Original research

Structural airway imaging metrics are differentially associated with persistent chronic bronchitis

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2020-215853).

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Received 24 July 2020
Revised 9 November 2020
Accepted 23 November 2020
Published Online First 6 January 2021

ABSTRACT

Background Chronic bronchitis (CB) is strongly associated with cigarette smoking, but not all smokers develop CB. We aimed to evaluate whether measures of structural airway disease on CT are differentially associated with CB.

Methods In smokers between ages 45 and 80 years, and with Global Initiative for Obstructive Lung Disease stages 0–4, CB was defined by the classic definition. Airway disease on CT was quantified by (i) wall area percent (WA%) of segmental airways; (ii) Pi10, the square root of the wall area of a hypothetical airway with 10 mm internal perimeter; (iii) total airway count (TAC) and (iv) airway fractal dimension (AFD), a measure of the complex branching pattern and remodelling of airways. CB was also assessed at the 5-year follow-up visit.

Measurements and main results Of 8917 participants, 1734 (19.4%) had CB at baseline. Airway measures were significantly worse in those with CB compared with those without CB: WA% 54.5 (8.8) versus 49.8 (8.3); Pi10 2.58 (0.67) versus 2.28 (0.59) mm; TAC 156.7 (81.6) versus 177.8 (91.1); AFD 1.477 (0.091) versus 1.497 (0.092) (all p<0.001). On follow-up of 5517 participants at 5 years, 399 (7.2%) had persistent CB. With adjustment for between-visits changes in smoking status and lung function, greater WA% and Pi10 were associated with significantly associated with persistent CB, adjusted OR per SD change 1.75, 95% CI 1.56 to 1.97; p<0.001 and 1.66, 95% CI 1.42 to 1.86; p<0.001, respectively. Higher AFD and TAC were associated with significantly lower odds of persistent CB, adjusted OR per SD change 0.76, 95% CI 0.67 to 0.86; p<0.001 and 0.69, 95% CI 0.60 to 0.80; p<0.001, respectively.

Conclusions Higher baseline AFD and TAC are associated with a lower risk of persistent CB, irrespective of changes in smoking status, suggesting preserved airway structure can confer a reserve against CB.

Key messages

What is the key question?
- Although chronic bronchitis (CB) is strongly associated with cigarette smoking, not all smokers develop CB.

What is the bottom line?
- In a cohort of current and former smokers, we demonstrated that higher total airway count and airway fractal dimension appear to confer a reserve against persistent CB.

Why read on?
- These findings support consideration of structural airway characteristics as risk factors for CB.

INTRODUCTION

Chronic bronchitis (CB) is a major component of COPD. Population data suggest CB affects between 3.4% and 22% of adults, with 10 million adults affected within the USA alone.[1 2] It is associated with substantial morbidity including dyspnoea, poor respiratory-quality of life and a high frequency of exacerbations.[3–9] Longer-term consequences include accelerated lung function decline,[6 8] a greater likelihood of airflow obstruction in those without airflow limitation at baseline,[10] and higher mortality than in those without CB.[6 10]

Cigarette smoking is the strongest risk factor for CB, conferring an approximately threefold higher risk compared with non-smokers.[2] It is, however, not known why only some smokers develop CB and others do not, given similar environmental exposures. Although differences in genetic predisposition is a possibility, twin studies show moderate familial aggregation in women only,[11] and genome-wide association studies have found borderline associations,[12] or associations that were no longer significant once current smoking or airflow obstruction was taken into account.[13] These findings raise important questions about the role of other risk factors as well as the existence of protective factors. It is plausible that the occurrence of CB represents a balance between gene-environment interactions and structural and functional reserve.

CB is associated with mucosal hypertrophy and thickening of the terminal airways.[3] CT findings of increased segmental and subsegmental airway wall thickness have been used as surrogates that reflect more distal airway remodelling.[14] Indeed, these measures of airway wall thickness on CT are greater in those with CB than in controls.[15] The deposition of cigarette smoke is patchy and likely depends on airway anatomy. Furthermore, some CT metrics that sample airways only at certain generations may not provide a complete measure of airway remodelling. Whether structural aspects of airway branching and remodelling confer

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To cite: Bhatt SP, Bodduluri S, Kizhakke Puliyakote AS, *et al*. *Thorax* 2021;**76**:343–349.

differential risk for CB has not been examined. In prior studies, thickened segmental airway walls were associated with CB but whether thickened airway wall predicates persistent CB even after smoking cessation is not known. Additional measures of airway disease have been described recently. Total airway count (TAC) is associated with lung function decline and may be associated with clinical airway disease.[16] We recently measured the fractal dimension of airways that takes into account the complex recurring branching patterns and airway remodelling.[17] Low airway fractal dimension (AFD) is associated with worse respiratory quality of life and functional capacity and also with frequent exacerbations, lung function decline, and mortality.[17] In this study, we aimed to evaluate whether measures of structural airway disease on CT are associated with CB, with the hypothesis that measures of airway remodelling are differently associated with persistent CB on long-term follow-up even after smoking cessation.

METHODS

Study population

We included adults enrolled in the Genetic Epidemiology of COPD (COPDGene) study, the details of which have been previously published.[18] Briefly, COPDGene is a large multicentre cohort that enrolled current and former smokers between the ages of 45 and 80 years from 21 centres across the USA. We analysed data from participants with Global Initiative for Obstructive Lung Disease (GOLD) stages 0 through 4; individuals with $FEV_1/FVC>/=0.70$ and FEV_1%predicted>/=80 but with respiratory symptoms were classified as GOLD 0. We excluded 1275 participants with Preserved Ratio Impaired Spirometry, with $FEV_1/FVC>/=0.70$ and $FEV_1<80\%$ predicted. All participants had a smoking burden of at least 10 pack years. Participants were classified as current smokers if they had smoked cigarettes within 30 days of study visit. At enrolment and at follow-up approximately 5 years later, all participants underwent lung function testing with prebronchodilator and postbronchodilator spirometry.

CB was defined using the classic definition of CB, the presence of cough and phlegm for at least 3 months a year for at least two consecutive years. We also defined CB using the responses to the chronic cough-related questions on the St. George's Respiratory Questionnaire (SGRQ)[19]; we classified individuals as having CB if they answered 'almost every day' or 'most days of the week' to both the questions 'over the last 4 weeks, I have coughed:' and 'over the last 4 weeks, I have brought up phlegm:'.[20 21] The SGRQ-based definition classifies more individuals as having CB than the classic definition, with comparable associations with airway disease and symptoms, but identifies more individuals at risk for future exacerbations than the classic definition.[21] The classic CB definition was used for the primary analyses.

CT image analysis

Volumetric CT scans were acquired at enrolment using multidetector CT scanners at full inspiration (total lung capacity) and end expiration (functional residual capacity or residual volume).[14 18] LungQ, V.1.0.0 (Thirona, Nijmegen, the Netherlands) and Pulmonary WorkStation V.2 software (VIDA Diagnostics, Coralville, Iowa, USA) were used to segment the lungs and airways from inspiratory CT scans.[22 23] The following measures of airway disease were calculated.

1. *Wall area per cent (WA%) of segmental airways:* the luminal area (A_I) and total airway cross-sectional area (A_T) were calculated, and the airway wall area estimated by $A_T - A_I$. Airway wall area per cent was calculated as $(WA\%) = [(A_T - A_I)/A_T] \times 100$.[24]
2. *Pi10:* the square root of the wall area of a hypothetical airway with 10 mm internal perimeter, was calculated by plotting the internal perimeters of all segmental and distal airways against the square root of their wall areas.[25]
3. *TAC:* the TAC of subtracheal airways was calculated by automated identification of branch points on the airway tree and summing number of branches.
4. *AFD:* AFD of the airway lumen was calculated using the Minkowski-Bougliand box-counting dimension using MATLAB software (MathWorks, Natick, Massachusetts, USA), as previously described.[17] Briefly, cubes of progressively increasing side length 's' were iteratively laid over the airway tree and the number of cubes 'n' that overlapped with the airway were identified at each successive iteration. The slope of the regression line between log (n) and log (1/s) was calculated to derive AFD. The greater the complexity of the airway tree, the higher the AFD.

Statistical analyses

We compared baseline characteristics of individuals with and without CB using Student's t-test for continuous variables and χ^2 test of proportions for categorical variables. To test associations of the four-airway metrics with presence of CB at baseline, we created binary logistic regression models with CB as the outcome and each airway metric as independent variable in separate models. All models were adjusted for age, gender, race, smoking status, pack-years of smoking, post-bronchodilator FEV_1, and CT scanner type. To test the association of each of the airway metrics with the presence of persistent CB at the 5-year follow-up visit, we created four categories: persistently no CB (CB(−) at both visits), resolved CB (CB(+) at baseline but CB(−) at follow-up), new CB (CB(−) at baseline and CB(+) at follow-up) and persistent CB (CB(+) at both visits). In multinomial logistic regression analyses, associations between each airway metric and the primary outcome of persistent CB were adjusted for age, gender, race, pack-years of smoking, change in smoking status, change in FEV_1, and CT scanner type. Persistently no CB was considered the reference group for these tests. Change in smoking status was categorised into one of four groups based on smoking status at the two visits: persistent smoker, quitter, resumed smoker and persistent former smoker. Persistent former smoker status was considered the reference variable. Similar models were created using the SGRQ-based CB classification. Two-sided alpha threshold of 0.05 was considered statistically significant, and all analyses were performed using SPSS (V.25.0) and R statistical package (V.3.2).

RESULTS

Subject characteristics

We included 8917 participants at baseline, with follow-up data available for 5517 at the 5-year visit. At baseline, 4407 (49.8%) had GOLD stage 0 disease, 791 (8.9%) GOLD 1, 1935 (21.7%) GOLD 2, 1175 (13.2%) GOLD 3 and 609 (6.8%) had GOLD 4 COPD. The mean (SD) smoking pack-years was 44.5 (25.1) and 4341 (48.7%) were active smokers. The prevalence of CB at baseline was 19.4% (1734/8917). The baseline characteristics of participants by presence of CB are shown in table 1.

At the follow-up visit, 33.9% remained active smokers, 12.1% quit and 2.3% had resumed smoking. CB was present in 802 of 5517 (14.5%) at the 5-year visit. 4187 (75.9%) had persistently

Table 1 Baseline characteristics of participants with and without chronic bronchitis

Parameters	Overall (n=8917)	No chronic bronchitis (n=7183)	Chronic bronchitis (n=1734)
Age (years)	59.9 (9.1)	60.0 (9.2)	59.5 (8.7)
Female (%)	4064 (45.6%)	3364 (46.8%)	700 (40.4%)
African American (%)	2838 (31.8%)	2391 (33.3%)	447 (25.8%)
Body mass index (kg/m^2)	28.4 (6.0)	28.4 (5.9)	28.3 (6.2)
Smoking pack-years	44.5 (25.1)	42.9 (24.2)	50.8 (27.3)
Current smokers (%)	4341 (48.7%)	3744 (52.1%)	597 (34.4%)
FEV_1 (L)	2.3 (1.0)	2.3 (1.0)	2.0 (1.0)
FEV_1%predicted	77.1 (27.0)	79.5 (26.4)	67.2 (26.9)
FVC (L)	3.4 (1.0)	3.4 (1.0)	3.3 (1.0)
FVC%predicted	89.1 (18.2)	90.1 (17.8)	84.9 (19.1)
FEV_1/FVC	0.65 (0.17)	0.66 (0.16)	0.59 (0.17)
GOLD severity, n (%)			
0	4407 (49.8%)	3851 (53.6%)	556 (32.1%)
1	791 (8.9%)	666 (9.3%)	125 (7.2%)
2	1935 (21.7%)	1405 (19.6%)	530 (30.6%)
3	1175 (13.2%)	821 (11.4%)	354 (20.4%)
4	609 (6.8%)	440 (6.1%)	169 (9.7%)
CT emphysema (%)*	7.0 (10.2)	6.7 (10.0)	8.4 (10.9)
Wall area % of segmental airways*	50.7 (8.6)	49.8 (8.3)	54.5 (8.8)
Pi10 (mm)*	2.34 (0.62)	2.28 (0.59)	2.58 (0.67)
Total airway count*	172.5 (87.4)	177.8 (91.1)	156.7 (81.6)
Airway fractal dimension*	1.493 (0.092)	1.497 (0.092)	1.477 (0.091)

*CT data available in n=8322 for CT emphysema, 8321 for wall area%, 8322 for Pi10, 8075 for total airway count and 8322 for airway fractal dimension.
GOLD, Global Initiative for Obstructive Lung Disease.

no CB, 528 (9.6%) had resolved CB, 403 (7.3%) had new CB and 399 (7.2%) had persistent CB. Table 2 shows a comparison between individuals in the four CB groups.

Airway metrics and CB at baseline

Airway measures were significantly worse in those with CB compared with those without CB: WA% 54.5 (8.8) versus 49.8 (8.3); Pi10 2.58 (0.67) versus 2.28 (0.59) mm; TAC 156.7 (81.6) versus 177.8 (91.1); AFD 1.477 (0.091) versus 1.497 (0.092) (all p<0.001). On bivariate regression, both WA% and Pi10 were associated with higher odds of having CB at baseline (OR for each SD change 1.74, 95% CI 1.64 to 1.84; p<0.001 and 1.61, 95% CI 1.52 to 1.69; p<0.001, respectively). Higher TAC at baseline was associated with lower odds of CB, OR for each SD change 0.73, 95% CI 0.68 to 0.79; p<0.001. Greater AFD was also associated with lower odds of CB (OR for each SD change 0.80, 95% CI 0.76 to 0.85; p<0.001). Figure 1 shows representative airways of individuals with and without CB.

On multivariable logistic regression with adjustment for age, gender, race, current smoking status, pack-years of smoking, FEV_1, and CT scanner type, WA% (adjusted OR for each SD change 1.34, 95% CI 1.25 to 1.43; p<0.001) and Pi10 (adjusted OR for each SD change 1.24, 95% CI 1.16 to 1.33; p<0.001) showed similar associations with the presence of CB, but TAC (adjusted OR for each SD change 0.95, 95% CI 0.88 to 1.03; p=0.227) and AFD (adjusted OR for each SD change 0.95, 95% CI 0.88 to 1.01; p=0.102) were not significantly associated with CB (figure 2).

Airway metrics and change in CB status at follow-up

On bivariate regression, both WA% and Pi10 at baseline were associated with higher odds of having persistent CB, with persistently no CB as the reference group (OR for each SD change 1.97, 95% CI 1.77 to 2.19; p<0.001 and 1.78, 95% CI 1.61 to 1.97; p<0.001, respectively). Higher TAC at baseline was associated with lower odds of persistent CB (OR for each SD change 0.70, 95% CI 0.62 to 0.81; p<0.001). Greater AFD was also associated with lower odds of persistent CB (OR for each SD change 0.79, 95% CI 0.71 to 0.88; p<0.001).

On multivariable logistic regression with adjustment for age, gender, race, change in smoking status (reference persistent non-smoker), pack-years of smoking, change in FEV_1 and CT scanner type, WA% (adjusted OR for each SD change 1.75, 95% CI 1.56 to 1.97; p<0.001), Pi10 (adjusted OR for each SD change 1.66, 95% CI 1.48 to 1.86; p<0.001), TAC (adjusted OR for each SD change 0.69, 95% CI 0.60 to 0.80; p<0.001) and AFD (adjusted OR for each SD change 0.76, 95% CI 0.67 to 0.86; p<0.001) were associated with persistent CB (figure 3). Similar associations were noted between these airway metrics and new CB as well, but with smaller effect sizes than for persistent CB (online supplemental table 1).

SGRQ-based definition of CB

The use of the SGRQ-based definition resulted in identification of greater number of individuals as having CB than the classic definition (30.7% vs 19.4%) (online supplemental table 2), and higher number of individuals were classified as having persistent CB at follow-up (14.9% vs 7.2%) (online supplemental table 3). The associations between airway metrics and baseline CB, as well as persistent CB at follow-up, were similar regardless of the CB definition used (online supplemental tables 4 and 5, figures 2 and 3).

DISCUSSION

In a cohort of current and former smokers, we demonstrated that CB is associated with increased airway wall thickness and lower TAC and AFDs. We also found that increased airway wall thickness is associated with persistent CB even with changes in smoking status, and with new onset CB. In contrast, a higher TAC and AFD appear to confer a reserve against persistent and new onset CB. These findings support consideration of structural airway characteristics as risk factors for CB and its persistence.

Cigarette smoking is the strongest risk factor for CB, with a lifetime cumulative incidence of approximately 40% reported in chronic smokers.[16] A number of other external exposures including environmental pollution,[26] workplace exposures[27] and biomass fuel,[28] are also risk factors. Despite these well-documented associations, host factors are also important given the variable likelihood of occurrence of CB with similar exposures. A number of genetic associations have been reported to explain some of the predisposition to CB. Genome-wide association studies revealed a novel locus on 11p15.5, including EFCAB4A, CHID1 and AP2A2, a region close to that encoding MUC6 and MUC2.[13] However, these associations did not hold true for CB when individuals with established airflow obstruction were excluded.[13] Other studies have either found modest associations or associations that did not reach genome-wide significance.[12 29] Cytotoxic T-lymphocyte antigen polymorphisms are associated with CB but not with airflow obstruction.[30]

Table 2 Baseline characteristics of participants by chronic bronchitis status at follow-up

Parameters	Overall (n=5517)	Persistent no CB (n=4187)	Resolved CB (n=528)	New CB (n=403)	Persistent CB (n=399)
Age (years)	60.4 (8.8)	60.6 (8.9)	59.6 (8.6)	60.2 (8.9)	59.7 (8.3)
Female (%)	2721 (49.3%)	2137 (51.0%)	233 (44.1%)	182 (45.2%)	169 (42.4%)
African American (%)	1518 (27.5%)	1181 (28.2%)	147 (27.8%)	111 (27.5%)	79 (19.8%)
Body mass index (kg/m^2)	28.7 (5.9)	28.7 (5.9)	28.8 (6.1)	28.6 (5.5)	28.4 (5.9)
Smoking pack-years	43.3 (23.9)	41.3 (23.0)	47.0 (23.7)	49.4 (26.1)	52.6 (27.0)
Smoking status (%)					
Persistent active	1868 (33.9%)	1241 (29.6%)	208 (39.5%)	185 (45.9%)	234 (58.6%)
Interval quit	667 (12.1%)	477 (11.4%)	122 (23.1%)	34 (8.4%)	34 (8.5%)
Interval new	126 (2.3%)	96 (2.3%)	7 (1.3%)	17 (4.2%)	6 (1.5%)
Persistent former	2855 (51.8%)	2373 (56.7%)	190 (36.1%)	167 (41.4%)	125 (31.3%)
FEV_1 (L)	2.3 (0.9)	2.4 (0.9)	2.2 (0.9)	2.2 (0.9)	2.0 (0.8)
FEV_1%predicted	80.1 (24.5)	82.8 (23.7)	72.2 (25.7)	74.2 (25.3)	68.2 (24.1)
FVC (L)	3.4 (1.0)	3.4 (1.0)	3.4 (1.0)	3.4 (1.0)	3.4 (1.0)
FVC%predicted	90.8 (16.6)	91.8 (16.1)	87.6 (18.0)	89.5 (17.8)	86.5 (17.2)
FEV_1/FVC	0.67 (0.15)	0.69 (0.15)	0.62 (0.16)	0.63 (0.15)	0.60 (0.15)
GOLD severity, n (%)					
0	2863 (51.9%)	2396 (57.2%)	208 (39.4%)	149 (37.0%)	110 (27.6%)
1	542 (9.8%)	434 (10.4%)	38 (7.2%)	44 (10.9%)	26 (6.5%)
2	1271 (23.0%)	826 (19.7%)	162 (30.7%)	122 (30.3%)	161 (40.4%)
3	659 (11.9%)	411 (9.8%)	91 (17.2%)	74 (18.4%)	83 (20.8%)
4	182 (3.3%)	120 (2.9%)	29 (4.5%)	14 (3.5%)	19 (4.8%)
CT emphysema (%)*	6.2 (8.9)	6.0 (8.6)	6.9 (9.4)	7.6 (10.0)	7.9 (9.3)
Wall area % of segmental airways*	49.7 (8.4)	48.6 (7.9)	53.1 (8.9)	51.9 (8.9)	54.2 (8.7)
Pi10 (mm)*	2.26 (0.59)	2.19 (0.55)	2.48 (0.67)	2.43 (0.64)	2.54 (0.65)
Total airway count*	180.7 (95.2)	186.2 (98.2)	166.8 (81.7)	161.6 (74.9)	161.2 (93.1)
Airway fractal dimension*	1.500 (0.093)	1.506 (0.093)	1.486 (0.099)	1.478 (0.089)	1.484 (0.088)
Change in FEV_1 (mL)†	39.8 (53.2)	37.3 (51.7)	41.9 (60.7)	50.8 (55.5)	50.1 (53.5)

*CT data available in n=5225 for CT emphysema, 5224 for wall area%, 5225 for Pi10, 5054 for total airway count and 5225 for airway fractal dimension.
†Change in FEV_1 data available in 4952.
GOLD, Global Initiative for Obstructive Lung Disease.

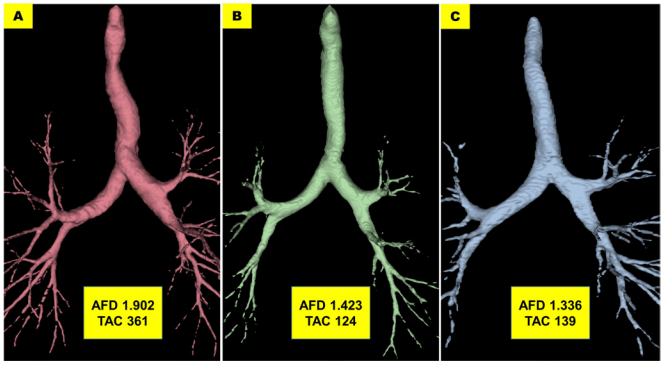

Figure 1 Airway fractal dimension (AFD) and total airway count (TAC) for representative participants with (A) persistently no chronic bronchitis at baseline and at follow-up (B) with chronic bronchitis at baseline but not at follow-up (resolved chronic bronchitis) and (C) persistent chronic bronchitis at both visits.

It is also important to note that CB is likely reversible in some individuals, at least with cessation of those exposures that are more easily quantifiable such as cigarette smoking.[31 32] Epidemiological studies suggest that within a year or two of quitting smoking, symptoms of CB and mucus hypersecretion return to levels close to those reported by non-smokers in many but not all adults.[31–33] These facts raise an important question: are there factors that confer a protective effect or reserve against the development and persistence of CB? It is pertinent to note that a number of pathophysiological alterations in the lung are accentuated or attenuated by structural changes in the lungs. For instance, mechanotransduction likely causes emphysema progression once emphysema has developed.[34] A number of measures of small and large airway disease are associated with accelerated decline in FEV_1.[16 17 35 36] In this study, we show that increased airway wall thickness was associated with the presence of CB. This is consistent with a previous study showing cross-sectional associations between airway wall remodelling and CB.[15] Regardless of how CB was defined, even after adjusting for

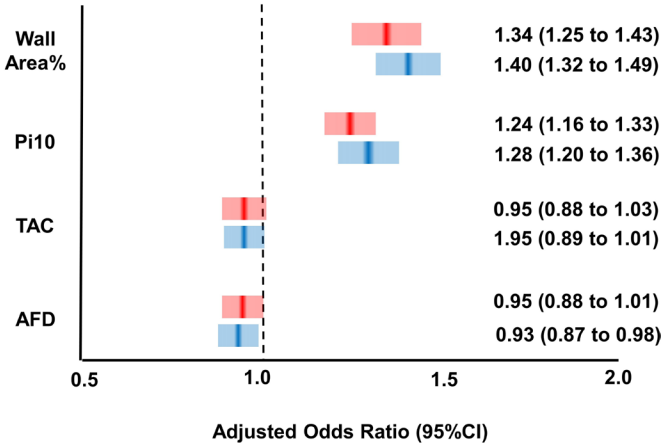

Figure 2 Multivariable* associations between airway metrics and chronic bronchitis (CB) at baseline. ORs are per one SD change in airway metric. Wall area% measured of segmental airways. *Adjusted for age, gender, race, smoking status, pack years of smoking, FEV_1, and CT scanner type. Central lines within the bars represent point estimates, and ends represent 95% CI. Red bars indicate results for the classic definition of CB and blue bars indicate results for the St. George's Respiratory Questionnaire-based definition of CB. AFD, airway fractal dimension; Pi10, square root of the wall area of a hypothetic airway with 10 mm internal perimeter; TAC, total airway count.

change in smoking status, greater airway wall thickness at baseline was temporally associated with resolved, new and persistent CB, but with higher odds for persistent bronchitis. This suggests that airway remodelling changes persist and may not resolve fully unlike symptoms. In contrast, higher AFD was associated with not only a lower odds of presence of CB at baseline, and also with a lower odds of its persistence at 5 years, irrespective of any changes in smoking status. Although CB itself can result in some of the observed airway remodelling, the longitudinal assessment of CB status and the relationship with baseline airway remodelling suggests that these airway metrics inform risk. Lower airway count and lower AFD at baseline were also associated

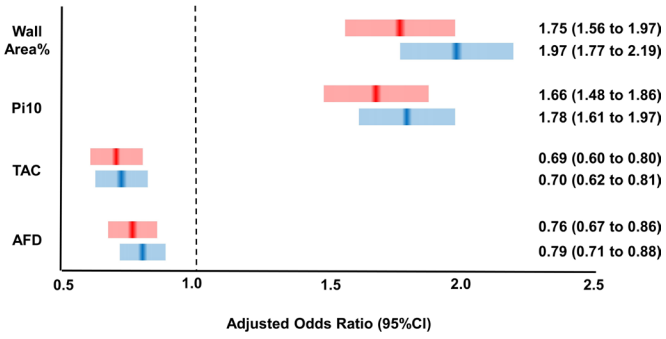

Figure 3 Multivariable associations between baseline airway metrics and persistent chronic bronchitis (CB) at 5-year follow-up. ORs are per one SD change in airway metric. Wall area% measured of segmental airways. *Adjusted for age, gender, race, smoking status (reference persistent no smoking), pack years of smoking, FEV_1, and CT scanner type. Central lines within the bars represent point estimates, and ends represent 95% CI. Red bars indicate results for the classic definition of CB and blue bars indicate results for the St. George's Respiratory Questionnaire-based definition of CB. AFD, airway fractal dimension; Pi10, Square root of the wall area of a hypothetic airway with 10 mm internal perimeter; TAC, total airway count.

with new CB but to a much lesser degree than persistent CB, again suggesting that some changes are likely irreversible, but also that preserved airway count and preserved airway branching tree confer a reserve against persistence of CB.

AFD provides a summary measure of the size and complex branching pattern of the airways. It is essentially a measure of the space-filling capacity of a structure. In the box-counting method we applied, more boxes of smaller sizes would be needed to fill in more complex structures. Thus, the AFD is affected by the size of the airways, luminal diameters and airway narrowing, loss of airway segments, tortuosity, and changes in branching angles. The human airways have a homothetic character such that there is a fixed relationship between parent and daughter branch diameters.[37] A change in this relationship due to upstream airway narrowing or loss may introduce changes in flow dynamics with more turbulence and differences in particle deposition. The branching pattern of airways also has considerable implications for smoke and drug deposition.[38] Harmful cigarette smoke particles may deposit more at bifurcations and abnormalities in airway geometry can alter the deposition patterns and density of both harmful particles as well as beneficial inhaled medications.[39 40] Of note, the seminal pathological study of CB by Reid suggested that mucosal involvement in CB is not uniform but a focal process with areas of significant goblet cell hypertrophy interspersed with normal mucosa.[41]

AFD is affected by both innate airway anatomy and later-life changes. Embryonic airway budding and early life morphogenesis are regulated by a number of genetic and cellular factors.[42] Airway narrowing and remodelling due to external exposures later in life, or changes in airway geometry induced by adjacent emphysema, may alter AFD.[17] Low AFD due to native airway structure or remodelling later in life may predispose individuals to a higher risk of CB in the setting of resumed or continued smoking. A recent study by Smith and colleagues suggested that the presence of central airway branch variation in the form of either additional accessory airways or missing branches predisposes to developing airflow obstruction and COPD.[43] Dysnapsis has also been shown to be a predictor of incident airflow obstruction.[44] TAC changes are likely permanent and confer a higher risk for CB and its persistence. Decimal changes in AFD imply a significant remodelling as AFD in non-smokers is 1.56 (SD 0.07) in the COPDGene study.[17] Our results may aid identification of and targeting individuals with CB who may need interventions consisting of just avoiding exposures versus more prolonged medical or interventional therapies.[45]

Our study has several strengths. The COPDGene study included well-characterised participants with a wide range of airflow obstruction. All spirometry and CT studies were subject to stringent quality control. We classified CB using two definitions. Although this led to differences in prevalence rates, the associations with airway metrics were similar, supporting the robustness of the results. Our study also has a few limitations. First, we defined persistence of CB using participant responses 5 years apart. CB status may have fluctuated in the interval between the two visits. Persistent CB status is less affected by this, but we may have missed some individuals who did not have CB at the second visit but changed status just prior to the follow-up visit. However, the use of both the classic definition and the SGRQ-based definition alleviates this concern. Second, we also did not have information on when participants quit smoking. This should not however affect the results significantly as symptoms of CB improve within weeks after quitting smoking, although not return to normal, and also because we applied the alternative SGRQ-based definition of CB which

has a shorter period of 1-month recall of symptoms compared with the classic 2-year definition. Third, COPDGene included non-Hispanic Whites and African Americans, and these findings should be tested in other populations.

CONCLUSIONS

Airway remodelling features are differentially associated with the presence of CB and its persistence over time, regardless of changes in smoking status. These structural risk factors may help identify individuals at differential risk, and hence targeting personalised preventative and therapeutic interventions.

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Acknowledgements The views expressed in this manuscript are those of the authors and so not necessarily reflect the position or policy of the Department of Veterans Affairs or the US Government.

Contributors Study concept and design: SPB, SB and VK. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: SPB. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: SPB. Study supervision: SPB and VK. SPB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This work was supported by NHLBI R01 HL151421 (SPB and AN), NHLBI K23HL133438 (SPB), and NIBIB R21EB027891 (SPB). SF is supported by the Department of Veterans Affairs (Award No. 14380). The COPDGene study is supported by NIH Grants U01 HL089897 and U01 HL089856. COPDGene is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pfizer, Siemens, and Sunovion.

Competing interests SPB has received consulting fees from GlaxoSmithKline and Sunovion. VK reports personal fees from Gala Therapeutics, ABIM Critical Care Test Writing Committee, AstraZeneca and Boehringer Ingelheim.

Patient consent for publication Not required.

Ethics approval Written informed consent was obtained from all participants prior to enrolment and the study protocol was approved by the institutional review boards of all participating centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. COPDGene data are available to investigators upon request through a study proposal.

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