# Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation

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ABSTRACT    Airway wall thickness and emphysema contribute to airflow limitation.

We examined their association with lung function decline and development of airflow limitation in 2021 male smokers with and without airflow limitation. Airway wall thickness and emphysema were quantified on chest computed tomography and expressed as the square root of wall area of a 10-mm lumen perimeter ($Pi_{10}$) and the 15th percentile method ($Perc_{15}$), respectively. Baseline and follow-up (median (interquartile range) 3 (2.9–3.1) years) spirometry was available.

$Pi_{10}$ and $Perc_{15}$ correlated with baseline forced expiratory volume in 1 s ($FEV_1$) (r=−0.49 and 0.11, respectively (p<0.001)). Multiple linear regression showed that $Pi_{10}$ and $Perc_{15}$ at baseline were associated with a lower $FEV_1$ after follow-up (p<0.05). For each SD increase in $Pi_{10}$ and decrease in $Perc_{15}$ the $FEV_1$ decreased by 20 mL and 30.2 mL, respectively. The odds ratio for developing airflow limitation after 3 years was 2.45 for a 1-mm higher $Pi_{10}$ and 1.46 for a 10-HU lower $Perc_{15}$ (p<0.001).

A greater degree of airway wall thickness and emphysema was associated with a higher $FEV_1$ decline and development of airflow limitation after 3 years of follow-up.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation and increased lung function decline [1]. Airflow limitation is caused by emphysema and airway wall remodelling (*i.e.* airway wall thickening and bronchiolar obliteration) [2]. COPD is a heterogeneous disease and it is recognised that the degree in which emphysema and airway wall disease contribute to the development of airflow limitation and lung function impairment varies within each individual [3, 4].

Quantitative computed tomography (CT) can been used to quantify the extent of emphysema and airway wall thickness. Several studies found associations of emphysema and airway wall thickness with lung function, the presence of COPD and clinical symptoms. Previous studies showed an association between CT quantified emphysema and a more rapid lung function decline in smokers and subjects with COPD [5–9].

However, whether airway wall thickness is independently associated with a stronger decline in lung function has not yet been studied. Chest CT examinations performed in clinical practice or for screening purposes may enable identification of subjects at risk for COPD or a rapid decline in lung function.

The objective of the present study was to determine the association of airway wall thickness and emphysema with lung function decline or development of forced expiratory volume in 1 s ($FEV_1$)/forced vital capacity (FVC) <0.70 after a follow-up period of 3 years in a cohort of former and current smokers without and with airflow limitation.

## Methods

### Participants

The study was conducted among male participants of the Dutch-Belgian Lung Cancer Screening Trial (NELSON) [10]. The NELSON trial is a population-based, CT screening trial for lung cancer. Inclusion criteria have been published previously [8]. In short, participants meeting the inclusion criteria of having smoked >10 cigarettes·day$^{-1}$ for >30 years or >15 cigarettes·day$^{-1}$ for >25 years and who were fit enough to potentially undergo thoracic surgery were invited to participate. Potential fitness for surgery was determined by the ability to walk up two flights of stairs. Baseline details on smoking habits were gathered through questionnaires, which included questions about duration of smoking, smoking history and smoking status at enrolment (current or former smoker). At the start of the study it was decided that this study provided the opportunity to also assess lung function. To investigate this in relation to CT measurements, spirometry was performed in a random sample at the University Medical Center Utrecht (Utrecht, the Netherlands) and the University Medical Center Groningen (Groningen, the Netherlands).

The NELSON trial was approved by the Dutch Ministry of Health on December 23, 2003 and by the ethics committee of the two participating hospitals (University Medical Center Utrecht and University Medical Centre Groningen) (approval number 03/040) The NELSON trial is registered at www.trialregister.nl (trial number ISRCTN63545820). Informed consent was obtained from all participants.

### Pulmonary function testing

Pulmonary function tests (PFTs) were carried out according to current European Respiratory Society and American Thoracic Society guidelines and included $FEV_1$, FVC and $FEV_1$/FVC [11]. Reversibility of airflow limitation was not assessed. PFTs were performed at baseline and follow-up. The PFTs were performed on the same day as the CT scan. Airflow limitation was defined according the 2012 Global Lung Function Initiative (GLI) equations as a z-score $< -1.645$ and secondary analyses according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as an $FEV_1$/FVC <70% [1, 12, 13]. Predicted values, standardised residuals and the lower limits of normal were calculated using the 2012 GLI equations [13].

### CT scanning

All participants received low-dose CT, with a 16-detector row multidetector CT scanner (Brilliance 16P; Philips Medical Systems, Cleveland, OH, USA or Sensation-16; Siemens Medical Solutions, Forchheim, Germany) at baseline and follow-up. Scan data were obtained in spiral mode, with 16×0.75 mm collimation and in full inspiration. No spirometric gating was applied [14]. Axial images were reconstructed with 1.0 mm thickness at a 0.7 mm increment. All scans were reconstructed with a soft reconstruction filter (Philips B; Philips Medical Systems, Cleveland, OH, USA; Siemens B30f; Siemens Medical Solutions, Forchheim, Germany) at a 512×512 matrix. Exposure settings were 30 mAs at 120 or 140 kVp, depending on the participant's weight. This low-dose CT protocol has previously been used to quantify emphysema in COPD patients and heavy smokers [8, 15, 16]. All quantifications were performed with CIRRUS Lung 12.03 (http://cirrus.diagnijmegen.nl).

*Quantification of emphysema*

The lungs were automatically segmented, and a noise reduction filter was applied to decrease the influence of noise on the quantitative measurements. Severity of emphysema was based on the 15th percentile method (Perc15). This technique provides the Hounsfield Units point below which 15% of the voxels are distributed. The lower the Perc15 values are, *i.e.* closer to −1000 HU, the more emphysema is present. To adjust for variations in inspiration level between participants during CT acquisition, Perc15 was adjusted to the predicted total lung capacity [17]. Total lung capacity was derived from appropriate reference equations [13]. We adjusted Perc15 by multiplying Perc15 with CT total lung volume and dividing this by the predicted total lung capacity. Throughout this article Perc15 refers to adjusted values for differences in inspiration levels.

*Quantification of airway wall thickness*

The airway tree was automatically segmented based on region growing and morphological operations [18, 19]. On average, airways up to the eighth generation were included in the segmentation. Throughout the entire segmented airway tree, cross-sectional image planes perpendicular to the local airway direction were defined at 1 mm spacing. Cross-sectional planes obtained from the trachea, main bronchi or bifurcations were discarded automatically as areas where accurate measurements were not possible. For all remaining cross-sections, accurate lumen and wall borders were determined by analysing intensity profiles of 72 rays pointing from the centre of the lumen outward using an intensity integration technique to account for partial volume effects [20]. On average this resulted in 800 cross-sections per scan. For each cross-section, the lumen perimeter and wall area were calculated. A linear regression of the square root of wall area *versus* the lumen perimeter was calculated for all cross-sections (fig. 1) [21]. The square root of wall area of a 10-mm lumen perimeter (Pi10) was calculated and used as a measurement of airway wall thickness. For each CT scan a random selection of cross-sections of the detected airway walls borders was visually inspected to verify measurement accuracy.

*Statistical analyses*

Mean±SD values were calculated for normally distributed data and median (interquartile range) for non-normally distributed data. T-tests and Chi-squared tests were used to test differences between groups as appropriate. Pearson's correlations were used to establish associations between variables at baseline. FEV1 at the end of the observation period was the primary end-point and was analysed by multiple linear regression analysis. Airway wall thickness (Pi10) and emphysema (Perc15) were the main explanatory factors. Adjustments were made for baseline FEV1, age, height, pack-years and smoking status (current/former smoker). In a second model, an interaction term between airway wall thickness and emphysema was added. In a third model, an interaction of smoking status and pack-years with Pi10 and emphysema was added.

Multiple linear logistic regression analysis was performed to examine if Perc15 and Pi10 were associated with the development of airflow limitation after follow-up in subjects without airflow limitation at baseline. Adjustment was made for FEV1 z-score, age, pack-years and smoking status. A p-value <0.05 was considered significant. All statistical analyses were performed using SPSS 20 (SPSS, Chicago, IL, USA).

## Results

### Baseline demographics and lung function

In total, 2211 subjects underwent CT and follow-up spirometry. Airway wall thickness measurements were not available in 190 subjects because of a technical failure, resulting in 2021 subjects being included in this study. There were no significant differences in age, pack-years, smoking status and FEV1 decline between subjects excluded because of missing airway wall thickness measurements and those who were included (data not shown).

Mean±SD age was 60.5±4.9 years. According to the GLI, 408 (20.2%) subjects had airflow limitation at baseline. Using the GOLD criteria, approximately one-third of the subjects (n=697; 34.5%) had airflow limitation. Mean±SD FEV1 was 3.64±0.37 L, which is −0.41±1.16 standardised residuals. Approximately half of the subjects were current smokers at the start of the study (n=1113; 55.1%), and the mean±SD of pack-years for the entire study group was 42.0±19.9. There was a significant difference in mean±SD FEV1 standardised residuals between current and former smokers, −0.42±1.16 and −0.26±1.17 (p=0.02), respectively. There was also a difference in pack-years, 39.2±16.0 and 40.9±17.3 (p=0.045), respectively. Further details on baseline demographics and lung function are presented in table 1.

### Baseline airway wall thickness and emphysema

Mean±SD Perc15 was −934.8±30.1 HU and Pi10 was 2.42±0.59 mm. According to the 2012 GLI equations, participants with airflow limitation had more emphysema and thicker airway walls than participants without airflow limitation (Perc15: −945.3±18.6 and −931.7±31.2 HU, respectively; Pi10: 2.83±0.59
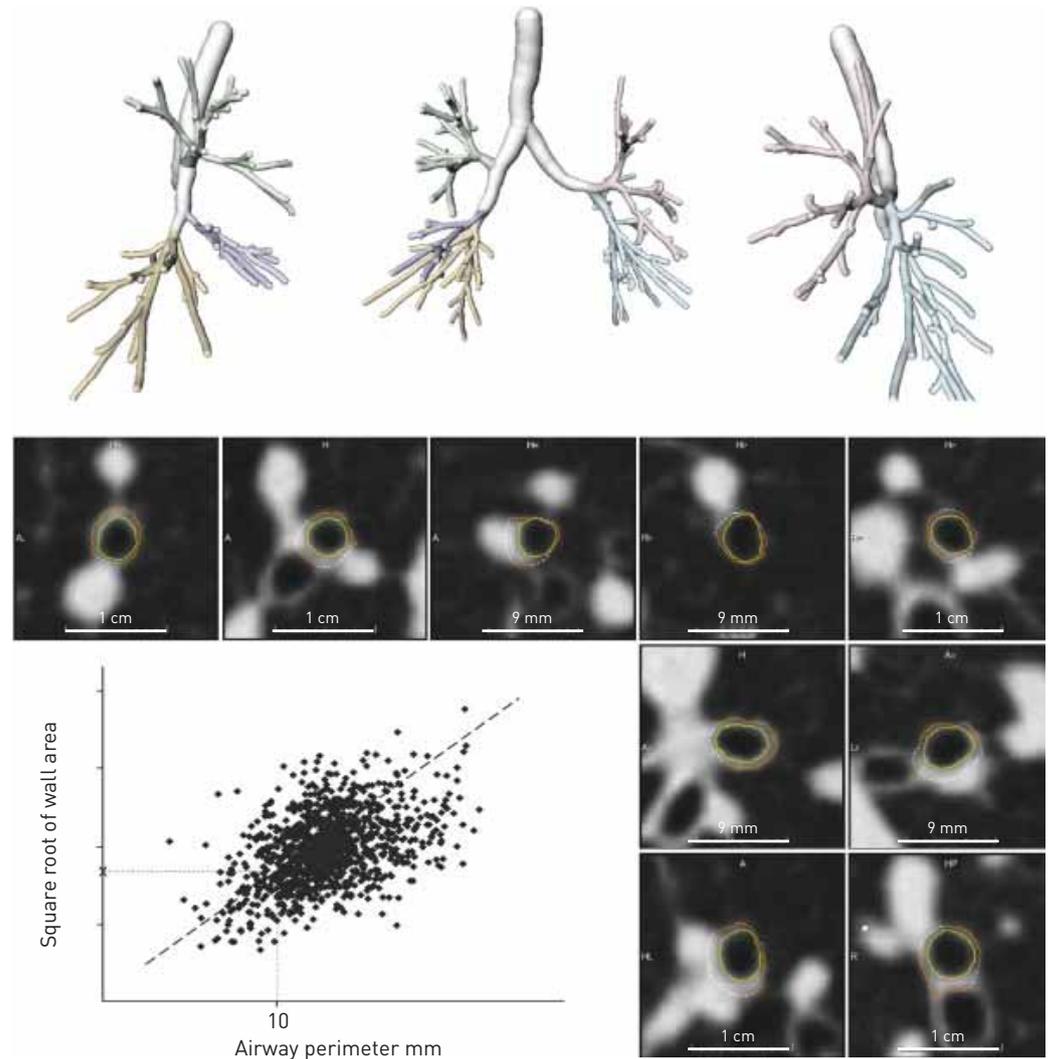
FIGURE 1 Illustration of the automatic quantification of airway wall thickness. The airway tree was automatically segmented based on region growing and morphological operations. Throughout the entire segmented airway tree, cross-sectional image planes perpendicular to the local airway direction were defined at 1-mm spacing. For all remaining cross-sections, accurate lumen and wall borders were determined by analysing intensity profiles of 72 rays pointing from the centre of the lumen outward using an intensity integration technique to account for partial volume effects. A linear regression of the square root of wall area *versus* the lumen perimeter was calculated for all cross-sections. The square root of wall area for a theoretical airway with 10-mm lumen perimeter was calculated, which was used as a measurement of airway wall thickness. Reproduced from [21] with permission from the publisher.

and 2.31±0.55 mm, respectively; all p<0.001). When using the GOLD criteria for airflow limitation the results were similar, but the differences were smaller (Perc15: −942.8±17.6 *versus* −930.6±34.3 HU; Pi10: 2.70±0.61 *versus* 2.27±0.53 mm; all p<0.001).

At univariate analysis, participants with a higher Pi10 and lower Perc15 had a lower FEV1 (r=−0.49 and 0.11, respectively, p<0.001). A 1-mm higher Pi10 resulted in a 25-mL lower FEV1 and a 10-HU lower Perc15 resulted in a 6-mL lower FEV1 (p<0.001). There was a low significant correlation between Perc15 and Pi10 (r=0.12, p<0.001). Current smokers had a higher Pi10 than former smokers; 2.53±0.61 mm and 2.37±0.58 mm, respectively (both p<0.001). Current smokers had a higher Perc15 than former smokers; −933.0±18.6 HU and −942.6±17.3 HU, respectively. No significant correlation was found between pack-years and Perc15 or Pi10.

### Follow-up measurements
#### Decline of FEV1

Median (interquartile range) time of follow-up was 3.0 (2.9–3.1) years. Mean±SD FEV1 decline was 197±71 mL. Multivariate analyses, with correction for baseline FEV1, years in study, height, pack-years,

**TABLE 1** Baseline demographics, pulmonary function and airway wall thickness and emphysema

| | |
|---|---|
| **Age years** | 59.8±5.3 |
| **Height cm** | 178±6.3 |
| **Pack-years** | 42.0±19.9 |
| **Current smoker** | 1113 (55.1) |
| **FEV1 L** | 3.64±0.37 |
| **FEV1 standardised residuals** | −0.41±1.16 |
| **FEV1/FVC z-score <−1.645** | 408 (20.2) |
| **FEV1/FVC <70%** | 697 (34.5) |
| **GOLD status** | |
| No COPD | 1488 (67.3) |
| GOLD I | 466 (21.1) |
| GOLD II | 222 (10) |
| GOLD III | 35 (1.5) |
| **Pi10 mm** | 2.42±0.59 |
| **Perc15 Hounsfield Units** | −934.8±30.1 |

Data are presented as mean±SD or n (%). FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; Pi10: square root of wall area of a 10-mm lumen perimeter; Perc15: 15th percentile method.

smoking status and age, showed that lower $Pi_{10}$ was associated with a lower $FEV_1$ after follow-up (p=0.002). A 1-mm higher $Pi_{10}$ resulted in a 34-mL lower $FEV_1$ after follow-up. Additionally, $Perc_{15}$ was associated with a lower $FEV_1$ after follow-up (p=0.006) and a 10-HU lower $Perc_{15}$ was associated with a 10-mL lower $FEV_1$ after follow-up. Smoking status, baseline $FEV_1$, age and height were also associated with $FEV_1$ after follow-up. The effect sizes of these parameters on $FEV_1$ after follow-up are presented in table 2. There was no significant interaction between $Pi_{10}$ and $Perc_{15}$ (p=0.703). When comparing the effects of $Pi_{10}$ and $Perc_{15}$ on $FEV_1$ by standardisation, the effect of one SD change in $Pi_{10}$ resulted in a 20-mL lower $FEV_1$ after follow-up and one SD change in $Perc_{15}$ resulted in a 30.2-mL lower $FEV_1$ after follow-up. Interactions of smoking status and pack-years with $Pi_{10}$ and $Perc_{15}$ were not significant (p>0.05).

*Development of airflow limitation at follow-up*

1613 (79.8%) participants had no airflow limitation at baseline according to the 2012 GLI equations, of which 172 (10.7%) developed airflow limitation at follow-up. Using the GOLD criteria this was 1324 (65.5%), of which 291 (22%) developed airflow limitation at follow-up. Subjects who developed airflow limitation (2012 GLI equations) at follow-up had significantly more emphysema (p<0.001) and thicker airway walls at baseline compared to those who did not develop airflow limitation ($Perc_{15}$: −937.6±17.4 *versus* −931.5±33.1 HU, respectively; $Pi_{10}$: 2.59±0.54 *versus* 2.28±0.55 mm, respectively).

Both $Perc_{15}$ and $Pi_{10}$ were significantly and independently associated with development of airflow limitation according to the 2012 GLI equations after 3 years of follow-up. A 10-HU lower $Perc_{15}$ resulted in an odds ratio of 1.46 and a 1-mm higher $Pi_{10}$ resulted in an odds ratio of 2.45 (both p<0.001). When

**TABLE 2** Results from the multiple linear regression analysis with forced expiratory volume in 1 s (FEV1) after follow-up as primary end-point

| Covariable | Increment or comparison | Changes in FEV1 after follow-up per unit change in covariable β | 95% CI | p-value |
|---|---|---|---|---|
| **Years in study** | +1 year | −38 mL | −60−−16 | 0.001 |
| **Baseline FEV1** | −10 mL | −8.8 mL | −8.6−−9.0 | <0.001 |
| **Smoking status** | Current *versus* former | −55 mL | −77−−33 | <0.001 |
| **Age years** | +1 year | −5 mL | −7−−3 | <0.001 |
| **Height cm** | +1 cm | +3 mL | 1−5 | 0.006 |
| **Pack-years** | +10 pack-years | −10 mL | −15−−5 | <0.001 |
| **Pi10 mm** | +1 mm | −34 mL | −56−−12 | 0.002 |
| **Perc15 Hounsfield Units** | 10 Hounsfield Units lower | −10 mL | −15−−5 | 0.006 |

Pi10: square root of wall area of a 10-mm lumen perimeter; Perc15: 15th percentile method.
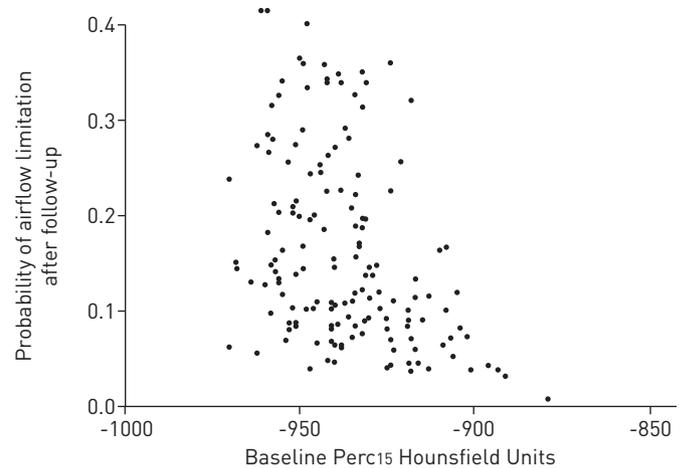
FIGURE 2 Results of the multivariable adjusted logistic regression analysis showing the probability of participants without airflow limitation at baseline having airflow limitation after follow-up according to the baseline 15th percentile method ($Perc_{15}$). Subjects with lower $Perc_{15}$ have a higher probability of airflow limitation after follow-up.

using the GOLD criteria for airflow limitation, a similar odds ratio for $Pi_{10}$ was found, but this was lower for $Perc_{15}$. A 10-HU lower $Perc_{15}$ resulted in an odds ratio of 1.26 and a 1-mm higher $Pi_{10}$ resulted in an odds ratio of 2.44 (both $p<0.001$). 289 subjects at baseline were classified as having airflow obstruction according to GOLD but not according to the 2012 GLI equations. In these subjects, the odds ratio of developing airflow limitation according to the 2012 GLI equations was 1.86 for 1-mm higher $Pi_{10}$ and 1.23 for 10-HU lower $Perc_{15}$ ($p=0.039$ and $0.024$, respectively). Figures 2 and 3 illustrate the multivariable adjusted probability of developing airflow limitation (2012 GLI equations) according to the baseline values of $Perc_{15}$ and $Pi_{10}$. Age, pack-years and smoking status were also independently associated with development of airflow limitation.

## Discussion

In this large study of former and current male smokers without and with mild airflow limitation, we showed that both emphysema and airway wall thickness are independently associated with a lower $FEV_1$ after an average 3-year follow-up period. In addition, we showed that emphysema and airway wall thickness were also associated with the development of airflow limitation in subjects without airflow limitation at baseline. These results indicate that the assessment of structural changes in the lungs by CT in former and current smokers may allow clinicians to identify subjects who will show a larger $FEV_1$ decline or will develop airflow limitation.
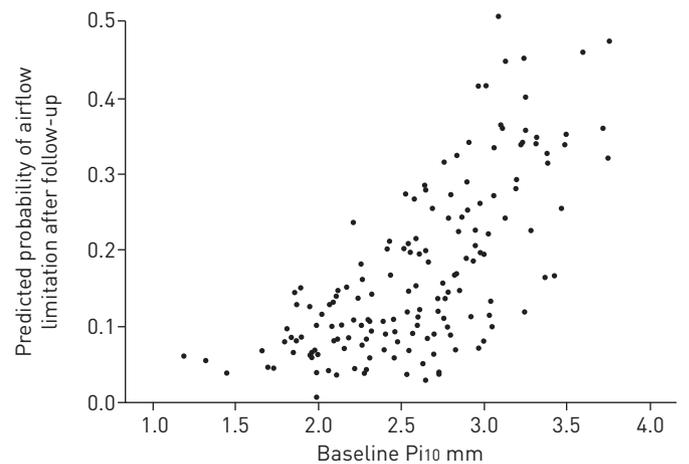


FIGURE 3 Results of the multivariable adjusted logistic regression analysis showing the probability of having airflow limitation after follow-up according to baseline square root of wall area of a 10-mm lumen perimeter ($Pi_{10}$) values in participants without airflow limitation at baseline. Participants with higher $Pi_{10}$ have a higher probability of airflow limitation after follow-up.

A few studies have examined the relationship between airway wall thickness on CT and lung function decline and development of COPD. OHARA et al. [22] demonstrated that increment in the percentage of airway wall area of the total lumen area was associated with annually higher changes in FEV1 in 83 male COPD subjects. However, they only reported results from univariate analyses and did not provide effect sizes. Other cross-sectional studies have shown that a higher airway wall thickness is associated with lower pulmonary function and the presence of COPD [5, 23–26].

Airway wall thickness has been associated with other outcome measures. GRYDELAND et al. [27] showed that higher airway wall thickness is related with respiratory symptoms (dyspnoea, cough and wheeze). HAN et al. [28] showed that higher airway wall thickness was associated with a greater risk of having an acute COPD exacerbation in COPD patients, independent of emphysema. In their study, each 1-mm increase of Pi10 was associated with a 1.8-times increase in annual exacerbation rate. MARTINEZ et al. [29] demonstrated that thicker airway walls were associated with higher scores on the St George's Respiratory Questionnaire and the BODE index (body mass index, airflow obstruction, dyspnoea and exercise capacity) [29]. Together, these studies showed that airway wall thickness is associated with clinically relevant outcomes.

The finding that CT-quantified emphysema is associated with accelerated lung function decline seems robust given the fact that several other groups have reported similar findings [5–9]. YUAN et al. [7] showed that there was a trend between automatically quantified low-attenuation areas on CT and follow-up lung function in smokers without COPD. Although their findings were not significant, the direction of effect is the same as ours. Our findings complement the findings of VESTBO et al. [6], which reported that COPD subjects with emphysema (defined as >10% low-attenuation areas < −950 HU) have an additional decline in FEV1 of $13\,mL\cdot year^{-1}$ compared to those without emphysema. In that study, subjects with moderate, severe or very severe COPD were included but subjects with an earlier stage of the disease were not, unlike in our study. Thus, we extend their observations to early emphysema.

COPD is defined by the presence of airflow limitation [1]. Airflow limitation is, however, caused by a complex interplay of structural lung changes, i.e. emphysema and large and small airway disease. The role of airway wall thickening seems to decrease in more severe COPD (GOLD III/IV) as the relative importance of airway wall thickening reduces in subjects with increasing COPD severity [3]. In our study, only subjects with mild COPD were included. Therefore, we could not truly examine if the relative importance of airway wall thickness decreases with increasing COPD severity. In addition, emphysema and airway wall thickening may already be present but not yet result in COPD. The clinical relevance of airway wall thickening in subjects without COPD is unclear to date, but as we showed that airway wall thickness is associated with FEV1, it may be clinically relevant in current and former smokers without COPD. Detecting and quantifying these structural changes by CT may become relevant in improving the prognosis of individual subjects [30].

Our study included smokers with and without mild airflow limitation who are probably in an early phase of the pathophysiological process of COPD. Recently, it was shown that small airways are probably affected earlier in the pathophysiological cascade of COPD [3]. Furthermore, airway wall thickness and emphysema were both independently associated with a lower FEV1 at follow-up. This indicates that it is of importance to assess both emphysema and airway wall thickness when analysing chest CT scans. However, the advantage of CT scans over the presence of symptoms of dyspnoea, cough and wheeze in predicting lung function decline and/or the development of COPD in a population of smokers needs to be addressed in future studies.

A strength of this study is the large number of included participants (n=2021) with and without mild airflow limitation and a median follow-up of 3 years. Another strength is the use of CT scans with low radiation exposure. In view of the annually increasing number of CT scans being performed, further knowledge on the prognostic value of structural lung changes present on CT scans may become increasingly important. If lung cancer screening may be implemented as a population-based screening, additional information next to lung cancer may improve the relevance of a (national) screening programme.

A limitation of the study is the use of pre-bronchodilator lung function values. However, because both baseline and follow-up spirometry were performed without bronchodilatation, this should not have had an effect on the assessment of FEV1 decline. Still, due to lack of post-bronchodilator spirometric values, a number of subjects could be falsely classified as having airflow limitation. Another limitation is that no females were included in the current study. A previous study showed that at a cross-sectional level, females have a lower Pi10 when compared to males [17]. However, it is not known if the association of Pi10 with lung function decline differs between females and males. Future studies could determine whether our findings can be generalised to females. Different exposure settings were used for subjects weighing <80 kg and >80 kg, which could have influenced Perc15 measurements. However, in this cohort of subjects without COPD or mild COPD we do not foresee a strong correlation between weight and lung function. Finally, 190 scans were not included in the analyses because of segmentation errors, such as problems with

the automatic identification of all bronchial walls. However, these subjects did not differ in clinical parameters with those included.

In conclusion, the current study indicates that more severe airway wall thickness and emphysema on CT scans are independently associated with accelerated FEV1 decline and with the development of airflow limitation in male smokers. Chest CT scans may gain a role in the selection of smokers with and without mild COPD who will suffer from more severe lung function decline and/or development of COPD.

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