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# Asthma and lung structure on CT: The MESA Lung Study

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## Abstract

**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 or before) or young adulthood (age 19 to 45) was associated with altered lung structure on computed tomography (CT) in later life.

**Methods—**The Multi-Ethnic Study of Atherosclerosis Lung Study recruited 3,965 participants and assessed asthma history using standardized questionnaires, spirometry following guidelines, and segmental airway dimensions and percent low attenuation areas on CT scans.

**Results—**Asthma with onset in childhood and young adulthood was associated with large decrements in the forced expiratory volume in one second among participants with a mean age of 66 years (−365 ml and −343 ml, respectively; P<0.001). Asthma with onset in childhood and young adulthood was associated with increased mean airway wall thickness standardized to an internal perimeter of 10 mm (Pi10) (0.1 mm, P<0.001 for both), predominantly from narrower segmental airway lumens (−0.39 mm and −0.34 mm, respectively; P<0.001). Asthma with onset in childhood and young adulthood also was associated with a greater percentage of low attenuation areas (1.69% and 4.30%, respectively; P<0.001). Findings were similar among never smokers except that differential percentage of low attenuation areas in child-onset asthma was not seen in them.

**Conclusion—**Asthma with onset in childhood or young adulthood, was associated with reduced lung function, narrower airways and, among asthmatics who smoked, greater percentage of low attenuation areas in later life.



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**Authors' contributions**: Dr. Donohue performed the statistical analysis and drafted the manuscript. Drs. Hoffman, Guo, Jacobs and Enright and Ms. Baumhauer provided data collection and critical revisions. Drs. Ahmed and Lovasi provided assistance with statistical analyses and critical revisions. Dr. Barr provided funding, data collection and critical revisions.

### MeSH terms

airway remodeling; airway structure; asthma; emphysema; epidemiology

## INTRODUCTION

Asthma prevalence exceeds ten percent 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 mortality (4) and defines chronic obstructive pulmonary disease (COPD) (5), 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 child-onset asthma have basement membrane thickening on endobronchial biopsy and relatively few have completely normal lung function at age 18–25 years old (8). The European Community Respiratory Health Survey found that a history of childhood asthma, among other factors, was associated with a larger decline 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 may contribute to airway wall thickening and irreversible airflow limitation (11–20). Early and repeated mechanical stress to alveoli from persistent asthma may lead to alveolar rupture, strain on adjacent alveolar walls and alveolar enlargement (21) with consequences in later life. The relationship of child-onset asthma to lung function in later life is poorly defined since the longest prospective cohort study of child- 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 or before) or young adulthood (age 19 to 45) 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 whites, African Americans, Hispanics, and Asians (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; St. Paul, Minnesota; Chicago; and Los Angeles. Exclusion criteria were clinical cardiovascular disease, weight exceeding 136 kg (300 lb), pregnancy, and 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 (Figure 1). Characteristics of MESA participants in the MESA Lung Study compared to not in the MESA Lung Study are reported in the Online Repository (Table E1); non-participants 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 was ascertained by self report using standard questionnaire items (23). Participants were asked, “Have you ever had asthma?” If so, 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-diagnosis of asthma. Child-onset asthma was defined as 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 twelve 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, had no current respiratory medication use, no wheezing in the last twelve months, and an $FEV_1/FVC \geq$ lower limit of normal.

### Spirometry

Spirometry was conducted in 2004–2006 in accordance with the American Thoracic Society/European Respiratory Society guidelines (24) (See Online Repository for details).

### CT Measures

CT scans were acquired as previously described and as detailed in the Online Repository (25).

**Airway Dimensions—**Airways were sampled by CT imaging perpendicular to the airway long axis (i.e., the airway lumen was approximately circular). They were measured in two dimensions using a modified full-width-half-maximum principle to identify the outer and inner airway wall borders (Figure 2) (26). Pi10 in the lower lobes was calculated following 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 = nine airways per participant). As is standard, airways with an internal perimeter ≤ 6 mm were excluded given the technical limitations of the CT scanners. The resulting regression line was used to calculate the standardized measure of airway wall thickness for a hypothetical airway with an internal perimeter of 10mm (Pi10) for each participant (27).

Since asthma may be related to narrowed airway lumens or thickened airway walls, (11) and standard CT measures of airway wall thickness such as Pi10 combine wall thickness with luminal diameter (by regressing airway wall thickness on inner perimeter, or taking the ratio of the two), 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 purposes of this study, the terms ‘airway wall thickness’ and ‘airway lumen diameter’ refer to the dimensions of a single airway for each participant, while ‘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, wall thickness) are adjusted for body size.

**Percentage of lung low attenuation areas (%LAA)—**%LAA (also known as percent emphysema) was defined as the percentage of the total lung voxels with attenuation < –910 Hounsfield units (HU) (28). %LAA reflects 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 Online Repository.

### Covariates

Age, gender, 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$^2$ 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. In order to account for the multiple comparisons (four measures of lung function and structure), statistical significance was defined post-hoc as a Bonferroni-corrected, two-tailed $P<0.0125$ for this test. If a statistically significant difference were detected for a given endpoint using this strict criteria, within-category comparisons were considered significant at a $P<0.05$. Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

## RESULTS

The mean age of the 3,371 participants was 65 years at the time of spirometry, 49% were male, and the race/ethic distribution was 34% white, 25% African-American, 23% Hispanic, and 18% Chinese-American. Fifty percent of the cohort never smoked cigarettes, 42% were former smokers and 8% currently smoked.

Of the 3,371 participants who met inclusion criteria, 446 had asthma and 2,925 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 to participants without asthma ($P< 0.001$) (Table II).

### Lung Structure

Participants with asthma had an increased Pi10 compared to participants without asthma (multivariate mean difference was 0.10 mm [95%CI: 0.06, 0.13]; P<0.001 for those with asthma onset in childhood, 0.09 mm [95%CI: 0.04, 0.13]; P<0.001 for those with asthma onset in young adulthood, and 0.05 mm [95%CI: 0.006, 0.09]; P<0.001 for those with onset after age 45 years).

Associations for Pi10, however, were predominantly due to lumen rather than wall size (Table II). Participants with asthma had narrower segmental airway lumens than participants without asthma (P< 0.001). In contrast to findings for airway lumens, segmental airway wall thickness was not significantly increased in asthma compared to participants without asthma (P=0.06).

### Percent Low Attenuation Areas

Participants with asthma had greater %LAA than participants without asthma (P<0.001), whether with onset in childhood, young adulthood or after age 45 years (Table II).

### Never Smokers

Findings were generally similar among the 50% of the cohort that never smoked cigarettes (Table III). Decrements 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 to the whole cohort was that %LAA was not increased in never smokers with child-onset asthma. As in the whole cohort, Pi10 was increased within each category of asthma (P<0.001).

### 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];P = 0.003), thicker airway walls (mean difference 0.001 mm [95%CI: 0.0003 to 0.002];P = 0.01) and increased %LAA (mean difference 0.15% [95%CI 0.11 to 0.20]; P < 0.001) 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 (Table E2).

### Lung Structure and Lung Function

In fully adjusted models, each increased ml of $FEV_1$ was associated with wider airway lumens (mean difference 0.03mm (95%CI 0.03 to 0.04); p < 0.001), was not associated with a change in airway wall thickness (mean difference 0.0005mm (95%CI −0.0003 to 0.00014; p = 0.2), and was associated with reduced %LAA (mean difference −0.4% (95%CI −0.5 to −0.4);p < 0.001).

### 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 below the lower limit of normal, respiratory medication use or wheezing in the last twelve months. When age of onset was varied, findings were generally similar (Online Repository Tables E3 and E4). When the threshold for %LAA was decreased to −950 HU results were similar (multivariate mean difference was 0.7% [95%CI: 0.2, 1.3] for those with asthma onset in childhood, 1.4% [95%CI: 0.7, 2.2] for those with asthma onset in young adulthood, and 1.3% [95%CI: 0.6, 1.9] for those with onset after age 45 years). Results were similar in analyses stratified by scanner type (Tables E5a and E5b). Results adjusted for medication use are reported in

Table E6 and for those with recurrent disease in Table E7. Results also were similar after adjusting for recent upper respiratory infection (Table E8), and stratified by current vs. former asthma (Table E9).

## 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 $FEV_1$ in later life among participants with asthma with onset in childhood and young adulthood was larger than that among participants with a history of cigarette smoking (−365 ml for child onset asthma and −343 ml for young adult onset asthma vs. −82 mL for participants who smoked) (31) in this multi-ethnic, 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 prior cross-sectional studies of self-reported asthma in older adults (3); these studies, however, did not report asthma age-of-onset and so it is unclear if they assessed early or late-onset asthma, or mis-classified 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 to participants without asthma in this general population sample. Though there is controversy about the optimal approach to measuring airways on CT (34), Nakano et al. showed that the relative change in smaller airways may be greater than what can be observed on CT in the larger airways, which would suggest associations of greater magnitude in airways smaller than measured in the present study (35). Furthermore, proximal airway changes may 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 remodeling (12) or because of bronchoconstriction and increased airway smooth muscle tone (37). We speculate that dysynapsis, or a relatively smaller airway size compared to lung volume, may explain these consistent findings for lung function and airway lumens in asthma.

Multiple prior studies have observed evidence of airway wall thickening on CT scan in patients with asthma (11, 14–20). However, most of these used the Pi10 and other metrics of airway wall thickness such as airway wall area percent that combine lumen with airway wall thickness and therefore it is unclear if 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 al.(11) found that patients with severe asthma had increased wall thickness percent and wall area percent compared to those with mild to moderate asthma or to those without asthma, but no difference between those with mild to moderate asthma vs. those without asthma. We did see an association between asthma and increased Pi10, but not between asthma and wall thickness. Our validated, reproducible approach to the measurement of segmental airway wall lumen diameter and thickness was similar to that utilized by Nakano et al (38), 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 may be due to the generally milder asthma phenotype found in this population based study.

Asthma onset in young adulthood was associated with increased %LAA, 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 remodeling (42); however, these results suggest that damage to 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 et al. posit a "pseudophysiologic emphysema" due to loss of lung elastic recoil (43). Exacerbations in older smokers accelerate progression of percent emphysema/%LAA (44). It is possible that these results are due to either chronic air trapping in stable asthma or acute hyperinflation during an exacerbation. Indeed, Gelb et al. found evidence of "pseudophysiologic emphysema," with reduced diffusing capacity and marked hyperinflation but minimal evidence of emphysema on autopsy in a study of ten participants with severe small airways disease (43). 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 infection. Further, visual assessment of CT scans from participants with persistent asthma demonstrated pulmonary emphysema among smokers and never-smokers (Figure 4).

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, the probability that misclassification of asthma was differential 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 child onset asthma, are supportive, as are our findings of narrower airway lumens and large decrements in lung function even among participants with remitted asthma. Post-bronchodilator spirometry was not conducted in this large population-based study, but mortality risk related to lung function is based on pre-bronchodilator measures.

Lung structure was measured on the lung regions of gated cardiac CT scans. The cardiac scans did not allow assessment of 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, three-dimensional scans. Variations in slice thickness and scanner resolution by scanner type may have affected airway measurement accuracy. However, this variability existed across all subgroups and scanner type was accounted for within the statistical models. Beam hardening may contribute to low attenuation around the pulmonary vessels, but would have been non-differential with respect to asthma subgroups. Expiratory CT scans were not obtained, and thus some of the %LAA may be due to air trapping.

Cross-sectional studies may have selection bias, but this is unlikely to explain the results since 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.

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## Abbreviations

| | |
|---|---|
| **%LAA** | percent low attenuation areas |
| **COPD** | chronic obstructive pulmonary disease |
| **CT** | computed tomography |
| **ETS** | environmental tobacco smoke |
| **$FEV_1$** | forced expiratory volume in one second |
| **FVC** | forced vital capacity |
| **HU** | Hounsfield units |
| **ICC** | intraclass correlation coefficient |
| **LLN** | lower limit of normal |
| **MESA** | Multi-Ethnic Study of Atherosclerosis |
| **Pi10** | wall thickness for a hypothetical airway with an internal perimeter of 10 mm |

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**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 to participants without asthma.

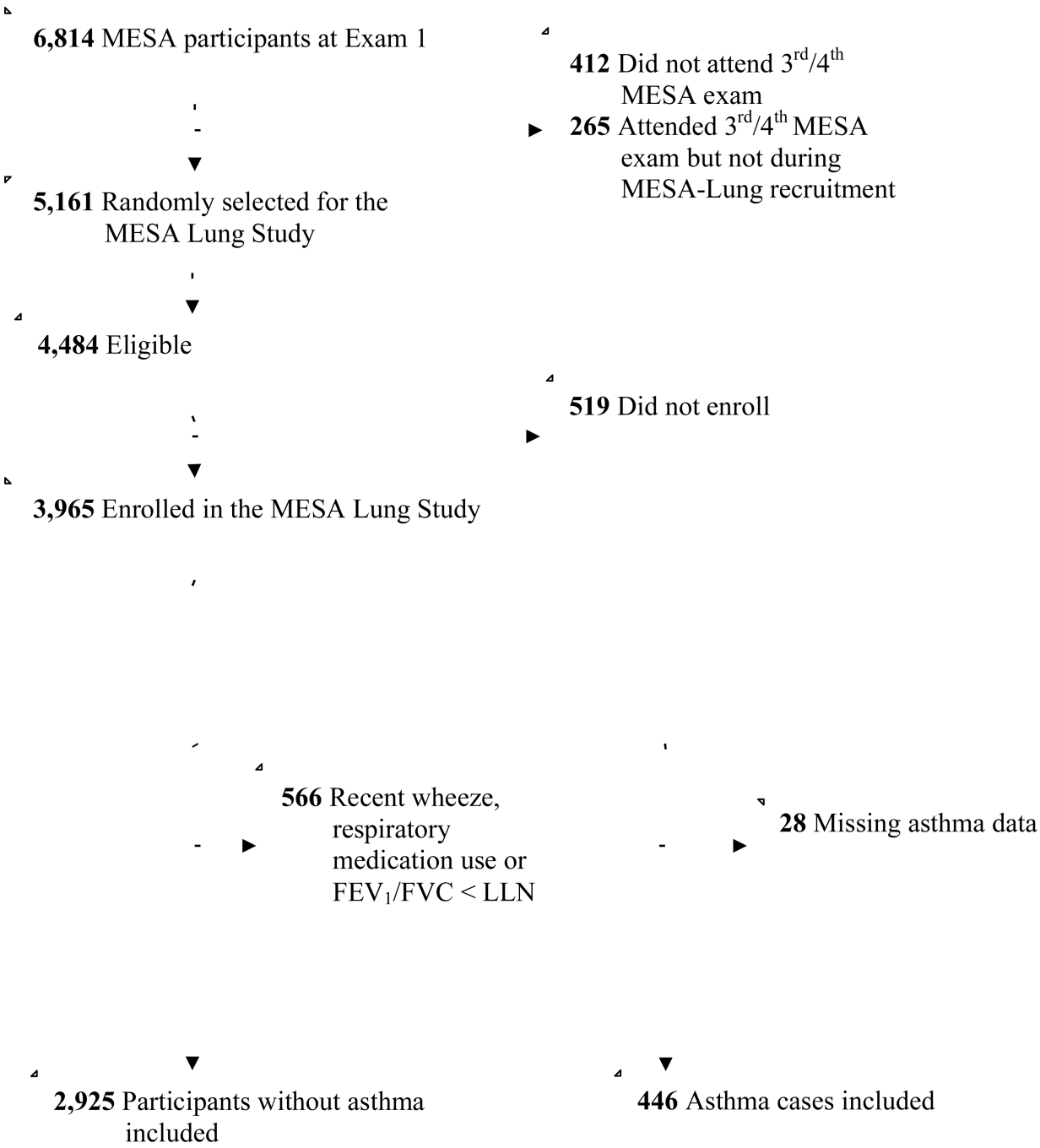



**Figure 1. The Study Sample**

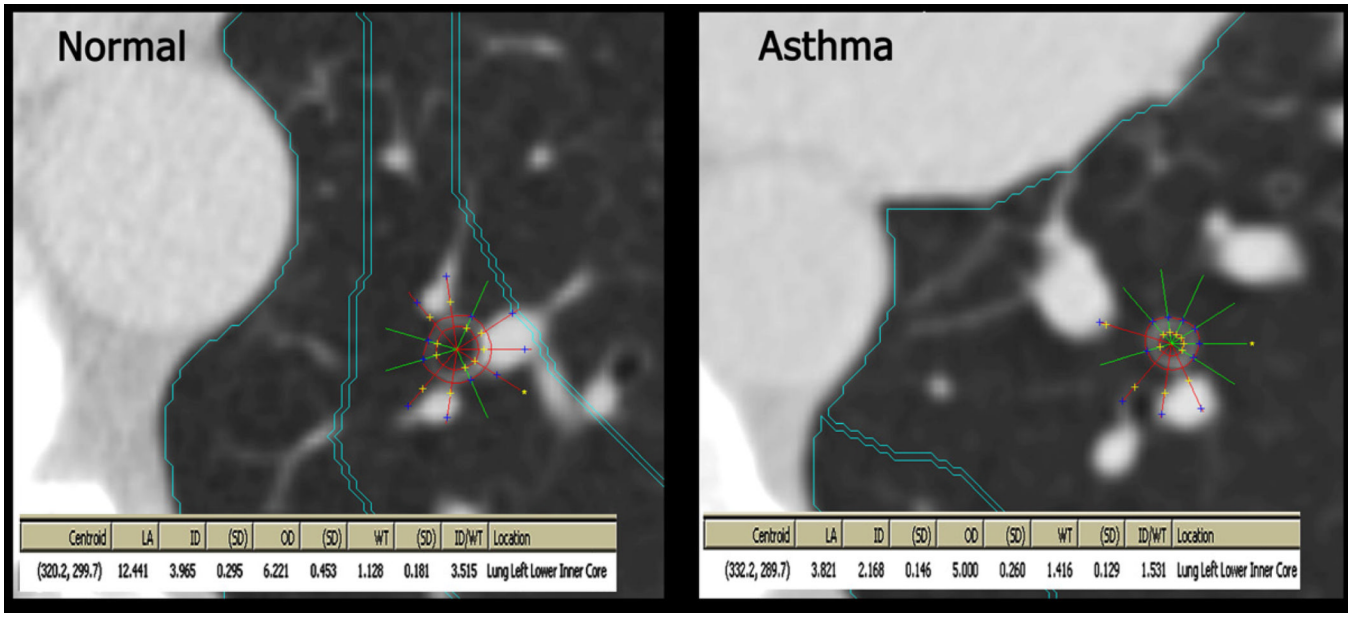
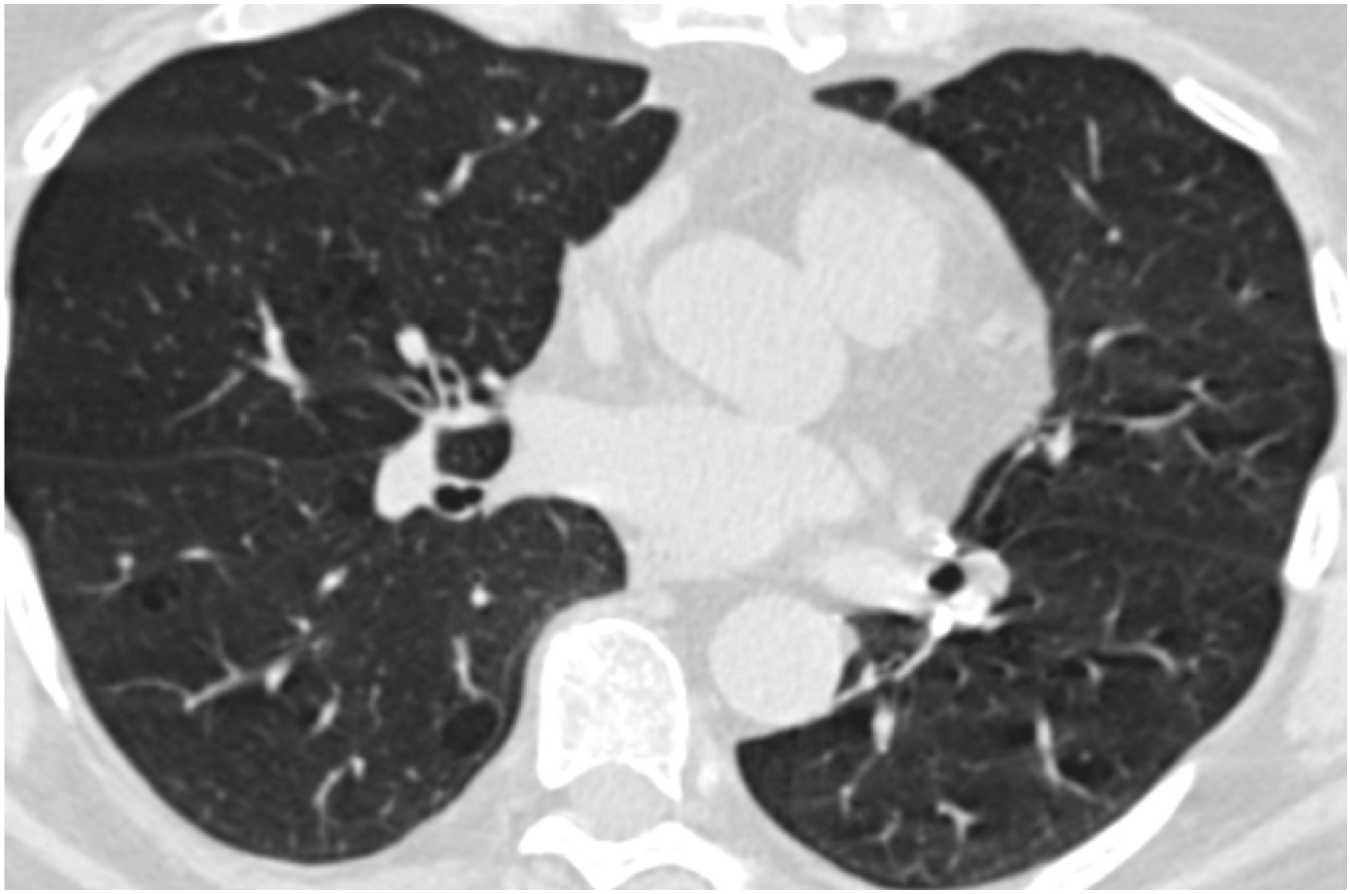



**Figure 2. Airway measurements on CT Scan**

Upon locating an airway perpendicular to the plane, a centroid was placed in the airway, from which the Pulmonary Analysis Software Suite generated rays and outer airway diameters. If a ray extended into adjacent tissue the analyst would exclude it and the PASS system would regenerate the inner and outer diameter to conform to the shape of the airway. The remaining rays were averaged to calculate wall thickness and lumen diameter.



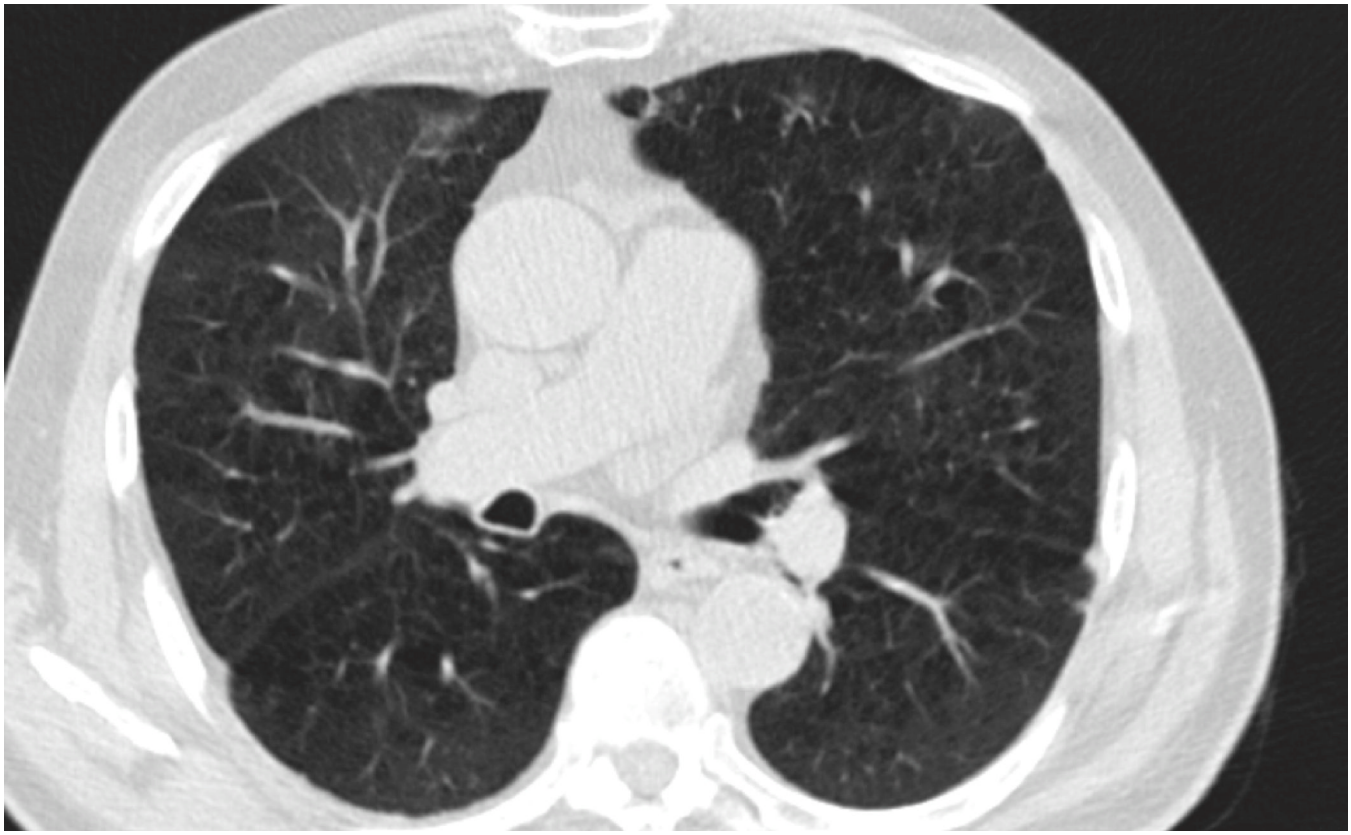


**Figure 3. Increased %LAA in Participants with Persistent Asthma**

## Table I

Characteristics of Participants Stratified by Asthma Age of Onset

| | No Asthma* | Child Onset Asthma ≤18 years† | Young Adult Onset Asthma 19 to 45 years‡ | Late Adult Onset Asthma > 45 years§ |
|---|---|---|---|---|
| N=3371 | 2925 | 217 | 102 | 127 |
| Age, mean (SD), years | 65 (10) | 63 (10) | 62 (10) | 68 (9) |
| Female gender — % | 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, years — % | | | | |
| < 12 | 17 | 11 | 19 | 17 |
| 12 | 18 | 10 | 12 | 20 |
| > 12 | 65 | 79 | 69 | 63 |
| Asthma age-of-onset, median (IQR) | n/a | 8 (4–13) | 35 (30–40) | 57 (50–64) |
| Age at remission, median (IQR) | n/a | 17 (12–25) | 40 (33–45) | 57 (50–67) |
| Taking asthma medications, — %¶ | 0 | 29 | 47 | 60 |
| Wheezing in last 12 months, — % | 0 | 35 | 48 | 54 |
| Current asthma, — % | 0 | 52% | 55% | 91% |
| Hay fever – % | 29 | 62 | 55 | 48 |
| Height, mean (SD), cm | 166 (10) | 167 (10) | 163 (8) | 163 (10) |
| Weight, mean (SD), lbs | 169 (37) | 182 (42) | 178 (39) | 175 (37) |
| Waist circumference, mean (SD), cm | 96 (13) | 100 (16) | 101 (16) | 103 (15) |
| Body mass index, mean (SD), $kg/m^2$ | 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, median (IQR) ng/ml | 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, — % | | | | |
| Multi-detector 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) |

| | **No Asthma*** | **Child Onset Asthma ≤18 years†** | **Young Adult Onset Asthma 19 to 45 years‡** | **Late Adult Onset Asthma > 45 years§** |
|---|---|---|---|---|
| FVC, mean % predicted (SD) | 97 (15) | 90 (16) | 90 (18) | 90 (19) |
| $FEV_1$/FVC % (SD) | 77 (7) | 71 (10) | 72 (11) | 69 (13) |

Abbreviations: SD, standard deviation; IQR, inter-quartile range; CT, computed tomography; ETS, environmental tobacco smoke; $FEV_1$, forced expiratory volume in one second; FVC, forced vital capacity

*No asthma = no history of asthma, no current respiratory medication use, no wheezing in the last twelve months, and an $FEV_1$/FVC ≥ lower limit of normal.

†Child onset asthma = report of first asthma symptoms or diagnosis before age 19 years

‡Young adult onset asthma = report of first asthma symptoms or diagnosis between ages 19 to 45 years

§Late adult onset asthma = report of first asthma symptoms or diagnosis between after age 45 years

¶Inhaled corticosteroids, β-agonists, leukotriene inhibitors

#Among ever smokers

**Among pipe smokers

**Table II**

Asthma age of onset, lung structure and function

| | ≤ 18 years n=217 | 19 to 45 years n=102 | > 45 years n=127 | P-value |
|---|---|---|---|---|
| $FEV_1$ (ml) | −365 (−419 to −310) *** | −343 (−420 to −266) *** | −359 (−428 to −289) *** | < 0.001 |
| 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) *** | < 0.001 |
| 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) | 0.06 |
| % LAA (%) | 1.69 (0.09 to 3.29) * | 4.30 (2.00 to 6.59) *** | 3.52 (1.45 to 5.58) *** | < 0.001 |

Results represent the mean difference compared to participants without asthma from linear regression models adjusted for age, sex, height, $height^2$, race/ethnicity, smoking status, pack-years, pipe-years, urine cotinine, household ETS, education, body mass index, waist circumference, occupational exposures, 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 vs. participants without asthma.

Where significant overall, subgroups were tested individually, with $p < 0.001$ = *** and $p < 0.05$ = *.

## Table III

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

| | ≤ 18 years n=107 | 19 to 45 years n=51 | > 45 years n=51 | P-value |
|---|---|---|---|---|
| $FEV_1$ (ml) | −293 (−364 to −221) *** | −237 (−338 to −137) *** | −307 (−407 to −207) *** | < 0.001 |
| 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) *** | < 0.001 |
| 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) | 0.09 |
| % LAA (%) | −0.68 (−2.83 to 1.47) | 3.52 (0.46 to 6.58) * | 3.44 (0.391 to 6.50) * | < 0.001 |

Results represent the mean difference compared to participants without asthma from linear regression models adjusted for age, sex, height, height2, race/ethnicity, smoking status, pack-years, pipe-years, urine cotinine, household ETS, education, body mass index, waist circumference, occupational exposures, 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 < 0.001 = *** and P < 0.05 = *.