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Long-term NO_2 exposures and cause-specific mortality in American older adults

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Abstract

Background—The impact of long-term exposure to nitrogen dioxide (NO_2) on cause-specific mortality is poorly understood.

Objective—To assess mortality risks associated with long-term NO_2 exposure and evaluate confounding of this association.

Methods—We examined the association between 12-month moving average NO_2 exposure and cause-specific mortality in 14.1 million US Medicare beneficiaries between 2000 and 2008. Associations were examined using age, gender, and race-stratified and state-adjusted Poisson regression models. We assessed the potential for confounding by $PM_{2.5}$ and behavioral covariates and unmeasured confounding by decomposing NO_2 into its spatial and spatio-temporal components.

Results—We found significant associations between 12-month NO_2 exposure and increased mortality from all-causes [risk ratio (RR): 1.052; 95% CI: 1.051, 1.054; per 10 ppb], cardiovascular (CVD) (1.133; 95% CI: 1.130, 1.137) and respiratory disease (1.050; 95% CI: 1.044, 1.056), all cancers (1.021; 95% CI: 1.017, 1.025), ischemic heart disease (IHD) (1.221; 95% CI: 1.217, 1.226), cerebrovascular (CBV) disease (1.092; 95% CI: 1.085, 1.100), and for the first time pneumonia (1.275; 95% CI: 1.263, 1.287). Associations generally remained positive and statistically significant after adjustment for $PM_{2.5}$ and behavioral factors.

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Disclosures

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.12.060.

Conclusions—Our findings provide additional evidence of the increased risk posed by long-term NO_2 exposures on increased mortality from all-causes, CVD, respiratory disease, IHD, CBV, and cancer and provide new evidence of their impact on mortality from pneumonia. Unmeasured confounding of these associations was present, however, demonstrating the need to understand sources of this confounding.

1. Introduction

Numerous studies have evaluated the associations of short-term exposure to ambient nitrogen dioxide (NO_2) with risk of all-cause, cardiovascular and respiratory mortality. A recent systemic review of 204 time-series study reported a 1.3% [95% confidence interval (CI) 0.1%, 1.9%], 1.7% (95% CI: 0.9%, 2.5%), and 2.0% (95% CI: 1.4%, 2.7%) for all-cause, cardiovascular, and respiratory mortality, respectively, per 10 parts per billion (ppb) increase in 24-hour NO_2 exposure (Mills et al., 2015). Significant elevated risks in cardiovascular and respiratory hospitalizations have also been shown to be associated with a 10 ppb increment in 24-h NO_2 exposure (Mills et al., 2015).

In contrast, few epidemiological studies have examined the association between long-term ambient NO_2 concentration and all-cause – and, especially, cause-specific – mortality (Faustini et al., 2014; Hoek et al., 2013). In a meta-analysis of 9 to 18 studies depending on the cause of mortality, Faustini et al. (Faustini et al., 2014) estimated that long-term NO_2 exposure was associated with 1.04 (95% CI: 1.02, 1.06), 1.13 (95% CI: 1.09, 1.18) and 1.03 (95% CI: 1.02, 1.03) increases in all-cause, cardiovascular, and respiratory mortality, respectively, with substantial heterogeneity in study-specific RRs, especially for cardiovascular mortality. Moreover, only a limited number of studies have examined the impact of long-term NO_2 exposure on specific sub-causes of cardiovascular, respiratory, and cancer mortality [e.g., cerebrovascular disease, chronic obstructive pulmonary disease (COPD) or lung cancer]. The lack of such studies is not surprising, given the relative few number of deaths from these specific sub-causes (e.g., 4.9% of Medicare enrollees between 2000 and 2008) and corresponding insufficient statistical power to draw meaningful conclusions in studies with small- and medium-sized cohorts. To address these data gaps, we analyzed data from a cohort of 14.1 million United States (U.S.) Medicare beneficiaries to examine the association of NO_2 exposure with three leading causes of death (and their specific sub-causes): cardiovascular disease (CVD), respiratory disease, and cancer, and investigated potential confounding and modification of the NO_2-mortality associations. We further assessed the potential for unmeasured confounding of our associations using the decomposition method described by Greven et al. (2011) and applied by Pun et al. (2017) in base and adjusted models. In brief, this method divides NO_2 exposures into its temporal and spatio-temporal components, assuming that each contribute equally to the effect of air pollution on the mortality.

2. Methods

2.1. Data source and study population

This study was approved by the Institutional Review Board of Northeastern University. We compiled beneficiary data for 14.1 million Medicare enrollees aged 65–120 years

living in the conterminous U.S. between December 2000 through December 2008 from the Centers for Medicare and Medicaid Services Medicare Enrollment file. For each enrollee, the beneficiary-specific information on date of birth, age, gender, race/ethnicity, monthly survival, and ZIP code of residence was extracted. Using the International Classification of Disease (ICD–10) codes, we identified deaths from non-accidental and accidental causes of mortality, as well as three major causes including CVD, respiratory disease, and cancer, which account for over 72% of all-cause mortality (Table 1). We also identified cause-specific deaths from the three major causes [i.e., ischemic heart disease (IHD), cerebrovascular disease (CBV), congestive heart failure (CHF), COPD, pneumonia, and lung cancer] using codes from the National Death Index.

2.2. Exposure assessment

We obtained daily NO_2 data from the EPA Air Quality System (AQS) for the conterminous U.S. between December 2000 and December 2008. We selected 407 eligible AQS monitors that had daily NO_2 measurements for 3+ calendar years, with each year having at least 9 months with at least 27 days with valid 24-h averages during the study period. Of the included monitors, 110 monitors were located in the Western U.S., and 141 and 156 in the Central and Eastern U.S., respectively.

To control for potential confounding by $PM_{2.5}$, we also obtained daily $PM_{2.5}$ estimates on a 6 × 6 km grid across the U.S. for each Medicare beneficiary from a set of well-validated spatio-temporal smoothing models (Yanosky et al., 2014). The $PM_{2.5}$ estimates from grid points closest to the eligible NO_2 monitors were matched to corresponding monitors. In the primary analysis, our exposure measures were calculated as the 12-month moving average of NO_2 or $PM_{2.5}$ concentrations preceding the month of death.

2.3. Covariates

For each beneficiary, we defined the urbanicity of their ZIP codes of residence using data from the Rural Health Research Center (USDA, http://depts.washington.edu/uwruca/ruca-uses.php), and classified ZIP codes into urban, micropolitan (including areas with populations between 10,000 and 49,999), or rural as defined using Categorization B. We also obtained county-level behavioral covariates from the Selected Metropolitan/Micropolitan Area Risk Trends of the Behavioral Risk Factor Surveillance System (BRFSS), which first become available in 2002 (CDC-BRFSS). Because only 261 of the 407 NO_2 monitors were located in a county with BRFSS data, the analysis of confounding by behavioral risk factors was restricted to the subset of beneficiaries living near these 261 monitors.

2.4. Statistical analyses

For each month between December 2000 and December 2008, we matched 12-month moving averages of NO_2 concentration for a given AQS monitor to eligible Medicare beneficiaries who lived in ZIP codes with a geographic centroid within a 6 mile radius of an eligible NO_2 monitor. When a ZIP code centroid was located within 6 miles of ≥ 2 valid monitors, the closest monitor was chosen. The number of beneficiaries and deaths for each 5-year age interval, monitor and study month were calculated, with ages 90 years and over collapsed into 1 interval to avoid excessive zero counts of deaths in the older age groups.

In our main analyses, we constructed Poisson regression models stratified by age (in 5-year age intervals), gender and race, and employed a back-fitting algorithm to estimate the association of 12-month moving average NO_2 exposure on cause-specific mortality nationwide (Greven et al., 2011; Pun et al., 2017; Buja et al., 1989). These models also controlled for state of residence to account for unmeasured covariates that may vary spatially. In supplemental models, we examined longer moving averages, ranging from 2 to 5 years. We also examined regional associations in three mutually exclusive and exhaustive geographical regions: 'East' of the Mississippi River, 'Center' between the Mississippi River and the Sierra Nevada mountain range, and 'West' of the Sierra Nevada mountain range (Greven et al., 2011).

Given strong correlations between NO_2 and $PM_{2.5}$, we assessed confounding of the association of NO_2 and mortality by $PM_{2.5}$ using a two-stage approach (Schwartz et al., 2015). In the first stage, we linearly regressed 12-month moving average NO_2 on 12-month moving average $PM_{2.5}$ concentrations. We subsequently used the residual, which represents NO_2 exposure that is unexplained by $PM_{2.5}$, in the second stage as the exposure measure in the Poisson regression models, with the resulting coefficient representing the NO_2-associated mortality risk after adjusting for $PM_{2.5}$. Further, we examined potential confounding by both $PM_{2.5}$ and behavioral factors, by additionally adjusting for behavioral covariates from BRFSS in a subset of the cohort. These covariates were selected a priori based on previous associations with either mortality or NO_2; they included monthly county-level prevalence of current smokers, diabetics, heavy drinkers (i.e., > two drinks per day), asthma, average median income and body mass index. Note that the spatial distribution of the monitors with BRFSS data was similar to that for all monitors, although with fewer monitors in the West (19.9% versus 27.0% overall) and more in the East (41.8% vs. 38.3% overall) (Table S1).

We examined the extent to which our findings remained affected by unmeasured confounding by decomposing NO_2 exposures into two orthogonal components, namely the "temporal" NO_2 and "spatio-temporal" NO_2, using a method described by Greven et al. (2011). "Temporal" NO_2 was calculated by subtracting the mean concentration of all monitors over the study period from the national average concentration for a given month, while the "spatio-temporal" NO_2 for a given month and site was calculated by subtracting temporal NO_2 and the average concentration at each site from the monthly NO_2 concentration at that site. In our base and $PM_{2.5}$- and BRFSS-adjusted models, we included "temporal" NO_2 and "spatio-temporal" NO_2 as the exposure measures and compared their effect estimates for each examined cause of death. As in Greven et al. (2011), we assumed that unmeasured confounding may exist if the effect estimates for "temporal" NO_2 and "spatio-temporal" NO_2 with mortality are unequal.

Effect estimates for NO_2 are expressed as the risk ratios of death in a given month per 10 ppb increase in 12-month moving average of NO_2. All statistical analyses were conducted using SAS Software version 9.4.

3. Results

Our study population included 14.1 million Medicare enrollees aged 65–120 residing in 556 ZIP codes, close to 407 monitors across the U.S., and accounted for 26% of all Medicare enrollees. The median number of enrollees per ZIP code in any given month was 25,685 (Table 1). There were 3.5 million deaths reported during the study period: 98% from non-accidental and 2% from accidental causes. CVD accounted for 41% of all non-accidental mortality, followed by cancer (22%) and respiratory (11%) mortality. IHD accounted for over half of all CVD-related deaths, with a median of 961 deaths per month and monitor, followed by mortality from CBV and CHF. Half of respiratory deaths were from COPD, and 30% from pneumonia. Lung cancer comprised 27% of all cancer deaths. Approximately 89%, 4%, and 2% of our cohort lived in urban, micropolitan, and rural areas respectively (5% had missing data). The annual median NO_2 and $PM_{2.5}$ concentrations for the conterminous U.S. over the study period were 14.2 ppb and 10.8 $\mu g/m^3$, respectively.

In base Poisson regression models stratified by age, gender and race, and adjusted for state, a 10 ppb increase in 12-month moving average of NO_2 was associated with increased mortality risk from all causes (RR: 1.052; 95% CI: 1.051, 1.054), and non-accidental causes (1.055; 95% CI: 1.053, 1.057), but decreased mortality from accidental causes nationwide (Table 2). NO_2-associated increased mortality risk was greatest from CVD-related causes (1.133; 95% CI: 1.130, 1.137); among them, NO_2 was linked to 1.092 (95% CI: 1.085, 1.100) and 1.221 (95% CI: 1.217, 1.226) times the risk of death from CBV and IHD, respectively. A smaller but significant RR was observed for respiratory mortality (1.050; 95% CI: 1.044, 1.056), with an NO_2-associated RR for pneumonia mortality of 1.275 (95% CI: 1.263, 1.287). NO_2-associated mortality risks were lowest for cancer mortality (1.021, 95% CI: 1.017, 1.025). In contrast, 12-month moving average NO_2 exposures were significantly associated with lower mortality risks from CHF (0.903; 95% CI: 0.893, 0.914), COPD (0.958; 95% CI: 0.950, 0.965), and lung cancer (0.983; 95% CI: 0.975, 0.990).

Similar association was found when longer moving averages were examined (Table S2) using the subset of beneficiaries living near the 369 monitors with valid 5-year measures. Further, the magnitude of the associations between NO_2 and cause-specific mortality varied by geographic region, with NO_2-associated RRs generally highest in the Central U.S., as compared to the East and West. Moreover, NO_2-associated RRs differed by the urbanicity of the beneficiaries' residences, with higher RRs for those living in urban (1.055, 95% CI: 1.053, 1.057) and micropolitan (1.097, 95% CI: 1.061, 1.135) as compared to rural neighborhoods (0.822, 95% CI: 0.626, 1.080) (Table S3).

Notably, in models controlling for 12-month moving average $PM_{2.5}$, U.S.-wide associations with NO_2 remained positive and statistically significant for non-accidental, CVD, IHD, CBV, respiratory, pneumonia, and cancer mortality, with similar or somewhat attenuated RRs (Table 2). However, the magnitude and robustness of the NO_2-mortality associations to adjustment for $PM_{2.5}$ differed by geographic region. After adjustment for $PM_{2.5}$, NO_2-associated RRs were generally similar or substantially higher in the Central U.S. as compared to other regions for all causes of mortality. RRs in multivariate models that

adjusted for both $PM_{2.5}$ and behavioral factors were similar to those from $PM_{2.5}$-adjusted models for most causes of death (Table S4).

When we used "temporal" and "spatio-temporal" NO_2 as the exposure measures in base (Table S5), $PM_{2.5}$-adjusted (Table 3), and $PM_{2.5}$- and BFRSS-adjusted models (Table S6), we found RRs associated with "spatio-temporal" NO_2 to be consistently lower than those for "temporal" NO_2, suggesting that unmeasured confounding remained, even after adjustment for $PM_{2.5}$ and behavioral covariates. Despite this, both "spatio-temporal" and "temporal" RRs were generally statistically significant and positive. They, however, differed by geographical region, with RRs for temporal NO_2 and spatio-temporal NO_2 tending to be highest in the Central U.S. or in the Western U.S. In the East, "spatio-temporal" RRs were significantly negative for all causes of death except COPD and lung cancer.

4. Discussion

In a U.S. Medicare cohort of 14.1 million beneficiaries and 3.5 million deaths, we found a 10 ppb increase in 12-month NO_2 exposure to be associated with increased risks for mortality from cardiovascular disease (11%) and respiratory disease (3%), and to a lesser extent from cancer (2%), after controlling for $PM_{2.5}$. We further observed that the impacts of NO_2 exposure on mortality are consistent across specific subcategories of these major diseases, including IHD, CBV disease, and for the first time, pneumonia. Our findings were generally consistent across geographic region and model specifications, although confounding by $PM_{2.5}$ and to a lesser extent behavioral factors was evident. Moreover, our results showing unequal RRs for "temporal" and "spatio-temporal" NO_2 even after adjustment for $PM_{2.5}$ and behavioral risk factors, suggesting that unmeasured confounding of our NO_2-mortality association remain, consistent with our previously reported findings for the association between $PM_{2.5}$ and mortality (Pun et al., 2017).

The findings of elevated NO_2-associated risks for all-cause (RR: 1.052; 95% CI:1.051, 1.054) and non-accidental (RR: 1.055; 95% CI:1.053, 1.057) mortality are generally consistent with findings from earlier studies, including those from Turner et al. (2016) in the extended follow-up of the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II), from Crouse et al. of a Canada-wide cohort (Crouse et al., 2015), and from smaller-scale studies of occupational (Hart et al., 2011) and European cohorts (Cesaroni et al., 2013; Beelen et al., 2008; Filleul et al., 2005; Heinrich et al., 2013). They, however, differ from those from three studies that reported null associations (Beelen et al., 2014a; Lipfert et al., 2006; Pope et al., 2002), with these null findings attributed to several factors, including the relatively low person-time with underlying disease (hypertensive) in the study of US veterans (Lipfert et al., 2006), potential confounding by $PM_{2.5}$ in the Pope et al. (2002) study, and geographical differences for the European cohort followed in Beelen et al. (2014a).

Our findings showing consistent associations between increased long-term NO_2 exposures and CVD-related mortality are supported by results from Turner et al. (2016) and Krewski et al. (2009), in their extended follow-up of the US-based American Cancer Society (ACS) Cancer Prevention Study II (CPS-II), which reported significant NO_2-associated, increased

mortality risks for CVD (1.03/10 ppb; 95% CI, 1.01, 1.06) in models adjusting for $PM_{2.5}$ and numerous individual-specific socio-economic and behavioral factors. Similarly, our results are largely consistent with those from Crouse et al. (2015), who found significant associations between NO_2 exposure and CVD and IHD mortality in single- and multi-pollutant models using data from the Canadian Census Health and Environment Cohort (CanCHEC) (Crouse et al., 2015). The $PM_{2.5}$-adjusted effect estimates for CVD (1.04, 95% CI 1.03, 1.06) and IHD (1.05, 95% CI 1.03, 1.07) mortality from the CanCHEC study were lower than those from our study. These lower effect estimates may be due to study-specific differences in the urbanicity of participant residences, as suggested by our findings of lower NO_2-associated RRs in rural areas. Given the larger proportion of rural lands in Canada as compared to the U.S., it is possible that a larger fraction of CanCHEC participants lived in rural areas as compared to our study (Crouse et al., 2015). Consistent with this theory, Hart et al. (Hart et al., 2011) found an increased risk of CVD mortality associated with NO_2 among a cohort of U.S. truckers (13.8%, 95% CI 3.3%, 253% after exclusion of long-haul drivers), with risk levels similar to our study but higher than that found in CanCHEC. These risks, however, were not robust to adjustment for $PM_{2.5}$ nor were they significant for IHD mortality. In studies conducted outside of North America, NO_2-associated CVD mortality risks also varied substantially. Null findings, for example, were reported in Dutch (Brunekreef et al., 2009) and panEuropean studies (Beelen et al., 2014b), while small positive and significant RRs were found in a Rome (1.05; 95% CI, 1.04, 1.07) (Cesaroni et al., 2013) and second Dutch (1.04; 95% CI, 0.97, 1.13) (Beelen et al., 2008) study and larger estimates in German (1.89; 95% CI, 1.28, 2.78) (Schikowski et al., 2007) and Chinese (5.43; 95% CI, 4.79, 6.16) (Zhang et al., 2011) studies. Factors contributing to these observed differences may result from the relatively small numbers of death from CVD in these studies and from population and geographical differences.

For respiratory mortality, we found significant and positive associations with long-term NO_2 exposure, with associations attenuated but remaining statistically significant after adjustment for $PM_{2.5}$, as was found in the CanCHEC, two European studies (Cesaroni et al., 2013; Beelen et al., 2008), and a Japan study (Katanoda et al., 2011). Notably, we showed NO_2-associated respiratory mortality risks to vary by region, with associations in the Western US for all respiratory and COPD mortality significantly negative. These findings are consistent with those from a California teachers study by Lipsett (Lipsett et al., 2011), which also did not find a significantly positive NO_2-respiratory mortality association. Factors that contribute to this observed geographical heterogeneity are not known, but may reflect unmeasured confounding.

Nonetheless, we observed consistently strong, increased NO_2-associated risks for pneumonia mortality (1.275; 95% CI, 1.263, 1.287), an important contributor to respiratory mortality among older adults, with stable RRs across geographic regions irrespective of model construct. While no other study has examined the impact of NO_2 on pneumonia mortality, our findings are supported by toxicological studies, which showed that NO_2 increases susceptibility to bacterial pathogens by damaging epithelial cells and reducing mucociliary clearance, thus reducing bronchial macrophages, natural killer cells, macrophages, and CD4 to CD8 ratios (*Integrated Science Assessment for Oxides of Nitrogen–Health Criteria*, 2016). Consistent with this increased susceptibility, Neupane et

al. (Neupane et al., 2010) showed NO_2 exposures to be associated with more than a two-fold increased risk of hospitalization from community-acquired pneumonia (Neupane et al., 2010).

Of note, we found long-term NO_2 exposure to be significantly associated with decreased risk of accidental mortality, which in this analysis, we treated as a negative control (Pun et al., 2017) to allow us to assess the potential bias and validity in RRs for mortality from other causes. We were able to treat it as such given our assumption that accidental death was independent of NO_2 exposure. Given this assumption, our observed inverse associations between NO_2 exposure and accidental mortality suggest that RRs for other causes of deaths were underestimated. Alternatively or in addition, it is possible that our observed inverse association between NO_2 exposure and accidental death reflects unmeasured confounding, for example by traffic density (van Beeck et al., 1991), which has been associated with both increased NO_2 exposure (Rose et al., 2009; Lamsal et al., 2013) and decreased accidental death (van Beeck et al., 1991). Since traffic density and other potential confounding factors are likely unique to NO_2 and accidental mortality, they may not be relevant to other causes of death.

Several limitations of our study warrant consideration. First, we used the ambient, nearest monitor NO_2 concentrations instead of personal measurement data, which may underestimate the chronic health risks (Yanosky et al., 2014). Second, we did not have information on beneficiary-level socio-economic status, behaviors, and health history, which could contribute to exposure misclassification and unmeasured confounding as evidenced by our different “temporal” and “spatio-temporal” RRs. It is unlikely, however, that unmeasured confounding alone is responsible for our significant associations between NO_2 and increased mortality, given (1) results from earlier cohort studies which also showed significant, positive associations between NO_2 and mortality even after adjustment for numerous individual-specific covariates and (2) our finding of similar RRs from models with and without adjusting for behavioral covariates from BRFSS. Further, while differences in spatio-temporal and temporal RRs are consistent with unmeasured confounding, the magnitude of this difference may overestimate the extent of this unmeasured confounding, given disparate variability in temporal and spatio-temporal NO_2. Lastly, our study cohort of elderly populations (age 65+ years old) living near NO_2 monitors may limit the generalizability of our findings to those living further away from monitors or to individuals from younger age groups.

There are substantial strengths of our study. With over 14 million Medicare beneficiaries with 3.5 million deaths, our study had sufficient power to detect associations between NO_2 exposures and cause-specific mortality. Several measures were taken to ensure the validity of our findings, including but not limited to 1) estimation of baseline hazards that vary with individual-level age, gender, race, and area of residence, 2) adjustment for state of residence, $PM_{2.5}$, and behavioral risk factors, and 3) our generally consistent NO_2-associated RRs by U.S. region (except for COPD, all cancer and lung cancer). Moreover, the assessment of unmeasured confounding lends support to the validity of adverse effects of NO_2 exposure, given that both “temporal” and “spatio-temporal” NO_2 were positively and significantly

associated with all-cause mortality, and mortality from CVD-related causes, pneumonia, and cancer.

5. Conclusion

In a large U.S. elderly cohort, we observed consistent associations of long-term NO_2 exposure with increased all-causes, CVD and cancer mortality. We also found first evidence of adverse and significant association of NO_2 with pneumonia morality, though findings for respiratory mortality were inconsistent. Associations were strongest for participants living in non-rural areas. Evidence of confounding by $PM_{2.5}$, behavioral factors, and unmeasured covariates was noted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of monitors, $PM_{2.5}$ data, number of Medicare enrollees and of deaths by cause among Medicare enrollees (ages 65–120) from Dec 2000–2008.

	ICD-10 code	Median[a]	n (%)
Monitoring stations NO_2		$_{9.69}$ 14.23 $_{18.63}$	407
$PM_{2.5}$		$_{8.42}$ 10.83 $_{13.63}$	
Medicare enrollees		$_{7327}$ 25,685 $_{55,127}$	14.1 million
All-cause deaths		$_{1053}$ 5118 $_{11,949}$	3.5 million (100.0)
Non-accidental	A–R	$_{1019}$ 5000 $_{11,772}$	3.4 million (97.9)
Accidental	V–Y	$_{29}$ 115 $_{256}$	73,318 (2.1)
All cardiovascular	I00–I99	$_{396}$ 2024 $_{4783}$	1.4 million (41.3)
Ischemic heart disease	I20–I25	$_{201}$ 961 $_{2417}$	796,890 (23.0)
Cerebrovascular disease	I60–I69	$_{80}$ 374 $_{852}$	239,866 (6.9)
Congestive heart failure	I50	$_{30}$ 124 $_{318}$	88,902 (2.6)
All respiratory	J00–J99	$_{118}$ 541 $_{1292}$	365,369 (10.5)
COPD	J40–J44	$_{67}$ 287 $_{668}$	179,735(5.2)
Pneumonia	J12–J18	$_{30}$ 136 $_{353}$	112,863 (3.3)
All cancer	C–D	$_{236}$ 1164 $_{2674}$	767,432 (22.2)
Lung cancer	C34	$_{67}$ 323 $_{698}$	203,481 (5.9)

[a] Values are medians among locations and months, with 25th and 75th percentile given in smaller print.

Table 2

Mortality risk ratios (95% CI) associated with a 10 ppb increase in one-year moving average NO_2 exposure: by region and cause of death and adjusted for $PM_{2.5}$.

Cause of death and region	Main model[a]	$PM_{2.5}$ adjusted model[b]
All-cause		
US	1.052 (1.051, 1.054)	1.044 (1.042, 1.047)
West	1.023 (1.021, 1.026)	0.992 (0.987, 0.996)
Center	1.121 (1.114, 1.127)	1.125 (1.119, 1.132)
East	1.064 (1.061, 1.066)	1.040 (1.037, 1.044)
Accidental		
US	0.938 (0.926, 0.951)	0.947 (0.931, 0.963)
West	0.861 (0.843, 0.879)	0.872 (0.843, 0.902)
Center	1.014 (0.980, 1.048)	0.993 (0.958, 1.030)
East	0.978 (0.960, 0.997)	0.975 (0.953, 0.998)
Non-accidental		
US	1.055 (1.053, 1.057)	1.046 (1.044, 1.049)
West	1.027 (1.024, 1.029)	0.994 (0.990, 0.999)
Center	1.124 (1.118, 1.130)	1.129 (1.122, 1.136)
East	1.065 (1.063, 1.068)	1.042 (1.038, 1.045)
All cardiovascular		
US	1.133 (1.130, 1.137)	1.113 (1.109, 1.117)
West	1.103 (1.099, 1.108)	1.031 (1.024, 1.038)
Center	1.243 (1.232, 1.254)	1.250 (1.238, 1.263)
East	1.141 (1.136, 1.146)	1.108 (1.103, 1.114)
Ischemic heart disease		
US	1.221 (1.217, 1.226)	1.192 (1.187, 1.198)
West	1.211 (1.204, 1.217)	1.107 (1.097, 1.117)
Center	1.316 (1.299, 1.333)	1.321 (1.302, 1.339)
East	1.216 (1.209, 1.222)	1.189 (1.181, 1.196)
Cerebrovascular disease		
US	1.092 (1.085, 1.100)	1.054 (1.045, 1.064)
West	1.035 (1.025, 1.045)	0.973 (0.957, 0.988)
Center	1.248 (1.222, 1.275)	1.253 (1.224, 1.282)
East	1.124 (1.112, 1.137)	1.025 (1.012, 1.039)
Congestive heart failure		
US	0.903 (0.893, 0.914)	0.894 (0.880, 0.907)
West	0.871 (0.853, 0.888)	0.832 (0.807, 0.859)
Center	0.946 (0.914, 0.978)	0.967 (0.932, 1.003)
East	0.916 (0.901, 0.931)	0.892 (0.875, 0.910)
All respiratory		
US	1.050 (1.044, 1.056)	1.030 (1.023, 1.038)
West	1.021 (1.013, 1.030)	0.974 (0.961, 0.987)

Cause of death and region	Main model[a]	$PM_{2.5}$ adjusted model[b]
Center	1.068 (1.050, 1.086)	1.073 (1.053, 1.092)
East	1.077 (1.069, 1.086)	1.037 (1.026, 1.047)
COPD		
US	0.958 (0.950, 0.965)	0.914 (0.905, 0.924)
West	0.975 (0.964, 0.986)	0.907 (0.890, 0.924)
Center	1.030 (1.007, 1.053)	1.035 (1.010, 1.060)
East	0.915 (0.903, 0.927)	0.868 (0.855, 0.881)
Pneumonia		
US	1.275 (1.263, 1.287)	1.290 (1.274, 1.306)
West	1.219 (1.203, 1.235)	1.200 (1.174, 1.227)
Center	1.188 (1.147, 1.230)	1.184 (1.139, 1.230)
East	1.362 (1.343, 1.381)	1.345 (1.322, 1.369)
All cancer		
US	1.021 (1.017, 1.025)	1.016 (1.011, 1.022)
West	0.984 (0.978, 0.990)	0.973 (0.963, 0.982)
Center	1.090 (1.077, 1.103)	1.091 (1.077, 1.106)
East	1.039 (1.034, 1.045)	1.013 (1.006, 1.019)
Lung cancer		
US	0.983 (0.975, 0.990)	0.959 (0.950, 0.969)
West	0.952 (0.940, 0.963)	0.925 (0.907, 0.943)
Center	1.058 (1.034, 1.082)	1.050 (1.024, 1.076)
East	0.991 (0.981, 1.002)	0.946 (0.933, 0.958)

[a] Age, gender, and race-stratified and state-adjusted Poisson regression models.

[b] Additionally adjusted for $PM_{2.5}$ using two-stage models.

Table 3

Mortality risk ratios (95% CI) associated with a 10 ppb increase in long-term spatio-temporal and temporal NO_2 in $PM_{2.5}$-adjusted health models: by region and cause of death.

Cause of death and region	Spatio-temporal NO_2[a]	Temporal NO_2[a]
All-cause		
US	1.009 (1.001, 1.016)	2.019 (1.992, 2.047)
West	0.992 (0.979, 1.006)	2.370 (2.280, 2.464)
Center	1.035 (1.017, 1.053)	1.655 (1.615, 1.696)
East	0.992 (0.982, 1.002)	1.623 (1.598, 1.648)
Accidental		
US	0.917 (0.873, 0.964)	0.872 (0.795, 0.956)
West	0.984 (0.887, 1.092)	0.844 (0.635, 1.122)
Center	0.821 (0.742, 0.908)	0.665 (0.574, 0.771)
East	1.014 (0.944, 1.088)	0.903 (0.811, 1.006)
Non-accidental		
US	1.011 (1.003, 1.018)	2.056 (2.029, 2.085)
West	0.992 (0.979, 1.006)	2.417 (2.324, 2.514)
Center	1.042 (1.024, 1.060)	1.697 (1.656, 1.740)
East	0.992 (0.981, 1.002)	1.643 (1.618, 1.669)
All cardiovascular		
US	1.042 (1.031, 1.054)	4.034 (3.949, 4.121)
West	1.026 (1.006, 1.048)	3.663 (3.452, 3.887)
Center	1.171 (1.139, 1.205)	3.143 (3.022, 3.269)
East	0.988 (0.972, 1.004)	2.647 (2.583, 2.713)
Ischemic heart disease		
US	1.058 (1.042, 1.074)	5.628 (5.468, 5.793)
West	1.045 (1.018, 1.074)	4.908 (4.533, 5.313)
Center	1.197 (1.197, 1.246)	4.204 (3.975, 4.445)
East	1.007 (1.007, 1.028)	3.238 (3.134, 3.346)
Cerebrovascular disease		
US	1.046 (1.018, 1.075)	5.806 (5.508, 6.121)
West	1.075 (1.024, 1.129)	4.059 (3.541, 4.652)
Center	1.183 (1.108, 1.264)	3.640 (3.327, 3.982)
East	0.994 (0.955, 1.035)	3.436 (3.223, 3.663)
Congestive heart failure		
US	1.026 (0.980, 1.075)	1.231 (1.132, 1.339)
West	1.035 (0.941, 1.138)	2.101 (1.604, 2.751)
Center	1.180 (1.062, 1.311)	1.455 (1.269, 1.668)
East	0.863 (0.810, 0.919)	1.835 (1.746, 1.929)
All respiratory		
US	0.978 (0.957, 1.000)	2.619 (2.511, 2.731)
West	0.935 (0.899, 0.973)	4.661 (4.160, 5.222)

Cause of death and region	Spatio-temporal NO_2 [a]	Temporal NO_2 [a]
Center	1.031 (0.979, 1.085)	1.927 (1.790, 2.075)
East	0.973 (0.942, 1.005)	1.835 (1.746, 1.929)
COPD		
US	0.987 (0.957, 1.019)	1.582 (1.491, 1.679)
West	0.928 (0.878, 0.981)	3.373 (2.878, 3.952)
Center	1.018 (0.950, 1.090)	1.558 (1.409, 1.723)
East	1.020 (0.972, 1.070)	1.131 (1.053, 1.216)
Pneumonia		
US	0.960 (0.922, 0.999)	6.867 (6.161, 7.413)
West	0.953 (0.893, 1.017)	10.081 (8.312, 12.225)
Center	1.084 (0.973, 1.207)	3.807 (3.281, 4.417)
East	0.914 (0.861, 0.970)	3.933 (3.592, 4.306)
All cancer		
US	1.019 (1.003, 1.035)	1.596 (1.551, 1.642)
West	1.002 (0.973, 1.032)	1.412 (1.300, 1.534)
Center	1.044 (1.006, 1.083)	1.415 (1.343, 1.491)
East	0.999 (0.978, 1.021)	1.444 (1.397, 1.493)
Lung cancer		
US	1.033 (1.002, 1.064)	1.535 (1.451, 1.623)
West	1.003 (0.946, 1.063)	1.614 (1.371, 1.902)
Center	1.089 (1.014, 1.170)	1.426 (1.291, 1.575)
East	1.017 (0.975, 1.061)	1.330 (1.247, 1.418)

[a] Age, gender, and race-stratified and state-adjusted Poisson regression models; additionally adjusted for $PM_{2.5}$ using two-stage models.