

CT airway remodelling and chronic cough

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ABSTRACT

Rationale Structural airway changes related to chronic cough (CC) are described in the literature, but so far reported data are rare and non-conclusive. Furthermore, they derive mainly from cohorts with small sample sizes. Advanced CT imaging not only allows airway abnormalities to be quantified, but also to count the number of visible airways. The current study evaluates these airway abnormalities in CC and assesses the contribution of CC in addition to CT findings on the progression of airflow limitation, defined as a decline in forced expiratory volume in 1 s (FEV1) over time.

Methods A total of 1183 males and females aged ≥ 40 years with thoracic CT scans and valid spirometry from Canadian Obstructive Lung Disease, a Canadian multicentre, population-based study has been included in this analysis. Participants were stratified into 286 never-smokers, 297 ever-smokers with normal lung function and 600 with chronic obstructive pulmonary disease (COPD) of different severity grades. Imaging parameters analyses included total airway count (TAC), airway wall thickness, emphysema as well as parameters for functional small airway disease quantification.

Results Irrespective of COPD presence, CC was not related to specific airway and lung structure features. Independent of TAC and emphysema score, CC was highly associated with FEV1 decline over time in the entire study population, particularly in ever-smokers ($p < 0.0001$).

Conclusion The absence of specific structural CT features independently from COPD presence indicate that other underlying mechanisms are contributing to the symptomatology of CC. On top of derived CT parameters, CC seems to be independently associated with FEV1 decline.

Trial registration number NCT00920348.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Data about structural airway features in chronic cough are scarce, derive from sample size studies and report controversial findings on possible presence of structural airway features in chronic cough. This study uses a large sample and makes use of advanced CT imaging parameters to evaluate structural changes in chronic cough and its contribution to airflow limitation on top of other already acknowledged CT parameters.

WHAT THIS STUDY ADDS

⇒ Regardless of the presence of chronic obstructive pulmonary disease, chronic cough was found being associated with forced expiratory volume in 1 s decline but not with specific structural airway features.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research effort is needed to detect other pathophysiological mechanisms that may contribute to the development of chronic cough. For practice, chronic cough could serve as a clinical biomarker for early airflow limitation, particularly in ever-smokers.

phenotypes of CC.³ Furthermore, CC impacts decline in forced expiratory volume in 1 s (FEV1) in longitudinal studies in smokers and patients with COPD.^{4–6} Despite this impact on morbidity, limited data are yet available about the relationship between airway and lung structural changes and CC.

Results of endobronchial biopsies revealed features of airway remodelling related to inflammatory changes and in particular mucosal inflammation by mast cell hyperplasia in non-asthmatic CC.^{7–9} Presence of increased airway wall thickness in terms of subbasement membrane thickening as well as increases in goblet cell area, vascularity and vessel size are described in both asthmatic and non-asthmatic CC.^{7–10} These changes contribute to the enhanced cough reflex in chronic non-asthmatic coughers and induce a vicious circle of cough persistence as cough

INTRODUCTION

Chronic cough (CC) is a prevalent clinical problem¹ with a significant impact on daily life and quality of life as well as a common reason worldwide to seek medical attention.² Besides being a cardinal symptom of chronic bronchitis within the chronic obstructive pulmonary disease (COPD), the role of CC was highlighted by recently published guidelines that defined different non-COPD



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Table 1 Subject demographics, pulmonary function and imaging measurements

Parameter (\pm SD unless specified)	Never-smoker (n=286)	At-risk (n=297)	GOLD I (n=361)	GOLD II + (n=239)
Subject demographic				
Age, years	66 (10)	66 (9.1)	68 (10) [†]	66 (11)
Female sex, n (%)	136 (48)	131 (44)	124 (34) ^{*†}	100 (42)
Caucasian, n (%)	266 (93)	282 (95)	347 (96)	223 (93)
Pack-years, years	0 (0)	21 (24) [*]	18 (23) [*]	26 (26) ^{*†‡}
BMI, kg/m ²	27 (4.6)	28 (5.1)	27 (4.5)	28 (6.2)
Current-smoker, n (%)	–	64 (22)	52 (14) [†]	61 (26)
History of asthma, n (%)	21 (7.3)	30 (10)	66 (18) ^{*†}	86 (36) ^{*†‡}
History of tuberculosis, n (%)	3 (1.0)	0 (0.0)	5 (1.4)	5 (2.1) [†]
History of HDHTDM, n (%)	97 (34)	105 (35)	131 (36)	115 (48) ^{*†‡}
History of bronchiectasis, n (%)	54 (19)	47 (17)	75 (21)	48 (20)
Pulmonary function				
FEV ₁ , % _{pred}	106 (15)	103 (14) [*]	96 (12) ^{*†}	69 (8.0) ^{*†‡}
FEV ₁ /FVC, %	78 (4.7)	77 (4.6)	64 (4.6) ^{*†}	59 (7.5) ^{*†‡}
RV/TLC, %	37 (7.6)	37 (7.3)	40 (8.9) ^{*†}	46 (9.3) ^{*†‡}
DL _{CO} , % _{pred}	115 (23)	113 (22)	109 (23) [*]	95 (24) ^{*†‡}
Chronic cough, n (%)	22 (7.6)	43 (14) [*]	52 (14) [*]	64 (27) ^{*†‡}
BDR FEV ₁ , %	3.7 (6.1)	3.4 (5.9)	6.6 (1.8) ^{*†}	10 (12) ^{*†‡}
BDR responder, n (%)	28 (10)	32 (11)	99 (27) ^{*†}	100 (42) ^{*†‡}
Imaging				
LAA ₈₅₆ , %	21 (17)	18 (15)	29 (16) ^{*†}	31 (19) ^{*†}
LAA ₉₅₀ , %	3.0 (2.9)	3.0 (3.2)	5.4 (4.9) ^{*†}	5.3 (5.0) ^{*†}
TAC, n	221 (73)	217 (68)	190 (66) ^{*†}	152 (53) ^{*†‡}
Pi10, mm	3.9 (0.15)	3.9 (0.13)	3.9 (0.13)	3.9 (0.12)
Inner area, mm ²	12 (4.6)	12 (3.2)	11 (3.1) ^{*†}	9.5 (2.6) ^{*†‡}
Wall area per cent, %	62 (2.9)	62 (2.8)	63 (3.0) [†]	64 (2.6) ^{*†‡}
DPM _{ISAD} , %	41 (17)	37 (17)	42 (13) ^{*†}	49 (15) ^{*†‡}
PRM _{ISAD} , %	21 (12)	15 (13)	29 (15) ^{*†}	29 (17) ^{*†}

Significance of difference (p<0.05).

*Significantly different from never-smoker.

†Significantly different from at risk.

‡Significantly different from GOLD I.

BDR, bronchodilator response; BMI, body mass index; DL_{CO}, diffusing capacity for carbon monoxide; DPM, disease probability measure; FEV₁, forced expiratory volume in 1 s; fSAD, functional small airway disease; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HDHTDM, heart disease, systemic hypertension or diabetes mellitus; LAA₈₅₆, low attenuation area of the lung with attenuation values below -856 HU on full-expiration CT; %_{pred}, per cent predicted; PRM, parametric response mapping; RV, residual volume; TAC, total airway count; TLC, total lung capacity.

itself may induce remodelling.¹⁰ Further, airway wall thickening and the degree of goblet cell hyperplasia in non-asthmatic cough correlated with increased cough sensitivity.^{10 11}

Advanced thoracic CT imaging now makes it possible to generate structural lung measurements that reflect both, emphysema and airway remodelling.¹² In patients with COPD, CT airway wall measurements have been shown to correlate significantly with physiological measurements, respiratory symptoms, COPD-related exacerbations,¹³ FEV₁ decline and all-cause mortality.¹⁴ Another CT measurement, the total airway count (TAC)

has been shown to correlate with COPD severity as well as FEV₁ decline.¹⁵ TAC was also associated with the number of terminal bronchioles and their distortion which were measured by micro-CT technique of excised lung specimens.¹⁶ Other novel approaches, such as the parametric response mapping (PRM) and disease probability measure (DPM), allow quantification of functional small airway disease.¹⁷ All of these CT measurements have been used to analyse structural changes in different chronic airway disease conditions as COPD, but to our knowledge, no studies have investigated the association between CT structural airway measures and CC. However, previous

Table 2 Comparison of subject demographic, pulmonary function and imaging measurements for those with or without chronic cough

Parameter (\pm SD unless specified)	No chronic cough (n=1002)	Chronic cough (n=181)	P value
Subject demographic			
Age, years	67 (9.9)	67 (9.7)	0.91
Female sex, n (%)	417 (42)	74 (41)	0.87
Caucasian, n (%)	941 (94)	177 (98)	0.03
Pack-years, years	15 (22)	23 (27)	<0.001
BMI, kg/m ²	27 (5.0)	27 (5.2)	0.66
Current-smoker, n (%)	125 (12)	52 (29)	<0.001
History of asthma, n (%)	154 (15)	49 (27)	<0.001
History of tuberculosis, n (%)	13 (1.3)	0 (0)	0.24
History of HDHTDM, n (%)	367 (37)	81 (45)	0.05
History of bronchiectasis, n (%)	181 (18)	43 (24)	0.08
Pulmonary function			
FEV ₁ , % _{pred}	96 (18)	88 (19)	<0.001
FEV ₁ /FVC, %	70 (9.2)	66 (9.5)	<0.001
RV/TLC, %	39 (9.0)	41 (9.0)	0.006
DL _{CO} , % _{pred}	110 (24)	99 (25)	<0.001
BDR FEV ₁ , %	5.8 (7.9)	5.8 (9.6)	0.91
BDR responder, n (%)	218 (22)	41 (23)	0.77
Imaging			
LAA ₈₅₆ , %	25 (18)	25 (17)	0.92
LAA ₉₅₀ , %	4.2 (4.4)	4.3 (3.7)	0.87
TAC, n	197 (69)	196 (79)	0.89
Pi10, mm	3.9 (0.14)	3.9 (0.11)	0.41
Inner area, mm ²	11 (3.6)	11 (3.5)	0.73
Wall area per cent, %	63 (3.0)	63 (3.0)	0.34
DPM _{fSAD} , %	42 (16)	42 (15)	0.85
PRM _{fSAD} , %	24 (17)	22 (13)	0.37

BDR, bronchodilator response; BMI, body mass index; DL_{CO}, diffusing capacity for carbon monoxide; DPM, disease probability measure; FEV₁, forced expiratory volume in 1 s; fSAD, functional small airway disease; FVC, forced vital capacity; HDHTDM, heart disease, systemic hypertension or diabetes mellitus; LAA₈₅₆, low attenuation area of the lung with attenuation values below -856 HU on full-expiration CT; %_{pred}, per cent predicted; PRM, parametric response mapping; RV, residual volume; TAC, total airway count; TLC, total lung capacity.

data suggest that CC is associated with the presence of emphysema on CT.¹⁸

Canadian Obstructive Lung Disease (CanCOLD) is a multicentre, population-based study including never-smokers, current or former smokers at risk of COPD, and participants with mild (Global Initiative for Chronic Obstructive Lung Disease, GOLD I) and moderate (GOLD II+) stages. Therefore, CanCOLD is very well suited to assess CT structural abnormalities associated with CC in persons at risk as well as in those with COPD. We hypothesise that CC is associated with CT airway wall thickness and emphysema.¹⁸ Furthermore, we

hypothesise that presence of CC and TAC independently contribute to the decline in lung function independent of the initial airflow level.

METHODS

Study design

The CanCOLD study (ClinicalTrials.gov: NCT00920348) is a longitudinal, observational, population-based multicentre study from nine sites across Canada investigating individuals >40 years of age randomly selected from the general population. For defining COPD, spirometry thresholds according to GOLD criteria were used.¹⁹ Participants were also asked by questionnaire about history of asthma, tuberculosis, bronchiectasis as well as heart disease, systemic hypertension or diabetes mellitus (HDHTDM). Detail information concerning study design, recruitment strategy and methodology of the CanCOLD study has been described elsewhere.²⁰ Patients or public were not involved in the design and conduct of this research.

Our analyses include 1183 individuals aged ≥ 40 years who had a total of four visits over a time frame of approximately 6 years; the mean time between visit 0 with visits 1, 2 and 3 was 2.5 ± 1.7 years, 4.4 ± 1.7 years and 5.9 ± 1.8 years, respectively. Our cohort consists of primarily four groups: (1) never-smokers with normal lung function: healthy persons who never smoked ($\leq 1/20$ pack-year of tobacco-smoking history) with no airflow limitation (FEV₁/forced vital capacity (FVC) ≥ 0.7); (2) ever-smokers with normal spirometry at risk for COPD: current or former smoker with no airflow limitation (FEV₁/FVC ≥ 0.7); (3) mild COPD (GOLD I): FEV₁/FVC < 0.7 and FEV₁pred $\geq 80\%$ and (4) moderate-to-severe COPD (GOLD II+): FEV₁/FVC < 0.7 and FEV₁pred $< 80\%$.

Chronic cough

CC was defined as cough on most days for at least 3 months in two consecutive years.^{1 21}

Lung function

Spirometry before and after bronchodilation was performed according to the American Thoracic Society/European Respiratory Society guidelines^{19 22} at four times (at baseline visit, and from baseline after 18 months, 36 months and 54 months) to measure the FEV₁ and FVC. Bronchodilator response (BDR FEV₁) was defined as the per cent change in FEV₁ after bronchodilator inhalation.

At baseline, body plethysmography was performed for measurement of residual volume (RV), total lung capacity (TLC) and the RV/TLC ratio as well as diffusing capacity of the lung for carbon monoxide (DLCO).¹⁹

Imaging

Thoracic CT scans were done at baseline visit. CT images were acquired at each of the nine sites using CT systems of various models with the participant supine at suspended



Table 3 Comparison of subject demographic, pulmonary function and imaging measurements for those with or without COPD and further those with or without chronic cough

Parameter (±SD unless specified)	No COPD (n=583)		P value	COPD (n=600)		P value
	No chronic cough (n=518)	Chronic cough (n=65)		No chronic cough (n=484)	Chronic cough (n=116)	
Subject demographic						
Age, years	66 (9.7)	67 (8.6)	0.51	68 (10)	67 (10)	0.34
Female sex, n (%)	241 (47)	26 (40)	0.36	176 (36)	48 (41)	0.34
Caucasian, n (%)	484 (93)	64 (98)	0.16	457 (94)	113 (97)	0.24
Pack-years, yrs	10 (19)	18 (27)	0.03	20 (24)	26 (26)	0.03
BMI, kg/m ²	27 (4.8)	28 (5.2)	0.46	28 (5.3)	27 (5.1)	0.28
Current-smoker, n (%)	51 (9.8)	13 (20)	0.02	74 (15)	39 (34)	<0.001
History of asthma, n (%)	42 (8.1)	9 (14)	0.16	112 (23)	40 (34)	0.02
History of tuberculosis, n (%)	3.0 (0.58)	0.0 (0.0)	1.00	10 (2.1)	0 (0)	0.22
History of HDHTDM, n (%)	177 (34)	25 (38)	0.49	190 (39)	56 (48)	0.09
History of bronchiectasis, n (%)	87 (17)	14 (22)	0.38	94 (19)	29 (25)	0.20
Pulmonary function						
FEV ₁ , % _{pred}	104 (15)	103 (16)	0.71	87 (17)	79 (15)	<0.001
FEV ₁ /FVC, %	77 (4.6)	76 (4.6)	0.08	63 (6.5)	61 (6.5)	0.01
RV/TLC, %	37 (7.4)	38 (7.8)	0.39	42 (9.8)	43 (9.1)	0.15
DL _{CO} , % _{pred}	115 (22)	106 (23)	0.003	105 (24)	95 (25)	<0.001
BDR FEV ₁ , %	3.5 (5.8)	4.1 (7.7)	0.43	8.1 (9.1)	6.7 (10)	0.16
BDR responder, n (%)	52 (10)	8.0 (12)	0.52	166 (34)	33 (28)	0.27
Imaging						
LAA ₈₅₆ , %	20 (16)	21 (17)	0.49	30 (18)	27 (16)	0.05
LAA ₉₅₀ , %	3.0 (3.1)	3.1 (2.4)	0.70	5.5 (5.0)	4.9 (4.2)	0.22
TAC, n	218 (69)	231 (81)	0.14	174 (62)	176 (70)	0.80
Pi10, mm	3.9 (0.14)	3.9 (0.13)	0.28	3.9 (0.14)	3.9 (0.10)	0.74
Inner area, mm ²	12 (4.0)	13 (3.7)	0.14	10 (3.0)	10 (3.0)	0.72
Wall area per cent, %	62 (2.9)	62 (2.6)	0.74	64 (2.9)	64 (2.9)	0.50
DPM _{ISAD} , %	39 (17)	38 (15)	0.45	45 (15)	45 (15)	0.70
PRM _{ISAD} , %	16 (13)	19 (14)	0.40	30 (17)	23 (12)	0.03
BDR, bronchodilator response; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DL _{CO} , diffusing capacity for carbon monoxide; DPM, disease probability measure; FEV ₁ , forced expiratory volume in 1 s; fSAD, functional small airway disease; FVC, forced vital capacity; HDHTDM, heart disease, systemic hypertension or diabetes mellitus; LAA ₈₅₆ , low attenuation area of the lung with attenuation values below -856 HU; % _{pred} , per cent predicted; PRM, parametric response mapping; RV, residual volume; TAC, total airway count; TLC, total lung capacity.						

full-inspiration and full-expiration from apex to base of the lung. The CT parameters for image acquisition are as follows: 100 kVp, 50 mAs, 0.5s gantry rotation, pitch of 1.375 and 1.0 or 1.25mm slice thickness, contiguous slices. The 'standard' or soft tissue reconstruction kernel was used for quantitative analysis.

CT image analysis was performed using commercially available software (Apollo V.2.0 software package, VIDA Diagnostics, Coralville, Iowa, USA). Gas trapping was quantified using full-expiration CT images as the low attenuation area of the lung below -856 HU (LAA856). For CT emphysema measurement, the percentage of the lung with LAA below -950 Hounsfield units (LAA950) was generated. The CT measured TAC was measured and obtained by summing all airway segments from the segmented airway tree.¹⁵

Pi10 was defined as the wall thickness of a theoretical airway with a lumen perimeter of 10 mm and was calculated using anatomically equivalent airways.¹⁹ The CT segmental airway wall percentage was calculated as the average measurement for the segmental bronchi right upper lobe apical segmental bronchus (RB1), middle lobe lateral segmental bronchus (RB4), right lower lobe posterior basilar segmental bronchus (RB10) and left lower lobe posterior basilar segmental bronchus (LB10) airways.²³ PRM and DPM were generated by registering images acquired at full-inspiration to images acquired at full-expiration and applying established thresholds.¹⁷

The CanCOLD study ClinicalTrials.gov registration number is NCT00920348.

Table 4 Multivariable logistic regression model for chronic cough with additional subject demographic covariates including FEV1

Model*	OR	95% CI		P value
		Lower	Upper	
LAA ₈₅₆ , %	0.995	0.984	1.006	0.38
LAA ₉₅₀ , %	0.976	0.932	1.023	0.31
TAC, n	1.003	1.000	1.006	0.047
Pi10, mm	2.191	0.619	7.76	0.22
Inner area, mm ²	1.049	1.000	1.101	0.052
Wall area per cent, %	0.982	0.918	1.051	0.60
DPM _{fSAD} , %	0.996	0.985	1.008	0.56
PRM _{fSAD} , %	0.984	0.959	1.009	0.21

*Adjusted by age; sex; race; pack-years; smoking status; body mass index; CT air volume; CT model, FEV1, history of asthma; history of tuberculosis; history of heart disease, systemic hypertension, or diabetes mellitus; bronchiectasis. DPM, disease probability measure; FEV1, forced expiratory volume in 1 s; fSAD, functional small airway disease; LAA856, low attenuation area of the lung with attenuation values below -856 HU; PRM, parametric response mapping; RPM, parametric response mapping; TAC, total airway count.

Statistical analysis

All statistical analyses were performed using SAS V.9.4 software. A one-way analysis of variance (ANOVA) with a Tukey test for multiple comparison correction was performed for statistical comparison between never-smokers, at risk, GOLD I and GOLD II+ COPD groups for participants' demographic, pulmonary function and CT measurements. For categorical variables, a Fisher's exact test was used. For comparison of the no CC and CC groups for all measurements, we used a Mann Whitney un-paired t-test. A multivariable logistic regression analysis for CC was performed using all CT measurements in separate models, adjusted by confounding variables (age, sex, race, pack-years, smoking status, body mass index (BMI), CT air volume, CT model, FEV1, history of asthma, history of tuberculosis, history of HDHTDM and bronchiectasis). A linear mixed effects model using the residual (restricted) maximum likelihood estimation method for the covariance parameters was performed for longitudinal FEV1 change; baseline variables included: age, sex, BMI, race, smoking status, FEV1, CC, TAC and LAA950; interaction terms for baseline TAC, LAA950, FEV1 and CC with time were included; time alone was also included in the model.

RESULTS

We evaluated baseline data of 1183 participants, aged ≥ 40 years. The study cohort consisted of 286 never-smokers with normal lung function, 297 ever-smokers with normal lung function at risk for COPD, and 600 individuals with COPD of different severity grades (n=361 GOLD I, n=239 GOLD II+).

In the GOLD I group, the female proportion was significantly lower than in the never-smoker and the at-risk group. Individuals with GOLD I were also older than at-risk participants. While CC in never-smokers was 7.6%, prevalence in at-risk individuals was almost twice as high (14%). Interestingly, the same prevalence of CC was found in the GOLD I group (14%). CC prevalence in the moderate-to-severe COPD group (GOLD II+) was again twice as high as in the former two groups (27%). COPD individuals of all stages had a lower FEV1 and FEV1/FVC values than individuals without COPD. COPD individuals of any stage reported more asthma than other groups while those with moderate-to-severe COPD had significantly more tuberculosis and HDHTDM. Individuals with COPD of any stage had significantly higher gas trapping and emphysema values (LAA856 and LAA950) as well as PRM and DPM than the non-COPD participants. TAC and the inner wall area decreased significantly with increasing COPD stage. Remarkably, Pi10 wall thickness did not differ between the four groups (table 1).

In table 2, comparisons between individuals without (n=1002) and with CC (n=181) are summarised. Participants with CC were more likely to be smokers and having a history of asthma. Regarding lung function, CC individuals had more reduced FEV1 and FEV1/FVC values. DLCO was higher in non-CC individuals. No differences in imaging parameters were found between those with and without CC.

Table 3 further shows characteristics of individuals with and without COPD, stratified for presence or absence of CC. In both groups, independently from the presence of COPD, individuals with CC were more likely to be current smokers, had more smoking pack years as well as lower DLCO and FEV1/FVC ratio. Concerning bronchial reversibility, there was no significant difference in BDR FEV1 between both groups.

Within the COPD group, individuals with CC reported more asthma and had lower FEV1% than those without CC. Regarding imaging parameters, only PRM was significantly reduced in CC individuals with COPD.

Associations of imaging parameters with CC are shown in table 4. Only TAC was statistically slightly associated with CC (OR 1.003, p=0.047). All other imaging parameters showed no significant associations with the presence of CC.

CC was significantly associated with FEV1 decline over time (table 5A). This finding is still consisting after adjusting for CT measured TAC (table 5B) and additionally for emphysema LAA950 (table 5C).

After splitting analyses separately for smoking status (table 5D,E), CC was significantly associated with FEV1 decline, independently from TAC and LAA950 in ever-smokers but not in non-smokers.

DISCUSSION

Our study could not identify airway and lung structure changes related to CC in non-COPD and COPD subjects

**Table 5** (A–E) Mixed effects multivariable regression models

Interactions	Estimate (95% CI)	SE	P value
(A) mixed effects multivariable regression models for longitudinal lung-function decline			
Model 1: FEV1*			
FEV1×time	−17.3 (−20.4 to −14.1)	1.59	<0.0001
Chronic cough×time	−17.3 (−24.4 to −10.1)	3.65	<0.0001
(B) Mixed effects multivariable regression models for longitudinal lung-function decline			
Model 1: FEV1†			
FEV ₁ ×time	−17.9 (−21.1 to −14.7)	1.64	<0.0001
Chronic cough×time	−17.0 (−24.1 to −9.9)	3.69	<0.0001
TAC×time	0.04 (0.002 to 0.07)	0.02	<0.0001
(C) Mixed effects multivariable regression models for longitudinal lung-function decline			
Model 1: FEV1‡			
FEV ₁ ×time	−17.6 (−20.8 to −14.4)	1.63	<0.0001
Chronic cough×time	−16.5 (−23.7 to −9.4)	3.64	<0.0001
TAC×time	0.04 (0.008 to 0.08)	0.01	0.02
LAA ₉₅₀ ×time	−0.80 (−1.4 to −0.23)	0.29	0.006
(D) Mixed effects multivariable regression models for longitudinal lung-function decline in ever-smokers			
Model 1: FEV1§			
FEV ₁ ×time	−28.7 (−33.3 to −24.1)	2.33	<0.0001
Chronic cough×time	−20.6 (−29.8 to −11.4)	4.70	<0.0001
TAC×time	0.07 (0.02 to 0.12)	0.03	0.007
LAA ₉₅₀ ×time	−0.84 (−1.6 to −0.10)	0.37	0.03
(E) Mixed effects multivariable regression models for longitudinal lung-function decline in non-smokers			
Model 1: FEV1¶			
FEV ₁ ×time	−6.2 (−10.5 to −2.0)	2.17	0.004
Chronic cough×time	−6.0 (−17.5 to −5.5)	5.87	0.30
TAC×time	0.01 (−0.03 to 0.06)	0.02	0.46
LAA ₉₅₀ ×time	−0.78 (−1.7 to −0.11)	0.45	0.09
*Adjusted by baseline age, sex, BMI, race, smoking status, FEV1, TAC, chronic cough.			
†Adjusted by baseline age, sex, BMI, race, smoking status, FEV1, TAC, chronic cough.			
‡Adjusted by baseline age, sex, BMI, race, smoking status, FEV1, chronic cough, TAC, LAA ₉₅₀ .			
§Adjusted by baseline age, sex, BMI, race, smoking status, FEV1, chronic cough, TAC, LAA ₉₅₀ .			
¶Adjusted by baseline age, sex, BMI, race, FEV1, chronic cough, TAC, LAA ₉₅₀ .			
BMI, body mass index; FEV1, forced expiratory volume in 1 s; LAA ₉₅₀ , low attenuation areas below −950 Hounsfield units; TAC, total airway count.			

using advanced imaging procedures. CC does not reflect differences in TAC or changes in the peripheral airway compartment. CC is besides TAC identified as strongly associated with FEV1 decline, particularly in ever-smokers.

The main finding of our study is the absence of airway and lung structure changes related to CC in non-COPD and COPD subjects based on advanced CT imaging parameters. These data differ from previous findings reporting central airway wall thickening in a small group of subjects with non-asthmatic cough.¹¹ Airway wall thickness in that study was defined by airway wall area and absolute wall thickness corrected for body surface area. In our study, airway dimensions were assessed by measuring airway wall area as well as wall thickness for a theoretical airway with 10mm perimeter. Data from biopsy studies in chronic non-asthmatic cough patients are also non-conclusive. Earlier data report normal

basement-membrane thickness in subjects with CC besides increased epithelial desquamation and inflammatory cells particularly mononuclear cells.²⁴ Others reported evidence of basement-membrane thickening in endotracheal biopsies in individuals with CC.^{7–9} A retrospective observational study conducted in France recently showed that one quarter of patients with CC had an abnormal chest CT scan: bronchiectasis, nodules and bronchial wall thickening were the most common findings.²⁵ Another study reported active and former smokers with CC had increased airway wall thickness and lower TAC. Of note, this study investigated chronic bronchitis and did not include never-smokers²⁶ Therefore, reported findings need to be interpreted cautiously due to differences in the definition of CC.

Our findings of normal airway dimensions are confirmed by PRM and DPM showing no differences in

quantitative small airway dimensions related to CC in normal subjects and those suffering from COPD. Our data could also not confirm previous conclusions on the clinical relevance of CT abnormalities reported in the CanCOLD cohort.¹⁸ In that study, it was reported that presence of emphysema was associated with CC as well as with chronic phlegm production, wheeze, dyspnoea, health status and risk of frequent exacerbations. To note is that these data were based on qualitative CT analysis: emphysema was zonally scored on a five-point scale (six zones) and presence of expiratory air-trapping, bronchial wall thickening and bronchiectasis were based on morphological criteria from the Fleischner glossary terms for thoracic imaging.²⁷ In our analysis, only quantitatively derived CT parameters are included.

Furthermore, our analysis includes more advanced CT derived parameters as TAC, PRM and DPM. Remarkable is the finding that PRM as marker of small airway dysfunction is more impaired in patients with COPD with CC.

Progressive abnormal decline in lung function as assessed by FEV1 is considered as a hallmark in the development of COPD. Several population studies have supported this causal link and identification of determinants of abnormal FEV1 decline over time became the focus of many studies.^{28–30} Most studies focused on the deleterious effects of smoking and the attenuation of FEV1 decline by stopping smoking habits. Earlier data demonstrate that subjects with CC had a decline in FEV1 well greater what would be expected in a population of non-smoking subjects and this decline in FEV1 occurred independently of changes in cough severity.³¹ Others reported that women with respiratory symptoms are more prone to a faster decline in FEV1.³² The role of individual CT parameters in relation to progression of COPD is also studied. The total number of airways quantified in vivo using CT seems to have the greatest influence on FEV1 decline and bronchodilator responsiveness.¹⁵ More recently, it was demonstrated that TAC is independently associated with annual decline in prebronchodilator and postbronchodilator FEV1.³³ Others reported that functional small airway disease assessed by PRM was associated with FEV1 decline.³⁴ Our data clearly illustrate that CC is strongly associated with FEV1 decline, particularly in smokers, on top of CT-derived parameters.

Recent data suggest that CC is more than a symptom, but is an important marker of incident development of airflow limitation in many population based studies.^{35–37} Particularly in patients suffering from COPD, it is demonstrated that CC itself is associated with lower FEV1, impaired diffusing capacity, more dyspnoea and worse health status. Furthermore, CC is considered as an independent risk factor for exacerbations of the disease, possibly linked to altered transient receptor potential (TRP) channel function.³⁸ The authors advocate to consider CC itself as a novel phenotype of COPD.³⁸ At least these data confirm that CC deserves a more prominent place in the diagnostic workup of at least patients with suspected underlying respiratory diseases.³⁹

Recently, the term pre-COPD was introduced to refer in particular to those subjects with symptoms of CC in the absence of airflow limitation.⁴⁰ Instead of lumping CC under the COPD umbrella, it seems more important to validate the individual and economic impact of CC itself and to overcome the unmet needs for alternative therapies for this disabling problem and to target underlying disease mechanisms.⁴¹

LIMITATIONS OF THE STUDY

We do acknowledge some potential limitations of our study.

We are aware that our used CC definition varies from the standard definition of clinical guidelines as cough lasting for at least 8 weeks.³ We used a 3-month duration definition that derived from a systematic review and meta-analysis in which the majority of studies also utilised a 3-month cut-off.¹

Further, we acknowledge that the presence of extrapulmonary causes of CC was not considered due to the study design. Conditions such as upper airway cough syndrome or gastro-oesophageal reflux disease which are not expected to have associated thoracic CT structural abnormalities may potentially bias our finding of not detecting specific CT features.

Due to our study design and available data, we are only able to describe statistical significances and associations but cannot claim causality for the reported results.

CONCLUSIONS

We conclude that irrespective of the presence of COPD, CC is not related to structural features in advanced CT scans. This absence of structural features indicates that there may be other pathophysiological concepts contributing to the development of CC and that there is a need for further studies. Furthermore, our data confirm that CC is independently from other derived CT parameters a condition highly associated with FEV1 decline.

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