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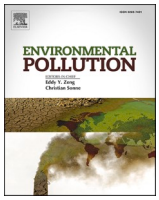

Short-term exposure to ambient nitrogen dioxide and fine particulate matter and cause-specific mortality: A causal modeling approach in four regions

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ABSTRACT

Ambient air pollution still represents a major health burden. While the link between short-term air pollution exposures and mortality has been well-documented globally, few studies have applied causal modeling approaches. Therefore, we aimed to quantify the relationship between day-to-day changes in ambient particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) levels and changes in daily natural, cardiovascular (including all-cardiovascular, cardiac, and stroke), as well as respiratory mortality rates using a causal modeling framework. Daily air pollution data and cause-specific death counts at the county, district, or municipality level from California (US), Jiangsu (China), Germany, and Lazio (Italy) were obtained for the years 2015–2019, including urban and rural populations. We used interactive fixed effects models to analyze the effects of air pollutants across different lag periods (0–2, 3–7, and 0–7 days after exposure) while accounting for both measured and unmeasured time-varying spatial unit-specific confounding factors. We observed increases in daily cardiovascular deaths (per 1 million people) per a 10 $\mu g/m^3$ increase in daily NO_2 at lag 0–7: 0.18 (95 % confidence interval: 0.02, 0.38) in California, 0.23 (0.14, 0.32) in Jiangsu, 0.48 (0.27, 0.70) in Germany, and −0.35 (−2.63, 1.92) in Lazio. For $PM_{2.5}$, the related increases in cardiovascular mortality rates were 0.00 (−0.18, 0.18) in California, 0.04 (0.00, 0.09) in Jiangsu, 0.22 (0.06, 0.37) in Germany, and 1.96 (0.76, 3.16) in Lazio. Additionally, associations were seen for natural, cardiac, stroke, and respiratory mortality, particularly pronounced among individuals aged 75 and older. These associations were strongest with prolonged exposures and remained consistent even in two-pollutant models. This study, using a causal modeling approach and including urban and rural populations, contributes to the growing body of evidence linking increases in short-term exposure to NO_2 and $PM_{2.5}$ with increased cause-specific mortality rates.

1. Introduction

Ambient air pollution is a major health risk, causing 4.5 million premature deaths annually globally (GBD 2019 Risk Factors Collaborators, 2020). The World Health Organization (WHO) rates short-term exposure to particulate matter (PM) with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) as causally linked to all-cause, cardiovascular, and respiratory mortality, while the effect of nitrogen dioxide (NO_2) on all-cause mortality is suggestive (WHO, 2021), but supported by recent systematic reviews confirming positive associations (Atkinson et al., 2014; Orellano et al., 2020; Wang et al., 2021).

Although initially affecting the respiratory system, air pollutants pose the highest attributable risk to the cardiovascular system (Brook et al., 2010), as shown in numerous epidemiological studies worldwide,

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even at low levels of exposure (Newby et al., 2015; Schwartz et al., 2017; Thurston et al., 2017). While the short-term effects of $PM_{2.5}$ on cardiovascular health are well established (Brook et al., 2010), the independent contribution of NO_2 is still widely debated (U.S. EPA, 2016).

Previous studies of the acute effects of NO_2 or $PM_{2.5}$ on cause-specific mortality have assessed metropolitan areas of the same country (Linares et al., 2018; Chen et al., 2019), multiple cities across the world (Liu et al., 2019; Meng et al., 2021), or single geographic regions (Stafoggia et al., 2020; Liu et al., 2021; Liu et al., 2022; Gariazzo et al., 2023). This focus might stem from a lack of air quality data in rural settings or sparse daily cause-specific mortality data with fine spatial resolution. However, epidemiological findings may lack generalizability because of potential disparities in population characteristics and source profiles of air pollutants in rural and urban areas, especially at very low concentrations (Gariazzo et al., 2023). Geographic differences in the association between NO_2 or $PM_{2.5}$ and cause-specific mortality emphasize the need for further research (Atkinson et al., 2014; Wang et al., 2021).

Most epidemiological studies have used time-series analyses to examine short-term effects (Atkinson et al., 2014; Orellano et al., 2020; Wang et al., 2021). However, these might be biased by unmeasured temporal confounding (Schwartz et al., 2017; Wei et al., 2020; Guo et al., 2023), suggesting that causal modeling approaches are needed.

The objective of the current study was to examine the association between daily changes in air pollution levels and day-to-day changes in cause-specific mortality rates in four different regions on three continents, including urban and rural populations: California, United States (US); Jiangsu Province, China (hereinafter Jiangsu); Germany; and Lazio Region, Italy (hereinafter Lazio). We used so-called interactive fixed effects (IFE) models (Ma et al., 2024) – a more flexible generalization of two-way fixed effects models – to investigate the association between short-term exposures to NO_2 and $PM_{2.5}$ and natural, all-cardiovascular, cardiac, stroke, as well as respiratory mortality rates. As a further objective, we explored potential variations in these effects based on sex, age, and urbanicity.

2. Methods

We used anonymized daily county-, district-, or municipality-level mortality records. This study received approval from the Yale Institutional Review Boards (IRB protocol ID: 2000029741) and adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (von Elm et al., 2007).

2.1. Mortality data

Daily cause-specific death counts by sex and age from 2015 to 2019 were collected in each spatial unit (county in California and Jiangsu; district in Germany; and municipality in Lazio) from national, state, or regional registries (eTable 1) based on each country's finest available administrative unit of mortality data. In Lazio, we limited our analysis to 79 (out of 378) municipalities, each with $\geq$10,000 population, to ensure an adequate number of deaths.

To define the mortality outcomes, we used both the 9th Revision (for Lazio, 2015–2018 only) and the 10th Revisions of the International Classification of Diseases. The outcomes include: Natural (i.e., non-accidental) (ICD-9: 1–799; ICD-10: A00-R99), cardiovascular (390–459; I00-I99), cardiac (390–429; I00-I52), cerebrovascular (430–438; I60-I69), and respiratory mortality (460–519; J00-J99). Using corresponding annual population size data (eTable 2), we computed daily cause-specific mortality rates at the spatial unit level for the entire population and population subgroups by sex (male and female) and age (0–74 and $\geq$ 75 years).

2.2. Environmental data

Daily mean concentrations of NO_2 and $PM_{2.5}$ were available from spatiotemporal models in 1 km $\times$ 1 km grid cells for Jiangsu (Huang et al., 2021; Huang et al., 2022), Germany (Flemming and Stern, 2004; Nordmann et al., 2020), and Lazio (Stafoggia et al., 2019; Stafoggia and Bellander, 2020), as well as data from air quality monitoring sites for California (U.S. EPA, 2020), including data from 32 (out of 58) counties with monitoring sites for both NO_2 and $PM_{2.5}$. For California, data from air quality monitoring sites were used since, at the time of our study, no high-resolution daily spatiotemporal data for NO_2 and $PM_{2.5}$ covering the whole of California were publicly available covering 2015 to 2019. For Jiangsu, Germany, and Lazio, we estimated daily mean pollutant concentrations in each spatial unit by calculating area-weighted averages within grids that intersected with respective spatial units. In California counties with multiple monitoring sites, average air pollution concentrations were calculated at the county level (eMethods 1).

We obtained hourly air temperature and dewpoint temperature data at a resolution of 0.1° $\times$ 0.1° (9 km $\times$ 9 km) from the ERA5-Land reanalysis dataset for all regions (Muñoz Sabater, 2019). Similar to the air pollution data, daily air temperature and dewpoint temperature averages and corresponding lags were computed for each spatial unit. Based on these data, we also calculated relative humidity and apparent temperature (eMethods 2).

2.3. Statistical analysis

We calculated descriptive statistics for air pollutants, air temperature, and cause-specific mortality rates. Spearman correlation coefficients were used to evaluate temporal variations.

Associations between air pollutants and cause-specific mortality were examined using a novel IFE model, a causal modeling approach. This model, detailed in Ma et al., controls for confounders varying across space (but not in time), for confounders varying across time (but not in space), and also for unmeasured time-varying spatial unit-specific confounders (Ma et al., 2024).

The outcome of our IFE model is the day-to-day difference in the spatial unit cause-specific mortality rate; the exposure is the day-to-day difference in the spatial unit average concentration of NO_2 or $PM_{2.5}$. The day-to-day change in air temperature on the same lag day as the air pollution variable is included as a natural cubic spline with five degrees of freedom (df). Day-to-day variations (i.e., first-order differences) were calculated to remove the long-term and seasonal trends of mortality rate, air pollution, and air temperature and to meet the stationarity and normality assumptions of the model. Further, the model includes a variable for time-invariant spatial unit effects and a variable for unmeasured time-varying spatial unit effects. More details on the IFE model are provided in the eMethods 3. The results of the IFE models are presented as expected changes in the day-to-day cause-specific mortality rate for each unit change in the daily air pollution level.

The short-term associations between changes in daily mortality rates and changes in exposure to air pollution were explored focusing on immediate (i.e., 0–2 days after exposure [lag0-2]), delayed [lag3-7], and prolonged [lag0-7] effects. In addition to single-pollutant models, we also conducted two-pollutant models, incorporating both NO_2 and $PM_{2.5}$ in the same model, to address possible mutual confounding and estimate independent effects. A univariate Cochran Q-test was performed to examine the heterogeneity of estimates across regions, and a random effects meta-analytical approach using restricted maximum likelihood (REML) was applied to calculate pooled estimates (Sera et al., 2019).

To identify potentially sensitive subpopulations, we examined effect modification by analyzing sex- (male and female) and age-stratified (0–74 years and $\geq$75 years) data. In addition, we performed stratified analyses to explore potential effect modification by urbanicity (urban and rural) as detailed in eTable 3. We cal culated z-scores to test whether there were significant differences in air pollutant effects between the groups (Ma et al., 2023).

We performed several sensitivity analyses to test the robustness of our results (e.g., different model parameters or confounding variables)

and also explored effects on cardiovascular mortality at each single lag day (eMethods 4).

All analyses were conducted using R software, version 4.1.3 (R Core Team, 2023). The IFE analyses were performed by applying the package *phtt* (Bada and Liebl, 2014).

A two-sided P-value <0.05 was considered statistically significant.

3. Results

3.1. Descriptive analysis

Overall, this analysis comprised 7,414,152 deaths from natural causes, including 2,904,720 and 721,325 deaths from cardiovascular and respiratory diseases, respectively, in California, Jiangsu, Germany, and Lazio from 2015 to 2019. Total numbers of cause-specific deaths by sex, age group, and urbanicity are presented in Table 1. Table 2 shows descriptive statistics of each region's daily cause-specific mortality rates, air pollution, and air temperature. The description of sex- and age-specific mortality rates are presented in eTable 4 and eTable 5. Descriptive statistics of mortality rates and environmental factors stratified by urbanicity are displayed in eTable 6. Fig. 1 illustrates the spatial distribution of NO_2 and $PM_{2.5}$ concentrations across the regions. The correlation among air pollutants and meteorological factors is displayed in eTable 7. There were no missing data in this study.

3.2. Association of air pollution with cause-specific mortality

The estimated associations between day-to-day changes in NO_2 and $PM_{2.5}$ levels and cause-specific mortality rates (per 1 million people) at different lags (0–2, 3–7, 0–7) from both single- and two-pollutant models are displayed in Fig. 2 and eTable 8. In single-pollutant models, increases in NO_2 or $PM_{2.5}$ were significantly associated with increased mortality rates across lags and different causes of death. Generally, estimates were strongest for natural mortality, showed considerably wider confidence intervals (CI) in Lazio than in the other three regions, and were most pronounced in prolonged lags (i.e., the 8-day average). Therefore, the estimates of lag0-7 were used as the main exposure in further analyses.

For example, we observed a relatively stable lag pattern across the four study regions for the effects of daily changes in air pollutants on daily changes in cardiovascular mortality rate. In single-pollutant models, the highest estimates were for lag0-7 for NO_2 in Germany (0.48 (95 % CI: 0.27, 0.70)) and $PM_{2.5}$ in Lazio (1.96 (95 % CI: 0.76, 3.16)). Cardiac mortality, as a subcategory of cardiovascular mortality, showed similar effect estimates and lag patterns, although the effects were commonly smaller. Changes in cerebrovascular mortality rates were more pronounced at the immediate lag0-2 and the prolonged lag0-7.

The lag pattern of the association between daily changes in air pollution and daily changes in respiratory mortality was inconsistent across study regions. It showed the highest effect estimates at lag0-7 for NO_2 in Germany (0.24 (95 % CI: 0.15, 0.34)) and $PM_{2.5}$ in Lazio (0.58 (95 % CI: 0.01, 1.15)).

The results from two-pollutant models were generally consistent with those from single-pollutant models, though the estimated coefficients for NO_2 in Lazio and $PM_{2.5}$ in Jiangsu were relatively smaller.

Table 1
Cause-specific deaths during the period 2015–2019 in the four study regions.

	Cause:	Natural	Cardiovascular	Cardiac	Cerebrovascular	Respiratory
California, US						
Total		1,055,977	373,760	293,788	68,222	103,837
Sex	Male	525,775	191,080	156,333	28,836	50,617
	Female	530,176	182,678	137,453	39,386	53,220
Age-group	0–74	391,830	113,870	92,794	16,712	30,012
	75+	664,077	259,869	200,977	51,507	73,817
Urbanicity	Urban	827,210	295,886	232,486	53,901	79,688
	Rural	228,767	77,874	61,302	14,321	24,149
Jiangsu, China						
Total		2,425,063	993,171	412,991	574,564	320,520
Sex	Male	1,327,688	497,304	201,556	292,371	178,480
	Female	1,097,336	495,843	211,424	282,180	142,036
Age-group	0–74	930,036	290,190	117,456	170,210	66,398
	75+	1,494,919	702,981	295,535	404,354	254,116
Urbanicity	Urban	1,192,833	467,781	191,700	273,087	142,288
	Rural	1,232,230	525,390	221,291	301,477	178,232
Germany						
Total		3,712,220	1,455,883	1,172,858	220,813	278,713
Sex	Male	1,764,397	636,519	518,366	89,771	146,269
	Female	1,947,823	819,364	654,492	131,042	132,444
Age-group	0–74	995,525	239,678	191,405	33,818	71,685
	75+	2,716,695	1,216,205	981,453	186,995	207,028
Urbanicity	Urban	2,472,450	922,206	735,300	145,373	189,989
	Rural	1,239,770	533,677	437,558	75,440	88,724
Lazio, Italy						
Total		220,892	81,906	61,959	16,922	18,255
Sex	Male	104,444	35,874	27,515	6,745	8,881
	Female	116,448	46,032	34,444	10,177	9,374
Age-group	0–74	55,945	13,317	10,167	2,327	2,624
	75+	164,947	68,589	51,792	14,595	15,631
Urbanicity	Urban	137,468	50,184	38,215	10,117	11,449
	Rural	83,424	31,722	23,744	6,805	6,806
All regions						
Total		7,414,152	2,904,720	1,941,596	880,521	721,325
Sex	Male	3,722,304	1,360,777	903,770	417,723	384,247
	Female	3,691,783	1,543,917	1,037,813	462,785	337,074
Age-group	0–74	2,373,336	657,055	411,822	223,067	170,719
	75+	5,040,638	2,247,644	1,529,757	657,451	550,592
Urbanicity	Urban	4,629,961	1,736,057	1,197,701	482,478	423,414
	Rural	2,784,191	1,168,663	743,895	398,043	297,911

Table 2
Daily county-/district-/municipality-level cause-specific mortality rates and environmental data, 2015–2019, in the four study regions.

	Mean (SD)	25th Percentile	Median (IQR)	75th Percentile
California, US (32 counties, total population 37,290,255, total area 247,411 km²)[a]				
Cause-specific mortality rate (per 1 million people)				
Natural	15.6 (7.2)	11.5	15.1 (7.6)	19.1
Cardiovascular	5.3 (3.9)	2.8	5.1 (4.2)	7.1
Cardiac	4.1 (3.4)	2.0	3.9 (3.6)	5.7
Cerebrovascular	1.0 (1.7)	0.0	0.0 (1.4)	1.4
Respiratory	1.6 (2.1)	0.0	1.1 (2.3)	2.3
Environmental factors				
NO_2 (μg/m³)	15.7 (11.4)	7.5	12.8 (13.6)	21.1
Urban	19.6 (13.1)	9.5	16.3 (16.9)	26.4
Rural	12.7 (8.9)	6.2	10.8 (10.9)	17.1
$PM_{2.5}$ (μg/m³)	9.9 (9.2)	5.3	8.0 (6.4)	11.7
Urban	9.3 (7.6)	5.4	8.0 (6.0)	11.4
Rural	10.4 (10.3)	5.3	8.1 (6.8)	12.1
Air temperature (°C)	16.3 (7.0)	11.2	15.7 (10.1)	21.2
Jiangsu, China (82 counties, total population 77,955,026, total area 102,010 km²)				
Cause-specific mortality rate (per 1 million people)				
Natural	17.2 (6.9)	12.4	16.4 (8.7)	21.1
Cardiovascular	6.9 (3.9)	4.2	6.4 (4.8)	9.0
Cardiac	2.8 (2.3)	1.2	2.5 (2.8)	4.0
Cerebrovascular	4.0 (2.7)	2.1	3.7 (3.4)	5.5
Respiratory	2.2 (2.2)	0.5	1.8 (2.9)	3.3
Environmental factors				
NO_2 (μg/m³)	32.2 (12.8)	23.1	29.8 (15.1)	38.2
Urban	36.2 (14.3)	26.0	33.2 (17.1)	43.1
Rural	28.2 (9.4)	21.1	26.7 (12.7)	33.8
$PM_{2.5}$ (μg/m³)	50.8 (27.8)	31.0	44.0 (31.8)	62.8
Urban	49.6 (28.0)	29.9	42.8 (31.7)	61.6
Rural	52.0 (27.5)	32.0	45.3 (32.0)	64.0
Air temperature (°C)	16.1 (9.1)	8.0	17.1 (15.7)	23.8
Germany (401 districts, total population 82,735,005, total area 357,672 km²)				
Cause-specific mortality rate (per 1 million people)				
Natural	25.0 (15.4)	14.8	23.3 (18.2)	33.0
Cardiovascular	10.2 (9.6)	2.2	8.6 (12.7)	15.0
Cardiac	8.3 (8.6)	0.0	7.0 (12.3)	12.3
Cerebrovascular	1.5 (3.5)	0.0	0.0 (0.0)	0.0
Respiratory	1.9 (4.0)	0.0	0.0 (2.1)	2.1
Environmental factors				
NO_2 (μg/m³)	12.2 (7.8)	6.7	10.1 (8.8)	15.5
Urban	15.0 (8.9)	8.5	12.7 (10.8)	19.3
Rural	9.5 (5.4)	5.7	8.2 (6.3)	12.0
$PM_{2.5}$ (μg/m³)	10.0 (7.0)	5.5	8.2 (6.8)	12.3
Urban	10.2 (7.1)	5.7	8.5 (6.9)	12.6
Rural	9.8 (7.0)	5.3	8.0 (6.7)	12.1
Air temperature (°C)	10.2 (7.4)	4.3	10.0 (11.9)	16.2
Lazio, Italy (79 municipalities, total population 5,104,384, total area 7268 km²)[b]				
Cause-specific mortality rate (per 1 million people)				
Natural	22.4 (34.1)	0.0	0.0 (40.2)	40.2
Cardiovascular	8.7 (21.3)	0.0	0.0 (0.0)	0.0
Cardiac	6.5 (18.4)	0.0	0.0 (0.0)	0.0
Cerebrovascular	1.9 (9.8)	0.0	0.0 (0.0)	0.0
Respiratory	1.8 (9.4)	0.0	0.0 (0.0)	0.0
Environmental factors				
NO_2 (μg/m³)	13.2 (6.3)	8.7	11.6 (7.5)	16.2
Urban	16.4 (7.1)	10.9	14.7 (9.5)	20.3
Rural	13.1 (6.2)	8.7	11.5 (7.4)	16.1
$PM_{2.5}$ (μg/m³)	13.3 (6.7)	9.2	11.8 (5.9)	15.0
Urban	13.3 (5.6)	9.7	12.1 (5.4)	15.2
Rural	13.3 (6.7)	9.1	11.7 (5.9)	15.0
Air temperature (°C)	15.3 (6.9)	10.1	14.9 (10.8)	20.9

IQR: Interquartile range; NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤2.5 μm; SD: Standard deviation.

[a] In California, only 32 (out of 58) counties with EPA air quality monitoring stations were included in the analysis.

[b] In Lazio, we only included 79 (out of 378) municipalities with a population ≥10,000.

We observed considerable heterogeneity of estimates across regions ranging from $I^2 = 0.00$ % to $I^2 = 90.54$ % (eTable 9). Therefore, pooled estimates should be interpreted with caution for some models (eTable 10).

3.3. Effect modification by sex, age, and urbanicity

We used lag0-7 to examine potential effect modifications by sex, age, and urbanicity. In subgroup analyses by sex, no consistent trend across study regions was observed, with few significant differences in effect estimates between males and females (Fig. 3 and eTable 11).

The results of the analyses by age group clearly showed stronger effects among people ≥75 years for NO_2 and $PM_{2.5}$, respectively, across all study regions (Fig. 3 and eTable 12). For example, in a single-pollutant model for Germany, the estimated change in the daily cardiovascular mortality rate (per 1 million people) in older people was 2.93 (95 % CI 1.24, 4.62) and 1.84 (95 % CI: 0.62, 3.06) per 10 μg/m³ increases in NO_2 and $PM_{2.5}$, respectively, but only 0.17 (95 % CI 0.08, 0.27) and 0.00 (95 % CI: 0.07, 0.07) in the younger age group. In both single- and two-pollutant models, apart from Lazio, the effect modification by age was more pronounced for NO_2 than for $PM_{2.5}$. Consistent significant effect modification was observed for NO_2 for natural, cardiovascular, cerebrovascular, and respiratory mortality in Jiangsu and Germany, and for $PM_{2.5}$ for natural and cardiovascular mortality in Germany and Lazio.

In stratified analyses by urbanicity, we found no consistent patterns of effect modification between urban and rural areas (Fig. 3 and eTable 13).

3.4. Sensitivity analyses

The results of the sensitivity analyses for cardiovascular mortality are displayed in eFig. 1 and summarized for all mortality outcomes in eTable 14. Our results remained robust in single-pollutant models when changing several model parameters or adjusting for additional variables. In two-pollutant models, the results were robust after restricting the analysis to counties or municipalities with a Spearman correlation coefficient smaller than 0.6 between the two pollutants. The effects of NO_2 and $PM_{2.5}$ on cardiovascular mortality at every single lag (0–7) from both single- and two-pollutant models are presented in eTable 15.

4. Discussion

In this observational study, we used the IFE model to estimate the short-term associations between daily changes in NO_2 or $PM_{2.5}$ and changes in daily cause-specific mortality rates for California, Jiangsu, Germany, and Lazio between 2015 and 2019. We found significant associations between increases in each air pollutant and cause-specific mortality rates across all study regions. Associations were most consistent for natural and cardiovascular mortality, showing pronounced prolonged effects (i.e., lag0-7). The estimated effects were comparable for men and women and urban and rural areas but larger for older people. Our results remained robust in two-pollutant models.

Our findings are generally consistent with the previous literature. For example, in studies of the Multi-Country Multi-City (MCC) Collaborative Research Network, a 10 μg/m³ increase in NO_2 concentration at lag1 was associated with a 0.46 %, 0.37 %, and 0.47 % increase in all-cause, cardiovascular, and respiratory mortality, respectively (Meng et al., 2021). For $PM_{2.5}$, a 10 μg/m³ increase in the two-day average

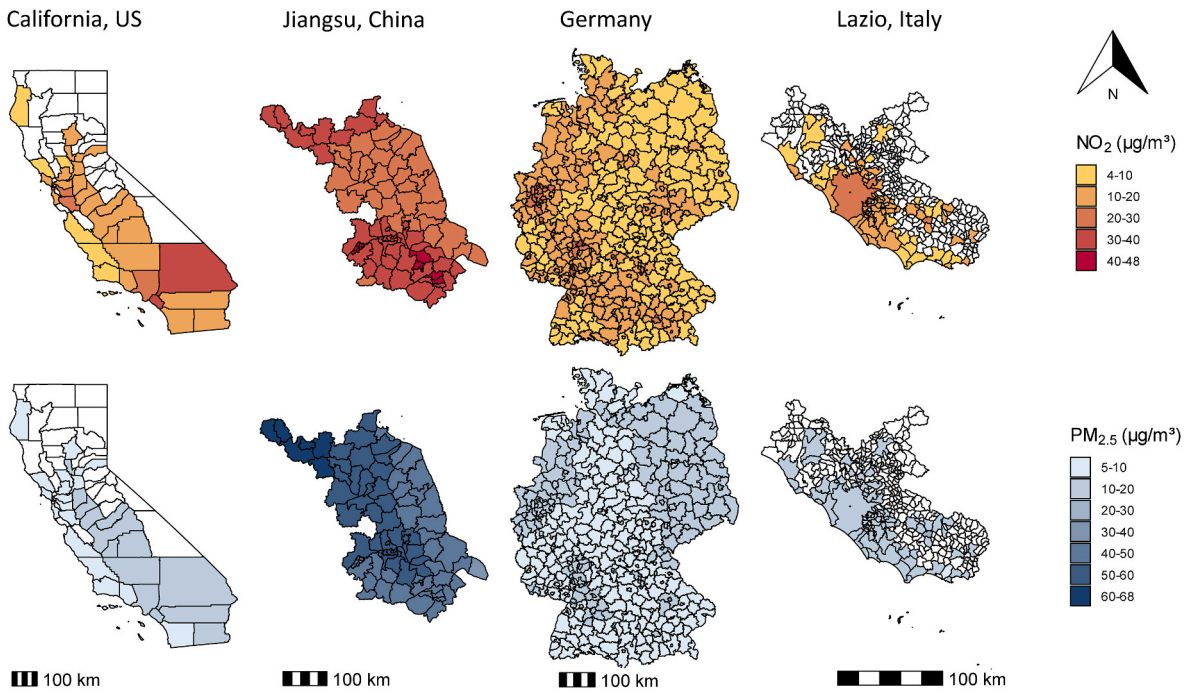

Fig. 1. Daily mean NO_2 and $PM_{2.5}$ concentrations in each spatial unit.
These maps display the daily average NO_2 and $PM_{2.5}$ concentrations in each county, district or municipality in California, US; Jiangsu, China; Germany; and Lazio, Italy (2015–2019). The white areas in California are counties that lacked air quality monitoring stations for both NO_2 and PM_2.; the white areas in Lazio represent municipalities with a population of less than 10,000.
NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\leq$2.5 μm.

(lag0-1) was associated with an increase of 0.44 %, 0.36 %, and 0.47 % (Liu et al., 2019). Our study's estimates cannot be directly compared to those from time-series or case-crossover studies due to differing interpretations of model coefficients. However, Ma et al. found similar results when comparing the IFE model to a traditional time-series model using the same data. Their findings indicate that short-term exposure to NO_2 or $PM_{2.5}$ was linked to increased all-cause mortality (Ma et al., 2024). This consistency between approaches lends further support to a (causal) relationship between short-term exposure to NO_2 and $PM_{2.5}$ and mortality from specific causes.

Consistent with previous studies on specific cardiovascular outcomes, we found positive associations with cardiac and cerebrovascular mortality for NO_2 and $PM_{2.5}$. For example, a Chinese study found that each 10 μg/m^3 increase in exposure to NO_2 and $PM_{2.5}$ was significantly associated with a 1.46 % and 4.14 % increase in odds of myocardial infarction mortality (Liu et al., 2021). In two-pollutant models, mutually adjusting for NO_2 and $PM_{2.5}$, a Swiss study found a strong association between the eight-day average (lag0-7) of NO_2 and stroke mortality (odds ratio (OR): 1.13, per 10 μg/m^3 increase in NO_2), particularly pronounced in ischemic (OR: 1.55) compared to hemorrhagic (OR: 1.03) stroke outcomes (Saucy et al., 2021). No association was found for $PM_{2.5}$. Chiusolo et al. reported positive associations between short-term NO_2 and cardiac and stroke mortality at lag0-5 for ten Italian cities (Chiusolo et al., 2011). However, a nationwide Italian study could not confirm these associations for NO_2 but identified a positive association between $PM_{2.5}$ and cardiac mortality (Gariazzo et al., 2023). While the association of $PM_{2.5}$ with cardiovascular mortality has been classified as causal by the WHO (WHO, 2021), the current evidence on the causal relationship between short-term NO_2 exposure and cardiovascular effects is limited due to insufficient studies (Orellano et al., 2020) and the remaining uncertainty about the independent effects of NO_2 on health (Mills et al., 2016; Forastiere and Peters, 2021; Saucy et al., 2021).

There has been a long discussion on whether NO_2 is a surrogate of other air pollutants, particularly $PM_{2.5}$, that can be co-emitted from the same sources (Brunekreef et al., 2021; Forastiere and Peters, 2021), and whether exposure to NO_2 independently causes adverse health effects (Mills et al., 2016; Forastiere and Peters, 2021; Saucy et al., 2021). Although statistically adjusting the NO_2 association for $PM_{2.5}$ cannot conclusively show an independent effect, gathering evidence might enhance our comprehension of the relationship (Stafoggia et al., 2017). In our study, associations between NO_2 and cause-specific mortality outcomes were generally robust to adjustment for $PM_{2.5}$ and, therefore, add to the supporting evidence for independent effects of short-term exposure to NO_2 on mortality (Mills et al., 2016).

To date, strong evidence exists regarding the respiratory effects of short-term exposure to NO_2, e.g., indicating that inhaling NO_2 can induce allergic inflammation, airway responsiveness, and oxidative stress, thereby triggering asthma attacks (U.S. EPA, 2016). However, the biological pathways underlying the extrapulmonary effects of NO_2 are not yet well understood, and the evidence does not distinctly describe independent NO_2 effects on biological processes leading to mortality (U.S. EPA, 2016; Forastiere and Peters, 2021). For cardiovascular effects, findings from experimental studies indicate changes in heart rate variability, increases in markers of inflammation and oxidative stress, and thrombin generation in plasma of humans and heart tissue of rats as potential nonspecific effects leading to myocardial infarction (Huang et al., 2012; Strak et al., 2013; U.S. EPA, 2016).

Three main pathways are hypothesized for how PM can exert effects on the cardiovascular system (Brook et al., 2010; Rückerl et al., 2011): 1) particles in the lung can induce subclinical systemic reactions such as the release of pro-inflammatory and pro-oxidative mediators leading to several local and systemic inflammatory processes, promoting endothelial dysfunction, a pro-coagulation state, and triggering atherosclerotic plaque; 2) particles settling within the pulmonary tree can directly stimulate neuronal reflexes, causing alterations in pulmonary and cardiac autonomic regulation. These changes in autonomic tone are often the most immediate reaction to the inhalation of air pollution and involve multiple reflex arcs; 3) after exposure, PM (i.e., ultrafine

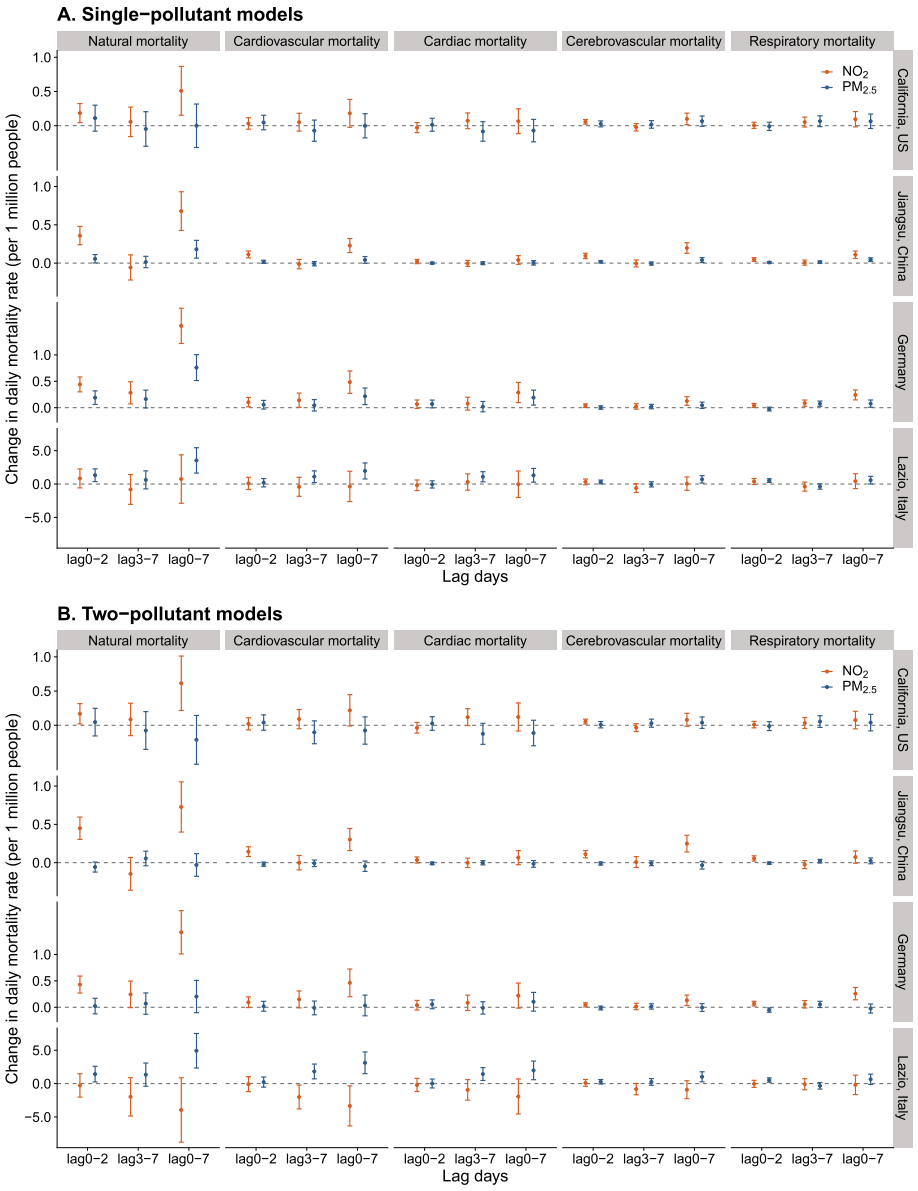

Fig. 2. Estimated change in daily cause-specific mortality rate (per 1 million people) associated with a 10 μg/m^3 increase in NO_2 or $PM_{2.5}$ concentration.
This figure shows the estimated change in daily cause-specific mortality rate (per 1 million people) per 10 μg/m^3 increase in NO_2 or $PM_{2.5}$ concentration from single-pollutant models (A) and two-pollutant models (B) on different lag days in Jiangsu, China; California, US; Germany; and Lazio, Italy (2015–2019). The error bars represent the 95 % confidence intervals. Due to the large differences in the magnitude of the confidence intervals, the y-axis for Lazio shows a different range to ensure readability.
Abbreviations as in Fig. 1.

particles) or particle constituents may quickly pass from the pulmonary epithelium into the circulation and interact directly with the cardiovascular system. These small particles may impact the vascular endothelium and atherosclerotic plaques and contribute to oxidative stress and local inflammation.

Our study highlighted elevated effect estimates at prolonged lags (lag0-7) observed across all studied cause-specific outcomes and study regions. Comparable lag patterns were observed in prior studies (Chiusolo et al., 2011; Saucy et al., 2021; Gariazzo et al., 2023), suggesting that increases in air pollution over several days might have particularly adverse impacts on mortality.

Higher risk estimates among older people have been reported previously (Liu et al., 2022; Gariazzo et al., 2023), which we confirmed in our study. These results reflect both the higher mortality rate and the increased susceptibility to short-term air pollution exposure among older people, probably due to reduced compensatory processes and a higher prevalence of comorbidities in the older population (Shumake et al., 2013).

Previous studies on the acute effects of air pollution on cause-specific mortality primarily focused on metropolitan areas (Linares et al., 2018; Liu et al., 2019; Meng et al., 2021). Our analyses encompassed both urban and rural areas, which is crucial as a substantial share of the population in our study regions resided in non-urban environments which may differ in their emission sources and pollutant concentrations. Recent studies conducted in Sweden (Stafoggia et al., 2020), Italy (Renzi et al., 2022), and the US (Kloog et al., 2014; Bravo et al., 2017) have provided evidence of harmful short-term effects of air pollution in rural and less urbanized areas. Corroborating prior findings, we showed that effect estimates from urban areas barely differed from those of rural areas, even though NO_2 concentrations in urban areas were considerably higher than in rural ones. Lacking data on particle composition, we can only speculate that the composition and potentially differential toxicity

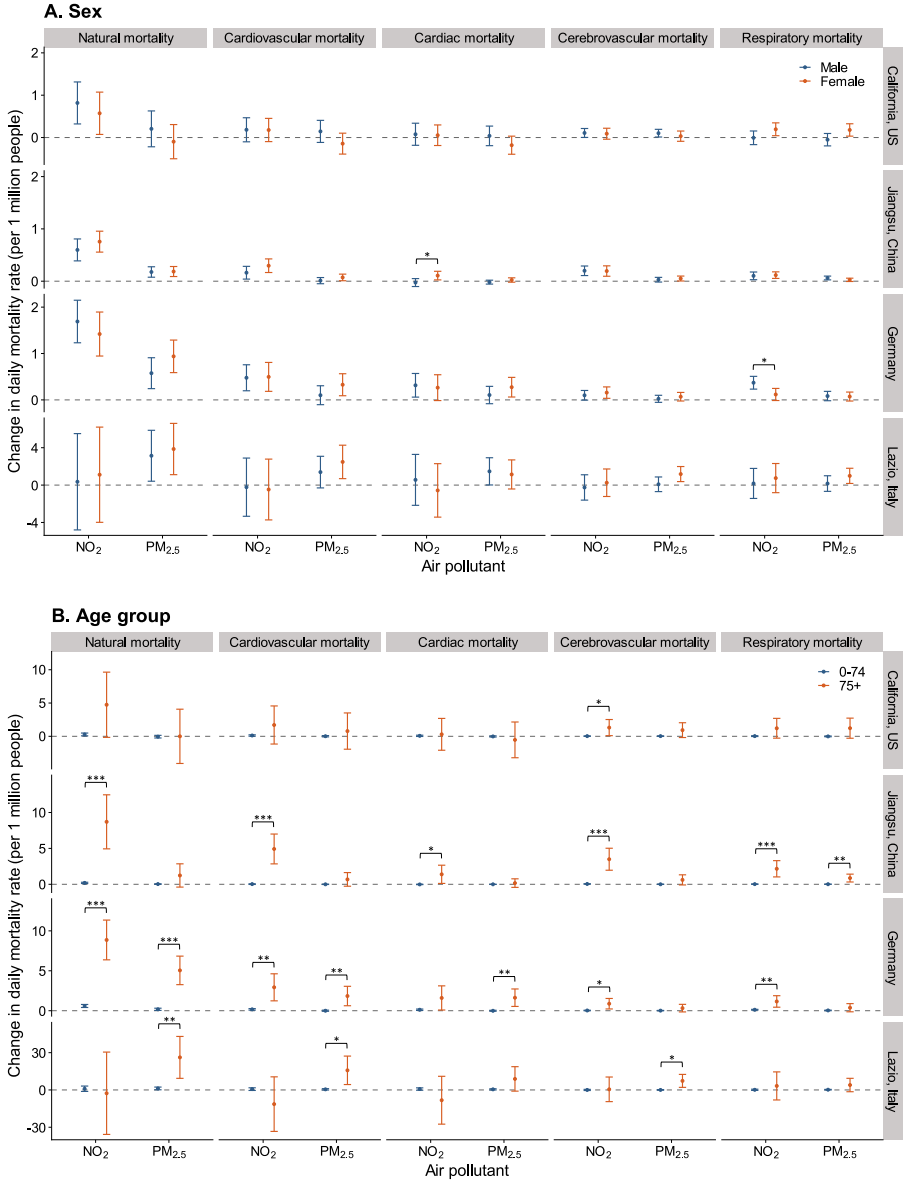

Fig. 3. Estimated change in daily cause-specific mortality rate (per 1 million people) associated with a 10 μg/m^3 increase in NO_2 or $PM_{2.5}$ concentration by effect modification.

This figure shows the estimated change in daily cause-specific mortality rate (per 1 million people) per 10 μg/m^3 increase in NO_2 or $PM_{2.5}$ concentration by sex (male, female) (A), by age group (0–74, ≥75 years) (B), and urbanicity (urban, rural areas) (C) from single-pollutant models on lag0-7 in Jiangsu, China; California, US; Germany; and Lazio, Italy (2015–2019). The error bars represent the 95 % confidence intervals. Due to the large differences in the magnitude of the confidence intervals, the y-axis for Lazio shows a different range to ensure readability. We tested the statistical differences in effect estimates between groups based on the z score calculated using the coefficients and standard errors for different groups. Significant differences are marked as follows:
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
Abbreviations as in Fig. 1.

of the particles (Kloog et al., 2014) have a different impact on the short-term association between air pollution and cause-specific mortality in urban and rural settings.

In Jiangsu, a region with high air pollution concentrations, we found that changes in daily $PM_{2.5}$ were accompanied by weaker associations with daily changes in mortality rate compared to Germany and Lazio, which have lower levels of air pollution. This finding has been reported in previous studies (Peters et al., 2000; Chen et al., 2012; Chen et al., 2017; Liu et al., 2019). It is hypothesized that in regions with higher long-term exposure to $PM_{2.5}$, populations may exhibit adaptive responses that could result in smaller estimate-per-unit changes in exposure (Peters et al., 2000; Liu et al., 2019).

This comprehensive multi-country study had several strengths, including applying standardized approaches to data collection and analyses in multiple locations. The availability of national, state, or regional cause-specific mortality data matched with highly resolved spatiotemporal exposure models (monitoring sites in California) allowed us to study large portions of the population in the four regions, providing estimates of associations for both urban and rural areas, the latter often neglected in former epidemiological studies. The large sample size and resulting statistical power enabled us to investigate cardiac and cerebrovascular deaths. Applying the novel IFE model allowed us to provide robust support for a causal association between short-term exposure to NO_2 and $PM_{2.5}$ and cause-specific mortality.

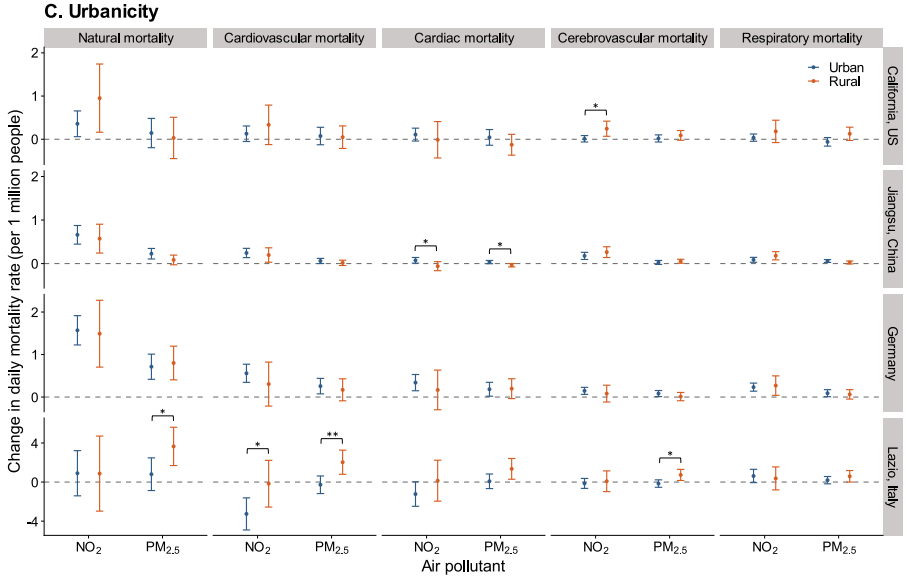

Fig. 3. (*continued*).

We acknowledge several limitations of this study. First, performing multiple analyses, we cannot rule out that some of our results are observed due to chance. Second, using air pollution data aggregated on a spatial unit level, this study could not account for variations within individual units. Despite high-quality air pollution models, the exposure estimates were subject to uncertainty. In California, only including counties with air quality monitoring stations did not allow us to attain full spatial coverage. Moreover, in California counties with multiple monitoring sites, average air pollution concentrations were calculated at the county level. However, no further spatial interpolation was conducted. Third, we acknowledge the occurrence of misclassification of cause of death statements on death certificates, which could bias our results. Fourth, due to data protection regulations, we were only able to analyze two age groups (0–74 years and ≥75 years), even though it might have been informative to examine more granular age groups in the 0–74 years range, especially children and adolescents, who are still developing and may be particularly vulnerable to the effects of poor air quality. Last, including four regions from three continents, we observed spatial heterogeneity in the association between short-term changes in air pollution and daily mortality rates across regions, which might be due to different PM components, long-term air pollution levels, regional climate, and population characteristics affecting susceptibility.

5. Conclusion

This study, using a causal modeling approach and including urban and rural populations, found that increased short-term NO_2 and $PM_{2.5}$ exposures were associated with increased mortality rates due to natural, cardiovascular, cardiac, cerebrovascular, and respiratory causes. The associations were particularly pronounced among individuals aged 75 and older and with prolonged exposures and remained consistent even in two-pollutant models. These findings emphasize the need of further improving ambient air pollution levels to yield greater public health benefits.

CRediT authorship contribution statement

Anne Marb: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Yiqun Ma:** Writing – review & editing, Visualization, Validation, Investigation, Formal analysis, Data curation. **Federica Nobile:** Writing – review & editing, Visualization, Validation, Investigation, Formal analysis, Data curation. **Robert Dubrow:** Writing – review & editing, Methodology, Investigation. **Patrick L. Kinney:** Writing – review & editing, Methodology, Investigation. **Massimo Stafoggia:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Kai Chen:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Annette Peters:** Writing – review & editing, Supervision, Methodology. **Susanne Breitner:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Anne Marb reports financial support was provided by Health Effects Institute and by Deutsche Forschungsgemeinschaft. Yiqun Ma, Federica Nobile, Robert Dubrow, Kai Chen, and Susanne Breitner report financial support support was provided by Health Effects Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2025.126059.

Data availability statement

The modeled air pollution data in Jiangsu (China), Germany, and Lazio (Italy) are available upon request, the station-based air pollution data in California (US) are publicly available on the US EPA website (https://www.epa.gov/outdoor-air-quality-data). The cause-specific mortality data in all four regions are confidential.

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