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Airway wall thickening on CT: Relation to smoking status and severity of COPD

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ABSTRACT

Airway wall thickening in cigarette smokers is thought to be a result of inflammatory changes and airway remodeling. This study investigates if CT-derived airway wall thickening associates to disease severity in smokers with and without COPD and if airway wall thickening is reversible by smoking cessation.

We examined 2000 smokers and 46 never-smokers who returned for a 5-year follow-up visit in the COPDGene-study. Multivariable regression analyses were performed at visit 1 to associate airway wall thickness (expressed as Pi10) with percent predicted forced expiratory volume in 1 s (FEV_1%-predicted), 6-min walking distance (6MWD), and St. George Respiratory Questionnaire (SGRQ). Longitudinal analyses were performed to assess the effect of smoking cessation on Pi10 using linear mixed models.

A higher Pi10 was significantly associated with worse FEV_1%-predicted, 6MWD, and SGRQ in all GOLD-stages. Longitudinal analyses showed that subjects that quit smoking significantly decreased in Pi10 (ΔPi10 = −0.18 mm, $p < 0.001$). Subjects that started smoking had a significant increase in Pi10 (ΔPi10 = 0.14 mm, $p < 0.001$).

Pi10 is a clinically relevant biomarker of smoking-related airway injury in smokers with and without COPD. The change in Pi10 with change in smoking status suggests that it can quantify a reversible component of smoking-related airway inflammation.

1. Introduction

With the increasing use of computed tomography (CT) in clinical practice and lung cancer screening, there is a growing interest in the added value of CT for the diagnosis of smoking related comorbidities, in particular coronary artery disease and chronic obstructive pulmonary disease (COPD) [1]. Earlier diagnosis of COPD could lead to earlier treatment and better prevention of exacerbations. Exacerbation prevention is especially important since exacerbations have been associated with an accelerated loss of lung function [2]. In this regard, there is a need for reliable CT biomarkers of COPD.

Quantitative CT measurements of emphysema are clear predictors of COPD. Non-emphysematous COPD can be identified by air trapping, which requires an additional expiratory CT scan, or by airway morphology. Airway wall thickness is readily quantifiable on inspiratory lung screening CT and has been shown to serve as a biomarker for the diagnosis of COPD [3] and to be associated with airflow obstruction [4–6].

Thickening of the airway walls in cigarette smokers is thought to be due to a combination of inflammatory changes and remodeling. However, it is unknown if these smoking-related airway changes are different in current smokers compared to former smokers, and whether smoking cessation can cause changes in airway wall thickness measured on CT. Airway measurements on CT are often expressed as airway wall thickness or luminal area of specific segmental and sub-segmental bronchi [6,7]. However, this requires an accurate set of labeled airway

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branches. Pi10 is an alternative measure of airway wall thickness and is calculated from a large number of airway lumen and airway wall measurements throughout the lungs. This measurement provides a useful summary score of the airway wall thickness for an individual patient [8]. Although a previous study has shown that Pi10 is a predictor of COPD [3], it is unclear if Pi10 is also associated with the severity of spirometric impairment and quality of life in smokers with and without COPD and in smokers with and without emphysema.

We hypothesized that higher Pi10 is associated with a worse disease state in smokers with and without COPD and in smokers with and without emphysema. Furthermore, we hypothesized that current smokers have thicker airway walls as compared to former smokers, which is reversible to some extent as an effect of smoking cessation.

2. Materials and methods

2.1. Study population

COPDGene is a multi-center study examining 10,371 smokers which has been described in previous work [9]. We included the first 2000 smokers and 46 never smokers who returned for a second examination at five-year follow-up. A written informed consent was obtained from each subject and the COPDGene study was approved by the institutional review board. Age, gender, Body Mass Index (BMI), pack years, and smoking status (current, former, or never) were recorded for each subject for both visits. Spirometry was used to assess the post-bronchodilator forced expiratory volume in 1 s (FEV_1 and FEV_1%-predicted) and the forced vital capacity (FVC) [10]. Airflow obstruction was defined by $FEV_1/FVC < 0.70$, where the corresponding GOLD-stage was determined by FEV_1%-predicted [11]. Bronchodilator responsiveness (BDR) was determined by a pre/post bronchodilator FEV_1 change ≥ 12%, with a minimum of 200 ml. Quality of life was assessed by 6 min walking distance (6MWD) [12] and the St George's Respiratory Questionnaire (SGRQ) [13].

2.2. CT imaging and quantification

Thin section thoracic CT scans were acquired at full inspiration (200 mAs) at both visits, using the same scanning protocol for all smokers and never smokers [9]. Quantification of airway wall thickness and emphysema was performed using Thirona lung quantification software (Thirona, the Netherlands, http://www.thirona.eu). Lungs and airways were automatically extracted from inspiratory CT scans and visually approved by trained analysts. A global measure for airway wall thickness was calculated from the extracted airways and expressed as the square root of wall area of a hypothetical airway with internal perimeter of 10 mm (Pi10) [8,14]. Emphysema was defined as the percentage of low-attenuation area below −950 Hounsfield units (LAA%-950) and the total lung capacity (TLC) was defined as the volume of the lung. Details on CT quantification are presented in the online data supplement (Section A).

2.3. Statistical analysis

Cross-sectional analysis was performed on all smokers at visit 1. Differences in baseline characteristics between current and former smokers were tested using an independent samples *t*-test or chi-squared test. Linear regression was used to investigate the univariate and multivariate associations between Pi10 and FEV_1%-predicted, 6MWD, and SGRQ, reported as standardized (sβ) and unstandardized regression coefficients (β). Multivariable models were adjusted for gender, age, BMI, pack years, TLC, BDR, smoking status, and LAA%-950. All multivariate analyses were repeated per GOLD-stage and for subgroups stratified by the presence of emphysema. An additional cross-sectional analysis was performed in which smokers in the upper Pi10 quartile were compared to smokers in the lower Pi10 quartile with regard to their FEV_1%-predicted, 6MWD, and SGRQ. This analysis was repeated per GOLD-stage. All differences were tested using independent sample t-tests. IBM SPSS statistics (version 23) was used for all cross-sectional analyses. Longitudinal analyses were performed to study the effects of smoking cessation on Pi10 using linear mixed models. Gender, age, BMI, pack years, TLC, BDR, and LAA%-950 were included in the model as covariates and the model was fit in R version 3.2.3 using the "lme4"-package [15]. Details on statistical analyses are presented in the online data supplement (Section B). All reported p-values are two-sided with a 0.05 significant level.

3. Results

3.1. Subject inclusion

From the first 2000 smokers enrolled in the COPDGene study, we excluded 39 subjects because of missing clinical data (19 subjects with missing 6MWD and 20 subjects with missing BDR) and 6 subjects because of failed CT quantification. This resulted in 1955 subjects eligible for the cross-sectional analyses of visit 1. To investigate Pi10 changes over time, we additionally excluded 79 subjects with significant changes of the lungs (such as intervening surgery or development of lung fibrosis) and included a control group of 46 never smokers. This resulted in 1922 subjects that were eligible for the longitudinal analyses.

3.2. Descriptive statistics

Demographics of the 1955 smokers included in the cross-sectional analysis are shown in Table 1. The mean age of this population was 60.5 years and 50.8% were male. A total of 872 subjects were diagnosed with COPD (181 subjects with GOLD1, 404 subjects with GOLD2, 221 subjects with GOLD3, and 66 subjects with GOLD4). From the remaining 1083 subjects, 862 subject were in the GOLD0 group and 221 subjects in the preserved ratio impaired spirometry (PRISm) group [16]. The average Pi10 was 2.26 mm (with a standard deviation of 0.58 mm) and increased with an increasing GOLD stage. A total of 865 subjects were smokers at the time of the first examination (visit 1). When stratifying by smoking status, Pi10 was significantly higher in current smokers in all GOLD stages.

For the 1922 subjects that were included in the longitudinal analyses, five groups were defined based on the change in smoking status over the five-year follow-up period: 631 subjects that were smokers at both visits (persistent current smoker); 993 subjects that were former smokers at both visits (persistent former smokers); 203 subjects that quit smoking after visit 1 (cessation smokers); 49 subjects that restarted smoking after visit 1 (relapsing smokers); and 46 subjects that had never smoked (never smokers). The mean age of the never smokers was 61.6 years and 42.9% were male subjects. Demographics of the never smokers are shown in the online data supplement (Section C, Table E1). At both visits, the average Pi10 was significantly higher in current smokers as compared to former smokers ($p < 0.001$), and the average Pi10 of the never smokers was significantly lower compared to both the current and former smokers (both $p < 0.001$).

3.3. Airway wall thickness as predictor of disease severity

In the univariate analysis, Pi10 was inversely related to FEV_1%-predicted ($s\beta = -0.60$, $p < 0.001$) and 6MWD ($s\beta = -0.34$, $p < 0.001$), and directly related to SGRQ ($s\beta = 0.43$, $p < 0.001$). Multivariable analyses (Table 2) confirmed the univariate analysis and showed that a higher Pi10 was significantly associated with a lower FEV_1%-predicted, a lower 6MWD, and a higher SGRQ (all $p < 0.001$). When stratifying by GOLD stage (i.e. GOLD 0, GOLD 1/2, GOLD 3/4, and PRISm), a higher Pi10 was significantly associated with a lower FEV_1%-predicted and a higher SGRQ in all GOLD stages and PRISm, and with a lower 6MWD in GOLD 0, GOLD 1/2 and GOLD 3/4. In order to investigate the role of

Table 1
Baseline demographics of all subjects (and stratified by smoking status) that were included in the cross-sectional analysis of visit 1. Data is given as mean ± standard deviation or as percentage of subjects.

	All smokers (n = 1955)	Current smokers (n = 865)	Former smokers (n = 1090)	p-value[a]
Demographic Characteristics				
Age (years)	60.5 ± 8.9	55.8 ± 7.4	64.2 ± 8.1	< 0.001
Gender (% male)	50.8	52.4	49.6	0.229
BMI (kg/m^2)	28.9 ± 6.0	28.3 ± 6.0	29.4 ± 5.9	< 0.001
Pack years (years)	43.7 ± 23.7	42.0 ± 22.3	45.2 ± 24.7	0.003
Clinical Characteristics and Quality of Life				
FEV_1% predicted (%)	78.3 ± 23.9	81.6 ± 22.0	75.7 ± 25.1	< 0.001
BD Responsiveness (% yes)	20.2	17.9	21.9	0.028
COPD (% yes)	44.6	37.3	50.4	< 0.001
GOLD stages				
GOLD 0 (%)	44.1	49.1	40.1	
GOLD 1 (%)	9.3	8.7	9.7	
GOLD 2 (%)	20.7	18.5	22.4	
GOLD 3/4 (%)	14.7	10.2	18.3	
PRISm (%)	11.3	13.5	9.5	
6MWD (m)	427.6 ± 116.5	414.9 ± 116.9	437.7 ± 115.2	< 0.001
GOLD 0	461.1 ± 112.3	433.4 ± 113.7	488.1 ± 104.1	< 0.001
GOLD 1	462.8 ± 105.7	453.1 ± 111.9	469.6 ± 101.0	0.303
GOLD 2	413.6 ± 107.1	412.1 ± 114.1	414.5 ± 102.5	0.824
GOLD 3/4	351.0 ± 102.3	336.3 ± 104.3	357.5 ± 101.0	0.107
PRISm	393.3 ± 113.0	386.1 ± 112.7	401.4 ± 113.3	0.315
SGRQ	23.5 ± 21.0	25.8 ± 21.4	21.8 ± 20.5	< 0.001
GOLD 0	14.7 ± 16.5	19.6 ± 18.6	10.1 ± 12.6	< 0.001
GOLD 1	16.6 ± 15.5	19.8 ± 17.4	14.1 ± 13.7	0.020
GOLD 2	29.1 ± 20.2	29.8 ± 20.6	28.7 ± 20.0	0.588
GOLD 3/4	43.0 ± 18.7	47.5 ± 19.2	41.1 ± 18.1	0.007
PRISm	28.2 ± 22.9	30.6 ± 22.9	25.6 ± 22.6	0.104
Imaging Characteristics				
TLC (L)	5.54 ± 1.43	5.32 ± 1.40	5.71 ± 1.42	< 0.001
Pi10 (mm)	2.26 ± 0.58	2.34 ± 0.60	2.21 ± 0.55	< 0.001
GOLD 0	1.95 ± 0.41	2.04 ± 0.43	1.86 ± 0.37	< 0.001
GOLD 1	2.06 ± 0.44	2.18 ± 0.48	1.97 ± 0.39	0.001
GOLD 2	2.53 ± 0.54	2.66 ± 0.61	2.45 ± 0.48	< 0.001
GOLD 3/4	2.81 ± 0.49	2.97 ± 0.56	2.74 ± 0.44	< 0.001
PRISm	2.46 ± 0.56	2.59 ± 0.56	2.31 ± 0.54	< 0.001
LAA%-950 (%)	6.71 ± 9.25	3.86 ± 6.14	8.98 ± 10.58	< 0.001

[a] p-value is given for the difference between current and former smokers. BMI = Body Mass Index; FEV_1 = Forced Expiratory Volume after 1 s; BD = bronchodilator; COPD = Chronic Obstructive Pulmonary Disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; 6MWD = 6 Minute Walking Distance; SGRQ = St George's Respiratory Questionnaire; TLC = total lung capacity; Pi10 = airway wall thickness expressed as the square root of wall area at airways with a perimeter of 10 mm; LAA%-950 = the percentage of low-attenuation lung area below −950 Hounsfield units.

gender in these multivariable models, we performed an additional analysis in which the entire cohort was stratified by gender. The results of these multiple linear regression analyses are presented in the online data supplement (Section C, Table E2). Stratification by gender for the entire cohort resulted in significant associations between Pi10 and all clinical variables for both males and females ($p < 0.001$).

Additional multivariable analyses were performed for groups stratified by both GOLD stage and the presence of emphysema, where presence of emphysema was defined by the 97.5% percentile of LAA%-950 of the never smokers (i.e. LAA%-950 = 5.77%). The results of these multiple linear regression analyses are presented in the online data supplement (Section C, Table E3). When stratifying the entire cohort based on the presence of emphysema, a higher Pi10 was significantly associated with a lower FEV_1%-predicted, a lower 6MWD, and a higher SGRQ (all $p < 0.001$) in subjects with and without emphysema. For subjects without emphysema, a higher Pi10 was significantly associated

Table 2
Effects of a 1 mm increase in Pi10 on FEV1%-predicted, 6MWD, and SGRQ using multivariate linear regression analyses. The effect sizes are given as unstandardized regressing estimate (β) and standardized regression estimate (sβ). The analysis was performed for the entire cohort and for groups stratified by GOLD stage.

	n	FEV_1% predicted, %		SGRQ, %		6MWD, m	
		β [95%CI]	sβ	β [95%CI]	sβ	β [95%CI]	sβ
Entire cohort	1955	−21.6 [-22.8 to −20.3]	−0.52**	10.4 [8.9–11.9]	0.29**	−40.4 [-48.7 to −32.1]	−0.20**
GOLD 0	862	−7.2 [-9.1 to −5.3]	−0.26**	3.9 [1.2–6.6]	0.10*	−19.1 [-37.0 to −1.1]	−0.07*
GOLD 1/2	585	−12.3 [-14.3 to −10.2]	−0.46**	6.1 [3.3–9.0]	0.17**	−22.0 [-37.3 to −6.7]	−0.11*
GOLD 3/4	287	−3.2 [-5.2 to −1.2]	−0.17*	4.3 [0.2–8.5]	0.11*	−26.1 [-51.1 to −1.1]	−0.12*
PRISm	221	−3.4 [-5.4 to −1.4]	−0.23**	6.5 [1.1–11.9]	0.16*	−20.0 [-45.7–5.8]	−0.10

All models were adjusted for gender, age, Body Mass Index, pack years, total lung capacity, bronchodilator responsiveness, smoking status, and LAA%-950. FEV_1 = Forced Expiratory Volume after 1 s; 6MWD = Six Minute Walking Distance; SGRQ = St George's Respiratory Questionnaire; n = number of subjects; Pi10 = airway wall thickness expressed as the square root of wall area at airways with a perimeter of 10 mm; LAA%-950 = the percentage of low-attenuation lung area below −950 Hounsfield units; β = unstandardized regressing estimate; 95%CI = 95%-confidence interval; sβ = standardized regression estimate; *$p < 0.05$. **$p < 0.001$.

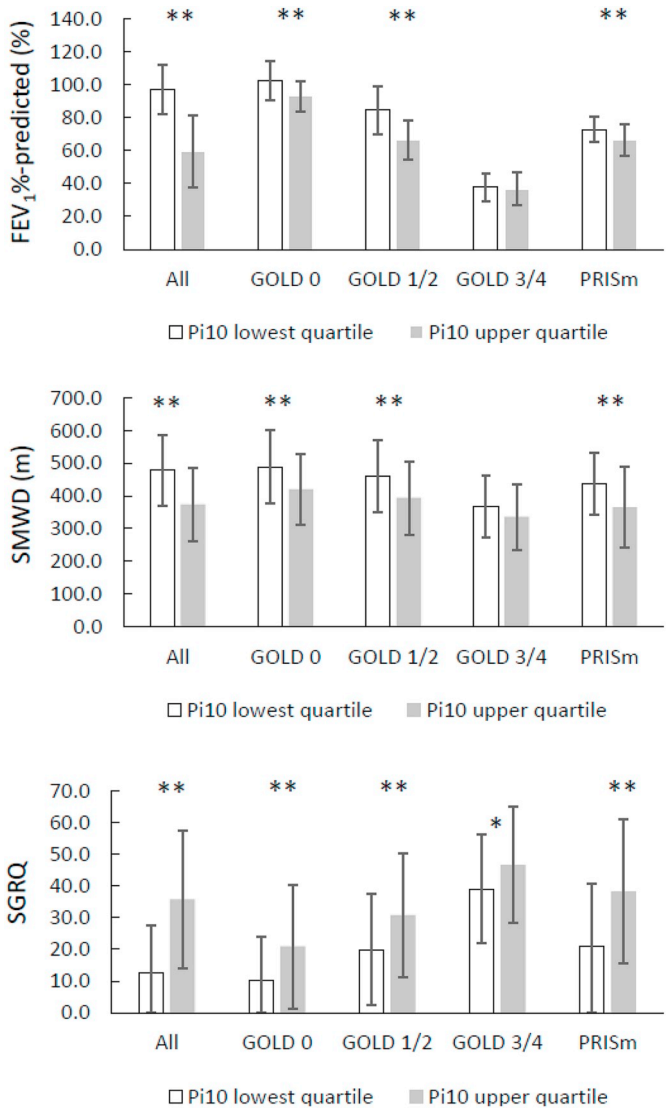

Fig. 1. FEV1%-predicted, 6MWD, and SGRQ for subjects stratified by the lower and upper Pi10 quartile. Error bars indicate the standard deviation. Significance is indicated for differences between the Pi10 quartiles. *p < 0.05. **p < 0.001.

with a lower FEV_1%-predicted and a higher SGRQ in all GOLD stages except GOLD 3/4, and a significant association for non-emphysematous subjects with 6MWD was only found in GOLD 0 and GOLD 1/2.

When dividing all smokers into subgroups based on the upper and lower Pi10 quartiles, FEV1%-predicted and 6MWD were significantly higher in the lower quartile (ΔFEV1%-predicted = 37.4%, Δ6MWD = 104.1 m, both $p < 0.001$), and SGRQ was significantly lower in the lower quartile (ΔSGRQ = −23.1, $p < 0.001$). These effects remained significant for smokers in GOLD 0, GOLD 1/2, and PRISm. For smokers in GOLD 3/4, this effect still remained but was only significant for 6MWD (Fig. 1).

To assess the relation between Pi10 and disease severity, we performed an additional experiment (presented in the online data supplement, Section D) investigating the value of Pi10 for COPD prediction models. We confirmed results a previous study by Mets et al. [3], showing that including Pi10 in prediction models for COPD significantly improves the accuracy of the prediction.

3.4. Effects of smoking cessation on airway wall thickness

The estimated longitudinal change in Pi10 in the five predefined smoking groups is shown in Fig. 2 and Table 3. Only the group with subjects that quit smoking after the first visit showed a significant decrease in Pi10 (ΔPi10 = −0.18 mm, $p < 0.001$), and only the group of subjects that started smoking after the first visit had a significant increase in Pi10 (ΔPi10 = 0.14 mm, $p = 0.002$). The change in Pi10 for the groups of never smokers, persistent current smokers and persistent former smokers was not statistically significant. In this model, age was not significantly associated with Pi10 change.

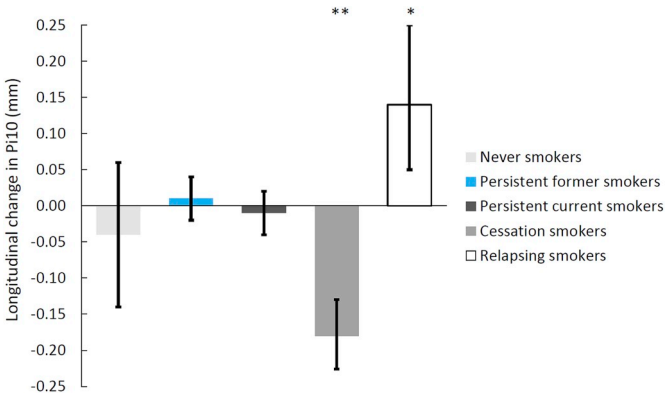

Fig. 2. Estimated longitudinal change in Pi10 stratified by change in smoking status. Pi10 change is the estimated change in Pi10 that is adjusted for gender, age, BMI, pack years, TLC, BDR, smoking status, and LAA%-950 at both visits using a linear mixed model. Whiskers of each bar indicate the 95% confidence interval. *p < 0.05. **p < 0.001.

4. Discussion

In this study, Pi10 was used to express a global state of airway wall thickening based on inspiratory CT. Our results showed that this measurement is a predictor of the severity of spirometric impairment and quality of life in all GOLD stages, where a high Pi10 was associated with a worse FEV_1%-predicted, SGRQ, and 6MWD. Furthermore, Pi10 significantly decreased in subjects that stopped smoking within the five-year follow-up period, whereas subjects that started smoking during this period significantly increased in Pi10. This strongly suggests that Pi10 can be a measure of smoking related airway wall thickening and can be reduced by a smoking cessation intervention.

The presented results support the hypothesis that Pi10 is significantly higher in current smokers compared to former smokers and that this significant difference is persistent throughout the GOLD stages. This effect is most likely because Pi10 in current smokers reflects a combination of airway inflammation and airway remodeling, while the effect of inflammation is less in former smokers. This conclusion is supported by the finding that Pi10 in subjects that have never smoked is significantly lower compared to both former and current smokers.

The presented results support previously studies that found inverse correlations with airway measurements and clinical characteristics such as FEV_1, FEV_1%-predicted and FEV_1/FVC [4–6,17]. We additionally showed that there is a significant association between Pi10 and quality of life (i.e. 6MWD and SQRQ). These associations were found to be similar for both males and females. Importantly, a high Pi10 was associated with a worse FEV_1%-predicted, SGRQ, and 6MWD even in subjects without spirometric impairment that are assumed to be disease free, confirming previous findings by Regan et al. [18], and suggesting that Pi10 may be a biomarker of smoking related airway injury in those without COPD. Furthermore, we showed that the associations between Pi10 and FEV_1%-predicted, SGRQ, and 6MWD remain for subjects without emphysema, suggesting that Pi10 can serve as an independent marker of disease severity in non-emphysematous COPD.

A study by Mets et al. [3] showed that Pi10 independently predicts the presence of COPD in a lung cancer screening cohort. We replicated

Table 3
Linear mixed model analyses identifying longitudinal Pi10 changes for a change in smoking status.

Group	n	Pi10		Pi10 change[a] [95%CI]	p-value[b]
		Visit 1	Visit 2		
Never smokers	46	1.69	1.72	−0.04 [-0.14, 0.06]	0.47
Persistent former smokers	993	2.20	2.24	0.01 [-0.02, 0.04]	0.53
Persistent current smokers	631	2.31	2.35	−0.01 [-0.04, 0.02]	0.46
Cessation smokers	203	2.39	2.27	−0.18 [-0.23, −0.13]	< 0.001
Relapsing smokers	49	2.17	2.33	0.14 [0.05, 0.23]	0.002

[a] Pi10 change is the estimated change in Pi10 that is adjusted for gender, age, BMI, pack years, TLC, BDR, and LAA%-950 at both visits using a linear mixed model.
[b] p-value of the estimated change in Pi10 are Bonferroni adjusted. n = number of subjects; Pi10 = airway wall thickness expressed as the square root of wall area at airways with a perimeter of 10 mm; LAA%-950 = the percentage of low-attenuation lung area below −950 Hounsfield units; BMI = body mass index; TLC = total lung capacity; BDR = bronchodilator responsiveness; 95%CI = 95%-confidence interval.

these results using the data from COPDGene and confirmed that including Pi10 significantly improves the prediction of the presence of COPD (this additional analysis and the results are described in Section D of the online data supplement). We further showed that the effect of Pi10 on the odds of having COPD was significantly higher in former smokers compared to current smokers.

Previous studies have shown that emphysema [19], bronchodilator responsiveness [20], and total lung capacity [21] on CT have an influence on airway wall thickness. We therefore adjusted for these factors in the linear regression and mixed model analyses. Even after accounting for the effects of emphysema, bronchodilator responsiveness and total lung capacity, Pi10 was found to be an independent predictor of the presence and severity of COPD. Our findings support the potential utility of Pi10 as an automatically computed biomarker that might be routinely used in subjects undergoing lung cancer screening, and potentially also in clinical trials of treatment for smoking-related airway diseases. The primary advantage of the Pi10 in this context is that it provides an index score that summarizes luminal perimeters and airway wall areas throughout the entire airway tree into a single number by which the airway can be directly compared between subjects.

In addition to the results on the association between smoking status and clinical traits, the effect of change in smoking status was evaluated. We showed that subjects who stopped smoking had a significant decrease in Pi10. On the other hand, subjects who recommenced smoking showed an increase in Pi10. The effect of smoking cessation on airway dimensions could be used to encourage patients to quit smoking; subsequent CT scans could be used to document the effect of smoking cessation on bronchial wall thickness. Additionally, Pi10 may be a useful biomarker for evaluating airway remodeling over time, especially in longitudinal studies where the effect of therapy is being evaluated.

A limitation of this study is that Pi10 can be influenced by airway wall thickness, bronchial lumen area, and the total size of the bronchial tree. This means that a high Pi10 can be a result of an increase in airway wall thickness, a decrease in luminal area, or both. Additionally, Pi10 provides no information on the spatial distribution of bronchial changes. Since Pi10 is a measure of the global state of the airways, lobar differences are not considered. It is therefore possible that including additional airway measures of generation-specific lumen area or wall thickness might further improve the prediction of presence and severity of smoking-related airway injury. However, obtaining these measures and performing quality assurance on them is more time-consuming than the automated Pi10 method presented here. A further limitation is that the effect of medications cannot be systematically assessed.

We conclude that Pi10 predicts the presence of airflow limitation and the severity of dyspnea, quality of life, and spirometric impairment in cigarette smokers. In addition, we found that Pi10 is higher in current smokers as compared to former smokers, which may be because of partially reversible smoking related inflammation. Pi10 can be used as a measure for smoking related airway injury that can provide important information regarding longitudinal changes in airway wall thickness.

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Take-home message

Airway wall thickening on CT may provide a marker of smoking-related airway injury, even in subjects without COPD.

CRediT authorship contribution statement

Jean-Paul Charbonnier: Conceptualization, Funding acquisition, Formal analysis, Formal analysis, Writing – review. **Esther Pompe:** Conceptualization, Funding acquisition, Formal analysis, Writing – review. **Camille Moore:** Formal analysis. **Stephen Humphries:** Formal analysis, Funding acquisition. **Bram van Ginneken:** Formal analysis, Funding acquisition. **Barry Make:** Conceptualization, Funding acquisition, Writing – review. **Elizabeth Regan:** Conceptualization, Funding acquisition. **James D. Crapo:** Conceptualization, Funding acquisition, Writing – review. **Eva M. van Rikxoort:** Conceptualization, Funding acquisition, Formal analysis, Writing – review. **David A. Lynch:** Conceptualization, Funding acquisition, Formal analysis, Writing – review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2018.11.014.

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