JAMA | Original Investigation

Association of Short-term Exposure to Air Pollution With Mortality in Older Adults

Qian Di, MS; Lingzhen Dai, ScD; Yun Wang, PhD; Antonella Zanobetti, PhD; Christine Choirat, PhD; Joel D. Schwartz, PhD; Francesca Dominici, PhD

IMPORTANCE The US Environmental Protection Agency is required to reexamine its National Ambient Air Quality Standards (NAAQS) every 5 years, but evidence of mortality risk is lacking at air pollution levels below the current daily NAAQS in unmonitored areas and for sensitive subgroups.

OBJECTIVE To estimate the association between short-term exposures to ambient fine particulate matter ($PM_{2.5}$) and ozone, and at levels below the current daily NAAQS, and mortality in the continental United States.

DESIGN, SETTING, AND PARTICIPANTS Case-crossover design and conditional logistic regression to estimate the association between short-term exposures to $PM_{2.5}$ and ozone (mean of daily exposure on the same day of death and 1 day prior) and mortality in 2-pollutant models. The study included the entire Medicare population from January 1, 2000, to December 31, 2012, residing in 39 182 zip codes.

EXPOSURES Daily $PM_{2.5}$ and ozone levels in a 1-km × 1-km grid were estimated using published and validated air pollution prediction models based on land use, chemical transport modeling, and satellite remote sensing data. From these gridded exposures, daily exposures were calculated for every zip code in the United States. Warm-season ozone was defined as ozone levels for the months April to September of each year.

MAIN OUTCOMES AND MEASURES All-cause mortality in the entire Medicare population from 2000 to 2012.

RESULTS During the study period, there were 22 433 862 million case days and 76 143 209 control days. Of all case and control days, 93.6% had $PM_{2.5}$ levels below 25 $\mu g/m^3$, during which 95.2% of deaths occurred (21 353 817 of 22 433 862), and 91.1% of days had ozone levels below 60 parts per billion, during which 93.4% of deaths occurred (20 955 387 of 22 433 862). The baseline daily mortality rates were 137.33 and 129.44 (per 1 million persons at risk per day) for the entire year and for the warm season, respectively. Each short-term increase of 10 $\mu g/m^3$ in $PM_{2.5}$ (adjusted by ozone) and 10 parts per billion (10^{-9}) in warm-season ozone (adjusted by $PM_{2.5}$) were statistically significantly associated with a relative increase of 1.05% (95% CI, 0.95%-1.15%) and 0.51% (95% CI, 0.41%-0.61%) in daily mortality rate, respectively. Absolute risk differences in daily mortality rate were 1.42 (95% CI, 1.29-1.56) and 0.66 (95% CI, 0.53-0.78) per 1 million persons at risk per day. There was no evidence of a threshold in the exposure-response relationship.

CONCLUSIONS AND RELEVANCE In the US Medicare population from 2000 to 2012, short-term exposures to $PM_{2.5}$ and warm-season ozone were significantly associated with increased risk of mortality. This risk occurred at levels below current national air quality standards, suggesting that these standards may need to be reevaluated.

Editorial page 2431

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 2489

Author Affiliations: Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Di, Dai, Zanobetti, Schwartz); Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Wang, Choirat, Dominici).

Corresponding Authors: Joel D. Schwartz, PhD, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Landmark Center West 404H, Boston, MA 02215 (jschwrtz@hsph.harvard.edu).

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In the United States, the Clean Air Act[1] requires a review of National Ambient Air Quality Standards (NAAQS) for fine particulate matter ($PM_{2.5}$) and ozone every 5 years.[2] In 2012, the annual and 24-hour NAAQS for $PM_{2.5}$ were set to 12 μg/m^3 and 35 μg/m^3, respectively. With no annual standard for ozone, the 8-hour NAAQS for ozone was set to 70 parts per billion (ppb). Currently, the review of these standards is ongoing, with public comments expected in the fall of 2017.[3]

Several studies have provided evidence that short-term exposures to $PM_{2.5}$ and ozone were associated with mortality,[4-8] but these studies primarily included large and well-monitored metropolitan areas. While the US Environmental Protection Agency (EPA) is considering more stringent NAAQS, evidence is needed to clarify the association between mortality risk and exposure levels below the daily NAAQS and in rural and unmonitored areas.

The Clean Air Act[1] also requires the US EPA to set standards to protect "sensitive subgroups." To estimate the health risk of short-term exposure to air pollution for specific subgroups (eg, underrepresented minorities and those with low socioeconomic status, such as persons eligible for Medicaid), a large population is necessary to achieve maximum accuracy and adequate statistical power.

A case-crossover study was conducted to examine all deaths of Medicare participants in the continental United States from 2000 throughout 2012 and estimate the mortality risk associated with short-term exposures to $PM_{2.5}$ and ozone in the general population as well as in subgroups. The study was designed to estimate the association between daily mortality and air pollution at levels below current daily NAAQS to evaluate the adequacy of the current air quality standards for $PM_{2.5}$ and ozone.

Key Points

Question What is the association between short-term exposure to air pollution below current air quality standards and all-cause mortality?

Finding In a case-crossover study of more than 22 million deaths, each 10-μg/m^3 daily increase in fine particulate matter and 10–parts-per-billion daily increase in warm-season ozone exposures were associated with a statistically significant increase of 1.42 and 0.66 deaths per 1 million persons at risk per day, respectively.

Meaning Day-to-day changes in fine particulate matter and ozone exposures were significantly associated with higher risk of all-cause mortality at levels below current air quality standards, suggesting that those standards may need to be reevaluated.

Methods

This study was approved by the institutional review board at the Harvard T.H. Chan School of Public Health. As a study of previously collected administrative data, it was exempt from informed consent requirements.

Study Population

Using claims data from the Centers for Medicare & Medicaid Services, all deaths among all Medicare beneficiaries were identified during the period 2000 to 2012, providing enough power to analyze the risk of mortality associated with $PM_{2.5}$ and ozone concentrations much lower than the current standards (**Table 1**). For each beneficiary, information was extracted on the date of death, age, sex, race, ethnicity, zip code of residence, and eligibility for Medicaid (a proxy for low income) to assess the associations of mortality with $PM_{2.5}$ and ozone concentrations in potentially vulnerable subgroups. Self-reported information on race and ethnicity was obtained from Medicare beneficiary files.

Outcome

The study outcome was all-cause mortality. Individuals with a verified date of death between January 1, 2000, and December 31, 2012, were included. Individuals with an unverified date of death, or still living after December 31, 2012, were excluded.

Study Design

We estimated the association between short-term exposure to $PM_{2.5}$ (adjusted by ozone) and short-term exposure to ozone (adjusted by $PM_{2.5}$) and all-cause mortality using a case-crossover design.[9] Specifically, "case day" was defined as the date of death. For the same person, we compared daily air pollution exposure on the case day vs daily air pollution exposure on "control days." Control days were chosen (1) on the same day of the week as the case day to control for potential confounding effect by day of week; (2) before and after the case day (bidirectional sampling) to control for time trend[10,11]; and (3) only in the same month as the case day to control for seasonal and subseasonal patterns.[10,12] Individual-level covariates and zip code–level covariates that did not vary day to day (eg, age, sex, race/ethnicity, socioeconomic status, smoking, and other behavioral risk factors) were not considered to be confounders as they remain constant when comparing case days vs control days.

Environmental Data

Daily ambient levels of $PM_{2.5}$ and ozone were estimated from published and validated air pollution prediction models.[13,14] Combining monitoring data from the EPA, satellite-based measurements, and other data sets, neural networks were used to predict 24-hour $PM_{2.5}$ and 8-hour maximum ozone concentrations at each 1-km ×1-km grid in the continental United States, including locations with no monitoring sites. Cross-validation indicated good agreement between predicted values and monitoring values (R^2 = 0.84 for $PM_{2.5}$ and R^2 = 0.76 for ozone) and at low concentrations (R^2 = 0.85 when constraining to 24-hour $PM_{2.5}$ <25 μg/m^3 and R^2 = 0.75 when constraining to daily 8-hour maximum ozone <60 ppb). Details have been published elsewhere.[13,14] Warm season was defined to be from April 1 to September 30, which is the specific time window to examine the association between ozone and mortality.

Meteorological variables, including air and dew point temperatures, were retrieved from North American Regional Reanalysis data and estimated daily mean values were determined for each 32-km × 32-km grid in the continental United States.[15]

For each case day (date of death) and its control days, the daily 24-hour $PM_{2.5}$, 8-hour maximum ozone, and daily air and dew point temperatures were assigned based on zip code of residence of the individual (eAppendix 1 in the Supplement). Because we estimated air pollution levels everywhere in the continental United States, the number of zip codes included in this study was 39 182, resulting in a 33% increase compared with the number of zip codes with a centroid less than 50 km from a monitor (n = 26 115).

Table 1. Baseline Characteristics of Study Population (2000-2012)

Baseline Characteristic	Value
Case days, No.	22 433 862
Control days, No.	76 143 209
Among All Cases (n = 22 433 862), %	
Age at death, y	
≤69	10.38
70-74	13.37
75-84	38.48
≥85	37.78
Sex	
Male	44.73
Female	55.27
Race/ethnicity	
White	87.34
Black	8.87
Asian	1.03
Hispanic	1.51
Native American	0.31
Medicaid Eligibility (n = 22 433 862), %	
Ineligible	77.36
Eligible	22.64

Statistical Analysis

The relative risk (RR) of all-cause mortality associated with short-term exposures to $PM_{2.5}$ (adjusted by ozone) and warm-season ozone (adjusted by $PM_{2.5}$) was estimated by fitting a conditional logistic regression to all pairs of case days and matched control days (eAppendix 2 in the Supplement).[9] The regression model included both pollutants as main effects and natural splines of air and dew point temperatures with 3 *df* to control for potential residual confounding by weather. For each case day, daily exposure to air pollution was defined as the mean of the same day of death (lag 0-day) and 1 day prior (lag 1-day), denoted as lag 01-day.[5,16,17] Relative risk increase (RRI) was defined as RR − 1. The absolute risk difference (ARD) of all-cause mortality associated with air pollution was defined as ARD = α × (RR − 1)/RR, where α denotes the baseline daily mortality rate (eAppendix 3 in the Supplement).

The robustness of the analysis results was assessed with respect to (1) choosing the *df* used for the confounding adjustment for temperature, (2) using lag 01-day exposure as the exposure metric, (3) the definition of warm season, and (4) using only air pollution measurements from the nearest EPA monitoring sites. Splines on meteorological variables with 6 and 9 *df* yielded results with a difference of less than 5% of the standard error (eFigure 1 in the Supplement). The main analysis, which used the lag 01-day exposure, yielded the lowest values of the Akaike Information Criteria values, indicating better fit to the data (eTable in the Supplement). Different definitions of warm season yielded similar risk estimates (eAppendix 4 in the Supplement), and using exposure mea-

Table 2. Relative Risk Increase and Absolute Risk Difference of Daily Mortality Associated With Each 10-μg/m³ Increase in $PM_{2.5}$ and Each 10-ppb Increase in Ozone

	Relative Risk Increase, % (95% CI)		Absolute Risk Difference in Daily Mortality Rates, No. per 1 Million Persons at Risk per Day (95% CI)[a]	
Air Pollutant Analysis	$PM_{2.5}$	Ozone[b]	$PM_{2.5}$	Ozone[b]
Main analysis[c]	1.05 (0.95-1.15)	0.51 (0.41-0.61)	1.42 (1.29-1.56)	0.66 (0.53-0.78)
Low-exposure analysis[d]	1.61 (1.48-1.74)	0.58 (0.46-0.70)	2.17 (2.00-2.34)	0.74 (0.59-0.90)
Single-pollutant analysis[e]	1.18 (1.09-1.28)	0.55 (0.48-0.62)	1.61 (1.48-1.73)	0.71 (0.62-0.79)
Nearest monitors analysis[f]	0.83 (0.73-0.93)	0.35 (0.28-0.41)	1.13 (0.99-1.26)	0.45 (0.37-0.53)

Abbreviations: $PM_{2.5}$, fine particulate matter; ppb, parts per billion.

[a] The daily baseline mortality rate was 137.33 per 1 million persons at risk per day; the warm-season daily baseline mortality rate was 129.44 per 1 million persons at risk per day.

[b] Ozone analyses included days from the warm season only (April 1 to September 30).

[c] The main analysis used the mean of daily exposure on the same day of death and 1 day prior (lag 01-day) as the exposure metric for both $PM_{2.5}$ and ozone, and controlled for natural splines of air and dew point temperatures with 3 *df*. The main analysis considered the 2 pollutants jointly included into the regression model and estimated the percentage increase in the daily mortality rate associated with a 10-μg/m³ increase in $PM_{2.5}$ exposure adjusted for ozone and the percentage increase in daily mortality rate associated with a 10-ppb increase in warm-season ozone exposure adjusted for $PM_{2.5}$.

[d] The low-exposure analysis had the same model specifications as the 2-pollutant analysis and was constrained for days when $PM_{2.5}$ was below 25 μg/m³ or ozone below 60 ppb.

[e] The single-pollutant analysis estimated the percentage increase in the daily mortality rate associated with a 10-μg/m³ increase in $PM_{2.5}$ exposure without adjusting for ozone and the percentage increase in the daily mortality rate associated with a 10-ppb increase in ozone exposure without adjusting for $PM_{2.5}$.

[f] $PM_{2.5}$ and ozone monitoring data were retrieved from the US Environmental Protection Agency Air Quality System, which provides the daily mean of $PM_{2.5}$ and daily 8-hour maximum ozone levels at each monitoring site. Daily ozone concentrations were averaged from April 1 to September 30. Individuals were assigned to the $PM_{2.5}$ and ozone levels from the nearest monitor site within 50 km. Those living 50 km from any monitoring site were excluded.

surements from the nearest monitors resulted in attenuated, but still significant, risk estimates (**Table 2**).

The subgroup analyses were conducted by sex (male and female), race/ethnicity (white, nonwhite, and others), age (≤69, 70-74, 75-84, and ≥85 years), eligibility for Medicaid, and population density (quartiles). We fitted separate conditional logistic regressions to the data for each subgroup and obtained subgroup-specific estimates of RR and ARD. We implemented a 2-sample test for assessing statistically significant differences in the estimated RR and ARD between categories within each subgroup (eg, female vs male), based on the point estimate and standard error (se) (eAppendix 5 in the Supplement):

$$Z = \frac{RR_{male} - RR_{female}}{\sqrt{se(RR_{male})^2 + se(RR_{female})^2}}$$

The goal was to estimate mortality rate increases (both RRI and ARD) at air pollution levels well below the current daily NAAQS. The analysis was restricted to days with daily air pollution concentrations below 25 μg/m^3 for $PM_{2.5}$ and 60 ppb for ozone. We chose 25 μg/m^3 and 60 ppb instead of the current daily NAAQS (35 μg/m^3 for daily $PM_{2.5}$ and 70 ppb for 8-hour maximum ozone) because levels of $PM_{2.5}$ and ozone on most of the days included in the analysis were already below the current safety standards.

Exposure-response curves were estimated between $PM_{2.5}$ or ozone and mortality by replacing linear terms for the 2 pollutants with penalized splines for both $PM_{2.5}$ and ozone.

All analyses were performed in R software version 3.3.2 (R Foundation). Computations were run on (1) the Odyssey cluster supported by the Faculty of Arts and Sciences Division of Science, Research Computing Group at Harvard University and (2) the Research Computing Environment supported by the Institute for Quantitative Social Science in the Faculty of Arts and Sciences at Harvard University.

Results

During the study period, there were more than 22 million case days (deaths) and more than 76 million control days (Table 1). Of all case and control days, 93.6% had $PM_{2.5}$ levels below 25 μg/m^3, during which 95.2% of deaths occurred (21 353 817 of 22 433 862), and 91.1% of days had ozone levels below 60 ppb, during which 93.4% of deaths occurred (20 955 387 of 22 433 862). The baseline daily mortality rates were 137.33 and 129.44 (per 1 million persons at risk per day [per 1M per day]) for the entire year and for the warm season, respectively. The mean time between case and control days was 12.55 days (range 7-28 days), with minimal differences in air and dew point temperatures between case and control days (0.003°C and 0.01°C, respectively). During the study period, the mean concentrations of $PM_{2.5}$ and ozone were 11.6 μg/m^3 and 37.8 ppb, respectively. **Figure 1** and **Figure 2** show the daily $PM_{2.5}$ and ozone time series by state, respectively.

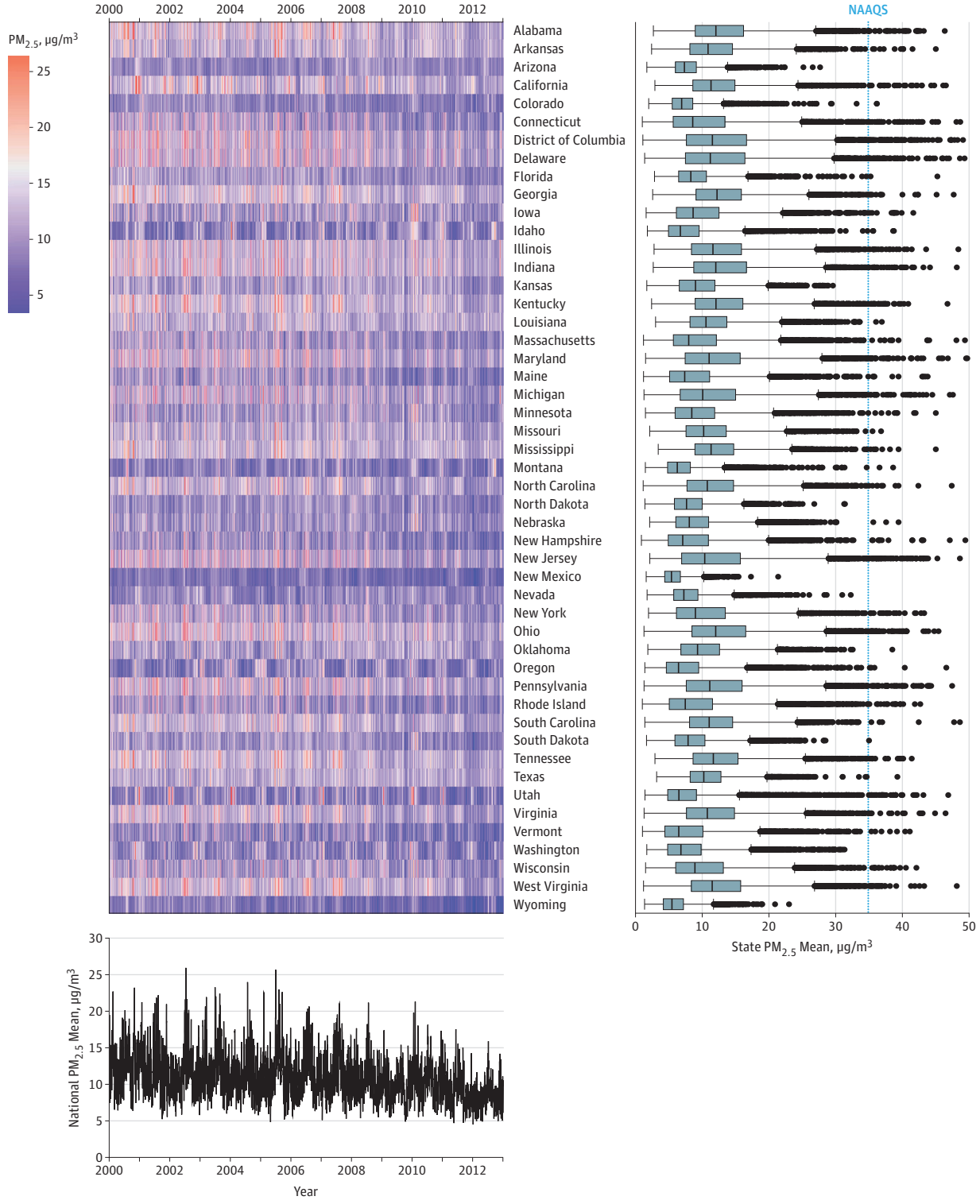
Each 10-μg/m^3 and 10-ppb increase in the lag 01-day exposure for $PM_{2.5}$ and warm-season ozone was associated with an RRI of 1.05% (95% CI, 0.95%-1.15%) and 0.51% (95% CI, 0.41%-0.61%) in the daily mortality rate. The ARDs were 1.42 (95% CI, 1.29-1.56) and 0.66 (95% CI, 0.53-0.78) per 1M per day. These associations remained significant when examining days below 25 μg/m^3 for $PM_{2.5}$ and below 60 ppb for ozone, with larger effect size estimates for both $PM_{2.5}$ and ozone (RRI: 1.61% [95% CI, 1.48%-1.74%] and 0.58% [95% CI, 0.46%-0.70%]; ARD: 2.17 [95% CI, 2.00-2.34] and 0.74 [95% CI, 0.59-0.90] per 1M per day, respectively) (Table 2). $PM_{2.5}$ was associated with higher mortality rate in some subgroups, including Medicaid-eligible individuals (RRI: 1.49% [95% CI, 1.29%-1.70%]; ARD: 3.59 [95% CI, 3.11-4.08] per 1M per day; interaction: $P < .001$), individuals older than 70 years (eg, for ≥85 years, RRI: 1.38% [95% CI, 1.23%-1.54%]; ARD: 5.35 [95% CI, 4.75-5.95] per 1M per day; interaction: $P < .001$), and females (RRI: 1.20% [95% CI, 1.07%-1.33%]; ARD: 1.56 [95% CI, 1.39-1.72] per 1M per day; interaction: $P = .02$) (**Figure 3** and **Figure 4**). The effect estimates for $PM_{2.5}$ increased with age. The effect estimate for black individuals was higher than that for white individuals ($P = .001$; eFigure 2 in the Supplement). For ozone, similar patterns were observed, but with less contrast between groups. No significant differences were found in the short-term associations between air pollution exposure ($PM_{2.5}$ and ozone) and mortality across areas with different population density levels (Figure 3 and Figure 4). Effect estimates using different lags of exposure are shown in eFigure 3 in the Supplement.

Figure 5 shows the estimated exposure-response curves for $PM_{2.5}$ and ozone. The slope was steeper at $PM_{2.5}$ levels below 25 μg/m^3 ($P < .001$), consistent with the low-exposure analysis (Table 2). Both $PM_{2.5}$ and ozone exposure-responses were almost linear, with no indication of a mortality risk threshold at very low concentrations. eFigure 4 in the Supplement shows the exposure-response curves for $PM_{2.5}$ when restricted to just the warm season and for ozone when not restricted to the warm season; results were similar.

Discussion

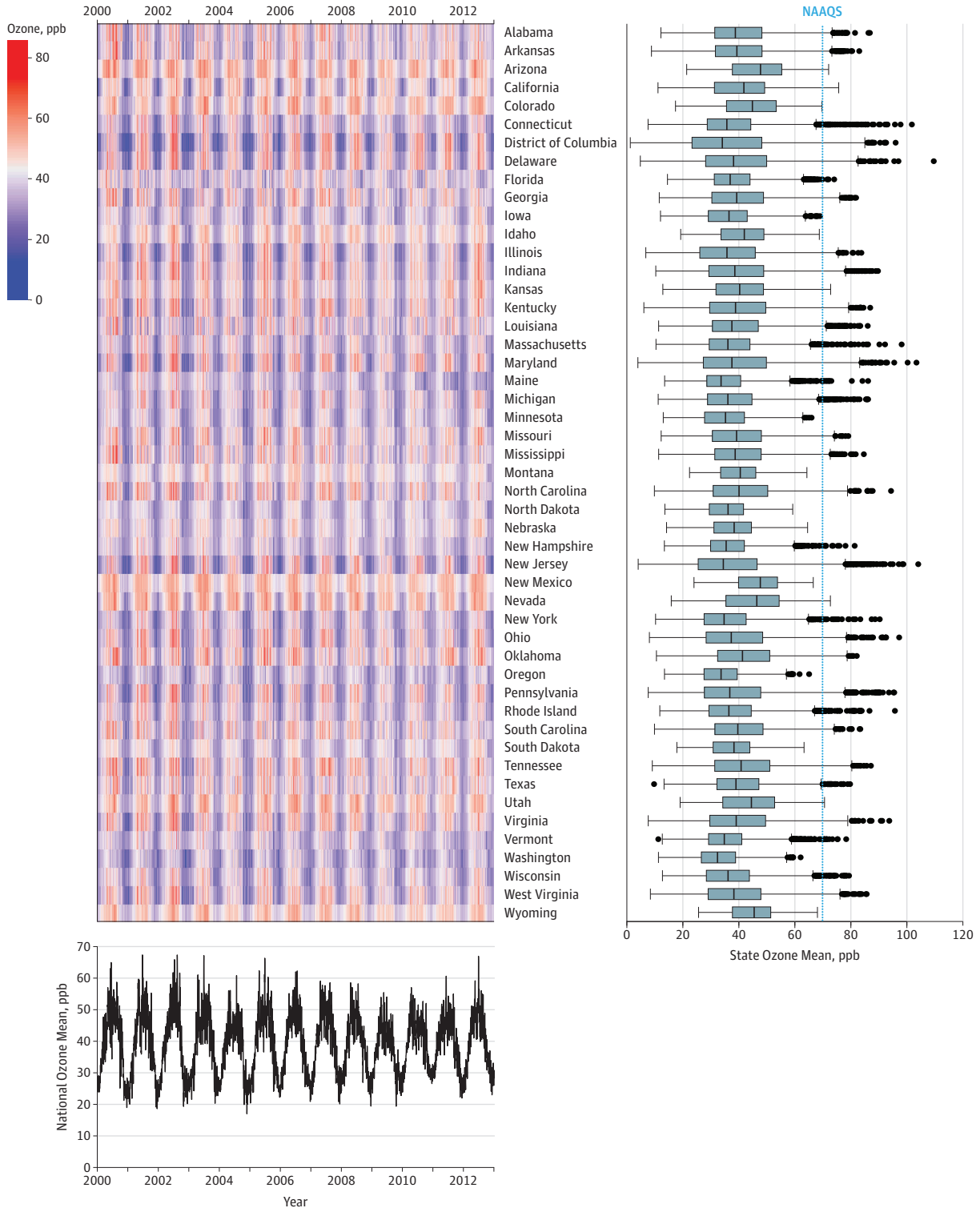
In this large case-crossover study of all Medicare deaths in the continental United States from 2000 to 2012, a 10-μg/m^3 daily increase in $PM_{2.5}$ and a 10-ppb daily increase in warm-season ozone exposures were associated with a statistically significant increase of 1.42 and 0.66 deaths per 1M per day, respectively. The risk of mortality remained statistically significant when restricting the analysis to days with $PM_{2.5}$ and ozone levels much lower than the current daily NAAQS.[18] This study included individuals living in smaller cities, towns, and rural areas that were unmonitored and thus excluded from previous time series studies. There were no significant differences in the mortality risk associated with air pollution among individuals living in urban vs rural areas. Taken together, these results provide evidence that short-term exposures to $PM_{2.5}$ and ozone, even at levels much lower than the current daily standards, are associated with increased mortality, particularly for susceptible populations.

Figure 1. Daily Mean $PM_{2.5}$ Concentrations in the Continental United States, 2000-2012



Daily mean fine particulate matter ($PM_{2.5}$) concentrations were calculated and plotted by state. The time-series plot at the bottom indicates the national daily mean values across all locations. Boxplots show the distribution of daily $PM_{2.5}$ levels for each state. The blue dashed line indicates the daily National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$ (35 µg/m^3). The line across the box, upper hinge, and lower hinge represent the median value, 75th percentile (Q3), and 25th percentile (Q1), respectively. The upper whisker is located at the smaller of the maximal value and Q3 + 1.5 × interquartile range; the lower whisker is located at the larger of the minimal value and Q1 – 1.5 × interquartile range. Any values that lie beyond the upper and lower whiskers are outliers.

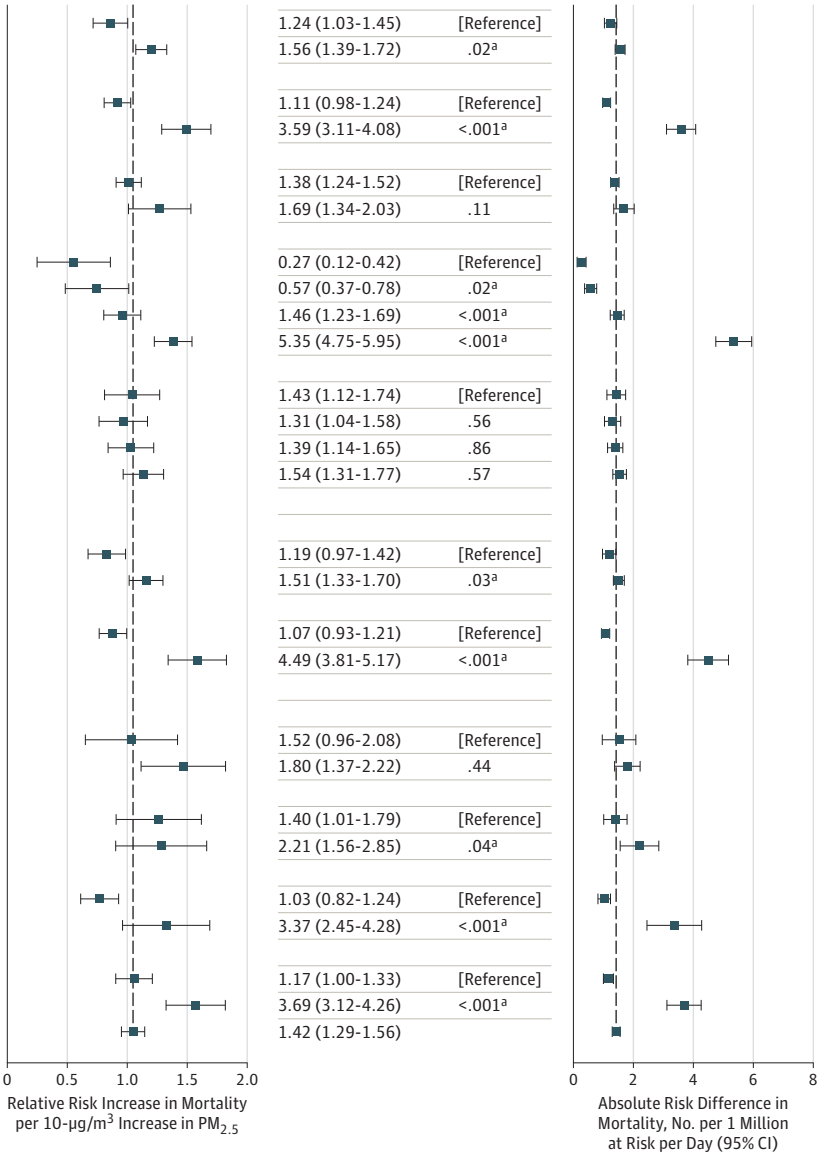
Figure 2. Daily 8-Hour Maximum Ozone Concentrations in the Continental United States, 2000-2012



Daily mean 8-hour maximum ozone concentrations were calculated and plotted by state. The time-series plot at the bottom indicates the national daily mean values across all locations. Boxplots show the distribution of daily ozone levels for each state. The blue dashed line indicates the daily National Ambient Air Quality Standards (NAAQS) for ozone (70 parts per billion [ppb]). The line across the box, upper hinge, and lower hinge represent the median value, 75th percentile (Q3), and 25th percentile (Q1), respectively. The upper whisker is located at the smaller of the maximal value and Q3 + 1.5 × interquartile range; the lower whisker is located at the larger of the minimal value and Q1 − 1.5 × interquartile range. Any values that lie beyond the upper and lower whiskers are outliers.

Figure 3. Relative Risk Increase and Absolute Risk Difference of Daily Mortality Associated With 10-μg/m^3 Increase in Fine Particulate Matter ($PM_{2.5}$)

Model	Relative Risk Increase in Mortality per 10-μg/m^3 Increase in $PM_{2.5}$, % (95% CI)	*P* Value for Effect Modification	Absolute Risk Difference in Mortality, No. per 1 Million at Risk per Day (95% CI)	*P* Value for Effect Modification
Sex				
Male	0.86 (0.72-1.00)	[Reference]	1.24 (1.03-1.45)	[Reference]
Female	1.20 (1.07-1.33)	<.001[a]	1.56 (1.39-1.72)	.02[a]
Medicaid eligibility				
Noneligible	0.92 (0.81-1.03)	[Reference]	1.11 (0.98-1.24)	[Reference]
Eligible	1.49 (1.29-1.70)	<.001[a]	3.59 (3.11-4.08)	<.001[a]
Race/ethnicity				
White	1.01 (0.91-1.12)	[Reference]	1.38 (1.24-1.52)	[Reference]
Nonwhite	1.27 (1.01-1.53)	.07	1.69 (1.34-2.03)	.11
Age, y				
≤69	0.55 (0.25-0.86)	[Reference]	0.27 (0.12-0.42)	[Reference]
70-74	0.75 (0.48-1.01)	.35	0.57 (0.37-0.78)	.02[a]
75-84	0.96 (0.80-1.11)	.02[a]	1.46 (1.23-1.69)	<.001[a]
≥85	1.38 (1.23-1.54)	<.001[a]	5.35 (4.75-5.95)	<.001[a]
Population density				
Low	1.04 (0.81-1.27)	[Reference]	1.43 (1.12-1.74)	[Reference]
Medium low	0.97 (0.76-1.17)	.64	1.31 (1.04-1.58)	.56
Medium high	1.03 (0.84-1.22)	.95	1.39 (1.14-1.65)	.86
High	1.13 (0.97-1.30)	.52	1.54 (1.31-1.77)	.57
Whites				
Sex				
Male	0.83 (0.67-0.99)	[Reference]	1.19 (0.97-1.42)	[Reference]
Female	1.16 (1.02-1.30)	.002[a]	1.51 (1.33-1.70)	.03[a]
Medicaid eligibility				
Noneligible	0.88 (0.77-1.00)	[Reference]	1.07 (0.93-1.21)	[Reference]
Eligible	1.58 (1.34-1.83)	<.001[a]	4.49 (3.81-5.17)	<.001[a]
Nonwhites				
Sex				
Male	1.03 (0.65-1.42)	[Reference]	1.52 (0.96-2.08)	[Reference]
Female	1.47 (1.12-1.82)	.01	1.80 (1.37-2.22)	.44
Medicaid eligibility				
Noneligible	1.26 (0.91-1.62)	[Reference]	1.40 (1.01-1.79)	[Reference]
Eligible	1.28 (0.90-1.66)	.94	2.21 (1.56-2.85)	.04[a]
Medicaid eligibility, males				
Noneligible	0.77 (0.61-0.93)	[Reference]	1.03 (0.82-1.24)	[Reference]
Eligible	1.32 (0.96-1.69)	.006	3.37 (2.45-4.28)	<.001[a]
Medicaid eligibility, females				
Noneligible	1.06 (0.90-1.21)	[Reference]	1.17 (1.00-1.33)	[Reference]
Eligible	1.57 (1.32-1.82)	<.001[a]	3.69 (3.12-4.26)	<.001[a]
Overall	1.05 (0.95-1.15)		1.42 (1.29-1.56)	



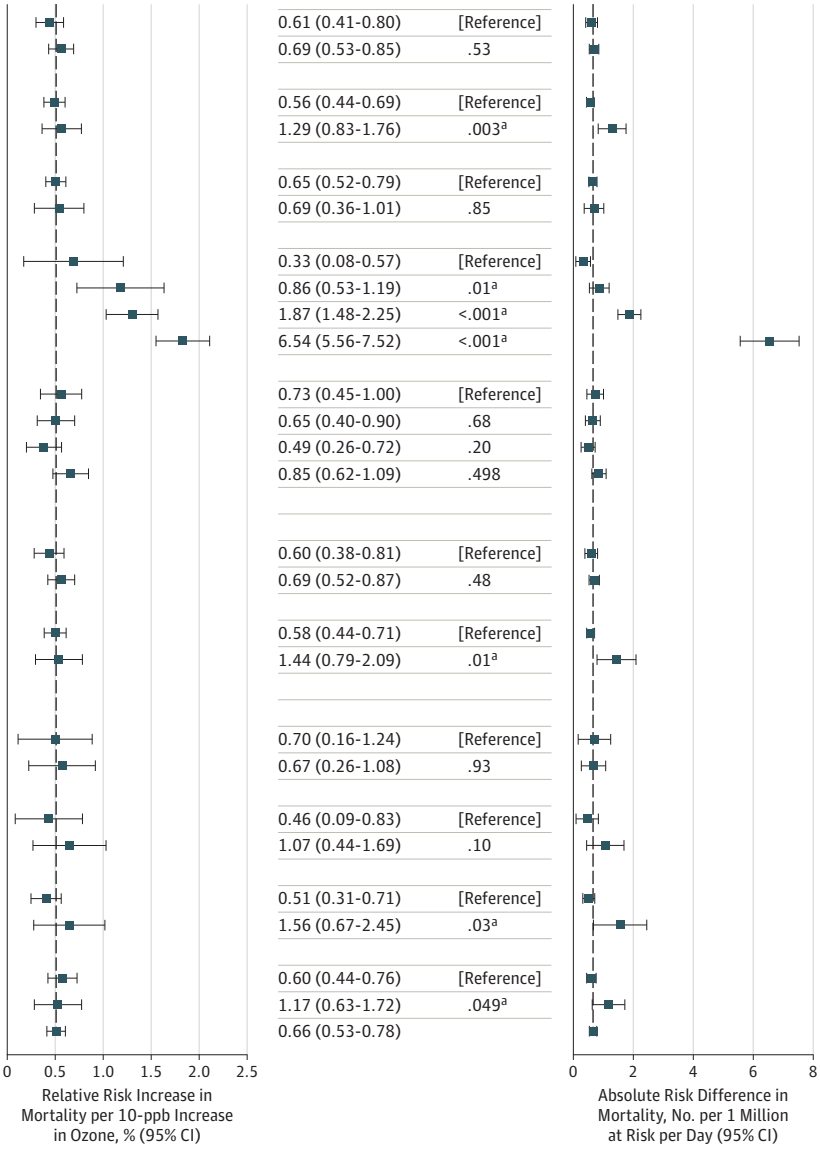
For the main analysis, subgroup analyses used a 2-pollutant analysis (with both $PM_{2.5}$ and ozone), based on the mean of daily exposure on the same day of death and 1 day prior (lag 01-day) as the exposure metric for $PM_{2.5}$, and controlled for natural splines of air and dew point temperatures (each with 3 *df*). Vertical lines indicate effects for the entire study population. Subgroup analyses were conducted for each subgroup (eg, male or female, white or nonwhite, Medicare eligible or Medicare ineligible, age groups, and quartiles of population density). For the main analysis and each subgroup, conditional logistic regressions were run to obtain relative risk increases and calculated absolute risk difference based on baseline mortality rates (eAppendix 2 in the Supplement). Numbers in the figure represent point estimates, 95% CIs, and *P* values for effect modifications. The reference groups were used when assessing effect modification.

[a] Statistically significant effect estimate (at 5% level) compared with the reference group.

The Clean Air Act[1] requires the administrator of the US EPA to set NAAQS at levels that provide "protection for at-risk populations, with an adequate margin of safety."[19] In this study, Medicaid-eligible individuals, females, and elderly individuals had higher mortality rate increases associated with $PM_{2.5}$ than other groups. Previous studies have found similar results in some subgroups.[20,21] Poverty, unhealthy lifestyle, poor access to health care, and other factors may make some subgroups more vulnerable to air pollution. The exact mechanism is worth exploring in future studies.

Figure 4. Relative Risk Increase and Absolute Risk Difference of Daily Mortality Associated With 10-Parts-per-Billion (ppb) Increase in Ozone

Model	Relative Risk Increase in Mortality per 10-ppb Increase in Ozone, % (95% CI)	*P* Value for Effect Modification	Absolute Risk Difference in Mortality, No. per 1 Million at Risk per Day (95% CI)	*P* Value for Effect Modification
Sex				
Male	0.44 (0.30-0.59)	[Reference]	0.61 (0.41-0.80)	[Reference]
Female	0.56 (0.43-0.69)	.23	0.69 (0.53-0.85)	.53
Medicaid eligibility				
Noneligible	0.49 (0.38-0.60)	[Reference]	0.56 (0.44-0.69)	[Reference]
Eligible	0.57 (0.36-0.77)	.53	1.29 (0.83-1.76)	.003[a]
Race/ethnicity				
White	0.51 (0.40-0.61)	[Reference]	0.65 (0.52-0.79)	[Reference]
Nonwhite	0.54 (0.28-0.80)	.81	0.69 (0.36-1.01)	.85
Age, y				
≤69	0.69 (0.17-1.21)	[Reference]	0.33 (0.08-0.57)	[Reference]
70-74	1.18 (0.73-1.63)	.16	0.86 (0.53-1.19)	.01[a]
75-84	1.30 (1.03-1.57)	.04[a]	1.87 (1.48-2.25)	<.001[a]
≥85	1.83 (1.55-2.11)	<.001[a]	6.54 (5.56-7.52)	<.001[a]
Population density				
Low	0.56 (0.35-0.78)	[Reference]	0.73 (0.45-1.00)	[Reference]
Medium low	0.51 (0.31-0.70)	.72	0.65 (0.40-0.90)	.68
Medium high	0.38 (0.20-0.57)	.22	0.49 (0.26-0.72)	.20
High	0.66 (0.48-0.85)	.49	0.85 (0.62-1.09)	.498
Whites				
Sex				
Male	0.44 (0.28-0.59)	[Reference]	0.60 (0.38-0.81)	[Reference]
Female	0.56 (0.42-0.70)	.24	0.69 (0.52-0.87)	.48
Medicaid eligibility				
Noneligible	0.50 (0.39-0.61)	[Reference]	0.58 (0.44-0.71)	[Reference]
Eligible	0.54 (0.29-0.78)	.78	1.44 (0.79-2.09)	.01[a]
Nonwhites				
Sex				
Male	0.50 (0.11-0.89)	[Reference]	0.70 (0.16-1.24)	[Reference]
Female	0.57 (0.22-0.92)	.79	0.67 (0.26-1.08)	.93
Medicaid eligibility				
Noneligible	0.43 (0.08-0.78)	[Reference]	0.46 (0.09-0.83)	[Reference]
Eligible	0.65 (0.27-1.03)	.42	1.07 (0.44-1.69)	.10
Medicaid eligibility, males				
Noneligible	0.40 (0.25-0.56)	[Reference]	0.51 (0.31-0.71)	[Reference]
Eligible	0.65 (0.28-1.02)	.24	1.56 (0.67-2.45)	.03[a]
Medicaid eligibility, females				
Noneligible	0.58 (0.42-0.73)	[Reference]	0.60 (0.44-0.76)	[Reference]
Eligible	0.53 (0.28-0.77)	.75	1.17 (0.63-1.72)	.049[a]
Overall	0.51 (0.41-0.61)		0.66 (0.53-0.78)	

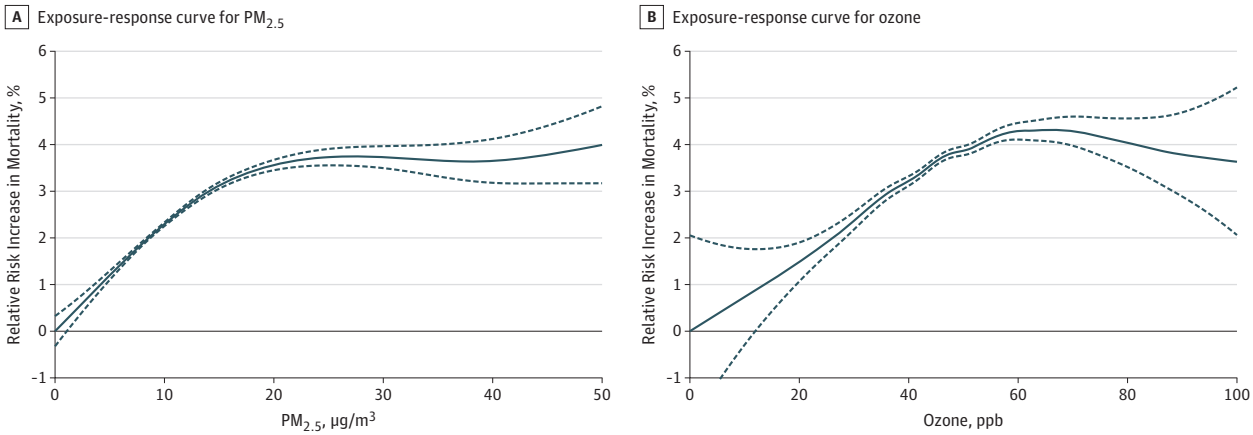


For the main analysis, subgroup analyses used a 2-pollutant analysis (with both $PM_{2.5}$ and ozone), based on the mean of daily exposure on the same day of death and 1 day prior (lag 01-day) as the exposure metric for ozone, and controlled for natural splines of air and dew point temperatures (each with 3 *df*). Vertical lines indicate effects for the entire study population. Subgroup analyses were conducted for each subgroup (eg, male or female, white or nonwhite, Medicare eligible or Medicare ineligible, age groups, and quartiles of population density). For the main analysis and each subgroup, conditional logistic regressions were run to obtain relative risk increases, and calculated absolute risk difference based on baseline mortality rates (eAppendix 2 in the Supplement). For ozone, analyses were restricted to the warm season (April to September). Numbers in the figure represent point estimates, 95% CIs, and *P* values for effect modifications. The reference groups were used when assessing effect modification.

[a] Statistically significant effect estimate (at 5% level) compared with the reference group.

The current NAAQS for daily $PM_{2.5}$ is 35 μg/m^3. When restricting the analysis to daily $PM_{2.5}$ levels below 25 μg/m^3, the association between short-term $PM_{2.5}$ exposure and mortality remained but was elevated. The current daily NAAQS for ozone is 70 ppb; when restricting the analysis to daily warm-season ozone concentrations below 60 ppb, the effect size also increased slightly. The exposure-response curves revealed a similar pattern. These results indicate

Figure 5. Estimated Exposure-Response Curves for Short-term Exposures to Fine Particulate Matter ($PM_{2.5}$) and Ozone



A 2-pollutant analysis with separate penalized splines on $PM_{2.5}$ (A) and ozone (B) was conducted to assess the percentage increase in daily mortality at various pollution levels. Dashed lines indicate 95% CIs. The mean of daily exposure on the same day of death and 1 day prior (lag 01-day) was used as metrics of exposure to $PM_{2.5}$ and ozone. Analysis for ozone was restricted to the warm season (April to September). Ppb indicates parts per billion.

that air pollution is associated with an increase in daily mortality rates, even at levels well below the current standards.

The exposure-response relationship between $PM_{2.5}$ exposure and mortality was consistent with findings of previous studies. One study combined exposure-response curves from 22 European cities and reported an almost linear relationship between $PM_{2.5}$ and mortality.[22] Another multicity study reported a linear relationship down to 2-µg/m^3 $PM_{2.5}$.[23] The present study found a similarly linear exposure-response relationship below 15-µg/m^3 $PM_{2.5}$ and a less steep slope above this level.

For ozone, the linear exposure-response curve with no threshold described in this study is consistent with earlier research. An almost linear exposure-response curve for ozone was previously reported with no threshold or a threshold at very low concentrations.[24] A study from the Netherlands also concluded that if an ozone threshold exists, it does so at very low levels.[25]

Findings from this study are also consistent with the literature regarding the observed effect sizes of both $PM_{2.5}$[5,8,16,26-28] and ozone.[7,20,29,30] This study further demonstrates that in more recent years, during which air pollution concentrations have fallen, statistically significant associations between mortality and exposures to $PM_{2.5}$ and ozone persisted.

The association of mortality and $PM_{2.5}$ exposure is supported by a large number of published experimental studies in animals[31-33] and in humans exposed to traffic air pollution,[34,35] diesel particles,[36] and unfiltered urban air.[37] Similarly, a review of toxicological studies and a recent panel study found that ozone exposure was associated with multiple adverse health outcomes.[38,39]

Strengths

This study has several strengths. First, to our knowledge, this is the largest analysis of daily air pollution exposure and mortality to date, with approximately 4 times the number of deaths included in a previous large study.[5] Second, this study assessed daily exposures using air pollution prediction models that provide accurate estimates of daily levels of $PM_{2.5}$ and ozone for most of the United States, including previously unmonitored areas. An analysis that relied only on exposure data from monitoring stations was found to result in a downward bias in estimates (Table 2). Third, the inclusion of more than 22 million deaths from 2000 to 2012 from the entire Medicare population provided large statistical power to detect differences in mortality rates in potentially vulnerable populations and to estimate mortality rates at very low $PM_{2.5}$ and ozone concentrations. Fourth, this study estimated the air pollution-mortality association well below the current daily NAAQS and in unmonitored areas, and it did not identify significant differences in the mortality rate increase between urban and rural areas. Fifth, this study used a case-crossover design that individually matched potential confounding factors by month, year, and other time-invariant variables and controlled for time-varying patterns, as demonstrated by the minimal differences in meteorological variables between case and control days.

Limitations

This study also has several limitations. First, the case-crossover design does not allow estimation of mortality rate increase associated with long-term exposure to air pollution. Long-term risks in the same study population have been estimated elsewhere.[40] Second, because this study used residential zip code to ascertain exposure level rather than exact home address or place of death, some measurement error is expected. Third, the Medicare population primarily consists of individuals older than 65 years, which limits the generalizability of findings to younger populations. However, because more than two-thirds of deaths in

the United States occur in people older than 65 years of age, and air pollution–related health risk rises with age, the Medicare population in this study includes most cases of air pollution–induced mortality. Fourth, Medicare files do not report cause-specific mortality. Fifth, the most recent data used in this study are nearly 5 years old, and it is uncertain whether exposures and outcomes would be the same with more current data.

Conclusions

In the US Medicare population from 2000 to 2012, short-term exposures to $PM_{2.5}$ and warm-season ozone were significantly associated with increased risk of mortality. This risk occurred at levels below current national air quality standards, suggesting that these standards may need to be reevaluated.

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Author Contributions: Mr Di had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mr Di and Dr Dai contributed equally to this study.
Concept and design: Di, Dai, Zanobetti, Schwartz, Dominici.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Di, Dai, Choirat, Dominici.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Di, Dai, Choirat, Schwartz, Dominici.
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