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Original research article

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Please cite this article as: Kirby M, Smith BM, Tanabe N, *et al*. Computed tomography total airway count predicts progression to COPD in at risk smokers. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00307-2021).

Computed Tomography Total Airway Count Predicts Progression to COPD in At Risk Smokers

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Sources of Support: Dr. Kirby gratefully acknowledges salary support from the Parker B. Francis Fellowship Program and the Canada Research Chair Program (Tier II), and funding support from the Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant. Dr. Coxson was a Roberta R Miller Fellow in Thoracic Imaging from the BC Lung Association.

We acknowledge the Canadian Institute of Heath Research (CIHR/Rx&D Collaborative Research Program Operating Grants- 93326); the Respiratory Health Network of the FRQS (RHN); the Canadian Respiratory Research Network (CRRN); the Canadian Lung Association (CLA)/Canadian Thoracic Society (CTS); British Columbia Lung Association; and industry partners including Astra Zeneca Canada Inc., Boehringer-Ingelheim Canada Inc.,

GlaxoSmithKline Canada Inc., Merck, Novartis Pharma Canada Inc., Nycomed Canada Inc., and Pfizer Canada Ltd for funding support.

“Take Home” Message:

CT total airway count (TAC) predicts incident COPD in at risk smokers, indicating that smokers exhibit early airway remodeling prior to abnormal spirometry and that CT TAC is a potential tool to help identify smokers at increased risk of COPD.

ABSTRACT

There is limited understanding of how to identify people at high risk of developing chronic obstructive pulmonary disease (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 10mm perimeter (Pi10), and low attenuation areas below -856HU (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 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 chronic obstructive pulmonary disease (COPD), but only 25-30% of smokers develop the irreversible airflow limitation that characterizes 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 remodeling. Tobacco smoke has been shown to induce pro-inflammatory responses in the lungs and impairs innate defense 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 caliber 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 occurs 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 likely contributes to small airway pathophysiology. However, it is unknown if 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 multi-center, population-based Canadian Cohort of Obstructive Lung Disease (CanCOLD) [11].

METHODS

Study Participants

The prospective, longitudinal and multi-center CanCOLD cohort study involved 9 sites from 6 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 9 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 one second (FEV_1)/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 if participants developed COPD at follow-up, participants were matched at the two subsequent time-points based on available CT imaging at baseline (visit 1) and follow-up spirometry (visit 2 and/or visit 3). Since only n=198 participants had both visit 1 and visit 2 time-points, 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 minutes after inhalation of a short-acting bronchodilator according to the American Thoracic Society [12] standards to measure the FEV_1, FVC, FEV_1/FVC and the forced expiratory flow between the 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, dyspnea, chest tightness) on health status [16] and the modified medical research council (mMRC) dyspnea scale was used to assess degree of baseline functional disability due to dyspnea [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 second 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 software package, VIDA Diagnostics, Inc., Coralville, Iowa, 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) (LAA_{856}) [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 (LAA_{950}) [19] and -910 HU (LAA_{910}). The total airway count (TAC) 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 10mm 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, FEV_1/FVC, CT LAA_{950}, CT air volume/total lung capacity, and CT model. A linear mixed effects model using the residual (restricted) maximum likelihood estimation method for the

covariance parameters was performed for longitudinal FEV_1, FVC and FEV_1/FVC change with each CT airway measurement (TAC, Pi10, wall area percent, LAA_{856}) included in a separate model. Time, an interaction term for time with the CT measurement were included in the model. FEV_1, FVC and FEV_1/FVC, and the interaction of the measurements with time, were also included in models for FEV_1, FVC and FEV_1/FVC, respectively. Models were adjusted for age, sex, height, race, smoking status, pack-years, LAA_{950}, and CT model. CT air volume/total lung capacity was used for TAC, Pi10 and wall area percent and CT air volume/residual volume was used for LAA_{856}. A sensitivity analysis also performed by adjusting multivariable regression models for self-reported history of asthma and tuberculosis.

RESULTS

There were 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 FEV_1/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, 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 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 between 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 developed 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: 4.50-4.99mm ($p<0.05$), 4.00-4.49mm ($p<0.05$), 3.50-3.99mm ($p<0.05$), and 3.00-3.49mm ($p<0.05$), 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 time-point. 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 ($p<0.05$).

Table 3 shows multivariable linear mixed effects regression models for longitudinal FEV_1, FVC and FEV_1/FVC decline (using the visit 1, visit 2 and visit 3 time-points) for CT airway measurements adjusted for potential baseline cofounding variables. A reduced CT TAC was significantly associated with greater longitudinal decline in FEV_1/FVC (p=0.03), but not FEV_1 (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 FEV_1, FVC or FEV_1/FVC decline ($p>0.05$), however smoking status was significant in the model for FEV_1 decline (p=0.01). There were no significant associations for Pi10, wall area percent or LAA_{856} with longitudinal decline in FEV_1, FVC or FEV_1/FVC. CT TAC also remained significantly associated with longitudinal FEV_1/FVC decline in a model including baseline FEV_1, and the interaction of FEV_1 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 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 cofounding variables, including asthma and tuberculosis, and showed reduced TAC remained statistically significantly associated with longitudinal decline in FEV_1/FVC (stand. β=0.003, p=0.03) and FVC (stand. β =-0.18, p=0.02).

DISCUSSION

Structural changes to the airways occurs 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 total airway count (TAC) is related to lung function decline [9] and reflects the loss and remodeling of the terminal bronchioles as measured using micro-CT of lung specimens [10], we aimed to determine if 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 more small airways; 3) at risk participants with reduced TAC had an approximately 2-times increased risk of developing incident COPD, and; 3) reduced TAC was significantly associated with greater longitudinal FEV_1/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 more small airways (7^{th} and 8^{th} generation). Interestingly, when the number of airways was stratified by lumen diameter, we showed this decline occurred in the airways 3.00-4.50mm in diameter, but significant no changes in the number of airways <3.00mm in diameter. Taken together, this may suggest that while there are fewer small airways (7^{th} and 8^{th} generation), there are also fewer mid-sized airways, which may suggest narrower lumen diameters.

Interesting, 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 minimize bias of symptom burden among ever-smokers without COPD when compared with other study bases, where participants may be more likely to enroll 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 remodeling 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 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 FEV_1/FVC and FVC, but not FEV_1 over an approximately 3-year follow-up in this at risk group. The finding that the FEV_1/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 FEV_1 relative to the FVC. In other words, in participants with higher TAC, FEV_1 and FVC fall in parallel, and therefore the FEV_1/FVC ratio remains constant over time, whereas in those with reduced TAC, the FEV_1 and FVC fall at different rates, resulting in a decline in the FEV_1/FVC ratio. Although we have previously demonstrated that CT TAC is significantly associated with longitudinal decline in FEV_1, 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 FEV_1/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 if 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, 25]. 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 [26]. 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 remodeling/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 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 personalized 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, non-disease related factors that may impact the TAC measurement. Other factors, such as lung volume during image acquisition [27], field-of-view [28], and others [29], have been shown to influence airway measurements. We acknowledge that even with standardized image acquisition parameters, the image quality may differ with different CT systems [27, 29], 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 [30], no phantoms were used to in this study. Importantly, there is currently no consensus on standardized 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 standardized image acquisition protocols for multicenter studies. In this study, to minimize the impact of these factors we used a standardized image acquisition protocol and breath-hold coaching [31], 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, there was only 56 (18%) of participants that became (incident) COPD. This number would likely 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 FEV_1/FVC decline, therefore can provide a greater understanding of the pathology that may influence FEV_1/FVC.

In conclusion, we showed that participants with reduced CT total airway count had a 2-times higher risk for developing COPD, and reduced total airway count was significantly associated with accelerated longitudinal FEV_1/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.

Declaration of Interests: All authors have authors no financial and personal relationships with other people or organizations that could inappropriately influence this work.

Acknowledgments: The authors would also like to thank the men and women who participated in the study and individuals in the ***CanCOLD Collaborative research Group**: Jonathon Samet (the Keck School of Medicine of USC, California, USA); Milo Puhan (John Hopkins School of Public Health, Baltimore, USA); Qutayba Hamid, Carolyn Baglole, Palmina Mancino, Pei-Zhi Li, Zhi Song, Dennis Jensen, Benjamin Mcdonald Smith (McGill University, Montreal, QC, Canada); Yvan Fortier and Mina Dligui (Sherbrooke University, Sherbrooke, QC, Canada); Kenneth Chapman, Jane Duke, Andrea S Gershon, Teresa To, (University of Toronto, Toronto, ON Canada); J Mark Fitzgerald, Mohsen Sadatsafavi (University of British Columbia, Vancouver, BC); Christine Lo, Sarah Cheng, Elena Un, Michael Cheng, Cynthia Fung, Nancy Haynes, Liyun Zheng, LingXiang Zou, Joe Comeau, Jonathon Leipsic, Cameron Hague (UBC James Hogg Research Center, Vancouver, BC, Canada); Brandie L Walker, Curtis Dumonceaux, (University of Calgary, Calgary, AB, Canada); Paul Hernandez, Scott Fulton, (University of Dalhousie, Halifax, NS, Canada); Shawn Aaron, Kathy Vandemheen, (University of Ottawa, Ottawa, ON, Canada); Denis O'Donnell, Matthew McNeil, Kate Whelan (Queen's University, Kingston, ON, Canada); Francois Maltais, Cynthia Brouillard (University of Laval, Quebec City, QC, Canada); Darcy Marciniuk, Ron Clemens, Janet Baran (University of Saskatchewan, Saskatoon, SK, Canada).

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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, yrs	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, yrs	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

SD=standard deviation; BMI=body mass index; FEV_1=forced expiratory volume in one second; $\%_{pred}$=percent predicted; FVC=forced vital capacity; RV=residual volume; TLC=total lung capacity; DL_{CO}=diffusing capacity for carbon monoxide; TAC=total airway count; LAA_{950}=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 10mm internal perimeter. Significance of difference ($p<0.05$).

Table 2. Odds Ratio Estimates for Development of Spirometric COPD

	COPD Development at V2			COPD Development at V3			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 V1, yrs (±SD)		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				0.96	0.67 – 1.36	0.80	1.00	0.71 – 1.41	0.99	0.88	0.64 – 1.23	0.46
Percent	0.83	0.54 – 1.28	0.40									
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

*Continuous Model: CT TAC, Pi10 and wall area percent were standardized.

Models included V1 age (yrs), sex (female), height (cm), Caucasian race, smoking status, pack-years, FEV_1/FVC (%), LAA_{950} (%), 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 LAA_{856}.

Table 3. Mixed Effects Multivariable Regression Models for Longitudinal FEV_1, FVC and FEV_1/FVC Change with CT measurements

Interactions	Estimate (95% CI)	Standard Error	P-value
FEV_1, ml			
TAC x time	-0.052	0.058	0.37
Pi10 x time	-15.80	25.14	0.53
Wall area percent x time	-0.70	1.40	0.62
LAA_{856} x time	-0.32	0.26	0.22
FVC, ml			
TAC x time	-0.18	0.08	**0.02**
Pi10 x time	-42.37	36.00	0.24
Wall area percent x time	0.73	1.97	0.71
LAA_{856} x time	-0.36	0.36	0.33
FEV_1/FVC, %			
TAC x time	0.003	0.001	**0.03**
Pi10 x time	-0.67	0.49	0.17
Wall area percent x time	-0.03	0.03	0.33
LAA_{856} x time	-0.002	0.005	0.75

Models included: time, V1 age (yrs), sex (female), height (cm), Caucasian race, smoking status, pack-years, LAA_{950} (%), CT model. FEV1 (ml), FVC (ml) and FEV_1/FVC (%), and the interaction of the measurements with time, were included in models for FEV_1, FVC and FEV_1/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 LAA_{856}.

FIGURE LEGENDS

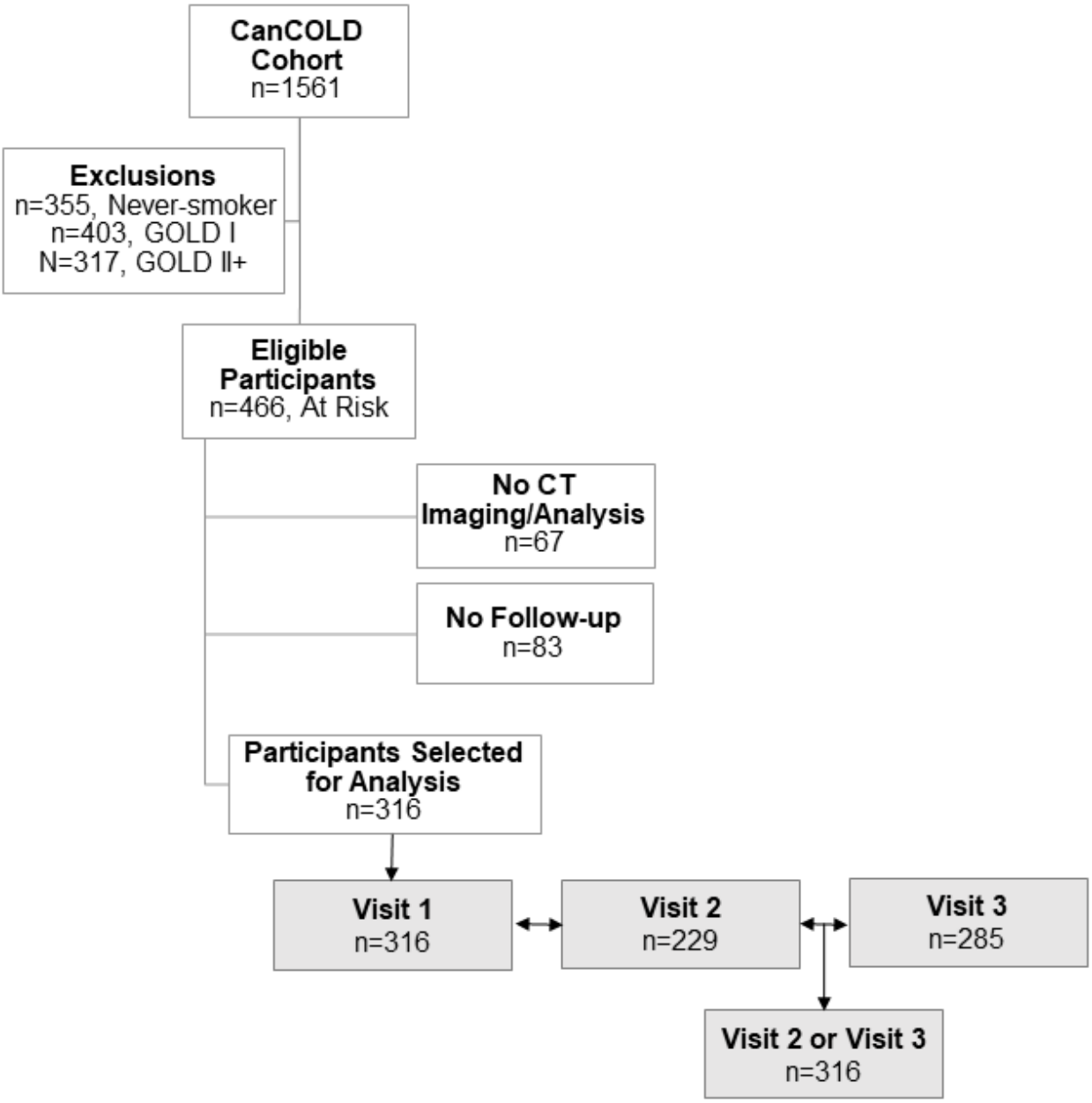

Figure 1. Consort Diagram
There were a total of n=1561 CanCOLD participants at Visit 1. The never-smokers (n=355) and participants with spirometrically defined COPD (n=720) were excluded; n=466 at risk participants were eligible. Of these, at risk participants without CT imaging/analysis (n=67) and without 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 time points, visit 2 (n=229) and visit 3 (n=285). Since only n=198 participants had both visit 1 and visit 2 time-points, 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).

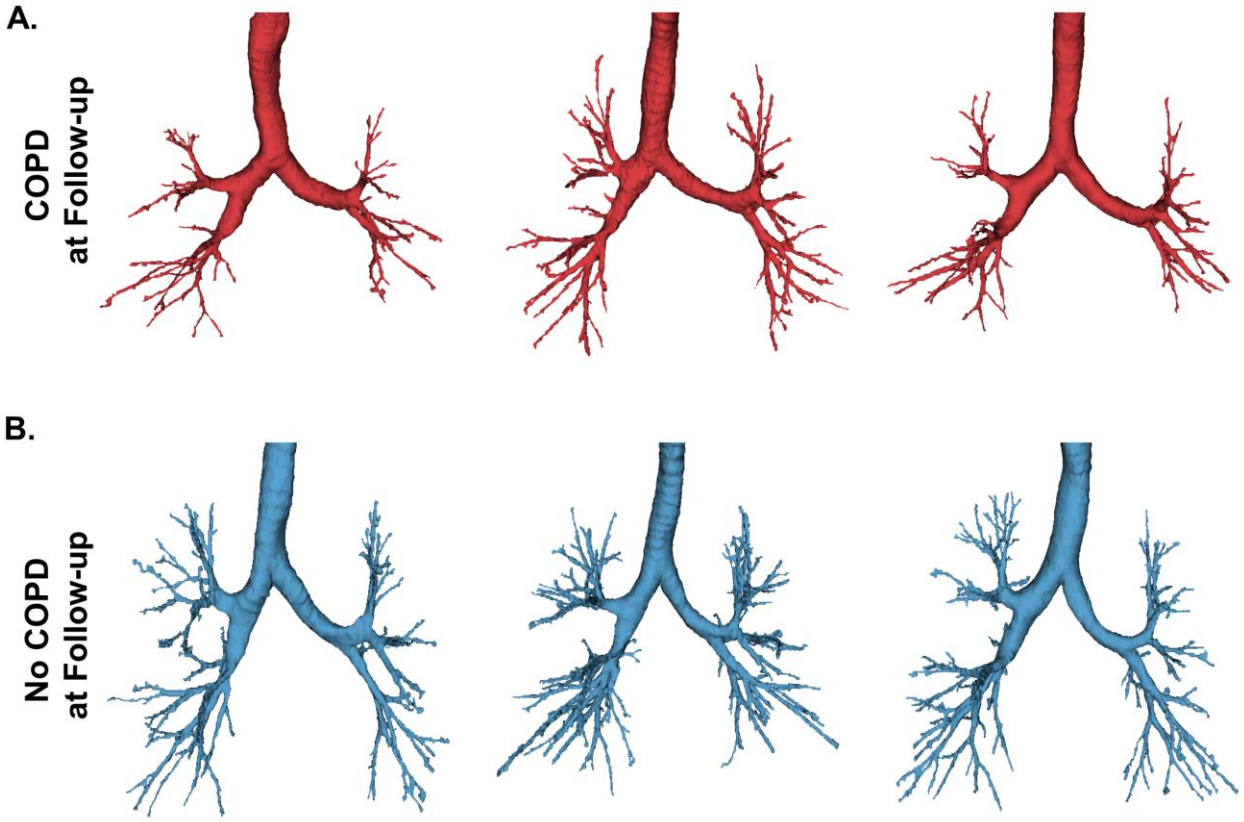

Figure 2. 3D CT Airway Tree Reconstructions for Representative Participants with (A) and without (B) COPD at Follow-up

A. Left: age=56 year old male current smoker; BMI=25 kg/m^2, FEV_1=77%$_{pred}$, TAC=136. Middle: age=70 year old male ex-smoker; BMI=29 kg/m^2, FEV_1=101%$_{pred}$, TAC=196. Right: age=54 year old male current smoker; BMI=26 kg/m^2, FEV_1=99%$_{pred}$, TAC=125.

B. Left: age=70 year old female ex-smoker; BMI=22 kg/m^2, FEV_1=97%$_{pred}$, TAC=219. Middle: age=73 year old male ex-smoker; BMI=26 kg/m^2, FEV_1=125%$_{pred}$, TAC=365. Right: age=50 year old male ex-smoker; BMI=25 kg/m^2, FEV_1=96%$_{pred}$, TAC=300.

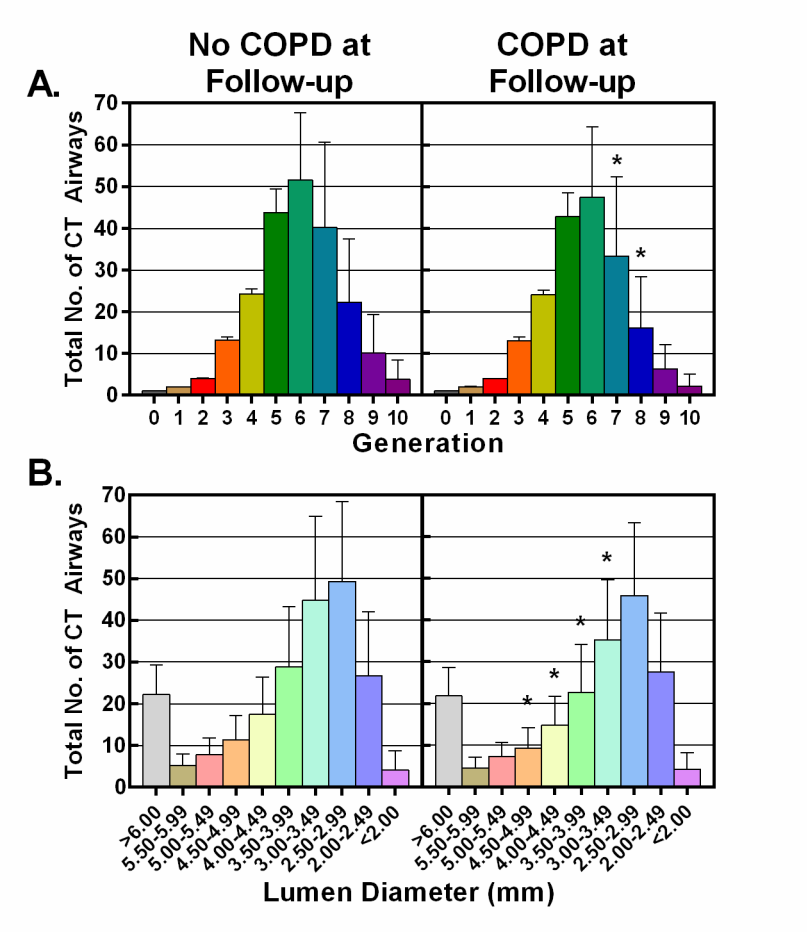

Figure 3. CT Airway Count by Generation and Airway Lumen Diameter for Participants (A) with COPD, and (B) without COPD at Follow-up

The plot summary data shows TAC measurements for airways color coded by airway generation (A) and by various sizes divided into discrete bins (B). Error bars represent the standard deviation of the airway counts for all participants.