Enfisema e funzione respiratoria dopo 20 anni di inquinamento

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Soltanto le concentrazioni ambientali di ozono e di ossidi d'azoto sono significativamente associate ad un aumento dei casi di enfisema o un peggioramento dello stesso, mentre è la presenza di ozono a peggiorare la funzione respiratoria

Storicamente l'inquinamento dell'aria esterna è sempre stato associato a malattie polmonari e cardiovascolari. Ma nel contesto attuale, con quale incisività le concentrazioni dei più comuni inquinanti inalati a lungo termine provocano nello specifico enfisema polmonare e peggioramento della funzione respiratoria?

L'enfisema polmonare rientra nelle malattie broncopolmonari croniche, in cui il grado del conseguente deficit respiratorio si attua in modo irreversibile.

In un recente studio statunitense le percentuali di peggioramento in quasi vent'anni di osservazione sono significative.

Le sostanze prese in esame sono state l'ozono, le polveri sottili più fini (PM2.5), gli ossidi di azoto ed il black carbon.

Lo studio ha analizzato la casistica per ogni singolo inquinante, per poi confrontare i risultati finali.

La ricerca è stata effettuata dal 2000 al 2018 in popolazioni residenti in 6 aree metropolitane degli USA, 5780 soggetti osservati negli ultimi 10 anni attraverso TAC e misurazioni della funzione respiratoria (calcolo FEV1).

Nel corso di questo periodo la qualità dell'aria è cambiata, anche per effetto di politiche di salute ambientale: in particolare nel lavoro in questione erano diminuite le concentrazioni medie di PM2.5 e ossidi d'azoto.

Per questo motivo nelle conclusioni gli studiosi americani evidenziano che soltanto le concentrazioni ambientali di ozono e di ossidi d'azoto sono significativamente associate ad un aumento dei casi di enfisema o un peggioramento dello stesso, mentre è la presenza di ozono a peggiorare la funzione respiratoria.

Testo di Alessia Marcocci

Original Investigation
August 13, 2019

Association Between Long-term Exposure to Ambient Air Pollution and Change in Quantitatively Assessed Emphysema and Lung Function

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Video (4:20)
Ambient Air Pollution and Change in Emphysema and Lung Function

Key Points

Question Is there an association between ambient air pollutants and progression of emphysema and changes in lung function in the general population?

Findings In this cohort study conducted between 2000 and 2018 that included 5780 participants in 6 US metropolitan regions followed up for a median of 10 years, there was a statistically significant association between baseline ambient concentrations of ambient ozone (O_3), fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_x), and black carbon with greater increases in emphysema assessed quantitatively using computed tomographic (CT) imaging. Concentrations of O_3 and NO_x, but not concentrations of $PM_{2.5}$, over study follow-up were also associated with increases in emphysema. Baseline ambient O_3 was significantly associated with a faster decline in forced expiratory volume in the first second (FEV_1).

Meaning Long-term exposure to ambient air pollutants, especially O_3, was significantly associated with increasing emphysema assessed quantitatively using CT imaging and with worsening lung function.

Abstract

Importance While air pollutants at historical levels have been associated with cardiovascular and respiratory diseases, it is not known whether exposure to contemporary air pollutant concentrations is associated with progression of emphysema.

Objective To assess the longitudinal association of ambient ozone (O_3), fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_x), and black carbon exposure with change in percent emphysema assessed via computed tomographic (CT) imaging and lung function.

Design, Setting, and Participants This cohort study included participants from the Multi-Ethnic Study of Atherosclerosis (MESA) Air and Lung Studies conducted in 6 metropolitan regions of the United States, which included 6814 adults aged 45 to 84 years recruited between July 2000 and August 2002, and an additional 257 participants recruited from February 2005 to May 2007, with follow-up through November 2018.

Exposures Residence-specific air pollutant concentrations (O_3, $PM_{2.5}$, NO_x, and black carbon) were estimated by validated spatiotemporal models incorporating cohort-specific monitoring, determined from 1999 through the end of follow-up.

Main Outcomes and Measures Percent emphysema, defined as the percent of lung pixels less than −950 Hounsfield units, was assessed up to 5 times per participant via cardiac CT scan (2000-2007) and equivalent regions on lung CT scans (2010-2018). Spirometry was performed up to 3 times per participant (2004-2018).

Results Among 7071 study participants (mean [range] age at recruitment, 60 [45-84] years; 3330 [47.1%] were men), 5780 were assigned outdoor residential air pollution concentrations in the year of their baseline examination and during the follow-up period and had at least 1 follow-up CT scan, and 2772 had at least 1 follow-up spirometric assessment, over a median of 10 years. Median percent emphysema was 3% at baseline and increased a mean of 0.58 percentage points per 10 years. Mean ambient concentrations of $PM_{2.5}$ and NO_x, but not O_3, decreased substantially during follow-up. Ambient concentrations of O_3, $PM_{2.5}$, NO_x, and black carbon at study baseline were significantly associated with greater increases in percent emphysema per 10 years (O_3: 0.13 per 3 parts per billion [95% CI, 0.03-0.24]; $PM_{2.5}$: 0.11 per 2 μg/m^3 [95% CI, 0.03-0.19]; NO_x: 0.06 per 10 parts per billion [95% CI, 0.01-0.12]; black carbon: 0.10 per 0.2 μg/m^3 [95% CI, 0.01-0.18]). Ambient O_3 and NO_x concentrations, but not $PM_{2.5}$ concentrations, during follow-up were also significantly associated with greater increases in percent emphysema. Ambient O_3 concentrations, but not other pollutants, at baseline and during follow-up were significantly associated with a greater decline in forced expiratory volume in 1 second per 10 years (baseline: 13.41 mL per 3 parts per billion [95% CI, 0.7-26.1]; follow-up: 18.15 mL per 3 parts per billion [95% CI, 1.59-34.71]).

Conclusions and Relevance In this cohort study conducted between 2000 and 2018 in 6 US metropolitan regions, long-term exposure to ambient air pollutants was significantly associated with increasing emphysema assessed quantitatively using CT imaging and lung function.

Introduction

Chronic lower respiratory disease is the fourth leading cause of death in the United States and third leading cause of death worldwide.[1,2] Most of this mortality is due to chronic obstructive pulmonary disease (COPD), defined by persistent airflow limitation, measured via spirometry, and pulmonary emphysema, defined by destruction of the lung parenchyma.[3] Emphysema can be measured quantitatively on computed tomographic (CT) imaging and can be observed without spirometric COPD.[4,5] The percentage of emphysema-like lung on CT scans ("percent emphysema") is associated with the degree of lung function impairment and symptoms as well as mortality in patients with COPD.[6] Percent emphysema is also associated with dyspnea and disease exacerbations independent of lung function among smokers[7] and with incident COPD and all-cause mortality among individuals without COPD in the general population.[4,8]

Ambient air pollution is a major risk factor for poor health worldwide.[9] The relationship of air pollution exposures with respiratory morbidity and mortality has been documented in the short-term[10] and, by a more limited number of prospective cohorts, in the long-term.[11,12] There is elevated

risk of death associated with ozone (O_3) and fine particulate matter less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) exposure in patients with COPD[11] and a faster decline in lung function associated with long-term exposure to traffic-related air pollutants in healthy populations.[13] No longitudinal studies of air pollution and emphysema progression on CT scan, to our knowledge, have been reported.

This cohort study examined the hypothesis that long-term exposure to air pollutants is associated with progression of percent emphysema shown on CT imaging, as well as decline in lung function, in a well-characterized, multiethnic cohort of adults.

Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited participants aged 45 to 84 years without clinical cardiovascular disease from 2000 to 2002 in 6 US metropolitan areas. Investigators recruited white, African American, Hispanic, and Chinese American participants to achieve prespecified recruitment goals by clinical site; race/ethnicity was based on participant self-identification. The MESA study included 4 race/ethnic categories to create a more representative and diverse population than was represented in prior National Heart, Lung, and Blood Institute cohort studies. The MESA Air Pollution Study (MESA Air) recruited additional participants with comparable ages and without cardiovascular disease from 2005 to 2007.[14] The MESA Lung Study enrolled a subsample of 3813 MESA participants from 2004 to 2006,[15] additional MESA participants from 2010 to 2012, and selected all MESA participants in 2017 to 2018. No selection criteria were related to risk or presence of lung disease. The current analysis includes all MESA participants with valid air pollutant exposure estimates, outcomes, and covariates.

The protocols were approved by the institutional review boards of the collaborating institutions. Written informed consent was obtained from all participants.

Percent Emphysema on CT

Percent emphysema was calculated based on all usable CT scans, including cardiac and full-lung scans. All MESA participants underwent a cardiac CT scan at baseline from 2000 to 2002. Cardiac CT scans were acquired at suspended full inspiration.[16] A second CT scan was conducted for 84% of participants in the cohort between 2002 and 2005 and for a subset of participants who did not have a prior scan in 2004 or 2005 and consented to a scan at this examination from 2005 to 2007. Participants in the MESA Lung Study underwent a full-lung CT scan at suspended full inspiration following a standardized protocol from 2010 to 2012[17] and from 2017 to 2018 with modification to account for scanner evolution.

Trained readers performed percent emphysema measurements at a central reading center, without knowledge of other participant information, using modified Pulmonary Analysis Software Suite for cardiac scans and the updated version, Apollo 1.2 (VIDA Diagnostics), for full-lung scans. For cardiac CT scans, which were performed in duplicate at each examination, the scan with the greater air volume was used except in cases in which 1 scan failed to meet quality control criteria.[18]

Percent emphysema was defined as the percentage of lung pixels below −950 Hounsfield units (HU), a threshold selected based on pathologic comparisons[5] and prognostic significance in this cohort.[4] The −950-HU threshold on all scans was adjusted for attenuation of air outside the chest to account for scanner variation.[18] Because cardiac CT images approximate 66% of lung volume (from the carina to the lung bases), the upper-third portion of full-lung scans was excluded to follow the

same lung region over time. Percent emphysema on cardiac scans was reproducible (scan-rescan intraclass correlation coefficient [ICC], 0.91), comparable between scanners (ICC, 0.94), and valid compared with full-lung CT scans (ICC, 0.93).[18]

CT technology changed over the 18 years of the study. Therefore, sensitivity analyses were performed using a hidden Markov measure field approach to the measurement of percent emphysema, which reduces interscanner and interprotocol variability by adapting the characteristics of each image under varying CT imaging protocols and differences in intensity distributions due to inspiration level.[19] In additional sensitivity analyses, scans with inspiratory levels less than 80% of the participant's maximum lung volume on scans were excluded and an alternative metric, the HU of the lowest 15th percentile of the lung frequency distribution (PD15), was examined in each participant. A higher PD15 value indicates less emphysema.

Lung Function

Spirometry was conducted in the MESA Lung Study from 2004 to 2006 and repeated twice from 2010 to 2012 and 2017 to 2018 in accordance with American Thoracic Society guidelines and with the same dry-rolling seal spirometers (Occupational Marketing Inc).[15] All results were reviewed by 1 investigator. Airflow obstruction was defined at the first measurement of lung function as forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) ratio less than 0.70.

Exposure Assessment

The method used to estimate long-term outdoor air pollution concentrations at each participant's home address has been previously described in detail.[20,21] In brief, spatiotemporal exposure models were developed for O_3, $PM_{2.5}$, and oxides of nitrogen (NO_x) in each study region based on measurements (1999-2018) from the US Environmental Protection Agency (EPA) Air Quality System and the spatially dense cohort-specific monitoring performed for MESA Air.[22] Mean outdoor concentrations of black carbon were estimated only for the years 2006 to 2008 because comparable air quality system data were not available at other times (the EPA's measurement method for black carbon was not stable over follow-up). City-specific models incorporated a large number of variables covering a wide diversity of geographic features, such as traffic, industrial emissions, population density, and land use. The performance of these models ranged from good to excellent as assessed by the overall cross-validation R^2 evaluated at participant residence locations (range, 0.59-0.92).

To account for strong temporal trends in some air pollutants and the knowledge that prior exposure can alter ventilatory function trajectories even after exposure stops (as seen with smoking[23]), 2 approaches were used to assign long-term mean exposure to each participant: (1) baseline exposure, assessed as pollutant concentration for the year of the baseline examination in 2000 (or 2006-2008 for black carbon) because this exposure measure more closely approximates prior epochs of this exposure and (2) exposure over follow-up, assessed as time-varying mean concentrations between the year of the baseline examination and follow-up time of the repeated outcome measure.

Statistical Analysis

The principal interest of the study was to assess the longitudinal relationship between long-term exposure to air pollutants and progression of percent emphysema and decline in lung function over time (assessed as the interaction between air pollutant and time in the model). As described in more

detail in the Supplement, these associations were estimated using linear mixed effects models with random intercept (and slope for the emphysema model).

The primary adjusted model for the percent emphysema and pulmonary function outcomes included cross-sectional terms, including baseline age, sex, race/ethnicity, study region, education, height, weight, body mass index (time-varying), smoking (status, pack-years, cigarettes per day for current smokers, and secondhand smoke exposure [both time-varying]), long-term mean city-specific temperature (time-varying), income, employment outside the home, physical activity, neighborhood socioeconomic status (SES) index,[24] and the interaction between SES and study region; longitudinal terms for interactions between these variables and study time (years since baseline); and a transient effects term. While most key covariates were 99% to 100% complete, 5% of participants were missing complete information to calculate pack-years of smoking. We assigned those participants a value of zero and adjusted for an indicator variable reflecting missing pack-years data; we performed sensitivity analyses to confirm that results were consistent between this approach and alternative approaches (excluding missing subjects and assigning the median value for pack-years). Scanner parameters (eg, CT scanner model, milliampere-second adjustment, pixel size) were also included in the percent emphysema model, while the model of lung function additionally controlled for occupational exposure to fumes and gases. Each of the air pollution exposure metrics (at baseline or over follow-up as described above) was investigated separately and included as a main effect and in interaction with time. The associations of exposure to air pollutants with outcomes were compared with the association of pack-years in the same model. In secondary analyses, the regression models were extended by also adjusting for some self-reported transient respiratory conditions (eg, cold, flu, bronchitis, pneumonia) in the lung function models and for high-attenuation areas on CT imaging (percentage of imaged lung volume with attenuation values between −600 and −250 HU) in the emphysema model.

Effect modification of the associations with air pollutants was examined for age, sex, race/ethnicity, obesity, smoking status, SES level, baseline airflow obstruction, study region, and scanner type using 3-way interaction terms between study time, the effect modifier, and exposure concentration. A significant difference between subgroups was indicated by a *P* value less than .05 for the *F* test of the 3-way interaction.

To examine whether pollutants acted independently or jointly on lung outcomes, a model with linear combinations was implemented based on estimates from the fully adjusted models that included all the pollutants simultaneously. Concentration-response curves were generated using a thin plate regression spline with 4 degrees of freedom for long-term exposure to the air pollutants assessed at baseline and during follow-up.

The significance threshold was .05 and all tests were 2-sided. Additional sensitivity analyses were conducted by (1) including copollutants to assess independent, combined, and multiplicative associations on the study outcomes, (2) adding an additional random intercept for neighborhood clusters, (3) examining the relationship between pollutants and relative progression of percent emphysema using a log-transformed outcome, (4) using alternative definitions for emphysema, (5) excluding data with low lung volume on CT scan, (6) examining the effect of missing data by excluding participants who underwent only 1 examination, and (7) restricting to participants who had both CT and spirometry measurements. Analyses were performed using SAS version 9.4 (SAS Institute).

Results

Study Participants and Air Pollutant Concentrations

This study included 7071 participants (6814 MESA participants and 257 MESA Air study participants). Of 7069 participants with percent emphysema measures, 6860 were assigned outdoor residential air pollution concentrations in the year of their baseline examination and during the follow-up period (eFigure 1 in the Supplement). Of these participants, 5780 (84%) had at least 1 follow-up CT scan over a median (range) of 10 (1-18) years. Air pollution concentrations could be assigned to 3636 of 3813 MESA Lung participants with at least 1 spirometric lung function assessment, 2772 (76%) of whom had a second spirometric assessment at a median of 10 years.

Of the 6860 participants at baseline, 3126 (46%) were lifelong nonsmokers, 2595 (38%) were white, and 4344 (63%) reported at least some college education (Table). Baseline median (interquartile range [IQR]) percent emphysema was 3% (4.5%) and the mean rate of change was 0.58 percentage points (95% CI, 0.38-0.78) over 10 years. The rate of change varied by site and exposure levels (eTable 1 in the Supplement). Regarding lung function, 826 of 3636 participants (22%) had airflow obstruction at baseline (eTable 2 in the Supplement) and the cohort exhibited a mean decline in FEV_1 of 309 mL (95% CI, 299-319) and in FVC of 331 mL (95% CI, 317-345) over 10 years.

Air pollution concentrations varied substantially across the study regions over 18 years (Figure 1 and Figure 2). While annual mean concentrations of $PM_{2.5}$ and NO_x declined over follow-up, O_3 concentrations did not (Figure 2). Correlations of residential ambient O_3 (2000-2018) with residential ambient $PM_{2.5}$ and NO_x within each study region were negative and of moderate degree ($r = -0.32$ for $PM_{2.5}$ and -0.42 for NO_x) (eTable 3 in the Supplement).

Air Pollution and Longitudinal Change in Percent Emphysema

Among the 6860 included participants, greater exposures to O_3, $PM_{2.5}$, and NO_x assessed at study baseline and to black carbon averaged through 2006 to 2008 were all significantly associated with an increased progression of percent emphysema over 10 years, per rounded IQR increment (O_3: 0.13 per 3 parts per billion [ppb] [95% CI, 0.03-0.24]; $PM_{2.5}$: 0.11 per 2 $\mu g/m^3$ [95% CI, 0.03-0.19]; NO_x: 0.06 per 10 ppb [95% CI, 0.01 to 0.12]; black carbon: 0.10 per 0.2 $\mu g/m^3$ [95% CI, 0.01-0.18]).

In the analyses of air pollutant exposure over follow-up, a 3 ppb–higher long-term mean O_3 exposure assessed over follow-up was significantly associated with an increased progression of 0.18 percentage points in percent emphysema over 10 years (95% CI, 0.08-0.28) (Figure 3). This increase is equal to the association of 29 pack-years of smoking (each 10 pack-years of smoking was significantly associated with an increased progression of 0.06 percentage points [95% CI, 0.02-0.11] of percent emphysema) or 3 years of aging in this cohort. The association between pollutant concentrations over follow-up and faster progression of percent emphysema was also statistically significant for NOx (increase, 0.12 percentage points per 10 ppb [95% CI, 0.04-0.19]), but not for $PM_{2.5}$ (increase, -0.04 per 2 $\mu g/m^3$ [95% CI, -0.15 to 0.08]).

Results for O_3, $PM_{2.5}$, and NO_x were not sensitive to accounting for neighborhood clusters, use of log-transformed outcome or alternative definitions of quantitatively assessed emphysema (ie, hidden Markov measure field, PD15), restriction to participants having both percent emphysema and lung function measures, or exclusion of data with low scan lung volume or participants with a single examination (eTables 4 and 5 in the Supplement). Addition of $PM_{2.5}$, NO_x, or black carbon as a covariate similarly did not weaken the associations with exposure to O_3 at baseline or over follow-up, nor did addition of O_3 affect the association with baseline $PM_{2.5}$.

Combining the associations of the multiple air pollutants on change in percent emphysema resulted in a greater magnitude of associations than when assessing associations of individual pollutants (Figure 4 and eTable 6 in the Supplement). The concentration-response function between long-term O_3 exposure assessed over follow-up and progression of percent emphysema has a sigmoidal appearance, most strongly linear in the area with the most participants (where CIs are narrower) and with suggestion of attenuation of the association at both lower and higher concentrations (where CIs are wider) (Figure 3). While there was no clear-cut evidence for effect modification across the subgroups studied (eTables 7-9 in the Supplement), greater progression of emphysema with O_3 assessed over follow-up was observed in the group with airflow limitation at baseline (increase of 0.35 percentage points [95% CI, 0.18-0.51]) compared with the group without airflow limitation (increase, 0.15 percentage points [95% CI, 0.03-0.27]).

Air Pollution and Longitudinal Change in Lung Function

Among 3636 participants, 3 ppb in long-term O_3 exposure assessed over follow-up was significantly associated with a 18.15-mL greater decline in FEV_1 (95% CI, 1.59-34.71) and a 40.19-mL greater decline in FVC (95% CI, 17.88-62.49) over 10 years (eTable 10 and eFigure 3 in the Supplement). These associations were robust when additionally adjusted for baseline respiratory symptoms. The associations were generally not sensitive to inclusion of copollutants. Associations between O_3 and FEV_1 and FVC were of greater magnitude among current smokers; associations for FEV_1 were of greater magnitude among participants with airflow obstruction at baseline (eTable 11 in the Supplement).

There was no significant association between other air pollutants and lung function decline or between O_3 and FEV_1/FVC ratio (eTable 10 in the Supplement). No indication of combined association was observed for FEV_1 and FVC with other pollutants (eFigure 4 in the Supplement). Associations with FEV_1 and FVC were statistically significant for exposure to O_3 at baseline, but not for the other pollutants (eTable 12 in the Supplement).

Discussion

Higher residential concentrations of O_3, $PM_{2.5}$, and NO_x at study baseline, of black carbon averaged from 2006 to 2008, and of O_3 and NO_x assessed over study follow-up were significantly associated with greater increases in percent emphysema, assessed via CT imaging, over a median of 10 years. Findings were most robust and of greatest magnitude for O_3. Because percent emphysema is related to respiratory symptoms, hospitalizations,[7] and mortality even among individuals without airflow obstruction,[4,6] these associations in a community-based population demonstrate novel evidence that air pollution contributes to worsening lung health.

Despite existing regulations to prevent short-term excursions of O_3 levels, long-term average concentrations of O_3, which were associated with changes in lung structure and function, did not decline during the years of observation. Absent new control strategies, these levels are not expected to decline as climate change advances.[25] This contrasts with the observed trends in $PM_{2.5}$ and NO_x that highlight the success of past regulatory initiatives to control these 2 pollutants. Because long-term concentrations of O_3 at current levels were strongly and consistently associated with both progression of emphysema and decline in lung function in this study, more effective control strategies to reduce O_3 concentrations may be needed to protect lung health.

Ground-level O_3 is a powerful oxidizing agent and common air pollutant worldwide. Toxicologic studies have shown that O_3 causes persistent pulmonary inflammation and structural alterations throughout the lung that may play a role in chronic lower respiratory disease, including

emphysema.[26] In a mouse model, exposure to O_3 for 6 weeks induced a chronic inflammatory process, with increased protease expression, epithelial apoptosis and alveolar enlargement, and destruction, mimicking emphysema.[27] In animals, $PM_{2.5}$ exposure leads to neutrophilic pulmonary inflammation and oxidative stress,[28] and in healthy adults, controlled exposure to $PM_{2.5}$ leads to increased systemic inflammation and endothelial microparticles, including those of lung origin.[29] This may be relevant because endothelial apoptosis causes emphysema in animals and endothelial microparticles have been linked to lower lung function and, specifically, percent emphysema in individuals with mild COPD and smokers without COPD.[30]

The current study found that faster progression of percent emphysema and decline in FEV_1 were significantly associated with long-term O_3 concentrations among the subset of participants with airflow limitation at baseline. This finding is consistent with prior studies demonstrating worse outcomes related to air pollution in patients with lung disease[31] and supports the conclusion in the 2013 EPA Integrated Science Assessment that individuals with lung disease are a high-risk group for O_3-related health effects.[32] Findings for O_3 and loss of lung function were greater among current smokers, perhaps because of additive effects of airway inflammation and oxidative stress.[33]

Higher exposures to $PM_{2.5}$ and NO_x at baseline and NO_x (and no other pollutants) over follow-up were also significantly associated with faster emphysema progression. When all pollutants were considered together, there was evidence that the association for O_3 was of the greatest magnitude, which is consistent with other literature,[12] and for an additive effect of copollutants, which is consistent with animal studies.[33]

Unlike O_3 and NO_x, $PM_{2.5}$ exposure over follow-up was not significantly associated with emphysema progression. Development of emphysema can be a slow, lifelong process and, once initiated, additional areas of emphysema in the adjacent lung can be produced from biomechanical forces, even in the absence of further exposures, such as cigarette smoke.[34] These findings might explain the increased rate of emphysema progression significantly associated with $PM_{2.5}$ at baseline but not during follow-up. Baseline measures likely reflect exposure at and prior to baseline, particularly for $PM_{2.5}$ concentrations, which declined substantially over the 10 years of follow-up. In addition, the changes in scanner technology over follow-up as $PM_{2.5}$ concentrations decreased may have made the follow-up analyses less sensitive for emphysema progression than the baseline analyses.

While O_3 exposure was significantly associated with decline in lung function, the other pollutants were not; statistical power for spirometry was smaller than for percent emphysema on CT because the number of observations for spirometry were less than half those for percent emphysema and occurred during the latter period of follow-up when nonozone pollutant concentrations had declined. While air pollutants, including O_3, $PM_{2.5}$, NO_x, and black carbon, have been associated consistently with respiratory events,[10,12] relatively few studies have reported a longitudinal association between O_3, $PM_{2.5}$, and NO_x and decline in lung function in older adults, and findings have not been completely consistent. Single-site studies have reported longitudinal associations between $PM_{2.5}$[13] and black carbon[35] and a faster decline in lung function, and a larger multi-center study in Europe found PM_{10} to be associated with a faster lung function decline.[36] However, another large European study did not find any longitudinal associations between air pollutants and lung function decline.[37]

To our knowledge, this is the first longitudinal study to assess the association between long-term exposure to air pollutants and progression of percent emphysema on CT in a large, community-based multiethnic cohort. Other strengths of this study include the large sample size, the long period

of follow-up, and the fine-scale assessment of residential-level outdoor air pollution concentrations from cohort-specific monitoring and advanced statistical modeling.

Limitations

This study has several limitations. First, outdoor air pollution concentrations, especially in the case of O_3, may not fully reflect individual air pollution exposures and dose in all microenvironments[38]; outdoor concentrations do not explain all variation in indoor concentrations, and most individuals spend the majority of their time indoors.[39] Second, percent emphysema was measured only in the lower two-thirds of the lung. However, percent emphysema measured in the lower two-thirds of the lung correlates well with full-lung percent emphysema (ICC, 0.93) in this cohort and a cohort of smokers,[18] and percent emphysema measured on cardiac scans was associated with dyspnea, spirometric obstruction, and mortality in this cohort.[4,8] Third, CT scanners changed over the 18 years of data collection; however, analyses using an advanced image processing approach designed to account for scanner variation yielded similar results, as did sensitivity analyses using various approaches to adjust for stratification by scanner type (eTables 4 and 5 in the Supplement). There is debate about the optimal parameterization of the histogram of the lung attenuation; however, sensitivity analyses using PD15 yielded consistent results. Fourth, no volume correction of CT data was performed,[40] given the debate over its utility and the partial lung imaging; however, results were consistent when participants with a difference greater than 20% in lung volume on CT scans were excluded.

Conclusions

In the United States between 2000 and 2018, long-term exposure to ambient air pollutants was significantly associated with increases in emphysema assessed quantitatively via CT imaging and lung function.

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