% were former smokers and 7.4% were current smokers. Mean lung function in the cohort was normal, with a mean percent-predicted FEV_1, FVC, and DLCO of 97.9±15.2%, 101.8±13.3%, and 96.6±15.7%, respectively. The mean FEV_1/FVC was 74.2±7.3%. In the Offspring subset who had follow-up spirometry, over an average interval of 5.7±0.4 years, FEV_1, FVC, and DLCO declined by a mean of 33.0±36.4 mL/year, 45.4±46.6 mL/year, and 0.36±0.52 mL/min/mmHg/year, respectively. For measures of airways disease, 167 participants (7.4%) met criteria for moderate-to-severe obstruction on spirometry, while 297 (13.0%) had CT evidence of emphysema.

Mean total (TBV) and small blood vessel volumes (BV5) were 143.1±30.8 mL and 55.9±11.5 mL, respectively, and the small vessel fraction (BV5/TBV) was 39.3±4.1%. Participants with airflow

obstruction had similar TBV, but lower BV5 and BV5/TBV compared to those without obstruction (Supplementary **Table S1**).

Associations with Measures of Pulmonary Function and Airways Disease

Associations of pulmonary blood vessel volumes and measures of pulmonary function and airways disease are reported in **Table 2** and **Table 3**. Lower blood vessel volume was consistently associated with worse pulmonary function in fully adjusted models. For example, per SD lower TBV, FEV_1 was 145.1 mL lower (95% CI: 117.6-172.6, p<0.0001), FVC was 248.8 mL lower (95% CI: 217.6-280.0, p<0.0001), and DLCO was 1.40 mL/min/mmHg lower (95% CI: 1.16-1.63, p<0.0001) (**Figure 2**). A similar pattern was observed for the small vessel fraction: more severe pruning (i.e. lower BV5/TBV) was associated with lower FEV_1 and FVC, but not with DLCO (**Figure 3**). We did not find any associations of radiographic pulmonary vascular volumes with annualized change in FEV_1, FVC, or DLCO (**Table 2**). The penalised splines for the associations of TBV and BV5 with continuous measures of lung function (FEV_1, FVC, and DLCO) showed linear relationships (Supplementary **Figures S1 and S2**). In addition, the spline of the association of BV5/TBV with FEV_1 and FVC was roughly linear (Supplementary **Figure S3**).

For measures of airways disease on spirometry and CT, we found that more severe CT pruning was associated with higher odds of obstruction in fully adjusted models (**Table 3**); each SD lower BV5/TBV was associated with 37% higher odds of obstruction (OR 1.37, 95% CI: 1.11-1.71, p=0.004). There was no association of CT pulmonary vascular volumes and emphysema on CT (**Figure 4**).

Table 2: Associations of CT Pulmonary Vascular Volumes and Measures of Pulmonary Function (Expressed Per Standard Deviation Lower Vascular Parameter)

Pulmonary Function Parameter	Participants in Analysis (n)	Total Blood Volume (TBV)		Small Vessel Blood Volume (BV5)		Small Vessel Fraction (BV5/TBV)	
		Difference per SD Lower TBV (95% CI)	p-value	Difference per SD Lower BV5 (95% CI)	p-value	Difference per SD Lower BV5/TBV (95% CI)	p-value
FEV_1 (mL)	2,255	-145.1 (-172.6, -117.6)	<0.0001	-125.7 (-148.8, -102.6)	<0.0001	-49.8 (-75.9, -23.7)	0.0002
FVC (mL)	2,255	-248.8 (-280.0, -217.6)	<0.0001	-217.8 (-243.9, -191.8)	<0.0001	-91.9 (-122.1, -61.7)	<0.0001
DLCO (mL/min/mmHg)	2,109	-1.40 (-1.63, -1.16)	<0.0001	-0.98 (-1.18, -0.78)	<0.0001	0.02 (-0.20, 0.25)	0.84
Change in FEV_1 (mL/year)	842	-0.09 (-4.07, 3.89)	0.96	-0.58 (-3.78, 2.61)	0.72	-0.92 (-4.25, 2.41)	0.59
Change in FVC (mL/year)	842	-0.23 (-5.30, 4.84)	0.93	-0.82 (-4.89, 3.25)	0.69	-0.54 (-4.78, 3.71)	0.80
Change in DLCO (mL/min/mmHg/year)	530	0.04 (-0.03, 0.11)	0.29	0.01 (-0.05, 0.07)	0.68	-0.03 (-0.09, 0.03)	0.34

*Results of linear regression models with adjustment for age, sex, height, weight, smoking status, total pack-years of cigarette exposure, personal educational attainment, occupation category, census tract median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation)

Table 3: Associations of Radiographic CT Pulmonary Vascular Volumes and Odds of Airways Disease (Expressed Per Standard Deviation Lower Blood Vascular Parameter)

Airways Disease Parameter	Participants in Analysis (n)	Total Blood Volume (TBV)		Small Vessel Blood Volume (BV5)		Small Vessel Fraction (BV5/TBV)	
		Odds Ratio per SD Lower TBV (95% CI)	p-value	Odds Ratio per SD Lower BV5 (95% CI)	p-value	Odds Ratio per SD Lower BV5/TBV (95% CI)	p-value
Presence of obstruction on spirometry	2,255	1.03 (0.80, 1.32)	0.82	1.21 (0.98, 1.49)	0.08	1.37 (1.11, 1.71)	0.004
Presence of emphysema on CT	2,291	0.87 (0.70, 1.08)	0.20	0.93 (0.77, 1.11)	0.42	1.09 (0.89, 1.33)	0.39

*Results of logistic regression models with adjustment for age, sex, height, weight, smoking status, total pack-years of cigarette exposure, personal educational attainment, occupation category, census tract median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation)

Secondary Analyses

In secondary analyses, we found no evidence that the associations of radiographic pulmonary vascular volumes with spirometry or trajectory of lung function differed by ever-smoking status (all $p_{interaction}>0.10$). For associations of absolute CT vascular volumes (TBV and BV5) and the presence of airways disease defined by spirometry or CT, we found inconsistent evidence of differential relationships based on smoking status. In the case of emphysema on CT, in ever-smokers there was an association with higher odds of emphysema per SD higher TBV (OR 1.26, 95% CI: 1.01-1.57), and this relationship was not seen in never-smokers ($p_{interaction}=0.03$). There was no evidence that the associations of CT pruning (BV5/TBV) with pulmonary function and airways disease differed by smoking status (all $p_{interaction}>0.10$).

In a sensitivity analysis restricted to participants with normal FEV_1 and FVC (≥80 percent-predicted), the pattern of associations of CT pulmonary blood vessel volumes and lung function was generally consistent. Associations of TBV and BV5 with FEV_1, FVC, and DLCO remained significant (all $p<0.0001$). For small vessel fraction, BV5/TBV was associated with FVC ($p<0.0001$), but the association with FEV_1 was attenuated ($p=0.099$).

Discussion

In this large cohort of community-dwelling and generally healthy adults, we found that more severe vascular pruning and lower pulmonary blood vessel volumes derived from automated CT image analysis were consistently associated with worse measures of lung health, including lower spirometric volumes, diffusing capacity, and/or greater odds of airflow obstruction on spirometry. These associations persisted when restricting the analysis to participants with normal spirometry, and did not

substantially differ based on the presence of ever-smoking exposure. This suggests that, even in populations where only a minority of individuals have abnormal lung function or airways disease, differences in pulmonary vascular volumes detectable by CT are associated with clinically relevant indicators of pulmonary health.

These results are consistent with previous work in cohorts of individuals with substantial airways disease, including COPDGene and the Severe Asthma Research Program, which also utilized a similar quantitative vascular image analysis technique as our study [1,2]. These studies have primarily focused on the relative volume of the smallest pulmonary vessels (the BV5/TBV fraction) as an indicator of the angiographic pruning that is known to occur in COPD. In these studies, a lower BV5/TBV (indicating more severe CT pruning) was consistently associated with more severe airways disease, including worse spirometry, higher GOLD stage, higher peripheral and sputum eosinophil percentage, higher odds of future asthma exacerbation during follow-up, presence of right-ventricular dysfunction on cardiac MRI (which may be a hemodynamic consequence of pruning and loss of the pulmonary vascular bed), and greater mortality during follow-up [1,2,19,33]. In a univariate analysis of participants of COPDGene, more severe CT pruning was correlated with higher percent low-attenuation area on CT, a quantitative densitometric measure of emphysema. In contrast, we found that CT pruning was not associated with presence of visually evident emphysema on CT, which may be explained in part by the low burden of emphysema in the generally healthy Framingham cohort compared to COPDGene. The use of quantitative densitometric measures, which may potentially provide complementary information regarding emphysematous changes, may have helped to clarify this discrepancy; however, the parameters used for image acquisition and reconstruction in Framingham resulted in substantial artefact in the estimated percent low-attenuation area of the lung [30], which limits the use of these measures in our analyses.

A related, but distinct, method of quantifying pulmonary vascular pruning on CT has also been reported in the literature. This method calculates the relative cross-sectional area, rather than volume, of the small pulmonary vessels from three individual CT slices (one each from the upper, middle, and lower sections of the lung). Using this area-based metric of vascular pruning, studies of individuals with COPD found that more severe pruning was associated with lower FEV_1, DLCO, and greater extent of emphysema (as defined by the percentage of attenuation values lower than -950 Hounsfield units on each CT slice) [14,18]. In a small group of 30 non-smoking people without airflow obstruction on spirometry, area-based pulmonary vascular pruning on CT was not associated with lower FEV_1 [34]. However, this was a univariate analysis in a small number of individuals, and does not necessarily contradict our finding that healthy non-smokers with lower BV5/TBV had worse lung function, on average.

Our study also adds to the more general body of literature utilizing CT imaging techniques to study the earliest pathologic changes in airways disease. Recently, Koo and colleagues used an innovative combination of conventional CT, micro-CT, and histology to show that individuals with mild and moderate COPD had decreased numbers of small airways compared to a control group of smokers with normal lung function [35]. Furthermore, when examining only tissue samples without emphysematous destruction (as defined by normal alveolar surface area on micro-CT), those with mild and moderate COPD still had fewer small airways compared to controls.

The remodeling and loss of airways in smokers with early COPD thus parallels the pulmonary vascular changes identified in smokers. Santos et al. demonstrated that structural abnormalities of the

small pulmonary arteries were evident in mild COPD, and even smokers without airflow obstruction – who would have been included in the control group in many COPD studies – had similar vascular morphometric characteristics [36]. In guinea pig models, tobacco exposure induced pulmonary vascular alterations, including early structural remodeling, which were seen before emphysematous changes occurred [37,38]. Our results contribute to this existing literature by demonstrating that lower pulmonary vascular volumes, particularly in the smallest detectable vessels, are associated with poorer spirometric lung function (lower FEV_1 and FVC), even when examining only those individuals with normal lung function. In addition, we found that these associations did not differ in smokers compared to non-smokers, which suggests that vascular abnormalities are also clinically relevant in the substantial minority of individuals with COPD who have not been exposed to tobacco [39] – a population in whom early pathologic changes are not well described.

Taken in context, the results of our study suggest that lower pulmonary blood vessel volumes may be an independent indicator of worse respiratory health – not only in individuals with substantial lung disease that might be expected to be at high-risk for vascular pathology, but also in populations with normal average lung function and without high burdens of tobacco exposure. Our findings may indicate that pulmonary vasculopathy (including vessel narrowing and obliteration) likely occurs alongside the loss of the small airways in early airways disease, including in those who have not yet fulfilled the traditional disease criteria. Further work is necessary to determine the temporality of this association, which cannot be determined from our results. We believe that these observations underline the potential importance of vascular volumes on CT as an imaging biomarker.

However, our findings should also be considered alongside our prior study [26], in which we found that tobacco exposure was associated with higher total and small vessel volumes on CT, both in

those with and without airflow obstruction – a result that was unexpected given that histologic results from humans and animal models demonstrated that tobacco exposure was associated with narrowing and obliteration of the small vessels. The exact explanation for this finding remains unclear: this association was robust to adjustment for a number of possible structural and functional factors (including airflow obstruction and cardiovascular disease), was consistent across multiple metrics of tobacco exposure, and was similar to a prior finding that was previously described in the Multi-Ethnic Study of Atherosclerosis (MESA) [26,40].

In contrast, in the present analysis we found an association of more severe CT-based vascular pruning with poorer lung health using models which were adjusted for both smoking status and total pack-years of cigarette exposure. In addition, in secondary analyses to test for effect modification by smoking status, we also found no evidence that our primary results were different in smokers compared to non-smokers. These results indicate that CT measures of pruning are an independent indicator of structural vascular changes associated with airways disease, including narrowing and loss of the small pulmonary vessels. However, given that tobacco exposure did not appear to manifest as straightforward pruning on CT in this same generally healthy population, we would caution that any analyses of structural vascular measures on CT must consider adjustment for cigarette smoke exposure. Further work is necessary to elucidate the factors underlying this potential discrepancy, and to ensure the consistent interpretation of similar vascular imaging measures in future analyses.

To our knowledge, our study is among the first to investigate associations of pulmonary vascular volumes on CT with pulmonary function and airways disease in a generally healthy population – not selected on the basis of smoking or lung disease – and is also one of the largest to examine quantitative image analysis of the pulmonary vasculature. Strengths of our study include the large cohort size, with

adjustment for a more detailed set of potential confounders than other reports in the literature. Additionally, our analyses included both absolute and relative pulmonary blood vessel volumes to assess for differences in the distribution of the vasculature, and generated these volumes from all the pulmonary vessels visible on modern CT imaging, which may provide a more comprehensive vascular profile compared to methods that assess individual sections in isolation. One particular strength is that all CTs were performed on the same model scanner, at one institution, and using a uniform protocol, thereby reducing bias introduced by differences in image acquisition and manufacturer-related reconstruction algorithms – a significant concern for radiographic biomarkers [41].

Our study has several limitations. The cross-sectional study design of our main analysis limits conclusions regarding the causality of the associations. Although our models adjusted for many potential confounders, residual confounding cannot be excluded. While the inspiratory, whole-lung CT scans enable interpretation of lung and pulmonary vascular images, a potential limitation of the imaging protocol is that the CTs were gated to optimize assessment of coronary artery calcification. Due to the original recruitment strategy targeting residents of the town of Framingham in Massachusetts, USA, our sample is entirely of European ancestry, and our findings may not be generalisable to the population at large.

Fundamental questions about the relationship between the pulmonary vascular system and airways disease remain unanswered. These include whether vascular abnormalities are passive changes secondary to an underlying non-vascular process, or whether they instead represent a key driver of COPD/emphysema, as has been suggested by histologic studies of a small series of human smokers and animal models [36–38]. Additionally, given that loss of pulmonary arterioles and small airways have each been shown to occur prior to emphysematous tissue loss [35,38], it may be possible that early

COPD is characterized by vasculopathy that is more closely linked to abnormalities in the small airways rather than the airspaces. Our finding that differences in radiographic blood vessel volumes are detectable on CT and are associated with lung health even in the absence of pulmonary disease is a novel contribution to the existing literature. These results may support the expanded use of this technique to study and potentially identify the early pulmonary vascular changes that contribute to poorer long-term outcomes, which may represent a target for disease-modifying interventions. In addition, given that this method of vascular quantification has been shown to have within-subject reproducibility [1] and can detect responses to treatment [42], it may be possible to use this technology to study how very early pulmonary vascular changes develop over time. Future directions for research in generally healthy cohorts such as Framingham may address associations of pulmonary vascular volumes with right-sided cardiac function, the relationship between central pulmonary vascular measures (such as the pulmonary artery-to-aorta ratio) and peripheral vascular ratios (including BV5/TBV), associations with quantitative measures of emphysema, and the impact of longitudinal pulmonary vascular changes on cardiopulmonary outcomes.

Conclusions

In this study of community-dwelling, generally healthy adults without high burdens of smoking or airways disease, lower total and peripheral vessel pulmonary blood vessel volumes were associated with poorer measures of lung health and/or greater odds of airflow obstruction. This suggests that quantitative CT assessment may be used to detect subtle pulmonary vasculopathy that occurs in the setting of subclinical and early pulmonary pathology.

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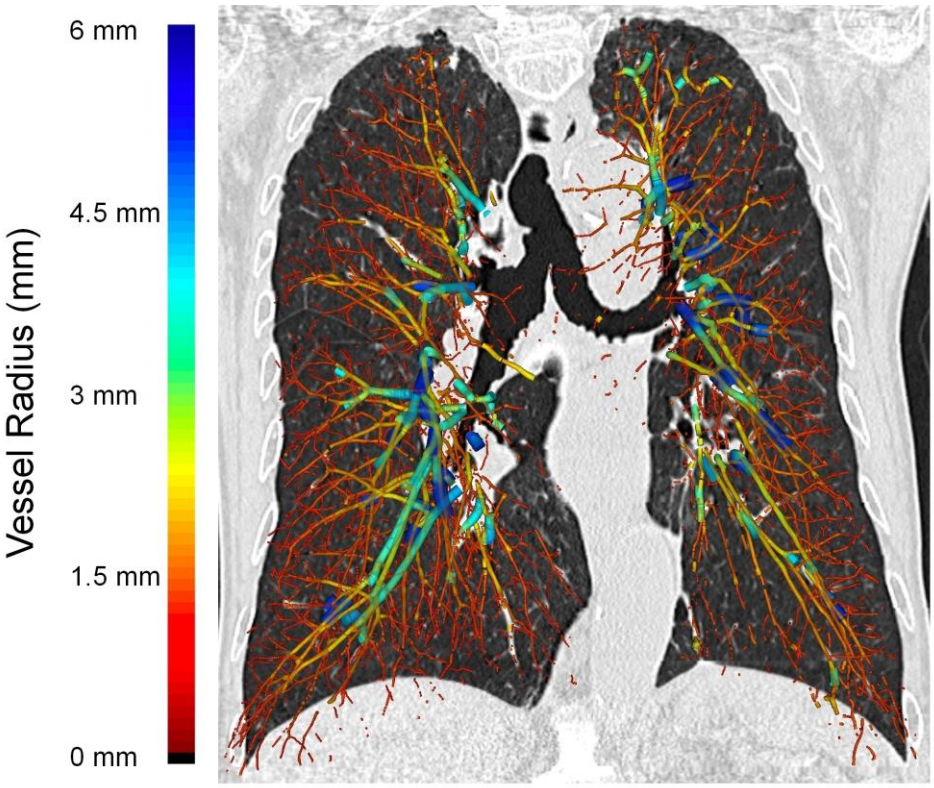
FIGURES

Figure 1: (Top) Coronal chest CT projection with overlaid volumetric reconstruction of the pulmonary vascular tree from a Framingham Heart Study participant. Vessels are color-coded by size. (Bottom) Representative quantitative histogram illustrating the distribution of vascular volume as a function of vessel size.



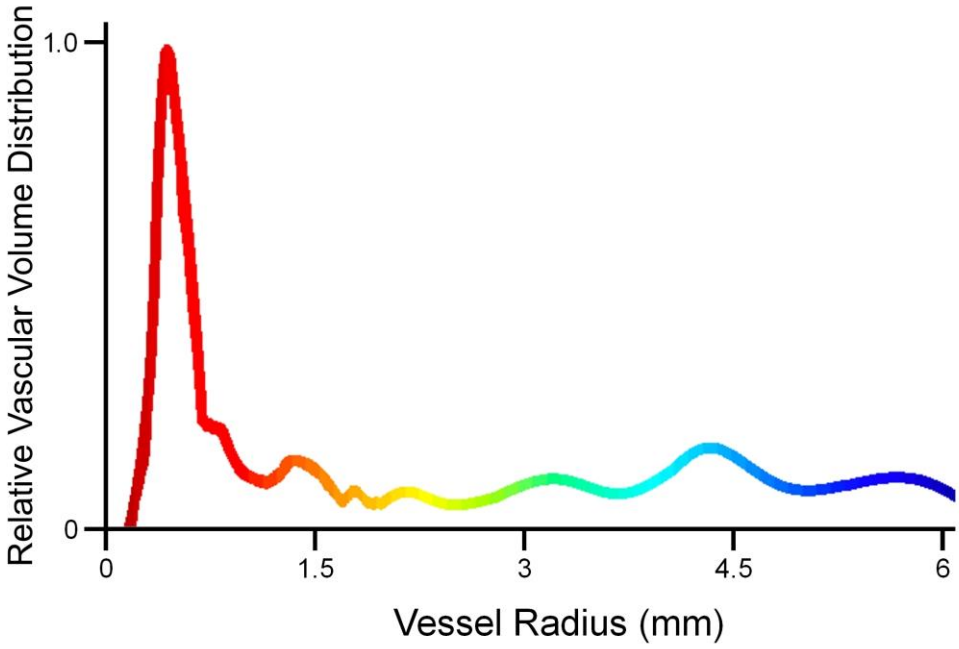
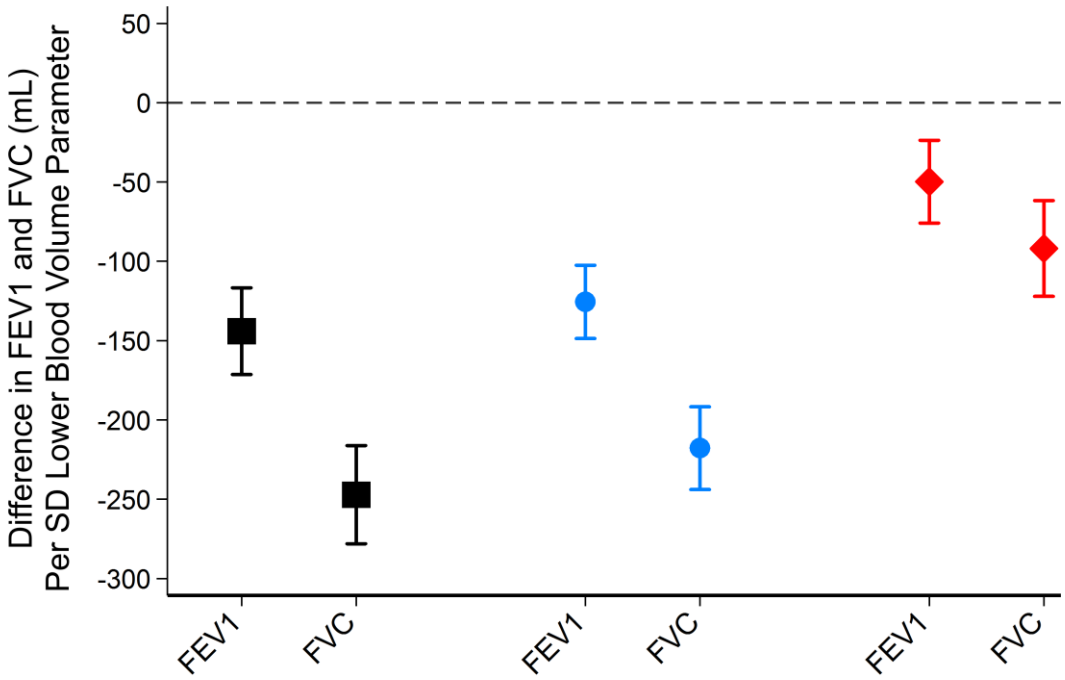


Figure 2: Associations of CT Pulmonary Vascular Volumes with Spirometry (Expressed Per Standard Deviation Lower Vascular Parameter)

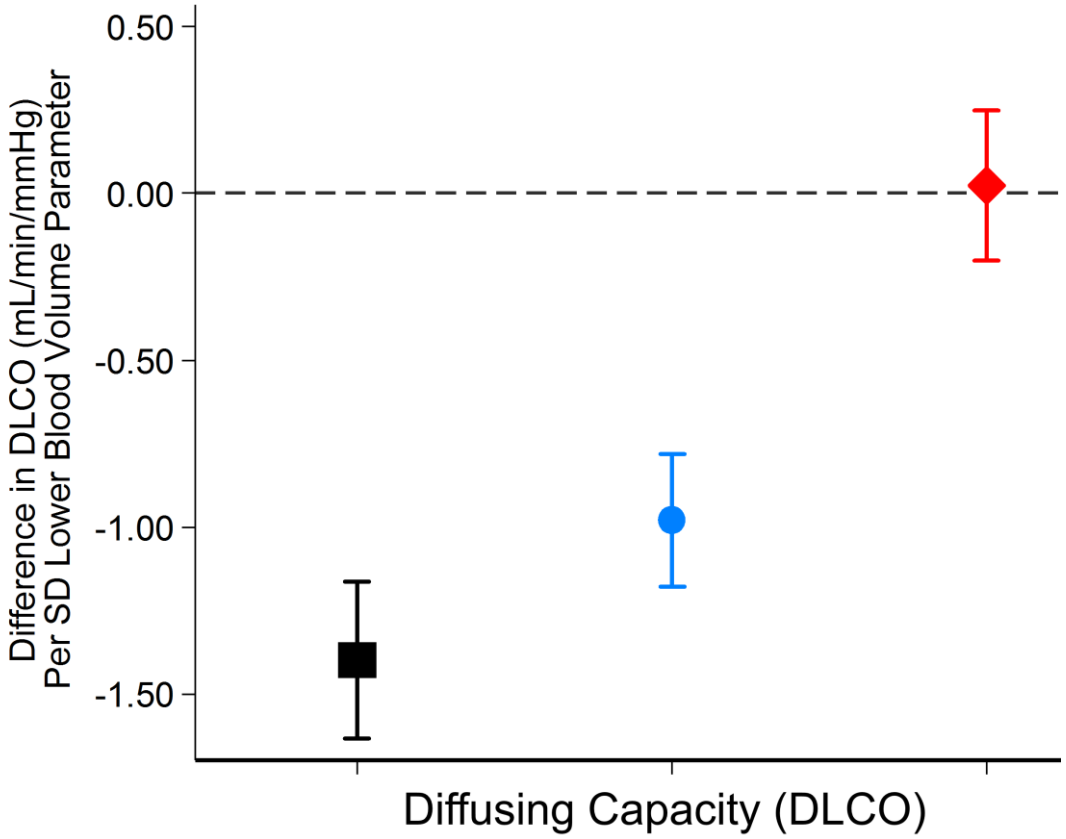
Legend:
■ Total blood vessel volume (TBV)
● Small vessel blood volume (BV5)
♦ Small vessel fraction (BV5/TBV)



*Results of linear regression models (expressed per standard deviation lower vascular volume parameter) with adjustment for age, sex, height, weight, smoking status, total pack-years of cigarette exposure, personal educational attainment, occupation category, census tract median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation)

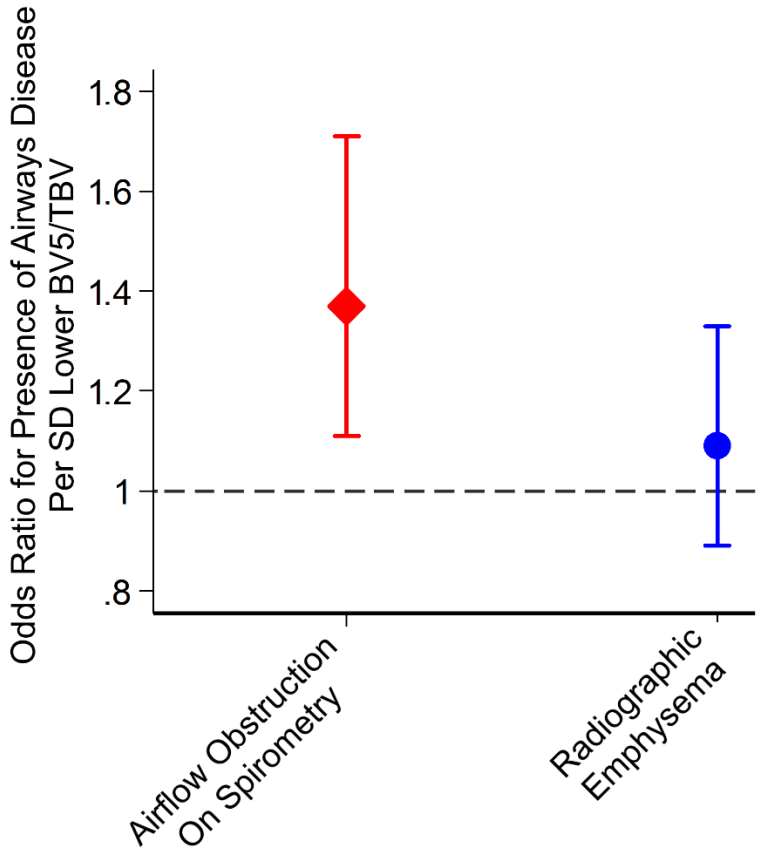
Figure 3: Associations of CT Pulmonary Vascular Volumes with Diffusing Capacity (Expressed Per Standard Deviation Lower Vascular Parameter)

Legend:
■ Total blood vessel volume (TBV)
● Small vessel blood volume (BV5)
♦ Small vessel fraction (BV5/TBV)



*Results of linear regression models (expressed per standard deviation lower vascular volume parameter) with adjustment for age, sex, height, weight, smoking status, total pack-years of cigarette exposure, personal educational attainment, occupation category, census tract median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation)

Figure 4: Associations of CT Pulmonary Vascular Pruning with Airways Disease



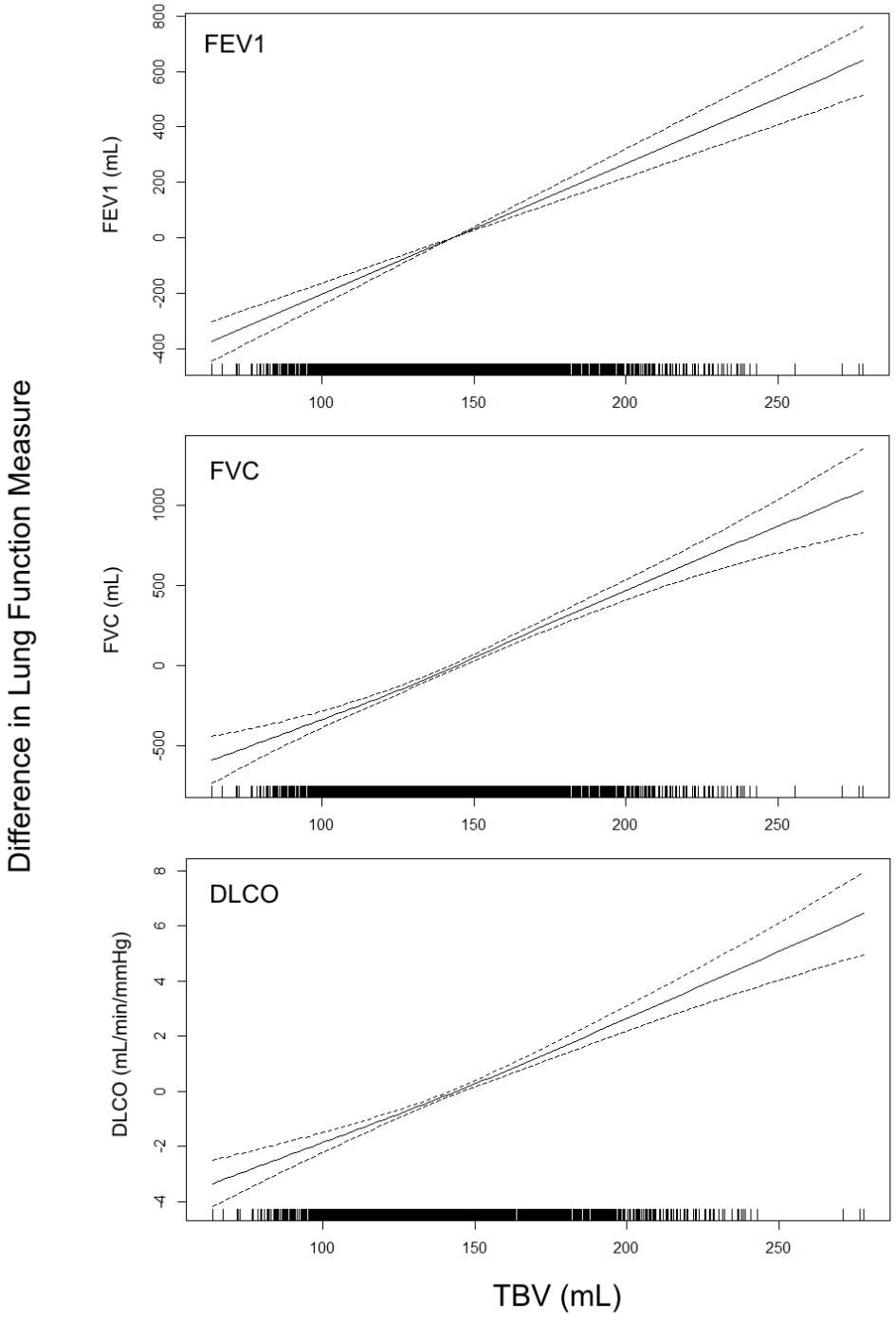
*Results of logistic regression models (expressed per standard deviation lower BV5/TBV) with adjustment for age, sex, height, weight, smoking status, total pack-years of cigarette exposure, personal educational attainment, occupation category, census tract median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation)

SUPPLEMENTARY MATERIAL

Supplementary Table S1: Comparison of Spirometry and CT Pulmonary Blood Vessel Volumes in Participants with Airflow Obstruction and Remainder of Cohort

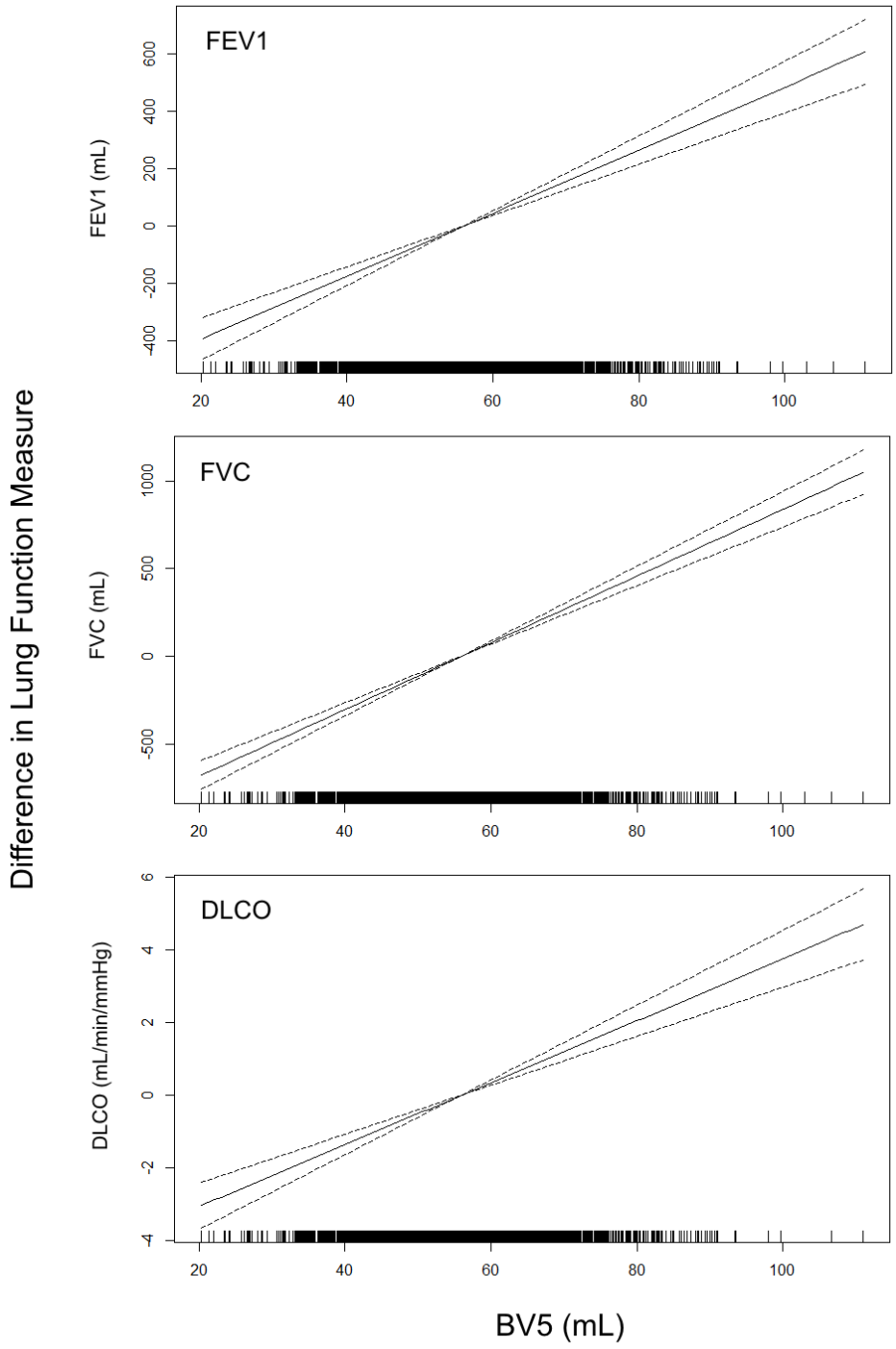
Lung Function Measure	**Participants with Airflow Obstruction (n=167)**	**Remainder of Cohort (n=2,088)**	**p-value (t-test)**
%-Predicted FEV_1	67.8 ± 10.1	100.3 ± 12.8	<0.0001
%-Predicted FVC	87.2 ± 11.1	103.0 ± 12.8	<0.0001
FEV_1/FVC (%)	59.4 ± 7.7	75.4 ± 5.8	<0.0001
%-Predicted DLCO	86.2 ± 18.3	97.4 ± 15.2	<0.0001
Blood Vessel Volumes			
BV5 (mL)	53.7 ± 11.3	56.1 ± 11.4	0.01
TBV (mL)	141.1 ± 31.4	143.3 ± 30.5	0.38
BV5/TBV (%)	38.4 ± 4.3	39.4 ± 4.0	0.002

Supplementary Figure S1: Differences in Measures of Lung Function by TBV



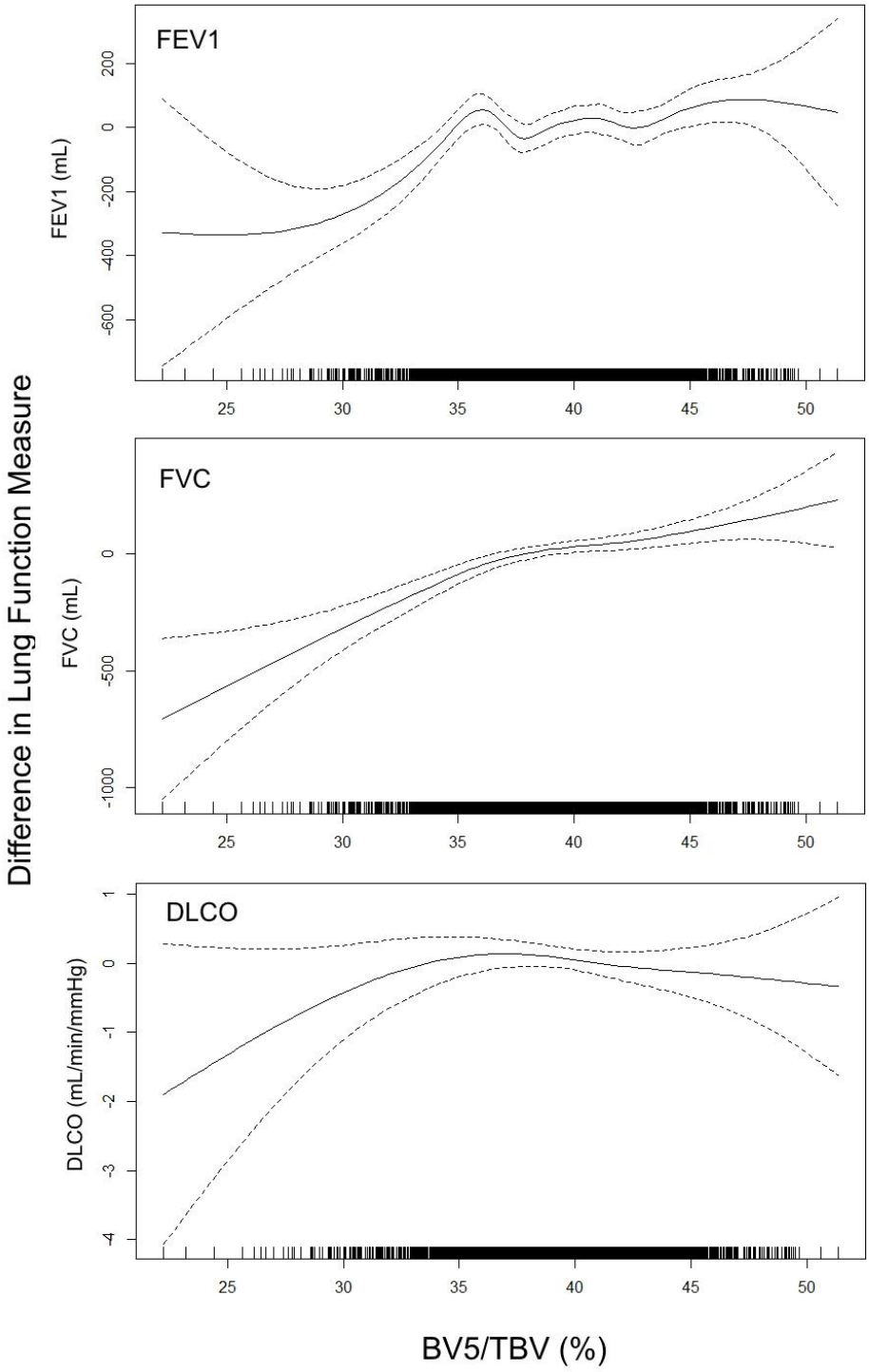
*Generalised additive model with penalised spline demonstrating differences in measures of lung function as a function of TBV. Data were fitted using a penalised spline with 1, 2.3, and 1.6 degrees of freedom for FEV_1, FVC, and DLCO, respectively. All models adjusted for age, sex, height, weight, personal educational attainment, occupation category, median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation). The solid line represents adjusted difference in lung function measure and dashed lines indicate the 95% confidence interval bands. The distribution of TBV is displayed by the rug plot along the x-axis.

Supplementary Figure S2: Differences in Measures of Lung Function by BV5



*Generalised additive model with penalised spline demonstrating differences in measures of lung function as a function of BV5. Data were fitted using a penalised spline with 1 degree of freedom each for FEV_1, FVC, and DLCO. All models adjusted for age, sex, height, weight, personal educational attainment, occupation category, median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation). The solid line represents adjusted difference in lung function measure and dashed lines indicate the 95% confidence interval bands. The distribution of BV5 is displayed by the rug plot along the x-axis.

Supplementary Figure S3: Differences in Measures of Lung Function by BV5/TBV



*Generalised additive model with penalised spline demonstrating differences in measures of lung function as a function of BV5/TBV. Data were fitted using a penalised spline with 7.6, 3.3, and 2.7 degrees of freedom for FEV_1, FVC, and DLCO, respectively. All models adjusted for age, sex, height, weight, personal educational attainment, occupation category, median neighborhood income, and Framingham Heart Study cohort (Offspring vs. Third Generation). The solid line represents adjusted difference in lung function measure and dashed lines indicate the 95% confidence interval bands. The distribution of BV5/TBV is displayed by the rug plot along the x-axis.