



Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking

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ABSTRACT: We investigated how quantitative high-resolution computed tomography (HRCT) measures of emphysema and airway wall thickness (AWT) vary with sex, age and smoking history.

We included 463 chronic obstructive pulmonary disease (COPD) cases and 431 controls. All included subjects were current or ex-smokers aged ≥ 40 yrs, and all underwent spirometry and HRCT examination. The HRCT images were quantitatively assessed, providing indices on lung density and airway dimensions.

The median (25–75th percentile) %LAA950 (% low-attenuation area < -950 HU) was 8.9 (3–19) and 4.7 (1–16) in male and female COPD cases, respectively, and 0.71 (0.3–1.6) and 0.32 (0.1–0.8) in male and female controls, respectively. %LAA950 was higher in ex-smokers and increased with increasing age and with increasing number of pack-years. The mean \pm SD standardised AWT was 0.504 ± 0.030 and 0.474 ± 0.031 in male and female COPD cases, respectively, and 0.488 ± 0.028 and 0.463 ± 0.025 in male and female controls, respectively. AWT decreased with increasing age in cases, and increased with the degree of current smoking in all subjects.

We found significant differences in quantitative HRCT measures of emphysema and AWT between varying sex, age and smoking groups of both control and COPD subjects.

KEYWORDS: Airway, chronic obstructive pulmonary disease, computed tomography, emphysema, sex, smoking

Chronic obstructive pulmonary disease (COPD) is a complex disorder in which numerous parameters interact to produce chronic airflow limitation [1]. There are differences in the extent and expression of COPD between individuals, and it is thought that genetics play a key role in the development of the disease [2]. These differences are exemplified in the differential response to cigarette smoke seen in males and females [3, 4]. However, most studies investigating the extent of COPD and the differences between sexes are based on lung function tests and respiratory symptoms [5, 6] which, unfortunately, do not provide a complete picture of COPD.

Quantitative computed tomography (CT) has become a popular technique to quantify the changes in lung structure, and to separate different subtypes of COPD according to the contribution of airways disease and emphysema [2, 7, 8]. Other studies have examined the sex effects on the anatomical changes and have found that females have less emphysema at all levels of airflow obstruction [3, 9]. However, there is very

limited data available on how CT derived airway wall thickness (AWT) varies with age, sex and smoking history [10, 11]. Such knowledge may work to increase our understanding of the natural course of COPD in males and females.

The objective of the present study was to quantify the emphysema and AWT in a large patient and community-based sample of ever-smokers, and to determine how these anatomical variables interact with sex, age and smoking to produce the clinical disorder known as COPD.

METHODS

This single centre study was conducted between January 2003 and January 2005 in Bergen, Norway. All subjects gave informed consent, and the local ethics committee and review board (Bergen) approved the study. The subjects included in the current study had all participated in the GenKOLS (Genetic COPD) study [12, 13], and constituted approximately half of the GenKOLS population (894 out of 1,909 subjects) who received an optional high-resolution CT (HRCT) scan. Subjects were recruited from a

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hospital patient register and from two general population studies [14, 15], and a total of 463 COPD cases and 431 controls were included. Enrolment criteria were: 1) self-reported Caucasian; 2) aged >40 yrs; 3) current or former smoker with ≥ 2.5 pack-yrs of smoking history; and 4) no severe α_1 -antitrypsin deficiency. Asthmatics were not excluded. For a complete list of inclusion and exclusion criteria refer to the supplementary data.

Subjects performed spirometry according to the American Thoracic Society standards [16], using a Vitalograph 2160 Spirometer (Vitalograph Ltd, Maids Moreton, UK) pre- and post-bronchodilation with 400 μ g salbutamol. Subjects were assessed at least 6 weeks after any respiratory infection, but were not asked to withhold regular medication. Local reference values for forced expiratory volume in 1 s (FEV₁) and forced expiratory vital capacity (FVC) were used [17]. COPD cases had post-bronchodilator FEV₁/FVC of <0.70 and an FEV₁ <80% predicted [1]. Controls had post-bronchodilator FEV₁/FVC of >0.70 and an FEV₁ >80% pred.

Computed tomography

The HRCT scans were all performed using a GE LightSpeed Ultra CT scanner (120 kVp, 200 mA; GE Healthcare, Milwaukee, WI, USA), at suspended full inspiration (apex to base) using 1-mm slice thickness at 20-mm intervals, producing an average of 13.4 ± 1.6 slices per subject. The CT scans were reconstructed using both a low spatial frequency reconstruction algorithm (standard) for density measurements, and a high spatial frequency algorithm (bone) for airway measurements. All images were transferred to the James Hogg iCAPTURE Centre (Vancouver, BC, Canada) for quantitative analysis as previously described [18, 19]. Briefly, the lungs were segmented from the chest wall and central blood vessels and airways using a modified border tracing algorithm with prior position knowledge [20]. CT derived lung volume was also obtained. To obtain a proxy for inflation level, the CT derived total lung volume was divided by the predicted total lung capacity [21]. The extent of emphysema was assessed using the percentage of lung voxels with X-ray attenuation values less than (low attenuation areas; %LAA) -950 Hounsfield units (HU) (%LAA950). The -950 HU cut-off has been shown to be appropriate for this CT acquisition technique [22], but the amount of emphysema was also calculated using cut-offs of -910 HU and -856 HU (data not shown). Airways cut in cross-section (short to long axis greater than 2:3) were identified on the CT scans and measured using the Full Width At Half Maximum algorithm [8]. To reduce technical errors associated with very small airways, only airways with an internal perimeter >6 mm were included. To avoid potential bias issues surrounding different distribution of airway sizes between subjects, a standardised measure for AWT was derived for each subject by plotting the square root of the airway wall area against the internal perimeter of each measured airway (fig. 1). The resulting regression line was used to calculate the square root of the wall area for a 'theoretical airway' with an internal perimeter of 10 mm (AWT-Pi10) [2].

Statistical analysis

Proportions were tested using Chi-squared tests, while the mean was compared using ANOVA and the median using the

Kruskal–Wallis test. The associations of ln(%LAA) and AWT-Pi10 to the explanatory variables were examined with multiple linear regression. In these analyses, the %LAA values were transformed using the natural logarithm, because both the %LAA values and the regression residuals were right skewed. The following interactions were tested separately, based on an *a priori* assessment: sex \times age, sex \times pack-yrs and age \times current smoking *versus* %LAA, and sex \times age and sex \times current smoking *versus* AWT-Pi10. We also tested the COPD case–control–status \times pack-yrs interaction *versus* both %LAA and AWT-Pi10 on the whole material. A significance level of 0.05 was applied. All analyses were performed with STATA 9 (StataCorp LP, College Station, TX, USA).

RESULTS

For both sexes, COPD cases were older than controls, more COPD cases were current smokers and their total number of pack-years was higher than the controls (table 1). The number of pack-years in both COPD cases and controls was higher in males than in females, while the prevalence of current smokers was higher in females than in males. Male and female COPD cases were equally distributed across the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages; ~60% classified as stage II, 28% as stage III and the rest as stage IV.

The median %LAA950 scores were higher in COPD cases and higher in males (table 2). AWT-Pi10 was higher in COPD cases and higher in males, regardless of disease status (table 2). Both lumen area and number of airways analysed was slightly higher in males, but there were no significant differences between COPD cases and controls.

The %LAA950 increased with increasing age in both COPD cases and controls (table 2). The AWT-Pi10 decreased slightly with increasing age in COPD cases, but did not vary by age in controls. %LAA950 was higher in ex-smokers than in current smokers. It also increased slightly with total smoking consumption in terms of pack-years, but did not vary by current number of cigarettes smoked daily. This pattern was seen regardless of disease status. The AWT-Pi10 increased slightly with higher daily cigarette consumption and increasing number of pack-years in both COPD cases and controls (table 2).

In the multiple linear regression analysis including sex, age and smoking, the relationships of sex and age to emphysema score and to the indices of AWT persisted (table 3). After adjusting for sex, age and daily cigarette consumption the %LAA950 score increased with number of pack-years in COPD cases, while the AWT-Pi10 increased with number of pack-years in controls. This adjusted analysis (table 3) also showed that the %LAA950 decreased with increasing daily number of cigarettes smoked in COPD cases. AWT-Pi10 did not vary significantly with current daily number of cigarettes smoked.

The number of airways examined in each subject was also added to the airway models without affecting the overall results. Body mass index, post-bronchodilator FEV₁ % predicted, CT-measured total lung volume and total lung volume as a fraction of total lung capacity predicted (proxy for inflation level) were added separately to the models of table 3. The explained variation was markedly increased, but the

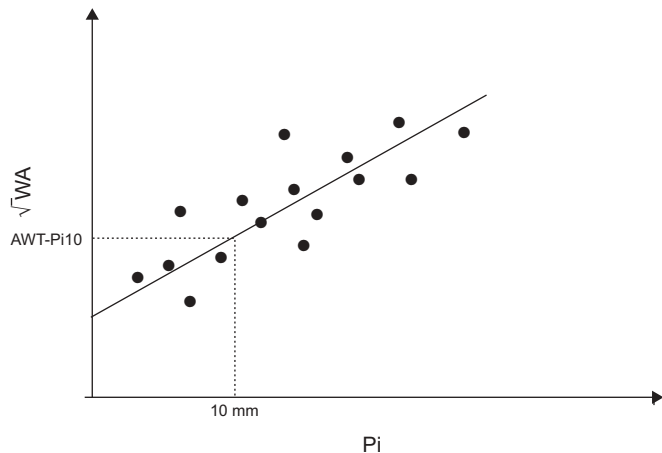


FIGURE 1. The calculation of AWT-Pi10. The square root of the wall area of each measured airway (\sqrt{WA}) was plotted against the internal perimeter (Pi) of that airway. This was performed separately for each subject. From the resulting regression line, a standardised measure of airway wall thickness for an airway with an internal perimeter of 10 mm was predicted (AWT-Pi10).

observed relationships remained overtly unchanged in size and direction.

We also calculated %LAA910 and %LAA856 (data not shown). They were analysed using the same multiple linear regression models shown in table 3, showing the same overall relationships found using %LAA950.

Interaction analysis

The *a priori* defined interaction terms were then added separately to the multiple regression models. Sex and age showed a significant interaction in their effect on %LAA950 among the controls, indicating that %LAA950 increased more rapidly with increasing age in females than in males (fig. 2). Age and current smoking groups showed a significant interaction in their effect on %LAA950 among COPD cases, indicating that %LAA950 increased more rapidly with increasing age in current smokers (fig. 3). Sex and pack-years did not interact in their relationship to emphysema. Nor did sex and current smoking habit interact in their relationship to AWT.

We also combined the COPD cases and controls and added case/control status as an explanatory variable to the models in table 3. Case/control status and pack-years showed a significant interaction in their effect on AWT-Pi10, indicating that the AWT increased more rapidly with increasing number of pack-years in controls than in COPD cases (fig. 4).

DISCUSSION

In the current study we used a large COPD case-control population to perform sub-group analyses of the quantitative CT data and found considerable sex, age and smoking related differences in the estimates of emphysema and AWT. These data show that there is more emphysema in males and ex-smokers and that the extent of emphysema increased with increasing age and number of pack-years, regardless of COPD case/control status. AWT was higher in males, and decreased slightly with increasing age in both COPD cases and controls.

TABLE 1 Characteristics of the study population

	COPD cases		Control subjects	
	Males	Females	Males	Females
Subjects n	299	164	231	200
Demographics				
Age yrs	65.2 ± 9.4	62.6 ± 9.0	55.7 ± 9.5	54.1 ± 8.9
Ex-smokers	53.2	46.3	62.3	52.5
Current smokers	46.8	53.7	37.7	47.5
<10 cigarettes·day ⁻¹	10.4	12.2	7.8	16.5
10–19 cigarettes·day ⁻¹	21.4	30.5	21.2	23.0
≥20 cigarettes·day ⁻¹	15.1	11.0	8.7	8.0
Pack-years	30.6 (21–43)	22.5 (16–32)	18.0 (10–27)	14.0 (8–23)
Height cm	175.3 ± 6.8	163.0 ± 5.9	178.2 ± 6.6	166.0 ± 5.8
Pre-BD FEV1 % pred	49.5 ± 17.4	49.9 ± 16.4	91.9 ± 9.1	93.0 ± 8.9
Post-BD FEV1 % pred	52.6 ± 17.4	53.1 ± 16.1	94.5 ± 8.8	96.0 ± 9.1
GOLD classification				
Stage II	58.2	62.8		
Stage III	28.1	28.1		
Stage IV	13.7	9.2		

Data are presented as mean ± SD, per cent or median (25th–75th percentiles), unless otherwise stated. COPD: chronic obstructive pulmonary disease; BD: bronchodilator; FEV1: forced expiratory volume in 1 s; % pred: % predicted; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Interaction analysis showed that the emphysema score increased more with increasing age in females and in current smokers. It also showed that the AWT increased more with increasing number of pack-years in the control group.

Sex differences

The data from this study confirm previous findings that there are more cases of emphysema in males than in females [3, 9] and expands the previous results by including control subjects with no airflow obstruction. This sex difference is contrary to the findings of GEVENOIS *et al.* [23], who did not find any sex difference in CT lung densitometry; however, that study may have been underpowered by only including 42 subjects.

The higher emphysema score in males could have several explanations. Emphysema quantification is very sensitive to the level of inspiration, but even though males have larger lungs [17], there are no indications that males inspired deeper, and we did adjust the analyses for inspirational level. Environmental cause is another possible explanation, as males are more exposed to occupational airborne agents, which are potentially harmful to the lungs [24]. When our study group was in the first decade of life, the male smoking prevalence was two to three times that of females. As sons spend more time with their fathers than daughters do, they were more likely to be exposed to passive smoking [25]. There are data to suggest that passive smoking in childhood may have independent effects on the lungs in adult age [26]. Our findings could also be explained by residual confounding from smoking, but we were not able to examine the sex difference in never-smokers only, as these were not included in the study.

TABLE 2 Quantitative high-resolution computed tomography parameters by sex, age and smoking groups

	% Low-attenuation areas < -950 HU		AWT-Pi10 cm [#]	
	COPD cases	Controls	COPD cases	Controls
Subjects n	462	428	438	407
All subjects	7.02 (2.23–17.80)	0.52 (0.21–1.28)	0.494 ± 0.033	0.477 ± 0.029
Sex				
Males	8.86	0.71	0.505	0.488
Females	4.74	0.32	0.474	0.463
p-value	0.0018	0.0001	<0.0001	<0.0001
Age yrs				
<50	1.32	0.27	0.501	0.477
50–59	3.56	0.45	0.501	0.476
60–69	8.95	0.91	0.486	0.480
≥70	12.24	1.35	0.495	0.470
p-value	0.0001	0.0001	0.0025	0.4380
Smoking				
Ex-smokers	9.72	0.65	0.493	0.477
Current smokers	4.86	0.35	0.495	0.476
p-value	0.0001	0.0001	0.4740	0.5683
Current smokers				
<10 cigarettes·day ⁻¹	6.02	0.31	0.480	0.473
10–19.9 cigarettes·day ⁻¹	4.28	0.36	0.499	0.473
≥20 cigarettes·day ⁻¹	5.33	0.26	0.501	0.487
p-value	0.1080	0.3414	0.0033	0.0493
Pack-years				
<15	4.74	0.54	0.485	0.473
15–29.9	6.29	0.45	0.491	0.476
≥30	8.94	0.70	0.500	0.489
p-value	0.0733	0.3638	0.0033	0.0003

Data for all parameters are presented as median (25th–75th percentile) or mean ± sd. Data for % low-attenuation areas < -950 HU are presented as median and for AWT-Pi10 (airway wall thickness for an airway with an internal perimeter of 10 mm) as mean. The p-values were calculated using Kruskal–Wallis (low-attenuation area) and ANOVA (AWT-Pi10). HU: Hounsfield units; COPD: chronic obstructive pulmonary disease. #: standardised measurement of airway wall thickness. The bold p-values indicate significance.

However, we did compare subjects with <10 pack-yrs, and observed the same difference between males and females as in the entire sample (data not shown). Therefore, we find the residual confounding possibility less likely.

To our knowledge, we are the first to describe sex differences in CT measurements of airway dimensions. Our findings contradict the histological results in a subgroup of 101 subjects from the NETT study (the National Emphysema Treatment Trial), in which females had higher total wall area relative to luminal perimeter [3]. However, these studies are not comparable because the subjects in the NETT study were highly selected candidates for lung volume reduction surgery. Furthermore, the NETT subjects were all ex-smokers with no significant sputum production, while our study comprised a community-based sample of both current and ex-smokers with a wide range of respiratory symptoms and pulmonary function. Finally, the NETT data is based on airways <2 mm in diameter measured using histology of the resected and most emphysematous part of the lungs, while our CT examination was based on airways >2 mm in diameter from all regions of the lungs.

The sex difference in environmental exposures, described previously for the emphysema score, could also explain the airway differences. Furthermore, males have larger lungs than females [17], and that is the probable explanation of why we measure a slightly larger number of airways with slightly larger lumens in males. However, AWT-Pi10 adjusts for this difference and, after adding height or CT derived total lung volume to the model, the sex difference persisted. One could argue that the CT derived total lung volume is dependent on the degree of inspiration. Hence, we also adjusted for the CT derived total lung volume as a fraction of expected total lung capacity. Still the sex difference in AWT persisted, supporting the fact that this is a genuine sex difference, unrelated to the difference in size between sexes.

Age differences

The increasing emphysema score with ageing found in our study is in line with previous cross-sectional [23] and longitudinal [27] surveys. None of these studies examined if age and sex interacted in their effect on emphysema score, while we found that the sex difference in emphysema score

TABLE 3 Multivariate linear regression models, with % low-attenuation areas < -950 Hounsfield units (HU) and AWT-Pi10 as dependent variables in chronic obstructive pulmonary disease (COPD) cases and controls

	COPD cases		Controls	
	coefficient	p-value	coefficient	p-value
% Low-attenuation areas < -950 HU[#]				
Subjects n	462		428	
Intercept	-1.062 ± 0.464	<0.05	-3.438 ± 0.373	<0.001
Male	0.272 ± 0.130	<0.05	0.674 ± 0.113	<0.001
Age per 10 yrs	0.397 ± 0.070	<0.001	0.450 ± 0.065	<0.001
Pack-years per 10 pack-yrs	0.085 ± 0.039	<0.05	0.011 ± 0.048	>0.05
Smoking groups		<0.05		>0.05
Ex-smokers	0		0	
Current				
<10 cigarettes·day ⁻¹	-0.181 ± 0.200	>0.05	-0.349 ± 0.181	>0.05
10–19.9 cigarettes·day ⁻¹	-0.451 ± 0.155	<0.01	-0.099 ± 0.146	>0.05
≥20 cigarettes·day ⁻¹	-0.430 ± 0.207	<0.05	-0.458 ± 0.235	>0.05
Adjusted R ²	0.1421		0.2159	
AWT-Pi10[‡]				
Subjects n	438		407	
Intercept	0.497 ± 0.011	<0.001	0.472 ± 0.009	<0.001
Male	0.031 ± 0.003	<0.001	0.024 ± 0.003	<0.001
Age per 10 yrs	-0.004 ± 0.001	<0.05	-0.003 ± 0.001	<0.05
Pack-years per 10 pack-yrs	-0.0002 ± 0.0009	>0.05	0.005 ± 0.001	<0.001
Smoking groups		<0.01		>0.05
Ex-smokers	0		0	
Current				
<10 cigarettes·day ⁻¹	-0.011 ± 0.005	<0.05	0.002 ± 0.004	>0.05
10–19.9 cigarettes·day ⁻¹	0.007 ± 0.004	>0.05	-0.007 ± 0.003	<0.05
≥20 cigarettes·day ⁻¹	0.005 ± 0.005	>0.05	-0.001 ± 0.005	>0.05
Adjusted R ²	0.2121		0.2218	

Data are presented as coefficient ± SE, unless otherwise stated. AWT-Pi10: airway wall thickness for an airway with an internal perimeter of 10 mm. #: log-transformed; ‡: standardised measure of airway wall thickness.

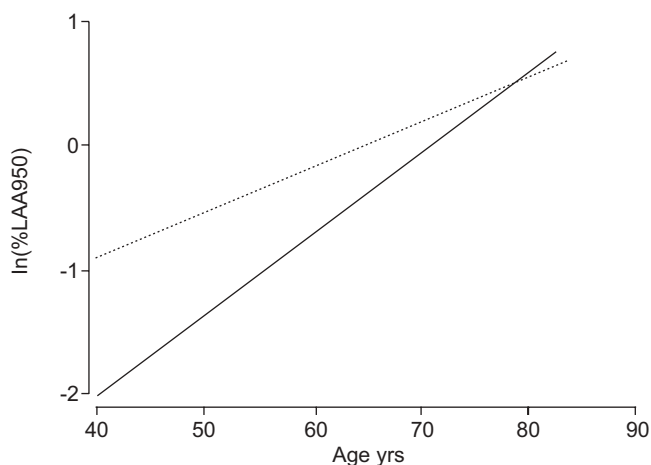


FIGURE 2. The relationship of log-transformed % low-attenuation areas < -950 Hounsfield units (%LAA950) and age in controls when pack-years and current smoking levels were held constant. There was a significant interaction between age and sex ($p=0.007$).: males; —: females.

declined significantly with increasing age among the controls (fig. 2). This may have several explanations. It could indicate that the natural ageing of the lung gradually reduces the relative importance of environmental risk factors to which males are more exposed. It could also be a selection effect more pronounced in males than females as the age–sex interaction was only present in the control group. Finally, it could be related to the fact that the increased deposition of body fat associated with ageing is mainly abdominal in males, and more evenly distributed in females [28, 29]. This increased amount of abdominal fat in ageing males could, in the supine CT measurement position, press the diaphragm cranially, causing increased pulmonary density and reducing the percentage of tissue with a density < -950 HU. In support of this, we also found that CT measured lung volume was slightly reduced in elderly male controls. It is also worth mentioning that age was a stronger predictor for emphysema than smoking was in both COPD cases and controls, and this is in line with data recently reported in the BOLD study (Burden of Chronic Obstructive Lung Disease) [30].

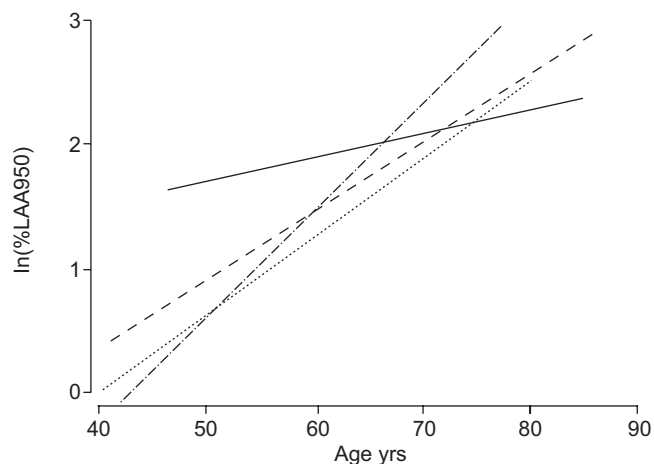


FIGURE 3. The relationship of log-transformed % low-attenuation areas < -950 Hounsfield units (%LAA950) and age in chronic obstructive pulmonary disease cases when pack-years and sex were held constant. There was a significant interaction between age and current smoking status ($p=0.006$). —: ex-smoker; - - - -: current smoker, <10 cigarettes·day $^{-1}$; ·····: current smoker, $10-20$ cigarettes·day $^{-1}$; · - · - ·: current smoker, ≥ 20 cigarettes·day $^{-1}$.

Smoking-related differences

Increasing number of pack-years smoked was associated with increased emphysema score in COPD cases, even after adjusting for sex, age and current smoking status (table 3). This is in accordance with the study by SOEJIMA *et al.* [27], which followed 83 smokers with annual CT for 5 yrs, even though they did not adjust for age. These data are also in line with previous respiratory physiological studies which report that pack-years are an independent predictor for indices of emphysema [31]. The association between emphysema and pack-years, as well as the greater increase of emphysema with increasing age in current smokers (fig. 3), was seen in our COPD cases only. However the controls had smoked, and were smoking significantly less and had significantly less emphysema than the COPD cases.

The decrease in %LAA950 associated with increased current daily smoke consumption in COPD cases (tables 2 and 3) is most probably due to a survivor effect, where those with more advanced disease would be more likely to reduce or quit smoking.

No clear trend was seen for the quantity of current smoking. However, the number of pack-years was related to increasing AWT in controls (table 3; fig. 4). This could imply that the observed airway wall thickening, which on average was larger among COPD cases, is caused by different underlying pathophysiological mechanisms in COPD cases than controls [32–35]. However, our study is cross-sectional, and to clarify these relationships a longitudinal design is needed.

Strengths and limitations of the study

The strength of this study is that it is a single centre study, and all control subjects were sampled from a community study with high response rates [36–38]. Furthermore, surveys of nonresponders have shown that the study samples are representative of the population at large with respect to sex, age and smoking [36], and we think that the external validity of

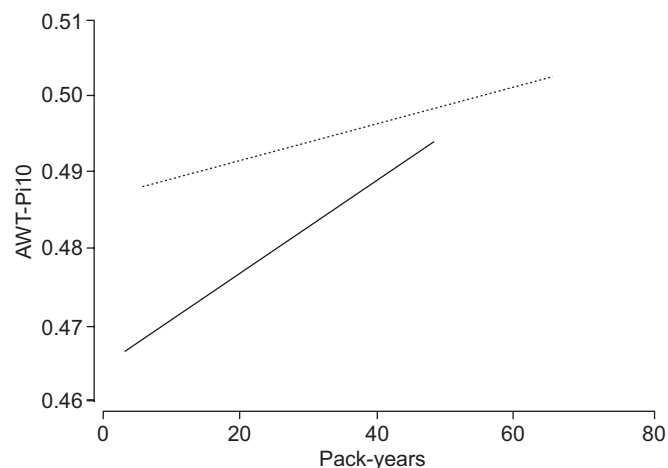


FIGURE 4. The relationship of AWT-Pi10 (standardised measure of airway wall thickness for an airway with an internal perimeter of 10 mm) and pack-years when age, current smoking level and sex were held constant. There is a significant interaction between pack-years and case-control status ($p=0.003$). ·····: chronic obstructive pulmonary disease cases; —: controls.

our findings is high. Finally, all CT scans were performed with the same scanner.

However, there are some limitations to this study. 1) Even though subjects with a total smoking history as low as 2.5 pack-yr were included in the study, we did not include never-smokers. 2) There were more male COPD cases, and the COPD cases were older, but all these differences have been adjusted for in the multivariate analyses. 3) The study did not include GOLD stage I. However, GOLD stages II–IV are those regarded as clinically important [30]. 4) The CT scans were not spirometrically gated, but it has been shown that the repeatability of quantitative CT tests is high and not likely to improve by using spirometric gating [39]. Furthermore, all analyses were adjusted for inflation level. 5) We were not able to determine the generations of the airways measured, and the generations might have differed between those with small and large lungs. However, adjustments for lung volume, lumen size or number of airways measured did not alter the relationships observed in table 3. Finally, it has been shown that CT measurements of small airway wall dimensions using the technique employed here are extremely variable [40]. Therefore, we only used larger airways in our analysis. While it is well established that COPD is a small airways disease [41, 42], studies have shown that the inflammatory response seen in small airways can also be seen in large airways [43], and that CT estimates of AWT are correlated with histological measurements of small airway wall dimensions [8]. Therefore, we are confident that our results do reflect the changes that are occurring in the small airways.

In conclusion, this study shows that the sex, age and smoking composition of the study population has strong effects on the quantitative CT measures of emphysema and AWT, and must be considered when comparing CT studies. As long as these population characteristics are taken into account, quantitative CT is a valuable tool for further characterisation of not only COPD phenotypes, but also healthy subjects to understand the natural history of the lung.

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STATEMENT OF INTEREST

Statements of interest for H.O. Coxson, S.G. Pillai and S. Sharma and the study itself can be found at www.erj.ersjournals.com/misc/statements.dtl

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