

## Age and Small Airway Imaging Abnormalities in Subjects with and without Airflow Obstruction in SPIROMICS

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### Abstract

**Rationale:** Aging is associated with reduced FEV<sub>1</sub> to FVC ratio (FEV<sub>1</sub>/FVC), hyperinflation, and alveolar enlargement, but little is known about how age affects small airways.

**Objectives:** To determine if chest computed tomography (CT)-assessed functional small airway would increase with age, even among asymptomatic individuals.

**Methods:** We used parametric response mapping analysis of paired inspiratory/expiratory CTs to identify functional small airway abnormality (PRM<sup>FSA</sup>) and emphysema (PRM<sup>EMPH</sup>) in the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) cohort. Using adjusted linear regression models, we analyzed associations between PRM<sup>FSA</sup> and age in subjects with or without airflow obstruction. We subdivided participants with normal spirometry based on respiratory-related impairment (6-minute-walk distance <350 m, modified Medical Research Council ≥2, chronic bronchitis, St. George's Respiratory Questionnaire >25, respiratory events requiring treatment [antibiotics and/or steroids or hospitalization] in the year before enrollment).

**Measurements and Main Results:** Among 580 never- and ever-smokers without obstruction or respiratory impairment, PRM<sup>FSA</sup> increased 2.7% per decade, ranging from 3.6% (ages 40–50 yr) to 12.7% (ages 70–80 yr). PRM<sup>EMPH</sup> increased nonsignificantly (0.1% [ages 40–50 yr] to 0.4% [ages 70–80 yr]; *P* = 0.34). Associations were similar among nonobstructed individuals with respiratory-related impairment. Increasing PRM<sup>FSA</sup> in subjects without airflow obstruction was associated with increased FVC (*P* = 0.004) but unchanged FEV<sub>1</sub> (*P* = 0.94), yielding lower FEV<sub>1</sub>/FVC ratios (*P* < 0.001). Although emphysema was also significantly associated with lower FEV<sub>1</sub>/FVC (*P* = 0.04), its contribution relative to PRM<sup>FSA</sup> in those without airflow obstruction was limited by its low burden.

**Conclusions:** In never- and ever-smokers without airflow obstruction, aging is associated with increased FVC and CT-defined functional small airway abnormality regardless of respiratory symptoms.

**Keywords:** spirometry; imaging analysis; aging; geriatrics; lung function

(Received in original form April 27, 2016; accepted in final form August 25, 2016)

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Author Contributions: C.H.M., A.A.D., C.M., C.P., N.M., and C.T.C. contributed to conceiving and writing the manuscript, data analysis, and clinical interpretation of the data. J.L.C., C.B.C., R.E.K., R.P., P.G.W., E.R.B., N.N.H., R.G.B., G.J.C., E.A.K., E.A.H., B.D.R., C.J.G., F.J.M., and M.K.H. contributed to acquisition of the data, conceiving and writing the manuscript, data analysis, and clinical interpretation of the data. All authors reviewed and approved the final draft of the manuscript.

Am J Respir Crit Care Med Vol 195, Iss 4, pp 464–472, Feb 15, 2017

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Originally Published in Press as DOI: 10.1164/rccm.201604-0871OC on August 26, 2016

Internet address: www.atsjournals.org

## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Hyperinflation and reductions in the FEV<sub>1</sub>/FVC ratio have been reported in association with lung aging in healthy never-smokers, although the exact mechanism for these changes has not been well defined.

### What This Study Adds to

**the Field:** Computed tomography-defined functional small airway abnormality increased with age and was associated with lower FEV<sub>1</sub>/FVC ratio, primarily because of greater FVC, even among asymptomatic subjects with FEV<sub>1</sub>/FVC ratio greater than 0.7.

Greater life expectancy has been associated with an increased prevalence of chronic diseases (1), including chronic obstructive pulmonary disease (COPD), bringing new health care needs and challenges. One of these challenges is to understand the “normal” process of aging and to separate it from “disease.” Lung aging is a complex process previously noted to involve loss of elastic recoil, air trapping (2), decreased vital capacity, increased residual volume (3), and homogeneous hyperinflation (4). These changes, considered normal age-related phenomena, are also present in emphysema-predominant COPD, although with greater severity, including actual destruction of alveolar structures and thickening of the airways. The resemblance between emphysema and age-related changes has led some authors to hypothesize that accelerated lung aging (“senile lung,” sometimes known as “senile emphysema”) is part of COPD

pathogenesis (5, 6), a matter that is still intensely debated (7). Despite great interest in the changes at the level of the air sacs, less is known about the impact of aging on the peripheral airways, a major site of airflow resistance and an early target in the development of COPD (8).

New methods and algorithms of lung imaging continue to be proposed to evaluate COPD, with the goal of delineating phenotypic characteristics associated with clinical outcomes (9–11) and disease progression (12, 13). One strength of the recently introduced parametric response mapping (PRM) computed tomography (CT) analysis method is its ability to distinguish emphysematous from nonemphysematous gas trapping, with the latter termed functional small airways abnormality (PRM<sup>FSA</sup>) (14–17). Given the limited available information about the impact of aging on small airways (8, 18, 19), identifying age-related changes is an important goal with direct implications in defining lung diseases.

In this analysis, we use clinical, functional, and imaging data from participants in a well-characterized cohort to test the hypotheses that abnormalities of the functional small airways are part of normal aging and that early obstructive lung disease accelerates age-related changes. Specifically, we (1) quantified the extent of PRM<sup>FSA</sup> in never- and ever-smokers with neither physiologic nor clinical pulmonary abnormalities, (2) tested whether the extent of CT-defined abnormalities increased with aging, and (3) determined whether age-related differences in PRM<sup>FSA</sup> vary by presence of airflow obstruction. Parts of the results have been presented in abstract form at the 2016 American Thoracic Society International Conference on May 16, 2016, San Francisco, California (20).

## Methods

### Design and Study Participants

This study is a cross-sectional analysis of baseline data from participants in SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study), a multicenter cohort study that has enrolled 2,981 participants across four strata (never-smokers and ever-smokers without COPD, with mild/moderate COPD, and with severe COPD) with the goals of identifying new COPD subgroups and intermediate markers of disease progression. Complete details of SPIROMICS design and protocols have been reported in detail elsewhere (21). The protocols for SPIROMICS have been approved by the institutional review board at each participating institution. For the current analysis, we selected participants, both ever- and never-smokers, without airflow obstruction, based on the spirometry definition of a fixed ratio of FEV<sub>1</sub> over FVC greater than or equal to 0.7 and FEV<sub>1</sub>% predicted greater than the lower limit of normal. Additionally, we excluded subjects with FVC below the lower limit of normal.

Participants were considered asymptomatic if they did not report any symptom or clinical marker of respiratory-related impairment (22) (chronic bronchitis symptoms [23]; dyspnea score  $\geq 2$  on the modified Medical Research Council [mMRC] scale [24]; distance walked in 6 min  $< 350$  m; St. George's Respiratory Questionnaire total score  $> 25$  points [25]; and acute respiratory events in the year before enrollment, defined as use of antibiotic and/or steroid or hospital admission for a respiratory “flare-up”). Subjects reporting any of these complaints or markers of lung impairment were considered symptomatic. For some additional analyses, aimed at testing the

Supported by funding from National Institutes of Health (NIH) NHLBI 3R01HL122438-02S1 and K23 HL128936 (C.H.M.); by funding from NIH NHLBI grant K01HL118714 and the Brigham and Women's Hospital Minority Faculty Career Development Award (A.A.D.); by Merit Review Award I01 CX000911 from the Clinical Research and Development Service, Department of Veterans Affairs (J.L.C.); by funding from NIH SBIR grant R44HL008837 (C.J.G.); by National Institute of Aging grant 5K08AG031837 and by the Claude D. Pepper Older Americans Independence Center at the University of Michigan (C.T.C.); and by funding from NIH NHLBI grant R01HL122438-01 (M.K.H.). SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) is funded by contract from the NHLBI (HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, HHSN268200900020C). The funding agencies did not have any role on the analysis and interpretation of the findings, or in the drafting or approval of the manuscript.

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This article has an online supplement, which is accessible from this issue's table of contents at [www.atsjournals.org](http://www.atsjournals.org)

age-by-disease interaction, we also included subjects with mild to moderate airflow obstruction ( $FEV_1/FVC < 0.7$ , and  $FEV_1 > 50\%$  predicted).

### Data Collection

SPIROMICS participants provided demographic information (age, sex, race), smoking history (ever- or never-smoker, smoking within the last month, lifetime cumulative smoking in pack-years), dyspnea severity (using the mMRC), medical history, and respiratory symptoms at enrollment, using validated questionnaires. Comorbid conditions, including asthma, were considered present if the participant answered yes to the question "Have you ever been diagnosed by a physician with [condition name]?" Anthropometric data on height and weight were acquired at enrollment, following standardized protocols. SPIROMICS uses post-bronchodilator spirometry values, with spirometry performed following American Thoracic Society recommendations on a pneumotachograph spirometer, with predicted values based on Hankinson reference equations (26).

### Imaging Analysis

PRM analysis of paired inspiratory and expiratory CTs was used to identify and quantify extent of functional small airway abnormality (PRM<sup>FSA</sup>) and emphysema (PRM<sup>EMPH</sup>). Briefly, the PRM method (27) consists of three key steps: (1) image acquisition per SPIROMICS protocol, (2) image processing, and (3) classification. During image processing, lung parenchyma and airways are segmented to restrict the focus of the registration process to the lungs. Deformable registration is performed to spatially align the expiration with the inspiration scan, allowing them share the same spatial geometry. Classification of voxel-by-voxel attenuation maps into discrete zones allows for quantification of global measures of normal parenchyma, PRM<sup>FSA</sup>, and PRM<sup>EMPH</sup>. Classification is determined by imposing two thresholds:  $-950$  HU on inspiration scans, with lesser values denoting emphysema; and  $-856$  HU on expiration scan, with lesser values denoting nonemphysematous gas trapping. These thresholds are applied to a joint histogram formed using all voxel pairs within the registered inspiration-expiration images. Three discrete classifications are

identified: (1) healthy lung parenchyma, (2) PRM<sup>FSA</sup>, and (3) PRM<sup>EMPH</sup>. PRM has been validated as a technique to identify abnormality even in those without spirometric obstruction (15, 28). PRM was performed using the Imbio Lung Density Analysis software application (Imbio, LLC, Minneapolis, MN). Extent of normal parenchyma, PRM<sup>EMPH</sup>, and PRM<sup>FSA</sup> is described as percentage of the whole lung area.

### Statistical Analysis

We performed descriptive statistics for demographic, clinical, and imaging variables (means with SD and proportions). Linear regression was used to identify the effect of age (in decades) on the presence of PRM<sup>FSA</sup>, in unadjusted models and models adjusted, based on previous knowledge, for covariates relevant to lung function and structure (sex, race, height, smoking status, cumulative smoking history, and history of asthma, with additional adjustment for clinical center and scanner). Initial analyses were restricted to subjects without airflow obstruction, contrasting those with versus without symptoms. In a second step, we compared the extent of PRM<sup>FSA</sup> between participants with versus without airflow obstruction and tested for airflow obstruction-by-age interactions. We performed three subgroup analyses, restricting the population to (1) never-smokers with no symptoms and no asthma; (2) participants without airflow obstruction and neither respiratory symptoms nor asthma; and (3) participants without history of wheezing before 16 years of age. Last, we tested the impact of PRM<sup>FSA</sup> on  $FEV_1$ , FVC, and the  $FEV_1/FVC$  ratio in models adjusted for variables known to be associated with lung function (age, sex, race, height, and emphysema percentage). All analyses were performed using Stata version 12 (Stata Corp., College Station, TX).

## Results

### Characteristics of Participants

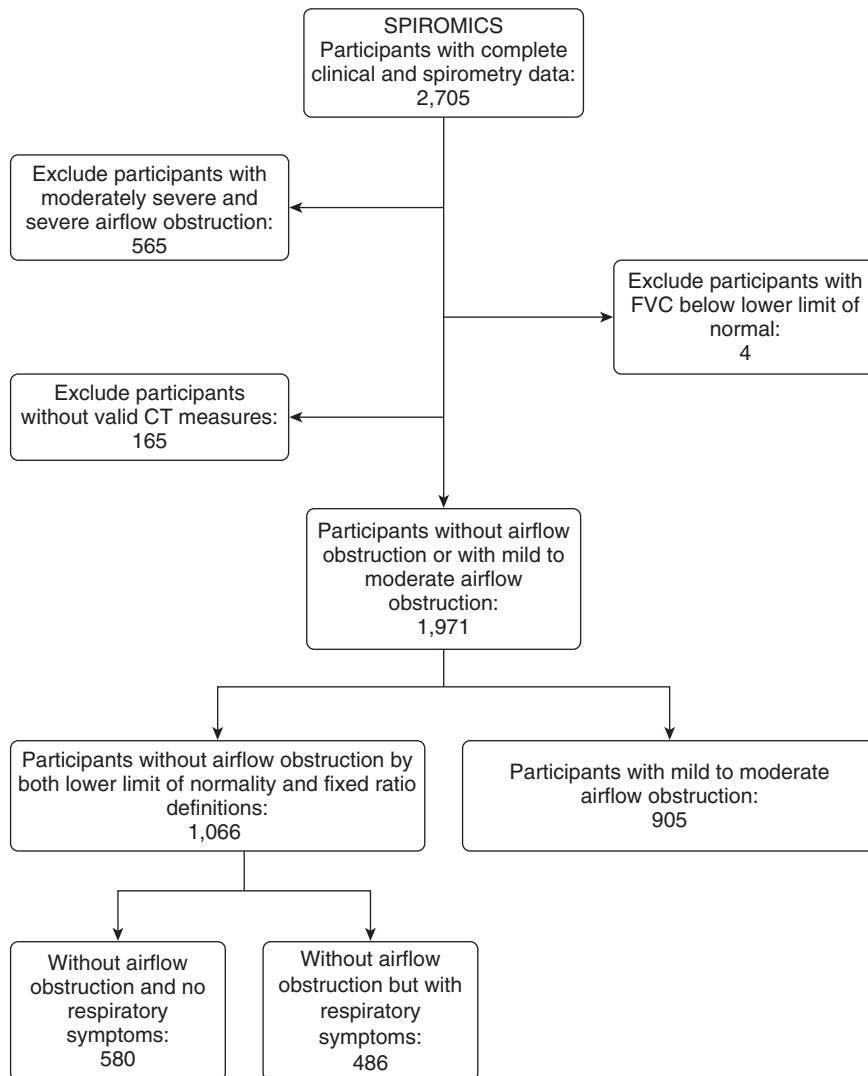
By September 2014, SPIROMICS had enrolled 2,705 subjects with complete clinical data and valid spirometry. Given our interest in normal aging and early disease, we excluded 565 participants with moderately severe or severe airflow

obstruction (Global Initiative for Chronic Obstructive Lung Disease spirometry stages 3 and 4), 165 participants whose PRM measures were unavailable, and four with FVC below the lower limit of normal, leaving 1,971 subjects for the current analyses, 1,066 without airflow obstruction by both the fixed ratio and lower limit of normal and 904 subjects with obstructive spirometry, Global Initiative for Chronic Obstructive Lung Disease stages 1 and 2. The flow of participants is described in Figure 1. Among the 1,066 subjects without airflow obstruction, ever- and never-smokers, 580 were asymptomatic, based on not reporting any of five markers of symptoms or respiratory-related impairment (22) (chronic bronchitis symptoms [23], dyspnea score  $\geq 2$  on the mMRC scale [24], acute respiratory events in the year before enrollment, distance walked in 6 min  $< 350$  m, and St. George's Respiratory Questionnaire total score  $> 25$  points [25]).

Overall, subjects had age 60.1 years (mean, SD, 9.9 yr), 53.3% females, and more than 24% of African American race. As expected,  $FEV_1\%$  predicted (mean, 96.3%; SD, 13.7%) and  $FEV_1$  absolute value (mean, 2.78 L; SD, 0.73) were within the normal range. The asymptomatic group had a statistically significant higher  $FEV_1\%$  predicted (99.3 vs. 92.7% among those with symptoms;  $P < 0.05$ ), higher frequency of never-smokers (26.6 vs. 6.0% among those with symptoms;  $P < 0.05$ ), lower frequency of current-smokers (30.1 vs. 52.2% among those with symptoms;  $P < 0.05$ ) and a lower frequency of comorbidities (Table 1).

### Functional Small Airway Abnormalities Increase with Advancing Age

PRM mapping showed that in subjects (both ever- and never-smokers) without airflow obstruction, most of the lung parenchyma was normal, with a low PRM<sup>FSA</sup> burden ( $8.3 \pm 8.0\%$ ) that was similar in those without symptoms ( $8.2 \pm 7.7\%$ ) compared with those with symptoms ( $8.3 \pm 8.4\%$ ;  $P = 0.81$ ). There was also paucity of emphysematous changes (PRM<sup>EMPH</sup>  $0.5 \pm 1.6\%$ ). PRM<sup>FSA</sup> increased with advancing age, in univariate analysis by 3.1% (95% confidence interval [CI], 2.6–3.5%) for decade of age. This association was maintained and remained significant, at 2.7% higher per decade (95% CI, 2.2–3.2%),



**Figure 1.** Flow of participants in SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study). CT = computed tomography.

in multivariate models adjusted for sex, race, height, smoking status, smoking history, history of asthma, clinical center, and CT scanner model (Table 2). Importantly, the increase of  $PRM^{FSA}$  by age was of similar magnitude among nonobstructed subjects with (2.6%; 95% CI, 1.7–3.5%) or without (2.7%; 95% CI, 2.02–3.4%) symptoms or respiratory-related impairment, in multivariate models equally adjusted.

Given that air sac dilation resembling emphysema has been described with aging, we also tested the burden of  $PRM^{EMPH}$  and its association with age in those without airflow obstruction, using similar models to those used to investigate airway abnormalities. We found that the

extent of  $PRM^{EMPH}$  is low, ranging from 0.01% at age 40–50 years to 0.4% at age 70–80 years. Moreover, among subjects without airflow obstruction, the increase in  $PRM^{EMPH}$  (per 10 yr of age) was quite low at 0.1% (95% CI, 0–0.2%) (see Table E1 in the online supplement).

To understand better the impact of smoking on  $PRM^{FSA}$  among subjects without airflow obstruction and to test whether smoking history alters the association between age and  $PRM^{FSA}$ , we also compared never-, former-, and current-smokers in models additionally adjusted for demographics, history of asthma, clinical center, and CT scanner model. Not only did the results not change

the age and  $PRM^{FSA}$  associations, but we also found a limited contribution of smoking history and intensity to the presence of FSA in these subjects with normal post-bronchodilator spirometry (see Table E2).

### Associations of Age with Functional Small Airway Abnormalities Are Maintained in Subgroup Analyses

Based on the different frequency of asthma between never- and ever-smokers, and between subjects with and without symptoms, we tested if  $PRM^{FSA}$  increased with advancing age in subgroups excluding subjects with respiratory symptoms and those with asthma. We found that the associations detected among never-smokers without respiratory symptoms were of similar magnitude after additionally excluding subjects with history of asthma (2.8; 95% CI, 1.7–3.9). Similarly, restricting the analyses to subjects without airflow obstruction, never- and ever-smokers, without symptoms showed similar associations (2.7; 95% CI, 2.0–3.4) to analyses further restricted to exclude participants with asthma (2.7; 95% CI, 2.0–3.5). Exclusion of participants reporting wheezing early in life (at age  $\leq 15$  yr) the age and  $PRM^{FSA}$  association was still maintained, both in the group of never-smokers without airflow obstruction (2.4; 95% CI, 1.3–3.6) and among never- and ever-smokers without airflow obstruction (2.7; 95% CI, 2.1–3.2) (see Table E3).

### Functional Small Airway Abnormalities Impact $FEV_1$ and FVC

Next, in subjects without airflow obstruction, never- and ever-smokers, we analyzed the associations between  $PRM^{FSA}$  and  $FEV_1$  or FVC, in models adjusted for age, sex, race, height, smoking history, smoking status, history of asthma, and  $PRM^{EMPH}$ . We found that an increase in  $PRM^{FSA}$  of 1% was not associated with a significant change in  $FEV_1$  ( $\beta = 1.9$  ml; 95% CI,  $-1.6$  to 5.5 ml;  $P = 0.35$ ). However,  $PRM^{FSA}$  significantly impacted FVC, with a 1% increase in  $PRM^{FSA}$  being associated with 9.4-ml greater (95% CI, 5.0–13.7 ml) FVC. As a consequence of this differential impact on  $FEV_1$  and FVC, an increase of 1% in  $PRM^{FSA}$  has a net effect of decreasing



**Table 1.** Characteristics of SPIROMICS Participants without Airflow Obstruction (N = 1,066)

	All Subjects	Without Respiratory Impairment* (n = 580)	With Respiratory Impairment* (n = 486)
<b>Demographics</b>			
Age, yr, mean (SD)	60.1 (9.9)	60.2 (10.0)	59.9 (9.8)
Females, % <sup>†</sup>	53.3	49.5	57.8
African American, % <sup>†</sup>	24.2	19.7	29.6
Body mass index, kg/m <sup>2</sup> , mean (SD) <sup>†</sup>	28.8 (5.1)	28.0 (4.7)	29.6 (5.4)
<b>Smoking status</b>			
Never-smokers, % <sup>†</sup>	17.2	26.6	6.0
Former smoker, %	42.6	43.3	41.8
Currently smoking, % <sup>†</sup>	40.2	30.1	52.2
<b>Smoking history</b>			
Pack-years smoked, mean (SD) <sup>†</sup>	36.2 (27.3)	30.6 (25.9)	42.9 (27.5)
<b>Respiratory function</b>			
FEV <sub>1</sub> , L, mean (SD) <sup>†</sup>	2.78 (0.73)	2.92 (0.71)	2.61 (0.71)
FEV <sub>1</sub> % predicted, mean (SD) <sup>†</sup>	96.3 (13.7)	99.3 (12.9)	92.7 (13.8)
<b>Comorbidities, %</b>			
Hypertension <sup>†</sup>	42.4	37.1	48.8
Anxiety or depression <sup>†</sup>	32.2	24.7	41.2
Gastroesophageal reflux disease <sup>†</sup>	28.0	23.4	33.5
Diabetes mellitus <sup>†</sup>	12.5	7.9	17.9
Asthma <sup>†</sup>	15.0	6.2	25.5
Coronary artery disease	4.7	3.3	6.4
Sleep apnea <sup>†</sup>	16.4	14.5	18.7
Peripheral vascular disease <sup>†</sup>	5.6	2.6	9.3

*Definition of abbreviation:* SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study.

\*Participants were considered to be without respiratory-related impairment (21) if they did not report chronic bronchitis symptoms (22), dyspnea score greater than or equal to two on the modified Medical Research Council scale (23), distance walked in 6 minutes greater than 350 m, St. George's Respiratory Questionnaire total score less than or equal to 25 points (24), and acute respiratory events in the year before enrollment, defined as use of antibiotic and/or steroid or hospital admission for a respiratory "flare-up."

<sup>†</sup>P less than 0.05.

the FEV<sub>1</sub>/FVC ratio by 0.15% (95% CI, -0.19 to -0.10%).

In the same models, increasing age was associated with decreases in both FEV<sub>1</sub> and FVC, but there was no interaction

between age and PRM<sup>FSA</sup>. The effect of PRM<sup>EMPH</sup> is not to be dismissed: in our analysis, a 1% increase in PRM<sup>EMPH</sup> was associated with a 19-ml lower FEV<sub>1</sub>, no effect on FVC, and a 0.41% lower

**Table 2.** Multivariate Models of the Impact of Age on Extent of CT-defined Functional Small Airway Abnormality (PRM<sup>FSA</sup>) in Subjects Free of Airflow Obstruction (N = 1,066)\*

	β (95% CI)
<b>Demographics</b>	
Age (per 10-yr increment)	2.7 (2.2 to 3.2)
Female (vs. male)	-1.1 (-2.3 to 0.1)
African American race (vs. non-Hispanic white)	-0.4 (-1.7 to 0.8)
Smoking history (per 10 pack-years)	0.1 (-0.1 to 0.3)
<b>Smoking status</b>	
Never-smoker	Reference
Former smoker	0.3 (-1.3 to 1.9)
Currently smoker	-0.8 (-2.4 to 0.7)
History of asthma (vs. no history of asthma)	-0.4 (-1.7 to 0.9)

*Definition of abbreviations:* CI = confidence interval; CT = computed tomography; FSA = functional small airway abnormality; PRM = parametric response mapping.

\*The models were additionally adjusted for height, clinical center, and scanner.

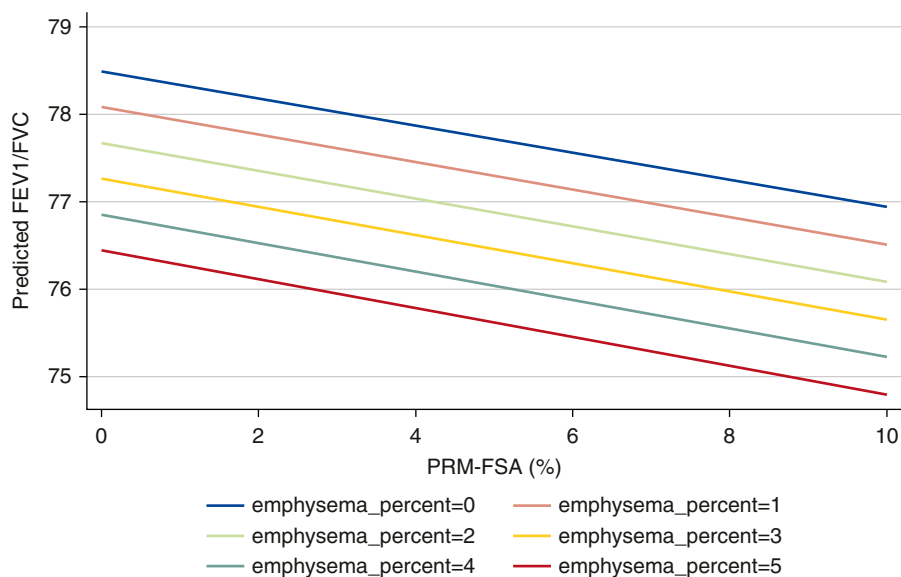
FEV<sub>1</sub>/FVC. Nevertheless, among participants without airflow obstruction, the higher burden of PRM<sup>FSA</sup> (mean, 8.3%) compared with a low emphysema burden (Figure 2), with almost 99% nonobstructed participants had emphysema less than or equal to 5%, makes the PRM<sup>EMPH</sup> contribution of lesser importance in this group of individuals.

### In Established Airflow Obstruction Age Has Greater Impact on the Extent of Small Airway Abnormalities

Finally, we compared the impact of age on PRM<sup>FSA</sup> between the group of 1,066 SPIROMICS participants without airflow obstruction and 905 participants with mild to moderate airflow obstruction (FEV<sub>1</sub>/FVC <0.7 and FEV<sub>1</sub> >50% predicted), including never- and ever-smokers whose demographic and clinical characteristics are presented in Table E4. We found that the extent of PRM<sup>FSA</sup> is significantly greater (P = 0.002 for the interaction term) at any age among those with airflow obstruction (Figure 3; see Figure E1), indicating that the contribution of aging to greater PRM<sup>FSA</sup> is different in presence of established obstruction. Thus, in models adjusted for FEV<sub>1</sub>% predicted, sex, race, height, smoking status, smoking history, history of asthma, clinical center, and scanner, there was a 4.2% higher PRM<sup>FSA</sup> per decade of age (95% CI, 3.3–5.1%) among subjects with obstruction, versus only a 2.7% higher PRM<sup>FSA</sup> per decade of age (95% CI, 2.2–3.2%) among those without airflow obstruction (see Figure E2). We also found a significant interaction between age and airflow obstruction in determining the extent of PRM<sup>EMPH</sup> (P = 0.006 for the interaction term), although the difference per decade of age was of lower magnitude (see Figure E3).

## Discussion

In this investigation of a well-characterized group of never- and ever-smokers, our cross-sectional analysis of imaging data using the PRM technique identified several novel findings about lung aging. First, in subjects without airflow obstruction, a modest degree of PRM<sup>FSA</sup> was associated with greater age, regardless of the presence of symptoms or respiratory-related impairment, an association maintained in



**Figure 2.** Changes in FEV<sub>1</sub>/FVC ratio across varying levels of computed tomography–defined small airway abnormality (parametric response mapping with functional small airways abnormality [PRM<sup>FSA</sup>]) and emphysema among subjects without airflow obstruction. Increasing percentage of PRM<sup>FSA</sup> (*x*-axis) is associated with decreasing FEV<sub>1</sub>/FVC ratio (*y*-axis), an effect that persists at any degree of emphysema severity, as shown by the similar slope of the lines describing the burden of emphysema.

different subgroups by history of smoking or asthma. Second, we found a significant association between airway abnormality (as defined by PRM<sup>FSA</sup>) and increased FVC. Third, we also demonstrate greater effect of age on the extent of PRM<sup>FSA</sup> among subjects with airflow obstruction, such that for the same degree of airflow obstruction, older subjects have greater small airway abnormality.

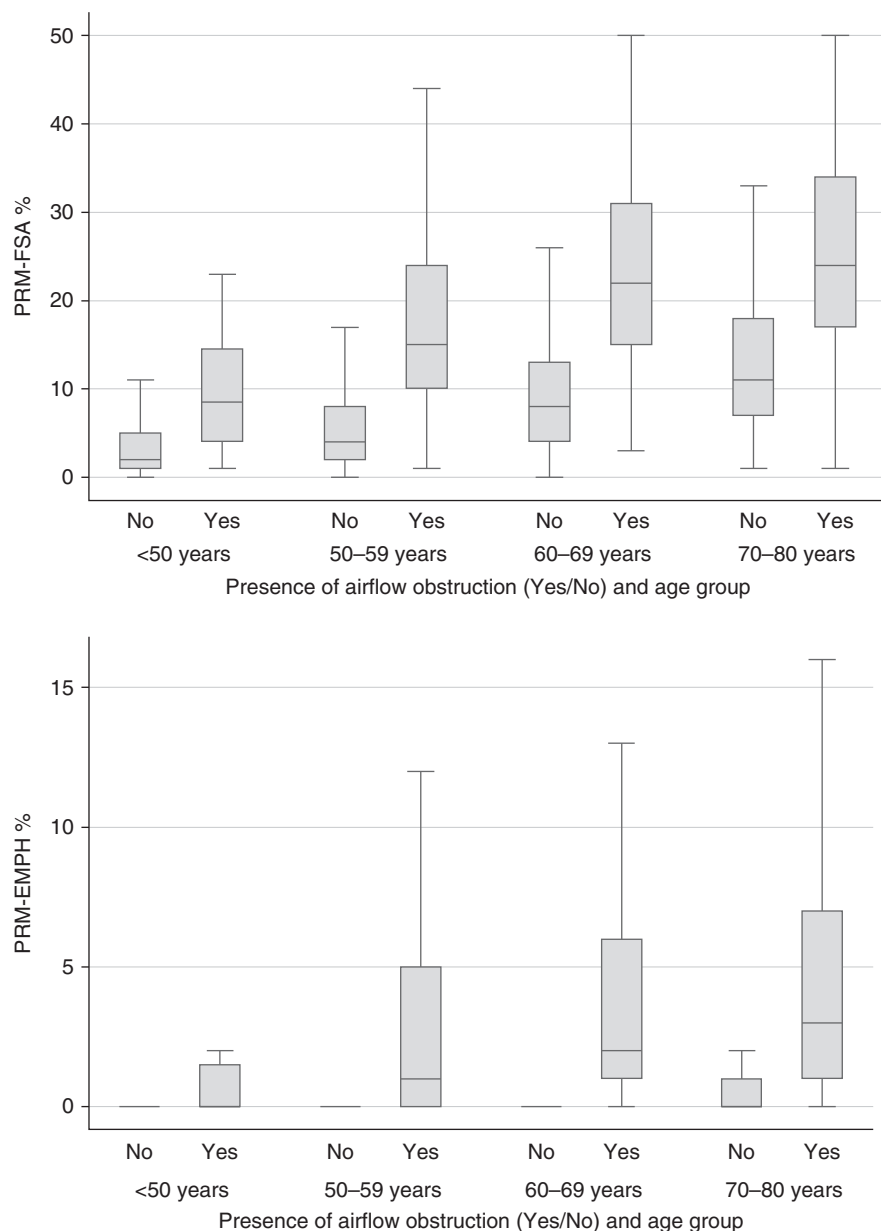
Hence, our data support the hypotheses that in this cohort (1) early events of lung aging in subjects without airflow obstruction or respiratory symptoms are represented by imaging abnormalities related with small airways, with minimal extent of emphysematous changes; (2) in older subjects without respiratory disease, nonclinically significant signs of small airway disease, which can be detected by PRM analysis, can bias spirometry values toward a spurious obstruction, when defined by the fixed FEV<sub>1</sub>/FVC ratio method (29); and (3) that the impact of age on imaging-derived markers of small airway abnormality is particularly relevant among subjects who have airflow obstruction compatible with a diagnosis of COPD.

With a growing number of older adults needing medical care, understanding age-related changes to the lungs is needed to differentiate between healthy aging and

disease, in particular when a new diagnostic method becomes available. With advancing age, respiratory physiologic studies (3, 30, 31) show a loss of elastic recoil, hyperinflation and air trapping, and linearly increased residual volume and decreased vital capacity. Probably the best known effect of normal aging of the lungs is progressive enlargement of the alveolar ducts and distal alveoli resembling emphysematous changes (31). Despite the paucity of inflammatory infiltration of the airways or changes in collagen and elastin content in the healthy elderly (32), it has become customary to label (erroneously) this process as “senile emphysema,” whereas a more precise term might be “senile lung” changes (7, 18). We found that the burden of CT-defined emphysema, as determined by PRM<sup>EMPH</sup>, was low in our selected group of participants with normal spirometry, even among those with respiratory-related impairment. Using a novel method to quantify emphysema noninvasively in a large sample, we provide new evidence to the long-lasting discussion about the interpretation of emphysema-like changes in the healthy elderly, and suggest that in the absence of toxic exposures and concurrent specific susceptibility factors (7), emphysema development is not an age-related condition.

Little regarding aging of the distal airways has been previously described. A previous report suggests that numbers of small airways may be reduced in subjects with senile lung (18). The paucity of information contrasts with growing evidence of the role of peripheral airways as an early target of physiologic changes in COPD (33), and early evidence of increasing resistance of the peripheral airways with advancing age (8, 34). More recently, studies using thin-section CT imaging have reported more frequent bronchial wall thickening in older adults, compared with their younger counterparts, independent of smoking history (35). Boudewijn and colleagues described an association between increasing age and more PRM<sup>FSA</sup>, in a study of 49 current- and 47 never-smokers, mean age 40 years (19). We confirmed the age and PRM<sup>FSA</sup> association, and extend those findings by examining a larger population of more advanced age, even without respiratory impairment.

Our results are important to the venerable and ongoing controversy over the different methods and thresholds currently used to identify and define abnormal spirometric values compatible with airflow obstruction, most commonly the fixed ratio and the lower limit of normal methods. Comparisons of both methods in older adults have shown a rate of discordance as high as 54% (36–38). It has been argued that some degree of hyperinflation caused by age-related changes of emphysema contributes to an age-related FEV<sub>1</sub> decline, resulting in greater overdiagnosis of obstruction when using the fixed ratio definition. In the current sample of subjects without clinically evident lung impairment, we have demonstrated that small airway abnormalities have greater impact on FVC, with minimal changes on FEV<sub>1</sub>, and that the resulting lower ratio could be a function of a change in the denominator (FVC), not just in the numerator (FEV<sub>1</sub>). A plausible interpretation of our findings is that the fixed ratio definition overestimates obstruction in the healthy elderly primarily because of the impact of “silent” small airway abnormalities on the expiratory measures captured by spirometry, not just the consequence of senile emphysema-like changes. Furthermore, comparison of our PRM<sup>FSA</sup> and PRM<sup>EMPH</sup> results, and especially their disparate changes in groups of different ages, implies that small airway



**Figure 3.** Distribution of parametric response mapping-determined small airway abnormality ( $PRM^{FSA}$ , top) and emphysema ( $PRM^{EMPH}$ , bottom) by age and presence of airflow obstruction. At any age, those without airflow obstruction (represented by group *No*) have significantly less small airway abnormality (*y-axis*, top) and emphysema (*y-axis*, bottom) than subjects of similar age with mild airflow obstruction (*Yes*).

changes, rather than senile emphysema-like changes, are the main contributors to this effect.

The finding of greater  $PRM^{FSA}$  extent among subjects with clinical disease and obstructive physiology, compared with those free of clinical and spirometric definitions of COPD, points toward a crucial role of small airways in the development and progression of tobacco-

related obstructive lung disease (33, 34). Among participants in the current study, the impact of aging was both present and magnified among those with obstructive disease, resulting in even greater  $PRM^{FSA}$ . Conversely, the finding of little to no difference in abnormal airway burden between smokers and nonsmokers of the same age before the development of overt obstruction agrees with current concept of

COPD susceptibility. These novel findings suggest that the pathologic mechanisms involved in COPD are not just the result of exposure and accelerated aging (39, 40), but instead that COPD progression results from “accelerated aging” only among susceptible individuals (4, 41). Whether such susceptibility in turn stems entirely from genetic predisposition, or instead might result in part from stochastic interactions between the immune system and an individual’s personal history and temporal order of respiratory infections, requires further study.

Our work is subject to several limitations. First, there was no tissue confirmation of the  $PRM^{FSA}$  measures, making it impossible to distinguish air sacs dilation from actual destruction. Whether there are intrinsic age-related structural abnormalities in the peripheral airways, or if the imaging findings of  $PRM^{FSA}$  represent age-related changes in lung elasticity, remains unknown and the evidence provided by this study cannot provide a final answer to that question; studies to validate PRM measurements histologically are under way. Second, SPIROMICS participants are volunteers, not a representative population sample, raising questions about subtle self-selection bias. Against that possibility is our demonstration of similar outcomes regardless of the presence of respiratory impairment, which we defined robustly by inclusion of several measures of patient-reported symptoms and outcomes, and the similar findings when controlling for the effect of asthma and early life wheezing. The cross-sectional nature of our analyses is a current limitation; longitudinal analysis of this cohort would greatly extend its power. Nevertheless, published work demonstrating an association between  $PRM^{FSA}$  and prospectively assessed lung function decline (28) supports the validity of this metric. Major strengths of the analysis include the large number of participants, use of well-defined criteria to judge presence or absence of abnormal lung function and lung impairment, and detailed analytic models with inclusion of most factors known to be associated with lung function and morphology.

### Conclusions

Analysis of paired inspiratory and expiratory chest CTs using PRM showed

that functional small airway abnormality increases with age, about 2% per decade after the age of 50 years, even in never-smokers with normal lung function and free of respiratory symptoms. This abnormality

results in a decreased FEV<sub>1</sub>/FVC ratio, caused mostly by a relative increase in the FVC. Among individuals with mild to moderate COPD, aging is associated with significantly greater imaging-based

evidence of functional small airway abnormality. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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