Short Term Exposure to Air Pollution and Mortality in the US: A Case-Crossover Analysis

Rongqi Liu (rliu@hsph.harvard.edu)  
Harvard T H Chan School of Public Health  https://orcid.org/0000-0002-0601-2032

Yaguang Wei  
Harvard T H Chan School of Public Health

Xinye Qiu  
Harvard T H Chan School of Public Health

Anna Kosheleva  
Harvard T H Chan School of Public Health

Joel D. Schwartz  
Harvard T H Chan School of Public Health

Research

Keywords: air pollutant, particulate matter, ozone, nitrogen dioxide, mortality

Posted Date: December 22nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1138337/v1

License: ©  This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background: Studies examining the association of short-term air pollution exposure and daily deaths have typically been limited to cities and used citywide averages for exposure. This study aims to estimate the associations between short-term exposures to fine particulate matter (PM$_{2.5}$), ozone (O$_3$), and nitrogen dioxide (NO$_2$) and all-cause and cause-specific mortality in multiple US states including rural areas.

Methods: We conducted a time-stratified case-crossover study examining the entire population of seven US states from 2000-2015, with over 3 million non-accidental deaths. Daily predictions of PM$_{2.5}$, O$_3$, and NO$_2$ at 1x1 km grid cells across the contiguous US were linked to mortality based on census track and residential address. For each pollutant, we used conditional logistic regression to quantify the association between exposure and the relative risk of mortality conditioning on meteorological variables and other pollutants.

Results: A 10 $\mu$g/m$^3$ increase in PM$_{2.5}$ exposure at the moving average of lag 0-1 day and 10 ppb increase in NO$_2$ exposure at lag 0-3 day were significantly associated with a 0.67% (95%CI: 0.34-1.01%) and 0.20% (95%CI: 0.00-0.39%) increase in the risk of all-cause mortality, respectively. A marginally significant association for mortality was observed with each 10 ppb increase in O$_3$ exposure at lag 0-3 day. The adverse effects of PM$_{2.5}$ on all-cause mortality persisted when restricting the analysis at lower levels. PM$_{2.5}$ was also significantly associated with respiratory mortality and cardiovascular mortality.

Conclusions: Short-term exposure to PM$_{2.5}$ and NO$_2$ is associated with increased risks for all-cause mortality. Our findings delivered evidence that risks of death persisted at levels below currently permissible.

Introduction

Globally, the burden of death attributable to fine particulate matter (PM$_{2.5}$) is estimated to be more than 4 million annually, representing 7.6% of total global deaths [1, 2]. Short-term exposure to PM$_{2.5}$ is associated with mortality from all-causes [3–5], stroke [6], asthma [7, 8], and chronic obstructive pulmonary disease [9–11]. Exposure to O$_3$ and NO$_2$ has also been linked to chronic respiratory diseases, impaired lung function, and all-cause mortality [12–16].

However, previous studies of the acute effect of PM$_{2.5}$ have been restricted to well-monitored metropolitan areas where the population is large enough to power the studies [17, 18]. Many time-series which examined the acute effect of O$_3$ and NO$_2$ on daily deaths had the same limitations [14, 15, 19]. Hence the effects in rural areas and unmonitored areas have been under-examined. In addition, these time-series studies assigned the same exposure to everyone in the same city, entailing limited spatial resolution and considerable exposure error. Fewer studies have examined all three of these pollutants together, with only one using causal modeling methods [20], and studies below the World Health Organization Air Quality Guidelines (WHO AQG) are less common.

In this study, we aimed to study the entire population of all ages in seven US states, use census tract or finer exposure data, and examine the lag structure between short-term air pollution exposure and all-cause and cause-specific mortality using a time-stratified case-crossover design. The study population covered states in the Midwest and Northeast areas between 2000 and 2015, with over 3 million deaths. We have also implemented several causal methods, specifically negative exposure controls, negative outcome controls, and propensity scores to provide more evidence for the causality of any associations.

Methods

Study Population

This study used non-accidental mortality data across seven states of the US: Georgia, Indiana, Kansas, Massachusetts, Michigan, New Jersey, and Ohio. Death certificate data were obtained from each state’s department of health and included date of death, age, sex, race, education, marital status, the cause of death, and either the census tract number or the latitude and longitude of the residential address at the date of death. The study outcomes were all-cause and cause-specific mortality due to cardiovascular disease (ICD-10: I00 to I99) and respiratory disease (ICD-10: J00 to J99).
Air pollution exposures and meteorological covariates

Daily concentrations of PM$_{2.5}$, O$_3$, and NO$_2$ at 1 km x 1 km grid cells in the contiguous US were predicted using a well-validated hybrid prediction model that incorporates satellite remote sensing, chemical transport models, meteorological variables, and land-use terms, with out-of-sample predicted $R^2$ of 0.86, 0.90, and 0.79 respectively [21, 22]. With this model, predictions were generated across the entire contiguous US, including locations with no monitoring sites. Temperature and absolute humidity were retrieved from Phase 2 of the North American Land Data Assimilation System, and daily mean values were determined for each 12 km x 12 km grid across the continental United States [23]. These air pollution and meteorological estimations were linked to each individual according to the residential address and the date of death.

Study Design

We utilized a case-crossover design with "case day" defined as the date of death, and "control day" defined as the same day of the week within the same month and year where death did not occur. "Control day" was chosen bidirectional time stratified (i.e. both before and after the case day, but in the same month) to control for confounding by time trend [23]. For each individual, we compared daily air pollution exposure on the case day to control days. By virtue of the study design, individuals serve as their own controls and any subject-level covariates that remain constant on case and control days (i.e., age, gender, race, socioeconomic status, comorbidities, smoking history, cholesterol levels, obesity, etc.), as well as any seasonal and sub-seasonal patterns, are controlled for by design.

Statistical Analysis

We used conditional logistic regression models to assess the associations between acute air pollutant exposures and mortality. For each case day, single-day lag exposures (lag 0 to lag 3) for each pollutant were examined to select the most robust lag pattern. Temperature was included as same day temperature, a moving average of lag1-3, and an additional quadratic term. Humidity was included as same day humidity and a moving average of lag1-3. Exposures after the death (lead) were included as negative exposure controls: they clearly cannot have caused the death, but if there is an omitted time-varying confounder that is correlated with the air pollution on the day of death, it is likely also correlated with the pollutant on the following day. Hence control for lead 1-day can at least partially control for that omitted confounder. The lag periods selected for inclusion are based on epidemiologic literature reporting evidence of immediate effects of air pollution on mortality (i.e., within a few days after pollution exposure) [24, 25]. We evaluated the effect of each pollutant in single-pollutant models, double-pollutant models, and three-pollutant models. We estimated the percent increase in mortality and its 95% confidence intervals (CIs) associated with each 10 µg/m$^3$ increase in exposure of PM$_{2.5}$ or 10 ppb increase in exposures to O$_3$ and NO$_2$. In addition to the negative exposure control, we analyzed deaths due to non-alcoholic fatty liver disease (NAFLD), which served as a negative outcome control to examine potential omitted confounding [26].

We repeated the analyses restricting to deaths with exposure levels below the 2020 World Health Organization Air Quality Guidelines (WHO AQG) for each pollutant to examine whether the associations persisted at levels currently permissible (25 µg/m$^3$ for PM$_{2.5}$, 100 µg/m$^3$ for O$_3$, 200 µg/m$^3$ for NO$_2$).

Effect modification analysis

To identify potentially susceptible populations, we examined modifications among subgroups of sex (male and female), race (White, Black, and Other), age ($\leq$45, 45-65, 65-75, and $\geq$75 years), education (less than, equal to, or greater than high school), and urbanicity (urban, rural). Population density for each census tract was calculated using the total population and land area, and urbanicity was defined based on whether census tract population density exceeds the 25th percentile of the overall density of the entire study population.

Sensitivity analyses

Sensitivity analyses were conducted to examine the robustness of our results. First, we evaluated different lag periods for temperature and humidity and chose the estimate of moving average in the final model based on the most significant estimates of
individual lag patterns. Second, we calculated the time-varying propensity scores for each air pollutant and used inverse probability weighting, which makes the air pollutant independent of all of the confounders, to re-estimate the associations.

All analyses were done in the statistical environment R4.0.3 [27], with the “survival” package (version 3.2-7) to fit the conditional logistic regression [28]. This study was approved by the institutional review board at Harvard T.H. Chan School of Public Health.

Results

Variable Distribution and Descriptive statistics

A total of 3,063,192 deaths were identified between 2000 and 2015 with a complete record of the date of death as well as corresponding geographical coordinates. Table 1 presents the summary statistics for the total population examined and for each state. Among all subjects who died during the study period, 46.9% were male and 12.8% were of the non-white race. The mean age at death was 75.6 years, ranging from 1.9 to 117.0 years, with 77% of the cases occurring in people 65 years or older. Of all deaths, 1,053,304 (34.4%) deaths were from cardiovascular diseases, and 323,309 (10.6%) deaths were from respiratory diseases.
Table 1
Descriptive characteristics and event day exposures from 2000 to 2015 in the US and in each state included in the study.

|                | Total  | OH     | MA     | NJ     | GA     | KS     | IN     | MI     |
|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| N              | 3,063,192 | 691,180 | 986,257 | 355,231 | 311,146 | 63,462 | 99,035 | 556,881 |

|                |        |        |        |        |        |        |        |        |
|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Sex            |        |        |        |        |        |        |        |        |
| Male           | 46.9%  | 47.3%  | 45.9%  | 46.2%  | 48.0%  | 46.9%  | 47.3%  | 48.0%  |
| Female         | 53.1%  | 52.7%  | 54.1%  | 53.8%  | 52.0%  | 53.1%  | 52.7%  | 52.0%  |

| Age (years)    |        |        |        |        |        |        |        |        |
|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| 75.6 (18.1)    | 75.1 (16.5) | 77.4 (20.4) | 75.9 (16.2) | 72.1 (18.1) | 76.4 (17.2) | 74.5 (16.8) | 74.9 (16.6) |

| Race           |        |        |        |        |        |        |        |        |
| White          | 87.2%  | 88.4%  | 92.8%  | 84.3%  | 71.7%  | 92.0%  | 91.8%  | 84.7%  |
| Black          | 10.8%  | 10.9%  | 4.0%   | 12.6%  | 27.3%  | 4.8%   | 7.6%   | 13.6%  |
| Other          | 2.0%   | 0.7%   | 3.1%   | 3.2%   | 1.0%   | 3.2%   | 0.6%   | 1.6%   |

| Education      |        |        |        |        |        |        |        |        |
| < HS*          | 21.2%  | 24.4%  | 17.8%  | 24.5%  | 11.7%  | 24.4%  | 15.8%  | 26.9%  |
| HS             | 44.6%  | 49.0%  | 51.2%  | 49.9%  | 14.3%  | 42.1%  | 23.9%  | 45.0%  |
| > HS           | 25.0%  | 23.9%  | 29.9%  | 24.9%  | 11.5%  | 32.3%  | 11.0%  | 26.6%  |

| Urbanicity     |        |        |        |        |        |        |        |        |
| Urban          | 75.1%  | 70.6%  | 83.5%  | 91.6%  | 67.2%  | 32.8%  | 41.3%  | 68.8%  |
| Rural          | 24.9%  | 29.4%  | 16.5%  | 8.4%   | 32.8%  | 67.2%  | 58.7%  | 31.2%  |

| Case Day Exposure |        |        |        |        |        |        |        |        |
| PM_{2.5} (µg/m³) | 10.4 (6.15) | 11.8 (5.90) | 8.66 (5.67) | 11.7 (7.36) | 11.8 (5.45) | 9.71 (4.74) | 13.0 (6.60) | 9.63 (5.90) |
| O₃ (ppb)        | 37.7 (11.0) | 38.0 (10.5) | 37.0 (11.0) | 37.2 (12.0) | 41.3 (12.6) | 38.0 (10.6) | 38.2 (13.2) | 36.6 (8.52) |
| NO₂ (ppb)       | 21.2 (12.1) | 18.4 (10.1) | 22.4 (11.8) | 31.9 (13.4) | 15.3 (10.7) | 16.3 (10.0) | 17.5 (9.95) | 20.3 (10.8) |
| Temperature (Kelvin) | 284 (10.3) | 284 (10.4) | 283 (9.61) | 284 (9.63) | 290 (9.21) | 285 (11.2) | 284 (11.2) | 282 (10.7) |
| Humidity (g/cm³) | 0.0073 (0.0045) | 0.0076 (0.0045) | 0.0068 (0.0042) | 0.0076 (0.0046) | 0.0095 (0.0047) | 0.0077 (0.0048) | 0.0075 (0.0046) | 0.00667 (0.0042) |

*Definition of abbreviations: HS=High school.

For sex, race, and education, data were presented as a percentage to the total. For age and case-day exposure, data were presented as mean (standard deviation).

Table 1 also presents the distribution of air pollutants and meteorological covariates on case days. The mean daily ambient air pollutant concentrations over the study period were 10.3 µg/m³ for PM_{2.5}, 37.7 ppb for O₃, and 21.2 ppb for NO₂. Concentrations varied year-to-year and between states, likely due to meteorology and wind patterns, and spatial variability in local sources of pollution.

**Results for single, double and multi-pollutant air pollutant models**
The individual effect of each air pollutant on all-cause mortality for different lag periods unadjusted for the other pollutants was shown in Supplementary Figure 1. The effect was most robust for PM$_{2.5}$ on lag 0 and lag 1, O$_3$ from lag 0 to lag 2, and NO$_2$ from lag 0 to lag 2, respectively. Therefore, we defined our baseline all-pollutant model to include the moving averages of exposure on these specified days. Figure 1 presents the result for percent increase in all-cause mortality in single-, double-, and three-pollutant models. Individually, all three pollutants were significantly associated with an increase in all-cause mortality. Upon controlling for either O$_3$ or NO$_2$ in double pollutant models, and for both in the three-pollutant model, the effect of PM$_{2.5}$ attenuated slightly, although it remained significant. The effect of O$_3$ and NO$_2$ attenuated to marginally significant after adjusting for other co-pollutants.

Table 2 presents the results of the analyses for all-cause mortality using the moving average of air pollutants and adjusting for all other pollutants, temperature, absolute humidity, and the leads of each pollutant. In the three-pollutant model, the percent increases for all-cause mortality associated with each 10-µg/m$^3$ increase of PM$_{2.5}$ exposure at lag 0-1 day, and 10 ppb increase in NO$_2$ exposure at lag 0-2 day were significant, at 0.67% (95%CI: 0.34-1.01%), and 0.20% (95%CI: 0.00-0.39%), respectively. Each 10 ppb increase in O$_3$ exposure at lag 0-2 day was associated with a 0.21% (95%CI: 0.00-0.42%) increase in all-cause mortality, although the association was only marginally significant. For PM$_{2.5}$, we found larger effect sizes for respiratory deaths, at 1.18% (95%CI: 0.07-2.28%) per 10 µg/m$^3$ increase. PM$_{2.5}$ was also significantly associated with deaths from cardiovascular causes (Table 2, Figure 2). We saw no significant association of any exposure with the negative outcome control.

| Model                  | Cases (n) | PM2.5 (µg/m$^3$) | %   | 95% CI     | p     | O3 (ppb) | %   | 95% CI     | p     | NO2 (ppb) | %   | 95% CI     | p     |
|------------------------|-----------|------------------|-----|------------|-------|----------|-----|------------|-------|-----------|-----|------------|-------|
| Three pollutant Model  | 13,474,216| 0.67             | 0.34| 1.01       | <0.01 | 0.21     | 0.00| 0.42       | 0.06  | 0.20      | 0.00| 0.39       | <0.05 |
| Low Exposure*          | 11,919,986| 0.67             | 0.25| 1.08       | <0.01 | 0.18     | -0.08| 0.44       | 0.17  | 0.12      | -0.10| 0.34       | 0.27  |
| Cardiovascular†        | 1,053,304 | 0.67             | 0.09| 1.25       | 0.02  | 0.23     | -0.15| 0.61       | 0.23  | -0.10     | -0.46| 0.25       | 0.57  |
| Respiratory†           | 323,309   | 1.18             | 0.07| 2.28       | 0.04  | 0.41     | -0.33| 1.15       | 0.28  | 0.72      | -0.01| 1.45       | 0.05  |

Values are percent increase (95% CI) for 10 µg/m$^3$ increase in PM$_{2.5}$, 10 ppb in O$_3$, and 10 ppb in NO$_2$. All models were adjusted for temperature and absolute humidity. Lag periods for all models were lag 0-1 for PM$_{2.5}$, lag 0-2 for O$_3$, and lag 0-2 for NO$_2$.

* The low exposure model analysis had the same model specifications as the baseline model analysis and was restricted to days with PM$_{2.5}$ below 25 µg/m$^3$, O$_3$ below 50 ppb, and NO$_2$ below 106.4 ppb.

† Mortality due to cardiovascular disease (International Classification of Disease, 10th edition [ICD-10] codes I00 to I99) and respiratory disease (ICD-10 codes J00 to J99).

Restriction to Effects Below Standard

Of all case and control days, 98.0% days had PM$_{2.5}$ levels below the WHO AQG standard of 25 µg/m$^3$, 89.5% days had ozone levels below the standard of 50 ppb (100 µg/m$^3$), and 100% days had NO$_2$ levels below the standard of 106.4 ppb (200 µg/m$^3$). 11,919,986 (88.47%) days had all three pollutant levels below the WHO AQG. When restricted to days with all exposure below standards, the results remained significant for PM$_{2.5}$ (Table 2, Figure 2).

Effect Modification
Figure 3 presents the effect of each air pollutant among each individual subgroup of education, sex, age group, race, and urbanicity. Although we did not observe significant incremental effect modification (Supplementary Table 1), females, people of Black, with low educational attainment and those residing in rural areas appeared more vulnerable to the effect of all three air pollutants.

**Sensitivity Analysis**

Temperature and absolute humidity on lag days 1 to 3 had robust associations with all-cause mortality (Supplementary Table 2) and the moving averages of these days were selected for the final model, along with terms for same-day temperature and humidity. We also added a non-linear quadratic term for same-day temperature in the final model. When propensity scores and inverse probability weighting were used to estimate the association between air pollution exposures and all-cause mortality, the results for PM$_{2.5}$ and NO$_2$ increased as compared to the baseline model. A 10 µg/m$^3$ increase in PM$_{2.5}$ and 10 ppb unit increase in NO$_2$ were now associated with 1.09% (95%CI: 0.81-1.38%) and 0.56% (0.39-0.73%) increases in all-cause mortality, respectively. The estimates for O$_3$ diminished to 0.09 (95% CI: 0.99-0.28%) per 10 ppb increase and was insignificant (Supplementary Table 3).

**Discussion**

In this study, we conducted a time-stratified case-crossover analysis for major air pollutants to estimate the associations of short-term PM$_{2.5}$, O$_3$, and NO$_2$ exposures with mortality for the entire population of seven US states, which covered over 3 million deaths between 2000 to 2015. These estimates were not only restricted to major cities but include smaller cities and rural areas. We found an independent and significant effect for PM$_{2.5}$ and NO$_2$, where a 10 µg/m$^3$ and 10 ppb increase was significantly associated with a 0.67% and 0.20% increase in the risk of all-cause mortality, respectively. The association for PM$_{2.5}$ remained significant when restricting the analysis to days with pollutant levels lower than the 2020 WHO AQG[29], indicating that current standards are not sufficient to protect the general population. We controlled for negative exposure control (exposure after death) in the main analysis, and we saw no association for the negative outcome control (mortality due to NAFLD), suggesting that our analysis was robust against residual confounding. Results of the causal modeling analysis remained consistent with those of the main analysis, suggesting that the observed associations may infer causal relationships.

Although other publications have investigated the effect of air pollutants utilizing a case-crossover design [30–32], none was on the scale in terms of area and age coverage comparable to the present study. In addition, our high exposure resolution has not yet been provided by existing literature. A case-crossover study of Medicare participants by Di et al. used spatially resolved air pollution at the ZIP code level [21] which had a coarser resolution as compared to our census tract level exposure (about one-third of the population of a ZIP code). Our effect estimates for PM$_{2.5}$ and O$_3$ were lower than that of Di’s (1.05% and 0.51% respectively), but we also adjusted an additional air pollutant NO$_2$ as well as incorporated negative exposure controls, negative outcome controls, and propensity score methods. The observed associations between PM$_{2.5}$ and mortality were robust to adjustment by co-pollutants and weather variables. In addition, while Di restricted the study to the US Medicare population of people 65 years and older, our study included people of all ages, providing increased generalizability.

The effect of PM$_{2.5}$ was were in agreement with those obtained by a study across 112 US cities from 1999–2005, which identified a 0.98% (95% CI: 0.75-1.22%) increase in mortality with each 10 µg/m$^3$ increase in PM$_{2.5}$ [33]. Although our estimation for O$_3$ was only marginally significant, the estimate was on par with that observed in a study of 48 US cities, which found a 0.3% (95% CI: 0.2-0.4%) increase in total mortality with each 10-ppb increase in O$_3$ [15]. However, similar to other previous US studies [18, 34–38], those daily air pollutant exposure data were obtained from local ambient monitoring stations. As a result, all individuals residing in the metropolitan area were assigned the same exposure, leading to substantial measurement error. In comparison, the present study did not use central monitors, thereby providing a finer resolution and more accurate exposure data for all individuals, including individuals living in smaller cities, rural communities or unmonitored areas that would be misclassified in earlier time-series studies. We observed a larger, although insignificant, effect for PM$_{2.5}$ and NO$_2$ in rural areas as compared to urban areas, suggesting the need for improved rural monitoring to contrast the adverse effect in urban versus rural regions, and the need to examine sources of rural vulnerability.
Findings from this study were also consistent with the effect sizes of PM$_{2.5}$ observed in other countries [39–41]. However, our estimates for PM$_{2.5}$ were higher than the 0.22% increase in 272 Chinese cities [42] and the 0.55% increase in 10 Mediterranean metropolitan areas [43]. Those regions have higher PM$_{2.5}$ concentrations, and the lower effect sizes may be due to a nonlinear dose-response, with lower slopes at high concentrations, which has been reported previously [44]. On the other hand, our estimates for NO$_2$ were lower than the 0.9% increase in previously reported levels [19], although the study did not control for O$_3$ and PM$_{2.5}$. These discrepancies may also be partly explained by differences in population structure, the number of cities, age category, and air pollutant measurement method involved.

The past WHO AQG daily standard was 25 µg/m$^3$ for PM$_{2.5}$, 50 ppb for O$_3$, and 106.4 ppb for NO$_2$. In comparison, the United States has a less restrictive standard for PM$_{2.5}$ and NO$_2$ (35 µg/m$^3$ for PM$_{2.5}$, 70 ppb for O$_3$, and 100 ppb for NO$_2$). When restricting the analysis to a PM$_{2.5}$ concentration below the past WHO standards, its effect size increased. The EPA recently proposed to maintain the current national particulate matter standards due to insufficient evidence for effect at lower concentrations [45]. Our findings showed that even at levels below the standards, PM2.5 pollution is significantly associated with an increase in daily mortality rates, including after incorporation of multiple causal modeling methods.

In addition to all-cause mortality, we also found a significant association with cardiovascular and respiratory mortality for PM$_{2.5}$. Exposure to air pollution has been consistently associated with death due to chronic obstructive pulmonary disease (COPD), death due to pneumonia, as well as emergency room visits for asthma [14, 15, 19, 46], and our estimates for respiratory mortality are in line with previously reported estimates. Many studies have reported associations between exposure to PM$_{2.5}$ and cardiovascular deaths [19, 47] and provided evidence that these disease processes can be mediated through a combination of inflammatory, autonomic, and vascular changes [48, 49].

Profound racial and socioeconomic disparities in PM$_{2.5}$ exposure have been well documented in prior studies, where the burden of death associated with PM$_{2.5}$ exposure was disproportionately borne by the elderly [35, 50] and people of races other than white [51, 52]. Our effect modification analysis suggested a slightly elevated, although insignificantly different, association between PM$_{2.5}$ and all-cause mortality among females, people of lower educational attainment, those residing in rural areas, and people of Black race. This is in addition to the effects of higher exposure in minorities. Greater attention is needed to address the issue faced by minorities who might also be least equipped to deal with the adverse health consequences of air pollution.

Attention has recently focused on causal methods of analysis for observational data. Causal modeling seeks to mimic a randomized controlled trial by making exposure independent of all confounders but can fail if there are omitted confounders. Case-crossover analyses, by matching each person to themselves, on a nearby day without the event make exposure independent of all fixed or slowly changing individual covariates by design, and hence render exposure independent of many unmeasured confounders. In addition, we used negative exposure and outcome controls to capture omitted time-varying confounders, and a marginal structural model to control for measured, time-varying confounders. These methods strengthened the evidence for a causal association between air pollution and daily mortality.

This study has several limitations. First, there is a lack of data differentiating exposure at residence and exposure elsewhere. However, in this study, 77% of the deaths occurred in people over the age of 65 and we, therefore, expected little workplace or commuting exposure, and a higher relevance for residential exposure [53]. As a result, the extent of misclassification was reduced. Moreover, the National Human Activity Pattern Survey in the U.S. reported that U.S. adults spent 69% of their time at home and 8% of the time outside their home [54]. Second, we did not have individual data on behavioral factors, medication, and specific health histories or treatments. By design, these cannot be confounders, but this limited our ability to investigate potential modifications by these characteristics. Third, we did not investigate potential confounding by other co-pollutants such as sulfur dioxide (SO$_2$) and carbon monoxide (CO). However, the levels of SO$_2$ and CO are low in the US [55, 56]. In addition, Dominici et al. [57] adjusted for all O$_3$, NO$_2$, SO$_2$, and CO but found no change in the magnitude of the effect between particular matter and mortality, suggesting there is little evidence that the effect of particulate matter is confounded by the additional pollutants.

Despite its limitations, the study adds to our understanding of the effect of short-term air pollution exposure. The most important strength of this study is the high resolution of exposure data covering the multiple states, even in areas without air monitoring.
stations. This provided accurate estimates of daily levels of air pollution and meteorological conditions, allowing us to examine the entire population of these states instead of only larger cities, and reduced exposure misclassification compared to prior studies with a central-monitor approach. Second, our analysis on the whole population of seven US states avoids potential selection bias and ensures the generalizability of the results. Finally, we used several causal modeling techniques, including negative exposure and negative outcome controls, as well as marginal structural models to increase the likelihood of a causal association.

Conclusions

In this analysis of the entire population in seven US states with over three million deaths, we found that short-term exposures to PM$_{2.5}$, O$_3$, and NO$_2$ were individually associated with an increased risk of all-cause mortality. The effect of air pollution persisted even at low ambient concentrations, suggesting that the current daily standards may need to be revised to reduce the global burden of mortality due to air pollution. The use of multiple causal techniques increases the likelihood of causal relationships between the short-term air pollution exposures and mortality.

Declarations

*Ethics approval and consent to participate*: Not applicable

*Consent for publication*: Not applicable

*Availability of data and materials*: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

*Competing interests*: The authors declare that they have no competing interests

*Funding*: This work was supported by U.S. EPA grant RD-83587201.

*Author Contributions*: R.L and J.D.S: contributed to study concept and design; R.L, Y.W, X.Q, R.K, and J.D.S: were involved in data collection; R.L, Y.W, X.Q, and J.D.S: contributed to data analysis; R.L: drafted the manuscript. All authors participated in interpretation of data, manuscript writing, and critical revision.

References

1. Cohen AJ, Brauer M, Burnett R, Ross Anderson H, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. The Lancet. 2017. pp. 1907–1918. doi:10.1016/s0140-6736(17)30505-6

2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380: 2224–2260. doi:10.1016/S0140-6736(12)61766-8

3. Kloog I, Ridgway B, Koutrakis P, Coull BA, Schwartz JD. Long- and short-term exposure to PM2.5 and mortality: using novel exposure models. Epidemiology. 2013;24: 555–561. doi:10.1097/EDE.0b013e318294beaa

4. Wong C-M, Vichit-Vadakan N, Kan H, Qian Z. Public Health and Air Pollution in Asia (PAPA): A Multicity Study of Short-Term Effects of Air Pollution on Mortality. Environmental Health Perspectives. 2008. pp. 1195–1202. doi:10.1289/ehp.11257

5. Guaita R, Pichiule M, Maté T, Linares C, Díaz J. Short-term impact of particulate matter (PM2.5) on respiratory mortality in Madrid. Int J Environ Health Res. 2011;21: 260–274. doi:10.1080/09603123.2010.544033

6. Shah ASV, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ. 2015;350: h1295. doi:10.1136/bmj.h1295
7. Lewis TC, Robins TG, Dvonch JT, Keeler GJ, Yip FY, Mentz GB, et al. Air pollution-associated changes in lung function among asthmatic children in Detroit. Environ Health Perspect. 2005;113: 1068–1075. doi:10.1289/ehp.7533

8. Liu Y, Pan J, Zhang H, Shi C, Li G, Peng Z, et al. Short-Term Exposure to Ambient Air Pollution and Asthma Mortality. Am J Respir Crit Care Med. 2019;200: 24–32. doi:10.1164/rccm.201810-1823OC

9. Liu S, Zhou Y, Liu S, Chen X, Zou W, Zhao D, et al. Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China. Thorax. 2017;72: 788–795. doi:10.1136/thoraxjnl-2016-208910

10. Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. Occup Environ Med. 2015;72: 42–48. doi:10.1136/oemed-2014-102266

11. Li M-H, Fan L-C, Mao B, Yang J-W, Choi AMK, Cao W-J, et al. Short-term Exposure to Ambient Fine Particulate Matter Increases Hospitalizations and Mortality in COPD: A Systematic Review and Meta-analysis. Chest. 2016;149: 447–458. doi:10.1378/chest.15-0513

12. Naess Ø, Nafstad P, Aamodt P, Claussen B, Rosland P. Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. Am J Epidemiol. 2007;165: 435–443. doi:10.1093/aje/kwk016

13. Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, et al. Ambient PM2.5, O3, and NO2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect. 2015;123: 1180–1186. doi:10.1289/ehp.1409276

14. Jerrett M, Burnett RT, Arden Pope C, Ito K, Thurston G, Krewski D, et al. Long-Term Ozone Exposure and Mortality. New England Journal of Medicine. 2009. pp. 1085–1095. doi:10.1056/nejmoa0803894

15. Zanobetti A, Schwartz J. Mortality displacement in the association of ozone with mortality: an analysis of 48 cities in the United States. Am J Respir Crit Care Med. 2008;177: 184–189. doi:10.1164/rccm.200706-823OC

16. Rice MB, Ljungman PL, Wilker EH, Gold DR, Schwartz JD, Koutrakis P, et al. Short-term exposure to air pollution and lung function in the Framingham Heart Study. Am J Respir Crit Care Med. 2013;188: 1351–1357. doi:10.1164/rccm.201308-1414OC

17. Rappazzo KM, Joodi G, Hoffman SR, Pursell IW, Mounsey JP, Cascio WE, et al. A case-crossover analysis of the relationship of air pollution with out-of-hospital sudden unexpected death in Wake County, North Carolina (2013–2015). Sci Total Environ. 2019;694: 133744. doi:10.1016/j.scitotenv.2019.133744

18. Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, et al. Ambient air pollution and the risk of acute ischemic stroke. Arch Intern Med. 2012;172: 229–234. doi:10.1001/archinternmed.2011.732

19. Chen R, Yin P, Meng X, Wang L, Liu C, Niu Y, et al. Associations Between Ambient Nitrogen Dioxide and Daily Cause-specific Mortality: Evidence from 272 Chinese Cities. Epidemiology. 2018;29: 482–489. doi:10.1097/EDE.0000000000000829

20. Schwartz J, Fong K, Zanobetti A. A national multicity analysis of the causal effect of local pollution, NO2, and PM 2.5 on mortality. Environ Health Perspect. 2018;126: 087004. Available: https://ehp.niehs.nih.gov/doi/abs/10.1289/EHP2732

21. Di Q, Dai L, Wang Y, Zanobetti A, Choirat C, Schwartz JD, et al. Association of Short-term Exposure to Air Pollution With Mortality in Older Adults. JAMA. 2017;318: 2446–2456. doi:10.1001/jama.2017.17923

22. Di Q, Kloog I, Koutrakis P, Lyapustin A, Wang Y, Schwartz J. Assessing PM2.5 Exposures with High Spatiotemporal Resolution across the Continental United States. Environ Sci Technol. 2016;50: 4712–4721. doi:10.1021/acs.est.5b06121
23. Mitchell KE, Lohmann D, Houser PR. The multi-institution North American Land Data Assimilation System (NLDAS): Utilizing multiple GCIP products and partners in a continental distributed hydrological …. Journal of. 2004. Available: https://agupubs.onlinelibrary.wiley.com/doi/abs/10.1029/2003JD003823@10.1002/(ISSN)2169-8996.GCIP3

24. EPA. Provisional Assessment of Recent Studies on Health Effects of Particulate Matter Exposure: National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency; 2012. Available: https://play.google.com/store/books/details?id=7nCezQEACAAJ

25. EPA. Policy Assessment for the Review of the National Ambient Air Quality Standards for. US Environmental Protection Agency. 2016. Available: https://www.epa.gov/sites/production/files/2019-09/documents/draft_policy_assessment_for_pm_naaqs_09-05-2019.pdf

26. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology. 2010;21: 383–388. doi:10.1097/EDE.0b013e3181d61eeb

27. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2020. Available: https://www.R-project.org

28. Therneau TM. A Package for Survival Analysis in R. 2020. Available: https://CRAN.R-project.org/package=survival

29. WHO | Air quality guidelines – global update 2005. 2019 [cited 31 May 2021]. Available: https://www.who.int/airpollution/publications/aqg2005/en/

30. Villeneuve PJ, Burnett RT, Shi Y, Krewski D, Goldberg MS, Hertzman C, et al. A time-series study of air pollution, socioeconomic status, and mortality in Vancouver, Canada. Journal of Exposure Science & Environmental Epidemiology. 2003. pp. 427–435. doi:10.1038/sj.jea.7500292

31. Stafoggia M, Bellander T. Short-term effects of air pollutants on daily mortality in the Stockholm county - A spatiotemporal analysis. Environ Res. 2020;188: 109854. doi:10.1016/j.envres.2020.109854

32. Liu X, Bertazzon S, Villeneuve PJ, Johnson M, Stieb D, Coward S, et al. Temporal and spatial effect of air pollution on hospital admissions for myocardial infarction: a case-crossover study. CMAJ Open. 2020;8: E619–E626. doi:10.9778/cmajo.20190160

33. Zanobetti A, Schwartz J. The effect of fine and coarse particulate air pollution on mortality: a national analysis. Environ Health Perspect. 2009;117: 898–903. doi:10.1289/ehp.0800108

34. Lee M, Koutrakis P, Coull B, Klooq I, Schwartz J. Acute effect of fine particulate matter on mortality in three Southeastern states from 2007-2011. J Expo Sci Environ Epidemiol. 2016;26: 173–179. doi:10.1038/jes.2015.47

35. Franklin M, Zeka A, Schwartz J. Association between PM2.5 and all-cause and specific-cause mortality in 27 US communities. J Expo Sci Environ Epidemiol. 2007;17: 279–287. doi:10.1038/sj.jes.7500530

36. Rosenthal FS, Carney JP, Olinger ML. Out-of-hospital cardiac arrest and airborne fine particulate matter: a case-crossover analysis of emergency medical services data in Indianapolis, Indiana. Environ Health Perspect. 2008;116: 631–636. doi:10.1289/ehp.10757

37. Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med. 1993;329: 1753–1759. doi:10.1056/NEJM199312093292401

38. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter with different sources with daily mortality in six U.S. cities. Environ Health Perspect. 2000;108: 941–947. doi:10.1289/ehp.00108941

39. Michikawa T, Ueda K, Takami A, Sugata S, Yoshino A, Nitta H, et al. Japanese Nationwide Study on the Association Between Short-term Exposure to Particulate Matter and Mortality. Journal of epidemiology. 2019;29: 471–477.
40. Janssen NAH, Fischer P, Marra M, Ameling C, Cassee FR. Short-term effects of PM2.5, PM10 and PM2.5–10 on daily mortality in the Netherlands. Sci Total Environ. 2013;463-464: 20–26. doi:10.1016/j.scitotenv.2013.05.062

41. Ueda K, Nitta H, Ono M, Takeuchi A. Estimating mortality effects of fine particulate matter in Japan: a comparison of time-series and case-crossover analyses. J Air Waste Manag Assoc. 2009;59: 1212–1218. doi:10.3155/1047-3289.59.10.1212

42. Chen R, Yin R, Meng X, Liu C, Wang L, Xu X, et al. Fine Particulate Air Pollution and Daily Mortality. A Nationwide Analysis in 272 Chinese Cities. Am J Respir Crit Care Med. 2017;196: 73–81. doi:10.1164/rccm.201609-1862OC

43. Samoli E, Stafoggia M, Rodopoulou S, Ostro B, Declercq C, Alessandrini E, et al. Associations between fine and coarse particles and mortality in Mediterranean cities: results from the MED-PARTICLES project. Environ Health Perspect. 2013;121: 932–938. doi:10.1289/ehp.1206124

44. Samoli E, Analitis A, Touloumi G, Schwartz J, Anderson HR, Sunyer J, et al. Estimating the exposure–response relationships between particulate matter and mortality within the APHEA multicity project. Environ Health Perspect. 2005;113: 88–95. Available: https://ehp.niehs.nih.gov/doi/abs/10.1289/ehp.7387

45. Epa US, OAR. National Ambient Air Quality Standards (NAAQS) for PM. 2020 [cited 21 Jan 2021]. Available: https://www.epa.gov/pm-pollution/national-ambient-air-quality-standards-naaqs-pm

46. Goldberg MS, Burnett RT, Brook J, Bailar JC 3rd, Valois MF, Vincent R. Associations between daily cause-specific mortality and concentrations of ground-level ozone in Montreal, Quebec. Am J Epidemiol. 2001;154: 817–826. doi:10.1093/aje/154.9.817

47. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med. 2006;173: 667–672. doi:10.1164/rccm.200503-443OC

48. Pope CA 3rd, Hansen ML, Long RW, Nielsen KR, Eatough NL, Wilson WE, et al. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect. 2004;112: 339–345. doi:10.1289/ehp.6588

49. Liao D, Duan Y, Whitsel EA, Zheng Z-J, Heiss G, Chinchilli VM, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. Am J Epidemiol. 2004;159: 768–777. doi:10.1093/aje/kwh109

50. Zeka A, Sullivan JR, Vokonas PS, Sparrow D, Schwartz J. Inflammatory markers and particulate air pollution: characterizing the pathway to disease. Int J Epidemiol. 2006;35: 1347–1354. doi:10.1093/ije/dyl132

51. Zanobetti A, Bind M-AC, Schwartz J. Particulate air pollution and survival in a COPD cohort. Environ Health. 2008;7: 48. doi:10.1186/1476-069X-7-48

52. Bell ML, Ebisu K. Environmental inequality in exposures to airborne particulate matter components in the United States. Environ Health Perspect. 2012;120: 1699–1704. doi:10.1289/ehp.1205201

53. Leech JA, Nelson WC, Burnett RT, Aaron S, Raizenne ME. It’s about time: A comparison of Canadian and American time–activity patterns. J Expo Sci Environ Epidemiol. 2002;12: 427–432. doi:10.1038/sj.jeea.7500244

54. Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P, et al. The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. J Expo Anal Environ Epidemiol. 2001;11: 231–252. doi:10.1038/sj.jeea.7500165

55. Epa US, OAR. Sulfur dioxide trends. 2016 [cited 28 Jan 2021]. Available: https://www.epa.gov/air-trends/sulfur-dioxide-trends
56. Epa US, OAR. Carbon Monoxide Trends. 2016 [cited 28 Jan 2021]. Available: https://www.epa.gov/air-trends/carbon-monoxide-trends

57. Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM. Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study: Mortality Among Residents Of 90 Cities. Journal of Toxicology and Environmental Health, Part A. 2005. pp. 1071–1092. doi:10.1080/15287390590935932

**Figures**

**Figure 1**

Presents the result for percent increase in all-cause mortality in single-, double-, and three-pollutant models. Individually, all three pollutants were significantly associated with an increase in all-cause mortality.

**Figure 2**

For PM$_{2.5}$, we found larger effect sizes for respiratory deaths, at 1.18% (95%CI: 0.07-2.28%) per 10 µg/m$^3$ increase. PM$_{2.5}$ was also significantly associated with deaths from cardiovascular causes. When restricted to days with all exposure below standards, the results remained significant for PM$_{2.5}$.

**Figure 3**

Presents the effect of each air pollutant among each individual subgroup of education, sex, age group, race, and urbanicity.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterial.docx](#)