Influence of asthma onset on airway dimensions on ultra-high-resolution CT in chronic obstructive pulmonary disease

Abstract

Purpose

Asthma onset before 40 years of age is associated with distinct clinical manifestations in COPD patients, but its morphological features remain unestablished. This study aimed to explore airway morphology in COPD patients with asthma onset before 40 years of age by using ultra-high-resolution CT (U-HRCT), which allows more accurate quantitation of the lumen and wall in smaller airways than conventional CT.

Materials and Methods

Clinical data of 500 consecutive patients undergoing full inspiratory U-HRCT (1024x1024 matrix and 0.25 mm slice thickness) were retrospectively analyzed. COPD patients without asthma, COPD patients with asthma onset at age < or ≥ 40 years and non-COPD smoker controls (N=137, 29, 34, and 22, respectively) were enrolled. The length, lumen area (LA), wall thickness and area (WA), and wall area percent (WA%) of the segmental (3^{rd}-generation) to sub-sub-segmental (5^{th}-generation) bronchus and the low attenuation volume percent (LAV%) were measured.

Results

LA and WA were smaller in the 4^{th} and 5^{th}-generation in COPD patients than in non-COPD controls, regardless of asthma onset. LA was smaller and WA% was larger in the 4^{th}- and 5^{th}-generation airways in COPD with asthma onset before 40 years than COPD without asthma, whereas WA did not differ between them. In multivariate analyses, asthma onset before 40 years was associated with smaller LA in COPD patients independent of demographics, use of inhaled corticosteroid and long-acting bronchodilators, airflow limitation, and LAV%.

Conclusions

Asthma onset before 40 years of age could be associated with greater lumen narrowing of the airways in COPD.

Keywords

Lung, Airway, Chronic obstructive pulmonary disease, Asthma, Computed tomography

Introduction

Chronic obstructive pulmonary disease (COPD) is a major lung disease that is diagnosed by simply detecting airflow limitation on spirometry but is characterized by heterogeneity in clinical and radiological manifestations and treatment responses[1]. This heterogeneity has prompted us to explore "treatable traits" in each patient[2]. Studies have shown that asthma onset is common in patients with COPD[3] and is associated with severe symptoms, frequent exacerbations, and poor mortality in COPD[3-5]. Importantly, asthma onset before age 40 years is widely used to identify a subgroup of COPD patients with a "treatable trait" who may benefit from inhaled corticosteroid (ICS) therapy in addition to a standard long-acting bronchodilator (LABD) therapy, such as a long-acting muscarinic antagonist and beta-agonist[4,6,7]. However, despite these distinct clinical features, the pathogenesis of COPD with asthma onset before age 40 years is not fully understood.

Structural assessment is essential for better understanding the pathogenesis of COPD subtypes including COPD with asthma. While the peripheral small airway is a major pathological site of COPD[8], thickening of the inner wall of the proximal cartilaginous airways associated with increased inflammation is a histological feature of COPD[9]. Moreover, luminal narrowing of the proximal cartilaginous airways due to wall thickening, mucus plugging, smooth muscle hypertrophy, and inflammation is commonly found in asthma[10]. Therefore, it is possible that asthma onset before age 40 years would have additional impacts on the proximal airway dimensions in COPD.

Computed tomography (CT) is readily accessible and informative for evaluating the airways and parenchyma separately[11]. CT studies have shown that luminal narrowing of proximal airways is a common feature in both COPD and asthma[12-15] but is more severe in asthma than in COPD[16]. Moreover, the lumen size of the segmental airways (3rd-generation) is smaller in smokers with childhood-onset asthma than in those without an asthma history[17], and the lumen area (LA) is smaller in patients with COPD and asthma than in patients with COPD alone[18]. In contrast, CT studies on both asthma and COPD have shown inconsistent results regarding wall thickening[13-15,19-21].

The difficulty in accurately quantifying the airway wall originates from the limited resolution of CT scans[22]. In conventional 512 x 512 matrix CT, the wall thickness is overestimated when evaluating smaller airways. Furthermore, the number of airways identifiable on conventional CT is reduced even in the 5th-generation airways in patients with COPD and asthma[23-25], inducing selection bias in measurements of airway dimensions[21]. However, this shortcoming has been mitigated by the recent introduction of ultra-high-resolution CT (U-HRCT)[26]. U-HRCT provides a 1024×1024 matrix image at a 0.25 mm slice thickness with no increase in radiation exposure[27] and enables accurate measurement of the lumen and wall sizes in peripheral airways >1.0 mm in diameter and >0.5 mm in wall thickness[28,29].

We hypothesized that asthma onset prior to COPD development drives structural alteration of the airways and contributes to the establishment of distinct subtypes of COPD. The aim of this study was to compare the lumen and wall sizes of 3rd- to 5th-generation airways in COPD patients with asthma onset before 40 years of age to those in COPD patients without asthma onset and non-COPD smoker controls by using U-HRCT images.

Material and methods

Patient enrollment and ethics statement

This is a retrospective cross-sectional study using clinical data from 500 consecutive subjects who underwent inspiratory chest U-HRCT at our hospital between February 2018 and October 2019. Medical history, spirometry, and U-HRCT records were reviewed, and all smokers with COPD and non-COPD smokers without any history of lung disease (smoker controls) were included in the present analyses. Smokers were defined as those with a smoking history of at least 10 pack-years[4,18]. A diagnosis of COPD was confirmed by a postbronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70%[30]. The smoker controls had an FEV_1/FVC ratio >70% and a percent of predicted FEV_1 (%FEV_1) >80%. Asthma onset was confirmed based on patient-reported diagnosis of asthma at age < 40 or ≥ 40 years. The exclusion criteria were alpha-1 antitrypsin

deficiency, other lung diseases such as interstitial pneumonia, atelectasis, and bronchiectasis, and a prior history of surgical lung resection. A commercially available Aquilion Precision scanner (Cannon Medical Systems, Otawara, Japan) was used for U-HRCT scans[27,29], and a Chestac-8900 (Chest M.I., Inc., Tokyo, Japan) was used for spirometry. The predicted FVC and predicted FEV_1 were calculated with the LMS method[31]. The study was approved by the ethics committee of our institution (approval No. R1660), and informed consent was waived due to the retrospective use of the data.

U-HRCT scan protocol

The Aquilion Precision scanner provided 1024×1024 matrix images with a 0.25 mm slice thickness using 0.25×0.25 mm detector elements in the superhigh-resolution (SHR) mode under the conditions of 120 kVp, 0.5 second exposure time, 350 mm field of view, and autoexposure control [27,28,32]. The U-HRCT images were reconstructed with the full iterative reconstruction method, namely, the forward-projected model-based iterative reconstruction solution (FIRST) algorithm for quantitation of airway dimensions[33]. Moreover, conventional 512×512 matrix images with a 1 mm slice thickness were also reconstructed using the smooth reconstruction algorithm (FC13) for quantitation of emphysematous change. The volume CT dose index ($CTDI_{vol}$) was approximately 10 mGy.

U-HRCT analyses

As shown in Figure 1, the airway length between two branching points, lumen and wall size of the segmental (3rd-generation), sub-segmental (4th-generation), and sub-sub-segmental (5th-generation) airways of the right apical, middle lateral, and lower posterior paths (RB1, RB4, and RB10) were measured on U-HRCT images using custom-made software, as previously reported[28]. Briefly, the centerline of the lumen was established 3-dimensionally, and cross-sectional images perpendicular to the centerline were generated for the middle two-thirds of each airway segment. The edges of the airway wall were automatically determined on all the cross-sectional images based on the full-width at half-maximum principle[20,28], and the lumen area (LA), wall thickness (WT), and wall area (WA) were measured and averaged for each segment. The WA% was

calculated using the following formula: 100*WA/(sum of LA and WA)[16,18,32]. The average length, LA, WT, WA and WA% from all identifiable segments of the RB1, RB4, and RB10 paths were used in the present analyses.

Lung volume on CT (CT-TLV) and the percentage ratio of voxels < −950 HU to total lung voxels, namely, the low attenuation volume percent (LAV%), were also measured on conventional 512×512 matrix images reconstructed by smooth kernel (FC13) using the SYNAPSE VINCENT volume analyzer (FUJIFILM, Tokyo, Japan)[18].

Statistical analysis

Statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) for Statistical Computing[34]. Data are expressed as the mean ± standard deviation (SD) unless otherwise indicated. A p value less than 0.05 was considered statistically significant. Continuous variables and categorical variables were compared using one-way analysis of variance followed by post hoc Tukey's multiple comparison method and the Chi-squared test, respectively. To assess whether asthma onset is associated with LA of the 4^{th}- and 5^{th}-generation airways in COPD, multiple linear regression models were constructed including the presence of asthma onset diagnosed at an age of either < 40 years or ≥ 40 years, age, sex, smoking status, smoking pack-year, the presence of increased blood eosinophils (>300/μl), the use of ICS, the use of LABD, and either $\%FEV_1$ or LAV% as independent variables.

Results

Of 500 consecutive subjects who were screened, 200 patients with COPD and 22 non-COPD smoker controls without any history of lung disease were included in the analyses (Figure 2). Based on patient-reported past history of asthma, patients with COPD were classified into those without asthma onset and those with asthma onset at age < 40 years or ≥ 40 years. Table 1 shows the demographics of the subjects. Age, sex, height, weight, smoking pack-years, and the ratio of LABD use did not differ among the 4 groups. In contrast, %FVC and $\%FEV_1$ were lower in COPD patients with asthma onset at the age

of < 40 years than in the other groups. LAV% and CT-TLV were greater in COPD patients with asthma onset at the age ≥ 40 years and COPD patients with no asthma onset, but there was no significant difference in LAV% between COPD patients with no asthma and those with asthma onset at age < 40 years. The ratio of ICS use was greater in COPD patients with asthma onset at ages < 40 and ≥ 40 years than in those with no asthma onset.

In measurements of airway dimensions (Table 2), the number of airways measurable on U-HRCT and airway length of the 3rd-, 4th-, and 5th-generation airways did not differ among the 4 groups, whereas LA was lower and WA% was higher in the 4th- and 5th-generation airways of COPD patients with asthma onset at age < 40 years than in those of COPD patients with no asthma onset or smoker controls. WA in the 3rd-, 4th-, and 5th-generation airways did not differ between COPD patients with no asthma and those with asthma onset at age < 40 years. These comparisons of LAV%, LA, WA, and WA% in the 5th-generation airways are also shown in Figure 3, and the representative U-HRCT images of the 5th-generation airways (Figure 4) also show a smaller lumen size in COPD patients with asthma onset at age < 40 years compared to COPD patients without asthma onset. Furthermore, COPD patients with asthma onset at age < 40 years were divided into those with and without childhood-onset (age < 20 years) asthma (n=20 and 9, see Figure E1, Supplemental Digital Content). There was no difference in LA or WA between these two groups.

In multivariable linear regression analysis (Table 3), asthma onset at age < 40 years was significantly associated with lower LA in the 5th-geneartion airways, independent of age, height, smoking status, pack-years, ICS use, LABD use the presence of blood eosinophils >300, %FEV$_1$ and LAV%. The similar association of asthma onset at age < 40 years with lower LA was also found when using LA in the 4th generation airways (see Table E1, Supplemental Digital content). Moreover, in multivariable analysis that adjusted for the same variables, asthma onset at age < 40 years was significantly associated with higher WA% in the 4th generation, but not in the 5th-generation (see Table E2,

Supplemental Digital Content).

Discussion

The present U-HRCT analyses show that regardless of asthma onset, the lumen and wall areas were smaller in patients with COPD than in non-COPD smokers who had similar smoking histories. In addition, asthma onset before age 40 years had significant impacts on luminal narrowing in the 4th- and 5th-generation airways in patients with COPD, independent of %FEV$_1$, LAV%, the use of ICS and/or LABD, and the presence of higher blood eosinophils. These findings confirm a significant impact of asthma onset prior to COPD diagnosis on airway size in COPD and may provide the structural background underlying previous clinical findings that childhood asthma is an important risk factor for future development of COPD[35] and that asthma onset before age 40 years is associated with frequent exacerbations in patients with COPD[6].

The 3rd- to 5th-generation of RB1, RB4, and RB10 airways were clearly visualized owing to the improvement in both in-plain and z-axis resolutions, and the number of 3rd- to 5th-generation airways measured on U-HRCT did not differ among the 4 groups. This unbiased sampling of target airways on U-HRCT is a major advantage over previous conventional CT studies, in which even the number of 5th-generation airways was reduced in COPD patients compared to controls[23,25], and the sampling bias could skew quantitative evaluations of those airways[21]. Moreover, the mean (SD) WTs for the 5th-generation airways were 0.96 (0.08), 0.90 (0.06), 0.89 (0.09), and 0.90 (0.07) mm in the 4 groups, suggesting that the WT of the 5th-generation airways was over the lower limit of quantitation for the walls (0.6 mm) on U-HRCT, whereas the WT of approximately more than half of these airways was below the lower limit of quantitation (1.0 mm) and overestimated on conventional CT[22,28].

Since airways are stretched during inspiration, insufficient full inspiration at CT scans potentially affects quantitative measurements of the lumen and wall areas on the 2-dimensional cross-sectional images of a target airway which were reconstructed from

inspiratory CT scans. However, because the airway length between two branching points for the 3rd- to 5th-generation airways did not differ among the 4 groups, we postulate that the extent of the 3-dimensional stretch of the measured airways during inspiratory CT scans is similar among the groups, and may not affect the present comparisons. . The comparisons of airway dimensions show that the LA in the 4th- and 5th-generation airways but not the 3rd-generation airways was smaller in COPD patients with asthma onset before 40 years of age than in COPD patients without asthma onset (Table 2 and Figure 3). The finding was further confirmed by the multivariate regression analysis that adjusted for age, sex, height, smoking status, ICS use, LABD use, and either %FEV_1 or LAV%. These findings extend a previous conventional CT-based report on the association between childhood-onset asthma and smaller 3rd-generation airways in smokers[17] and suggest that a smaller lumen might occur in the peripheral airways than in the central airways in COPD patients with asthma onset before 40 years of age.

The WT did not differ between COPD patients with and without asthma onset in this study. This is partially consistent with a previous conventional CT study[18] that showed no difference in the WT of the 5th-generation airways between asthma-COPD patients and COPD patients. However, a previous study also showed that the WT was greater in the 3rd- and 4th-generation airways in asthma-COPD patients than in COPD patients. This could be affected by the different inclusion criteria, where those authors defined asthma-COPD using variable symptoms and bronchiolar reversibility but not a history of asthma. Moreover, the different resolution of the CT scans (conventional CT vs U-HRCT) could affect the results because U-HRCT allows for accurate measurements of the WT with less overestimation than conventional CT[28,32].

Regardless of asthma onset, both the lumen and wall areas were smaller in the 3 groups of COPD patients, compared to those in the control group. This is consistent with previous reports that showed that the wall areas of the central airways are smaller in COPD patients than in non-COPD patients[15,21]. Notably, the 5th generation airways in the 3 groups of COPD patients showed smaller lumen and wall areas, but larger WA%, compared to the

control group. Considering that the WA% was determined by the ratio of wall area to the sum of wall and lumen area, a combination of decreased wall area and increased WA% in the 3 COPD groups could be because while both the lumen and wall areas are reduced in COPD, the degree of reduction in the lumen area is relatively greater than that in the wall area.

The blood eosinophil count and the ratio of ICS use, but not LABD use, differed between COPD patients with no asthma onset and those with asthma onset at the age < 40 and ≥ 40 years. While airway dimensions on CT could be affected by higher blood eosinophil count [36] and treatments with ICS and LABD[37], the result of the multivariable analysis confirmed that asthma onset before 40 years of age was associated with a smaller lumen of the 4th– and 5th-generation airways even after adjusting for the presence of blood eosinophils >300/μL and the use of ICS and/or LABA.

The lumen area was decreased and the WA% was increased in COPD with asthma onset at age < 40 years compared to COPD without asthma onset, whereas the wall area did not differ between the two groups. The mechanism by which luminal narrowing is not accompanied by an increase in wall area in COPD with asthma onset at age < 40 years is beyond the scope of this study. Because a smaller airway size is associated with lower lung function even in healthy persons[38] and low baseline lung function in younger age predisposes individuals to airway disease development[39], we speculate that persons with a smaller airway size at a younger age may carry a higher risk of asthma onset before 40 years and subsequent COPD development compared to those with normal airway size.

Some limitations need to be described. First, due to the retrospective nature of the analyses, clinical symptoms and exacerbations were not consistently collected for all the subjects. We were not able to examine whether the morphological changes could have impacts on clinical symptoms and exacerbations. Second, the sample size of controls and COPD patients with asthma onset at age < 40 or ≥ 40 years was not large. Third, the majority of subjects were male. Whether the present findings can be generalized to both males and females is not clear. We acknowledge that the present findings need to be

validated in a future larger study.

In conclusion, the present U-HRCT data show that asthma onset before age 40 years is associated with a smaller lumen of the 4th- and 5th-generation airways in COPD, which might be a key morphological factor underlying the distinct clinical manifestation of COPD patients with asthma onset before age 40 years.

References

1. Faner R, Agusti A. Multilevel, Dynamic Chronic Obstructive Pulmonary Disease Heterogeneity. A Challenge for Personalized Medicine. *Ann Am Thorac Soc.* 2016;13 Suppl 2:S466-S470.
2. McDonald VM, Fingleton J, Agusti A, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *Eur Respir J.* 2019;53(5).
3. Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med.* 2013;107(7):1053-1060.
4. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. *Respir Res.* 2011;12:127.
5. Jo YS, Hwang YI, Yoo KH, et al. Effect of Inhaled Corticosteroids on Exacerbation of Asthma-COPD Overlap According to Different Diagnostic Criteria. *J Allergy Clin Immunol Pract.* 2020.
6. Hayden LP, Hardin ME, Qiu W, et al. Asthma Is a Risk Factor for Respiratory Exacerbations Without Increased Rate of Lung Function Decline: Five-Year Follow-up in Adult Smokers From the COPDGene Study. *Chest.* 2018;153(2):368-377.
7. Sin DD, Miravitlles M, Mannino DM, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. *Eur Respir J.* 2016;48(3):664-673.
8. Hogg JC, Pare PD, Hackett TL. The Contribution of Small Airway Obstruction to the Pathogenesis of Chronic Obstructive Pulmonary Disease. *Physiol Rev.* 2017;97(2):529-552.
9. Tiddens HA, Pare PD, Hogg JC, Hop WC, Lambert R, de Jongste JC. Cartilaginous airway dimensions and airflow obstruction in human lungs. *Am J Respir Crit Care Med.* 1995;152(1):260-266.

10. James AL, Pare PD, Hogg JC. The mechanics of airway narrowing in asthma. *Am Rev Respir Dis.* 1989;139(1):242-246.
11. Labaki WW, Martinez CH, Martinez FJ, et al. The Role of Chest Computed Tomography in the Evaluation and Management of the Patient with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2017;196(11):1372-1379.
12. Tanabe N, Vasilescu DM, Kirby M, et al. Analysis of airway pathology in COPD using a combination of computed tomography, micro-computed tomography and histology. *Eur Respir J.* 2018;51(2):1701245.
13. Postma DS, Brightling C, Baldi S, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. *Lancet Respir Med.* 2019;7(5):402-416.
14. Gupta S, Hartley R, Khan UT, et al. Quantitative computed tomography-derived clusters: redefining airway remodeling in asthmatic patients. *J Allergy Clin Immunol.* 2014;133(3):729-738 e718.
15. Washko GR, Diaz AA, Kim V, et al. Computed tomographic measures of airway morphology in smokers and never-smoking normals. *J Appl Physiol (1985).* 2014;116(6):668-673.
16. Shimizu K, Hasegawa M, Makita H, Nasuhara Y, Konno S, Nishimura M. Comparison of airway remodelling assessed by computed tomography in asthma and COPD. *Respir Med.* 2011;105(9):1275-1283.
17. Diaz AA, Hardin ME, Come CE, et al. Childhood-onset asthma in smokers. association between CT measures of airway size, lung function, and chronic airflow obstruction. *Ann Am Thorac Soc.* 2014;11(9):1371-1378.
18. Karayama M, Inui N, Yasui H, et al. Physiological and morphological differences of airways between COPD and asthma-COPD overlap. *Sci Rep.* 2019;9(1):7818.
19. Niimi A, Matsumoto H, Amitani R, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med.* 2000;162(4 Pt 1):1518-1523.
20. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med.* 2000;162(3 Pt 1):1102-1108.
21. Smith BM, Hoffman EA, Rabinowitz D, et al. Comparison of spatially matched airways reveals thinner airway walls in COPD. The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study and the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax.* 2014;69(11):987-996.
22. Oguma T, Hirai T, Niimi A, et al. Limitations of airway dimension measurement on images obtained using multi-detector row computed tomography. *PLoS One.*

2013;8(10):e76381.
23. Kirby M, Tanabe N, Tan WC, et al. Total Airway Count on Computed Tomography and the Risk of Chronic Obstructive Pulmonary Disease Progression. Findings from a Population-based Study. *Am J Respir Crit Care Med.* 2018;197(1):56-65.
24. Eddy RL, Svenningsen S, Kirby M, et al. Is Computed Tomography Airway Count Related to Asthma Severity and Airway Structure-function? *Am J Respir Crit Care Med.* 2020.
25. Diaz AA, Valim C, Yamashiro T, et al. Airway count and emphysema assessed by chest CT imaging predicts clinical outcome in smokers. *Chest.* 2010;138(4):880-887.
26. Yanagawa M, Hata A, Honda O, et al. Subjective and objective comparisons of image quality between ultra-high-resolution CT and conventional area detector CT in phantoms and cadaveric human lungs. *Eur Radiol.* 2018;28(12):5060-5068.
27. Xu Y, Yamashiro T, Moriya H, Muramatsu S, Murayama S. Quantitative Emphysema Measurement On Ultra-High-Resolution CT Scans. *Int J Chron Obstruct Pulmon Dis.* 2019;14:2283-2290.
28. Tanabe N, Oguma T, Sato S, et al. Quantitative measurement of airway dimensions using ultra-high resolution computed tomography. *Respir Investig.* 2018;56(6):489-496.
29. Tanabe N, Shima H, Sato S, et al. Direct evaluation of peripheral airways using ultra-high-resolution CT in chronic obstructive pulmonary disease. *Eur J Radiol.* 2019;120:108687.
30. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *Eur Respir J.* 2017;49(3).
31. Kubota M, Kobayashi H, Quanjer PH, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. *Respir Investig.* 2014;52(4):242-250.
32. Mikayama R, Shirasaka T, Yabuuchi H, et al. Effect of scan mode and focal spot size in airway dimension measurements for ultra-high-resolution computed tomography of chronic obstructive pulmonary disease: A COPDGene phantom study. *Phys Med.* 2020;70:102-108.
33. Nishiyama Y, Tada K, Nishiyama Y, et al. Effect of the forward-projected model-based iterative reconstruction solution algorithm on image quality and radiation dose in pediatric cardiac computed tomography. *Pediatr Radiol.* 2016;46(12):1663-1670.
34. *R: A Language and Environment for Statistical Computing. URL http://www.R-project.org/.* [computer program]. 2015.

35. Tagiyeva N, Devereux G, Fielding S, Turner S, Douglas G. Outcomes of Childhood Asthma and Wheezy Bronchitis. A 50-Year Cohort Study. *Am J Respir Crit Care Med.* 2016;193(1):23-30.
36. Hastie AT, Martinez FJ, Curtis JL, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. *Lancet Respir Med.* 2017;5(12):956-967.
37. Suzuki T, Tada Y, Kawata N, et al. Clinical, physiological, and radiological features of asthma-chronic obstructive pulmonary disease overlap syndrome. *Int J Chron Obstruct Pulmon Dis.* 2015;10:947-954.
38. Green M, Mead J, Turner JM. Variability of maximum expiratory flow-volume curves. *J Appl Physiol.* 1974;37(1):67-74.
39. Lange P, Celli B, Agusti A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med.* 2015;373(2):111-122.

Figure captions

Figure 1. Quantitative of airway dimensions using ultra-high-resolution CT

A target airway was selected (yellow arrow), and then the software automatically established the centerline of the lumen 3-dimensionally, and measured airway length between two branching points. Cross-sectional images perpendicular to the centerline were generated for the middle two-thirds of each airway segment, and lumen (green) and wall (blue) were segmented, quantified, and averaged for the airway.

Figure 2. Patient flow chart

U-HRCT = ultra-high-resolution computed tomography. FEV_1 = forced expiratory volume in one second. FVC = forced vital capacity. $\%FEV_1$ = % of predicted FEV_1

Figure 3. Emphysema and dimensions of the sub-sub-segmental airways in COPD and non-COPD patients

(A) Low attenuation volume percent (LAV%), (B) lumen area, (C) wall thickness, and (D) wall area percent (WA%) of the sub-sub-segmental airways (5^{th}-generation) were compared with Tukey's all-pairwise comparison. Patients with COPD were divided into 137 COPD patients without asthma onset (COPD No asthma), 29 COPD patients with asthma onset at age < 40 years and 34 COPD patients with asthma onset at age ≥ 40 years. A middle line of box indicates the median value, and upper and lower lines of box indicate the 75th and 25th percentile. Upper and lower whiskers extends to the largest and smallest values. * indicates $p<0.05$ compared to the control group. P values were calculated based on the Tukey's multiple comparisons.

Figure 4. Representative U-HRCT images of the sub-sub-segmental (5^{th}-generation) airways in COPD patients with asthma onset before age 40 years and COPD patients without asthma onset.

Representative cross-sections of the sub-sub-segmental (5^{th}-generation) airways of the right apical bronchus in male former smokers. (A) COPD patients with asthma onset before age 40 years (%FEV_1 = 57%, low attenuation volume percent [LAV%]=0.3%, lumen area = 6.9mm^2, wall area percent [WA%] = 64%). (B) COPD patients with asthma onset before age 40 years and severe emphysema (%FEV_1 = 20% and LAV%=43%, lumen area = 4.7mm^2, WA%=67%). (C) COPD patients without asthma onset and mild emphysema (%FEV_1 = 68%, LAV%=15%, lumen area = 9.8mm^2, WA%=53%). (D) COPD patients without asthma onset and moderate emphysema (%FEV_1 = 55%, LAV%=31%, lumen area = 9.0mm^2, WA% =56%). Of note, the 5^{th}-generation airways of COPD with asthma onset before age 40 years (A and B) show a smaller lumen area and greater ratio of the wall area to the sum of lumen and wall areas, as assessed as WA%, compared to those of COPD without asthma onset (C and D).

List of Supplemental Digital Content

Figure 1

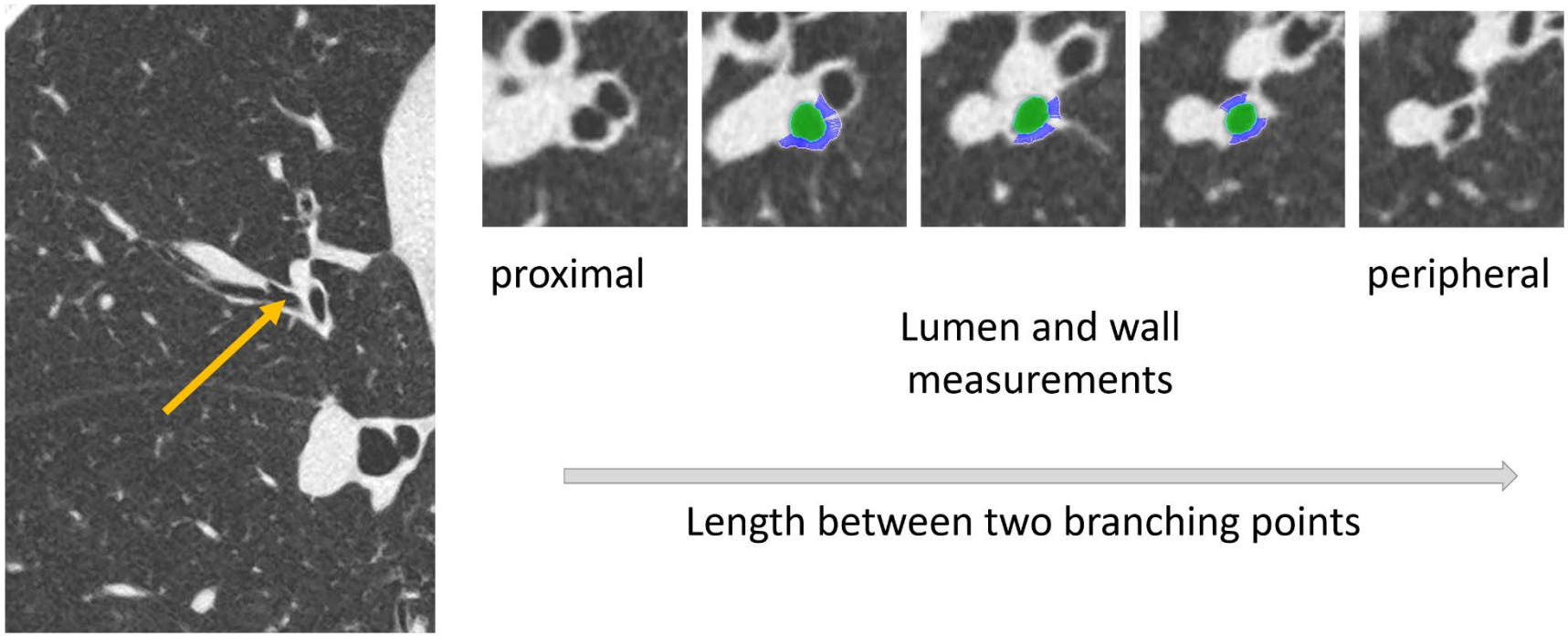

proximal
peripheral
Lumen and wall measurements
Length between two branching points

Figure 2

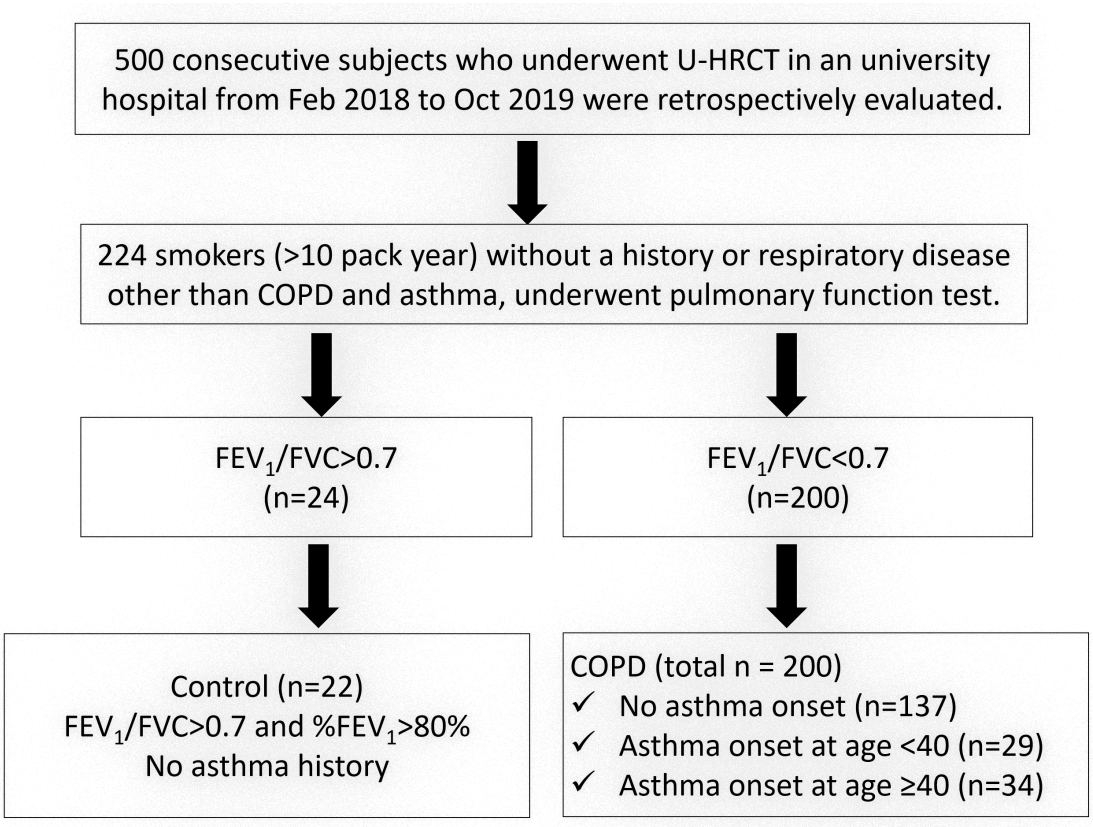

500 consecutive subjects who underwent U-HRCT in an university hospital from Feb 2018 to Oct 2019 were retrospectively evaluated.
224 smokers (>10 pack year) without a history or respiratory disease other than COPD and asthma, underwent pulmonary function test.
FEV1/FVC>0.7 (n=24)
FEV1/FVC<0.7 (n=200)
Control (n=22)
FEV1/FVC>0.7 and %FEV1>80%
No asthma history
COPD (total n = 200)
✓ No asthma onset (n=137)
✓ Asthma onset at age <40 (n=29)
✓ Asthma onset at age ≥40 (n=34)

Figure 3

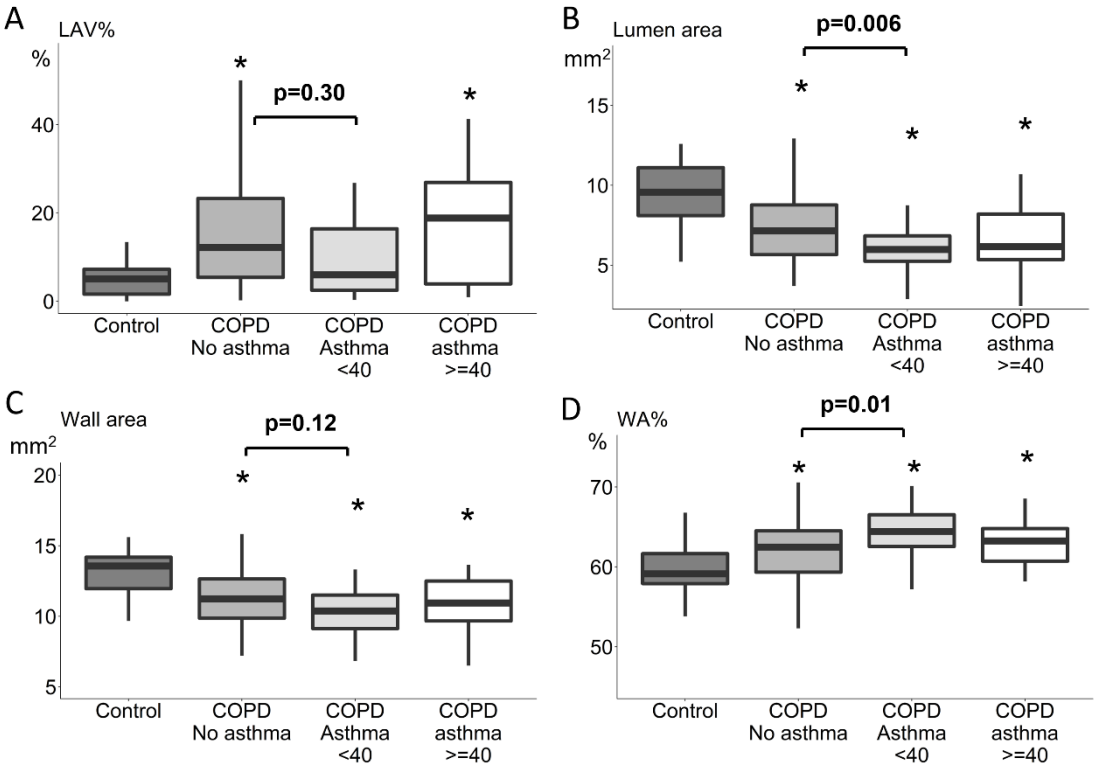
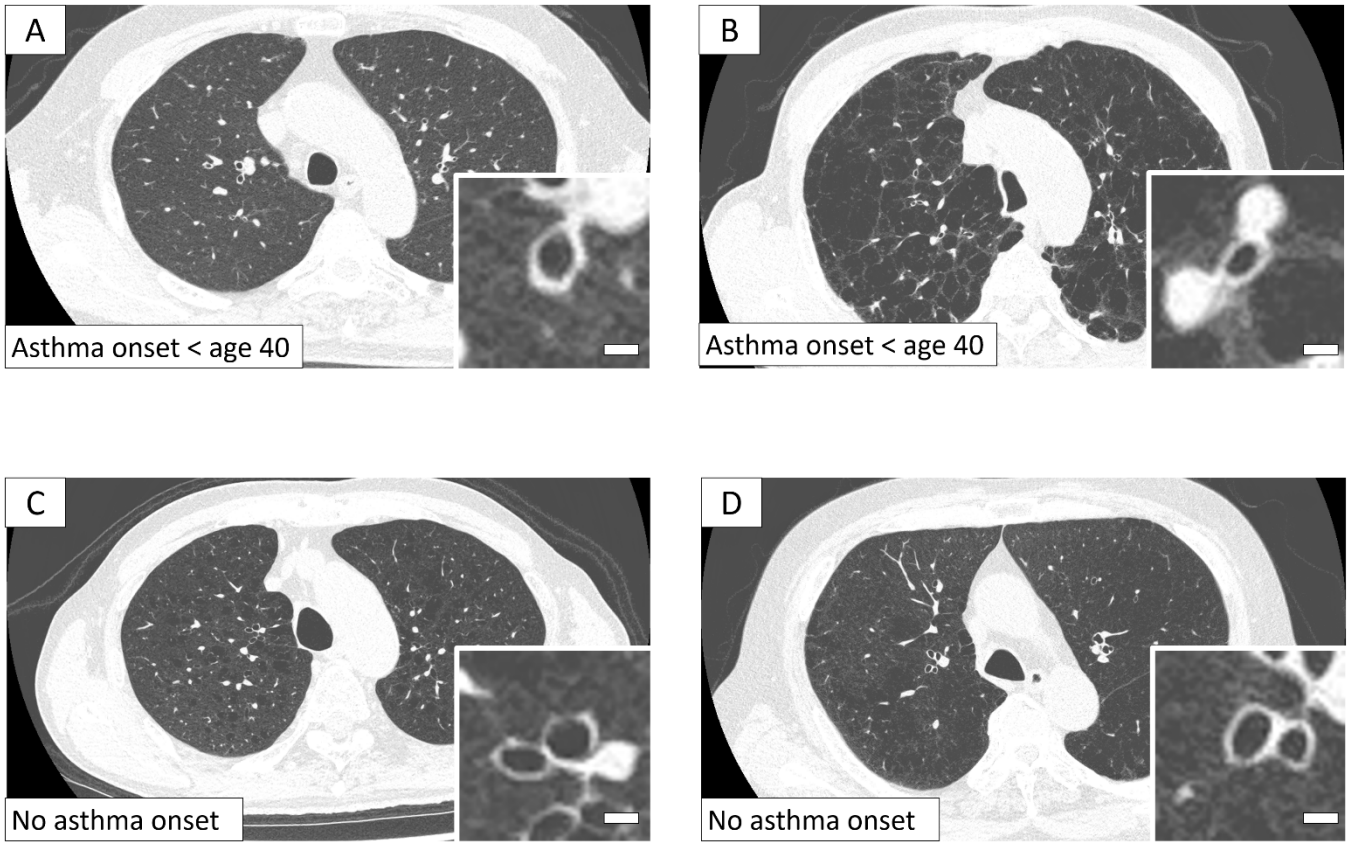

A
LAV%
%
40
20
0
p=0.30
Control
COPD No asthma
COPD Asthma <40
COPD asthma >=40
B
Lumen area
mm2
15
10
5
p=0.006
C
Wall area
mm2
20
15
10
5
p=0.12
D
WA%
%
70
60
50
p=0.01

Figure 4


A
Asthma onset < age 40
B
Asthma onset < age 40
C
No asthma onset
D
No asthma onset

Tables

Table 1. Demographic data of the study subjects (n=222)

	Smoker Control	COPD No Asthma	COPD Asthma <40	COPD Asthma ≥40	P value
N	22	137	29	34	
Age	72 (8)	73 (8)	72 (8)	73 (6)	0.97
Male, n (%)	94%	94%	93%	94%	0.34
Height, cm	163 (6)	165 (6)	164 (7)	165 (6)	0.45
Weight, kg	63 (9)	63 (11)	62 (10)	64 (11)	0.92
Current smoker, %	9%	23%	10%	9%	0.08
Pack-years	54 (26)	61 (30)	57 (37)	58 (40)	0.69
%FVC, %	101 (13)	95 (21)	86 (14)*†	95 (19)	0.034
%FEV_1, %	98 (13)	68 (22)*	59 (19)*†	65 (19)*	<0.001
FEV_1/FVC, %	74 (3)	53 (12)*	52 (14)*	52 (12)*	<0.001
Eosinophils, /μL	202 (137)	215 (181)	302 (198)*†	292 (196) *†	0.024
Eosinophils >300/μL, %	22%	20%	38%	45%	0.035
CT-TLV, L	4.8 (1.1)	5.6 (1.0) *	5.4 (1.2)	5.6 (0.9) *	0.010
LAV%, %	5 (4)	16 (14) *	12 (14)	16 (13) *	0.001
Medication					
LABD, %	-	68%	72%	82%	0.22
ICS, %	-	30%	69%	97%	<0.001

Data are expressed as the mean (standard deviation, SD) unless otherwise indicated. FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; CT-TLV = lung volume on CT. LAV% = low attenuation volume percent; LABD = long-acting bronchodilator; ICS = inhaled corticosteroid. * and † indicate $p<0.05$ compared to

controls and COPD patients without asthma onset, respectively, based on post hoc Tukey’s multiple comparison.

Table 2. Airway dimensions on ultra-high-resolution CT in control smokers and COPD patients with and without asthma onset.

		Smoker Control (n=22)	COPD No Asthma (n=137)	COPD Asthma <40 (n=29)	COPD Asthma ≥40 (n=34)
No. of airways (measurable on U-HRCT)	3rd	3.0 (0.0)	3.0 (0.0)	3.0 (0.0)	3.0 (0.0)
	4th	5.8 (0.5)	5.9 (0.3)	5.9 (0.4)	6.0 (0.2)
	5th	10.7 (1.5)	10.7 (1.3)	10.7 (1.5)	10.2 (1.0)
Length (mm)	3rd	9.1 (2.3)	9.7 (1.8)	10.0 (2.3)	9.6 (2.0)
	4th	7.9 (1.7)	8.6 (1.6)	8.2 (1.9)	8.0 (1.4)
	5th	6.4 (1.5)	6.6 (1.5)	6.5 (1.5)	7.0 (1.4)
Lumen area (mm^2)	3rd	25.9 (7.3)	23.4 (6.5)	20.1 (4.8)*	22.6 (6.2)
	4th	15.9 (4.2)	12.7 (3.6)*	10.3 (2.5)*†	12.0 (3.6)*
	5th	9.8 (2.9)	7.4 (2.1)*	6.0 (1.4)*†	6.8 (2.2)*
Wall thickness (mm)	3rd	1.29 (0.17)	1.32 (0.18)	1.36 (0.18)	1.36 (0.24)
	4th	1.08 (0.10)	1.03 (0.09)	1.04 (0.13)	1.05 (0.12)
	5th	0.96 (0.08)	0.90 (0.06)*	0.89 (0.09)*	0.90 (0.07)*
Wall area (mm^2)	3rd	28.6 (5.7)	28.3 (5.7)	27.6 (6.8)	29.0 (7.6)
	4th	18.9 (2.9)	16.3 (2.8)*	15.4 (3.4)*	16.6 (3.6)*
	5th	13.6 (2.7)	11.3 (1.8)*	10.4 (2.1)*	11.0 (2.1)*
WA% (%)	3rd	52.7 (5.7)	55.0 (5.3)	58.4 (4.7)*†	56.2 (5.7)
	4th	55.5 (4.8)	57.7 (4.3)	60.8 (4.3)*†	59.3 (4.4)*
	5th	59.4 (3.5)	62.0 (3.6)*	64.2 (3.2)*†	63.1 (3.0)*

Data are expressed as the mean (standard deviation, SD). Patients with COPD are classified into those without asthma onset (COPD No Asthma), those with asthma onset at age <40 years (COPD Asthma <40), and those with asthma onset at age ≥40 years (COPD Asthma ≥40). WA% = wall area percent. * and † indicate $p<0.05$ compared to

control and COPD without asthma onset, respectively, based on Tukey’s multiple comparison.

Table 3. Multivariable analysis to explore relative impacts of asthma onset on lumen area of the sub-sub-segmental airways in patients with COPD (n=200)

Models	Variables		Estimate (SE)	P value
#1. Lumen area (5^{th})	$\%FEV_1$	per 1%	0.04 (0.01)	<0.01
	Asthma	None	reference	
		age <40	-0.84 (0.40)	0.039
		age ≥40	-0.24 (0.42)	0.56
#2. Lumen area (5^{th})	LAV%	per 1%	0.002 (0.01)	0.87
	Asthma	None	reference	
		age <40	-1.03 (0.44)	0.022
		age ≥40	-0.08 (0.46)	0.86

Each multivariate linear regression model was adjusted by age, sex, height, smoking status, pack-year, use of inhaled corticosteroid, use of long-acting bronchodilators, and presence of higher blood eosinophils (>300 μl). 5^{th} = at the sub-sub-segmental airways (5^{th}-generation). %FEV1 = % of predicted forced expiratory volume in 1 second. LAV% = low attenuation volume %. SE = standard error.