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CHEST

Longitudinal airway remodeling in active and past smokers in a lung cancer screening population

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Abstract

Objectives To longitudinally investigate smoking cessation-related changes of quantitative computed tomography (QCT)–based airway metrics in a group of heavy smokers.

Methods CT scans were acquired in a lung cancer screening population over 4 years at 12-month intervals in 284 long-term ex-smokers (ES), 405 continuously active smokers (CS), and 31 subjects who quitted smoking within 2 years after baseline CT (recent quitters, RQ). Total diameter (TD), lumen area (LA), and wall percentage (WP) of 1st–8th generation airways were computed using airway analysis software. Inter-group comparison was performed using Mann-Whitney *U* test or Student's *t* test (two groups), and ANOVA or ANOVA on ranks with Dunn's multiple comparison test (more than two groups), while Fisher's exact test or chi-squared test was used for categorical data. Multiple linear regression was used for multivariable analysis.

Results At any time, TD and LA were significantly higher in ES than CS, for example, in 5th–8th generation airways at baseline with 6.24 mm vs. 5.93 mm ($p < 0.001$) and 15.23 mm^2 vs. 13.51 mm^2 ($p < 0.001$), respectively. RQ showed higher TD (6.15 mm vs. 5.93 mm, n.s.) and significantly higher LA (14.77 mm^2 vs. 13.51 mm^2, $p < 0.001$) than CS after 3 years, and after 4 years. In multivariate analyses, smoking status independently predicted TD, LA, and WP at baseline, at 3 years and 4 years ($p < 0.01$–0.001), with stronger impact than pack years.

Conclusions Bronchial dimensions depend on the smoking status. Smoking-induced airway remodeling can be partially reversible after smoking cessation even in long-term heavy smokers. Therefore, QCT-based airway metrics in clinical trials should consider the current smoking status besides pack years.

Key Points

- *Airway lumen and diameter are decreased in active smokers compared to ex-smokers, and there is a trend towards increased airway wall thickness in active smokers.*
- *Smoking-related airway changes improve within 2 years after smoking cessation.*
- *Smoking status is an independent predictor of airway dimensions.*

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Abbreviations

ANOVA	Analysis of variance
AS	All smokers
ATS	American Thoracic Society
BMI	Body mass index
coeff.	Regression coefficient
COPACETIC	COPD Pathology: Addressing Critical Gaps, Early Treatment & Diagnosis and Innovative Concepts
COPD	Chronic obstructive pulmonary disease
COPDGene	The Genetic Epidemiology of COPD study
CS	Continuous smokers
CT	Multidetector computed tomography
DFG	German Research Council
ECSC	European Coal and Steal Community
ERS	European Respiratory Society
ES	Ex-smokers
FEV1	Forced expiratory volume in 1 s
FEV1/FVC	Tiffenau Index
FEV1%	Forced expiratory volume in 1 s (percent predicted)
FVC	Forced vital capacity
G	Airway generation
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HU	Hounsfield units
LA	Luminal area
LUSI	Lung Cancer Screening Intervention Trial
LV	Lung volume
M	Male sex
PFT	Pulmonary function testing
Pi10	Standardized airway wall thickness at an internal perimeter of 10 mm
QCT	Quantitative CT
RQ	Recent quitters
st. coeff.	Standardized regression coefficient
TD	Total diameter
WA	Wall area
WP	Relative wall thickness
YACTA	Yet another CT analyzer

Introduction

Chest multidetector computed tomography (CT) is well established for phenotyping smoking-related lung diseases such as cigarette smoke-induced chronic obstructive pulmonary disease (COPD) [1–5]. It allows for the characterization of two main imaging features of COPD: airway remodeling and emphysema [6, 7], which both contribute significantly to airflow limitation and disease exacerbation to a variable degree [8, 9]. It has long been known that airflow limitation as measured by spirometry may improve within the first 2 years and that the rate of its decline thereafter is lower when COPD patients quit smoking [10, 11], indicating that reversibility of airflow limitation may be related to subsiding inflammation and improved airway remodeling, while emphysema is considered an irreversible lung damage. Quantitative computed tomography (QCT) allows for the quantification of lung emphysema and airway dimensions, and CT-based assessment of the parenchyma now plays a key role in directing patients with severe emphysema towards interventional lung volume reduction therapy [12, 13]. In comparison, QCT of the airways has not yet found its way into clinical COPD management, but it provides valuable outcome measures which are already used within clinical trials to assess response to therapy with novel drugs (ClinicalTrials.gov Identifier: NCT01480661, NCT03268226). Besides, it is used in several large observational cohort studies to investigate disease mechanisms of COPD [4, 14–16]. A main focus of research in QCT studies has been the documentation of longitudinal deterioration of emphysema in the absence of pharmacological treatment for emphysema [17, 18]. Previous work has demonstrated that active smokers have a quicker progression of emphysema severity than ex-smokers with COPD [19, 20], and it has also been shown that, in long-term heavy smokers, smoking cessation leads to a decrease in lung density, which may be related to clearance of smoking-induced inflammation [21, 22]. On the other hand, QCT of the airways has been performed in few studies demonstrating the influence of airway remodeling on COPD severity [1, 9, 14, 23]. More subtle than in COPD, airway changes related to smoking have been described in non-COPD patients [24–26]. However, the quantitative influence of active smoking on airway dimensions as determined by QCT remains unknown. Further, long-term changes of airway dimensions in sustained smoking have not been studied yet, as opposed to emphysema progression in smokers. Although some preliminary studies indicate that airway dimensions in COPD patients on QCT may be influenced by bronchodilators [27], a potential reversibility of airway remodeling in smokers with or without being diagnosed with COPD who stop active smoking has not been demonstrated yet. Consequently, the aim of our study was to longitudinally compare airway dimensions on annual QCT over a period of 4 years in a large cohort of active and former heavy smokers recruited from the first German Lung Cancer Screening Intervention Trial (LUSI) [28]. Further, short-term effects of smoking cessation on

airway dimensions on QCT in a subgroup of heavy smokers were assessed, based on the hypothesis that smoking cessation does not only reduce active pulmonary parenchymal inflammation [21] but also leads to improved airway remodeling.

Materials and methods

Study population

The study was carried out among 720 heavy smokers (50–69 years of age) from the LUSI population who underwent annual screening CT over a period of 4 years as described previously [21, 28–30]. Spirometry performed at baseline and volumetric low dose non-contrast chest CT data with 1.0-mm slice thickness and sharp convolution kernel reconstructions at baseline as well as years 1–4 were required for inclusion into this sub-study. All subjects included in the study had identical CT acquisition parameters at baseline (Acquilion 16, Canon Medical Systems Corp.) as well in years 2, 3, and 4 (Definition Flash, Siemens Healthineers AG), whereas data from year 1 represent image data from both CT scanners due to the exchange of the scanner hardware. Further details are provided with the online supplement.

Smoking habits and cessation

A standardized smoking cessation counseling was offered to each participant upon study inclusion as described previously [28–30]. Smoking habits of each participant were assessed every 12 months using a standardized questionnaire. Based on these data, 2 subgroups were created at baseline: (1) "Ex-smokers" (ES) defined by having quitted smoking at least 1 year before study baseline. (2) "All smokers" (AS) defined as active smokers at the time of study baseline. Further, the latter group of AS was subdivided at 3 years as follows: (3) "Continuous smokers" (CS) defined as subjects who continued active smoking throughout the study period, i.e., from baseline to 4 years. (4) "Recent quitters" (RQ) defined as subjects who smoked at baseline, but ceased to smoke between baseline and 2 years, i.e., 1 year before CT scanning at 3 years, and remained non-smokers until 4 years. Further details are provided with the online supplement.

Airway measurements

Non-commercial fully automatic airway analysis software YACTA ("Yet another CT analyzer," Version 2.8.0.14, programming by O.W.) was applied to CT data as previously described [23, 31–33], to segment the entire tracheobronchial tree down to the 8th airway generation and to calculate the various metrics of airway geometry [34] using the parameter-free integral-based method (IBMpf). User interaction or manual correction of the segmentations was not required. The following previously described airway parameters were calculated for the 1st–8th generation separately: total diameter (TD), luminal area (LA), wall area (WA), and the ratio of wall area to the sum of wall and lumen area (wall percentage, WP). Additionally, a standardized measure for airway wall thickness was derived by plotting the square root of the airway wall area against the internal perimeter of the airway for every measured airway location. By using the resulting regression line, the square root of the wall area for a "theoretical airway" with an internal perimeter of 10 mm was determined and defined as Pi10 [35]. Besides, the most distal airway generation measurable by QCT software was documented for each CT dataset.

Statistical analysis

Computational results were inspected by a reader with more than 7 years of experience in chest radiology and QCT, as well as by the YACTA programmer. SigmaPlot (Systat Software Inc.) was used for data analysis. Data are presented as mean ± standard deviation for normal or as median ± median average deviation for skewed distributions, unless otherwise specified. Inter-group comparison (two groups) was carried out using Mann-Whitney *U* test or Student's *t* test, while categorical data were analyzed using Fisher's exact test or chi-squared test as appropriate. Inter-group comparison of more than two groups was performed using analysis of variance (repeated measures ANOVA or ANOVA on ranks) and post hoc analysis (Dunn's multiple comparison test) as appropriate. Of note, CS were assessed inclusive of RQ (group AS) at baseline, years 1 and 2, and separately thereafter in years 3 and 4. Data from baseline as well as 2-, 3-, and 4-year follow-up were subjected to multiple linear regression analysis with TD, LA, WA, WP, and Pi10 as dependent variables. The following parameters served as independent variables: lung volume, sex, smoking status (current smoker), BMI, FEV1%, age, and pack years. A p value < 0.05 was considered statistically significant, including adjustment for multiple comparison with the Bonferroni-Holm method as appropriate [36]. Further details are provided with the online supplement.

Results

Patient characteristics

From the 2029 subjects recruited for the LUSI study [28], 720 fulfilled all inclusion criteria. The median age of the study population at baseline was 57.2 years. At baseline, inter-group comparison using Mann-Whitney *U* test (for skewed distributions) or Student's *t* test (for normal distributions) revealed that ES (56.7 ± 5.6 years) were slightly younger than

Table 1 Patient characteristics at baseline

	Ex-smokers (ES)	All smokers (AS)	*p*	Continuous smokers (CS)	Recent quitters (RQ)	*p*
n =	284	436		405	31	
Age (years)	56.7 ± 5.6*	59.4 ± 5.4	< 0.001	59.7 ± 5.4	55.5 ± 4.7*	< 0.001
Male/female	201/80	266/168	n.s.	245/158	21/10	n.s.
Pack years	41.3 ± 18.7	38.4 ± 15.2	n.s.	38.1 ± 15.0	42.5 ± 16.9	n.s.
BMI (kg/m^2)	28.2 ± 4.0*	26.2 ± 4.4	< 0.001	26.2 ± 4.3	25.5 ± 3.0	n.s
COPD (*n*)	37	55	n.s.	53	2	n.s.
FEV1 (l)	3.0 ± 0.7	2.9 ± 0.7	< 0.05	2.8 ± 0.7	3.0 ± 0.8	n.s.
FEV1 (%)	94.9 ± 15.2	93.2 ± 16.8	< 0.05	93.1 ± 16.8	94.9 ± 18.2	n.s.
FEV1/FVC	79.6 ± 10.5	80.5 ± 11.8	n.s.	80.2 ± 11.8	84.6 ± 10.7	< 0.05

Data are presented as mean ± standard deviation. Inter-group comparison was performed using Mann-Whitney *U* test or Student's *t* test for continuous variables as appropriate. Categorical variables (male/female, COPD) were analyzed using chi-squared test to assess inter-group differences. Percentage values refer to the predicted volumes [57]. Of note, RQ and CS are contained in the group of AS at baseline, but baseline data are shown separately also to demonstrate that there are no meaningful differences between these subgroups at baseline. *$p < 0.001$ vs. CS

BMI body mass index, *FEV1* forced expiratory volume in 1 s, *FEV1/FVC* Tiffeneau index

the group of AS (59.4 ± 5.4 years, $p < 0.001$) (Table 1). Subjects forming the groups of RQ (55.5 ± 4.7 years) and CS (59.7 ± 5.4) out of AS after 2 years showed significantly different age at baseline ($p < 0.001$). All groups consisted of heavy smokers with a similar amount of pack years smoked. Slight but significant differences concerning FEV1% predicted were observed only between ES and AS at baseline with 94.9 ± 15.2 vs. 93.2 ± 16.8 ($p < 0.05$). Chi-squared test revealed that the relation of male to female subjects and the prevalence of COPD were not significantly different between ES, AS, CS, and RQ (Table 1).

Effects of smoking cessation on airway dimensions

First, we investigated smoking-related effects on airway dimensions on QCT by comparing ES with the group of AS each at baseline and at 1 and 2 years, and consecutively ES with CS and RQ at 3 and 4 years. At baseline and 1 and 2 years, long-term ES had significantly higher TD and LA compared to active smokers (AS) for subsegmental 5th to 8th generation airways ($p < 0.001$) (Figs. 1e and 2e), with similar results for the more proximal airway generations including the trachea ($p = 0.632$ to $p < 0.001$) (Figs. 1a–d and 2a–d). WP was similar between ES and AS for 5th to 8th generation airways ($p =$ 0.825–0.040) (Fig. 3e), mainly due to an increase of wall area (see also online supplement and Fig. S1), but there was a trend towards lower WP in ES for the more proximal airways ($p = 0.560$ to $p < 0.05$) (Fig. 3a–d). Pi10 tended to be lower in ES compared to AS at baseline and year 1, and was significantly lower at the 2-year follow-up ($p < 0.05$) (Fig. 4).

Of note, baseline airway measurements were similar between future CS and RQ. Only WA was significantly smaller in RQ at baseline compared to CS ($p < 0.001$). Data are shown in the supplement.

At 3 and 4 years, we observed the acute effects of smoking cessation in the group of subjects who recently quit smoking after study baseline (RQ) in comparison to those who continued smoking throughout the study (CS) and to the long-term ex-smokers (ES). In analogy to the abovementioned observations, RQ had immediately higher TD and LA for all airway generations compared to CS, which remained mostly insignificant due to a high variability ($p = 0.731$ to $p < 0.001$), but even was significant for LA for subsegmental airways ($p < 0.001$) (Figs. 1 and 2). Importantly, means for TD and LA of RQ approximated those of ES at 3 and 4 years. There was also a trend towards decreased WP in RQ compared to CS, again approximating the mean values of ES for all airway generations ($p = 0.978$ to $p = 0.015$) (Fig. 3). Also, we observed a tendency towards increased WA in RQ (Fig. S1), similarly to ES. Pi10 tended to decrease in RQ compared to CS at 3 and 4 years, now showing similar values as ES (Fig. 4), but the difference was statistically insignificant. Detailed WA plots (Fig. S1) and related explanations are provided with the online supplement.

Predictors of quantitative airway metrics

Multiple linear regression analysis was performed at baseline and at 2, 3, and 4 years to identify significant predictors of quantitative airway metrics for Pi10, as well as TD, LA, and WP of subsegmental airways (5th to 8th generation airways). In this context, lung volume, sex (m), smoking status (current smoker), BMI, FEV1%, age, and the amount of pack years served as independent variables (Tables 2, 3, 4, and 5). Among these independent variables, only the smoking status (active smoker)

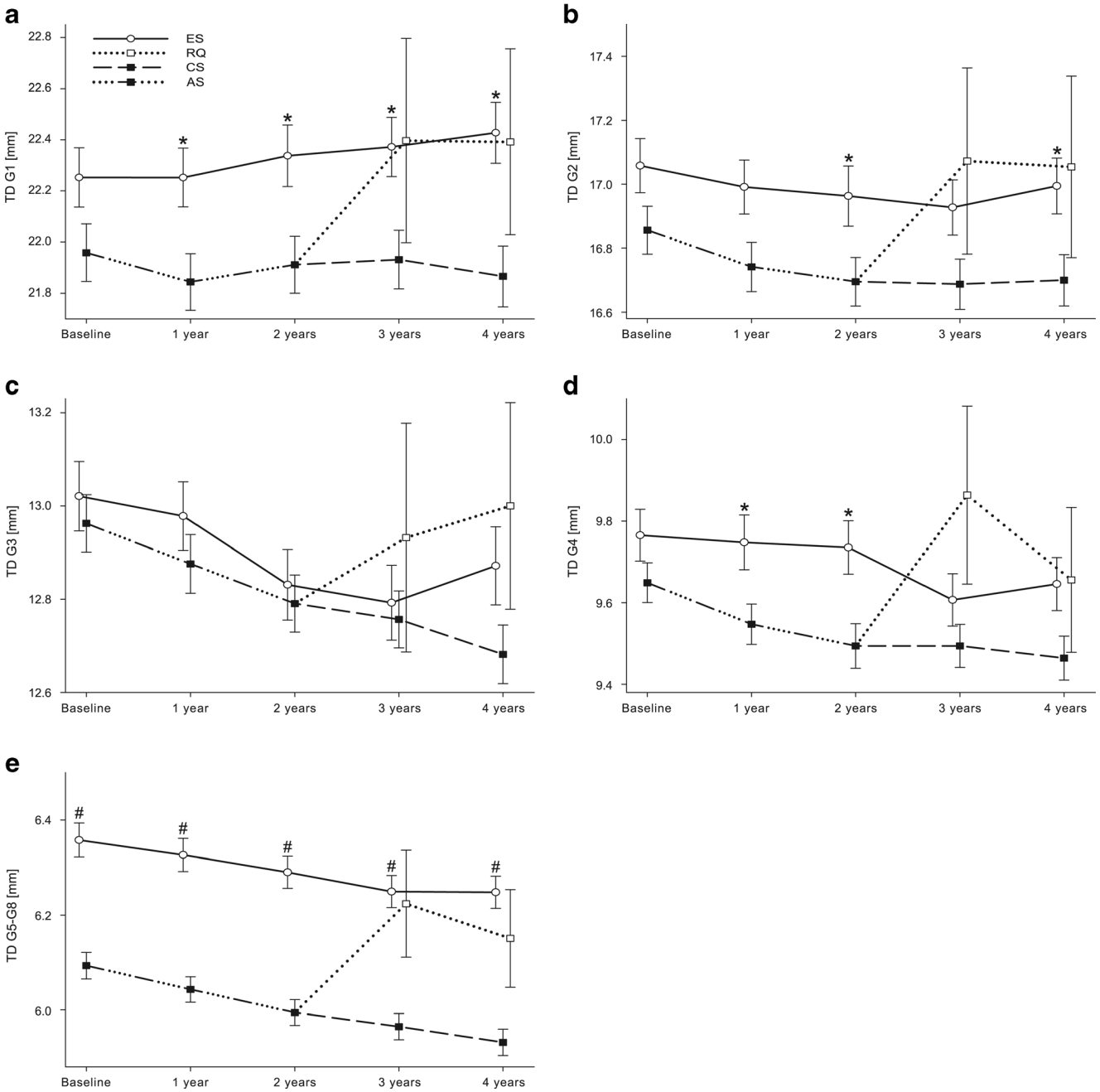

Fig. 1 Effects of smoking cessation on total diameter (TD). Data are given as mean ± standard error of the mean for 1st (**a**), 2nd (**b**), 3rd (**c**), 4th (**g**), and 5th to 8th (**e**) airway generation (G). Please note that 1st generation equals to trachea, and 5th to 8th generation refers to subsegmental airways accordingly. ES ex-smokers, RQ recent quitters, CS continuous smokers, AS all smokers. *$p < 0.05$ vs. AS or CS, #$p < 0.001$ vs. AS or CS

($p < 0.01$–0.001) and FEV1% (each $p < 0.001$) were significant predictors of Pi10, TD, LA, and WP for 5th to 8th generation airways (Tables 2, 3, 4, and 5) at any point in time. Age was shown to be a significant predictor of Pi10, TD for 5th–8th generation, LA for 5th–8th generation, and WP for 5th–8th generation (each $p < 0.05$–0.001), except for Pi10 at year 2, for WP for 5th–8th generation at year 2, and TD for 5th–8th generation at year 4. Male sex was also a significant predictor of the dependent variables TD, LA, and WP for 5th–8th generation (each $p < 0.001$) (Tables 3, 4, and 5), while only a weak association with Pi10 was found at the 2- and 3-year follow-up ($p < 0.05$) (Table 2). BMI was found to significantly predict Pi10, TD, and WP for 5th–8th generation (each $p < 0.001$) (Tables 2, 3, and 5) while only weak associations with LA for 5th–8th generation were found (at the 4-year follow-up, $p < 0.05$) (Table 4). The amount of pack years did not show meaningful associations with the dependent

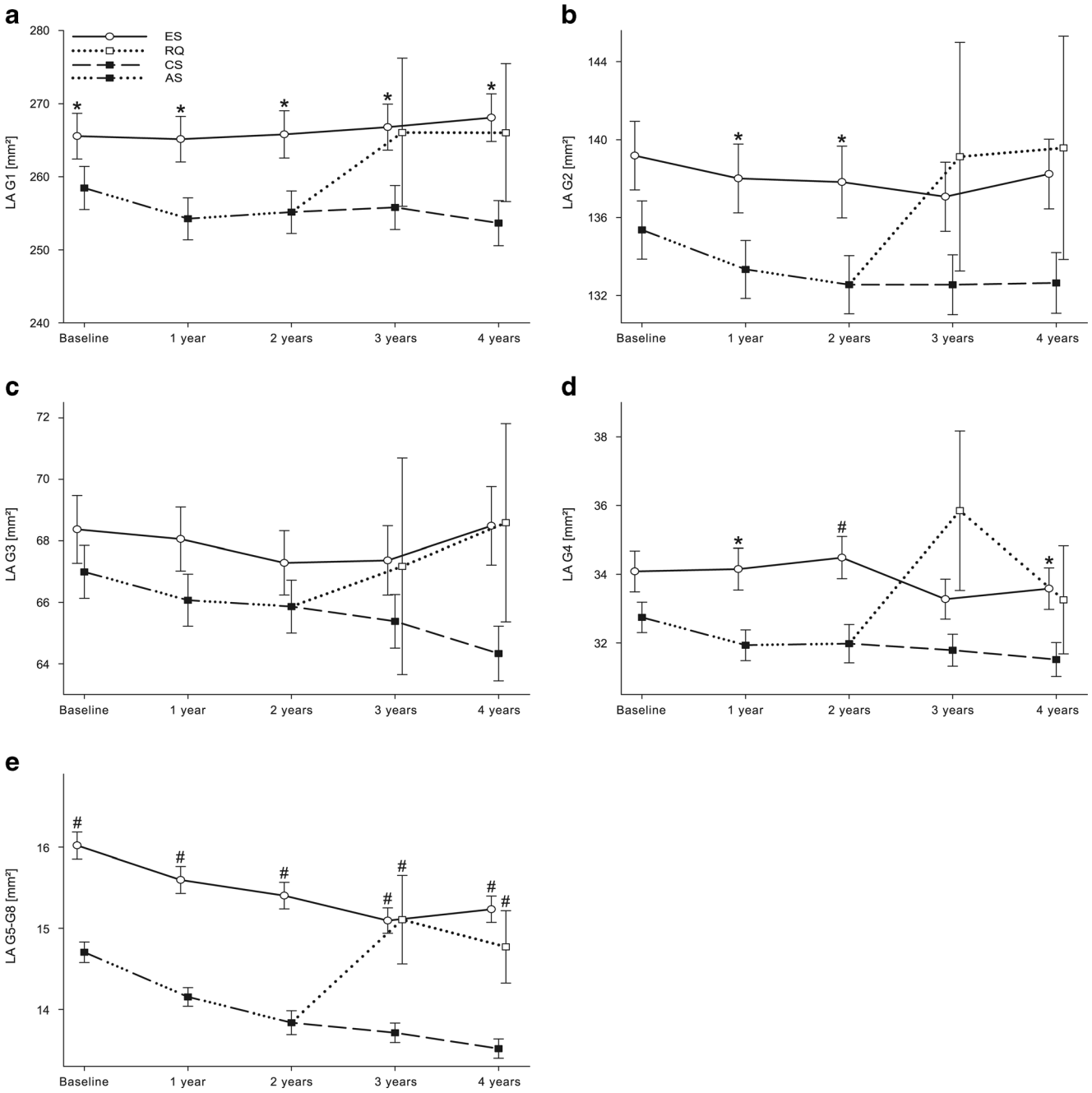

Fig. 2 Effects of smoking cessation on luminal area (LA). Data are given as mean ± standard error of the mean for 1st (**a**), 2nd (**b**), 3rd (**c**), 4th (**g**), and 5th to 8th (**e**) airway generation (G). Please note that 1st generation equals to trachea, and 5th to 8th generation refers to subsegmental airways accordingly. ES ex-smokers, RQ recent quitters, CS continuous smokers, AS all smokers. $^{*}p < 0.05$ vs. AS or CS, $^{\#}p < 0.001$ vs. AS or CS

variables, except with TD for 5th–8th generation at 3 and 4 years and LA for 5th–8th generation at 4 years (each $p < 0.05$). The lung volume appeared to be a significant predictor of LA and WP for 5th–8th generation, and Pi10 (each $p < 0.001$) at any time point. However, the lung volume did not show meaningful associations with TD for 5th–8th generation (Table 3). With a standardized regression coefficient between −0.199 and −0.088, the smoking status was at least the fourth strongest out of seven potential predictors of Pi10, TD, LA or WP in subsegmental airways (Tables 2, 3, 4, and 5). Interestingly, the smoking status was a stronger predictor of the dependent variables than pack years (standardized regression coefficient = 0.005–0.071) or age (0.013–0.127) at most time points (Tables 2, 3, 4, and 5). In general, FEV1% was the strongest predictor of Pi10, LA, and WP with a standardized regression coefficient between −0.429 and 0.113. Multivariable analyses for

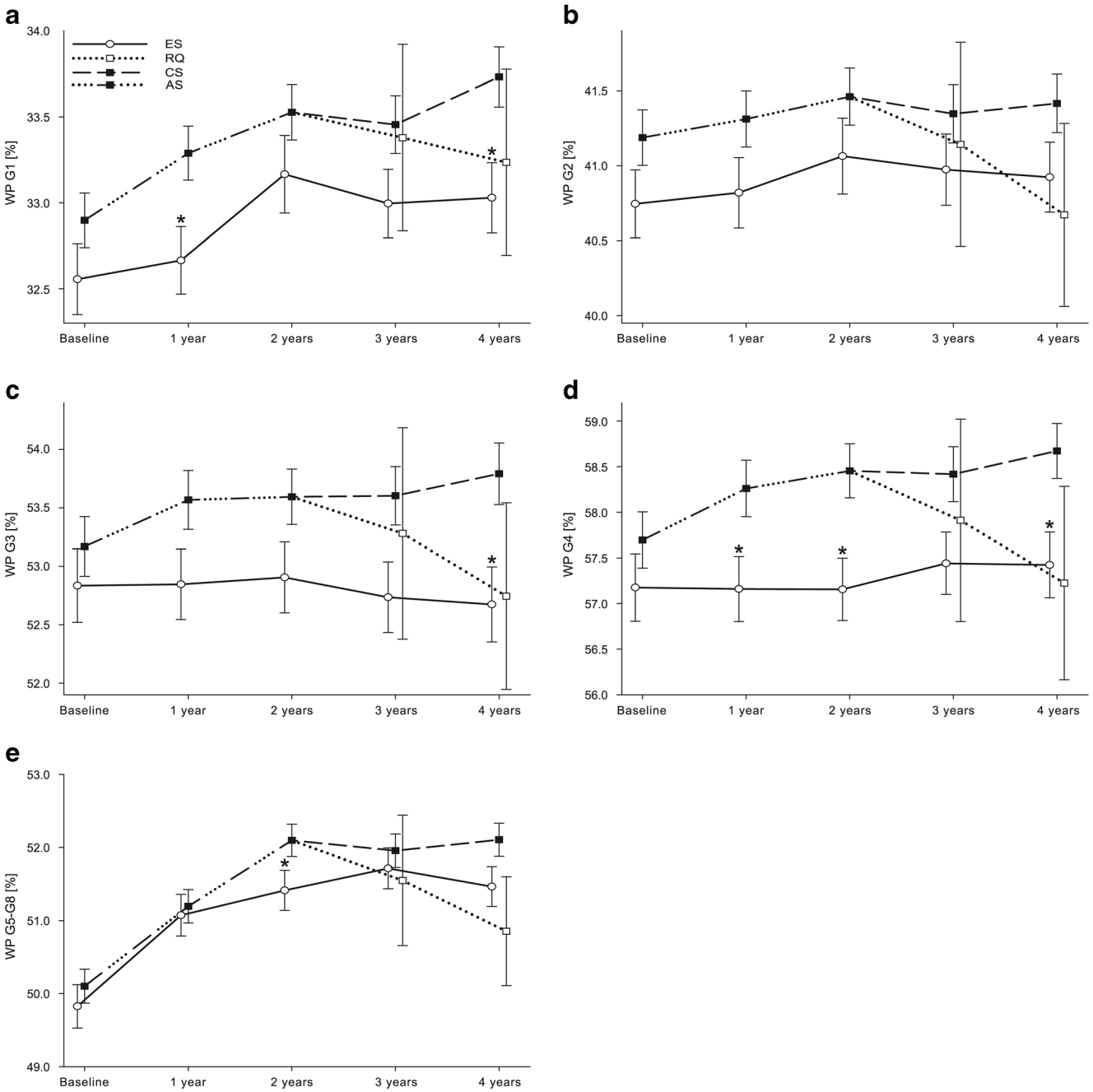

Fig. 3 Effects of smoking cessation on wall percentage (WP). Data are given as mean ± standard error of the mean for 1st (**a**), 2nd (**b**), 3rd (**c**), 4th (**g**), and 5th to 8th (**e**) airway generation (G). Please note that 1st generation equals to trachea, and 5th to 8th generation refers to subsegmental airways accordingly. ES ex-smokers, RQ recent quitters, CS continuous smokers, AS all smokers. *$p < 0.05$ vs. AS or CS, #$p < 0.001$ vs. AS or CS

WA performed in an analogous manner are provided with the online supplement (Table S2).

Discussion

The aim of the study was to longitudinally compare QCT-based airway metrics between two large groups of active and former long-term heavy smokers from a lung cancer screening population over a period of 4 years. ES per definition stopped smoking at least 2 years before study onset. At baseline, the group of ES showed larger bronchial caliber and lumen (i.e., less bronchial narrowing) in all airway generations compared to AS, and this inter-group difference was consistently maintained until the follow-up at 4 years (Figs. 1 and 2). By analogy, ES showed slightly lower wall percentage, with significant inter-group differences being found mainly in larger airways (Fig. 3). As bronchial narrowing is usually the result of

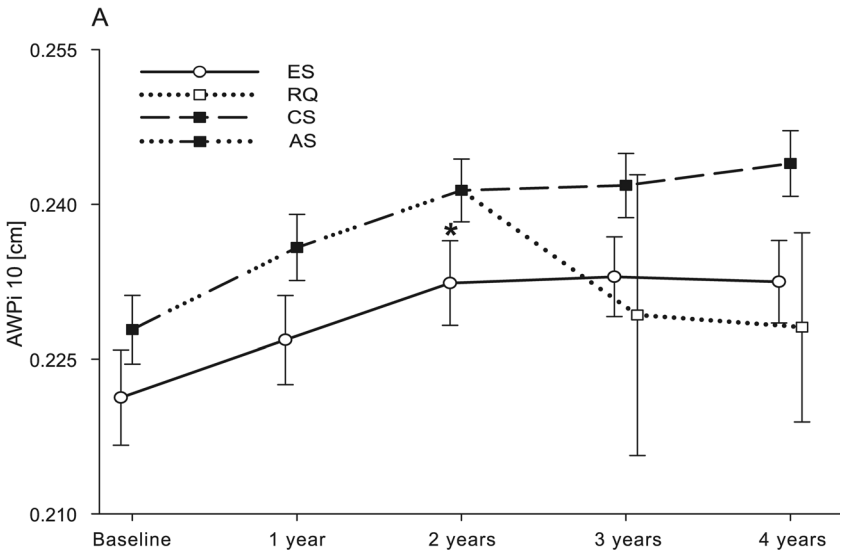

Fig. 4 Effects of smoking cessation on standardized airway wall thickness (Pi10). Data are given as mean ± standard error of the mean for 1st to 8th airway generation (G). Please note that 1st generation equals to trachea, and 5th to 8th generation refers to subsegmental airways accordingly. ES ex-smokers, RQ recent quitters, CS continuous smokers, AS all smokers. *$p < 0.05$ vs. AS or CS, #$p < 0.001$ vs. AS or CS

chronic inflammation with bronchoconstriction and bronchial remodeling, the increased bronchial diameter and lumen observed in ex-smokers suggest that such smoking-related changes of airway geometry can be partly reversible after smoking cessation, with a long-lasting effect (at least 4 years).

Although ES and AS did not differ in clinical parameters at baseline, especially in pack years smoked (Table 1), it was required to confirm that solely smoking status was responsible for the observed differences in airway metrics, independently from other influencing factors. We thus aimed at investigating short-term effects of smoking cessation on airway dimensions in initially active smokers from the AS group, who then quitted smoking within the first 2 years of the 4-year time span of periodical CT scans. This means that by definition, the resulting group of recent quitters (RQ) had ceased to smoke at least 2 years before the last annual CT scan in the 4th year. Airway dimensions of RQ were then compared with the remaining AS subjects who continued to smoke over the 4-year time span (CS), with the hypothesis to reproduce the differences observed between AS and ES made at baseline. At baseline, airway dimensions were similar between future CS and RQ, except for WA in 5th to 8th generation airways, which was smaller in RQ. After smoking cessation, measures for bronchial narrowing and WP of RQ tended to improve at years 3 and 4, becoming very similar to those of ES (Figs. 1, 2, and 4). Due to the small number of subjects in the group of RQ, some of the observed differences between RQ and CS were statistically insignificant. However, lumen area of 5th to 8th generation airways had significantly improved at year 3, reflecting reversibility of narrowing of subsegmental airways in long-term heavy smokers within a short time span after smoking cessation. In this group of recent quitters, a significant improvement in airway dimensions over continuously active smokers was still measurable at the 4-year follow-up, underlining the long-lasting nature of smoking cessation effects on airway geometry.

Table 2 Predictors of Pi10 based on multiple linear regression analysis

Pi10	Baseline		2 years		3 years		4 years	
	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.
Lung volume (ml)	− 0.0000113	− 0.250***	− 0.0000177	− 0.353***	− 0.0000171	− 0.338***	− 0.0000131	− 0.261***
Sex (M)	0.00630	0.041	0.0121	0.0875*	0.0122	0.090*	0.00653	0.048
Current smoker	0.0192	0.129***	0.0193	0.144***	0.0213	0.165***	0.0195	0.152***
BMI (kg/m^2)	0.00406	0.240***	0.00438	0.288***	0.00407	0.274***	0.00416	0.280***
FEV1%	− 0.00186	− 0.416***	− 0.00160	− 0.397***	− 0.00168	− 0.427***	− 0.00168	− 0.429***
Age (years)	− 0.00143	− 0.112***	− 0.000641	− 0.0559	− 0.00130	− 0.117***	− 0.00135	− 0.121***
Pack years	− 0.000250	− 0.057	− 0.0000257	− 0.00656	0.0000195	0.005	− 0.0000397	− 0.010
	$R^2 = 0.283$		$R^2 = 0.347$		$R^2 = 0.351$		$R^2 = 0.322$	

Coeff. regression coefficient, *St. Coeff.* standardized regression coefficient, *BMI* body mass index, *FEV1%* forced expiratory volume in 1 s in percent predicted

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3 Predictors of TD of 5th to 8th generation airways based on multiple linear regression analysis

TD G5-G8	Baseline		2 years		3 years		4 years	
	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.
Lung volume (ml)	− 0.0000237	− 0.057	0.0000184	0.0367	0.00000253	0.004	0.00000651	0.0123
Sex (M)	0.579	0.413***	0.466	0.338***	0.496	0.361***	0.466	0.328***
Current smoker	− 0.121	− 0.088**	− 0.196	− 0.146***	− 0.166	− 0.126***	− 0.166	− 0.122***
BMI (kg/m^2)	0.0467	0.301***	0.0440	0.289***	0.0405	0.266***	0.0464	0.295***
FEV1%	0.00463	0.113***	0.00536	0.133***	0.00632	0.157***	0.00568	0.137***
Age (years)	0.0120	0.103**	0.0147	0.128***	0.00776	0.067*	0.00155	0.0131
Pack years	0.00123	0.031	0.000880	0.0224	0.00274	0.071*	0.00260	0.0667*
	$R^2 = 0.318$		$R^2 = 0.310$		$R^2 = 0.291$		$R^2 = 0.283$	

Coeff. regression coefficient, *St. Coeff.* standardized regression coefficient, *BMI* body mass index, *FEV1%* forced expiratory volume in 1 s in percent predicted

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

The observed inter-group differences with higher LA and TD in ES and RQ did not translate into substantial inter-group differences in WP, mainly due to an increase of WA (Fig. S1), especially in 5th–8th generation airways. By analogy, QCT analyses in 311 participants of the MESA COPD study (3rd to 6th generation airways) and 1248 participants of the SPIROMICS study (1st to 6th generation airways) revealed significantly greater wall areas in controls (current or former smokers without COPD) compared to COPD patients, and WA tended to decrease with increasing COPD severity [39], reflecting bronchial remodeling with reduction of smooth muscle, change in extracellular matrix, loss of cartilage, or reduced bronchial vascular volume due to chronic inflammation in long-term smokers [40–42]. Following these findings and the results from our study, we speculate that smoking cessation does not only lead to increased total diameter and lumen area of the subsegmental airways (G5–8 in our study), but also leads to an increase in total wall area (but not wall percentage) on CT, which is reflective of a regeneration towards a normal airway wall architecture. Besides, the increased LA and TD after smoking cessation may also reflect subsiding bronchoconstriction [43]. These results correspond to outcomes of clinical studies in COPD patients, which showed that smoking-induced low-grade inflammation in airways can return to levels seen in non-smokers [37]. However, in COPD patients, inflammation tends to be stronger and persists longer after smoking cessation than in asymptomatic smokers [38], which made up the majority of our study population.

Importantly, in multivariate analyses, the smoking status was shown to be an independent predictor of quantitative measures of subsegmental airway geometry. In detail, active smoking was shown to be a positive predictor of bronchial wall thickening, and a positive predictor of bronchial narrowing (negative predictor of the bronchial caliber diameter and lumen area) (Tables 3, 4, and 5). Consequently, the

Table 4 Predictors of LA of 5th to 8th generation airways based on multiple linear regression analysis

LA G5-G8	Baseline		2 years		3 years		4 years	
	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.
Lung volume (ml)	0.000366	0.157***	0.000842	0.275***	0.000697	0.240***	0.000757	0.255***
Sex (M)	1.859	0.235***	1.039	0.123**	1.137	0.148***	1.198	0.150***
Current smoker	− 1.160	− 0.151***	− 1.631	− 0.199***	− 1.417	− 0.192***	− 1.520	− 0.199***
BMI (kg/m^2)	0.00502	0.005	− 0.00190	− 0.00204	− 0.000167	− 0.0001	0.0293	0.033*
FEV1%	0.0820	0.355***	0.0744	0.302***	0.0833	0.370***	0.0815	0.350***
Age (years)	0.0831	0.127***	0.0850	0.121***	0.0684	0.107**	0.0371	0.055**
Pack years	0.0127	0.056	0.00245	0.0102	0.00796	0.037	0.00485	0.022*
	$R^2 = 0.250$		$R^2 = 0.253$		$R^2 = 0.275$		$R^2 = 0.280$	

Coeff. regression coefficient, *St. Coeff.* standardized regression coefficient, *BMI* body mass index, *FEV1%* forced expiratory volume in 1 s in percent predicted

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 5 Predictors of WP of 5th to 8th generation airways based on multiple linear regression analysis

WP G5-G8	Baseline		2 years		3 years		4 years	
	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.	Coeff.	St. Coeff.
Lung volume (ml)	− 0.00129	− 0.245***	− 0.00213	− 0.350***	− 0.00209	− 0.326***	− 0.00219	− 0.348***
Sex (M)	2.815	0.158***	3.220	0.192***	3.597	0.211***	3.026	0.179***
Current smoker	1.995	0.115***	2.309	0.142***	2.196	0.135***	2.262	0.139***
BMI (kg/m^2)	0.676	0.343***	0.667	0.360***	0.628	0.334***	0.631	0.337***
FEV1%	− 0.192	− 0.368***	− 0.176	− 0.360***	− 0.190	− 0.382***	− 0.188	− 0.379***
Age (years)	− 0.110	− 0.074*	− 0.0543	− 0.0389	− 0.118	− 0.083*	− 0.102	− 0.072*
Pack years	− 0.0209	− 0.041	0.00301	0.0063	0.0108	0.022	0.0203	0.043
	$R^2 = 0.311$		$R^2 = 0.364$		$R^2 = 0.349$		$R^2 = 0.354$	

Coeff. regression coefficient, *St. Coeff.* standardized regression coefficient, *BMI* body mass index, *FEV1%* forced expiratory volume in 1 s in percent predicted

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

present study indicates a significant impact of smoking and smoking cessation on the structure of main to subsegmental airways. Interestingly, the smoking status showed stronger associations with bronchial dimensions than aging or the total amount of pack years smoked. The impact of smoking cessation on functional aspects of the bronchial system was not in the focus of this study, but has been subject to several clinical studies, and their findings are concordant to our results. Smaller studies have reported an increase of FEV1 [44] or decrease airway hyperresponsiveness [45] during the first year after smoking cessation. More importantly, Xu et al examined 8191 smokers and ex-smokers describing effects of smoking behavior over a 6-year follow-up period [46]. They summarized that smoking cessation avoids further loss of pulmonary function at an expedited rate. Former smokers could accomplish rates of FEV1 decline comparable to never-smokers [46]. By analogy, Anthonisen et al studied 5887 subjects with early COPD longitudinally over 5 years using standardized smoking cessation programs [47]. Their results exposed that maintained smoking cessation provided the largest benefit for smaller declines in FEV1 [47]. Murray et al showed an exponential relationship between lung function decline in smokers and average cigarette amount [48]. Ultimately, smoking cessation reduces respiratory symptoms and decelerates lung function decline but does not fully eliminate the risk of disease progression [49].

The present study also has some limitations. Effects of smoking cessation and improved airway remodeling on lung function (for example spirometry) or other clinical outcome have not been investigated in this work. Spirometry was not available for follow-up time points because it was not part of the main study goal which was lung cancer screening. Due to the inevitable exchange of the CT scanner during the 1-year follow-up (newer scanner generation from other manufacturer), potentially heterogeneous airway measures had to be expected at 1 year, since images were acquired with 2 different scanners during this first follow-up. In this context, scanners from different manufacturers provide different image characteristics, resulting in substantial inter-scanner variability of QCT measurements [50–52]. Consequently, data from year 1 are of limited value for inter-group comparison and multivariable analysis. Additionally, absolute values of QCT measurements acquired at baseline and data acquired at later time points (years 2–4) may not be directly comparable due to the newer scanner generation used at later time points. To avoid potential bias, the investigation of effects from smoking and cessation on airway dimensions was therefore mainly based on inter-group comparisons between ES, AS, CS, and RQ at different time points. Consequently, longitudinal intra-group comparisons were not in the focus of this study and were only performed for the 2-, 3-, and 4-year follow-up, since these measurements were performed on the same CT scanner. During this short time span, we observed statistically significant longitudinal intra-group changes at several time points, and airway generations (as mentioned in the supplement), but the observed longitudinal differences were very small and showed no clear trend. Besides, TD and LA tended to increase from baseline until year 2 in ES and AS, while WP tended to decrease. These changes can be attributed partly to the exchange of the CT scanner. The performance of the software tool concerning airway segmentation and analysis of distal airway generations was very similar between groups and time points (Table S1). Due to fully automatic airway analysis software, the intrinsic variability of QCT measurements is extremely low and may at most originate from CT scanning procedures or changes in body fluid balance. In this context, short-term reproducibility studies showed insignificant differences in airway dimensional measurements which were markedly below the observed inter-group differences observed in our cohort [32, 53, 54].

Several studies recommended to normalize airway dimensions to lung volume, since the lung volume depends on height, body weight, and gender [26, 55, 56]. Consequently, we performed lung volume-based normalization for every airway measurement and each patient (data not shown). By comparing assets and distributions normalized results yielded no impact on the results of this study. We assume that variability of geometrical structures of bronchi and variability given by height and lung volume produce comparable size ranges.

Conclusion

Our findings indicate that bronchial lumen and bronchial diameter are decreased in active smokers compared to long-term ex-smokers and that there is a trend towards decreased airway wall area in active smokers, most likely reflecting inflammation and airway remodeling. We demonstrate for the first time that smoking-related airway changes can improve even in long-term heavy smokers after smoking cessation, and the effects seem to be long lasting, which is in line with clinical data on improved lung function after smoking cessation. Importantly, the smoking status was identified as a significant predictor of airway dimensions, independent of confounding factors such as age or amount of pack years smoked. Consequently, smoking-associated airway inflammation and remodeling can be adequately measured by quantitative CT, and the smoking status has a significant impact on quantitative CT-based airway analyses. Therefore, the current smoking status should be considered besides pack years when interpreting quantitative CT data of the airways in smokers.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Mark O. Wielpütz.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap The study subjects have been previously reported in J Thorac Oncol. 2015 Jun;10(6):890–6, J Cancer Res Clin Oncol. 2012 Sep;138(9):1475–86, J Cancer Res Clin Oncol. 2016 May;142(5):959–68, Eur Radiol. 2018 Feb;28(2):807–815, Cancer Prev Res (Phila). 2015 Sep;8(9):777–85, and Eur J Radiol. 2014 Mar;83(3):600–5. 376 participants have been reported in a study investigating effects of smoking cessation on lung density (Eur Radiol. 2018 Feb;28(2):807–815). Up to 49 participants were previously included in a study investigating the potential value of MRI for lung nodule detection (Eur J Radiol. 2014 Mar;83(3):600–5). These studies investigated data or aspects significantly different from the present manuscript.

Methodology
- retrospective study
- observational
- performed at one institution

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