## Original Contribution

# Association of Environmental Tobacco Smoke Exposure in Childhood With Early Emphysema in Adulthood Among Nonsmokers

## The MESA-Lung Study

**Gina S. Lovasi\*, Ana V. Diez Roux, Eric A. Hoffman, Steven M. Kawut, David R. Jacobs, Jr., and R. Graham Barr**

\* Correspondence to Dr. Gina S. Lovasi, Mailman School of Public Health, 722 West 168th Street, Room 804, New York, NY 10032
(e-mail: gl2225@columbia.edu).

Mechanical stress to alveolar walls may cause progressive damage after an early-life insult such as exposure to environmental tobacco smoke (ETS). This hypothesis was examined by using data from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort aged 45–84 years, free of clinical cardiovascular disease, recruited from 6 US sites in 2000–2002. The MESA-Lung Study assessed a fractal, structural measure of early emphysema ("alpha," lower values indicate more emphysema) and a standard quantitative measure ("percent emphysema") from cardiac computed tomography scans. Childhood ETS exposure was assessed retrospectively as a report of living with one or more regular indoor smokers. Analyses included 1,781 nonsmokers (<100 cigarettes, 20 cigars, or 20 pipefulls in their lifetime and urinary cotinine levels <100 ng/mL); mean age was 61 years (standard deviation, 10), and 65% were women. Childhood ETS exposure from 2 or more smokers (17%) compared with none (52%) was associated with 0.05 lower alpha and 2.8 higher percent emphysema ($P$ for trend = 0.04 and 0.01, respectively) after adjustment for demographic, anthropometric, parental, and participant characteristics, as well as adult exposures (e.g., cumulative residential air pollution exposure, exposure to ETS as an adult). Childhood ETS exposure was associated with detectable differences on computed tomography scans of adult lungs of nonsmokers.

cohort studies; diagnostic imaging; emphysema; lung; residence characteristics; spirometry; time; tobacco smoke pollution

Abbreviations: CT, computed tomography; ETS, environmental tobacco smoke; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; HU, Hounsfield units; MESA, Multi-Ethnic Study of Atherosclerosis.

Emphysema is defined anatomically as the destruction of alveolar walls and permanent enlargement of airspaces distal to the terminal bronchioles (1). Emphysema overlaps appreciably, but incompletely, with chronic obstructive pulmonary disease, which is defined by airflow obstruction that is not fully reversible (2). Combined, emphysema and chronic obstructive pulmonary disease are projected to become the third leading cause of death worldwide by 2020 (3, 4), and their global prevalence is estimated to be approximately 10% (2).

Emphysema can be diagnosed on histopathology or on computed tomography (CT) scans and can be subdivided into 2 major types (5). Centriacinar/centrilobular emphysema occurs predominantly in the lung apices. The major risk factor for centrilobular emphysema, as for chronic obstructive pulmonary disease, is cigarette smoking (6, 7). Panlobular emphysema generally occurs diffusely or in the lower lobes and occurs not infrequently in nonsmokers (7, 8). In a series of consecutive autopsies of older accident victims, for example, 10 of 72 lung specimens from nonsmokers exhibited moderate panlobular emphysema (7).

The major known cause of panlobular emphysema is alpha 1-antitrypsin deficiency (9), which affects fewer than

0.1% of individuals in population-based studies. Other risk factors for panlobular emphysema among nonsmokers have not been well described (6), in part because of the lack of population-based cohorts with quantitative measures of emphysema.

The mechanical hypothesis of emphysema posits that emphysema may develop and progress because of simple mechanical strain on alveolar walls (10, 11). The absence of a given alveolar wall increases mechanical strain on surrounding alveolar walls, predisposing them to rupture. Adjacent alveoli connected by loss of their interalveolar septum form an emphysematous sac, which places additional strain on neighboring alveolar walls. Emphysematous sacs therefore propagate and enlarge. Mishima et al. (10) found that the reduction in number of alveoli and increase in average sac size in a lattice model followed a fractal pattern. The same fractal relation between emphysematous hole number and size was observed on CT scans of patients with early chronic obstructive pulmonary disease.

Under this mechanical hypothesis, as well as other theories that frame early life as a sensitive period (12, 13), early insults should have a disproportionately large impact on the development of emphysema. One such early-life insult may be exposure to environmental tobacco smoke (ETS) in the childhood home. We therefore examined whether ETS exposure in childhood was associated with diffuse early emphysema and diffuse percent emphysema on CT scan in a large, population-based cohort of adults. We restricted the analysis to participants who denied a significant smoking history given our interest in emphysema in nonsmokers and to minimize potential confounding by smoking in adulthood.

## MATERIALS AND METHODS

### Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter, prospective cohort study designed to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease. Details on the study design have been published previously (14). The study enrolled 6,814 men and women who were classified as African American, Chinese, Hispanic, or non-Hispanic white based on self-reported race and ethnicity. Participants were recruited from 6 communities in the United States: Forsyth County, North Carolina; northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles, California. All participants were aged 45–84 years when recruited in 2000–2002. Exclusion criteria included clinical cardiovascular disease, any cardiovascular procedure, weight >300 pounds (135 kg), pregnancy, or impediment to long-term participation. The protocols of MESA and all studies described herein were approved by the institutional review boards of all collaborating institutions and the National Heart, Lung, and Blood Institute (Bethesda, Maryland).

The MESA-Lung Study enrolled 3,965 participants of 4,483 randomly selected from all MESA participants who consented to genetic analyses, underwent baseline measures of endothelial function, and attended an examination during the MESA-Lung Study recruitment period in 2004–2006 (99%, 89%, and 91% of the MESA cohort, respectively). Chinese participants were oversampled, resulting in a sample that was 24% Chinese, 30% non-Hispanic white, 22% non-Hispanic black, and 23% Hispanic.

The present study included 1,781 MESA-Lung participants who met all of the following criteria. They reported that they had smoked fewer than 1) 100 cigarettes, 2) 20 cigars, and 3) 20 pipefulls in their lifetime. In addition, they confirmed this information at least a second time during a clinic visit at least 18 months later, and their urinary cotinine levels were <100 ng/mL at the time of the CT scan.

### Early emphysema and percent emphysema

Quantitative measures of early emphysema were performed on the lung fields of cardiac CT scans, which imaged approximately 70% of the lung volume from the carina to the lung bases. Cardiac CT scans were performed at full inspiration on multidetector CT and electron-beam CT scanners in 2000–2002, following a standardized protocol (15). Two scans were performed on each participant; the scan with higher air volume was used for analyses, except that, when the 2 scans had discordant quality control scores, the higher quality scan was used (11).

Image attenuation was assessed by using modified Pulmonary Analysis Software Suite (16, 17) at a single reading center by trained readers without knowledge of other participant information. To correct for variations in scanner calibration and in the way different scanners handle scatter and beam hardening, we measured the attenuation of air outside and inside the body for each scan. Air outside the body, which should have a mean attenuation of −1,000 Hounsfield units (HU), was sampled in a region well away from the body, scanner table, and blankets. The attenuation of each pixel in the lung regions was then corrected to have the value equal measured pixel attenuation × (−1,000/mean air attenuation), from which emphysema measures were calculated. For our main analysis, emphysema measures were corrected for air attenuation outside the body and were calculated by using a threshold of −910 HU to define emphysema-like lung; sensitivity analyses were performed by using emphysema measures corrected for air attenuation within the body and by using an alternative threshold of −950 HU.

Early emphysema was defined by a measure termed "alpha" (10, 11). Emphysematous holes on CT scan were defined as connected voxels within a scanned slice falling below −910 HU. Alpha is defined as the slope of the log-log relation of hole size ($x$-axis) versus number of holes discernible in the lung field of a CT scan. This relation is linear (mean $r^2$ on MESA scans = 0.97) and increases (approaching zero) with the degree of severity as multiple small holes merge to form fewer, larger holes. The slope of this log-log relation is termed "$d$" in studies by Mishima et al. (10), and alpha is equal to $d \times (-1)$. In our data, the coefficient of variation of alpha from paired cardiac scans was 4.3%, and the intraclass correlation coefficient was 0.88 (18).

Percent of emphysema-like lung (also known as percent low attenuation area and hereafter referred to as percent emphysema) was defined as the percentage of voxels in the lung that fell below −910 HU. This threshold was derived from comparisons to pathologic specimens (19). The intraclass correlation coefficient for percent emphysema was 0.94. Alpha and percent emphysema from cardiac scans correlated with those measures from full-lung scans from 42 MESA participants (e.g., 0.88 for alpha and 0.93 for percent emphysema on multidetector CT scanner data) (18).

For secondary analyses, apical and basal lung segments were defined as the cephalad or caudal eighths of the lung divided along the z-axis scan coverage of the cardiac CT scan, enabling estimation of apical-basilar difference in percent emphysema. The correlation of this measure with apical-basilar difference in percent emphysema from full lung scans is 0.76 (18).

### Spirometry

Spirometry was conducted in 2004–2006 in accordance with American Thoracic Society/European Respiratory Society guidelines (20). Tests were conducted by using a dry-rolling-sealed spirometer and software that performed automated quality checks in real time (Occupational Marketing, Inc., Houston, Texas). All spirometry examinations were reviewed by one investigator, and each test was graded for quality (21). The intraclass correlation coefficient of both forced expiratory volume in 1 second ($FEV_1$) and forced vital capacity (FVC) on random 10% repeat testing was 0.99.

### Childhood ETS exposure and parental smoking

Childhood ETS exposure was based on participants' retrospective reports in response to the question, "In your childhood, did you live with a regular cigarette smoker who smoked in your home?" Participants also reported the number of smokers ("In your childhood, how many smokers lived in your home?"), and childhood ETS was categorized as none, one regular smoker in the home, or two or more regular smokers in the home. Parental smoking was classified as neither mother nor father, father only, mother only, or both mother and father based on a separate item that asked whether each parent smoked ("Did or does he/she smoke cigarettes?").

### Demographic characteristics and other covariates

Most covariates, including age, gender, race, ethnicity, and country of birth, were self-reported. Participants were asked to report their educational attainment (8 categories, from which years of education was estimated (22)). Asthma was defined as self-report of physician-diagnosed asthma, with symptom onset before age 45 years. Occupational exposure to dust was assessed by asking, "Have you ever been exposed at work to dust?" Environmental tobacco exposure in adulthood was measured with the following 2 items: "As an adult, have you ever lived with a regular cigarette smoker (not including yourself) who smoked in your home?" and "As an adult, have you ever regularly spent time, when you were not at home, indoors where people were smoking cigarettes (for example, at work)?"

Urinary cotinine was measured by immunoassay (Immulite 2000 Nicotine Metabolite Assay; Diagnostic Products Corp., Los Angeles, California). Air pollution was assessed by using a 20-year residential history to approximate the cumulative exposure to particles with a diameter smaller than 10 μm based on data from the US Environmental Protection Agency's Aerometric Information Retrieval System; exposure for the 20-year period was summarized by using an area-under-the-curve calculation (23). Height was measured to the nearest 0.1 cm, and weight was measured to the nearest pound (1 pound = 0.45 kg).

### Statistical analysis

All outcomes were analyzed by using generalized linear regression with robust variance estimates. Models of percent emphysema, which was highly skewed, used a gamma error distribution.

Regression models were adjusted for personal, familial, and environmental characteristics that either 1) had the potential to confound the associations of interest because of their role as a common prior cause of both childhood ETS exposure and adult respiratory health or 2) were potential precision variables, outside of the causal pathway of interest but likely to explain some of the variance in the adult respiratory outcomes. The specific adjustment variables included age, sex, race/ethnicity, height, body mass index, whether the participant was born in the United States, mother's and father's educational attainment (whether each completed high school), participant's educational attainment (a grouped linear variable with 5 categories), history of asthma before the age of 45 years, cumulative residential air pollution exposure, living with a smoker as an adult, occupational exposures (dichotomous indicators for secondhand smoke and dust), and urinary cotinine (a dichotomous indicator of detectable levels to indicate recent ETS exposure). The continuous covariates age, height, and body mass index were modeled with linear and centered quadratic terms. Models also adjusted for CT scanner type and, if multidetector CT scanner, weight above 100 kg (220 pounds) since the dose of radiation, measured in milli-ampere seconds, was increased for these participants (15).

For model adjustment, missing data on covariates (father's education, $n = 92$; mother's education, $n = 56$; paternal smoking, $n = 117$; maternal smoking, $n = 34$; birth outside of the United States, $n = 3$; participant's education, $n = 3$; ETS in the adult household, $n = 1$; cumulative air pollution exposure, $n = 406$; occupational ETS exposure, $n = 20$; and occupational dust exposure, $n = 5$) were estimated by multiple imputation (24). Five imputed data sets were created, and their results were recombined such that regression confidence intervals reflected uncertainty from missing covariate data. Analyses were performed with Stata 10.0 software (Stata Corp., College Station, Texas).

### RESULTS

The study sample included 1,781 participants who did not smoke (Table 1). The mean age was 61 years, and 65% were

**Table 1.**   Characteristics of Participants,[a] by Childhood ETS[b] Exposure, in the Multi-Ethnic Study of Atherosclerosis, United States, 2000–2006

| | No Childhood ETS Exposure (n = 923) | One Smoker in the Childhood Home (n = 559) | Two or More Smokers in the Childhood Home (n = 299) |
|---|---|---|---|
| Male sex | 35 | 34 | 37 |
| Age, years | 62 (10) | 61 (10) | 59 (10) |
| Adult height, cm | 163 (10) | 164 (9) | 165 (10) |
| Body mass index, kg/m$^2$ | 27 (5) | 28 (6) | 28 (5) |
| White race/ethnicity | 24 | 33 | 39 |
| Chinese race/ethnicity | 28 | 25 | 16 |
| Black race/ethnicity | 22 | 22 | 23 |
| Hispanic race/ethnicity | 27 | 20 | 21 |
| Born outside of the United States | 55 | 42 | 37 |
| Father completed high school | 44 | 42 | 51 |
| Mother completed high school | 37 | 40 | 42 |
| Neither parent smoked | 74 | 6 | 7 |
| Only the father smoked | 20 | 75 | 19 |
| Only the mother smoked | 4 | 14 | 6 |
| Both the mother and father smoked | 2 | 5 | 68 |
| Asthma before age 45 years | 8 | 8 | 11 |
| Education, years | 13 (4) | 14 (4) | 14 (4) |
| Lived with a smoker as an adult | 30 | 41 | 38 |
| Occupational exposure to secondhand smoke | 32 | 38 | 44 |
| Occupational exposure to dust | 29 | 29 | 40 |
| AUC for cumulative residential PM$_{10}$ exposure | 35 (8) | 35 (8) | 34 (7) |
| Cotinine levels below detection threshold (≤7.07 ng/mL) | 86 | 87 | 79 |
| Cotinine levels detectable (>7.07 and <100 ng/mL) | 14 | 13 | 21 |

Abbreviations: AUC, area under the curve; ETS, environmental tobacco smoke; PM$_{10}$, particles with a diameter smaller than 10 μm.

[a] Values are expressed as percentage or mean (standard deviation).

[b] Childhood ETS was defined by retrospective reports in response to the question, "In your childhood, did you live with a regular cigarette smoker who smoked in your home?" and a follow-up question on the number of smokers in the childhood home.

female. Participants were born between 1917 and 1957 (median: 1940). Approximately half of participants reported childhood ETS exposure from at least one regular smoker in their childhood home. Participants reporting childhood ETS exposure were somewhat younger, more likely to be non-Hispanic white, and less likely to have been born outside the United States. However, childhood ETS did not appear to be associated with adult educational attainment or an estimate of cumulative residential exposure to air pollution (specifically, particles with a diameter smaller than 10 μm). Participants who reported a smoker in the childhood home were

more likely to report that their mother, father, or both smoked. For participants who reported childhood ETS exposure but no parental smoking, the regular smoker may have been another household member; however, we did not have additional information on number of members of the household.

**Childhood ETS exposure**

The number of smokers in the childhood home was classified as none, one, or two more and was monotonically

**Table 2.**    Associations of Childhood ETS[a] Exposure With CT Measures of Early Emphysema in the Multi-Ethnic Study of Atherosclerosis, United States, 2000–2006

| | No. | Mean (SD) | Unadjusted Model | | Adjusted Model[b] | | P for Trend |
|---|---|---|---|---|---|---|---|
| | | | Difference | 95% CI | Difference | 95% CI | |
| Alpha[c] | | | | | | | |
| No childhood ETS exposure | 923 | 1.24 (0.30) | Reference | | Reference | | 0.04 |
| One smoker in the childhood home | 559 | 1.22 (0.30) | −0.02 | −0.06, 0.01 | −0.01 | −0.04, 0.01 | |
| Two or more smokers in the childhood home | 299 | 1.19 (0.31) | −0.05 | −0.09, −0.01 | −0.03 | −0.07, 0.00 | |
| Percent emphysema[c] | | | | | | | |
| No childhood ETS exposure | 923 | 17.1 (11.9) | Reference | | Reference | | 0.01 |
| One smoker in the childhood home | 559 | 18.3 (12.5) | 1.1 | −0.2, 2.4 | 0.7 | −0.4, 1.8 | |
| Two or more smokers in the childhood home | 299 | 20.0 (13.5) | 2.8 | 1.1, 4.5 | 2.1 | 0.4, 3.7 | |
| Apical-basilar difference in percent emphysema | | | | | | | |
| No childhood ETS exposure | 922 | 2.77 (6.92) | Reference | | Reference | | 0.42 |
| One smoker in the childhood home | 558 | 2.36 (7.00) | −0.41 | −1.14, 0.33 | −0.21 | −0.91, 0.50 | |
| Two or more smokers in the childhood home | 299 | 1.67 (7.41) | −1.10 | −2.05, 0.14 | −0.34 | −1.24, 0.56 | |

Abbreviations: CI, confidence interval; CT, computed tomography; ETS, environmental tobacco smoke; SD, standard deviation.

[a] Childhood ETS was defined by retrospective reports in response to the question, "In your childhood, did you live with a regular cigarette smoker who smoked in your home?" and a follow-up question on the number of smokers in the childhood home.

[b] Adjusted for sex, race/ethnicity, age, height, body mass index, whether the participant was born in the United States, mother's and father's educational attainment, participant's educational attainment, history of asthma before age 45 years, cumulative residential air pollution exposure, living with a smoker as an adult, occupational exposures to secondhand smoke and dust, and urinary cotinine.

[c] Refer to the Materials and Methods section of the text for a definition.

associated with both alpha and percent emphysema after adjusting for all covariates (Table 2). The magnitude of the estimated differences in emphysema measures was modest, equal to approximately one-tenth of a standard deviation for alpha. In contrast, there was no association of childhood ETS exposure with apical-basilar difference in emphysema after adjustment.

In contrast to findings for alpha and percent emphysema, there were no significant associations of childhood ETS exposure with lung function. The adjusted lung function differences comparing participants exposed to childhood ETS from 2 or more smokers with those without any childhood ETS exposure were 20 mL (95% confidence interval: −29, 69) for $FEV_1$, 51 mL for FVC (95% confidence interval: 11, 114), and −0.41 (95% confidence interval: −1.28, 0.46) for $FEV_1/FVC$ ratio × 100% after adjusting for sex, race/ethnicity, age, height, body mass index, whether the participant was born in the United States, mother's and father's educational attainment, participant's educational attainment, history of asthma before age 45 years, cumulative residential air pollution exposure, living with a smoker as an adult, occupational exposures to secondhand smoke and dust, and urinary cotinine.

**Parental smoking**

Parental history of smoking was classified as paternal smoking only, maternal smoking only, or both paternal and maternal smoking. There was a trend for participants reporting that one or both of their parents smoked to have a lower mean alpha and a higher percent emphysema (Table 3). Although the statistical power to detect an interaction between childhood ETS exposure and parental smoking history was low, parental smoking appeared to be most associated with CT-based measures among those who reported childhood ETS exposure based on reports of living with a regular smoker who smoked in the home (Figure 1).

**Sensitivity analyses**

We performed sensitivity analysis after excluding obese participants (body mass index >30 kg/m$^2$), for whom CT scan of the lungs may be less accurate (25). Results for the 1,288 nonobese participants were similar to the associations in the entire sample. There was no significant effect modification by participants' gender or race/ethnicity. A reanalysis of CT-based measures using inside-air-calibrated

**Table 3.**   Associations of Parental Smoking With CT Measures of Early Emphysema in the Multi-Ethnic Study of Atherosclerosis, United States, 2000–2006

| | No. | Mean (SD) | Unadjusted Model | | Adjusted Model[a] | | P for Trend |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | | Difference | 95% CI | Difference | 95% CI | |
| Alpha[b] | | | | | | | |
| Neither parent smoked | 726 | 1.24 (0.31) | Reference | | Reference | | 0.04 |
| Only the father smoked | 655 | 1.22 (0.29) | −0.02 | −0.05, 0.01 | −0.01 | −0.04, 0.02 | |
| Only the mother smoked | 134 | 1.21 (0.30) | −0.04 | −0.09, 0.02 | −0.03 | −0.08, 0.01 | |
| Both parents smoked | 247 | 1.18 (0.32) | −0.06 | −0.11, −0.01 | −0.04 | −0.07, 0.00 | |
| Percent emphysema[b] | | | | | | | |
| Neither parent smoked | 726 | 17.0 (12.0) | Reference | | Reference | | 0.03 |
| Only the father smoked | 655 | 18.1 (12.2) | 1.1 | −0.2, 2.4 | 0.7 | −0.4, 1.8 | |
| Only the mother smoked | 134 | 18.5 (11.9) | 1.5 | −0.7, 3.7 | 1.8 | −0.1, 3.7 | |
| Both parents smoked | 247 | 19.8 (14.1) | 2.8 | 0.9, 4.8 | 1.6 | −0.3, 3.5 | |
| Apical-basilar difference in percent emphysema | | | | | | | |
| Neither parent smoked[c] | 726 | 3.19 (6.98) | Reference | | Reference | | 0.12 |
| Only the father smoked | 653 | 2.16 (6.90) | −1.04 | −1.77, −0.30 | −0.93 | −1.62, −0.24 | |
| Only the mother smoked | 134 | 1.67 (7.35) | −1.52 | −2.88, −0.18 | −0.91 | −2.24, 0.42 | |
| Both parents smoked | 247 | 1.62 (7.21) | −1.57 | −2.61, −0.54 | −0.60 | −1.59, 0.39 | |

Abbreviations: CI, confidence interval; CT, computed tomography; SD, standard deviation.

[a] Adjusted for sex, race/ethnicity, age, height, body mass index, whether the participant was born in the United States, mother's and father's educational attainment, participant's educational attainment, history of asthma before age 45 years, cumulative residential air pollution exposure, living with a smoker as an adult, occupational exposures to secondhand smoke and dust, and urinary cotinine.

[b] Refer to the Materials and Methods section of the text for a definition.

[c] The reference group (neither parent smoked) is compared with 3 mutually exclusive categories of parental smoking (father only, mother only, both parents) modeled as indicator variables, and the trend is assessed for the order given.

measures to better account for possible distortion due to body size did not alter the pattern of results. In an analysis using the threshold of −950 HU instead of −910 HU to define emphysema-like lung areas, the associations of childhood ETS exposure with alpha and percent emphysema were in the same direction but were attenuated; the association with percent emphysema remained monotonic and statistically significant ($P = 0.001$), but the association with alpha did not.

## DISCUSSION

Compared with adult nonsmokers who reported no childhood ETS exposure, adult nonsmokers who reported greater childhood ETS exposure had greater degrees of diffuse emphysema measured quantitatively on CT scan. Reports that both parents smoked were likewise associated with early emphysema on CT scan. On the other hand, we found no difference in pulmonary function by degree of childhood ETS exposure.

To our knowledge, this population-based study is the first to examine the association of childhood ETS with early emphysema by CT scan in nonsmokers. One explanation for this observation can be found in Mishima et al.'s hypothesis (10) of mechanical tension with physical breakage of

alveolar walls. In addition, local tension on alveolar walls may also increase the chance of their breakage because of decreased pulmonary blood flow. However, our cross-sectional CT scan data did not enable us to distinguish this pattern of vulnerability and breakage from the mere persistence of initial injury due to incomplete repair. Our findings are also compatible with other pathways that could link childhood ETS exposure with emphysema-like lung patterns in adulthood, such as altered gene expression or developmental plasticity (26).

Previous studies have found evidence that childhood ETS exposure affects perinatal and childhood health outcomes (27) along with adult respiratory health outcomes, including lung function (28–30) and respiratory symptoms (31); however, most of these studies have been limited to younger adults. Childhood ETS exposure has been linked to lower $FEV_1$ (32, 33) or lower $FEV_1/FVC$ ratio (34–36) in childhood, and parental smoking has also been associated with worse lung function in young adulthood (28, 37). However, several studies have suggested that the effects of passive smoking on lung function may be heterogeneous across gender or racial groups (30, 35–37) or that childhood ETS is associated with higher FVC values in childhood (34, 36, 38). The lack of association between childhood ETS and lung function in our study does not
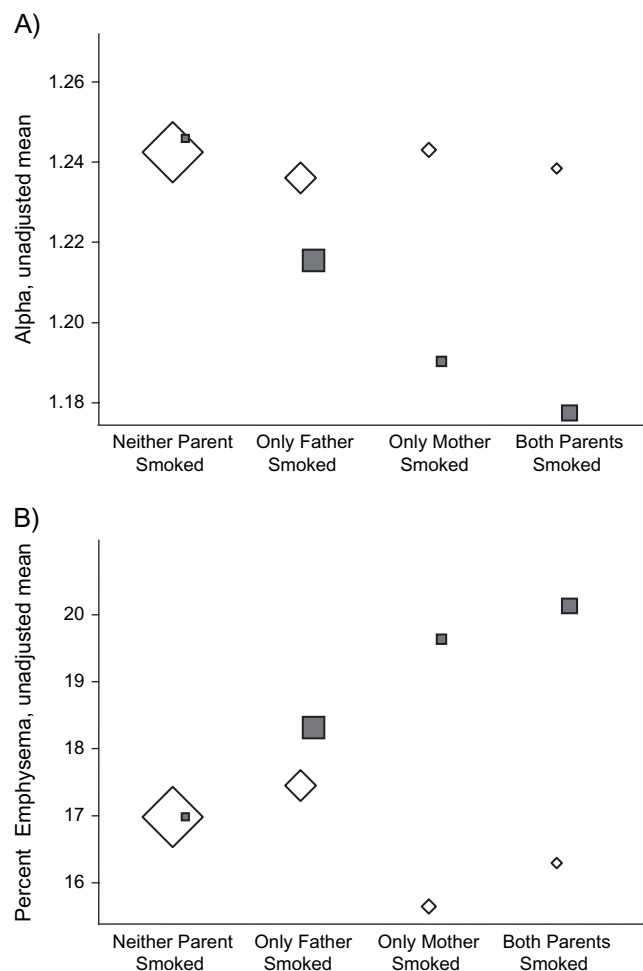
A)



B)



**Figure 1.** Association of childhood environmental tobacco smoke (ETS) exposure and parental smoking with early emphysema on computed tomography scan in the Multi-Ethnic Study of Atherosclerosis, United States, 2000–2006. Shown are unadjusted group means for A) alpha and B) percent emphysema (refer to the Materials and Methods section of the text for a definition of each) by parental smoking status and childhood ETS exposure. Squares: participants who reported childhood ETS exposure; diamonds: participants who did not report childhood ETS exposure. The sizes of the symbols correspond to the number of participants in each group.

were not part of this assessment. This exposure information is subject to misclassification bias, which could be differential if participants perceiving respiratory symptoms were more likely to report childhood ETS exposure. However, the reliance on subclinical measures of early emphysema in a relatively healthy cohort of adults makes differential misclassification bias an unlikely explanation for our findings. The exposure also provides no information with regard to timing during childhood, making it difficult to distinguish cumulative exposure from exposure in utero or during other sensitive periods. The persistence of an association between childhood ETS and early emphysema after restricting our analyses to those whose mothers did not smoke and the monotonic relation between number of smokers in the home and early emphysema both suggest that the effect we are detecting is for smoking in the home during childhood, rather than in utero exposure alone.

Second, the CT-based measurements of early emphysema were taken at a single point in time and were based upon partial-lung scans. However, 2 scans were acquired at the examination, and we previously validated the measures from MESA cardiac scans against full-lung scans (18). In addition, associations with the measure alpha differed depending on the threshold used to define areas of emphysema-like lung, suggesting some sensitivity of our results to the specification of our CT-based measures. Since this is the first large study known to examine these CT-based measures in a large, healthy cohort of adults, correspondence with clinically relevant disease categories cannot be assumed. However, percent emphysema is a standard quantitative measure of emphysema that is close to US Food and Drug Administration approval as a surrogate marker for emphysema, and we previously found good agreement between measures of diffuse emphysema on partial- and full-lung scans (18).

This study is further limited by the cross-sectional and observational nature of the data, and we cannot exclude the possibility that the small differences in emphysema on CT scan were due to residual confounding or confounding by unmeasured characteristics. Survival bias could have affected these cross-sectional results if some individuals with childhood ETS exposure and early emphysema did not survive to be eligible participants; however, this possibility would likely have biased our results toward the null. We excluded smokers based on questionnaire and cotinine data so that individual smoking did not overwhelm the relatively modest effect of childhood ETS exposure. Some participants who were former smokers may not have accurately reported their prior smoking history. However, given that approximately 2% of the cohort misreported their current smoking status (comparing self-report with cotinine levels), it is likely that this group is small.

Childhood ETS exposure in childhood was associated with CT measures of early emphysema in adulthood in a large multiethnic cohort. This finding suggests that the lungs may not recover completely from the effects of early-life exposures and adds to the literature on detrimental effects of ETS exposure.

contradict the results for early emphysema, since airflow obstruction and anatomic damage are theoretically and clinically distinguishable, but may suggest that emphysema is a more sensitive measure of damage compared with lung function in this relatively small and healthy cohort.

The unique strengths of this study—including the quantitative measures of emphysema in a racially and ethnically diverse, population-based cohort with a large number of nonsmokers—were offset by a number of limitations. First, our study relied on participants' recall of cohabitation with one or more cigarette smokers as a child and of parental smoking for the assessment of childhood ETS exposure. Other sources of ETS, including pipe and cigar smoke,

## ACKNOWLEDGMENTS

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