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Association of Dysanapsis With Chronic Obstructive Pulmonary Disease Among Older Adults

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IMPORTANCE Smoking is a major risk factor for chronic obstructive pulmonary disease (COPD), yet much of COPD risk remains unexplained.

OBJECTIVE To determine whether dysanapsis, a mismatch of airway tree caliber to lung size, assessed by computed tomography (CT), is associated with incident COPD among older adults and lung function decline in COPD.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study of 2 community-based samples: the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study, which involved 2531 participants (6 US sites, 2010-2018) and the Canadian Cohort of Obstructive Lung Disease (CanCOLD), which involved 1272 participants (9 Canadian sites, 2010-2018), and a case-control study of COPD: the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), which involved 2726 participants (12 US sites, 2011-2016).

EXPOSURES Dysanapsis was quantified on CT as the geometric mean of airway lumen diameters measured at 19 standard anatomic locations divided by the cube root of lung volume (airway to lung ratio).

MAIN OUTCOMES AND MEASURES Primary outcome was COPD defined by postbronchodilator ratio of forced expired volume in the first second to vital capacity (FEV_1:FVC) less than 0.70 with respiratory symptoms. Secondary outcome was longitudinal lung function. All analyses were adjusted for demographics and standard COPD risk factors (primary and secondhand tobacco smoke exposures, occupational and environmental pollutants, and asthma).

RESULTS In the MESA Lung sample (mean [SD] age, 69 years [9 years]; 1334 women [52.7%]), 237 of 2531 participants (9.4%) had prevalent COPD, the mean (SD) airway to lung ratio was 0.033 (0.004), and the mean (SD) FEV_1 decline was −33 mL/y (31 mL/y). Of 2294 MESA Lung participants without prevalent COPD, 98 (4.3%) had incident COPD at a median of 6.2 years. Compared with participants in the highest quartile of airway to lung ratio, those in the lowest had a significantly higher COPD incidence (9.8 vs 1.2 cases per 1000 person-years; rate ratio [RR], 8.12; 95% CI, 3.81 to 17.27; rate difference, 8.6 cases per 1000 person-years; 95% CI, 7.1 to 9.2; $P < .001$) but no significant difference in FEV_1 decline (−31 vs −33 mL/y; difference, 2 mL/y; 95% CI, −2 to 5; $P = .30$). Among CanCOLD participants (mean [SD] age, 67 years [10 years]; 564 women [44.3%]), 113 of 752 (15.0%) had incident COPD at a median of 3.1 years and the mean (SD) FEV_1 decline was −36 mL/y (75 mL/y). The COPD incidence in the lowest airway to lung quartile was significantly higher than in the highest quartile (80.6 vs 24.2 cases per 1000 person-years; RR, 3.33; 95% CI, 1.89 to 5.85; rate difference, 56.4 cases per 1000 person-years; 95% CI, 38.0 to 66.8; $P<.001$), but the FEV_1 decline did not differ significantly (−34 vs −36 mL/y; difference, 1 mL/y; 95% CI, −15 to 16; $P=.97$). Among 1206 SPIROMICS participants (mean [SD] age, 65 years [8 years]; 542 women [44.9%]) with COPD who were followed up for a median 2.1 years, those in the lowest airway to lung ratio quartile had a mean FEV_1 decline of −37 mL/y (15 mL/y), which did not differ significantly from the decline in MESA Lung participants ($P = .98$), whereas those in highest quartile had significantly faster decline than participants in MESA Lung (−55 mL/y [16 mL/y]; difference, −17 mL/y; 95% CI, −32 to −3; $P = .004$).

CONCLUSIONS AND RELEVANCE Among older adults, dysanapsis was significantly associated with COPD, with lower airway tree caliber relative to lung size associated with greater COPD risk. Dysanapsis appears to be a risk factor associated with COPD.

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Supplemental content

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Chronic obstructive pulmonary disease (COPD) is defined by airflow limitation that does not fully reverse[1] and is a leading cause of morbidity and mortality worldwide.[2] Smoking tobacco is a major COPD risk factor,[1] but despite decades of declining smoking rates in many countries,[3-5] the corresponding decreases in disease burden have been modest.[6,7] Furthermore, only a minority of lifetime smokers were found to have spirometry-defined COPD, and up to 30% occurred among people who never smoked in population-based observational samples from 1987 through 1988,[8] and 2005 through 2009.[9] Although other factors have been linked to COPD (eg, secondhand smoke, environmental or occupational pollutants, asthma),[1] much of the variation in COPD risk remains unexplained.

A 3-decade lung function trajectory study demonstrated that 50% of COPD among older adults arises from low baseline lung function, rather than from accelerated lung function decline.[10] Identifying factors associated with low baseline lung function may help account for a large proportion of COPD risk among older adults in the community.

Dysanapsis refers to a mismatch of airway tree caliber to lung size and was initially inferred from variation in spirometry among healthy adults.[11] Dysanapsis is believed to arise early in life,[11] has been implicated in obstructive lung disease susceptibility,[12,13] and can be quantified directly using computed tomography (CT).[14]

This study examined the hypothesis that dysanapsis quantified by CT as the ratio of mean airway lumen diameter to total lung volume (airway to lung ratio) would statistically account for a significant proportion of the variation in forced expired volume in the first second to forced vital capacity (FEV_1:FVC) ratio, and be associated with incident COPD among older adults in the general population. Furthermore, based on the 2 lung function trajectories leading to COPD described previously,[10] this study tested the hypothesis that patients with established COPD and lower airway to lung ratio would have slower lung function decline than those with a larger airway to lung ratio.

Key Points

Question Is dysanapsis, a mismatch of airway tree caliber to lung size, associated with subsequent risk of chronic obstructive pulmonary disease (COPD)?

Findings In this retrospective observational study involving 6529 older adults, a quantitative measure of dysanapsis (airway to lung ratio on computed tomography) was significantly associated with incident COPD (forced expiratory volume in the first second to forced vital capacity [FEV_1:FVC], <0.70 with respiratory symptoms), after adjusting for tobacco exposures and other standard risk factors.

Meaning Among older adults, dysanapsis appears to be a risk factor associated with COPD.

Methods

Study Participants

The main hypotheses were examined in a retrospective cohort study of 2 community-based samples with confirmation in a COPD case-control study; the last hypothesis was examined among patients with established COPD in the case-control study (eFigure 1 in the Supplement). Institutional review board approval was obtained at each study site. All participants provided written informed consent.

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective community-based study that recruited 6814 non-Hispanic white, black, Hispanic, and Chinese American participants, aged 45 through 84 years in the years 2000 through 2002 (examination 1) from the general population in 6 US communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; St Paul, Minnesota; and New York, New York). MESA is community-based but was not designed to be representative of the source populations.[15] Exclusion criteria included clinical cardiovascular disease and impediments to long-term follow-up. MESA Lung enrolled participants sampled from MESA who consented to undergo genetic analyses and completed an examination in the years 2004 through 2006 (examinations 3 and 4),[16] and all participants in the MESA Air substudy, which enrolled additional participants of comparable age from the same study sites and who were free of clinical cardiovascular disease in years 2005 through 2007.[17] MESA Lung participants had performed full-lung CT and spirometry in years 2010 through 2012 (examination 5), with a follow-up assessment in years 2016 through 2018 (examination 6).

The Canadian Chronic Obstructive Lung Disease (COLD) prevalence study used census data to recruit a random sample of noninstitutionalized adults 40 years or older from 9 communities in the years 2005 through 2009 (Calgary, Alberta; Halifax, Nova Scotia; Kingston, Ottawa, and Toronto, Ontario; Montreal and Quebec City, Quebec; Saskatoon, Saskatchewan; and Vancouver, British Columbia).[18] In years 2010 through 2014, the Canadian Cohort of Obstructive Lung Disease (CanCOLD)—a nested community-based case-control study that enrolled COLD participants with COPD, in addition to representative random subsets of COLD nonsmoking participants, and smoking participants without COPD matched on age and sex—performed full-lung CT and spirometry, with 18- and 36-month follow-up assessments (2011-2017).[19]

The Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) is a longitudinal case-control study that recruited participants with and without COPD, aged 40 through 80 years who reported 20 or more pack-years of smoking, recruited another 200 nonsmoking participants, at 12 US medical centers in the years 2010 through 2015 (Ann Arbor, Michigan; Baltimore, Maryland; Birmingham, Alabama; Chicago, Illinois; Denver, Colorado; Iowa City, Iowa; Los Angeles and San Francisco, California; New York, New York; Philadelphia, Pennsylvania; Salt Lake City, Utah; Winston-Salem, North Carolina), and performed full-lung CT and spirometry with up to 3 follow-up assessments in the years 2011 through 2016.[20] Participants were excluded if they had chronic lung diseases except asthma, body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 40, or prior surgical lung resection.

For each study, the first visit with full-lung CT was defined as the baseline visit for the present analysis (MESA Lung, examination 5; CanCOLD, visit 1; SPIROMICS, visit 1).

Dysanapsis Assessment by CT

Participants underwent inspiratory chest CT on helical scanners at baseline assessment. MESA Lung and SPIROMICS followed the same CT protocol (120 kV (peak) (kV[p]), 0.625-0.75 mm slice thickness, 0.5-second rotation time), and CanCOLD scans were acquired with 100 kV(p), 1.00-1.25 mm slice thickness, and 0.5-second rotation time.[21] Central airway tree lumen diameters at 19 standard anatomic locations (trachea to subsegments) and total lung volume were segmented and measured from inspiratory chest CT images using Apollo Software in all 3 studies by trained technologists unaware of other participant information (VIDA Diagnostics; see eMethods).[21-23]

Dysanapsis was assessed as the geometric mean of airway lumen diameters in centimeters measured at 19 standard anatomic locations divided by the cube-root of total lung volume in cubic centimeters (airway to lung ratio). Lower values indicate smaller airway tree caliber relative to lung size and higher values indicate larger airway tree caliber relative to lung size. Reproducibility of this measure on repeated CT scan was excellent (n = 96; rescan interval: 9-42 days; intraclass correlation coefficient, 0.92; 95% CI, 0.88-0.95). Long-term within-participant stability of the airway to lung ratio was quantified over a median interval 6.2 years in the MESA Lung cohort and did not vary significantly (n = 1399; mean [SD] of airway to lung ratio at the first assessment, 0.033 (0.004); and at the second assessment, 0.033 (0.004); mean difference, 0.00002; 95% CI, −0.0035 to 0.0035; eFigure 2 in the Supplement for the Bland-Altman plot).

To simplify interpretation, the percent-predicted airway tree size for each participant was quantified as the geometric mean of percent-predicted airway lumen diameters measured at 19 standard anatomic locations defined by externally validated, sex-stratified, airway-specific lumen diameter reference equations with terms for total lung volume, age, and height (eMethods, eTables 1-4, and eFigure 3 in the Supplement). A percent-predicted value of 100% can be considered the "normal" mean airway tree size given a participant's sex, lung volume, age, and height. A value less than 100% represents a smaller airway tree than predicted, and a value more than 100% represents a larger airway tree than predicted.

Outcomes

The primary study outcome was COPD defined initially by a postbronchodilator FEV_1:FVC ratio of less than 0.7 based on guidelines at the time of the study design (2017).[24] The guideline definition of COPD was updated in 2017 to require postbronchodilator FEV_1:FVC of less than 0.7 and presence of respiratory symptoms.[1] This updated COPD definition was included as a sensitivity analysis in the original draft of our manuscript but we changed it to the primary outcome in revisions to place emphasis on COPD of clinical importance in 2020. The original COPD definition is presented as a sensitivity analysis in the Supplement. Spirometry was performed at baseline following American Thoracic Society recommendations.[25] Questionnaire-assessed presence of respiratory symptoms included a COPD Assessment Test Score of 10 or more (range, 0-40),[26] chronic bronchitis (yes/no),[27] or modified Medical Research Council dyspnea score higher than 0 (range, 0-4).[28] Prevalent COPD was assessed in each study at the first visit with full-lung CT. Incident COPD was assessed in each study among participants with follow-up who did not have prevalent COPD. Secondary study outcomes were FEV_1:FVC, FEV_1, and FVC as continuous variables and were assessed in each study at the first visit with full-lung CT (cross-sectional analyses), in addition to follow-up spirometry assessments (longitudinal analyses).

Standard COPD Risk Factors

Primary Tobacco Smoke Exposures

Cigarette, pipe, and cigar smoking status (current, former, never) was self-reported in all studies and confirmed by urine cotinine measurement in MESA and SPIROMICS. Cigarette pack-years, pipe-years, and cigar-years were calculated by multiplying the number of years smoked by the mean number of daily cigarettes divided by 20, pipe bowls, and cigars, respectively.[16]

Secondhand Smoke Exposures, Occupational or Environmental Pollutants, and Asthma

Secondhand smoke exposure was assessed by self-report as living or working with a person who smokes regularly indoors as an adult and by the number of years of secondhand smoke exposure. Occupational exposure status to vapor gas, dust, or fumes at work, and physician diagnosis of asthma were self-reported. Among MESA Lung participants, individual estimates of long-term exposure to particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), oxides of nitrogen (NO_x), and ozone (O_3) were estimated over the 5-year period (2005-2012) prior to the baseline airway to lung ratio assessment (2010-2012) using validated spatiotemporal models based on continuous measurements acquired from government regulatory monitors and spatially dense supplemental data specific to the MESA Air Study.[29,30]

For study-specific risk factor variables, see eMethods in the Supplement.

Other Variables

Age and sex were assessed by questionnaire and self-reported by the participant. Race/ethnicity was assessed by fixed-category questionnaire items to adjust for pulmonary measures and to test for modification of associations. Height and weight were measured using standardized protocols. The percentage of emphysema-like lung (percent lung volume < −950 Hounsfield units) was quantified on CT images.[31]

Statistical Analysis

Participant characteristics were summarized by study. The CanCOLD participant characteristics and analyses were weighted by the inverse probability of selection from the population-based COLD study to provide community-based estimates.

The primary analysis assessed airway to lung ratio associations in the 2 community-based studies (MESA Lung and CanCOLD), and the secondary analysis included the subgroup of participants who never smoked (CanCOLD) and those with 20 or more pack-years of smoking (SPIROMICS).

The association between airway to lung ratio and baseline FEV_1:FVC ratio was assessed using a linear regression model that was first unadjusted, and then incrementally adjusted for (1) age, age × age, gender, height, height × height, and race/ethnicity; (2) primary tobacco smoke exposures (cigarette smoking status, pack-years, pipe smoking status, pipe-years, cigar smoking status, cigar-years); and, (3) secondhand smoke exposures, occupational or environmental pollutants, and asthma. The prevalence ratio for COPD was assessed using a modified Poisson regression model and adjusted for the above variables. The rate ratio for incident COPD among participants without COPD at baseline was calculated using the same approach with a follow-up interval offset. Multiple imputation was used to account for missing postbronchodilator and follow-up data in MESA Lung. The missing data on covariates were assumed to be missing at random. Based on this assumption, 100 imputed data sets were created using the fully conditional specification regression method. Each of the 100 imputed data sets was then analyzed in the usual way, and the parameter estimates were combined using the Rubin rule.[32] Given little missing data in the other 2 studies, missing covariate data were assigned an indicator variable and longitudinal analyses were limited to those with follow-up data.

Longitudinal FEV_1:FVC change was assessed using mixed-model regression with random intercepts and autoregressive covariance structure. Time was parameterized as years since airway to lung ratio assessment, and the model included baseline age, age × age, sex, height, height × height, race/ethnicity, time-varying primary tobacco and secondhand smoke exposures, occupational or environmental pollutants, asthma, airway to lung ratio, and interaction terms between the COPD risk factors with time. The same approach was used for analysis of longitudinal FEV_1 change among SPIROMICS participants with COPD.

To quantify the proportion of variation in baseline FEV_1:FVC statistically accounted for by standard COPD risk factors and by the airway to lung ratio, the adjusted R^2 was calculated from a linear regression model that was incrementally adjusted for (1) age, age × age, sex, height, height × height, and race/ethnicity; (2) primary tobacco smoke exposures (cigarette smoking status, pack-years, pipe smoking status, pipe-years, cigar smoking status, cigar-years); (3) secondhand smoke exposures, occupational or environmental pollutants, and asthma; and (4) the airway to lung ratio. The cumulative and incremental C statistic and continuous net reclassification index (NRI) improvement for incident COPD were calculated using the probabilities obtained from regression models adjusted for the variables above.[33]

Exploratory analyses assessed association modification by sex, and race/ethnicity for baseline and incident COPD, and FEV_1:FVC change was assessed with product terms. Sensitivity analyses (1) adjusted for percent emphysema, (2) replaced airway to lung ratio with percent-predicted airway tree size, (3) replaced FEV_1:FVC with FEV_1, and FVC, and (4) defined COPD by spirometry alone. Linearity of airway to lung-ratio associations with FEV_1:FVC and COPD were tested with 3- and 4-knot restricted cubic splines.

Analyses were performed using SAS version 9.4 (SAS Institute Inc). The significance threshold was .05 and 2-side *P* values are reported. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points and other analyses should be interpreted as exploratory.

Results

Characteristics of participants included in the airway to lung-ratio analyses are summarized by study in **Table 1** and by airway to lung ratio quartile (eTables 5-10 in the Supplement). MESA Lung participants (n = 2531) had a mean (SD) age of 69 years (9 years); 52.7% were women; 48.5% reported never smoking; race/ethnicity proportions were 38.8% non-Hispanic white, 26.0% black, 21.9% Hispanic; and 13.2% Chinese American; and 237 of 2531 (9.4%) had prevalent COPD. CanCOLD participants (n = 1272) had a mean (SD) age of 67 year (10 years); 44.3% were women; 51.3% reported never smoking; 93.8% were non-Hispanic white; and 171 (13.4%) had prevalent COPD. SPIROMICS participants reporting 20 or more pack-years of smoking (n = 2726) had a mean (SD) age of 63 years (9 years); 46.0% were women; 73.9% non-Hispanic white; and 1577 (57.9%) had prevalent COPD. Characteristics of included participants were generally similar to those lacking CT or spirometry (eTable 11 in the Supplement), although excluded MESA Lung participants were slightly older with lower lung function and excluded CanCOLD participants were more likely to be men and current smokers.

Spirometry was repeated prospectively over a median of 6.2 years in MESA lung (1458 of 2531 [57.6%]), 3.1 years in CanCOLD (1032 of 1272 [81.1%]), and 2.1 years SPIROMICS (2139 of 2726 [78.5%]). Participants without follow-up spirometry were more likely to be current smokers and have COPD; the MESA Lung and CanCOLD participants tended to be older, whereas SPIROMICS participants tended to be younger (eTable 12 in the Supplement). Among those free of COPD at baseline, 98 of 2294 (4.3%) in the MESA Lung Study, 113 of 752 (15.0%) in the CanCOLD study, and 237 of 933 (25.4%) in the SPIROMICS study had incident COPD detected.

Dysanapsis, FEV_1:FVC, and COPD in the Community-Based Studies

The mean (SD) airway to lung ratio was 0.033 (0.004) (98.3 [10.4] percent predicted) in the MESA Lung study and 0.032 (0.003) (95.7 [9.3] percent predicted) in the CanCOLD study. The **Figure** presents representative CT images showing the spectrum of airway to lung ratio and associated FEV_1:FVC among never smoking participants free of standard COPD risk factors.

In the MESA Lung Study, participants in the lowest quartile compared with those in the highest quartile of airway to

Table 1. Descriptive Characteristics of Study Participants Included in the Airway to Lung Ratio Association Analyses

Participant characteristics at baseline	No. (%) of participants		
	Community-based studies		SPIROMICS case-control study[c] (n=2726)
	MESA Lung [a] (n=2531)	CanCOLD[b] (n=1272)	
Age, mean (SD), y	69 (9)	67 (10)	63 (9)
Sex			
Women	1334 (52.7)	564 (44.3)	1253 (46.0)
Men	1197 (47.3)	708 (55.7)	1473 (54.0)
Height, mean (SD), cm	165 (10)	167 (9)	170 (10)
Body mass index, mean (SD)[d]	28 (5)	28 (5)	28 (5)
Race/ethnicity			
Non-Hispanic white	982 (38.8)	1193 (93.8)	2015 (73.9)
Non-Hispanic black	659 (26.0)	15 (1.2)	493 (18.1)
Hispanic	555 (21.9)	5 (0.4)	126 (4.6)
Chinese	335 (13.2)	44 (3.4)	26 (1.0)
Other	0	15 (1.2)	66 (2.4)
Cigarette smoking status			
Never	1227 (48.5)	652 (51.3)	0 (0.0)
Former	1084 (42.8)	475 (37.3)	1647 (60.4)
Current	220 (8.7)	145 (11.4)	1079 (39.6)
Pack-years of ever-smoking, median (IQR)	15 (5-34)	24 (11-42)	43 (31-60)
No. of participants	1168	597	
Pipe or cigar ever-smokers	304 (12.0)	157 (12.3)	297 (10.9)
Secondhand smoke exposure	1258 (49.7)	505 (39.7)	1135 (41.6)
Occupational exposure to vapor-gas, dust, or fumes	998 (39.4)	114 (8.9)	1134 (41.6)
Air pollution exposures, mean (SD)[e]			
No. of participants	2284		
$PM_{2.5}$, μm/m^3	12.3 (1.7)		
NO_x, ppb	30.7 (18.4)		
O_3, ppb	22.1 (4.3)		
Asthma diagnosis ever	209 (8.3)	227 (17.8)	545 (20.0)
FEV_1, mean (SD), L	2.3 (0.7)	2.6 (0.8)	1.9 (0.9)
Predicted FEV_1, mean (SD), %	96 (19)	94 (20)	66 (27)
FEV_1:FVC, mean (SD)	0.74 (0.08)	0.71 (0.08)	0.58 (0.16)
CT total lung volume, mean (SD), L	4.8 (1.3)	5.3 (1.3)	5.9 (1.5)
Prevalent COPD[f]	96 (4.4)	171 (13.4)	1577 (57.9)
Total No.	2170		
Emphysema, median (IQR), %[g]	1.4 (0.6-3.0)	2.3 (1.1-4.2)	3.2 (1.0-10.8)
Quantitative measures of dysanapsis			
Airway to lung ratio, mean (SD)[h]	0.033 (0.004)	0.032 (0.003)	0.032 (0.004)
Predicted airway tree size, mean (SD), %[i]	98.3 (10.4)	95.7 (9.3)	98.0 (11.1)
Follow-up spirometry analysis after baseline airway to lung ratio assessment			
No. of participants	1458	1032	2139
Total follow-up interval, median (IQR), y	6.2 (5.8-6.6)	3.1 (2.9-3.3)	2.1 (1.1-3.0)
No. of follow-up spirometry assessments, median (IQR)	1 (1-1)	2 (2-2)	2 (1-3)
Change in FEV_1:FVC, mean (SD), per 5 y	−0.01 (0.05)	−0.01 (0.09)	−0.04 (0.15)
Change in FEV_1, mean (SD), mL/y	−32 (40)	−36 (75)	−47 (14)
Follow-up incident COPD analysis after baseline airway to lung ratio assessment			
No. with incident COPD/No. without prevalent COPD (%)	31/1110 (2.8)	113/752 (15.0)	237/933 (25.4)
Total follow-up interval, median (IQR), y	6.2 (5.8-6.6)	3.1 (3.0-3.3)	2.1 (1.5-3.0)

Abbreviations: CanCOLD, Canadian Cohort of Obstructive Lung Disease; COLD, Canadian Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expired volume in the first second; FVC, forced vital capacity; IQR, interquartile range; MESA, Multi-Ethnic Study of Atherosclerosis; NO_x, oxides of nitrogen; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study.

[a] Multiple imputation accounts for the subset with missing postbronchodilator and follow-up data in the MESA Lung study (imputed participant characteristics are presented in eTable 11 in the Supplement).

[b] Weighted by the inverse ratio of probability of selection from COLD study.

[c] Excludes the nonsmokers.

[d] Calculated as the weight in kilograms divided by height in meters squared.

[e] Exposures were estimated during the 5-year period prior to assessment using validated spatiotemporal models based on continuous measurements acquired from government regulatory monitors and spatially dense supplemental data specific to the MESA Air study.

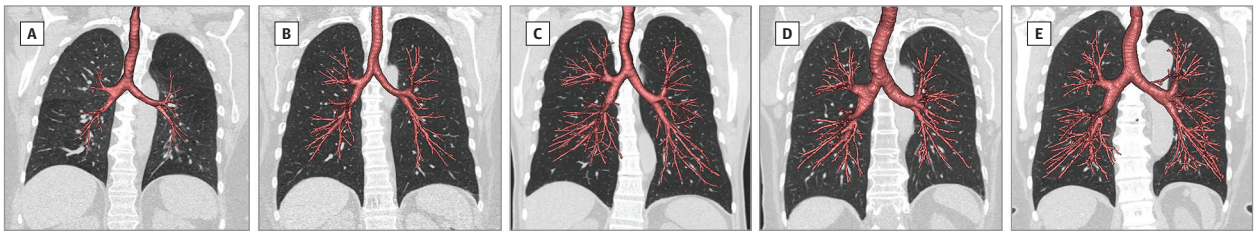
[f] Postbronchodilator FEV_1:FVC less than 0.70 and presence of respiratory symptoms.

[g] Percentage of lung pixels less than 950 Hounsfield units.

[h] See the Methods section for geometric mean calculations

[i] See the Methods section for the geometric calculations.

Figure. Representative CT Images Depicting the Spectrum of Dysanapsis Quantified as the Airway to Lung Ratio Among Older Adults Free of Standard COPD Risk Factors



Representative coronal CT images with segmented central airway trees (colored pink), and corresponding airway to lung ratio measures of dysanapsis and forced expired volume in the first second to forced vital capacity (FEV_1:FVC) ratio from participants free of standard chronic obstructive pulmonary disease (COPD) risk factors in the population-based Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. A, A participant in the first percentile (percent-predicted airway tree size, 78%) and FEV_1:FVC of 0.55. B, A participant in the 25th percentile (percent-predicted airway tree size, 91%) and FEV_1:FVC of 0.68. C, A participant in the 50th percentile (percent-predicted airway tree size,100%) and FEV_1:FVC of 0.80. D, A participant in the 75th percentile (percent-predicted airway tree size,105%) and FEV_1:FVC of 0.81. E, A participant in the 99th percentile (percent-predicted airway tree size, 120%) and FEV_1:FVC of 0.91. For geometric mean calculations, see the Methods section.

lung ratio had significantly lower FEV_1:FVC (0.69 vs 0.78; adjusted mean difference, −0.09; 95% CI, −0.10 to −0.08; $P < .001$) and had higher COPD prevalence (11.7% vs 2.9%; adjusted prevalence ratio, 4.06; 95% CI; 2.75 to 5.99; $P < .001$; adjusted prevalence difference, 8.9%; 95% CI, 7.5% to 9.8%). Findings were similar in unadjusted and partially adjusted analyses (**Table 2**).

In the CanCOLD study, participants in the lowest airway to lung ratio quartile also had a significantly lower FEV_1:FVC ratio (0.61 vs 0.72; adjusted mean difference, −0.09; 95% CI, −0.10 to −0.08; $P < .001$), and higher COPD prevalence (18.4% vs 6.5%; adjusted prevalence ratio, 2.83; 95% CI, 1.87 to 4.27; $P < .001$; adjusted prevalence difference, 11.9%; 95% CI, 8.6%-14.1%) than those in the highest quartile (Table 2).

Participants in the lowest quartile of airway to lung ratio also had a significantly higher COPD incidence in unadjusted and adjusted analyses in MESA Lung (9.8 vs 1.2 cases/1000 person-years; adjusted rate ratio [RR], 8.12; 95% CI, 3.81-17.27; adjusted rate difference, 8.6 cases/1000 person-years 95% CI, 7.1-9.2 cases/1000 person-years; $P < .001$), and in the CanCOLD study (80.6 vs 24.2 cases/1000 person-years; adjusted RR, 3.33; 95% CI, 1.89-5.85; adjusted rate difference, 56.4 cases/1000 person-years, 95% CI, 38.0-66.8 cases/1000 person-years; $P < .001$) compared with the highest quartile (Table 2).

There was no statistically significant association between airway to lung ratio and longitudinal FEV_1:FVC decline in either community-based study (adjusted mean FEV_1:FVC change per 5 years in MESA Lung, 0.00; 95% CI, 0.00 to 0.00; $P = .61$, and in the CanCOLD study, 0.00; 95% CI, −0.01 to 0.01; $P = .95$; Table 2).

Dysanapsis and the Statistical Accounting of Baseline FEV_1:FVC Variation and Incident COPD in the Community-Based Studies

In the MESA Lung study, the combination of age, age × age, sex, height, height × height, and race/ethnicity statistically accounted for 14.4% of the baseline FEV_1:FVC variation (95% CI, 14.2%-14.5%), primary tobacco smoke exposure variables (cigarette smoking status, pack-years, pipe smoking status, pipe-years, cigar smoking status, cigar-years) accounted for an additional 4.7% (95% CI, 4.6%-4.8%), and secondhand smoke, occupational or environmental pollutants, and asthma variables an additional 2.9% (95% CI, 2.8%-3.0%). The airway to lung ratio, when added to the above factors, statistically accounted for an additional 16.7% (95% CI, 16.6%-16.9%). The airway to lung ratio was also significantly associated with a C-statistic increment for incident COPD when added to the above factors (C statistic, 0.83 vs 0.76; difference, 0.07; 95% CI, 0.03-0.11; $P < .001$), and NRI improvement (0.60; 95% CI, 0.57-0.62; $P < .001$; **Table 3**).

In the CanCOLD study, the airway to lung ratio statistically accounted for the largest proportion of variation in baseline FEV_1:FVC when added to demographics and standard COPD risk factors (18.5%; 95% CI, 18.2%-18.8%; $P < .001$), and was statistically associated with C-statistic increment for incident COPD (C statistic, 0.74 vs 0.70; difference, 0.04; 95% CI, 0.01-0.08; $P = .03$) and NRI improvement (0.50; 95% CI, 0.47-0.53; $P < .001$; Table 3).

Dysanapsis Among Never Smoking CanCOLD Participants, and 20 Plus Pack-Year SPIROMICS Participants

Characteristics of the 520 CanCOLD study participants who never smoked , and 2726 SPIROMICS participants who smoked 20 or more pack-years are presented by airway to lung ratio quartile in eTables 8 and 9 in the Supplement, respectively. The mean (SD) airway to lung ratio was 0.031 (0.003) (94.2 [9.5] percent predicted) among CanCOLD study participants who never smoked, and 0.032 (0.004) (98.0 [11.1] percent predicted) among SPIROMICS participants with a smoking history of 20 or more pack-years.

Among both the CanCOLD study never-smoking participants and among SPIROMICS heavy-smoking participants, lower airway to lung ratio was significantly associated with lower baseline FEV_1:FVC, higher COPD prevalence, and higher COPD incidence in unadjusted and adjusted analyses but was not statistically associated with longitudinal FEV_1:FVC change (**Table 4**). Airway to lung ratio also statistically accounted for the largest proportion of variation in baseline FEV_1:FVC when added to standard COPD risk factors, and

Table 2. Airway to Lung Ratio Associations With FEV_1:FVC and Chronic Obstructive Pulmonary Disease in the Community-Based Studies

	MESA Lung	CanCOLD
Baseline FEV_1:FVC, No. of participants	2531	1272
Mean baseline difference, lowest to highest airway to lung ratio quartiles, (95% CI)[a,b]		
Unadjusted	−0.09 (−0.10 to −0.08)	−0.08 (−0.10 to −0.07)
Age, age × age, sex, height, height × height, and race/ethnicity	−0.09 (−0.10 to −0.08)	−0.10 (−0.11 to −0.08)
Primary tobacco smoke exposures	−0.09 (−0.10 to −0.08)	−0.09 (−0.11 to −0.08)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	−0.09 (−0.10 to −0.08)	−0.09 (−0.10 to −0.08)
Prevalent COPD, No. (%)	237 (9.4)	171 (13.4)
Prevalence ratio, lowest to highest airway to lung ratio quartiles, (95% CI)[a,c]		
Unadjusted	4.96 (3.83 to 7.62)	2.88 (1.91 to 4.35)
Age, age × age, sex, height, height × height, and race/ethnicity	5.16 (3.47 to 7.66)	3.33 (2.21 to 5.03)
Primary tobacco smoke exposures	4.62 (3.12 to 6.82)	3.11 (2.06 to 4.71)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	4.06 (2.75 to 5.99)	2.83 (1.87 to 4.27)
Prevalence difference, lowest to highest airway to lung ratio quartiles, (95% CI)[a]		
Unadjusted	16.9 (14.8 to 18.3)	16.9 (12.3 to 19.9)
Age, age × age, sex, height, height × height, and race/ethnicity	14.0 (12.4 to 15.1)	17.7 (13.8 to 20.3)
Primary tobacco smoke exposures	11.1 (9.6 to 12.1)	13.6 (10.3 to 15.8)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	8.9 (7.5 to 9.8)	11.9 (8.6 to 14.1)
No. with incident COPD/No. without prevalent COPD (%)	98/2294 (4.3)	113/752 (15.0)
Incidence rate ratio, lowest to highest airway to lung ratio quartiles, (95% CI)[a,c]		
Unadjusted	7.14 (3.27 to 15.61)	2.66 (1.55 to 4.56)
Age, age × age, sex, height, height × height, and race/ethnicity	8.90 (4.05 to 19.55)	3.52 (2.01 to 6.15)
Primary tobacco smoke exposures	8.62 (4.01 to 18.51)	3.42 (1.95 to 5.99)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	8.12 (3.81 to 17.27)	3.33 (1.89 to 5.85)
Incidence rate difference, lowest to highest airway to lung ratio quartiles, cases/1000 person-y, (95% CI)[a]		
Unadjusted	12.2 (9.8 to 13.3)	55.3 (31.3 to 69.2)
Age, age × age, sex, height, height × height, and race/ethnicity	11.3 (9.6 to 12.0)	67.1 (47.1 to 78.5)
Primary tobacco smoke exposures	10.2 (8.6 to 10.9)	61.8 (42.6 to 72.7)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	8.6 (7.1 to 9.2)	56.4 (38.0 to 66.8)
Follow-up FEV_1:FVC, No. of participants	2531	1032
Mean 5-y FEV_1:FVC change, lowest to highest airway to lung ratio quartiles, (95% CI)[a,d]		
Unadjusted	0.00 (0.00 to 0.00)	0.00 (−0.01 to 0.01)
Age, age × age, sex, height, height × height, and race/ethnicity	0.00 (0.00 to 0.00)	0.00 (−0.01 to 0.01)
Primary tobacco smoke exposures	0.00 (0.00 to 0.00)	0.00 (−0.01 to 0.01)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	0.00 (−0.01 to 0.00)	0.00 (−0.01 to 0.01)

Abbreviations: CanCOLD, Canadian Cohort of Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in the first second; FVC, forced vital capacity; MESA, Multi-Ethnic Study of Atherosclerosis.

[a] The lowest airway to lung ratio quartile was 25% of participants with the smallest and the highest quartile was 25% of participants with the largest airway tree caliber relative to lung volume.

[b] Differences were calculated using linear regression.

[c] The prevalence and incidence rate ratios were calculated using modified Poisson regression models.

[d] The annual change was calculated using mixed model regression with random intercepts.

Table 3. Baseline FEV_1:FVC Variation Statistically Accounted for, and Incident COPD C Statistic and NRI Increment With Standard COPD Risk Factors and Airway to Lung Ratio in the Community-Based Studies

	MESA Lung	CanCOLD
Baseline FEV_1:FVC, No.	2531	1272
Increment in proportion of baseline FEV_1:FVC % statistically accounted for, (95% CI)[a,b]		
Age, age × age, sex, height, height × height, and race/ethnicity	14.4 (14.2-14.5)	3.4 (3.3-3.5)
Primary tobacco smoke exposures	4.7 (4.6-4.8)	4.4 (4.3-4.5)
Secondhand smoke, occupational or environmental pollutants, and asthma	2.9 (2.8-3.0)	3.9 (3.9-4.0)
Airway to lung ratio	16.7 (16.6-16.9)	18.5 (18.2-18.8)
No. with incident COPD/No. without prevalent COPD (%)	98/2294 (4.3)	113/752 (15.0)
Cumulative C statistic for incident COPD for risk factors and airway to lung ratio, (95% CI)[b,c]		
Age, age × age, sex, height, height × height, and race/ethnicity	0.67 (0.66-0.67)	0.59 (0.58-0.59)
Primary tobacco smoke exposures	0.71 (0.71-0.72)	0.67 (0.67-0.67)
Secondhand smoke, occupational or environmental pollutants, and asthma	0.76 (0.76-0.77)	0.70 (0.70-0.71)
Airway to lung ratio	0.83 (0.82-0.83)	0.74 (0.74-0.75)
NRI improvement for incident COPD for risk factors and airway to lung ratio, (95% CI)[b,d]		
Age, age × age, sex, height, height × height, and race/ethnicity	0.58 (0.56-0.61)	0.31 (0.28-0.33)
Primary tobacco smoke exposures	0.37 (0.34-0.40)	0.41 (0.39-0.43)
Secondhand smoke, occupational or environmental pollutants, and asthma	0.37 (0.34-0.40)	0.28 (0.25-0.31)
Airway to lung ratio	0.60 (0.57-0.62)	0.50 (0.47-0.53)

Abbreviations: CanCOLD, Canadian Cohort of Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in the first second; FVC forced vital capacity; MESA, Multi-Ethnic Study of Atherosclerosis; NRI, net reclassification index.

[a] Statistically accounted for by standard COPD risk factors and airway to lung ratio were quantified as the increments in adjusted R^2 calculated using observed and predicted probabilities from regression models with addition of the variables indicated.

[b] CIs were estimated using bootstrap sampling with replacement technique.

[c] The cumulative C statistic for incident COPD was calculated using observed and predicted probabilities from regression models with addition of the variables indicated.

[d] The NRI improvement for incident COPD was calculated using observed and predicted probabilities from regression models with addition of the variables indicated. The NRI improvement quantifies whether the addition of a variable (or set of variables) to an existing model improves the prediction of an event. Larger values indicate the added variable(s) resulted in a net improvement in the predicted probability of the event (incident COPD).

significant C-statistic increment and NRI improvement for incident COPD (eTable 13 in the Supplement).

The 84 participants in the CanCOLD study who never smoked with prevalent COPD had a mean (SD) airway tree size of 91.5 cm (9.1 cm) percent predicted, whereas the 1149 participants in SPIROMICS who had 20 or more pack-years without prevalent COPD had a mean (SD) airway tree size of 103.7 cm (9.9 cm) percent predicted.

Dysanapsis and the Rate of FEV_1 Decline Among 20+ Pack-Year SPIROMICS Participants With COPD

Among 1206 SPIROMICS participants with prevalent COPD and follow-up spirometry, the mean (SD) rate of FEV_1 decline was −44 mL/y (15 mL/y) . Adjusted for demographics and standard COPD risk factors, those in the lowest airway to lung ratio quartile had a mean (SD) FEV_1 decline of −37 mL/y (15 mL/y), which did not differ significantly from that observed in the community-based studies (MESA Lung, −33 mL/y [31 mL/y]; adjusted difference, 0 mL/y; 95% CI, −8 to 8; P = .98; CanCOLD, −36 mL/y [75 mL/y]); adjusted difference, 2 mL/y; 95% CI, −7 to 10; P = .67). SPIROMICS participants with COPD in the highest airway to lung ratio quartile had a faster FEV_1 decline (−55 mL/y [16 mL/y]) than those in the lowest airway to lung ratio quartile (adjusted difference, −17 mL/y; 95% CI, −32 to −3 mL/y; P = .004).

Among 933 SPIROMICS participants without prevalent COPD, the mean (SD) rate of FEV_1 decline was −52 mL/y (12 mL/y) was not significantly different between those in the lowest and highest airway to lung ratio quartile (−45 vs −56 mL/y; adjusted difference, 10 mL/y; 95 %CI, −5 to 25 mL/y; P = .18).

Subgroup and Sensitivity Analyses

There was no statistical evidence of association modification by sex, or race/ethnicity for prevalent COPD (P for interaction >.17), incident COPD (P for interaction >.10), or longitudinal change in spirometry (P for interaction >.25). Analyses adjusted for percent emphysema or performed with percent-predicted airway tree size, COPD defined by spirometry alone, or analyses restricted to participants without imputed data yielded consistent results, as did replacing FEV_1:FVC with FEV_1, whereas the airway to lung

Table 4. Airway to Lung Ratio Associations With FEV_1/FVC and COPD Among Never-Smoking CanCOLD Participants and 20 Pack-Years or More SPIROMICS Participants[a]

	CanCOLD participants who never smoked	SPIROMICS participants with 20+ pack-years
Baseline FEV_1:FVC, No.	520	2726
Mean difference in baseline FEV_1:FVC, lowest to highest airway to lung ratio quartile, (95% CI)		
Unadjusted	−0.10 (−0.12 to −0.08)	−0.26 (−0.28 to −0.25)
Age, age × age, sex, height, height × height, and race/ethnicity	−0.11 (−0.13 to −0.09)	−0.26 (−0.28 to −0.25)
Primary tobacco smoke exposures	NA	−0.26 (−0.28 to −0.25)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	−0.10 (−0.12 to −0.08)	−0.26 (−0.27 to −0.25)
Prevalent COPD, No. (%)	84 (16.2)	1577 (57.8)
Prevalence ratio for COPD, lowest to highest airway to lung ratio quartile, (95% CI)		
Unadjusted	2.42 (1.29 to 4.53)	3.21 (2.83 to 3.63)
Age, age × age, sex, height, height × height, and race/ethnicity	2.95 (1.60 to 5.46)	3.18 (2.81 to 3.60)
Primary tobacco smoke exposures	NA	3.15 (2.78 to 3.57)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	2.57 (1.39 to 4.76)	3.06 (2.70 to 3.46)
Prevalence difference in COPD, lowest to highest airway to lung ratio quartile, % (95% CI)		
Unadjusted	13.1 (5.0 to 17.4)	60.6 (56.9 to 63.8)
Age, age × age, sex, height, height × height, and race/ethnicity	14.2 (8.0 to 17.5)	58.6 (55.0 to 61.7)
Primary tobacco smoke exposures	NA	58.2 (54.7 to 61.4)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	11.3 (5.1 to 14.6)	56.5 (52.8 to 59.6)
No. with incident COPD/No. without prevalent COPD (%)	42/372 (11.3)	237/933 (25.4)
Incidence rate ratio for COPD, lowest to highest airway to lung ratio quartile, (95% CI)		
Unadjusted	3.36 (1.32 to 8.52)	5.22 (3.40 to 8.01)
Age, age × age, sex, height, height × height, and race/ethnicity	4.00 (1.51 to 10.61)	5.99 (3.77 to 9.50)
Primary tobacco smoke exposures	NA	5.71 (3.56 to 9.17)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	3.66 (1.82 to 9.72)	5.48 (3.39 to 8.83)
Incidence rate difference for COPD, lowest to highest airway to lung ratio quartile, cases/1000 person-y, (95% CI)		
Unadjusted	49.9 (17.0 to 61.5)	41.0 (35.8 to 44.4)
Age, age × age, sex, height, height × height, and race/ethnicity	48.9 (21.9 to 59.1)	41.9 (37.0 to 45.0)
Primary tobacco smoke exposures	NA	40.1 (34.9 to 43.3)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	38.9 (14.7 to 48.0)	37.9 (32.7 to 41.1)
Follow-up FEV_1:FVC, No.	447	2139
Mean 5-y FEV_1:FVC change, lowest to highest airway to lung ratio quartile, (95% CI)		
Unadjusted	0.01 (−0.01 to 0.02)	0.01 (0.00 to 0.03)
Age, age × age, sex, height, height × height, and race/ethnicity	0.00 (−0.01 to 0.02)	0.01 (−0.01 to 0.02)
Primary tobacco smoke exposures	NA	0.01 (−0.01 to 0.02)
Secondhand smoke exposures, occupational or environmental pollutants, and asthma	0.00 (−0.02 to 0.02)	0.01 (−0.01 to 0.02)

Abbreviations: CanCOLD, Canadian Cohort of Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in the first second; FVC, forced vital capacity; NA, not applicable; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study.

[a] See Table 2 and Table 3 footnotes for an explanation of association measures.

ratio statistically accounted for little to none of the variation in FVC (eTables 14-18 in Supplement). Use of a nonlinear restricted cubic spline did not improve the model fit for airway to lung ratio associations with COPD when compared with a linear term.

Discussion

Dysanapsis quantified on CT was significantly associated with COPD risk among older adults in the community, with lower airway to lung ratio associated with higher COPD incidence. Airway to lung ratio statistically accounted for a greater proportion of variation in FEV_1:FVC than smoking and other COPD risk factors and yielded the highest net reclassification index improvement for incident COPD. These observations suggest that dysanapsis quantified as the airway to lung ratio on CT is a risk factor for COPD among older adults.

Dysanapsis, initially inferred from airflow variation in 56 healthy adults and subsequently confirmed using CT measurements, is believed to represent altered early-life mismatch of airway tree caliber to lung size.[11,14] The present study builds on these observations by showing that the airway to lung ratio is strongly and independently associated with COPD prevalence and incidence among older adults. This may help explain why only a minority of people with heavy smoking history develop COPD,[8,34] and why up to 30% of COPD occurs among people who never smoked.[9] Larger than predicted airway tree size may signal physiological reserve to sustain noxious particulate-pollutant-induced or asthma-induced airway narrowing (and associated reduction in airflow) without reaching the FEV_1:FVC threshold that defines COPD, as was seen in this study among participants without COPD despite heavy smoking history. Conversely, people with smaller than predicted airway tree size who never smoked may require no additional risk factor to meet the spirometric criteria for COPD.

Smaller airway to lung ratio was significantly associated with higher COPD incidence but was not significantly associated with longitudinal FEV_1:FVC change in the community samples. This finding is consistent with the observation that there are 2 major paths to development of COPD in older life: (1) low early-life lung function, which accounts for an estimated 50% of adult COPD risk, and (2) accelerated decline in lung function in adulthood due to long-term noxious exposures such as cigarette smoke.[10] Dysanapsis assessed quantitatively by CT among older adults may quantify a person's early life or baseline proximity to FEV_1:FVC of 0.70, that is, the first path to COPD. The lack of change in airway to lung ratio on CT over 6 years of aging and its lack of association with accelerated lung function decline in the general population is consistent with this thinking.

Also consistent is the finding that SPIROMICS participants with established COPD and smaller airway to lung ratio had the same average lung function decline as the community-based samples, whereas SPIROMICS participants with established COPD and larger airway to lung ratio had much faster decline in lung function. In other words, the same 2 major paths lead to 2 probabilistic types of patients with COPD: those with dysanapsis who do not have accelerated decline in lung function either before or after the development of COPD, and those with accelerated decline in lung function leading to COPD and persisting after its development.[10]

The magnitude of the airway to lung ratio association with COPD prevalence and incidence ratios were consistent in CanCOLD, and SPIROMICS, as was the lack of association with lung function change in all studies, whereas the airway to lung ratio prevalence and incidence ratios for COPD were somewhat higher in the MESA Lung Study. This may reflect the comparatively high baseline FEV_1:FVC among participants in the MESA Lung study, which may have reduced misclassification introduced from diagnostic instability of COPD.[35]

Limitations

This study has several limitations. First, airway to lung ratio was assessed after the period of lung development. Performing airway caliber measurements in early-life community-based samples is problematic owing to radiation risk. Nevertheless, CT-assessed airway to lung ratio among older adults exhibited stability over 6.2 years. Second, the airway to lung ratio measure may partly reflect emphysema-associated loss of airway tethering, airway remodeling, or lung hyperinflation. This is unlikely to explain the findings since (1) they were similar when adjusted for emphysema severity and among people who never smoked with very little emphysema; (2) dysanapsis was quantified mainly from cartilaginous airways, which are not believed to be the primary site of noxious particulate-induced COPD pathobiology and are less susceptible to airway tethering; and (3) the airway to lung ratio was associated with incident COPD independently.[36,37] Third, disease progression is multidimensional,[38] but the present analysis focused on lung function decline. Fourth, unmeasured, imprecisely measured, or differential susceptibility to COPD risk factors that alter the airway to lung ratio may inflate associations with COPD. However, there were detailed and standardized COPD risk factor assessments and analyses restricted to people who never smoked yielded similar results. Fifth, the airway tree reference equations were derived from a subset of participants included in the main association analyses of the MESA Lung study, which may affect generalizability. However, the reference equations were validated in the independent sample of SPIROMICS controls with no smoking history, and the findings were consistent in 2 independent studies. Sixth, the variance statistically accounted for and the NRI used to quantify the importance of the airway to lung ratio relative to other risk factors depend in part on study-specific associations and risk factor and outcome distributions; however, the airway to lung ratio variance accounted for and NRI improvement consistently exceeded each of the standard COPD risk factors in multiple community-based and clinical samples. Seventh, COPD status assessed at study visits (interval censoring) may have biased the COPD rate ratio estimates toward the null but would affect equally the estimates for the airway to lung ratio measure and other COPD risk factors. Eighth, differences among participants with missing baseline or follow-up data may introduce bias and limit generalizability. This is unlikely

given the consistent associations across multiple studies and sensitivity analyses. Ninth, it is possible that the findings in established COPD may be confounded by selection on COPD, a type of collider or index case bias[39,40]; however, they are the logical result of 2 paths to the development of COPD,[10] and we do not make inferences from patients with COPD to the general population.

Conclusions

Among older adults, dysanapsis was significantly associated with COPD, with lower airway caliber relative to lung size associated with greater COPD risk. Dysanapsis appears to be a risk factor associated with COPD.

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