Childhood-Onset Asthma in Smokers

Association between CT Measures of Airway Size, Lung Function, and Chronic Airflow Obstruction

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Abstract

Rationale and Objectives: Asthma is associated with chronic airflow obstruction. Our goal was to assess the association of computed tomographic measures of airway wall volume and lumen volume with the FEV_1 and chronic airflow obstruction in smokers with childhood-onset asthma.

Methods: We analyzed clinical, lung function, and volumetric computed tomographic airway volume data from 7,266 smokers, including 590 with childhood-onset asthma. Small wall volume and small lumen volume of segmental airways were defined as measures 1 SD below the mean. We assessed the association between small wall volume, small lumen volume, FEV_1, and chronic airflow obstruction (post-bronchodilator FEV_1/FVC ratio < 0.7) using linear and logistic models.

Measurements and Main Results: Compared with subjects without childhood-onset asthma, those with childhood-onset asthma had smaller wall volume and lumen volume ($P < 0.0001$) of segmental airways. Among subjects with childhood-onset asthma, those with the smallest wall volume and lumen volume had the lowest FEV_1 and greatest odds of chronic airflow obstruction. A similar tendency was seen in those without childhood-onset asthma. When comparing these two groups, both small wall volume and small lumen volume were more strongly associated with FEV_1 and chronic airflow obstruction among subjects with childhood-asthma in multivariate models.

Conclusion: In smokers with childhood-onset asthma, smaller airways are associated with reduced lung function and chronic airflow obstruction.
Clinical trial registered with www.clinicaltrials.gov (NCT00608764).

Keywords: airway wall volume; airway lumen volume; wall area percent

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There are several computed tomographic (CT) studies of central airway morphology in subjects with asthma (1–6). The results of these studies are inconsistent with subjects with asthma having larger, smaller, or similar-sized airways compared with control subjects (2, 4–6). A potential limitation of these investigations is the two-dimensional nature (2D) of the data with airway morphology expressed as wall thickness, wall area, or lumen area. These CT measures, however, are not analogous to airway size. For example, if airway wall thickening occurs on the lumenal side of the wall, such change would not be detected by measuring only the outer diameter of the airway. For this reason, more comprehensive assessments of CT bronchial volume (2D measures multiplied by length) may yield new insight into the associations of airway size and lung function in acute and chronic respiratory disease.

Recently, Gupta and colleagues (7) studied 65 subjects with mild-to-moderate or severe asthma using three-dimensional (3D) CT data. They found that subjects with asthma had smaller right upper lobe apical bronchus lumen volumes than control subjects and also tended to have smaller wall and total bronchial volumes. Although the latter two associations were likely limited by sample size, such analysis demonstrates the feasibility of using 3D airway measures and expands our understanding of the link between airway structure and function.

Based upon the prior reports of variable airway size in subjects with asthma and the work of Gupta and colleagues (7) presenting airway volumes rather than areas, we sought to explore the association between bronchial volume, lung function, and chronic airflow obstruction in smokers with and without childhood-onset asthma. We hypothesized that those with a history of childhood-onset asthma would have smaller airways than those without, and that bronchial size would be related to spirometric measures of lung function.

Materials and Methods

We used data from the COPDGene Study (8) to address this hypothesis. This study was designed to assess the genetic and epidemiological associations with chronic obstructive pulmonary disease (COPD) in non-Hispanic white and African American smokers 45–80 years of age (8). Subjects with active lung diseases other than asthma, emphysema, and COPD were excluded. COPDGene was approved by the institutional review board at each participating center, and all patients provided written informed consent. The current analysis was approved by the Partners Human Research Committee (Boston, MA) (2007P-000554).

Subject Selection

In this analysis, we selected smokers who had complete data on segmental airway volume from six bronchial paths (i.e., if a subject had missing airway volume data at any bronchial paths was not selected to this study) from the final 10,300_12MAR13 dataset (http://www.copdgene.org). We divided the smokers into two groups: those with and those without a history of childhood-onset asthma, defined as a self-reported physician diagnosis of asthma at age 18 years or younger. Subjects with asthma diagnosis after this age (n = 758) and those who did not report the age of this diagnosis were excluded from this analysis (n = 17). Subject selection is shown in Figure 1.

Clinical Evaluation

Demographic and clinical data, including standardized questionnaires (Medical History Questionnaire and Respiratory Disease Questionnaire) were collected (8). Subjects were considered to have had childhood-onset asthma if they responded "yes" to both of the following questions: "Have you ever had asthma?" and "Was it diagnosed by a doctor or other health professional?" Subjects with childhood-onset asthma were further classified as current or noncurrent subjects with asthma based on the response to the question "Do you still have it?" Subjects were considered to have had respiratory illness as a child if they responded "yes" to the following two questions: "Have you ever had pneumonia or bronchopneumonia [or] have you ever had an attack of bronchitis?" and "Was [this condition] diagnosed by a doctor or other health professional?" and if the illness was diagnosed at age 18 years or younger. A subject was considered to have had environmental exposure to a respiratory hazard at work if he/she responded affirmatively to any question regarding exposure at work (gas, smoke, chemical vapors, fumes) or had a dusty job.

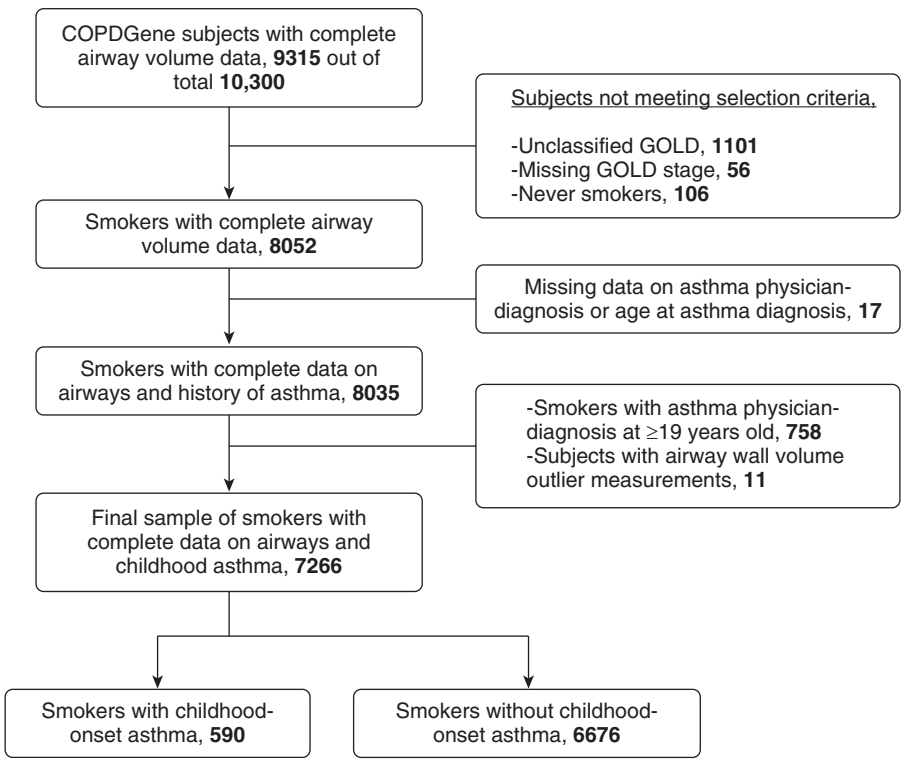

Figure 1. Diagram showing subject selection to this study. Unclassified GOLD (Global Initiative for Chronic Obstructive Lung Disease) is defined as low FEV_1 and normal FEV_1/FVC ratio.

All the questionnaires are available at www.copdgene.org.

Physiologic Evaluation

Spirometric measures of lung function were performed before and after the administration of albuterol, according to American Thoracic Society recommendations (9). Post-bronchodilator FEV_1 and FVC were expressed as percent of predicted values (10). Chronic airflow obstruction was defined as a post-bronchodilator FEV_1/FVC ratio less than 0.7 (11).

CT Scanning

All subjects underwent volumetric CT scanning without contrast in the supine position at coached full inspiration and relaxed exhalation. Data collected from inspiratory CT scans were analyzed. Images were acquired with CT protocols detailed in the online supplement (*see* also Reference 8).

CT Airway Analysis

Airway analysis on CT scan was performed with the dedicated software, Pulmonary Workstations 2 and Plus (VIDA Diagnostics, Coralville, IA [www.vidadiagnostics.com]) (12) at the Imaging Core for the COPDGene Study (Denver, CO). In our study, we used all available data for right main bronchus, left main bronchus, lobar bronchi (right upper lobe bronchus, intermediate bronchus, right lower lobe bronchus, left upper lobe bronchus, left lower lobe bronchus), and the segmental airways collected in six bronchial paths: right upper lobe apical bronchus; right middle lobe lateral bronchus; right lower lobe posterior basal bronchus; left upper lobe apicoposterior bronchus; superior lingular bronchus; and left lower lobe posterior basal bronchus. These segmental bronchi were selected based upon the consensus of COPDGene investigators and prior investigation (13–17).

Airway segmentations obtained with the software were then manually assessed for complete airway inclusion as well as correct and consistent labeling. Skipped branch points were also manually added as necessary to ensure accurate measurement of airway length. The segmental airway volume was calculated from CT measures of wall area, total bronchial area (wall area + lumen area), and airway length. Details of these measurements have been provided previously, including results of their validation in phantoms and *in vivo* CT scans of human lungs (18). In brief, the airway length (reported in mm) was measured as the distance between the branching point of the parent and child branches by placing a smoothed center line through the lumen. Thus, the software accounted for curved bronchial segments (i.e., if a bronchial segment is curved, then the length will be greater than the simple Euclidean distance between the parent- and child-branch points) (18). The total airway volume, wall volume, and lumen volume were computed as the total bronchial area, wall area, and lumen area multiplied by airway length, respectively.

Airway volume measurements are expressed in cubic millimeters, and segmental airways are reported as a mean from the six bronchial paths. The reproducibility of airway volume *in vivo* CT scans had a mean error of −0.05% (18). Airway volume measures are consistent with those from a recent study using VIDA software (7). The resultant wall volume and lumen volume measures were used to classify the central airways as small or medium-to-large size based on their value being lower or equal or above 1 SD below the mean of the entire cohort. We took this approach based on clinical and statistical bases. Clinically, it is plausible that, for an equivalent degree of bronchial injury, smaller airways of smokers (as measured by wall volume and lumen volume) with a history of childhood asthma may have increased risk for lower FEV_1 and chronic airflow obstruction. Statistically, on univariate analysis, wall volume and lumen volume below 1 SD from the mean had a large detrimental effect on FEV_1 ($\beta = -627$ ml and $\beta = -734$ ml; $P < 0.0001$ for both, respectively).

CT Quantification of Volume and Emphysema

CT measures of lung volume and low attenuation areas were performed with open source software Airway Inspector (www.airwayinspector.org). Lung volume measured on the full-inspiration CT scans was expressed as a percent of predicted total lung capacity (19). Emphysema was defined as percent of low attenuation areas less than −950 Hounsfield units on CT scan (20).

Statistical Analysis

Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Data are presented as means (±SD) or median (interquantile range) for continuous variables according to their distribution type and as frequency (%) for categorical variables. Comparisons of subjects' characteristics were performed using *t* test, Wilcoxon, and Chi-square tests, as appropriate. Regression plots between FEV_1 and lumen area, lumen volume, and wall volume were performed. Multivariate regression analyses by childhood-onset asthma status were performed to test the associations between outcomes, FEV_1, and chronic airflow obstruction, and the main predictors, small wall volume and small lumen volume. Details of the covariates are provided in the online supplement. Similar multivariate models with 2D CT measures of wall area and lumen area, both of which were dichotomized in the same manner as wall volume and lumen volume, were also performed. Finally, we conducted subgroup analyses among subjects diagnosed with asthma at age 10 years or younger, those without chronic airflow obstruction only, and those with childhood-onset asthma still reporting asthma, and those with childhood-onset asthma no longer reporting asthma.

Results

Out of 9,315 subjects with complete airway volume data available, 7,266 smokers were selected for this analysis with 590 having childhood-onset asthma (Figure 1). Subject characteristics are shown in Table 1. Compared with smokers without a history of childhood-onset asthma, those with childhood-onset asthma were more likely to be younger and African American and to have fewer pack-years of smoking. Subjects with childhood-onset asthma were also more likely to have a history of respiratory illness during childhood, maternal smoking during pregnancy, parental asthma, and environmental exposure at work. Smokers with childhood-onset asthma had a lower FEV_1 % predicted and FVC % predicted than smokers without childhood-onset asthma. These subjects also had higher frequency of spirometric diagnosis of chronic airflow obstruction.

Airways Dimensions by Childhood-Onset Asthma Status

In multivariate models, subjects with childhood-onset asthma had smaller mean

Table 1. Characteristics of all selected smoker participants (N = 7,266) by childhood-onset asthma status

Characteristics	With Childhood-Onset Asthma (n = 590)	Without Childhood-Onset Asthma (n = 6,676)	P Value
Age, yr	57 (51–65)	60 (52–67)	<0.0001
Male sex, %	55	57	0.31
African American race, %	44	30	<0.0001
Height, cm	170 ± 10	171 ± 9	0.29
BMI, kg/m^2	29 ± 6	28 ± 6	0.09
Pack-years of smoking	37 (25–53)	40 (28–55)	0.02
Current smoking status, %	55	52	0.23
Second-hand smoke exposure during childhood, %	84	82	0.41
Respiratory illness during childhood, %	39	16	<0.0001
Maternal smoking during pregnancy, %	26	22	0.006
Parental asthma, %	24	7	<0.0001
Environmental exposure at work, %	64	59	0.009
mMRC dyspnea score	2 (0–3)	1 (0–2)	<0.0001
FEV_1, % predicted	71 ± 27	80 ± 26	<0.0001
FVC, % predicted	86 ± 19	91 ± 18	<0.0001
FEV_1/FVC ratio	0.65 (0.51–0.76)	0.71 (0.58–0.79)	<0.0001
TLC_{CT}, % predicted	97 ± 16	97 ± 16	0.60
Emphysema on CT scan, %	2.5 (0.7–7.8)	2.3 (0.7–7.2)	0.78
Chronic airflow obstruction, %	61	47	<0.0001

Definition of abbreviations: BMI = body mass index; CT = computed tomography; mMRC = modified Medical Research Council; TLC_{CT} = total lung capacity measured on full-inspiration CT scans.
Data are presented as mean ± SD, median (interquantile range), and frequency (%) as appropriate. P values were calculated with t test, Wilcoxon test, and Chi-square test, respectively. Missing data: mMRC dyspnea score, 10; maternal smoking during pregnancy, 1; parental asthma, 1; second-hand smoke exposure during childhood, 3; environmental exposure at work, 3; TLC_{CT} % predicted, 3; emphysema on CT scan, 13.

lumen volume of the right main bronchus and all lobar bronchi ($P < 0.05$ for all comparisons). The difference in lumen volume of the left main bronchus was on the border of significance ($P = 0.06$). These subjects also had smaller mean wall volume of the right main bronchus, right upper lobe bronchus, and left lower lobe bronchus. The difference in wall volume was on the border of significance for the right lower lobe bronchus ($P = 0.09$) and left upper lobe bronchus ($P = 0.07$), and nonsignificant for the intermediate bronchus and left main bronchus (Table 2). Similarly, subjects with childhood-onset asthma had smaller wall area (difference, 1.3 mm^2), wall volume (difference, 16 mm^3), lumen volume (difference, 26.4 mm^3), and total airway volume (difference, 42.5 mm^3) of the averaged segmental airway measures than those without childhood-onset asthma. There were no significant differences in wall thickness or airway length between these groups; wall area percent was greater in those with childhood-onset asthma (Table 3).

When wall volume and lumen volume were examined by specific bronchial path, smoking subjects with asthma had smaller wall volume and lumen volume in all the paths ($P < 0.05$), with the exception of wall volume in left upper lobe apicoposterior bronchus (*see* Table E1 in the online supplement).

Association of Airway Size with FEV_1 and Chronic Airflow Obstruction by Childhood-Onset Asthma Status

Univariate regression analyses demonstrated that FEV_1 was directly related to lumen area, wall volume, and lumen volume with the slopes of these relationships being lower in those with childhood-onset asthma (Figure E1). This suggests that, for a given increase in FEV_1, the airway size increases less in the subjects with asthma than in the subjects without asthma. In models adjusted for demographics, smoking history, parental asthma, childhood respiratory illness, environmental exposure at work, and scanner type, the effect of small wall volume and lumen volume on FEV_1 was greater in subjects with childhood-onset asthma (for wall volume, −331 ml vs. −244 ml; for lumen volume, −534 ml vs. −435 ml). Similarly, the odds of chronic airflow obstruction for both small wall volume and small lumen volume were higher among subjects with childhood-onset asthma than those without childhood-onset asthma (small wall volume odds ratio, 2.10 vs. 2.02; small lumen volume odds ratio, 2.31 vs. 3.55) (Table 4). Similar, but stronger, results were observed when considering the effects of small wall area and small lumen area on both FEV_1 and chronic airflow obstruction (Table E2).

Finally, a subgroup analysis among subjects with asthma diagnosed at age 10 years or earlier (n = 482) showed comparable results for FEV_1 and chronic airflow obstruction (Table E3). The results in the subset of smokers without chronic airflow obstruction (n = 3,801) were similar to those of the entire study population, but the differences in the effects of lumen volume and wall volume on FEV_1 between those with and those without childhood-onset asthma were smaller (Table E4). Among subjects with childhood-onset asthma, the effects of lumen volume and wall volume on FEV_1 were greater in former than current subjects with asthma; wall volume was associated with chronic airflow obstruction only in the former subjects with asthma (Table E5). Former subjects with asthma also had greater emphysema on CT scan (6.9 vs. 5.3%; $P = 0.02$).

Discussion

In this study, we performed an extensive CT assessment of the extraparenchymal, lobar,

Table 2. Extraparenchymal bronchi and lobar bronchi dimensions in smokers by childhood-onset asthma status

	With Childhood-Onset Asthma Mean ± SD (mm^3)	Without Childhood-Onset Asthma Mean ± SD (mm^3)	Difference between Groups β ± SE (mm^3)	*P* Value
Right main bronchus				
Wall volume	3,145.7 ± 1,019.2	3,263.7 ± 1,106.7	−86.5 ± 38.6	0.02
Lumen volume	4,327.4 ± 1,347.4	4,545.7 ± 1,484.3	−166.9 ± 50.1	0.0009
Right upper lobe bronchus				
Wall volume	1,082.1 ± 329.9	1,129.3 ± 378.4	−36.1 ± 13.3	0.007
Lumen volume	1,145.2 ± 545.9	1,247.6 ± 541.8	−83.7 ± 20.9	<0.0001
Intermediate bronchus				
Wall volume	2,265.9 ± 650.0	2,322.5 ± 694.2	−29.0 ± 22.7	0.20
Lumen volume	2,790.9 ± 920.0	2,939.6 ± 990.3	−104.2 ± 32.4	0.001
Right lower lobe bronchus				
Wall volume	511.7 ± 212.6	524.9 ± 214.9	−14.9 ± 8.7	0.09
Lumen volume	398.2 ± 202.5	441.2 ± 213.4	−44.3 ± 8.8	<0.0001
Left main bronchus				
Wall volume	4,972.0 ± 1,409.5	5,008.5 ± 1,429.2	−3.7 ± 46.4	0.94
Lumen volume	6,433.8 ± 2,039.8	6,633.1 ± 2,038.9	−117.0 ± 63.3	0.06
Left upper lobe bronchus				
Wall volume	921.4 ± 303.3	956.1 ± 293.7	−18.9 ± 10.4	0.07
Lumen volume	964.0 ± 397.8	1,038.0 ± 380.8	−47.8 ± 14.0	0.0007
Left lower lobe bronchus				
Wall volume	920.8 ± 305.2	964.1 ± 313.6	−29.4 ± 11.7	0.01
Lumen volume	792.5 ± 340.1	885.3 ± 353.1	−78.9 ± 13.9	<0.0001

The difference (slope [β] ± SE) between smokers with and without history of childhood asthma (reference group) is from linear models adjusted for sex, race, height, and age.

and segmental airways in over 7,000 smokers with and without a history of childhood-onset asthma. We found that subjects with childhood-onset asthma had smaller airways than those without childhood-onset asthma. Furthermore, airway size was directly related to lung function in those with childhood-onset asthma, and inversely related to the risk of having chronic airflow obstruction. These results were substantiated in subjects whose asthma was diagnosed at or before 10 years of age and in those without chronic airflow obstruction.

Previous histopathologic studies have demonstrated mural inflammation and remodeling of the central airways in subjects with asthma. This has been associated with airway wall thickening on CT scan (2). However, our findings suggest that those subjects with childhood-onset asthma with the greatest spirometric impairment have the smallest airways, as measured by wall volume and lumen volume (Table 4). This apparent disconnect merits further discussion.

With our 2D measurements, we found that subjects with childhood-onset asthma had greater wall area percent than those without childhood-onset asthma (Table 3). These results are consistent with those reported by Aysola and colleagues (2) using CT data from the Severe Asthma Research Program. A potentially misleading aspect to the wall area percent is that it is a ratio influenced by both the numerator (wall area) and denominator (total bronchial area). In further exploration of the data presented by Aysola and colleagues, those subjects with severe asthma tended to have both a smaller wall area (44.1 mm^2 vs. 42.2 mm^2) and a smaller lumen area (45.9 mm^2 vs. 42 mm^2) than the subjects with moderate asthma. The ratio of wall area to total bronchial area was, however, increased, obscuring the overall trend in bronchial size. Their trends in wall area and lumen area suggest that airway remodeling may result in overall reductions of bronchial area (with relatively greater reductions in lumen area), or that people with smaller airways may be more prone to developing asthma.

Previously, we examined the relationship of airway structure and function in a cohort of never-smoking normal subjects from the COPDGene Study (21). We found that those subjects with the greatest wall area percent of the central airways had the lowest FEV_1. When examined in more detail, we found that subjects with lower lung function simply had smaller bronchial areas, and that, for a given reduction in total bronchial area, the lumen area tended to decrease faster than wall area. We suggested that the observed relationship between wall area and total bronchial area in never-smokers was a result of the natural scaling of biologic structures. Smaller airways simply have a greater wall-to-lumen or wall-to-total bronchial area ratio.

To ensure that our 2D observations in subjects with asthma were not due to forces acting orthogonally to the imaging plane (i.e., longitudinal stretch of the airways) we undertook a more comprehensive assessment using 3D CT measures of airway structure. Bronchial size was calculated as the product of area and bronchial length, and presented as wall volume and lumen volume. We found no difference in airway length between smokers with and without childhood-onset asthma, suggesting that elongation of the airways was not causing narrowing of the structures assessed on 2D analysis. In the absence of such artifact, smaller bronchial areas and bronchial volumes in those with childhood-onset asthma may be interpreted as evidence for

Table 3. Segmental airway dimensions in smokers by childhood-onset asthma status

	With Childhood-Onset Asthma Mean ± SD	Without Childhood-Onset Asthma Mean ± SD	Difference between Groups β ± SE	*P* Value
Wall thickness, mm	1.44 ± 0.13	1.45 ± 0.12	−0.004 ± 0.005	0.41
Wall area, mm^2	30.4 ± 6.1	31.7 ± 5.8	−1.3 ± 0.2	<0.0001
Wall area percent, %	62.5 ± 3.2	61.0 ± 3.0	1.6 ± 0.1	<0.0001
Airway length, mm	12.5 ± 2.2	12.5 ± 2.0	0.07 ± 0.08	0.39
Wall volume, mm^3	371.4 ± 92.5	388.7 ± 94.0	−16.0 ± 3.3	<0.0001
Lumen volume, mm^3	230.8 ± 76.9	257.4 ± 80.9	−26.4 ± 3.0	<0.0001
Total airway volume, mm^3	602.2 ± 165.5	646.1 ± 171.0	−42.5 ± 6.1	<0.0001

The difference (slope [β] ± SE) between smokers with and without history of childhood asthma (reference group) is from linear models adjusted for sex, race, height, age, pack-years of smoking, current smoking status, lung volume, emphysema on computed tomography scan, and scanner type.

these subjects having smaller airways. The difference in segmental airway volumes between those with and those without childhood-onset asthma persisted after accounting for relevant factors affecting airway morphology, including lung volume and the burden of emphysema on CT scan (17). These differences in wall volume and lumen volume are not likely due to smooth muscle tone, as, per protocol, subjects were imaged after performing spirometric testing with bronchodilator.

We further examined 3D CT measures of extraparenchymal airways, such as the right and left main bronchi. We chose these two bronchi with the hypothesis that their morphology was not as interdependent with the surrounding parenchyma as the intraparenchymal lobar and segmental airways. Again, subjects with childhood-onset asthma had smaller central airways; this finding persisted in multivariate regression analysis.

Another interesting finding in this study was that in, former subjects with asthma, the effect of small airway size (wall volume and lumen volume) on lung function was greater than in those with current asthma. In addition, small wall volume was strongly associated with chronic airflow obstruction in former subjects with asthma only (Table E5). Potential explanations for these findings include misclassification of asthma status and greater loss of elastic recoil in former subjects with asthma as they had more emphysema on CT scan.

Table 4. Association between bronchial size, lung function and chronic airflow obstruction in smokers with and without childhood-onset asthma

	FEV_1 (*ml*)				Chronic Airflow Obstruction			
	With Childhood-Onset Asthma		Without Childhood-Onset Asthma		With Childhood-Onset Asthma		Without Childhood-Onset Asthma	
	Mean ± SD	β (95% CI)	Mean ± SD	β (95% CI)	Total No. in Category/No. with Chronic Airflow Obstruction (%)	Adjusted OR (95% CI)	Total No. in Category/No. with Chronic Airflow Obstruction (%)	Adjusted OR (95% CI)
Small wall volume								
Yes	1,654 ± 727	−331 (−488 to −174)*	1,842 ± 733	−244 (−294 to −194)*	115/77 (67)	2.10 (1.27–3.46)†	1,025/568 (55)	2.02 (1.72–2.36)*
No	2,189 ± 936		2,472 ± 947		475/283 (60)		5,651/2,537 (45)	
Small lumen volume								
Yes	1,589 ± 728	−534 (−669 to −398)*	1,749 ± 767	−435 (−485 to −386)*	148/112 (76)	4.32 (2.64–7.08)*	946/625 (66)	3.55 (3.00–4.19)*
No	2,251 ± 923		2,478 ± 931		442/248 (56)		5,730/2,480 (43)	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
The multivariate model for FEV_1 was adjusted for sex, race, age, height, current smoking status, pack-years of smoking, second-hand smoke exposure and respiratory illness during childhood, maternal smoking during pregnancy, parental asthma, environmental exposure at work, and scanner type. The logistic model for chronic airflow obstruction included sex, age, pack-years of smoking, maternal smoking during pregnancy with the participant, respiratory illness during childhood, and environmental exposure at work as covariates. *P* values for the Hosmer and Lemeshow goodness-of-fit test for logistic models with small wall volume were 0.30 and 0.53 in subjects with and without childhood-onset asthma, respectively; corresponding *P* values for models with small lumen volume were 0.29 and 0.48.
*$P < 0.0001$.
†$P = 0.004$.

Overall, our findings support epidemiologic studies suggesting that asthma leads to chronic airflow obstruction (22–28). Early work (29) has suggested that, for a common exposure such as tobacco smoke, intrinsic bronchial structure may be responsible for the differential development of chronic bronchitis or emphysema. By using CT measures of airways, this theory has been substantiated in women (30), who have smaller bronchi relative to lung size compared with men. Low expiratory airflows attributed to a disproportionate (small) airway size relative to lung volume have also been described in healthy women during exercise (31) and in people living at altitude (32). Other studies have shown that low birth weight is linked to a greater risk of subsequent lung function impairment, asthma, and chronic obstructive airways disease (33–35). It is thought that this may due to delayed lung development with smaller bronchi that persist into adulthood (35).

Our study is not without limitations. There may be selection bias in the cohort, as the participating subjects with childhood-onset asthma may have more advanced disease than the general population of those with childhood-onset asthma, and there is an overrepresentation of COPD prevalence in the COPDGene Study. Thus, the generalizability of our findings to the entire population of childhood-onset asthma should be interpreted with caution. We also used a self-reported physician diagnosis of asthma, and misclassification is possible. However, more invasive techniques, such as methacholine challenge testing to diagnose asthma in subjects with FEV_1 of less than 70%, might be unsafe (36). In addition, the COPDGene study did not collect data on gestational age and birth weight, preventing us from accounting for these variables in our models. We also only used measures down only to the segmental airway level, which does not properly represent the heterogeneous morphology of the entire bronchial tree. The segmental airway volume measurements provided here, however, are similar to those reported by others using the same software (7). Finally, this is a cross-sectional analysis, and, as such, the changes we observed in the airways may be the consequence rather than the cause of the disease processes.

In summary, we analyzed data from the CT scans of over 7,000 smokers and found that those with childhood-onset asthma had the smaller airways than smokers without asthma. We further found that those with childhood-onset asthma who had the smallest airways were the most likely to have chronic expiratory airflow obstruction and the lowest FEV_1. Based upon our 2D and 3D data, as well as information from prior publications, these findings suggest that mural remodeling in subjects with childhood-onset asthma may result in smaller airways, and/or these subjects simply have smaller native airways, which predisposed them to smoking-induced airflow obstruction. Further longitudinal analyses are warranted to test this hypothesis. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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