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Long-Term Exposure to Low-Level NO_2 and Mortality among the Elderly Population in the Southeastern United States

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Background: Mounting evidence has shown that long-term exposure to fine particulate matter [PM ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$)] and ozone (O_3) can increase mortality. However, the health effects associated with long-term exposure to nitrogen dioxide (NO_2) are less clear, in particular the evidence is scarce for NO_2 at low levels that are below the current international guidelines.

Methods: We constructed a population-based full cohort comprising all Medicare beneficiaries (aged ≥65, $N = 13{,}590{,}387$) in the southeastern United States from 2000 to 2016, and we then further defined the below-guideline cohort that included only those who were always exposed to low-level NO_2, that is, with annual means below the current World Health Organization guidelines (i.e., ≤21 ppb). We applied previously estimated spatially and temporally resolved NO_2 concentrations and assigned annual means to study participants based on their ZIP code of residence. Cox proportional hazards models were used to examine the association between long-term exposure to low-level NO_2 and all-cause mortality, adjusting for potential confounders.

Results: About 71.1% of the Medicare beneficiaries in the southeastern United States were always exposed to low-level NO_2 over the study period. We observed an association between long-term exposure to low-level NO_2 and all-cause mortality, with a hazard ratio (HR) = 1.042 (95% CI: 1.040, 1.045) in single-pollutant models and a HR = 1.047 (95% CI: 1.045, 1.049) in multipollutant models (adjusting for $PM_{2.5}$ and O_3), per 10-ppb increase in annual NO_2 concentrations. The penalized spline indicates a linear exposure–response relationship across the entire NO_2 exposure range. Medicare enrollees who were White, female, and residing in urban areas were more vulnerable to long-term NO_2 exposure.

Conclusion: Using a large and representative cohort, we provide epidemiological evidence that long-term exposure to NO_2, even below the national and global ambient air quality guidelines, was approximately linearly associated with a higher risk of mortality among older adults, independent of $PM_{2.5}$ and O_3 exposure. Improving air quality by reducing NO_2 emissions, therefore, may yield significant health benefits. https://doi.org/10.1289/EHP9044

Introduction

Air pollution is among the most critical environmental and public health concerns worldwide (Chen and Kan 2008). The adverse health effects of exposure to ambient fine particulate matter [PM ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$)] (Akintoye et al. 2016; Chen and Hoek 2020; Shi et al. 2020) and ozone (O_3) (Turner et al. 2016) have been widely reported (Cesaroni et al.2012; Cohen et al. 2017; Danesh Yazdi et al. 2021; Silva et al. 2016; Wei et al. 2020) in previous epidemiological studies; however, the relationship between ambient nitrogen dioxide (NO_2) exposure and mortality is less understood. Although the risk associated with acute NO_2 exposure and premature mortality has been studied more extensively (Chen et al. 2012; Chiusolo et al. 2011; Mills et al. 2016; Samoli et al. 2006), the evidence remains limited for long-term NO_2 exposure. Fewer epidemiological studies have investigated the mortality risks associated with long-term NO_2 concentrations (Eum et al. 2019; Faustini et al. 2014; Hoek et al. 2013).

NO_2 gas, as one of the highly reactive nitrogen oxides (NO_x), primarily derives from high-temperature combustion processes. In the United States, motor vehicle emissions are the predominant source of NO_2, and high levels of NO_2 are observed along highways and in cities (Di et al. 2020). NO_2 can be coemitted on roadways with other traffic-related tailpipe and nontailpipe emissions, such as black carbon, organic carbon, and trace metals (WHO 2021). NO_2 is therefore often considered a surrogate for traffic-related air pollutants (Alotaibi et al. 2019). Other major sources of NO_2 also include power plants and off-road equipment (U.S. EPA 2011, 2020).

Recent evidence suggests that long-term exposure to NO_2 may be linked to premature mortality (COMEAP 2018; U.S. EPA 2019). Two recent systematic reviews, Huangfu and Atkinson (2020) and Huang et al. (2021), both reported a positive association between long-term NO_2 exposure and all-cause mortality, and they noted that more large-scale cohort studies exploring the concentration–response relationship are encouraged (Huang et al. 2021; Huangfu and Atkinson 2020). In addition, several more recent large cohort studies have reported positive associations between NO_2 and all-cause and cause-specific mortality, expanding the evidence base globally, including studies conducted in Europe (Samoli et al. 2021), Canada (Paul et al. 2020; Zhang et al. 2021), Netherlands (Klompmaker et al. 2020; Klompmaker et al. 2021), Denmark (So et al. 2020), Greece (Kasdagli et al. 2021), Japan (Yorifuji and Kashima 2020), and South Korea (Jung et al. 2020). Yet, among the growing body of literature, a high degree of regional heterogeneity has been observed. A few studies have assessed NO_2 exposure across a broad geographic area (Heinrich et al. 2013; Jerrett et al. 2013; Maheswaran et al. 2010), albeit at a relatively coarse spatial resolution. Thus, previous studies are limited in their ability to quantify the spatial variability of long-term exposure resulting from local variations in traffic-related emissions, which may impact overall measures of association. Further, although many studies have used multipollutant models to estimate associations with NO_2 after

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adjusting for other pollutants, these studies reported mixed results (Faustini et al. 2014; Huang et al. 2021; Stieb et al. 2021), and the independent association between NO_2 and all-cause mortality remains unclear (COMEAP 2018).

To protect public health from adverse health outcomes induced by air pollution, the World Health Organization (WHO) has set evidence-based guidelines on ambient air pollution to inform environmental policy and national air quality targets (WHO 2006). The target guidelines for NO_2 is currently set at an annual average of 40 $\mu g/m^3$ ($\sim$21 ppb) (WHO 2006). Similarly, in the United States, the National Ambient Air Quality Standards (NAAQS) are set and periodically revised by the U.S. Environmental Protection Agency on the basis of the best available scientific evidence, and the current NAAQS for annual mean NO_2 is 53 ppb (U.S. EPA 2021). However, it is not clear whether these standards are actually safe enough to protect public health.

We recently estimated temporally and spatially resolved NO_2 concentrations in the United States through an ensemble model that integrates multiple machine learning algorithms—including neural network, random forest, and gradient boosting—with a variety of predictor variables (e.g., satellite remote sensing and chemical transport models) (Di et al. 2020). This approach allows one to estimate daily NO_2 at a 1 km $\times$ 1 km resolution across the contiguous United States from 2000 to 2016 with an excellent prediction model performance. Therefore, we were able to assess long-term exposures of NO_2 for population-based cohort studies, with residents living far from monitors, as well as for those potentially exposed to low-level NO_2.

To address these critical gaps in knowledge, we conducted a large population-based cohort study encompassing all Medicare beneficiaries ($\geq$65 years of age) from 2000 to 2016 in the southeastern United States, using a high-resolution spatiotemporal ensemble model that can better capture air pollution data in rural and suburban areas. Focusing on the independent health effect of long-term exposure to low-level NO_2, we performed a multipollutant analysis to estimate the risk of all-cause mortality among the Medicare population associated with exposure (yearly average) to concentrations of NO_2 below the WHO annual guidelines of 40 $\mu g/m^3$ ($\sim$21 ppb) in an effort to better clarify the potential mortality risks attributable to air pollution levels below the current national and global ambient air quality guidelines.

Materials and Methods

Study Population

The study population comprised all Medicare beneficiaries who were $\geq$65 years of age over from 2000 to 2016 in seven southeastern U.S. states (Alabama, Florida, Georgia, Mississippi, North Carolina, South Carolina, and Tennessee). We constructed an open cohort from 1 January 2000 to 31 December 2016, with all-cause mortality as the outcome. We obtained individual-level characteristics, including the year and age of Medicare enrollment, date of death, current age, sex, race, ZIP code of residence, and Medicaid eligibility [a proxy for socioeconomic status (SES), that is, an individual eligible for both Medicare and Medicaid is likely to be of lower SES], from the Medicare beneficiary denominator file derived from the Centers for Medicare and Medicaid Services (CMS). The ZIP code of residence and calendar year were used for further exposure assignment. We further restricted the population to Medicare beneficiaries who were always exposed to low-level NO_2 (annual mean $\leq$21 ppb) over the study period (i.e., the low-exposure cohort). This study was approved by the CMS under the data use agreement (RSCH20-55733) and the institutional review board of Emory University (STUDY00000316), and a waiver of informed consent was granted.

Exposure

We applied previously estimated daily NO_2 concentrations at a 1 km $\times$ 1 km resolution in the United States from 2000 to 2016 using an ensemble model that integrated multiple machine learning algorithms and predictor variables (Di et al. 2020). Briefly, we respectively fit a neural network, a random forest, and a gradient boosting model with input predictor variables (satellite remote sensing, chemical transport models, meteorological variables, and multiple land-cover terms) and monitored NO_2 measurements to generate daily NO_2 predictions. This ensemble learning approach yielded a cross-validated mean R^2 of 0.79 and an average root mean square error of 7.2 ppb. For each ZIP code, daily NO_2 concentrations were averaged across all covered 1 km $\times$ 1 km grid cells with centroids that fell within the ZIP code boundary. We further calculated annual means (time-varying 1-y averages) and assigned these to Medicare beneficiaries according to their ZIP code of residence.

Covariates

Daily $PM_{2.5}$ and O_3 concentrations were previously estimated at a 1 km $\times$ 1 km resolution in the United States from 2000 to 2016 using the same ensemble model (Di et al. 2019; Requia et al. 2020). This trained model produced cross-validated mean R^2 values of 0.84 and 0.90 for $PM_{2.5}$ and O_3, respectively. We then aggregated daily predictions based on all covered 1-km^2 grid cells, and further calculated annual averages for $PM_{2.5}$ and warm-season averages for O_3 for each year relative to the ZIP code of residence. The warm season, defined as 1 May to 31 October, is a specific time window for examining the health effects of O_3 because the warm climate favors the formation and accumulation of O_3 in the atmosphere (Zhang et al. 2019).

We obtained eight ZIP code tabulation areas–level variables from the 2000 U.S. Census (U.S. Census 2002), 2010 U.S. Census (U.S. Census 2011), and the American Community Survey for 2005 to 2012 (U.S. Census 2020), and matched these variables to the ZIP code scale. The eight variables included median home value, percentage of owner-occupied housing units, median household income, population density, percentage of Black population, percentage of Hispanic population, percentage of those with a low education level (i.e., with less than a high school degree), and the percentage of those below the poverty level. Behavioral risk factors, including body mass index (BMI) and percentage of those who have ever smoked, were obtained at the county level from the Behavioral Risk Factor Surveillance System (BRFSS) between 2000 and 2016 (CDC 2020). We assigned county-level variables to a given ZIP code if the centroid was located within the county boundary. We linearly interpolated or extrapolated any missing data based on the available data (Junninen et al. 2004), in other words, all area-level variables were time-varying. These annual average data were assigned to individuals according to the ZIP code of residence.

Daily 1-km^2 resolution air temperature data were acquired for the southeastern United States between 2000 and 2016 from a national meteorology data product (Daymet, version 4) (Thornton et al. 2020). Daily temperature data were averaged for each ZIP code, and seasonal averages, including the mean temperature for summer (June–August) and winter (December–February), were calculated for each ZIP code and each year. We then assigned the seasonal mean temperature estimates to each participant according to the ZIP code of residence. Because more evidence has been found that seasonal temperature, particularly summer mean and winter mean temperature, has been associated with both all-cause mortality and air pollution levels (Duan et al. 2019; Park et al. 2011), we adjusted for summer and winter mean temperature in our main analyses.

Statistical Analysis

A counting process survival data set, based on the scheme presented by Andersen and Gill (1982), was constructed using the individual-level data. Namely, each observation represented a single person-year of mortality follow-up, with follow-up taking place at the beginning of the calendar year, whereas deaths were assessed at the end of each calendar year. We fit a series of single-, bi-, and tri-pollutant Cox proportional hazards models, with years of follow-up as the time scale, to estimate hazard ratios (HR) per 10-ppb increase in annual mean NO_2 exposure associated with all-cause mortality among the elderly population in both cohorts. All models were stratified by 5-y age categories, sex (female, male), and race (White, Black, and other), as well as by Medicaid eligibility, adjusting for indicators of calendar year, summer and winter mean temperature, median home value, median household income, population density, the proportion of owner-occupied housing units, and other demographic and behavioral risk factors, including the percentage of Black and Hispanic populations, education level, population below poverty level, BMI, and the proportion of those who were ever smokers.

To identify the most vulnerable subgroups, we evaluated effect modification by sex (female vs. male), race (White vs. Black vs. other), age (≥80 vs. <80 y), Medicaid eligibility (dual vs. nondual eligibility), urbanicity (quartiles of population density), and area-level SES indicator (a measure showing socioeconomic status; high SES vs. low SES) in tri-pollutant Cox models, by including interaction terms between these potential effect modifiers and NO_2. We included race as a covariate and effect modifier in our analysis to reflect the racial disparity. We applied the Wald test (Kaufman and MacLehose 2013) to assess whether one subgroup had a larger effect than another, and the $p < 0.05$ was chosen to suggest statistical significance. Dual eligibility subgroups refer to individuals who were eligible for both Medicare and Medicaid benefits, nondual otherwise. Area-level SES was defined as either below or above the median of the distribution of percentage below the poverty level. To assess the potential nonlinearity of the exposure–response relationship, we fit penalized spline regressions with penalized splines for NO_2, adjusting for all covariates and co-pollutants.

We performed the *m*-of-*n* bootstrap method to calculate statistically robust confidence intervals and account for potential spatial dependency in the Cox model. Given that the model treats the observations as independent, it may not adequately capture spatial patterns. *M*-of-*n* bootstrapping was performed by randomly sampling *m* ZIP codes of a total of *n* ZIP codes for each bootstrap replicate ($m =$ 2 times the square root of *n*, 500 replicates in total) (Bickel et al.2012). Doing so, breaks down the underlying spatial dependence as randomly sampled ZIP codes were not necessarily adjacent in each bootstrapped sample, yielding more robust standard errors and thus 95% confidence intervals. Therefore, it is least likely that our findings are influenced by spatial correlation.

We conducted several sensitivity analyses to assess the robustness of our results. First, we fit alternative models, excluding different covariates, including co-pollutant, time trends, SES, meteorology variables, behavioral risk factors, and baseline hazard stratification. We also tested how sensitive our models might be to adjust for space with a spatial smoother and with a state-level adjustment. We then compared the results of these models to examine the influence of potential confounders. Second, we evaluated the potential heterogeneity of associations by each U.S. state. Third, we fit single-pollutant penalized spline models, and tested whether the exposure–response relationship held under both scenarios (i.e., single-pollutant vs. multipollutant models).

The Medicare data set was stored and analyzed in the Rollins High-Performance Computing Cluster at Emory University, with Health Insurance Portability and Accountability Act compliance. R software, version 4.0.2 (R Development Core Team) was used in this study. The results were rounded to three decimal places to differentiate the upper and lower bounds of the confidence intervals. The estimated results with $p < 0.05$ were considered statistically significant.

Results

We included a total of 13,590,387 Medicare enrollees residing in 10,193 ZIP codes and 1,701 counties in the southeastern United States, with 107,291,652 person-years of follow-up in our full cohort study between 2000 through 2016. Each ZIP code had a mean [± standard deviation (SD)] of 1,485 ± 2,815 Medicare beneficiaries. A total of 4,898,015 (36.0%) participants died between 2000 and 2016. Among the full cohort, 9,669,469 (71.1%) Medicare enrollees living in 7,541 ZIP codes were always exposed to annual mean NO_2 concentrations below WHO air quality guidelines (21 ppb), with 2,814,617 (29.1%) deaths in 69,077,046 person-years of follow-up. The median follow-up years for the full cohort and the below-WHO guidelines cohort were 8 and 7 y, respectively. Nearly all (99.95%) of the Medicare enrollees were always exposed to annual mean NO_2 concentrations below the U.S. NAAQS (53 ppb). Detailed characteristics of the study population and summary statistics for all covariates are presented in Table 1 and Table S1.

Overall, from 2000 to 2016, the mean annual NO_2 concentration across the southeastern United States was 13.7 ppb, with an interquartile range (IQR) of 9.3 ppb (Table 2). The spatial distribution of long-term NO_2 concentrations is presented in Figure 1, which appears to depict patterns consistent with major roadways (Figure S1) and NO_2 concentrations at 1-km resolution (Figure S2). The SDs of the 1-km NO_2 concentrations within ZIP code areas are shown in Figure S3. The temporal trend of long-term NO_2 concentrations by state is shown in Figure S4. At the beginning of the study period, the lowest annual NO_2 levels were observed in Mississippi, with the highest annual levels observed in Florida. We observed a declining trend of NO_2 concentrations over the study period, apart from elevated levels between 2009 and 2011.

Overall, long-term exposure to NO_2, even at low levels, was significantly and positively associated with mortality in all statistical analyses (Table 3). In single-pollutant models, we observed a HR = 1.042 [95% confidence interval (CI): 1.040, 1.045] per 10-ppb increase in NO_2 concentrations. After adjusting for $PM_{2.5}$ and O_3, the results for NO_2 were similar (the estimated results for $PM_{2.5}$ and O_3 are presented in Table S2). The observed relationship between long-term NO_2 concentrations and mortality appears to be approximately linear across the exposure distribution, because the concentration–response curve does not suggest a threshold for mortality at low concentrations of NO_2, the slope of the curve does not level off at high concentrations at least in the range examined, and the nonlinearity derived from the penalized spline fitting is within the model uncertainty (Figure 2).

In effect modification analyses, we observed significantly higher risks among White individuals (HR = 1.060; 95% CI: 1.050, 1.071) ($p_{Interaction} < 0.001$), women (HR = 1.077; 95% CI: 1.062, 1.091) ($p_{Interaction} < 0.001$), and those residing in urban areas (HR = 1.057; 95% CI: 1.038, 1.076) ($p_{Interaction} < 0.001$). In addition, measures of association were higher among the relatively younger individuals (<80 years of age), although not significant ($p_{Interaction} = 0.056$). Further details are presented in Figure 3 and Table S3.

In our sensitivity analyses, excluding time trends changed the HR the most compared with the main analysis (HR excluding

Table 1. Descriptive statistics of full cohort ($N = 13{,}590{,}387$) and below-WHO guidelines cohort ($N = 9{,}669{,}469$) created from Medicare beneficiary denominator from 2000 to 2016 in seven southeastern U.S. states.

	Full cohort		Below-WHO guidelines cohort[a]	
Categories	*N*	%	*N*	%
Full cohort				
Deaths	4,898,015	36.0	2,814,617	29.1
Total population	13,590,387	100	9,669,469	100
Total person-years	107,291,652	100	69,077,046	100
Median follow-up year	8		7	
Age at entry (y)				
65–74	13,527,082	99.5	9,632,655	99.6
75–84	53,181	0.4	30,404	0.3
85–94	9,523	0.07	6,008	0.06
≥95	599	0.004	402	0.004
Sex				
Male	5,943,391	43.7	4,321,795	44.7
Female	7,646,996	56.3	5,347,674	55.3
Race				
White	11,217,509	82.5	8,073,062	83.5
Black	1,745,096	12.8	1,190,084	12.3
Other[b]	627,782	4.6	406,323	4.2
Medicaid eligibility				
Dual-eligible	1,718,169	12.6	1,154,668	11.9
Non–dual-eligible	11,872,218	87.4	8,514,801	88.1

Note: The seven states include Alabama, Florida, Georgia, Mississippi, North Carolina, South Carolina, and Tennessee. WHO, World Health Organization.
[a]The cohort was restricted to populations who were always exposed to annual mean NO_2 levels below the current WHO guidelines, i.e. 40 $\mu g/m^3$.
[b]Other included Asian, Hispanic, American Indian or Alaskan Native, and unknown.

time trend = 1.251; 95% CI: 1.248, 1.254; Table S4). Analyses stratifying by state yielded consistently positive associations between long-term NO_2 exposure and mortality, with the highest HR observed among Medicare beneficiaries in North Carolina (HR = 1.067; 95% CI: 1.060, 1.074; Table S5). Last, the single-pollutant and multipollutant penalized spline models yielded almost identical splines, both suggesting approximately linear exposure–response relationships for annual NO_2 and all-cause mortality (Figure 2; Figure S5).

Table 2. Spatial and temporal variability of annual NO_2 levels (in ppb) in years 2000–2016.

		Percentile						
Categories	Min	5th	25th	50th	75th	95th	Max	Mean
Overall	0.58	5.25	8.36	12.09	17.68	27.10	56.95	13.65
By year								
2000	3.32	8.26	14.11	20.17	25.62	34.34	52.47	20.30
2001	4.06	7.51	11.65	17.39	23.74	33.56	49.62	18.45
2002	2.82	6.19	9.91	15.45	21.60	30.69	42.82	16.37
2003	2.71	5.28	8.97	14.06	20.60	29.67	52.11	15.32
2004	2.07	7.19	10.23	14.45	19.49	27.79	46.07	15.48
2005	3.33	6.07	9.04	13.49	19.50	27.43	44.91	14.72
2006	2.11	5.44	7.90	12.13	19.28	26.50	41.54	13.97
2007	1.93	4.70	6.57	9.97	17.11	27.09	42.75	12.41
2008	2.42	6.12	8.00	11.18	16.63	25.13	35.97	12.87
2009	0.93	4.74	6.33	9.30	14.56	21.00	30.62	10.78
2010	0.58	5.23	8.03	10.92	15.18	23.52	36.62	12.14
2011	3.98	7.37	10.25	12.58	15.64	22.95	41.41	13.49
2012	2.94	7.77	10.00	11.85	14.59	21.15	49.47	12.86
2013	2.37	4.67	7.01	9.51	12.82	19.18	56.95	10.44
2014	2.39	4.51	6.62	9.54	14.34	21.12	39.01	10.99
2015	0.97	4.78	7.78	10.48	13.83	20.05	32.08	11.16
2016	1.09	3.84	6.31	9.36	14.03	20.84	31.44	10.59
By state								
Alabama	2.21	4.71	6.96	9.77	14.45	21.50	37.55	11.17
Florida	1.98	7.28	11.35	14.87	19.32	25.50	45.19	15.54
Georgia	2.58	5.64	8.56	11.90	19.24	32.37	52.47	14.86
Mississippi	2.24	4.63	6.78	9.52	13.87	20.19	29.85	10.70
North Carolina	0.58	5.58	8.87	12.70	19.01	29.06	46.07	14.54
South Carolina	2.97	5.55	8.23	11.17	16.00	25.38	37.71	12.78
Tennessee	0.94	4.55	6.87	10.08	16.90	27.71	56.95	12.58

Note: NO_2, nitrogen dioxide.

Discussion

In this large-scale population-based cohort study, we observed a significant and independent association between long-term exposure to NO_2 and all-cause mortality among the Medicare population even at NO_2 levels below global and national guidelines. We further observed a roughly linear trend in mortality risk after adjusting for $PM_{2.5}$ and O_3, indicating no apparent evidence of a threshold value. We also observed larger measures of association among White populations, women, and urban residents, indicating potential susceptibility among these groups.

Our results of an increased NO_2-associated all-cause mortality risk (HR = 1.047; 95% CI: 1.045, 1.049, per 10-ppb increase in annual average NO_2) are broadly consistent with previous cohort studies (Table S6), particularly among those using spatiotemporal exposure assessments (Cesaroni et al. 2013; Crouse et al. 2015; Eum et al. 2019; Faustini et al. 2014; Fischer et al. 2015; Hart et al. 2011; Hoek et al. 2013; Jerrett et al. 2013; Klompmaker et al. 2021; Nieuwenhuijsen et al. 2018; Paul et al. 2020; Samoli et al. 2021; Turner et al. 2016). In a recent Medicare cohort study, Eum et al. (2019) examined the impact of NO_2 exposure and mortality by region of the United States between 2000 and 2008 using ground-based monitoring data for NO_2 measures and a bipollutant Poisson regression model adjusted for $PM_{2.5}$ (Eum et al. 2019). Overall, they reported an increased all-cause mortality risk with similar measures of association per 10-ppb increase in annual average NO_2 (HR = 1.052; 95% CI: 1.051, 1.054).

Other U.S.-based studies have previously reported comparable results, including the American Cancer Society's Cancer Prevention Study II follow-up study reported by Turner et al. (2016) (HR = 1.01; 95% CI: 1.00, 1.03 per 10-unit increase) and Jerrett et al. (2013) (HR = 1.032; 95% CI: 1.008, 1.057 per an IQR increase of 4.1167 ppb) (Jerrett et al. 2013; Turner et al. 2016), whereas larger measures of association have been observed in single-pollutant models reported in the Nurses' Health Study (Hart et al. 2013) (HR = 1.10; 95% CI: 1.05, 1.15). Our results are additionally supported by the recent Ontario Population Health and Environment Cohort study (Paul et al. 2020) and a previous Canada-wide study (Crouse et al. 2015).

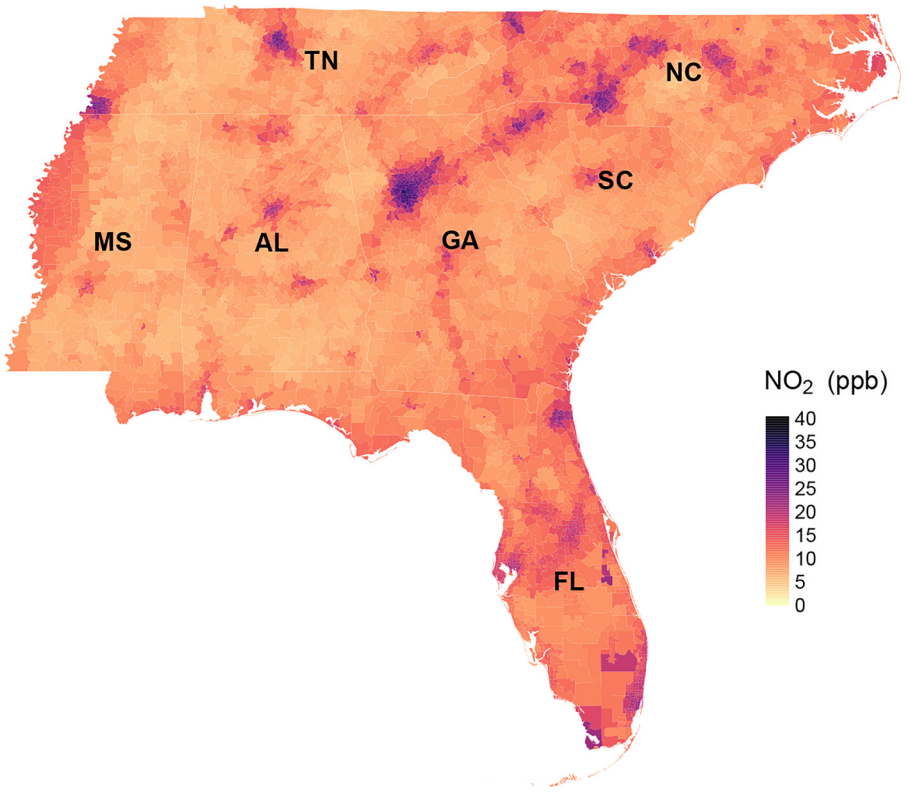

Figure 1. The spatial distribution of 17-y mean concentrations of annual NO_2 at ZIP code level in the southeastern United States (2000–2016). Note: NO_2, nitrogen dioxide.

Many previous studies have similarly observed positive associations at low annual average concentrations of NO_2 (Eum et al. 2019; Hart et al. 2013; Jerrett et al. 2013; Turner et al. 2016), including several recent international studies, such as those in Canada (Crouse et al. 2015; Paul et al. 2020; Zhang et al. 2021), Denmark (Hvidtfeldt et al. 2019; So et al. 2020), Netherlands (Beelen et al. 2008; Klompmaker et al. 2021), United Kingdom (Carey et al. 2013; Tonne and Wilkinson 2013), France (Sanyal et al. 2018), Japan (Yorifuji and Kashima 2020), and South Korea (Jung et al. 2020).

However, because so few previous studies have included estimates for NO_2-associated mortality risks using multipollutant models, recent studies with more significantly positive measures

Table 3. Estimated hazard ratio of mortality (95% CI) associated with an increase of 10 ppb in NO_2 concentration using Cox proportional hazards model for both full cohort and below-WHO guidelines cohort.

Models	Full cohort ($N = 13{,}590{,}387$) HR (95% CI)	Below-WHO guidelines cohort[a] ($N = 9{,}669{,}469$) HR (95% CI)
Single-pollutant[b]	1.042 (1.039, 1.044)	1.042 (1.040, 1.045)
Bi-pollutant (+$PM_{2.5}$)[c]	1.042 (1.040, 1.044)	1.042 (1.040, 1.045)
Bi-pollutant (+O_3)[d]	1.047 (1.045, 1.049)	1.047 (1.045, 1.050)
Tri-pollutant[e]	1.047 (1.044, 1.049)	1.047 (1.045, 1.049)

Note: Estimates are based on 10 ppb increments for NO_2. CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; WHO, World Health Organization.

[a]The cohort was restricted to populations who were always exposed to annual mean NO_2 levels below the current WHO guidelines, i.e., 40 $\mu g/m^3$.

[b]Single-pollutant model: stratified by age at entry (5-y categories), sex (female, male), race (White, Black, and other), Medicaid eligibility, and adjusted for calendar year, summer and winter mean temperature, median home value, median household income, population density, the proportion of owner-occupied housing units, the percentage of Black and Hispanic populations, education level, population below poverty level, body mass index, and the proportion of those who were ever smokers. The descriptive statistics for these variables are provided in Table 1 and Table S1.

[c]Bi-pollutant (+$PM_{2.5}$): single-pollutant model further adjusted for annual mean of $PM_{2.5}$.

[d]Bi-pollutant (+O_3): single-pollutant model further adjusted for annual warm-season average of O_3.

[e]Tri-pollutant: single-pollutant model further adjusted for annual mean of $PM_{2.5}$ and annual warm-season average of O_3.

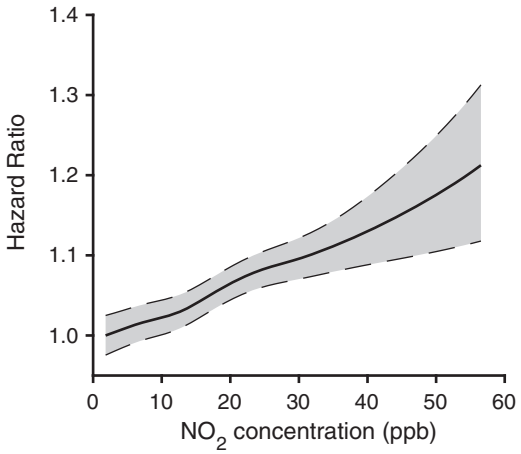

Figure 2. The exposure–response relationship between long-term exposure to NO_2 and all-cause mortality, derived from tri-pollutant models with adjustment of annual mean of $PM_{2.5}$, annual warm-season average of O_3, age at entry (5-y categories), sex (female, male), race (White, Black, and other), Medicaid eligibility, calendar year, summer and winter mean temperature, median home value, median household income, population density, the proportion of owner-occupied housing units, the percentage of Black and Hispanic populations, education level, population below poverty level, body mass index, and the proportion of those who were ever smokers. The descriptive statistics for these variables are provided in Table 1 and Table S1. Shaded areas indicate the 95% confidence bands. Note: NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; O_3, ozone.

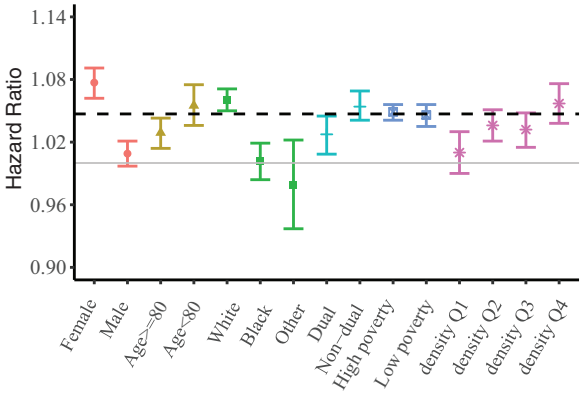

Figure 3. The hazard ratios of mortality associated with a 10-ppb increase in NO_2 concentrations for study subgroups. Density Q1–Q4 stand for low population density, low-medium population density, medium-high population density, and high population density, respectively. The numeric data for these measures of associations are provided in the Table S3. Note: NO_2, nitrogen dioxide; Q, quartile.

of association (Jung et al. 2020; Kasdagli et al. 2021; Yorifuji and Kashima 2020; Zhang et al. 2021) may be less reliable, potentially overestimating associations with NO_2 given the high correlation between co-pollutants. In a recent critical review and meta-analysis, Huangfu and Atkinson (2020) assessed the results of 24 international cohort studies on NO_2-associated mortality risk and reported an overall relative risk of 1.02 (95% CI: 1.01, 1.04) per 10-$\mu g/m^3$ increase in NO_2 for all-cause mortality (Huangfu and Atkinson 2020). In addition, Huang et al. (2021) reported a pooled HR = 1.06 (95% CI: 1.04, 1.08) for all-cause mortality per 10-ppb increase in annual NO_2 exposure (Huang et al. 2021). Likewise, two other meta-analyses, Faustini et al. (2014) and Hoek et al.(2013), respectively reported pooled HRs of 1.04 (95% CI: 1.02, 1.06) and 1.05 (95% CI: 1.03, 1.08) for all-cause mortality per 10-$\mu g/m^3$ increase in NO_2.

Although other factors—such as geographical differences, pollutant composition, and relative urbanicity, in addition to methodological differences that challenge the ability to make comparisons across studies, may impact the variability of measures of association (Hoek et al. 2013), multipollutant models—may provide a more accurate characterization of associated effects. However, at present, it is unclear whether the mortality effects observed in previous studies reflect an independent NO_2 association (COMEAP 2018), underscoring the potentially important contribution of our analysis to the literature. More work is necessary in this regard to better determine the causality of health effects and whether long-term average concentrations of NO_2 are adequately representative of complex pollutant mixtures.

Few studies have assessed the shape of the exposure–response relationship between NO_2 and mortality (Huangfu and Atkinson 2020). Our findings demonstrating evidence of linearity across the exposure distribution are supported by results from other recent studies (Dirgawati et al. 2019; Hanigan et al. 2019), suggesting that long-term exposure to NO_2, even at levels below current guidelines, is associated with increased mortality.

Another important finding from our study relates to the differential association observed in subgroup analyses. We found a higher average risk of mortality among White populations when compared with other races. One possible reason is that White populations, although less socially vulnerable and presumably, on average, healthier, might be less resilient to NO_2. This is consistent with the finding from other race/ethnicity health disparities studies (Breslau et al. 2006). We also found higher mortality risks among women compared with men, which is at odds with the results reported by Crouse et al. (2015); however, too few studies have investigated differential effects of NO_2-associated mortality risk by sex; thus, further investigation is warranted. Last, the effect of modification of age was not apparent, which was similar to the study of NO_2 and mortality in three Canadian cities (Chen et al. 2013).

Long-term exposure to NO_2 has been associated with acute and chronic respiratory diseases (Abbey et al. 1993), such as increased bronchial hyperresponsiveness (Jammes et al. 1998), increased respiratory infection (Liang et al. 2020), and decreased lung function (Nori-Sarma et al. 2021). Biological evidence has been reported for plausible mechanisms regarding the health effects of NO_2. One critical review suggests that NO_2 inhalation can induce lung function changes, accelerate pulmonary infections, and aggravate existing lung diseases by triggering a pro-inflammatory response, which is an innate immune response (Hesterberg et al. 2009). Moreover, an *in vitro* study found that NO_2 can enhance oxidative stress and lead to the generation of reactive oxygen and nitrogen species (Ayyagari et al. 2007), and another study found NO_2 could deteriorate the cardiovascular and immune systems in mice (Bevelander et al. 2007).

To the best of our knowledge, few studies have restricted ambient NO_2 exposure below current annual guidelines to investigate the exposure–response relationship between NO_2 and mortality in a large-scale population-based study (Chen et al. 2013; Sanyal et al. 2018; Yorifuji and Kashima 2020). Our study includes all Medicare beneficiaries in the southeastern United States, which includes all residents exposed to low-level NO_2 in both rural and urban areas. Our large, representative sample size provides ample statistical power to characterize complex spatiotemporal patterns among populations exposed to low-level pollution concentrations. Taken together, our results may provide a more confident characterization of the independent mortality effects of NO_2 through the use of single-, bi-, and multipollutant modeling and a rigorous statistical approach for deriving confidence intervals through an *m*-of-*n* bootstrapping approach (as a comparison, Table S7 shows the standard errors before and after bootstrapping).

Several limitations of this study should be acknowledged. First, as with any exposure assessment at an ecologic scale, the potential for exposure misclassification is of particular concern. The use of ZIP codes to estimate long-term exposure to NO_2 concentrations may not correlate well with individual-level exposure. Although the comparison of major roadways (Figure S1), 1-km^2 NO_2 concentrations (Figure S2), and ZIP code-scale NO_2 concentrations (Figure 1) suggests that even though ZIP code-level NO_2 may serve as a good indicator of traffic pollution at the larger scale, large differences in NO_2 could still occur within a major source area, for example, at locations near major roadways. As such, a 1-km^2 scale of NO_2 exposure may still be too coarse a resolution given the decay gradient of NO_2, which limits the ability to capture local or small-area variations in traffic-related pollution and proximity to roads. Second, the Medicare data do not provide the underlying cause of death necessary for understanding possible causal pathways. Third, given the use of administrative data, we cannot exclude the possibility of outcome misclassification due to coding errors or residual confounding bias on account of individual-level risk factors for mortality, such as smoking, alcohol consumption, and physical activity, which were not ascertained in this study. However, this was a semi-individual study because of the exposure aggregation, and these behaviors have been shown in personal exposure studies (Weisskopf and Webster 2017) to be uncorrelated with outdoor exposure levels; they are correlated only through neighborhood-level SES. Therefore, controlling for neighborhood SES and, secondarily, for neighborhood obesity and smoking, is appropriate for confounding adjustment. That said, we must admit that our neighborhood

smoking and obesity information is not ideal, because we have only the information gathered on a county level from the BRFSS, and residual confounding remains a concern. Fourth, our findings may not be generalized to younger age groups or represent the vast differences across the United States, where the pollution composition and demographic characteristics vary significantly. Furthermore, having controlled for O_3 and $PM_{2.5}$, we cannot rule out the possibility that NO_2 may be an indicator of other traffic-related air pollutants, such as ultrafine particles, soot, and trace metals or other potential noise-related confounding factors (Beckerman et al. 2008; Moshammer et al. 2020).

In conclusion, we found an association between long-term exposure to NO_2 and all-cause mortality, independent of $PM_{2.5}$ and O_3 exposure. Our findings contribute to the evidence base of the increased risk of mortality associated with traffic-related air pollution. Nevertheless, our results should be taken as part of a growing, although insufficiently studied, area of air pollution epidemiology. Further research is needed to study the association between long-term NO_2 exposure and mortality, particularly at low levels, with improved methods and measurements of exposure (e.g., improved with increasing spatial monitoring density). Reconsidering both national and international NO_2 emissions guidelines may yield significant health benefits.

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