

Asthma and lung structure on computed tomography: The Multi-Ethnic Study of Atherosclerosis Lung Study

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Background: The potential consequences of asthma in childhood and young adulthood on lung structure in older adults have not been studied in a large, population-based cohort.

Objective: The authors hypothesized that a history of asthma onset in childhood (age 18 years or before) or young adulthood (age 19–45 years) was associated with altered lung structure on computed tomography in later life.

Methods: The Multi-Ethnic Study of Atherosclerosis Lung Study recruited 3965 participants and assessed asthma history by using standardized questionnaires, guideline-based spirometry, and segmental airway dimensions and percentage of low attenuation area (%LAA) on computed tomographic scans. **Results:** Asthma with onset in childhood and young adulthood was associated with large decrements in FEV₁ among participants with a mean age of 66 years (–365 mL and –343 mL, respectively; $P < .001$). Asthma with onset in childhood and young adulthood was associated with increased mean airway wall thickness standardized to an internal perimeter of 10 mm (0.1 mm, $P < .001$ for both), predominantly from narrower segmental airway lumens (–0.39 mm and –0.34 mm, respectively; $P < .001$). Asthma with onset in childhood and young adulthood also was associated with a greater %LAA (1.69% and 4.30%, respectively; $P < .001$). Findings were similar among never smokers, except that differential %LAA in childhood-onset asthma were not seen in them.

Conclusion: Asthma with onset in childhood or young adulthood was associated with reduced lung function, narrower airways,

and among asthmatic patients who smoked, greater %LAA in later life. (*J Allergy Clin Immunol* 2013;131:361–8.)

Key words: Airway remodeling, airway structure, asthma, emphysema, epidemiology

Asthma prevalence exceeds 10% in the developed world and is increasing rapidly in the developing world.¹ Asthma is thought to contribute to low lung function in later life,^{2,3} which predicts mortality⁴ and defines chronic obstructive pulmonary disease (COPD),⁵ which is now the third-leading cause of death in the United States.⁶

The majority of children with asthma experience clinical remission and are symptom free by early adulthood.⁷ Nonetheless, those with remitted childhood-onset asthma have basement membrane thickening on endobronchial biopsy, and relatively few have completely normal lung function at age 18 to 25 years.⁸ The European Community Respiratory Health Survey found that a history of childhood asthma, among other factors, was associated with a larger decrease in lung function and increased risk of COPD later in life, and the Burden of Obstructive Lung Disease group similarly found that childhood respiratory disease was a risk factor for COPD among never smokers.^{9,10}

Case-control studies suggest that asthma might contribute to airway wall thickening and irreversible airflow limitation.^{11–20} Early and repeated mechanical stress to alveoli from persistent asthma might lead to alveolar rupture, strain on adjacent alveolar walls, and alveolar enlargement,²¹ with consequences in later life. The relationship of childhood-onset asthma to lung function in later life is poorly defined because the longest prospective cohort study of childhood-onset asthma has follow-up to a mean age of 42 years,² and no such studies have evaluated lung structure. We therefore examined asthma with onset in childhood and young adulthood in a cross-sectional analysis of a population-based cohort of older adults. We hypothesized that a history of asthma onset in childhood (age 18 years or before) or young adulthood (age 19–45 years) would be associated with altered lung structure on computed tomography (CT) in later life. For completeness, we also report results for participants with asthma onset after age 45 years.

METHODS

Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter cohort study of subclinical cardiovascular disease in white, African American, Hispanic, and Asian subjects.²² Between 2000 and 2002, MESA recruited 6814 men and women 45 to 84 years of age from Forsyth County, North Carolina; New York City; Baltimore, Maryland; St Paul, Minnesota; Chicago, Illinois; and Los Angeles, California. Exclusion criteria were clinical cardiovascular disease, weight exceeding 136 kg (300 lb), pregnancy, and

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Abbreviations used

COPD: Chronic obstructive pulmonary disease
 CT: Computed tomography
 ETS: Environmental tobacco smoke
 HU: Hounsfield units
 ICC: Intraclass correlation coefficient
 LAA: Low attenuation area
 MESA: Multi-Ethnic Study of Atherosclerosis
 Pi10: Wall thickness for a hypothetical airway with an internal perimeter of 10 mm

impediment to long-term participation. Written informed consent was obtained from all participants. The protocols were approved by the institutional review boards of all collaborating institutions and by the National Heart, Lung, and Blood Institute.

The MESA Lung Study enrolled MESA participants who underwent an examination between 2004 and 2006 (Fig 1). Characteristics of MESA participants in the MESA Lung Study compared with those not in the MESA Lung Study are reported in Table E1 in this article's Online Repository at www.jacionline.org; nonparticipants in the MESA Lung Study were somewhat older and more likely to be white or African American, but the prevalence of asthma was similar in both groups.

Asthma

Asthma and respiratory history were ascertained by means of self-report by using standard questionnaire items.²³ Participants were asked the following: "Have you ever had asthma?" If yes, participants were asked at what age they "developed first asthma symptoms" and at what age a "doctor first diagnosed asthma." Ninety-nine percent of participants who reported asthma also reported a physician's diagnosis of asthma. Childhood-onset asthma was defined as a report of first symptoms or diagnosis of asthma at or before age 18 years and young adult-onset asthma as onset of symptoms or diagnosis between age 19 and 45 years.

Remission of asthma was defined as "10-year (or more) period without asthma symptoms." Participants who reported a remission were asked about "age at first recurrence of asthma symptoms." Recurrence was defined as participants with a history of remission who subsequently reported use of respiratory medication at the time of the visit or wheezing in the prior 12 months. Participants without a remission were defined as having persistent asthma.

Participants without asthma

Participants were classified as being without asthma if they reported no history of asthma and had no current respiratory medication use, no wheezing in the last 12 months, and an FEV₁/forced vital capacity ratio of the lower limit of normal or greater.

Spirometry

Spirometry was conducted in 2004-2006 in accordance with the American Thoracic Society/European Respiratory Society guidelines (see the [Methods](#) section in this article's Online Repository at www.jacionline.org for details).²⁴

CT measures

CT scans were acquired as previously described and as detailed in the [Methods](#) section in this article's Online Repository.²⁵

Airway dimensions. Airways were sampled by using CT imaging perpendicular to the airway long axis (ie, the airway lumen was approximately circular). They were measured in 2 dimensions by using a modified full-width/half-maximum principle to identify the outer and inner airway wall borders (Fig 2).²⁶ Wall thickness for a hypothetical airway with an

internal perimeter of 10 mm (Pi10) in the lower lobes was calculated according to the standard method. Individual regression plots were created for each participant, plotting the square root of the wall area against the corresponding internal perimeter for each measured airway belonging to that participant (mean, 9 airways per participant). As is standard, airways with an internal perimeter of 6 mm or less were excluded given the technical limitations of the CT scanners. The resulting regression line was used to calculate the standardized measure of airway Pi10 for each participant.²⁷

Because asthma might be related to narrowed airway lumens or thickened airway walls¹¹ and standard CT measures of airway wall thickness, such as Pi10, combine wall thickness with lumen diameter (by regressing airway wall thickness on inner perimeter or taking the ratio of the 2), we assessed airway lumen diameter and airway wall thickness separately in a single segmental lower-lobe (LB10 or RB10) airway for each participant. Thus for the purposes of this study, the terms "airway wall thickness" and "airway lumen diameter" refer to the dimensions of a single airway for each participant, whereas Pi10 is a measure derived from both the wall thicknesses and lumen diameters of multiple airways per participant. All analyses of individual airway dimensions (lumen and wall thickness) are adjusted for body size.

Percentage of lung low attenuation areas. The percentage of low attenuation area (%LAA; also known as percentage of emphysema) was defined as the percentage of total lung voxels with attenuation of less than -910 Hounsfield units (HU).²⁸ The %LAA reflects the emphysematous and hyperinflated lung in addition to distal airway lumens.²⁹

Additional details regarding scanner types, slice thickness and reconstruction kernels, Pi10 calculations, individual airway measurements, and %LAA can be found in the [Methods](#) section in this article's Online Repository.

Covariates

Age, sex, race/ethnicity, educational attainment, and family history were self-reported. Assessment of other covariates has been previously described, including anthropometry,³⁰ current smoking, pack years and pipe years,³¹ environmental tobacco smoke (ETS) and occupational exposures,²³ and particulate matter.³²

Statistical analysis

Participants with asthma were categorized according to onset of asthma. Linear regression models regressed measures of lung function and structure on asthma categories. Initial regression models adjusted for age, sex, height, height squared, and race/ethnicity. Additional adjustment was performed for the following potential confounders: smoking status, pack years, cotinine, pipe years, household ETS, education, body mass index, waist circumference, occupational exposures, family history of emphysema, and particulate matter exposure. Models for CT measures also were adjusted for CT scanner type and tube current in milliamperes as precision variables. Differences in lung function and structure across categories of asthma were tested with the -2 log-likelihood test of nested models. Statistical significance was defined *post hoc* as a Bonferroni-corrected, 2-tailed *P* value of less than .0125 for this test to account for the multiple comparisons (4 measures of lung function and structure). If a statistically significant difference were detected for a given end point by using these strict criteria, within-category comparisons were considered significant at a *P* value of less than .05. Analyses were performed with SAS 9.1 software (SAS Institute, Cary, NC).

RESULTS

The mean age of the 3371 participants was 65 years at the time of spirometry, 49% were male, and the race/ethnic distribution was 34% white, 25% African American, 23% Hispanic, and 18% Chinese American. Fifty percent of the cohort never

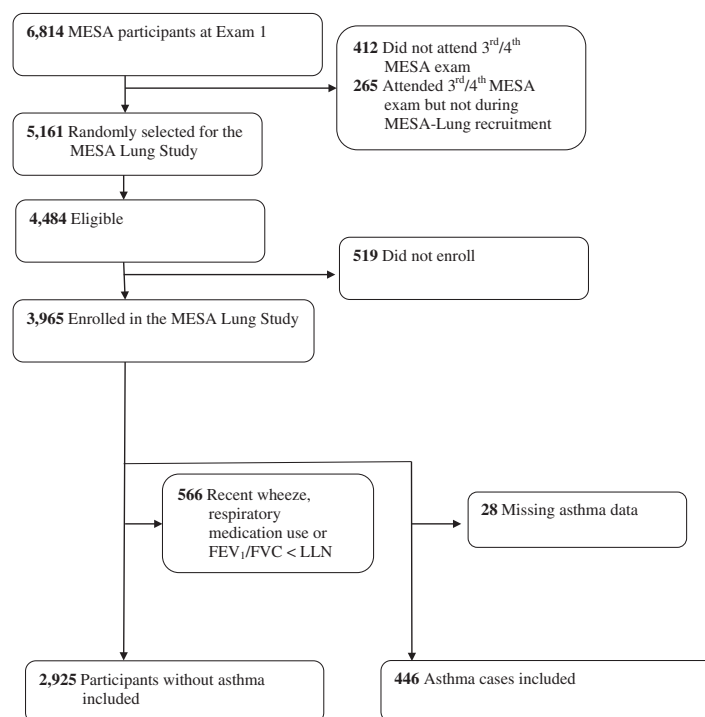


FIG 1. Study sample. FVC, Forced vital capacity; LLN, lower limit of normal.

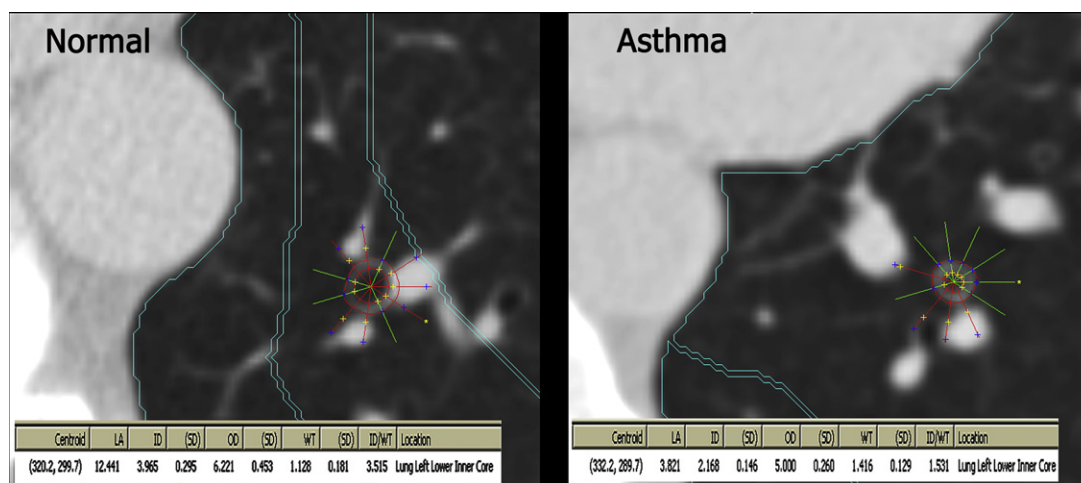


FIG 2. Airway measurements on CT scans. On locating an airway perpendicular to the plane, a centroid was placed in the center of the airway, from which the Pulmonary Analysis Software Suite generated rays and inner and outer airway diameters. If a ray extended into adjacent tissue, the analyst would manually exclude it, and the Pulmonary Analysis Software Suite system would regenerate the inner and outer diameters to better conform to the shape of the airway. The remaining rays were averaged to calculate airway wall thickness and lumen diameter.

smoked cigarettes, 42% were former smokers, and 8% currently smoked.

Of the 3371 participants who met the inclusion criteria, 446 had asthma, and 2925 did not. Two hundred seventeen participants reported asthma onset in childhood and 102 as young adults.

Participants with young adult-onset asthma were more likely to be female, have shorter height, and report ETS exposure (Table I). Smoking history did not vary appreciably across categories of asthma.

Lung function

As expected, participants with asthma onset at any age, including in childhood or young adulthood, had significantly lower lung function in later life compared with participants without asthma ($P < .001$, Table II).

Lung structure

Participants with asthma had an increased Pi10 value compared with participants without asthma: multivariate mean difference of

TABLE I. Characteristics of participants stratified by asthma age of onset

	No asthma*	Childhood-onset asthma ≤18 y†	Young adult-onset asthma 19-45 y‡	Late adult-onset asthma >45 y§
N = 3371	2925	217	102	127
Age (y), mean (SD)	65 (10)	63 (10)	62 (10)	68 (9)
Female sex (%)	50	48	79	67
Race/ethnicity (%)				
White	34	38	38	40
Chinese American	19	11	6	10
African American	25	31	29	21
Hispanic	23	20	28	29
Education (%)				
<12 y	17	11	19	17
12 y	18	10	12	20
>12 y	65	79	69	63
Asthma age of onset (y), median (IQR)	NA	8 (4-13)	35 (30-40)	57 (50-64)
Age at remission (y), median (IQR)	NA	17 (12-25)	40 (33-45)	57 (50-67)
Taking asthma medications (%)	0	29	47	60
Wheezing in last 12 mo (%)	0	35	48	54
Current asthma (%)	0	52	55	91
Hay fever (%)	29	62	55	48
Height (cm), mean (SD)	166 (10)	167 (10)	163 (8)	163 (10)
Weight (lbs), mean (SD)	169 (37)	182 (42)	178 (39)	175 (37)
Waist circumference (cm), mean (SD)	96 (13)	100 (16)	101 (16)	103 (15)
Body mass index (kg/m ²), mean (SD)	28 (5)	29 (6)	31 (7)	30 (6)
Cigarette smoking status (%)				
Never	51	50	50	40
Past	42	39	41	47
Current	8	11	9	13
Cigarette pack years, median (IQR)¶	13 (3-30)	16 (5-35)	12 (6-23)	24 (6-44)
Pipe years, median (IQR)#	21 (9-70)	48 (25-120)	9 (8-25)	18 (4-30)
Urine cotinine (ng/mL), median (IQR)	7 (7-11)	7 (7-19)	7 (7-22)	7 (7-12)
Household ETS (%)	69	70	77	67
Occupational exposures to dust (%)	34	46	45	39
Family history of emphysema (%)	3	7	6	10
CT scanner type (%)				
Multidetector CT	39	41	35	39
Electron-beam CT	61	59	65	61
Particulate matter <10 μm (%), mean (SD)	16 (7)	15 (7)	17 (7)	15 (8)
FEV ₁ , mean % predicted (SD)	98 (16)	83 (18)	83 (21)	82 (23)
FVC (% predicted), mean (SD)	97 (15)	90 (16)	90 (18)	90 (19)
FEV ₁ /FVC (% [SD])	77 (7)	71 (10)	72 (11)	69 (13)

FVC, Forced vital capacity; IQR, interquartile range; NA, not available.

*No asthma is defined as no history of asthma, no current respiratory medication use, no wheezing in the last 12 months, and an FEV₁/FVC ratio of the lower limit of normal or greater.

†Childhood-onset asthma is defined as report of first asthma symptoms or diagnosis before age 19 years.

‡Young adult-onset asthma is defined as report of first asthma symptoms or diagnosis between ages 19 and 45 years.

§Late adult-onset asthma is defined as report of first asthma symptoms or diagnosis after age 45 years.

||Inhaled corticosteroids, β-agonists, and leukotriene inhibitors.

¶Among ever smokers.

#Among pipe smokers.

0.10 mm (95% CI, 0.06-0.13 mm; $P < .001$) for those with asthma onset in childhood; 0.09 mm (95% CI, 0.04-0.13 mm; $P < .001$) for those with asthma onset in young adulthood; and 0.05 mm (95% CI, 0.006-0.09 mm; $P < .001$) for those with onset after age 45 years.

However, associations for Pi10 were predominantly due to lumen rather than wall size (Table II). Participants with asthma had narrower segmental airway lumens than participants without asthma ($P < .001$). In contrast to findings for airway lumens, segmental airway wall thickness was not significantly increased in asthmatic patients compared with that seen in participants without asthma ($P = .06$).

%LAA

Participants with asthma had greater %LAA than participants without asthma ($P < .001$), irrespective of onset in childhood, young adulthood, or after age 45 years (Table II).

Never smokers

Findings were generally similar among the 50% of the cohort who never smoked cigarettes (Table III). Decreases in lung function related to asthma with onset in childhood or young adulthood were large, and findings for the lumen were statistically significant. The only major difference compared with the whole cohort

TABLE II. Asthma age of onset, lung structure, and lung function

	≤18 y (n = 217)	19-45 y (n = 102)	>45 y (n = 127)	P value
FEV ₁ (mL)	−365 (−419 to −310)†	−343 (−420 to −266)†	−359 (−428 to −289)†	<.001
Single airway lumen diameter (mm)	−0.39 (−0.58 to −0.2)†	−0.34 (−0.61 to −0.07)*	−0.52 (−0.76 to −0.28)†	<.001
Single airway wall thickness (mm)	0.01 (−0.01 to 0.04)	0.02 (−0.02 to 0.05)	−0.02 (−0.06 to 0.009)	.06
%LAA	1.69 (0.09 to 3.29)*	4.30 (2.00 to 6.59)†	3.52 (1.45 to 5.58)†	<.001

Results represent the mean difference compared with participants without asthma from linear regression models adjusted for age, sex, height, height squared, race/ethnicity, smoking status, pack years, pipe years, urine cotinine, household ETS, education, body mass index, waist circumference, occupational exposures, and particulate matter exposure. Lung structure models (lumen diameter, wall thickness, and %LAA) were additionally adjusted for tube current in milliamperes and CT scanner type. The %LAA model was additionally adjusted for family history of emphysema. *P* values represent the −2 log likelihood test for overall significance among asthma age of onset subgroups versus participants without asthma. Where significant overall, subgroups were tested individually as follows: **P* < .05 and †*P* < .001.

TABLE III. Asthma age of onset, lung structure, and lung function in never smokers

	≤18 y (n = 107)	19-45 y (n = 51)	>45 y (n = 51)	P value
FEV ₁ (mL)	−293 (−364 to −221)†	−237 (−338 to −137)†	−307 (−407 to −207)†	<.001
Single airway lumen diameter (mm)	−0.35 (−0.62 to −0.08)*	−0.28 (−0.64 to 0.08)	−0.77 (−1.14 to −0.40)†	<.001
Single airway wall thickness (mm)	0.01 (−0.02 to 0.05)	0.02 (−0.02 to 0.07)	−0.03 (−0.08 to 0.02)	.09
%LAA	−0.68 (−2.83 to 1.47)	3.52 (0.46 to 6.58)*	3.44 (0.391 to 6.50)*	<.001

Results represent the mean difference compared with participants without asthma from linear regression models adjusted for age, sex, height, height squared, race/ethnicity, smoking status, pack years, pipe years, urine cotinine, household ETS, education, body mass index, waist circumference, occupational exposures, and particulate matter exposure. Lung structure models (lumen diameter, wall thickness, and %LAA) were additionally adjusted for tube current in milliamperes and CT scanner type. The %LAA model was additionally adjusted for family history of emphysema.

**P* < .05 and †*P* < .001.

was that %LAA was not increased in never smokers with childhood-onset asthma. As in the whole cohort, Pi10 values were increased within each category of asthma (*P* < .001).

Exploratory analysis of duration, remission, recurrence, or persistence of asthma

Each year of duration of asthma was associated with narrower airway lumens (mean difference, −0.01 mm [95% CI, −0.02 to −0.003 mm]; *P* = .003), thicker airway walls (mean difference, 0.001 mm [95% CI, 0.0003–0.002 mm]; *P* = .01), and increased %LAA (mean difference, 0.15% [95% CI, 0.11% to 0.20%]; *P* < .001) in fully adjusted models. Even participants with remitted asthma had evidence of narrow airway lumens and large decrements in lung function; participants with persistent asthma had evidence of increased %LAA (see Table E2 in this article's Online Repository at www.jacionline.org).

Lung structure and lung function

In fully adjusted models, each increased milliliter of FEV₁ was associated with wider airway lumens (mean difference, 0.03 mm [95% CI, 0.03–0.04 mm]; *P* < .001), was not associated with a change in airway wall thickness (mean difference, 0.0005 mm [95% CI, −0.0003 to 0.00014 mm]; *P* = .2), and was associated with reduced %LAA (mean difference, −0.4% [95% CI, −0.5 to −0.4]; *P* < .001).

Sensitivity analyses

Results were similar when inclusion criteria for the control group were relaxed to include any participant without a history of asthma, even if they had lung function of less than the lower limit of normal, respiratory medication use, or wheezing in the last 12 months. When age of onset was varied, findings were generally similar (see Tables E3 and E4 in this article's Online Repository at

www.jacionline.org). When the threshold for %LAA was decreased to −950 HU, results were similar: multivariate mean difference was 0.7% (95% CI, 0.2% to 1.3%) for those with asthma onset in childhood; 1.4% (95% CI, 0.7% to 2.2%) for those with asthma onset in young adulthood; and 1.3% (95% CI, 0.6% to 1.9%) for those with onset after age 45 years. Results were similar in analyses stratified by scanner type (see Tables E5 and E6 in this article's Online Repository at www.jacionline.org). Results adjusted for medication use are reported in Table E7, and results for those with recurrent disease are reported in Table E8 (both available in this article's Online Repository at www.jacionline.org). Results also were similar after adjusting for recent upper respiratory tract infection (see Table E9 in this article's Online Repository at www.jacionline.org) and stratified by current versus former asthma (see Table E10 in this article's Online Repository at www.jacionline.org).

DISCUSSION

A history of asthma, particularly in childhood and young adulthood, was associated both with large decrements in lung function in later life and narrower segmental airways in this large, population-based cohort study. In addition, asthma onset in young adulthood was associated with increased %LAA.

The mean decrement in FEV₁ in later life among participants with asthma with onset in childhood and young adulthood was greater than that among participants with a history of cigarette smoking (−365 mL for childhood-onset asthma and −343 mL for young adult-onset asthma vs −82 mL for participants who smoked)³¹ in this multiethnic, predominantly urban US cohort. This finding confirms that asthma in childhood and young adulthood is a major correlate of lung function later in life.

Our findings for lung function are consistent with those of prior cross-sectional studies of self-reported asthma in older adults³; however, these studies did not report asthma age of onset, and

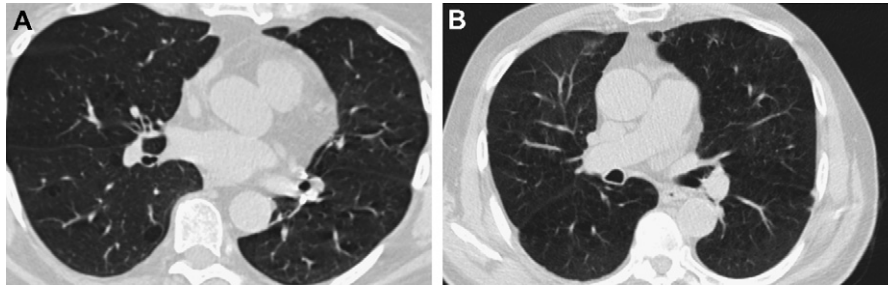


FIG 3. Increased %LAA in participants with persistent asthma. **A,** Never smoker. **B,** Smoker.

therefore it is unclear whether they assessed early- or late-onset asthma or misclassified COPD.³³

A novel finding of this study is that mean segmental airway lumen diameter was narrower among participants with asthma onset in childhood and young adulthood compared with that seen in participants without asthma in this general population sample. Although there is controversy about the optimal approach to measuring airways on CT,³⁴ Nakano et al³⁵ showed that the relative change in smaller airways might be greater than what can be observed on CT scans in the larger airways, which would suggest associations of greater magnitude in airways smaller than measured in the present study. Furthermore, proximal airway changes might lead to regional ventilatory defects.³⁶ This finding suggests either that participants with asthma had narrower airways throughout their lives that predisposed them to asthma or that asthma also contributed to narrow airways, either through airway remodeling¹² or because of bronchoconstriction and increased airway smooth muscle tone.³⁷ We speculate that dysynapsis or a relatively smaller airway size compared with lung volume can explain these consistent findings for lung function and airway lumens in asthma.

Multiple prior studies have observed evidence of airway wall thickening on CT scans in patients with asthma.^{11,14-20} However, most of these used Pi10 and other metrics of airway wall thickness, such as airway wall area percentage, that combine lumen with airway wall thickness, and therefore it is unclear whether their results were driven by smaller airway lumens or thicker airway walls. In addition, most of these studies were case-control studies in which the cases had fairly severe asthma. For example, Aysola et al¹¹ found that patients with severe asthma had increased wall thickness percentages and wall area percentages compared with those with mild-to-moderate asthma or those without asthma but that there was no difference between those with mild-to-moderate asthma versus those without asthma. We did see an association between asthma and increased Pi10 values but not between asthma and wall thickness. Our validated and reproducible approach to the measurement of segmental airway wall lumen diameter and thickness was similar to that used by Nakano et al³⁸ and suggests that in participants with asthma, composite measures, such as Pi10, are driven more by narrowing of the airway lumens than by thickening of the airway walls. Alternatively, it might be due to the generally milder asthma phenotype found in this population-based study.

Asthma onset in young adulthood was associated with increased %LAA, which is consistent with prior small case-control studies.^{39,40} Asthma is a known risk factor for COPD.⁴¹ This risk is due in part to airway remodeling⁴²; however, these results suggest that damages to the lung parenchyma might also contribute.

The mechanical hypothesis of emphysema posits that early and repeated injury leads to alveolar rupture, strain on adjacent alveoli, and propagation of emphysematous sac enlargement.²¹ Conversely, Gelb and Zamel⁴³ posit a “pseudophysiologic emphysema” caused by loss of lung elastic recoil. Exacerbations in older smokers accelerate progression of percentage of emphysema/%LAA.⁴⁴ It is possible that these results are due to either chronic air trapping in subjects with stable asthma or acute hyperinflation during an exacerbation. Indeed, Gelb and Zamel⁴³ found evidence of “pseudophysiologic emphysema” with reduced diffusing capacity and marked hyperinflation but minimal evidence of emphysema on autopsy in a study of 10 participants with severe small airways disease. However, participants in our study were drawn from a population-based sample and thus would, on average, have had milder disease and were scanned when clinically stable. Furthermore, results were similar after controlling for recent upper respiratory tract infection. Furthermore, visual assessment of CT scans from participants with persistent asthma demonstrated pulmonary emphysema among smokers and never smokers (Fig 3).

The present study has a number of limitations. Some degree of misclassification of the age of onset of asthma is likely in this cross-sectional study of adults given the retrospective ascertainment of asthma. However, it is probable that misclassification of asthma was minimized (although not ruled out) given the use of the cohort design and the subclinical outcome measures. Furthermore, our findings of large decrements in lung function among participants with self-reported asthma, including those with childhood-onset asthma, are supportive, as are our findings of narrower airway lumens and large decrements in lung function, even among participants with remitted asthma. Postbronchodilator spirometry was not conducted in this large population-based study, but mortality risk related to lung function is based on prebronchodilator measures.

Lung structure was measured on the lung regions of gated cardiac CT scans. The cardiac scans did not allow assessment of the upper lobes, but cardiac gating reduced the motion artifact typical in the left lower lobe of full lung scans, allowing more precise measures in these lobes. Three-dimensional airway reconstructions were not possible for these scans; however, we validated the location of the airways against full-lung, 3-dimensional scans. Variations in slice thickness and scanner resolution by scanner type might have affected airway measurement accuracy. However, this variability existed across all subgroups, and scanner type was accounted for within the statistical models. Beam hardening can contribute to low attenuation around the pulmonary vessels but would have been

nondifferential with respect to asthma subgroups. Expiratory CT scans were not obtained, and thus some of the %LAA might be due to air trapping.

Cross-sectional studies might have selection bias, but this is unlikely to explain the results because the study was population based and participants were not selected by asthma status. Although MESA is population based, patients with subclinical cardiovascular disease were excluded; this is unlikely to bias results for asthma because asthma is not related to subclinical cardiovascular disease.

In conclusion, a history of asthma in childhood and young adulthood, in addition to later adulthood, was associated with significant alterations in both lung function and lung structure in later life. All categories of asthma were associated with narrower segmental airways, whereas asthma onset between ages 19 and 45 years was associated with increased %LAA.

This manuscript has been reviewed by the MESA Investigators for scientific content and consistency of data interpretation with previous MESA publications. We thank the other investigators, the staff, and the participants of MESA for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

Key messages

- Asthma with onset in childhood and young adulthood was associated with narrower segmental airway lumens.
- Participants with asthma who smoked had reduced lung attenuation compared with participants without asthma.

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METHODS

Spirometry

Tests used a dry rolling-sealed spirometer with real-time automated quality checks (Occupational Marketing, Houston, Tex) and were all overread by a single investigator.^{E1} The intraclass correlation coefficient (ICC) of both FEV₁ and forced vital capacity on random 10% repeat testing was 0.99. Percent predicted values for lung function were calculated by using Hankinson reference equations, with a 0.88 correction for Asian subjects.^{E1,E2}

CT methods

Lung structure was assessed on the lung fields of cardiac CT scans, which included approximately 70% of the lung volume from the carina to the bases. The scans were gated to the cardiac cycle, thereby reducing cardiac-related motion artifacts. Two scans were obtained for each participant on separate breath holds. Three sites used a multidetector CT scanner (4-slice), and 3 sites used an Imatron C-150XL CT scanner (GE-Imatron, San Francisco, Calif). Image slices were obtained with the patient in the supine position, without couch angulation. A minimum of 35 contiguous images were obtained, starting above the left main coronary artery to the bottom of both ventricles. Slice thicknesses were 2.5 or 3 mm. A single breath hold was used to obtain each scan. Raw image data were reconstructed by using a section thickness of 3 mm, a field of view of 35 cm, and a matrix of 512 × 512. The nominal section thickness was 3.0 mm for electron-beam CT and 2.5 mm for 4-detector row CT. Spatial resolution, or a voxel, was 1.15 mm³ for multidetector row CT (0.68 × 0.68 × 2.50 mm) and 1.38 mm³ for electron-beam CT (0.68 × 0.68 × 3.00 mm). A modified version of the Pulmonary Analysis Software Suite^{E3} with semiautomated airway analysis^{E4} was used to assess lung structure at a single reading center by trained readers without knowledge of the participant's information. The scan with the greater volume of lung air was used for analyses, except in cases of discordant scan quality, when the higher-quality scan was analyzed.^{E5}

Pi10

We excluded participants for whom we had fewer than 6 airways measures, and therefore the minimum number of airways included in a Pi10 calculation was 6, with a mean of 8.6 and a maximum of 41 airways per participant. Ninety-five percent of participants had fewer than 15 airway measures. Most scans required about 5 to 15 minutes of operator time for airway measurement.

Single airway: Lumen diameter and wall thickness

To obtain LB10 or RB10, we selected the airway with the largest lumen diameter in the basilar one third of the CT scan. We verified this selection method among a random sample of 31 MESA participants who underwent full-lung CT scans at the time of a cardiac scan. The selected airway was either LB10 or RB10 for 95% of participants. The ICCs for the segmental airway lumen diameter and airway wall thickness in a 10% random sample on replicate CT scans were 0.94 and 0.73, respectively. Intrascanner intrareader ICCs were not differential by scanner type. ICCs for airway lumen were 0.96 versus 0.97 for EBT versus MDCT scanners, and ICCs for airway wall thickness were 0.71 vs 0.76 for EBT versus MDCT scanners.

%LAA

To correct for scanner variation, we measured the attenuation of air outside the body on each scan. The attenuation of each lung pixel was then corrected as measured pixel attenuation × (−1000/mean air attenuation). Sensitivity analyses were performed by using %LAA measures at a threshold of −950 HU. %LAA from MESA cardiac scans have been previously validated compared with full-lung scans.^{E5} The ICC of %LAA on 100% replicate scans was 0.94.

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TABLE E1. Characteristics of participants in the MESA Lung Study and in MESA but not in the MESA Lung Study

	MESA Lung Study (n = 3965)	Other MESA (n = 2849)
Age (y), mean (SD)	61 (10)	63 (11)
Female sex (%)	51	56
Race/ethnicity (%)		
White	35	43
Chinese American	16	6
African American	26	30
Hispanic	23	21
Height (cm), mean (SD)	167 (10)	166 (10)
Weight (lbs), mean (SD)	172 (38)	175 (39)
Cigarette smoking status (%)		
Never	52	48
Past	36	38
Current	12	14
Asthma (%)	9	10

TABLE E2. Asthma age of onset, lung structure, and lung function

	Childhood-onset asthma ≤ 18 y		Young adult-onset asthma 19-45 y		Late adult-onset asthma >45 y	
	Remitted* (n = 91)	Persistent† (n = 48)	Remitted‡ (n = 26)	Persistent§ (n = 55)	Remitted (n = 10)	Persistent (n = 99)
FEV ₁ (mL)	-203 (-283 to -123), P < .001	-438 (-548 to -328), P < .001	-157 (-305 to -10), P = .04	-290 (-393 to -186), P < .001	-87 (-325 to 150), P = .5	-363 (-440 to -286), P < .001
Single airway lumen diameter (mm)	-0.41 (-0.69 to -0.13), P = .004	-0.26 (-0.66 to 0.14), P = .2	-0.32 (-0.83 to 0.19), P = .2	-0.35 (-0.73 to 0.02), P = .06	-1.31 (-2.24 to -0.39), P = .006	-0.52 (-0.79 to -0.24), P < .001
Single airway wall thickness (mm)	-0.01 (-0.05 to 0.02), P = .4	0.05 (0.00 to 0.10), P = .06	-0.02 (-0.09 to 0.04), P = .5	0.03 (-0.02 to 0.08), P = .2	-0.02 (-0.14 to 0.11), P = .1	-0.03 (-0.07 to 0.003), P = .07
%LAA	-0.46 (-2.85 to 1.94), P = .7	5.50 (2.19 to 8.81), P = .001	4.00 (-0.43 to 8.41), P = .08	7.59 (4.49 to 10.7), P < .001	-2.61 (-9.73 to 4.51), P = .5	4.67 (2.34 to 6.98), P < .001

Results are adjusted for age, sex, height, height squared, race/ethnicity, smoking status, pack years, pipe years, urine cotinine, household ETS, education, body mass index, waist circumference, occupational exposures, particulate matter exposure, tube current in milliamperes, and CT scanner type. %LAA models were additionally adjusted for family history of emphysema.

*Childhood-onset asthma, remitted is defined as report of first asthma symptoms or diagnosis before age 18 years, report of a 10-year or longer period without asthma symptoms, no current respiratory medication use, and no wheezing in the last 12 months.

†Childhood-onset asthma, persistent is defined as report of first asthma symptoms or diagnosis before age 18 years and no report of a 10-year or longer period without asthma symptoms.

‡Young adult-onset asthma, remitted is defined as report of first asthma symptoms or diagnosis between age 19 and 44 years, report of a 10-year or longer period without asthma symptoms, no current respiratory medication use, and no wheezing in the last 12 months.

§Young adult-onset asthma, persistent is defined as report of first asthma symptoms or diagnosis between age 19 and 44 years and no report of a 10-year or longer period without asthma symptoms.

TABLE E3. Asthma age of onset, lung structure, and lung function for onset as children, adolescents, or adults

	≤12 y (n = 177)	13-19 y (n = 25)	>19 y (n = 244)
FEV ₁ (mL)	−346 (−405 to −287) [†]	−486 (−640 to −332) [†]	−354 (−405 to −302) [†]
Single airway lumen diameter (mm)	−0.43 (−0.64 to −0.22) [†]	0.13 (−0.46 to 0.72)	−0.46 (−0.64 to −0.28) [†]
Single airway wall thickness (mm)	0.01 (−0.02 to 0.04)	0.03 (−0.05 to 0.11)	−0.01 (−0.03 to 0.02)
%LAA	0.56 (−1.20 to 2.31)	5.89 (1.36 to 10.41)*	4.14 (2.61 to 5.68) [†]

**P* < .05 and [†]*P* < .001.

TABLE E4. Asthma age of onset, lung structure, and lung function for onset as children, adolescents, or young adults or late adult-onset asthma

	≤12 y (n = 185)	13-45 y (n = 145)	>45 y (n = 127)
FEV ₁ (mL)	-344 (-403 to -286) [†]	-376 (-444 to -308) [†]	-359 (-428 to -290) [†]
Single airway lumen diameter (mm)	-0.44 (-0.64 to -0.24) [†]	-0.29 (-0.53 to -0.05) [*]	-0.52 (-0.76 to -0.28) [†]
Single airway wall thickness (mm)	0.01 (-0.02 to 0.04)	0.02 (-0.01 to 0.05)	-0.02 (-0.06 to 0.01)
%LAA	1.00 (-0.73 to 2.72)	4.64 (2.63 to 6.66) [†]	3.52 (1.45 to 5.59) [†]

^{*}*P* < .05 and [†]*P* < .001.

TABLE E5. Asthma age of onset, lung structure, and lung function among those with EBT scans

	≤18 y (n = 127)	19-45 y (n = 66)	>45 y (n = 77)
FEV ₁ (mL)	−349 (−420 to −278)‡	−398 (−494 to −303)‡	−331 (−420 to −242)‡
Single airway lumen diameter (mm)	−0.33 (−0.57 to −0.1)‡	−0.35 (−0.68 to −0.02)*	−0.54 (−0.82 to −0.25)‡
Single airway wall thickness (mm)	0.00 (−0.04 to 0.03)	0.02 (−0.03 to 0.07)	−0.01 (−0.05 to 0.03)
%LAA	1.12 (−0.82 to 3.01)	4.08 (1.42 to 6.74)†	2.32 (−0.16 to 4.80)

**P* < .05, †*P* < .01, and ‡*P* < .001.

TABLE E6. Asthma age of onset, lung structure, and lung function among those with MDCT scans

	≤18 y (n = 90)	19-45 y (n = 36)	>45 y (n = 50)
FEV ₁ (mL)	-378 (-462 to -293) [‡]	-219 (-348 to -89) [‡]	-396 (-506 to -285) [‡]
Single airway lumen diameter (mm)	-0.50 (-0.82 to -0.18) [†]	-0.31 (-0.76 to -0.14)	-0.54 (-0.96 to -0.11) [*]
Single airway wall thickness (mm)	0.01 (-0.03 to 0.05)	0.01 (-0.04 to 0.08)	-0.06 (-0.11 to -0.01)
%LAA	2.46 (-0.29 to 5.21)	4.49 (0.29 to 8.69) [*]	5.38 (1.77 to 8.99) [†]

* $P < .05$, $^{\dagger}P < .01$, and $^{\ddagger}P < .001$.

TABLE E7. Asthma age of onset, lung structure, and lung function adjusted for asthma medication use (inhaled corticosteroids, β -agonists, and leukotriene inhibitors)

	≤ 18 y (n = 217)	19-45 y (n = 102)	>45 y (n = 127)
FEV ₁ (mL)	-282 (-340 to -224) [‡]	-209 (-293 to -125) [‡]	-185 (-267 to -103) [‡]
Single airway lumen diameter (mm)	-0.36 (-0.57 to -0.15) [‡]	-0.29 (-0.59 to 0.01)	-0.44 (-0.74 to -0.14) [†]
Single airway wall thickness (mm)	0.01 (-0.02 to 0.03)	0.01 (-0.03 to 0.05)	-0.03 (-0.07 to 0.01)
%LAA	0.67 (-1.06 to 2.39)	2.69 (0.18 to 5.20) [*]	1.39 (-1.08 to 3.86)

^{*} $P < .05$, [†] $P < .01$, and [‡] $P < .001$.

TABLE E8. Asthma age of onset, lung structure, and lung function among participants with recurrent disease

	≤18 y (n = 49)	19-45 y (n = 9)	>45 y (n = 7)
FEV ₁ (mL)	-478 (-586 to -370) [†]	-490 (-740 to -240) [†]	-466 (-749 to -182) [†]
Single airway lumen diameter (mm)	-0.37 (-0.74 to 0.00)*	-0.44 (-1.45 to 0.58)	-0.81 (-1.74 to 0.12)
Single airway wall thickness (mm)	0.01 (-0.04 to 0.7)	0.04 (-0.09 to 0.18)	0.07 (-0.06 to 0.19)
%LAA	5.32 (2.08 to 8.56) [†]	-1.15 (-8.65 to 6.36)	-1.36 (-9.87 to 7.14)

* $P < .05$ and $^{\dagger}P < .001$.

TABLE E9. Asthma age of onset, lung structure, and lung function adjusted for recent cold or flu

	≤18 y (n = 217)	19-45 y (n = 102)	>45 y (n = 127)
FEV ₁ (mL)	−364 (−418 to −310)‡	−342 (−419 to −265)‡	−358 (−427 to −288)‡
Single airway lumen diameter (mm)	−0.38 (−0.58 to −0.19)‡	−0.34 (−0.61 to −0.07)†	−0.50 (−0.75 to −0.26)‡
Single airway wall thickness (mm)	0.01 (−0.01 to 0.04)	0.02 (−0.02 to 0.05)	−0.02 (−0.06 to 0.009)
%LAA	1.71 (0.11-3.31)*	4.31 (2.01-6.60)‡	3.54 (1.47-5.61)‡

Results represent the mean difference compared with participants without asthma from linear regression models adjusted for age, sex, height, height squared, race/ethnicity, smoking status, pack years, pipe years, urine cotinine, household ETS, education, body mass index, waist circumference, occupational exposures, particulate matter exposure, asthma medication use, and recent cold or flu. Lung structure models (lumen diameter, wall thickness, and %LAA) were additionally adjusted for tube current in milliamperes and CT scanner type. The %LAA model was additionally adjusted for family history of emphysema.

* $P < .05$, † $P < .01$, and ‡ $P < .001$.

TABLE E10. Asthma age of onset, lung structure, and lung function adjusted for recent cold or flu

	Former asthma (n = 225)	Current asthma (n = 229)
FEV ₁ (mL)	−325 (−378 to −273)*	−380 (−433 to −326)*
Single airway lumen diameter (mm)	−0.43 (−0.62 to −0.25)*	−0.39 (−0.58 to −0.20)*
Single airway wall thickness (mm)	0.01 (−0.03 to 0.02)	0.01 (−0.02 to 0.03)
%LAA	0.64 (−0.93 to 2.21)	5.21 (3.62 to 6.79)*

Results represent the mean difference compared with participants without asthma from linear regression models adjusted for age, sex, height, height squared, race/ethnicity, smoking status, pack years, pipe years, urine cotinine, household ETS, education, body mass index, waist circumference, occupational exposures, particulate matter exposure, asthma medication use, and recent cold or flu. Lung structure models (lumen diameter, wall thickness, and %LAA) were additionally adjusted for tube current in milliamperes and CT scanner type. The %LAA model was additionally adjusted for family history of emphysema.

* $P < .001$.