



Computed tomography total airway count predicts progression to COPD in at-risk smokers

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Shareable abstract (@ERSpublications)

Computed tomography (CT) total airway count (TAC) predicts incident COPD in at-risk smokers, indicating that smokers exhibit early airway remodelling prior to abnormal spirometry and that CT TAC is a potential tool to help identify smokers at increased risk of COPD <https://bit.ly/2UTw314>

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Abstract

There is limited understanding of how to identify people at high risk of developing COPD. Our objective was to investigate the association between computed tomography (CT) total airway count (TAC) and incident COPD over 3 years among ever-smokers from the population-based Canadian Cohort Obstructive Lung Disease (CanCOLD) study.

CT and spirometry were acquired in ever-smokers at baseline; spirometry was repeated at 3-year follow-up. CT TAC was generated by summing all airway segments in the segmented airway tree (VIDA Diagnostics, Inc.). CT airway wall area, wall thickness for a theoretical airway with 10 mm perimeter (Pi10), and low attenuation areas below -856 HU (LAA_{856}) were also measured. Logistic and mixed effects regression models were constructed to determine the association for CT measurements with development of COPD and forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) decline, respectively.

Among 316 at-risk participants evaluated at baseline (65 ± 9 years, 40% female, 18 ± 19 pack-years), incident COPD was detected in 56 participants (18%) over a median 3.1 ± 0.6 years of follow-up. Among CT measurements, only TAC was associated with incident COPD ($p=0.03$), where a 1-SD decrement in TAC increased the odds ratio for incident COPD by a factor of two. In a multivariable linear regression model, reduced TAC was significantly associated with greater longitudinal FEV_1/FVC decline ($p=0.03$), but no other measurements were significant.

CT TAC predicts incident COPD in at-risk smokers, indicating that smokers exhibit early structural changes associated with COPD prior to abnormal spirometry.

Introduction

Smoking is an established risk factor for COPD, but only 25–30% of smokers develop the irreversible airflow limitation that characterises COPD [1, 2]. In those smokers without COPD, up to 50% report respiratory symptoms [3, 4], and 4% experience exacerbations, and these events are associated with the use of respiratory medications and self-perceived poor health outcomes [5]. Therefore, there is evidence that structural changes may precede the development of airflow limitation in smokers.

Evidence is mounting that smokers without airflow limitation have evidence of airway remodelling. Tobacco smoke has been shown to induce pro-inflammatory responses in the lungs and impairs innate



defence mechanisms in smokers without COPD [6]. Even in asymptomatic smokers, an increased number of inflammatory cells and structural changes in the mucosa of the airways has been reported [7]. Using computed tomography (CT) imaging, significantly thicker airway walls relative to total airway calibre have been shown in smokers without COPD compared to never-smokers [3], and among smokers with symptoms compared to those who remain asymptomatic [4]. Further, dimensions of the airway wall measured using CT in smokers are associated with development of overt COPD [8]. A better understanding of the structural changes that occur in the airway tree of smokers may provide a greater understanding of those at an increased risk of COPD.

Recently, studies have shown that the number of central airways quantified using CT (referred to as the total airway count, TAC), is significantly reduced in COPD [9], and is associated with longitudinal lung function decline [9], and with the number of terminal bronchioles measured using micro-CT of excised lung specimens [10], and therefore probably contributes to small airway pathophysiology. However, it is not known whether reduced airway count in at-risk smokers with normal spirometry is associated with development of COPD. In this study, our objective was to investigate the association of CT TAC acquired at baseline with development of COPD over 3 years in ever-smokers with normal spirometry from the multicentre population-based Canadian Cohort of Obstructive Lung Disease (CanCOLD) [11].

Methods

Study participants

The prospective, longitudinal and multicentre CanCOLD cohort study involved nine sites from six Canadian provinces [11]. Participants greater than 40 years of age were enrolled in the study by random digit dialling of the general population. At each of the nine study sites, institutional review board approval and written informed consent were obtained from all participants. Figure 1 shows a consort diagram for participant selection. Participants had Visit 1 images acquired and pulmonary function tests completed between May 2010 and August 2015. Never-smokers were defined as those with a lifetime exposure of <1/20 pack-years. Out of n=1561 CanCOLD participants enrolled at Visit 1, n=466 participants were ever-smokers (current or former smokers) without airflow limitation defined using spirometry (forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) <0.70). Of these, at-risk participants without CT imaging/analysis (n=67) and without follow-up (n=83) were excluded; n=316 participants were selected for analysis. To determine whether participants developed COPD at follow-up, participants were matched at the two subsequent timepoints based on available CT imaging at baseline (Visit 1) and follow-up spirometry (Visit 2 and/or Visit 3). Because only n=198 participants had both Visit 1 and Visit 2 timepoints, and some participants had only Visit 2 (n=31) or only Visit 3 (n=87), we also considered participants that had any follow-up (n=316).

Pulmonary function tests

Spirometry was performed before and 10–15 min after inhalation of a short-acting bronchodilator according to the American Thoracic Society [12] standards to measure FEV₁, FVC, FEV₁/FVC and the forced expiratory flow between 25% and 75% of the FVC (FEF_{25–75}). Whole body plethysmography was also performed for measurement of the residual volume (RV), total lung capacity (TLC) and the RV/TLC ratio. The diffusing capacity of the lung for carbon monoxide (DL_{CO}) was also acquired [13].

The St George's Respiratory Questionnaire (SGRQ) was used to measure the impact on overall health, daily life and perceived well-being [14, 15]. The COPD Assessment Test (CAT) was used to assess the global impact of COPD (cough, sputum, dyspnoea, chest tightness) on health status [16] and the modified Medical Research Council (mMRC) dyspnoea scale was used to assess degree of baseline functional disability due to dyspnoea [17].

CT image acquisition and analysis

CT images were acquired with the participant supine at suspended full inspiration and full expiration from apex to base of the lung [9, 11]. CT systems with different makes/models were used at the different sites. The CT protocol for image acquisition was: 100 kVp, 50 mAs, 0.5 s gantry rotation, pitch of 1.375 and 1.0 or 1.25 mm slice thickness, contiguous slices, and the “standard” or soft reconstruction kernel.

CT image analysis

CT image analysis was performed using commercially available software (Apollo 2.0, VIDA Diagnostics, Inc., Coralville, IA, USA). For images acquired at full expiration, CT gas trapping was quantified as the low attenuation area of the lung below –856 Hounsfield units (HU) (LAA₈₅₆) [18]. For full-inspiration CT images, CT total air volume (TLV) and CT emphysema were quantified; CT emphysema was quantified using the LAA below –950 HU (LAA₉₅₀) [19] and –910 HU (LAA₉₁₀). The total airway count (TAC)

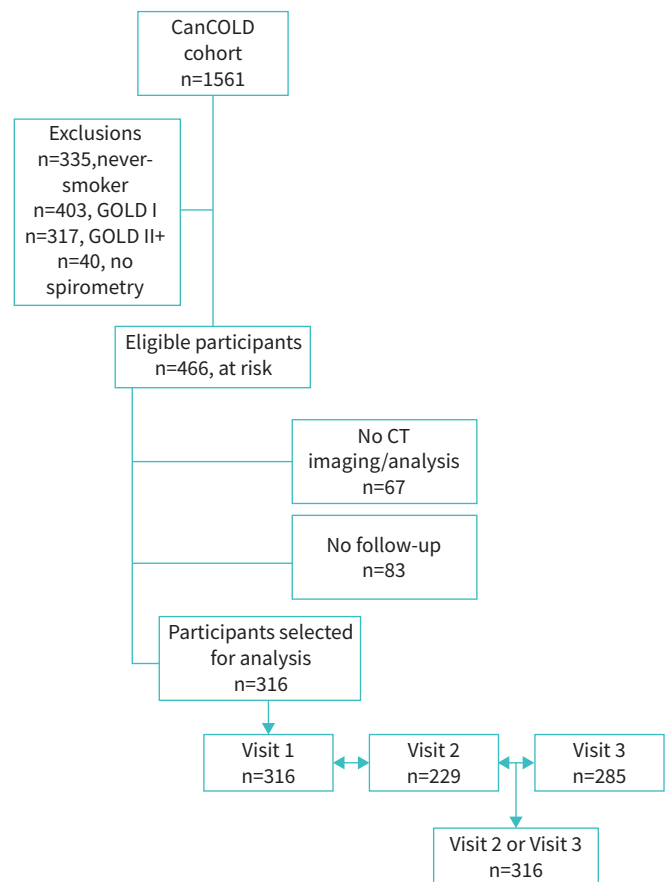


FIGURE 1 Consort diagram. There was a total of $n=1561$ Canadian Cohort Obstructive Lung Disease (CanCOLD) participants at Visit 1. The never-smokers ($n=335$) and participants with spirometrically-defined COPD ($n=720$) were excluded; $n=466$ at-risk participants were eligible. Of these, at-risk participants without CT imaging/analysis ($n=67$) and without follow-up at Visit 2 or Visit 3 ($n=83$) were excluded. A total of 316 participants were selected for analysis. For longitudinal comparison of spirometry measurements, participants were matched at the two subsequent timepoints, Visit 2 ($n=229$) and Visit 3 ($n=285$). Because only $n=198$ participants had both Visit 1 and Visit 2 timepoints, and some participants had only Visit 2 ($n=31$) or only Visit 3 ($n=87$), we also considered participants that had any follow-up ($n=316$).

measurement has been previously described in detail [9]. Briefly, the airway tree was first automatically segmented, and the airway segmentation was visually verified by a highly trained analyst and edited if required. A second analyst then performed peer review of the segmentation for quality control. From the segmented and visually verified airway tree segmentation mask, the TAC measurement was obtained by summing all airway segments; a segment was defined as the section of the airway between branch points. The high repeatability of CT airway counts has been previously reported [20]. The Pi10, defined as the wall thickness of a theoretical airway with a lumen perimeter of 10 mm, was generated [9]. The CT sub-segmental airway wall percentage was calculated as the average measurement for RB1, RB4, RB10, LB1 and LB10 airways [20].

Statistical analysis

SAS 9.4 software (Cary, NC, USA) was used for statistical analysis. Unpaired t-tests were performed for statistical comparison between at-risk participants that did or did not develop COPD at follow-up for Visit 1 participant demographic, pulmonary function and CT measurements. A Mann–Whitney test was used for groups that failed the Shapiro–Wilk normality test. For categorical variables, a Fisher’s exact test was used. For the logistic regression, COPD development at Visit 2, Visit 3, the last visit (Visit 2 or 3) and at any visit (Visit 2 or 3) were the outcome variables, and CT airway measurements were the predictors, adjusted by potential confounding variables from Visit 1 including: age, sex, height, race, smoking status, pack-years, FEV₁/FVC, CT LAA₉₅₀, CT air volume/TLC and CT model. A linear mixed effects model using the residual (restricted) maximum likelihood estimation method for the covariance parameters was performed for

longitudinal FEV₁, FVC and FEV₁/FVC change with each CT airway measurement (TAC, Pi10, wall area percent, LAA₈₅₆) included in a separate model. Time, an interaction term for time with the CT measurement, were included in the model. FEV₁, FVC and FEV₁/FVC, and the interaction of the measurements with time, were also included in models for FEV₁, FVC and FEV₁/FVC, respectively. Models were adjusted for age, sex, height, race, smoking status, pack-years, LAA₉₅₀ and CT model. CT air volume/TLC was used for TAC, Pi10 and wall area percent and CT air volume/RV was used for LAA₈₅₆. A sensitivity analysis was also performed by adjusting multivariable regression models for self-reported history of asthma and tuberculosis.

Results

There was a total of n=316 ever-smokers without COPD (at risk) evaluated at baseline (Visit 1). A total of 229 participants returned for follow-up at Visit 2 and 37 participants (16%) had spirometrically-defined COPD; a total of 285 participants returned for follow-up at Visit 3 and 54 participants (19%) had spirometrically-defined COPD. In all 316 that returned for follow-up at Visit 2 or Visit 3, 56 participants (18%) had spirometrically-defined COPD at their last follow-up visit. There were 19 participants that had spirometrically-defined COPD at Visit 2 but not Visit 3; the FEV₁/FVC in these 19 participants was on the threshold of spirometrically-defined COPD: mean (minimum, maximum) = 73.3% (70.3%, 74.8%). Therefore, in addition to considering development of COPD at Visit 2, Visit 3 or the last follow-up, for selected analyses we also included whether they had spirometric COPD at any follow-up.

As shown in table 1, there were significantly more current smokers amongst those that developed COPD (p=0.04) at their last follow-up compared to those that did not develop COPD, however there were no

TABLE 1 CanCOLD Visit 1 subject demographic, pulmonary function and imaging measurements

Parameter (±sd unless specified)	At-risk (n=316)	No COPD at follow-up (n=260)	COPD at follow-up (n=56)	p-value
Subject demographic				
Age, years	65 (9)	65 (9)	65 (10)	0.91
Female sex, n (%)	126 (40)	107 (41)	19 (34)	0.37
Caucasian, n (%)	300 (95)	248 (95)	52 (93)	0.50
Pack-years, years	18 (19)	18 (19)	22 (19)	0.053
BMI, kg·m ⁻²	28 (5)	28 (5)	27 (5)	0.29
Height, cm	168 (9)	168 (9)	168 (10)	0.87
Current smoker, n (%)	64 (20)	47 (18)	17 (30)	0.04
Pulmonary function				
FEV ₁ , % _{pred}	99 (16)	99 (16)	96 (17)	0.16
FVC, % _{pred}	97 (16)	96 (15)	98 (17)	0.32
FEV ₁ /FVC, %	77 (5)	78 (5)	73 (3)	<0.0001
FEF ₂₅₋₇₅ , L	2.46 (1.01)	2.56 (1.05)	1.96 (0.55)	<0.0001
RV, L	2.27 (0.57)	2.22 (0.54)	2.54 (0.62)	0.0005
TLC, L	6.14 (1.28)	6.07 (1.25)	6.48 (1.39)	0.049
RV/TLC, %	37 (7)	37 (7)	40 (8)	0.02
DL _{CO} , % _{pred}	111 (23)	112 (24)	109 (20)	0.67
Symptoms				
CAT score	5.9 (5.1)	6.0 (4.9)	5.4 (5.9)	0.07
SGRQ, total	9.2 (11.0)	9.5 (11.2)	10.4 (14.2)	0.61
MRC	1.3 (0.5)	1.2 (0.5)	1.4 (0.7)	0.21
Imaging				
TLV, L	4.48 (1.08)	4.40 (1.05)	4.84 (1.19)	0.005
TAC, n	213 (65)	218 (66)	193 (59)	0.01
LAA ₉₁₀ , %	19 (11)	18.7 (11.0)	21.9 (13.3)	0.16
LAA ₉₅₀ , %	2.9 (3.1)	2.9 (3.1)	3.3 (2.9)	0.15
Pi10, mm	3.93 (0.14)	3.96 (0.15)	3.96 (0.13)	0.51
Wall area percent, %	65.3 (2.6)	65.3 (2.5)	65.4 (2.8)	0.62
LAA ₈₅₆ , %	18 (15)	18 (15)	20 (15)	0.25

BMI: body mass index; FEV₁: forced expiratory volume in 1 s; %_{pred}: percent predicted; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; DL_{CO}: diffusing capacity for carbon monoxide; TAC: total airway count; LAA₉₅₀: low attenuation area of the lung with attenuation values below -950 HU on full-inspiration CT; Pi10: the square root of the airway wall area for a theoretical airway with 10 mm internal perimeter. Significance of difference : p<0.05.

significant differences between those with and without COPD at follow-up for age ($p=0.91$), sex ($p=0.37$), race ($p=0.50$), pack-years ($p=0.053$), BMI ($p=0.29$) or height ($p=0.87$). At-risk participants that developed COPD at follow-up were not significantly different from those that did not develop COPD at follow-up for $FEV_1\%_{pred}$ ($p=0.16$), $FVC\%_{pred}$ ($p=0.32$) or $DL_{CO}\%_{pred}$ ($p=0.67$), however those that developed COPD at follow-up had significantly worse FEV_1/FVC ($p<0.0001$), FEF_{25-75} ($p<0.0001$) and RV/TLC ($p=0.02$). There was no difference between those that did or did not develop COPD at follow-up for CAT score, SGRQ total or MRC ($p>0.05$). For the imaging measurements, only TAC was significantly reduced in at-risk participants with COPD at follow-up ($p=0.01$), but no difference was shown for any other CT airway or emphysema measurements ($p<0.05$).

Figure 2 shows the 3D airway tree reconstructions for representative participants that did and did not develop COPD at follow-up. Participants that developed COPD show 3D airway tree reconstructions with fewer airway segments than participants that did not develop COPD at follow-up. Figure 3 shows the airway counts by generation and airway lumen diameter for participants that did not develop COPD at follow-up. As shown in figure 3a, participants that developed COPD at follow-up had significantly fewer 7th and 8th generation airways ($p<0.05$), but no other differences in the number of airways within each generation. Figure 3b shows there were also significantly fewer airways with diameters that ranged between: 4.50 and 4.99 mm ($p<0.05$), 4.00 and 4.49 mm ($p<0.05$), 3.50 and 3.99 mm ($p<0.05$), and 3.00 and 3.49 mm ($p<0.05$), but the airways of other sizes were not significantly different.

Table 2 shows the odds ratio estimates for the development of spirometric COPD using CT measurements, and adjusting by potential confounding variables. For a 1-SD decrement in TAC the odds ratio for incident COPD increased by a factor of 1.82 ($p=0.03$) at Visit 3; for a 1-SD decrement in TAC the odds ratio for incident COPD at the last visit increased by a factor of 1.66 ($p=0.03$). There were no significant associations for $Pi10$, wall area percent and LAA_{856} with incident COPD at any follow-up timepoint. Further, CT TAC remained significantly associated with incident COPD at Visit 3 and the last visit in a multivariable regression model including FEV_1 as a confounding variable ($p<0.05$).

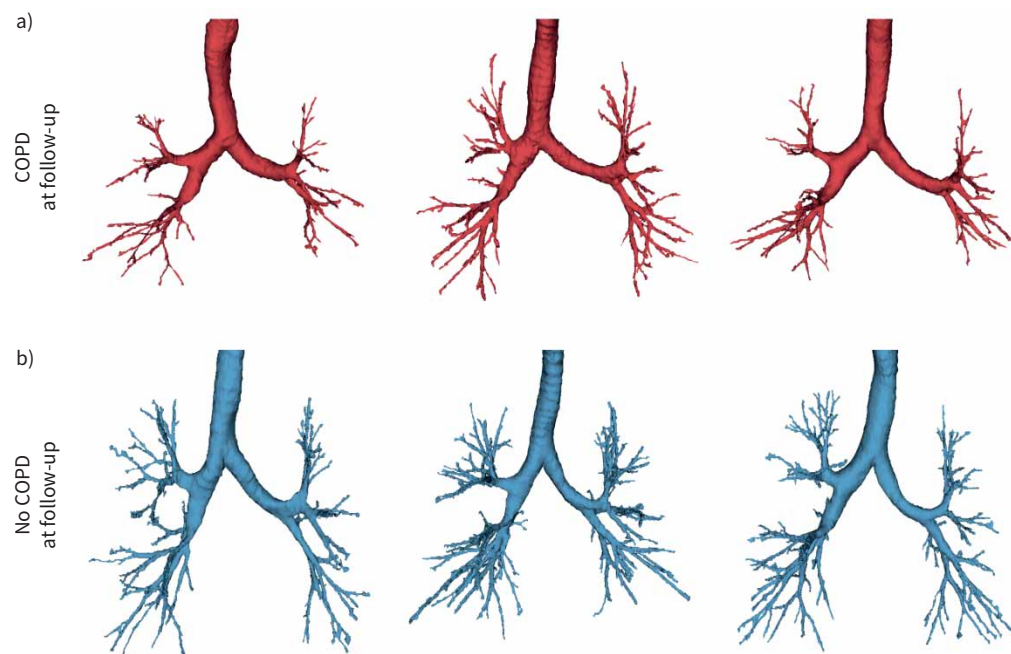


FIGURE 2 3D CT airway tree reconstructions for representative participants with (a) and without (b) COPD at follow-up. a) Left: 56-year-old male current smoker; BMI=25 kg·m⁻², FEV₁=77%_{pred}, TAC=136. Middle: 70-year-old male ex-smoker; BMI=29 kg·m⁻², FEV₁=101%_{pred}, TAC=196. Right: 54-year-old male current smoker; BMI=26 kg·m⁻², FEV₁=99%_{pred}, TAC=125. b) Left: 70-year-old female ex-smoker; BMI=22 kg·m⁻², FEV₁=97%_{pred}, TAC=219. Middle: 73-year-old male ex-smoker; BMI=26 kg·m⁻², FEV₁=125%_{pred}, TAC=365. Right: 50-year-old male ex-smoker; BMI=25 kg·m⁻², FEV₁=96%_{pred}, TAC=300. BMI: body mass index; CT: computed tomography; FEV₁: forced expiratory volume in 1 s; TAC: total airway count.

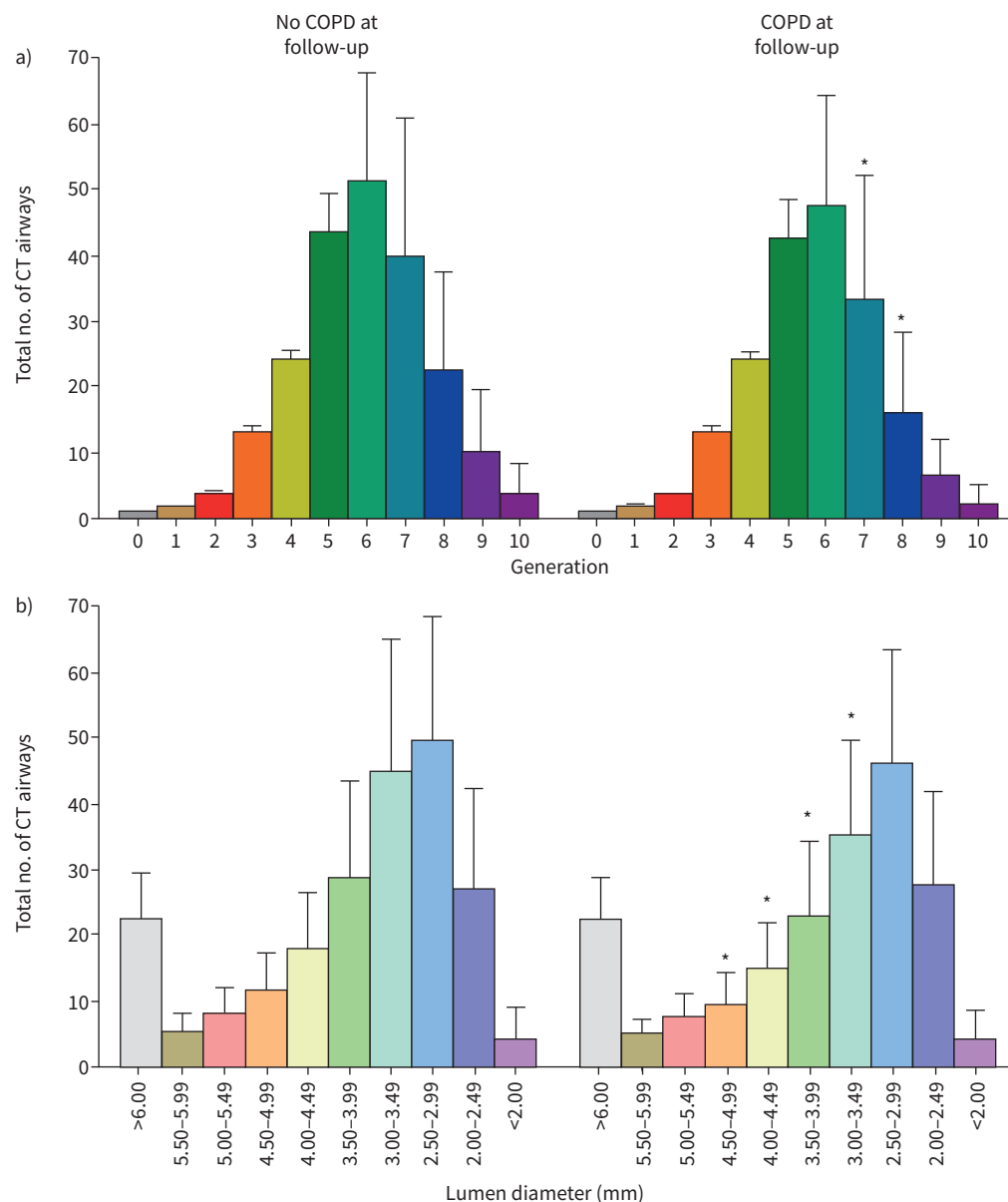


FIGURE 3 CT airway count by generation and airway lumen diameter for participants **a)** with COPD, and **b)** without COPD at follow-up. The plot summary data shows TAC measurements for airways colour coded by airway generation **(a)** and by various sizes divided into discrete bins **(b)**. Error bars represent the SD of the airway counts for all participants.

Table 3 shows multivariable linear mixed effects regression models for longitudinal FEV₁, FVC and FEV₁/FVC decline (using the Visit 1, Visit 2 and Visit 3 timepoints) for CT airway measurements adjusted for potential baseline confounding variables. A reduced CT TAC was significantly associated with greater longitudinal decline in FEV₁/FVC (p=0.03), but not FEV₁ (p=0.37). For FVC, reduced CT TAC was associated with a reduced longitudinal decline in FVC (p=0.03). Among Visit 1 measurements, sex and smoking status were not significant predictors of FEV₁, FVC or FEV₁/FVC decline (p>0.05), however smoking status was significant in the model for FEV₁ decline (p=0.01). There were no significant associations for Pi10, wall area percent or LAA₈₅₆ with longitudinal decline in FEV₁, FVC or FEV₁/FVC. CT TAC also remained significantly associated with longitudinal FEV₁/FVC decline in a model including baseline FEV₁, and the interaction of FEV₁ with time ($\beta=0.003$, p=0.03).

To determine if the CT TAC measurement may be impacted by other respiratory diseases, we performed a sensitivity analysis adjusting for self-reported asthma and tuberculosis, as well as removing the participants

TABLE 2 Odds ratio estimates for development of spirometric COPD

	COPD development at Visit 2			COPD development at Visit 3			COPD development at last visit			COPD development at any visit		
	Point estimate	95% confidence limits	p-value	Point estimate	95% confidence limits	p-value	Point estimate	95% confidence limits	p-value	Point estimate	95% Confidence limits	p-value
N	229			285			316			316		
Time from Visit 1, years (\pmsd)	1.7 (0.2)			3.2 (0.3)			3.1 (0.6)			2.9 (0.7)		
Models[#]												
TAC	1.44	0.81–2.57	0.21	1.82	1.14–2.92	0.01	1.66	1.05–2.60	0.03	1.45	0.96–2.19	0.08
Pi10	0.73	0.45–2.28	0.20	1.02	0.69–1.51	0.92	0.95	0.65–1.38	0.78	0.96	0.67–1.38	0.84
Wall area percent	0.83	0.54–1.28	0.40	0.96	0.67–1.36	0.80	1.00	0.71–1.41	0.99	0.88	0.64–1.23	0.46
LAA ₈₅₆	1.34	0.60–2.97	0.48	1.03	0.57–1.85	0.92	0.97	0.54–1.72	0.91	1.18	0.68–2.06	0.55

Models included Visit 1 age (years), sex (female), height (cm), Caucasian race, smoking status, pack-years, FEV₁/FVC (%), LAA₉₅₀ (%), CT model. CT air volume/total lung capacity (%) was added as a confounding variable for TAC, Pi10 and wall area percent. CT air volume/residual volume (%) was added as a confounding variable for LAA₈₅₆. [#]Continuous model: CT TAC, Pi10 and wall area percent were standardised.

with asthma (n=30) and tuberculosis (n=2) and repeating the analysis. Multivariable logistic regression analysis showed that even after adjusting for evidence of other respiratory diseases, TAC was significantly associated with incident COPD at Visit 3 (point estimate=1.76, p=0.02) and the last visit (point estimate=1.64, p=0.03). Further, when participants with reported asthma and tuberculosis were removed, TAC remained significantly associated with incident COPD at the last visit (point estimate=1.65, p=0.04). We also performed the multivariable linear mixed effects regression model that adjusted for potential baseline confounding variables, including asthma and tuberculosis, and showed reduced TAC remained statistically significantly associated with longitudinal decline in FEV₁/FVC (stand. β =0.003, p=0.03) and FVC (stand. β =-0.18, p=0.02).

TABLE 3 Mixed effects multivariable regression models for longitudinal FEV₁, FVC and FEV₁/FVC change with CT measurements

Interactions	Estimate (95% CI)	SE	p-value
FEV₁, mL			
TAC×time	-0.052	0.058	0.37
Pi10×time	-15.80	25.14	0.53
Wall area percent×time	-0.70	1.40	0.62
LAA ₈₅₆ ×time	-0.32	0.26	0.22
FVC, mL			
TAC×time	-0.18	0.08	0.02
Pi10×time	-42.37	36.00	0.24
Wall area percent×time	0.73	1.97	0.71
LAA ₈₅₆ ×time	-0.36	0.36	0.33
FEV₁/FVC, %			
TAC×time	0.003	0.001	0.03
Pi10×time	-0.67	0.49	0.17
Wall area percent×time	-0.03	0.03	0.33
LAA ₈₅₆ ×time	-0.002	0.005	0.75

Models included: time, Visit 1 age (years), sex (female), height (cm), Caucasian race, smoking status, pack-years, LAA₉₅₀ (%), CT model. FEV₁ (mL), FVC (mL) and FEV₁/FVC (%), and the interaction of the measurements with time, were included in models for FEV₁, FVC and FEV₁/FVC, respectively. CT air volume/total lung capacity (%) was used for TAC, Pi10 and wall area percent and CT air volume/residual volume (%) was used for LAA₈₅₆.

Discussion

Structural changes to the airways occur in smokers [3, 4, 6, 7], and even young smokers [21], despite the fact that only 25–30% of those that smoke go on to develop COPD [1, 2]. Therefore, a better understanding of the pre-clinical changes that occur in the airway tree is required and may help identify those at an increased risk of developing COPD. Based on previous studies demonstrating the CT TAC is related to lung function decline [9] and reflects the loss and remodelling of the terminal bronchioles as measured using micro-CT of lung specimens [10], we aimed to determine whether CT TAC was associated with incident COPD in at-risk ever-smokers. We report: 1) CT TAC was significantly reduced in at-risk participants that developed COPD at follow-up compared to those that did not develop COPD, but there were no differences for other CT measurements, and this reduction in airway number occurred in the smaller airways; 2) at-risk participants with reduced TAC had an approximately two-times increased risk of developing incident COPD; and 3) reduced TAC was significantly associated with greater longitudinal FEV₁/FVC decline.

Here we have shown that at-risk participants that develop overt COPD have reduced airway count on CT compared to those that do not develop COPD during the follow-up interval, and that the decline in airway count is driven primarily by a reduction in the smaller airways (7th and 8th generation). Interestingly, when the number of airways was stratified by lumen diameter, we showed that this decline occurred in airways 3.00–4.50 mm in diameter, but there were no significant changes in the number of airways <3.00 mm in diameter. Taken together, this may suggest that while there are fewer small airways (7th and 8th generation), there are also fewer mid-sized airways, which may suggest narrower lumen diameters.

Interestingly, we showed no difference in symptoms between those that developed COPD at follow-up compared to those that did not develop COPD, and this may be due to the lower symptom burden in the population-based CanCOLD sample. An important advantage of population-based studies is they can minimise bias of symptom burden among ever-smokers without COPD when compared with other study bases, where participants may be more likely to enrol due to their symptoms. It has been shown that bronchial biopsy specimens of asymptomatic smokers without COPD have increased thickness of the tenascin and lamina layers, and decreased structural integrity of the epithelial layers compared to never-smokers [7]. These structural changes in the airway walls have also been correlated with the number of mast cells in the epithelium, lamina propria and smooth muscle in asymptomatic smokers, but not never-smokers [22]. Taken together, these findings suggest that airway remodelling occurs in smokers, even those that remain asymptomatic, and that reduced CT airway count may identify individuals at risk of developing COPD.

We also demonstrated that reduced airway count on CT in at-risk smokers with normal lung function at baseline was associated with an increased risk of developing spirometrically-defined COPD over a relatively short duration follow-up. Oelsner and colleagues [8] investigated participants from the Multi-Ethnic Study of Atherosclerosis (MESA) study [23] and showed that in participants with normal spirometry, increased CT Pi10 at baseline predicted increased risk of incident spirometry-defined COPD over 5 years. In our study, we did not find that Pi10 was able to predict incident COPD. This may be due to the smaller number of subjects included in our study with follow-up, and the shorter follow-up duration. We do note that for TAC, the odds ratio for COPD development at Visit 3 (3.2±0.3 years) was significant, while it was not significant at Visit 2 (1.7±0.2 years).

We also demonstrated that CT TAC was associated with longitudinal decline in FEV₁/FVC and FVC, but not FEV₁ over an approximately 3-year follow-up in this at-risk group. The finding that the FEV₁/FVC ratio is declining at a faster rate, while FVC declines at a lower rate, in those with reduced TAC may suggest a disproportionate fall in FEV₁ relative to the FVC. In other words, in participants with higher TAC, FEV₁ and FVC fall in parallel, and therefore the FEV₁/FVC ratio remains constant over time, whereas in those with reduced TAC, the FEV₁ and FVC fall at different rates, resulting in a decline in the FEV₁/FVC ratio. Although we have previously demonstrated that CT TAC is significantly associated with longitudinal decline in FEV₁, this study included COPD participants [9]. Nevertheless, our results indicate that at-risk participants with reduced CT TAC are more likely to have a decline in their FEV₁/FVC ratio in a short period of time.

This study is strengthened by the relatively large number of at-risk smokers included due to the population study design of CanCOLD [11], and the short duration follow-up intervals investigated. We must acknowledge, however, that it remains unclear whether the lower airway count is due solely to smoking-related pathologies, such as increased number of inflammatory cells and structural changes to the airway wall components [7, 24]. An alternative explanation is that low TAC is, at least in part, due to the

inherent airway tree structure. Individuals not exposed to traditional COPD risk factors, such as smoking, who exhibited dysanapsis on CT, *i.e.* small airways relative to their lung size, have been shown to have an increased risk of developing COPD [25]. We note that dysanapsis on CT is thought to be a measure of inherent airway tree structure, measured as the mean airway lumen diameter divided by the total lung volume, while CT TAC is thought to reflect the remodelling/loss of airways. An advantage of CT TAC is that it may reflect airway wall thickening and airway lumen narrowing, as well as airway destruction. A limitation of this study is that we do not know if these participants have a history of being premature or had low weight at birth, which may contribute to development of COPD and could potentially be associated with CT TAC. Long-term studies in children or young adults are required to determine if airway tree structural variability is exhibited early in life, and if reduced airway counts are associated with increased risk of developing lung disease.

We also note that the CT TAC measurement has yet to be investigated longitudinally, either in the short term to assess measurement reproducibility, or longer term to determine whether TAC decreases over time with disease progression, or if TAC increases in response to treatment. Investigating CT TAC measurements longitudinally in COPD participants is an important goal of future studies. We also acknowledge that it is important to investigate the risk of COPD progression in former *versus* current smokers, as well as in males *versus* females, separately, to provide a better understanding of differences in longitudinal lung function decline in these groups, and, possibly, the potential for personalised risk assessment. It is also important for future studies to investigate the association between CT airway measurements with longitudinal decline in body plethysmography and diffusion capacity measurements, particularly RV and RV/TLC. Another limitation is that there are other nondisease-related factors that may impact the TAC measurement. Other factors, such as lung volume during image acquisition [26], field of view [27], and others [28], have been shown to influence airway measurements. We acknowledge that even with standardised image acquisition parameters, the image quality may differ with different CT systems [26, 28], resulting in variability in the CT measurements. Although airway phantoms can assess the calibration of several CT scanner parameters, and may be used to correct for measurement bias between each scanner [29], no phantoms were used in this study. Importantly, there is currently no consensus on standardised airway phantoms. Reducing CT airway measurement variability is an important goal, and groups such as the Quantitative Imaging Biomarkers Alliance (QIBA) are developing guidelines for standardised image acquisition protocols for multicentre studies. In this study, to minimise the impact of these factors we used a standardised image acquisition protocol and breath-hold coaching [30], and we have adjusted for these potentially confounding variables in our models. Finally, we also acknowledge that due to the relatively short duration of follow-up, only 56 (18%) of participants became (incident) COPD. This number would probably increase over a longer duration of follow-up. Future studies using longer duration follow-ups should be performed to confirm these findings. Nevertheless, our findings indicate that CT TAC was significantly and independently associated with developing incident COPD and longitudinal FEV₁/FVC decline, and can therefore provide a greater understanding of the pathology that may influence FEV₁/FVC.

In conclusion, we showed that participants with reduced CT total airway count had a two-times higher risk for developing COPD, and reduced TAC was significantly associated with accelerated longitudinal FEV₁/FVC decline. These findings add to a growing body of evidence that smokers exhibit early structural changes associated with COPD prior to abnormal spirometry, and suggests CT TAC is a potential tool to help identify smokers at increased risk of COPD.

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