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Long-term air pollution exposure and incident stroke in American older adults: A national cohort study

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Abstract

Aims: Stroke is a leading cause of death and disability for Americans, and growing evidence suggests that air pollution may play an important role. To facilitate pollution control efforts, the National Academy of Sciences and the World Health Organization have prioritized determining which air pollutants are most toxic. However, evidence is limited for the simultaneous effects of multiple air pollutants on stroke.

Methods and results: We constructed a nationwide population-based cohort study, using the Medicare Chronic Conditions Warehouse (2000–2017) and high-resolution air pollution data, to investigate the impact of long-term exposure to ambient $PM_{2.5}$, NO_2, and ground-level O_3 on incident stroke. Hazard ratios (HR) for stroke incidence were estimated using single-, bi-, and tri-pollutant Cox proportional hazards models. We identified ~2.2 million incident stroke cases among 17,443,900 fee-for-service Medicare beneficiaries. Per interquartile range (IQR) increase in the annual average $PM_{2.5}$ (3.7 μg/m^3), NO_2 (12.4 ppb), and warm-season O_3 (6.5 ppb) one-year

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Author contributions

L.S. designed research and directed its implementation; T.M. and L.S. analyzed data, T.M. and P.L. made the figures and tables, T.M., L.S., M. D.·Y, P.L., W.R., Q.D., Y.W., and J.S. prepared datasets. T.M. lead the writing of the manuscript, with input from all authors.

Declaration of Competing Interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gloepi.2022.100073.

prior to diagnosis, the HRs were 1.022 (95% CI: 1.017–1.028), 1.060 (95% CI: 1.054–1.065), and 1.021 (95% CI: 1.017–1.024), respectively, from the tri-pollutant model. There was strong evidence of linearity in concentration-response relationships for all three air pollutants in single-pollutant models. This linear relationship remained robust for NO_2 and O_3 in tri-pollutant models while the effect of $PM_{2.5}$ attenuated at the lower end of concentrations.

Conclusion: Using a large nationwide cohort, our study suggests that long-term exposure to $PM_{2.5}$, NO_2, and O_3 may independently increase the risk of stroke among the US elderly, among which traffic-related air pollution plays a particularly crucial role.

Keywords

Air pollution; Stroke; Incidence; Medicare

Introduction

Stroke is the number one cause of long-term disability and the second leading cause of death worldwide [1,2]. According to the Global Burden of Disease Study (GBD), there were approximately 11.9 million incidents, 104.2 million prevalent, and 6.2 million fatal cases of stroke globally in 2017, with 132.1 million stroke-related disability-adjusted life-years (DALYs) [3]. Since stroke is characterized by high mortality, high morbidity, and contributes to severe burden disease, identifying and intervening on modifiable risk factors of stroke is of great significance for public health.

An increasing number of epidemiologic studies have assessed the association between air pollution and stroke evaluated by hospital admission incidence, and mortality [4–6]. Recent studies examining relationship of air pollution on nonfatal stroke have shifted their focus from short-term to long-term exposures [7–14]. However, the results were inconsistent, and the associations between exposure to air pollution and stroke have not been fully understood. Moreover, these studies mainly focused on particulate matter exposures (particulate matter with aerodynamic diameter < 2.5μm or < 10 μm [$PM_{2.5}$ or PM_{10}]) [9,10,12,14–17]; while investigations of gaseous air pollutants (such as nitrogen dioxide [NO_2]; ground-level ozone [O_3]) or simultaneous effects of multi-pollutants are scarce. Most of the studies that looked at multi-pollutants often explored a single pollutant at a time [8,11,13], and only a few evaluated air pollutants jointly in multi-pollutant models to investigate the potential independent associations between air pollution types and stroke risk [7,18–20]. To facilitate the targeting of pollution control efforts, the National Academy of Sciences (NAS) and the World Health Organization (WHO) have prioritized determining which air pollutants are most toxic.

To address this gap, we constructed a nationwide population-based cohort among the American Medicare population (aged ≥65 years), combined with high-resolution air pollution datasets, to examine the association of stroke incidence with annual average $PM_{2.5}$, NO_2, and warm-season O_3 during the calendar year prior to diagnosis year. To better measure stroke incidence, we leveraged all Medicare claims across the contiguous United States (2000–2017) and further required a one-year “clean” period without events of interest to identify first diagnosis of stroke.

Methods

Study population

Health data were obtained from the two databases, namely the Medicare denominator file and the Medicare Chronic Conditions Warehouse (CCW), both from the Centers for Medicare and Medicaid Services (CMS). The Medicare denominator file (i.e., the enrollment file) contains enrollment records for each Medicare beneficiary in each year, including age, sex, race, Medicaid eligibility (a proxy for socioeconomic status - SES), the date of death (if any), and ZIP code of residence. Age, Medicaid eligibility, and ZIP code of residence are updated annually. The CCW database provides the date of the first occurrence with a stroke diagnosis code across the available Medicare claims. Based on the Medicare denominator file and the CCW database, we constructed an open cohort including all Medicare beneficiaries aged 65 and over with continuous enrollment [1] in Medicare Fee-for-Service (FFS) program; and [2] in both Medicare Part A (hospital insurance) and Part B (medical insurance) in the contiguous United States between 2000 and 2017. Namely, we excluded those with any time in Medicare Advantage Plan (Part C) over the study period since claim records are not available for these beneficiaries; and excluded those only enrolled in Medicare Part A or Part B. These exclusions were included because the CCW relies on FFS, Part A, and Part B to identify cases. If we relaxed these restrictions to broaden the cohort, the chance of missing stroke diagnoses among those additional participants brought into the analysis could be high.

In addition to the above-mentioned inclusion and exclusion criteria, we further required a “clean” period of one year after enrollment, during which there was no diagnosis code for stroke. For example, a participant entering Medicare in 2000 would be required to be stroke-free until 2011; follow-up for disease incidence began only then. We also excluded the one-year “clean” period from person-time to avoid immortal time bias. By removing potentially prevalent cases in their first years of follow-up, a diagnosis after that “clean” period more likely approximates disease “incidence”. We considered that a “clean” period of one year represent a reasonable time window to ensure a person was stroke diagnosis free prior to the Medicare diagnosis [21]; however, we also explored longer clean periods of 2 years and 4 years in sensitivity analyses. The person-time for the corresponding “clean” period was also excluded from the sub-cohorts. Therefore, study subjects entered the cohort on January 1st of the year following the “clean” period and were followed until first diagnosis of the outcome of interest across all Medicare claims, death, or end of follow-up. Cohort sizes and summary statistics for the study population with different clean periods are shown in Supplementary Table S1. Our research is approved by Emory’s IRB (#STUDY00000316) and the Centers for Medicare & Medicaid Services (CMS) under the data use agreement (#RSCH-2020–55,733). The Medicare dataset was stored and analyzed in Emory Rollins School secure cluster environment (HPC), with Health Insurance Portability and Accountability Act (HIPAA) compliance.

Outcome classification

The primary outcome of interest for this study was the time to stroke. The CCW database includes a pre-defined indicator for stroke, which is identified using an algorithm

that incorporates information from all available Medicare claims (such as inpatient and outpatient claims, Carrier file, skilled nursing facility, and home health-care claims) indicating that an individual was diagnosed with stroke (Chronic condition algorithms) [22]. We extracted the date of the first occurrence with a stroke diagnosis code for each study subject from the CCW database and defined the outcome stroke as the first occurrence of stroke diagnosis (reoccurrences of stroke were not considered in this study).

Exposure assessment

High-resolution ambient $PM_{2.5}$, NO_2, and O_3 concentrations for the entire contiguous United States were derived using spatiotemporal ensemble models that integrated three different machine learning algorithms, including a neural network, a random forest, and a gradient boosting machine [23–25]. The ensemble-based model used over one hundred predictors, including satellite measurements, land-use terms, meteorological variables, and chemical transport model predictions to estimate daily levels of the pollutants on a scale of 1 km × 1 km [26–28]. The quality of the estimates was assessed using 10-fold cross-validation against monitoring measurements values from the Environmental Protection Agency (EPA), Air Quality Systems (AQS) across the United States. The resulting R^2 values for annual predictions of $PM_{2.5}$, NO_2, and O_3 were 0.89, 0.84, and 0.86, respectively, yielding strong model performance [26–28]. We averaged these 1-km resolution predictions for each pollutant at ZIP code scale, because ZIP code is the smallest level of geography in the Medicare data and ZIP code of residence is updated annually. We then calculated annual averages for $PM_{2.5}$, NO_2, and warm-season O_3 (May 1 to October 31) concentrations in each ZIP code, for each calendar year and defined long-term exposure in our study as the annual averages of air pollutants. All Medicare beneficiary's outcome data for each calendar year were linked to the annual averaged exposures one year ago (i.e., one-year lag exposure) according to the residential ZIP code in the previous year such that any annual residential mobility changes by ZIP code were considered. We also explored different lagged exposures, including two-year, one-year, and zero-year lag exposure, in sensitivity analyses.

Covariates

We obtained individual-level covariates, including sex, race, age at entry, and Medicaid eligibility, from the Medicare denominator file. Based on individual age at entry, a 5-year age at entry group variable was created. We also included neighborhood-level covariates which have both been associated with ambient air pollution and implicated in cerebrovascular diseases into the analyses. These included ZIP code-level SES variables (population density, proportion of the population > 65 years of age living below the poverty line, proportion of the population listed as Black, median household income, proportion of housing units occupied by the owner, and proportion of the population > 65 years of age who had not graduated from high school), meteorological variables (annual mean temperature and annual mean relative humidity), land-use variable normalized difference vegetation index (NDVI) values, and county-level behavioral risk factors (mean body mass index and smoking rate) and health care capacity variables (number of hospitals and active medical doctors), as well as a geographical region (categorized as five U.S. region: West, Southwest, Midwest, Northeast, and Southeast). Specifically, SES variables were derived from the 2000 U.S. Census, 2010 U.S. Census, and the American Community

Survey for 2005–2012; meteorological data were acquired from the North American Regional Reanalysis data (NARR) for 2000–2017; NDVI values were retrieved from NASA's MODIS satellite (MOD13C2) for 2000–2017; behavioral risk factors were obtained from the Behavioral Risk Factor Surveillance System (BRFSS) between 2000 and 2016; and health care capacity data were obtained from the 2010, 2015, and 2018 American Hospital Association Annual Survey Database. We linearly interpolated or extrapolated the missing values based on the data available [29]. We also obtained co-morbidity conditions (hypertension and diabetes) from the CCW database. These covariates have been suggested to associate with air pollution and stroke [30,31], and we included them as candidate confounders in sensitivity analyses.

Statistical analysis

We estimated the relationship between long-term exposure to $PM_{2.5}$, NO_2, O_3, and incident stroke using a series of stratified Cox proportional-hazards models with a generalized estimating equation (GEE). The co-efficient for the exposure variable was the parameter of interest, and years of follow-up were the time scale. Specifically, we fitted single-pollutant, bi-pollutant, and tri-pollutant models and estimated hazard ratios (HRs) per interquartile-range (IQR) increase in the annual average of $PM_{2.5}$, NO_2, and warm-season O_3 concentrations in the one-year period prior to diagnosis. All three pollutants were of interest because some prior studies have shown associations between each of them and stroke [4,32–34]. GEE was used to adjust for residual autocorrelation within ZIP code with the use of robust standard errors (and 95% CI confidence intervals). To allow for flexible strata-specific baseline hazard functions, we stratified all models on four individual characteristics, including sex, race (white, black, other), Medicaid eligibility, and 5-year categories of age at study entry. We included 13 ZIP code-level and county-level time-varying covariates, including SES, behavioral risk factors, health care capacity, land-use, and meteorological variables in the model to adjust for potential confounding. Potential residual temporal and spatial trends were controlled by respectively including indicator variables for calendar years and geographical regions.

To assess the shape of the concentration-response (C-R) relationship between each air pollutant and stroke, we respectively fitted penalized splines [35] for $PM_{2.5}$, NO_2, and O_3, adjusting for all covariates included in the tri-pollutant models. We also compared the C-R relationship using the single-pollutant models for each air pollutant without adjustment for co-pollutants. To identify subpopulations who might be more vulnerable than others, we examined six potential effect modifiers (gender, race (white, black), Medicaid eligibility, age (<75, ≥ 75), neighborhood-level household income, and education) by stratification.

Additionally, we estimated the attributable fraction (AF) of stroke cases due to $PM_{2.5}$, NO_2, and O_3 air pollution, for those in the US exposed to an additional IQR of $PM_{2.5}$ (a difference of 3.7 $\mu g/m^3$), NO_2 (12.4 ppb), and O_3 (6.5 ppb), beyond current levels in US cities with relatively low exposure (i.e., 7 $\mu g/m^3$ for $PM_{2.5}$, 4 ppb for NO_2, and 30 ppb for O_3, the counterfactual) [36], using results from the tri-pollutant model, and using standard AF calculations when the entire population is exposed (RR-1)/RR (see Steenland and Armstrong 2006 [37]).

We conducted a series of sensitivity analyses to test the robustness of our main findings. First, we assessed the alternative exposure time windows by comparing the results using different lags (2-, 1-, and 0-year lags), in which exposure was assigned either as the annual exposure at 2 years prior to case, or 1 year prior, or 0 year prior. Second, we repeated the analyses using a sub-cohort of a longer "clean" period of 2 years and 4 years, i.e., thinking that excluding cases with a diagnosis during their first 2 years or 4 years of enrollment would increase the probability that we are capturing the first diagnosis and thus more closely estimating disease incidence, albeit at the cost of a smaller number of years of subjects and cases. Additionally, to evaluate whether the associations we observed were robust to different levels of confounding adjustment, we fitted the models with different set of covariates and modeled the potential residual temporal trend as a linear term for calendar years instead of categorical year. We also tested how sensitive our models might be to adjusting for space with a spatial smoother and with a state-level adjustment. Lastly, to evaluate whether the associations we observed can be attributed to comorbidities also linked to air pollution, we additionally adjusted for the comorbidities (including diabetes and hypertension), and restricted analyses to subjects without the comorbidities.

All computational analyses were run on the Rollins High-Performance Computing (HPC) Cluster at Emory University. R software, version 4.0.2, was used for all analyses.

Results

Study population characteristics

Table 1 provides descriptive information on the stroke cohort for main analysis. Data were analyzed for Medicare beneficiaries who were 65 years and older between Jan 1, 2000, and Dec 31, 2017, and met the inclusion and exclusion criteria (see Methods). The cohort was followed requiring a one-year "clean" period without stroke events to better capture stroke incidence. A total of 2,240,586 incident stroke cases were identified in 2001–2017 (as we applied a one-year "clean" period) among 17,443,900 studied subjects with 144,611,520 person-years of follow-up (Table 1). Most of the participants (88.2%) entered the cohort between ages 65 and 74, and the mean age at entry was 69.1 years (SD 4.8). The median follow-up was 8 years. Supplementary Table S2 summarized the new study subjects that entered the cohort serially over time and the mean age of the cohort increased gradually from 73.3 to 75.8 years. There were slightly more women than men, and most participants were white. More than 90% were not Medicaid-eligible, indicating that most participants were above the poverty level. Most of the observations came from the southern and midwestern regions of the contiguous United States.

Air pollution levels

The annual average levels of $PM_{2.5}$ and NO_2 were 9.4 μg/m^3 and 17.5 ppb across the contiguous United States from 2000 to 2016, which were both below the U.S. Environmental Protection Agency (EPA) annual standards of 12 μg/m^3 and 53 ppb. About 66% and 99% of the participants were always exposed to annual $PM_{2.5}$ and NO_2 below the national standards over the follow-up period. The annual warm-season (May–October) average O_3 was 42.8 ppb. We examined warm-season O_3 because O_3 is a temperature-

dependent variable (i.e. the level of O_3 rises significantly as the weather warms) and warm-season O_3 is often used in epidemiological studies for assessing long-term health effects [38]. While the EPA does not have an annual standard for ozone, the daily 8-h period standard for ozone is 70 ppb [39], indicating the warm-season O_3 levels in the cohort were generally below the EPA daily standard. Fig. 1 showed the distribution of the three air pollutants across the contiguous United States over the study period, estimated by the exposure models used in our analysis. $PM_{2.5}$ was the highest in the eastern region and West Coast of the United States, primarily reflected pollution transported over large distances. Warm-season O_3 was highest in the western region. High NO_2 was concentrated in urban centers, suggesting it mainly indicated local fossil fuel combustion sources, especially motorized traffic. Supplementary Table S3 shows the detailed distribution of the exposure levels. The three pollutants in this cohort were modestly correlated with the highest correlation observed between $PM_{2.5}$ and NO_2. The Spearman's rank correlations between pollutants (average annual exposure at ZIP code level) were $PM_{2.5}$ and NO_2 0.38, $PM_{2.5}$ and O_3 0.28, NO_2 and O_3 0.21.

Health effect estimates

Fig. 2 provides our main analysis results from the Cox proportional hazards models stratified by individual characteristics, adjusting for neighborhood-level socioeconomic status (SES), behavioral risk factors, health care capacity variables, land-use variables, and residual temporal and spatial trends (see Methods). Long-term exposure to $PM_{2.5}$, NO_2, and warm-season O_3 was associated with an increased risk of incident stroke in all models with or without adjusting for co-pollutants. An interquartile range (IQR) increase in the annual average NO_2 (12.4 ppb) preceding one-year diagnosis was associated with an increased risk of stroke (HR = 1.073, 95% CI: 1.068–1.079) in the single pollutant model, with effect sizes changing little in models adjusting for other pollutants. An IQR increase in annual average $PM_{2.5}$ (3.7 $\mu g/m^3$) was associated with an HR of 1.056 (95% CI: 1.051–1.061) in the single pollutant model, dropping to 1.022 (1.017–1.028) in the tri-pollutant model. An IQR increase in annual average warm-season O_3 (6.5 ppb) was associated with an HR of 1.035 (95% CI: 1.031–1.039) in the single-pollutant model, dropping to 1.021 (1.017–1.024) in the tri-pollutant model.

Concentration-response relationships

Fig. 3 showed the concentration-response (C-R) relationships between long-term $PM_{2.5}$, NO_2, and warm-season O_3 exposures and stroke incidence derived from the single-pollutant and the tri-pollutant models and the distribution of each pollutant in the cohort. The C-R relationships of NO_2 for stroke were approximately linear across the exposure distribution from both the single- and tri-pollutant models (Fig. 3, a2 and b2), although a slightly steeper slope was observed in the single-pollutant model. For $PM_{2.5}$, the C-R curve from the single-pollutant model showed a linear relationship for increasing annual mean $PM_{2.5}$ concentrations (Fig. 3, a1). When controlling for multi-pollutants, however, we observed a positive linear relationship for $PM_{2.5}$ and stroke incidence HR at concentrations above 11 $\mu g/m^3$ with an attenuated slope (Fig. 3, a2). For concentrations below 11 $\mu g/m^3$ (representing 75% of the distribution of the $PM_{2.5}$), the C-R curve from the tri-pollutant model is close to the null (Fig. 3, a2). The C-R relationship of O_3 for stroke from the single-pollutant

model showed a linear relationship across the exposure distribution and the associations level off at higher concentrations (Fig. 3, a3). This C-R relationship of O_3 persisted when controlling for multi-pollutants (Fig. 3, b3). Across the 0.1th to 99.9th percentile of the exposure distribution, NO_2 showed the strongest and most robust effect on stroke among all pollutants. The C-R relationship of NO_2 for stroke was almost linear, with no signal of threshold down to 4 ppb (1st percentile) in both single- and tri-pollutant models.

Effect modifications

We examined six potential effect modifiers [gender, race (white, black), Medicaid eligibility, age (<75, ≥75), neighborhood-level household income, and education]. Fig. 4 showed subgroup-specific hazard ratios for each pollutant from the tri-pollutant model, based on stratification of the potential effect modifiers. The same analyses derived from the single-pollutant models are shown in Fig. S1. Overall, the magnitude of HR differences between subgroups was small. We observed an increased hazard of stroke for women vs. men, Blacks vs. Whites, and Medicaid eligible vs. Medicaid ineligible in relation to NO_2. At the same time, those living in areas with lower median household incomes and lower education were found to have a higher association between stroke and NO_2. All these effect modifiers except race were robust to both the tri-pollutant and single-pollutant modeling (Fig. S1). We did not observe such effect modification patterns in relation to $PM_{2.5}$ or O_3. Regarding differences in HR by gender, although non-significant for $PM_{2.5}$ and O_3 in both the tri-pollutant and single-pollutant models, females had a general stronger association between stroke for all air pollutant exposures than males. Finally, we found little evidence of an interaction between air pollutant exposures and age in relation to stroke.

Attributable fraction

The strongest relationship we found with stroke was for NO_2 among the three pollutants. If the U.S. NO_2 levels could be lowered by 12.4 ppb, which is the IQR, then the attributable fraction (AF) for stroke due to current exposure levels, based on our main results from tri-pollutant models assuming a linear relationship, would be 6%. Namely, assuming there is a causal relationship, an estimated 6% of stroke cases would be avoided if NO_2 levels decreased by 12.4 ppb, which is approximately the difference between our large cities like Los Angeles and New York, and smaller cities like Portland and New Haven [36]. Likewise, if the U.S. $PM_{2.5}$ and O_3 levels could be reduced by 3.7 $\mu g/m^3$ (IQR) and 6.5 ppb (IQR), an estimated 2% and 2% of stroke cases would be avoided assuming a causal relationship.

Sensitivity analyses

Associations between long-term exposure to $PM_{2.5}$, NO_2, O_3, and stroke were robust to a series of sensitivity analyses. First, the use of alternative exposure windows (annual exposure 2, 1, or 0 years prior to stroke diagnosis, i.e., lags 2, 1, or 0) all supported a positive association with $PM_{2.5}$, NO_2, and O_3, though HRs varied in magnitude and attenuated with increasing lag periods (Supplementary Table S4). Second, two sub-cohorts with more stringent “clean” periods were constructed by excluding anyone who had a diagnosis for stroke in their first 2 years or 4 years of follow-up. Descriptive information of the sub-cohorts is summarized in Supplementary Table S1 and these new sub-cohorts yielded similar results to the main analyses (Supplementary Table S4). Third, the

observed associations with stroke were robust to different levels of confounding adjustment (Supplementary Table S5). Except for O_3, the association with stroke became negative when the model did not adjust for meteorological variables, including ZIP code level annual temperature, and relative humidity. Lastly, the additional adjustment for comorbidities such as diabetes and hypertension attenuated the associations between air pollutants and stroke to some extent, while the effects of $PM_{2.5}$, NO_2, O_3 remained robust in the single- and multi-pollutant models (Supplementary Table S6). However, these pollutants have been associated with hypertension and diabetes, so this may be controlling for a mediator.

Discussion

In this large, national population-based Medicare cohort, we found long-term exposure to $PM_{2.5}$, NO_2, and warm-season O_3 were associated with an increased risk of first incident stroke, in both single-pollutant models and models adjusting for co-pollutants. Among the three air pollutants studied, NO_2 had a larger effect on stroke risk than $PM_{2.5}$ or O_3 at the scale of interquartile range increase in concentrations in all models. NO_2 also had the most robust association with an increased risk of stroke, while the effect estimates of both $PM_{2.5}$ and O_3 attenuated after adjustment for co-pollutants.

The shapes of the concentration-response relationship between air pollutant exposure and stroke were investigated in both single- and tri-pollutant models. In the single-pollutant models, risks of first diagnosis with stroke linearly increased with increasing $PM_{2.5}$, NO_2, and O_3 concentrations, suggesting no safe threshold for harmful pollution. The concentration-response (C-R) shapes remained robust for NO_2 and O_3 in the tri-pollutant models while the effect of $PM_{2.5}$ attenuated at the lower end of concentrations. Similar results about the C-R shapes of $PM_{2.5}$ and NO_2 were observed in a pooled analysis of six European cohorts within the ELAPSE (the multicenter study Effects of Low-level Air Pollution: A study in Europe) project [40]. The reduction of the $PM_{2.5}$ hazard ratio at low concentrations did not imply that particles had no effect, as adjustment for NO_2 might also have adjusted for particles co-emitted with NO_2, including those from motorized traffic and other fossil fuel combustion sources [40,41]. While for the robust association for NO_2, this may reflect the direct effects of NO_2 or correlated combustion-related particles such as ultrafine particles [40,41]. The study population had low annual NO_2 exposures relative to the current national standard (53 ppb) and low warm-season O_3 exposures relative to the daily 8-h period standard (70 ppb). Nevertheless, our data suggest that lowering levels of pollution would have substantial public health benefits. In the subgroup analyses, female, black people, lower-income, and lower educated populations were susceptible subgroups for the effect of NO_2, reflecting a general pattern of increased susceptibility among those of lower SES [19,20]. In single-pollutant models, females had a higher risk of stroke to $PM_{2.5}$ and O_3, consistent with previous studies suggesting that the association between air pollution and cardiovascular diseases are stronger in women than in men [42,43]. Since the magnitude of HR differences between subgroups were relatively small, the subgroup health effects should be interpreted cautiously.

Most of the evidence on the effects of air pollution on stroke comes from time-series and case-crossover studies of cerebrovascular mortality [4–6,34]. Previous studies on the long-

term health effects have reported mixed results. Two prior Medicare population-specific studies of air pollutant exposure and cardiovascular outcomes are generally consistent with our results. Danesh Yazdi et al. (2019) [20] focused on the Medicare beneficiaries in the southeastern region of the United States and found both $PM_{2.5}$ and O_3 to be risk factors for stroke hospitalizations on the multiplicative scale, reporting a HR of 1.031 (95%CI: 1.030–1.032) and 1.012 (1.012–1.013) per unit increase in annual $PM_{2.5}$ and O_3 in the bi-pollutant models. A more recent study that expanded the study population to the entire Medicare cohort across the contiguous United States and studied the simultaneous effects for $PM_{2.5}$, NO_2, and O_3 found only $PM_{2.5}$ and NO_2 to be positive for ischemic stroke risk on an additive scale [19]. The discrepancies about the effect of O_3 on stroke could be due to the difference in cohort construction and outcome assessments. Our study included hospitalizations, physician's visits, and nursing home data to better ascertain stroke incidence, while the previous study only used hospital admission data [19]. In addition, that study only examined ischemic stroke, whereas we examined all strokes. A national sample cohort study in South Korea also found a significantly increased risk of stroke with long-term exposure to $PM_{2.5}$ and NO_2, in both single and multi-pollutant models [44]. A pooled analysis of six population-based European cohort studies within ELAPSE also found incidence of stroke was associated with $PM_{2.5}$ and NO_2 [40]. Conversely, the South Korea study [44] found a significant negative relationship between O_3 and stroke incidence while the ELAPSE study [40] found no association with O_3, in contrast with our results that found O_3 to be harmful. But we noticed that the study population in both the South Korean cohort [44] and the pooled European cohort [40] are younger, the mean age at baseline (SD) was 42(SD 15) and 54 (SD 9), respectively. Researchers looking at long-term exposure to ambient air pollutants and cerebrovascular disease within the European Study of Cohorts of Air Pollution Effects (ESCAPE) data found marginally significant associations between exposure to $PM_{2.5}$ and the incidence of stroke, with a significant relationship seen for those 60 or above [13]. Although they found non-significant associations for NO_2 in their single-pollutant models, a study in the Danish, Diet, Cancer and Health cohort that was included in the ESCAPE study found a borderline significant association between NO_2 and incident stroke [45]. Last, three meta-analyses reported per 10-$\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$ levels were associated with 5% (95% CI: 2–8%) [4], 13% (11–15%) [5], and 23% (10–26%) [6] increase in the hazard of stroke incidence, which are comparable to our effect estimates of 6% (5–8%) increased hazard per 10-$\mu g/m^3$ increase in $PM_{2.5}$. One meta-analysis evaluated the effect for NO_2 and found a significant but much smaller increased hazard of stroke incidence per 10 ppb increases in NO_2 compared with our results (0.4% (95% CI: 0.0–0.6%) vs. 4.8% (4.3–5.2%)) [4]. Furthermore, they did not find a significant association between O_3 and stroke incidence [4]. These inconsistent results compared to our study might be due to the relatively limited number of studies focusing on the health effects of gaseous air pollutants (NO_2 and O_3) [7,8,11,13,18,45] compared to particulate matter [9,10,12,14–17].

Air pollution has been shown to harm respiratory and cardiovascular systems through mechanisms including systemic inflammation, oxidative stress, and altered cardiac autonomic and vascular function [46–49]. However, the effects of exposure to multiple air pollutants on cerebral vessels are more uncertain and the mechanism by which any effect

on cerebrovascular disease is mediated is yet to be elucidated. Postmortem examination has reported evidence of particle-associated inflammation in the brain [50,51]. Although subclinical outcomes could not be examined in our Medicare cohort, these mechanisms underscore the biological plausibility of our finding that long-term exposure to $PM_{2.5}$, NO_2, and O_3 is independently associated with incident stroke. Hypertension and diabetes, established risk factors for stroke and also linked to air pollution, are hypothesized to be on a biological pathway of the air pollution effects leading to stroke, with systemic inflammation providing a common link [30,31]. In our study, diabetes and hypertension attenuated the associations between air pollutants and stroke to some extent while the effects of $PM_{2.5}$, NO_2, O_3 remained positive in the single- and multi-pollutant models (Table S5), suggesting hypertension and diabetes could be mediators. However, a formal mediation analysis would be important to confirm these findings.

Our study has several strengths. First, our study accounted for multiple air pollutants ($PM_{2.5}$, NO_2, and O_3), which were estimated from prediction models on a final scale [26–28], allowing us to compare the dependent and independent associations between stroke and air pollutant groups. Second, the population-based Medicare cohort has a large sample size that gave us ample statistical power to detect effects even though they are small, which is often the case in environmental studies. The use of all available Medicare claims not restricting to hospital admissions is likely to capture cases better and reduce the chance for outcome misclassification. In addition, we used a conservative method by requiring a one-year “clean” period and restricting the analysis to Medicare beneficiaries with continuous enrollment in Medicare FFS, and Part A (hospital insurance) and Part B (medical insurance) programs throughout the study period. We also excluded those who enrolled in the Medicare Part C plan since claims in Part C were inaccessible for us [52]. These stringent inclusion and exclusion criteria can increase the possibility that the cases were newly diagnosed and thus better approximate disease incidence. Lastly, we were able to control for a comprehensive set of individual- and neighborhood-level covariates. We controlled potential residual temporal trends by including indicator variables for calendar years to better account for the potential nonlinear trends in cerebrovascular disease incidences [53–55].

Our study also had several limitations. The first limitation is the potential for exposure error since we assessed only ambient outdoor air pollution concentrations based on participants’ ZIP code of residence, individual-level exposure was not feasible. However, the exposure prediction model we used has excellent predictive accuracy, which may reduce the exposure error [26–28]. Furthermore, a possible exposure misclassification is likely to be non-differential with respect to stroke incidence and have a net bias towards the null [56–58]. Second, our study is subject to unmeasured and residual confounding. We could not control for risk factors for cardiovascular diseases at the individual level such as smoking, physical activity, socioeconomic deprivation, and education, which may confound the association between air pollution and stroke [33]. However, individual smoking and other predictors have been shown in personal exposure studies [59] to be uncorrelated with ambient exposure levels, and are only correlated through neighborhood level covariates, and we believe we have controlled for a rich set of those covariates. Third, outcome misclassification is possible because Medicare is an administrative claims database primarily collected for payment purposes [52]. We expect this misclassification to be non-differential

and should bias the results to the null because such errors are unlikely to be related to air pollution exposure. Fourth, we assessed overall stroke only and were not able to study stroke further in its subtypes, such as ischemic stroke and hemorrhagic stroke. In sensitivity analyses, we controlled two common stroke risk factors (hypertension and diabetes) and observed attenuation in effect estimates, but we neglected that the risk factors profiles for stroke subtypes can be different [60,61]. Epidemiological studies that evaluated the heterogeneous effects of air pollution on stroke subtypes are still limited [62–65]. Given the etiological heterogeneity in stroke, future study of subtype-specific effects would be warranted. Furthermore, we did not consider the possible impact of loss to follow-up due to dropout or death on our findings. Air pollution exposure is an established cause of mortality [66,67], so that older participants are likely to represent a population that is "selected" for characteristics that place them at lower risk for stroke, resulting in underestimation of the relation of exposure with stroke risk [13]. Finally, we only studied the Medicare FFS population who continuously enrolled in both Part A and Part B programs, and never enrolled in Part C program. Some population characteristics differences were observed between our cohort and other Medicare cohorts with different inclusion and exclusion criteria (Supplementary Table S7), suggesting our results may not be generalizable to the entire US Medicare population and further work is needed to determine how study population composition can impact the association [68].

Conclusion

In conclusion, our study provides strong epidemiological evidence that long-term exposure to $PM_{2.5}$, NO_2, and O_3 are independently associated with a higher risk of incident stroke among the US elderly population. The strongest relationship we found with incident stroke was for NO_2 among the three pollutants, suggesting that traffic-related air pollution may play a particularly significant role in increased risks of stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data availability

The rules governing the Medicare dataset prohibit any sharing of the health datasets being used for our epidemiologic research. Restricted by our Data Use Agreement with the U.S. Centers for Medicare & Medicaid Services, the Medicare data that support the findings of this study are neither sharable nor publicly available. Academic and non-profit researchers who are interested in using Medicare data should contact the U.S. Centers for Medicare & Medicaid Services directly to obtain their own datasets upon completion of a Data Use Agreement.

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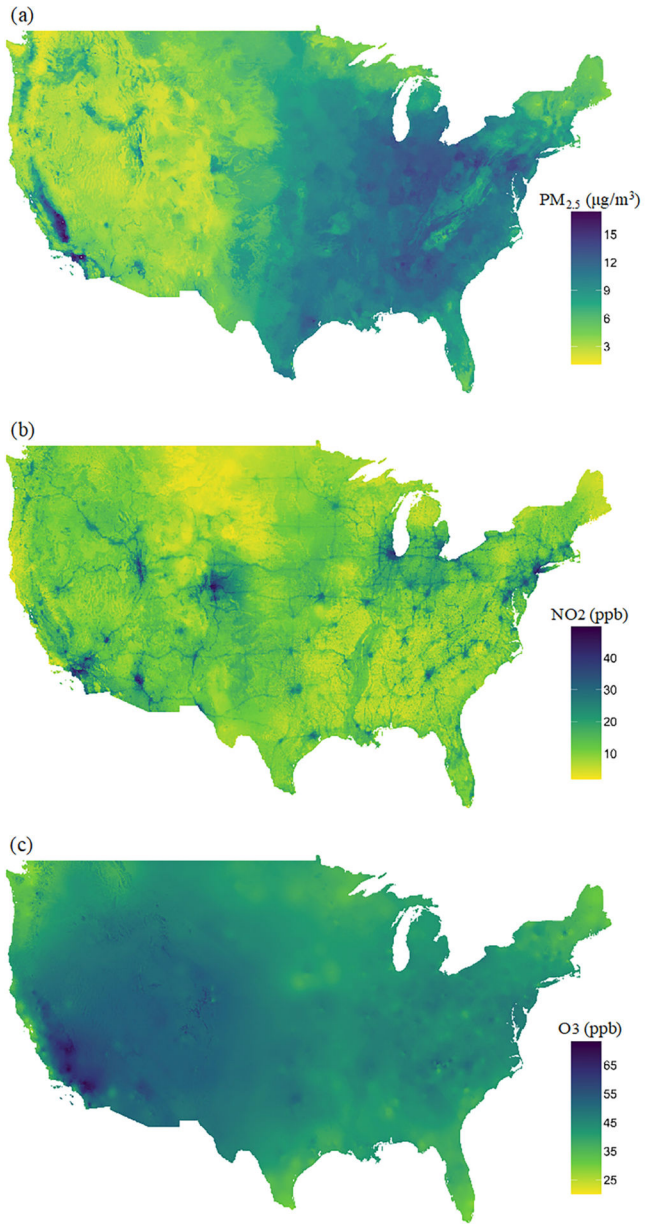

Fig. 1.

Average concentrations of (a) annual $PM_{2.5}$ (μg/m^3), (b) annual NO_2 (ppb), and (c) warm-season O_3 (ppb) across the contiguous United States over the study period (2000–2016).

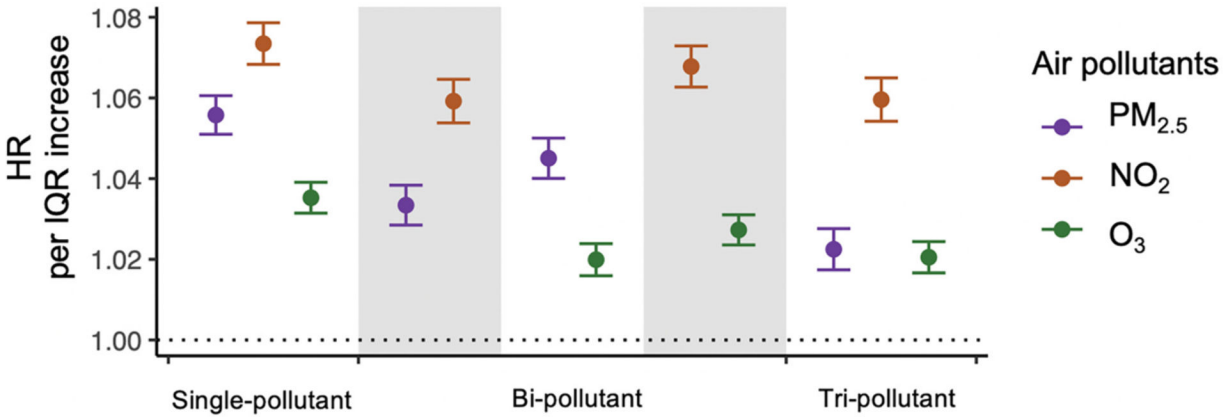

Fig. 2.

Hazard ratios of stroke incidence associated with annual $PM_{2.5}$ (a), or annual NO_2 (b), or warm-season O_3 (c) concentration expressed per IQR increment. The estimated hazard ratios were obtained using single-pollutant, bi-pollutant, and tri-pollutant models, respectively. IQR, interquartile range. HR, hazard ratio.

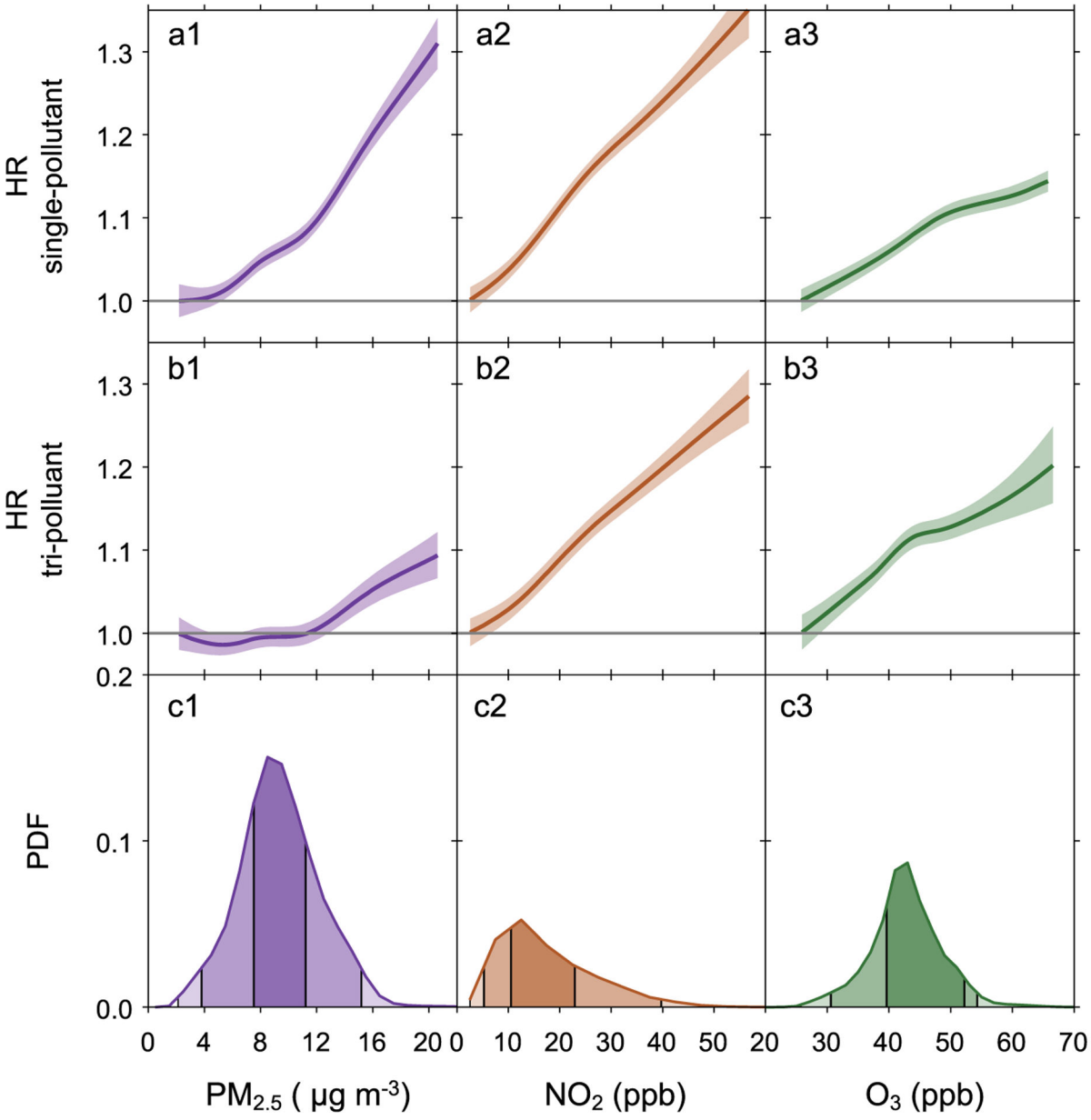

Fig. 3.

Concentration–response relationships between long-term $PM_{2.5}$, NO_2, and O_3 exposures and stroke incidence from (a) single pollutant models and (b) tri-pollutant models, and (c) probability distribution functions (PDF) of long-term $PM_{2.5}$, NO_2, and O_3 exposures. (a, b) The concentration-response curves, derived from the single-pollutant or tri-pollutant models, are shown for the concentration ranges between 0.1th to 99.9th percentiles of the pollutants, i.e. with 0.2% poorly constrained extreme values excluded. (c) The PDF shows the distribution of each exposure in the cohort and the shading areas (from the darkest to the lightest) represent pollutant concentration ranges of the IQR (i.e., 25th to 75th percentiles), 95% (2.5th to 97.5th), and 99.8% (0.1th to 99.9th), respectively. IQR, interquartile range. HR, hazard ratio.

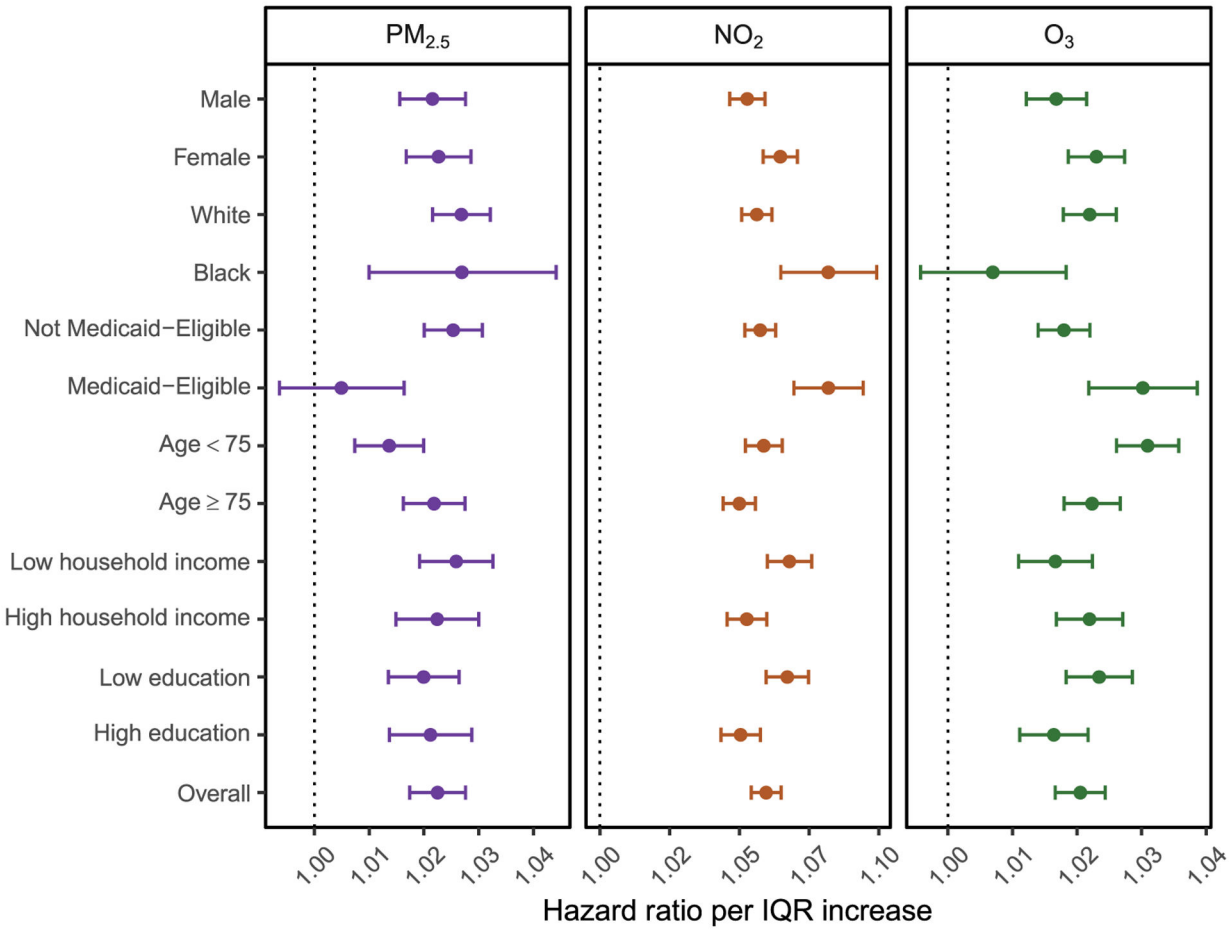

Fig. 4.

Hazard ratios of stroke incidence associated with an IQR increase in annual $PM_{2.5}$, annual NO_2, and warm-season O_3 concentration by study subgroups. All results were derived from the tri-pollutant models. The grey shades indicate the 95% CIs of the overall effect estimates. “Household income” denotes median household income at zip-code level, “Low household income” represents the subgroup with median household income lower than the population median while “High household income” represents the subgroup with median household income higher than the population median. “Education” denotes the proportion of the population > 65 years of age who had not graduated from high school at zip-code level, “Low education” represents the subgroup with the proportion of less educated people higher than the population proportion median while “High education” represents the subgroup with the proportion of less educated people lower than the population proportion median. IQR, interquartile range. HR, hazard ratio. CI, confidence interval.

Table 1

Descriptive statistics for the study population.

Variables	Full cohort	
	Number	%
Years of clean period	1	
Total population	17,443,900	100
Total Stroke cases	2,240,586	12.8
Total person-years	144,611,520	
Median follow-up year	8	
Age at entry (years)		
65–74	15,378,824	88.2
75–115	2,065,076	11.8
Mean (SD)	69.1 (4.8)	
Sex		
Male	7,291,664	41.8
Female	10,152,236	58.2
Race		
White	15,405,416	88.3
Black	1,039,110	6.0
Other[a]	999,374	5.7
Medicaid eligibility		
Dual-eligible	1,177,587	6.8
Non-dual eligible	16,266,313	93.2
Region		
Northeast	3,672,246	21.1
Southeast	4,781,586	27.4
Midwest	4,130,490	23.7
West	2,934,175	16.8
Southwest	1,921,509	11.0
Body-mass index (kg/m^2)	27.5 (1.0)	
Ever smoked (%)	46.2 (7.4)	
Below poverty level (%)	12.4 (7.3)	
Not graduated from high school (%)	13.8 (8.2)	
Median household income (US$1000)	57.1 (23.7)	
Air pollutants[b]		
Annual $PM_{2.5}$ ($\mu g/m^3$)	9.4 (3.7)	
Annual NO_2 (ppb)	17.5 (12.4)	
Warm-season O_3 (ppb)	42.8 (6.5)	

Note: Data are n (%) or mean (SD), except otherwise specified.

[a] Other included Asian, Hispanic, American Indian or Alaskan Native, and unknown.

[b] Presented as mean concentration (interquartile range) over the study period.