Air Pollution and Mortality in the Medicare Population

Qian Di, M.S., Yan Wang, M.S., Antonella Zanobetti, Ph.D., Yun Wang, Ph.D., Petros Koutrakis, Ph.D., Christine Choirat, Ph.D., Francesca Dominici, Ph.D., and Joel D. Schwartz, Ph.D.

ABSTRACT

BACKGROUND

Studies have shown that long-term exposure to air pollution increases mortality. However, evidence is limited for air-pollution levels below the most recent National Ambient Air Quality Standards. Previous studies involved predominantly urban populations and did not have the statistical power to estimate the health effects in underrepresented groups.

METHODS

We constructed an open cohort of all Medicare beneficiaries (60,925,443 persons) in the continental United States from the years 2000 through 2012, with 460,310,521 person-years of follow-up. Annual averages of fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [$PM_{2.5}$]) and ozone were estimated according to the ZIP Code of residence for each enrollee with the use of previously validated prediction models. We estimated the risk of death associated with exposure to increases of 10 μg per cubic meter for $PM_{2.5}$ and 10 parts per billion (ppb) for ozone using a two-pollutant Cox proportional-hazards model that controlled for demographic characteristics, Medicaid eligibility, and area-level covariates.

RESULTS

Increases of 10 μg per cubic meter in $PM_{2.5}$ and of 10 ppb in ozone were associated with increases in all-cause mortality of 7.3% (95% confidence interval [CI], 7.1 to 7.5) and 1.1% (95% CI, 1.0 to 1.2), respectively. When the analysis was restricted to person-years with exposure to $PM_{2.5}$ of less than 12 μg per cubic meter and ozone of less than 50 ppb, the same increases in $PM_{2.5}$ and ozone were associated with increases in the risk of death of 13.6% (95% CI, 13.1 to 14.1) and 1.0% (95% CI, 0.9 to 1.1), respectively. For $PM_{2.5}$, the risk of death among men, blacks, and people with Medicaid eligibility was higher than that in the rest of the population.

CONCLUSIONS

In the entire Medicare population, there was significant evidence of adverse effects related to exposure to $PM_{2.5}$ and ozone at concentrations below current national standards. This effect was most pronounced among self-identified racial minorities and people with low income. (Supported by the Health Effects Institute and others.)

From the Departments of Environmental Health (Q.D., Yan Wang, A.Z., P.K., J.D.S.) and Biostatistics (Yun Wang, C.C., F.D.), Harvard T.H. Chan School of Public Health, Boston. Address reprint requests to Dr. Dominici at Harvard T.H. Chan School of Public Health, Biostatistics Department, Bldg. 2, 4th Flr., 655 Huntington Ave., Boston, MA 02115, or at fdominic@hsph.harvard.edu.

THE ADVERSE HEALTH EFFECTS ASSOCI-
ated with long-term exposure to air pollu-
tion are well documented.[1,2] Studies sug-
gest that fine particles (particles with a mass
median aerodynamic diameter of less than 2.5 μm
[$PM_{2.5}$]) are a public health concern,[3] with expo-
sure linked to decreased life expectancy.[4-6] Long-
term exposure to ozone has also been associated
with reduced survival in several recent studies,
although evidence is sparse.[4,7-9]

Studies with large cohorts have investigated
the relationship between long-term exposures to
$PM_{2.5}$ and ozone and mortality[4,9-13]; others have
estimated the health effects of fine particles at
low concentrations (e.g., below 12 μg per cubic
meter for $PM_{2.5}$).[14-18] However, most of these
studies have included populations whose socio-
economic status is higher than the national aver-
age and who reside in well-monitored urban areas.
Consequently, these studies provide limited infor-
mation on the health effects of long-term expo-
sure to low levels of air pollution in smaller
cities and rural areas or among minorities or
persons with low socioeconomic status.

To address these gaps in knowledge, we con-
ducted a nationwide cohort study involving all
Medicare beneficiaries from 2000 through 2012,
a population of 61 million, with 460 million
person-years of follow-up. We used a survival
analysis to estimate the risk of death from any
cause associated with long-term exposure (yearly
average) to $PM_{2.5}$ concentrations lower than the
current annual National Ambient Air Quality
Standard (NAAQS) of 12 μg per cubic meter and
to ozone concentrations below 50 parts per billion
(ppb). Subgroup analyses were conducted to iden-
tify populations with a higher or lower level of
pollution-associated risk of death from any cause.

METHODS

MORTALITY DATA

We obtained the Medicare beneficiary denomi-
nator file from the Centers for Medicare and
Medicaid Services, which contains information
on all persons in the United States covered by
Medicare and more than 96% of the population
65 years of age or older. We constructed an open
cohort consisting of all beneficiaries in this age
group in the continental United States from
2000 through 2012, with all-cause mortality as
the outcome. For each beneficiary, we extracted

the date of death (up to December 31, 2012), age
at year of Medicare entry, year of entry, sex, race,
ZIP Code of residence, and Medicaid eligibility
(a proxy for low socioeconomic status). Persons
who were alive on January 1 of the year follow-
ing their enrollment in Medicare were entered
into the open cohort for the survival analysis.
Follow-up periods were defined according to
calendar years.

ASSESSMENT OF EXPOSURE TO AIR POLLUTION

Ambient levels of ozone and $PM_{2.5}$ were estimated
and validated on the basis of previously pub-
lished prediction models.[19,20] Briefly, we used an
artificial neural network that incorporated satel-
lite-based measurements, simulation outputs from
a chemical transport model, land-use terms,
meteorologic data, and other data to predict
daily concentrations of $PM_{2.5}$ and ozone at un-
monitored locations. We fit the neural network
with monitoring data from the Environmental
Protection Agency (EPA) Air Quality System
(AQS) (in which there are 1928 monitoring sta-
tions for $PM_{2.5}$ and 1877 monitoring stations for
ozone). We then predicted daily $PM_{2.5}$ and ozone
concentrations for nationwide grids that were
1 km by 1 km. Cross-validation indicated that
predictions were good across the entire study
area. The coefficients of determination (R^2) for
$PM_{2.5}$ and ozone were 0.83 and 0.80, respectively;
the mean square errors between the target and
forecasting values for $PM_{2.5}$ and ozone were 1.29 μg
per cubic meter and 2.91 ppb, respectively. Data
on daily air temperature and relative humidity
were retrieved from North American Regional
Reanalysis with grids that were approximately
32 km by 32 km; data were averaged annually.[21]

For each calendar year during which a person
was at risk of death, we assigned to that person
a value for the annual average $PM_{2.5}$ concentration,
a value for average ozone level during the warm
season (April 1 through September 30), and values
for annual average temperature and humidity ac-
cording to the ZIP Code of the person's residence.
The warm-season ozone concentration was used
to compare our results with those of previous
studies.[10] In this study, "ozone concentration"
refers to the average concentration during the
warm season, unless specified otherwise.

As part of a sensitivity analysis, we also ob-
tained data on $PM_{2.5}$ and ozone concentrations
from the EPA AQS and matched that data with

each person in our study on the basis of the nearest monitoring site within a distance of 50 km. (Details are provided in Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

STATISTICAL ANALYSIS

We fit a two-pollutant Cox proportional-hazards model with a generalized estimating equation to account for the correlation between ZIP Codes.[22] In this way, the risk of death from any cause associated with long-term exposure to $PM_{2.5}$ was always adjusted for long-term exposure to ozone, and the risk of death from any cause associated with long-term exposure to ozone was always adjusted for long-term exposure to $PM_{2.5}$, unless noted otherwise. We also conducted single-pollutant analyses for comparability. We allowed baseline mortality rates to differ according to sex, race, Medicaid eligibility, and 5-year categories of age at study entry. To adjust for potential confounding, we also obtained 15 ZIP-Code or county-level variables from various sources and a regional dummy variable to account for compositional differences in $PM_{2.5}$ across the United States (Table 1, and Section 1 in the Supplementary Appendix). We conducted this same statistical analysis but restricted it to person-years with $PM_{2.5}$ exposures lower than 12 μg per cubic meter and ozone exposures lower than 50 ppb (low-exposure analysis) (Table 1, and Section 1 in the Supplementary Appendix).

To identify populations at a higher or lower pollution-associated risk of death from any cause, we refit the same two-pollutant Cox model for some subgroups (e.g., male vs. female, white vs. black, and Medicaid eligible vs. Medicaid ineligible). To estimate the concentration-response function of air pollution and mortality, we fit a log-linear model with a thin-plate spline of both $PM_{2.5}$ and ozone and controlled for all the individual and ecologic variables used in our main analysis model (Section 7 in the Supplementary Appendix). To examine the robustness of our results, we conducted sensitivity analyses and compared the extent to which estimates of risk changed with respect to differences in confounding adjustment and estimation approaches (Sections S2 through S4 in the Supplementary Appendix).

Data on some important individual-level covariates were not available for the Medicare co-

hort, including data on smoking status, body-mass index (BMI), and income. We obtained data from the Medicare Current Beneficiary Survey (MCBS), a representative subsample of Medicare enrollees (133,964 records and 57,154 enrollees for the period 2000 through 2012), with individual-level data on smoking, BMI, income, and many other variables collected by means of telephone survey. Using MCBS data, we investigated how the lack of adjustment for these risk factors could have affected our calculated risk estimates in the Medicare cohort (Section 5 in the Supplementary Appendix). The computations in this article were run on the Odyssey cluster, which is supported by the FAS Division of Science, Research Computing Group, and on the Research Computing Environment, which is supported by the Institute for Quantitative Social Science in the Faculty of Arts and Sciences, both at Harvard University. We used R software, version 3.3.2 (R Project for Statistical Computing), and SAS software, version 9.4 (SAS Institute).

RESULTS

COHORT ANALYSES

The full cohort included 60,925,443 persons living in 39,716 different ZIP Codes with 460,310,521 person-years of follow-up. The median follow-up was 7 years. The total number of deaths was 22,567,924. There were 11,908,888 deaths and 247,682,367 person-years of follow-up when the $PM_{2.5}$ concentration was below 12 μg per cubic meter and 17,470,128 deaths and 353,831,836 person-years of follow-up when the ozone concentration was below 50 ppb. These data provided excellent power to estimate the risk of death at air-pollution levels below the current annual NAAQS for $PM_{2.5}$ and at low concentrations for ozone (Table 1).

Annual average $PM_{2.5}$ concentrations across the continental United States during the study period ranged from 6.21 to 15.64 μg per cubic meter (5th and 95th percentiles, respectively), and the warm-season average ozone concentrations ranged from 36.27 to 55.86 ppb (5th and 95th percentiles, respectively). The highest $PM_{2.5}$ concentrations were in California and the eastern and southeastern United States. The Mountain region and California had the highest ozone concentrations; the eastern states had lower ozone concentrations (Fig. 1).

Table 1. Cohort Characteristics and Ecologic and Meteorologic Variables.

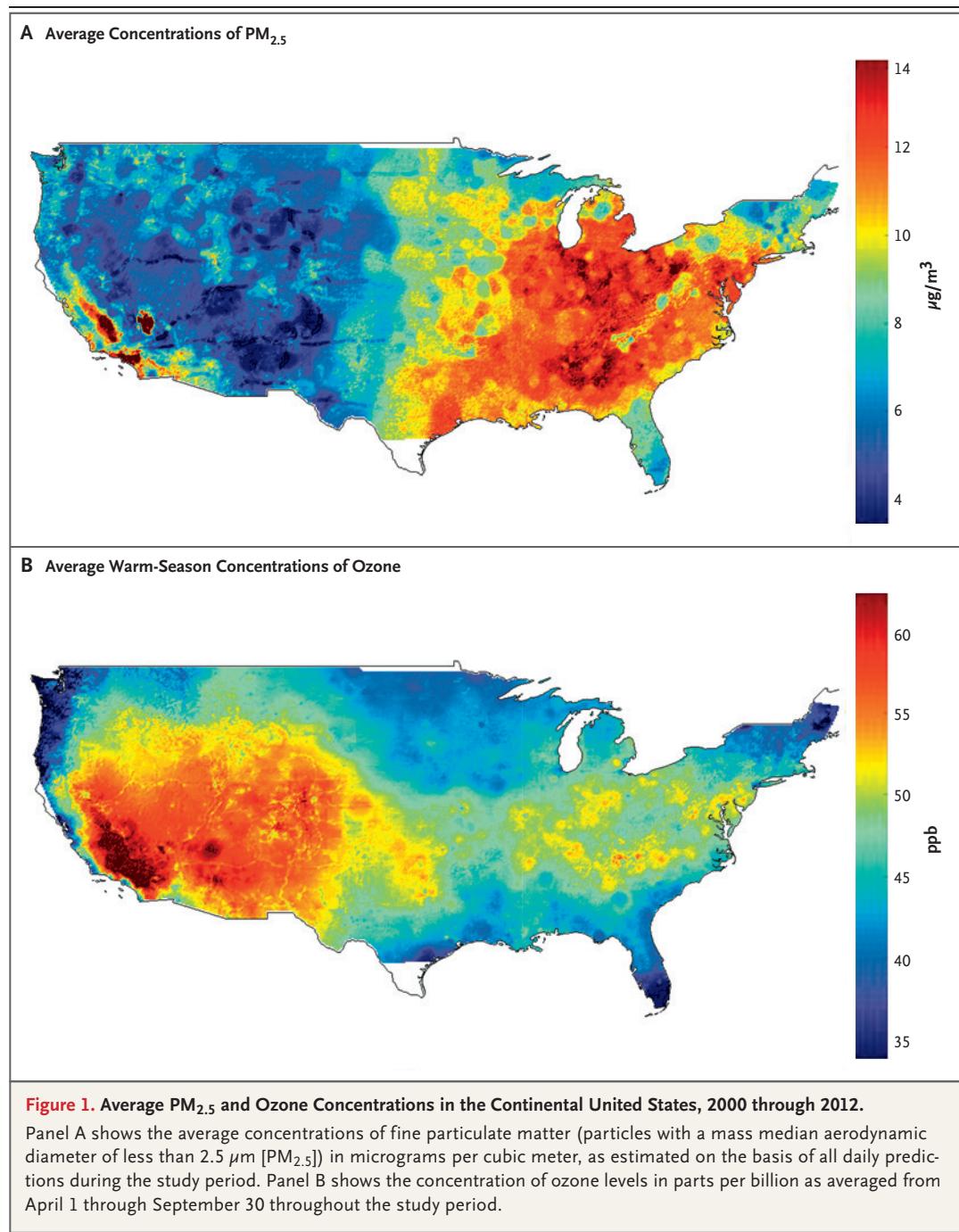| Characteristic or Variable	Entire Cohort	Ozone Concentration		PM₂.₅ Concentration	
		≥50 ppb*	<50 ppb	≥12 μg/m³	<12 μg/m³
Population					
Persons (no.)	60,925,443	14,405,094	46,520,349	28,145,493	32,779,950
Deaths (no.)	22,567,924	5,097,796	17,470,128	10,659,036	11,908,888
Total person-yr†	460,310,521	106,478,685	353,831,836	212,628,154	247,682,367
Median yr of follow-up	7	7	7	7	7
Average air-pollutant concentrations‡					
Ozone (ppb)	46.3	52.8	44.4	48.0	45.3
PM₂.₅ (μg/m³)	11.0	10.9	11.0	13.3	9.6
Individual covariates‡					
Male sex (%)	44.0	44.3	43.8	43.1	44.7
Race or ethnic group (%)§					
White	85.4	86.6	85.1	82.0	88.4
Black	8.7	7.2	9.2	12.0	5.9
Asian	1.8	1.8	1.8	2.1	1.6
Hispanic	1.9	2.0	1.9	1.9	1.9
Native American	0.3	0.6	0.3	0.1	0.6
Eligible for Medicaid (%)	16.5	15.3	16.8	17.8	15.3
Average age at study entry (yr)	70.1	69.7	70.2	70.1	70.0
Ecologic variables‡					
BMI	28.2	27.9	28.4	28.0	28.4
Ever smoked (%)	46.0	44.9	46.2	45.8	46.0
Population including all people 65 yr of age or older (%)					
Hispanic	9.5	13.4	8.4	8.4	10.0
Black	8.8	7.2	9.3	13.3	6.3
Median household income (1000s of $)	47.4	51.0	46.4	47.3	47.4
Median value of housing (1000s of $)	160.5	175.8	156.3	161.7	159.8
Below poverty level (%)	12.2	11.4	12.4	12.5	12.0
Did not complete high school (%)	32.3	30.7	32.7	35.3	30.6
Owner-occupied housing (%)	71.5	71.3	71.6	68.6	73.2
Population density (persons/km²)	3.2	0.7	3.8	4.8	2.2
Low-density lipoprotein level measured (%)	92.2	92.0	92.2	92.2	92.2
Glycated hemoglobin level measured (%)	94.8	94.6	94.8	94.8	94.8
≥1 Ambulatory visits (%)¶	91.7	92.2	91.6	91.7	91.7
Meteorologic variables‡					
Average temperature (°C)	14.0	14.9	13.8	14.5	13.7
Relative humidity (%)	71.1	60.8	73.9	73.7	69.6

* Summary statistics were calculated separately for persons residing in ZIP Codes where average ozone levels were below or above 50 ppb and where PM₂.₅ levels were below or above 12 μg per cubic meter. The value 12 μg per cubic meter was chosen as the current annual National Ambient Air Quality Standard (NAAQS) (e.g., the "safe" level) for PM₂.₅. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters) and ppb parts per billion.
† The number for total person-years of follow-up indicates the sum of individual units of time that the persons in the study population were at risk of death from 2000 through 2012.
‡ The average values for air pollution levels and for ecologic and meteorologic variables were computed by averaging values over all ZIP Codes from 2000 through 2012.
§ Data on race and ethnic group were obtained from Medicare beneficiary files.
¶ The variable for ambulatory visits refers to the average annual percentage of Medicare enrollees who had at least one ambulatory visit to a primary care physician.

Figure 1. Average PM₂.₅ and Ozone Concentrations in the Continental United States, 2000 through 2012.

Panel A shows the average concentrations of fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [PM₂.₅]) in micrograms per cubic meter, as estimated on the basis of all daily predictions during the study period. Panel B shows the concentration of ozone levels in parts per billion as averaged from April 1 through September 30 throughout the study period.

In a two-pollutant analysis, each increase of 10 μg per cubic meter in annual exposure to PM₂.₅ (estimated independently of ozone) and each increase of 10 ppb in warm-season exposure to ozone (estimated independently of PM₂.₅) was associated with an increase in all-cause mortality of 7.3% (95% confidence interval [CI], 7.1 to 7.5) and 1.1% (95% CI, 1.0 to 1.2), respec- tively. Estimates of risk based on predictive, ZIP- Code–specific assessments of exposure were slightly higher than those provided by the near- est data-monitoring site (Table 2). When we re- stricted the PM₂.₅ and ozone analyses to location- years with low concentrations, we continued to see significant associations between exposure and mortality (Table 2). Analysis of the MCBS

Table 2. Risk of Death Associated with an Increase of 10 μg per Cubic Meter in PM$_{2.5}$ or an Increase of 10 ppb in Ozone Concentration.*

Model	PM$_{2.5}$	Ozone
	hazard ratio (95% CI)	
Two-pollutant analysis		
Main analysis	1.073 (1.071–1.075)	1.011 (1.010–1.012)
Low-exposure analysis	1.136 (1.131–1.141)	1.010 (1.009–1.011)
Analysis based on data from nearest monitoring site (nearest-monitor analysis)†	1.061 (1.059–1.063)	1.001 (1.000–1.002)
Single-pollutant analysis‡	1.084 (1.081–1.086)	1.023 (1.022–1.024)

* Hazard ratios and 95% confidence intervals were calculated on the basis of an increase of 10 μg per cubic meter in exposure to PM$_{2.5}$ and an increase of 10 ppb in exposure to ozone.

† Daily average monitoring data on PM$_{2.5}$ and ozone were obtained from the Environmental Protection Agency Air Quality System. Daily ozone concentrations were averaged from April 1 through September 30 for the computation of warm-season averages. Data on PM$_{2.5}$ and ozone levels were obtained from the nearest monitoring site within 50 km. If there was more than one monitoring site within 50 km, the nearest site was chosen. Persons who lived more than 50 km from a monitoring site were excluded.

‡ For the single-pollutant analysis, model specifications were the same as those used in the main analysis, except that ozone was not included in the model when the main effect of PM$_{2.5}$ was estimated and PM$_{2.5}$ was not included in the model when the main effect of ozone was estimated.

subsample provided strong evidence that smoking and income are not likely to be confounders because they do not have a significant association with PM$_{2.5}$ or ozone (Section 5 in the Supplementary Appendix).

SUBGROUP ANALYSES

Subgroup analyses revealed that men; black, Asian, and Hispanic persons; and persons who were eligible for Medicaid (i.e., those who had low socioeconomic status) had a higher estimated risk of death from any cause in association with PM$_{2.5}$ exposure than the general population. The risk of death associated with ozone exposure was higher among white, Medicaid-eligible persons and was significantly below 1 in some racial subgroups (Fig. 2). Among black persons, the effect estimate for PM$_{2.5}$ was three times as high as that for the overall population (Table S3 in the Supplementary Appendix). Overall, the risk of death associated with ozone exposure was smaller and somewhat less robust than that associated with PM$_{2.5}$ exposure. We also detected a small but significant interaction between ozone exposure and PM$_{2.5}$ exposure (Table S8 in the Supplementary Appendix). Our thin-plate–spline fit indicated a relationship between PM$_{2.5}$, ozone, and all-cause mortality that was almost linear, with no signal of threshold down to 5 μg per

cubic meter and 30 ppb, respectively (Fig. 3, and Fig. S8 in the Supplementary Appendix).

DISCUSSION

This study involving an open cohort of all persons receiving Medicare, including those from small cities and rural areas, showed that long-term exposures to PM$_{2.5}$ and ozone were associated with an increased risk of death, even at levels below the current annual NAAQS for PM$_{2.5}$. Furthermore, the study showed that black men and persons eligible to receive Medicaid had a much higher risk of death associated with exposure to air pollution than other subgroups. These findings suggest that lowering the annual NAAQS may produce important public health benefits overall, especially among self-identified racial minorities and people with low income.

The strengths of this study include the assessment of exposure with high spatial and temporal resolution, the use of a cohort of almost 61 million Medicare beneficiaries across the entire continental United States followed for up to 13 consecutive years, and the ability to perform subgroup analyses of the health effects of air pollution on groups of disadvantaged persons. However, Medicare claims do not include extensive individual-level data on behavioral risk fac-
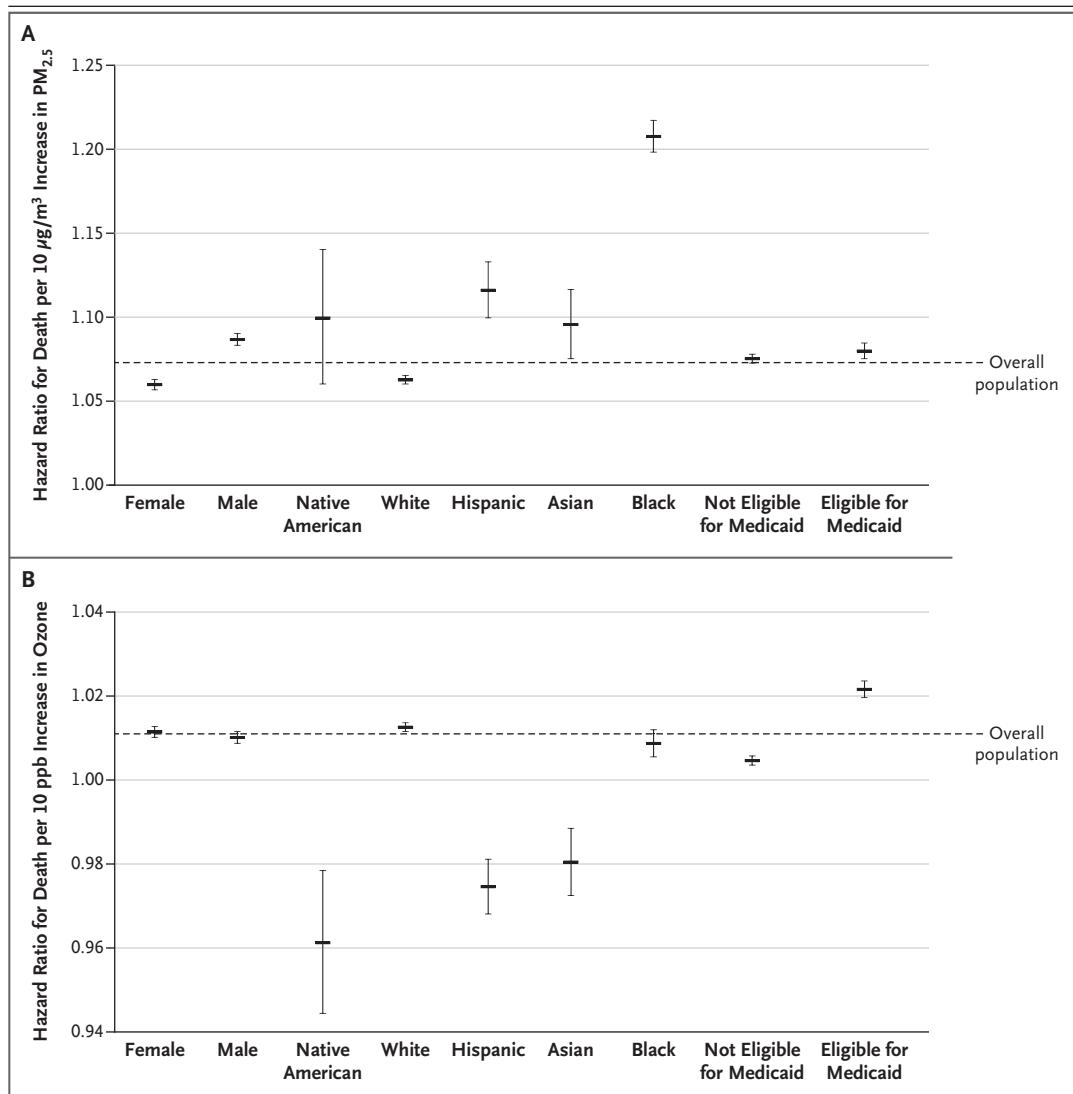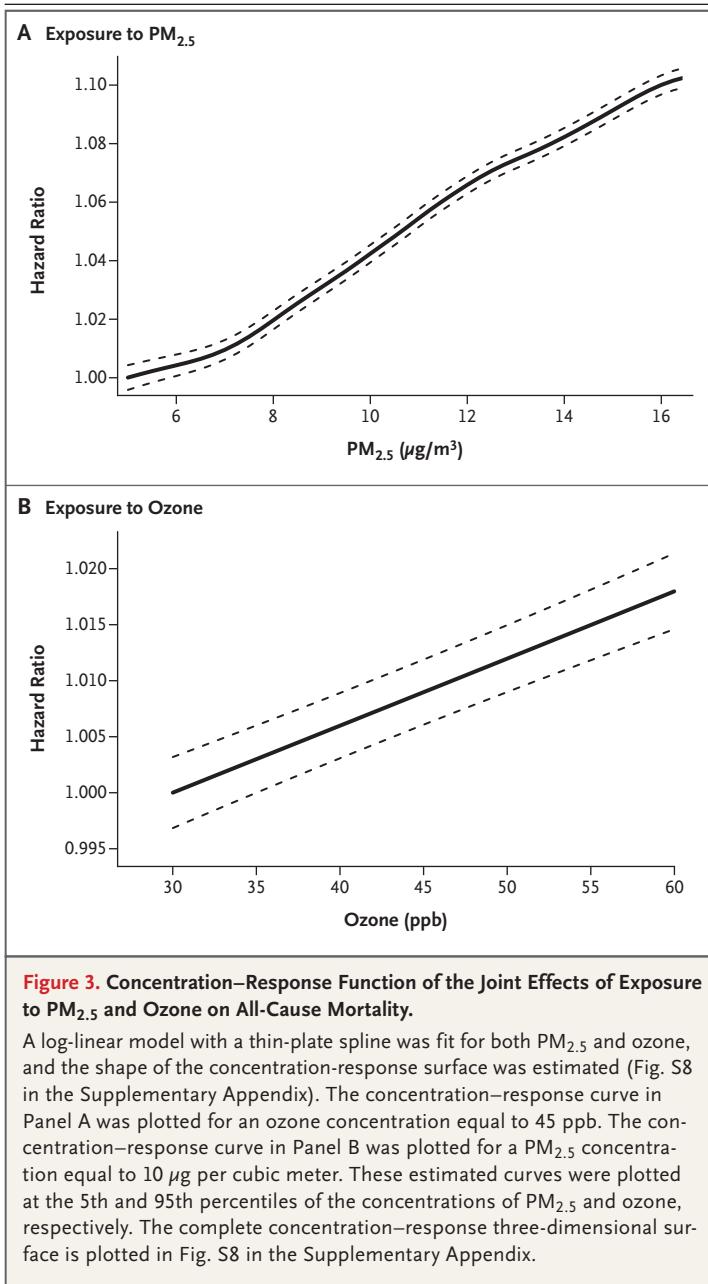
Figure 2. Risk of Death Associated with an Increase of 10 μg per Cubic Meter in PM₂.₅ Concentrations and an Increase of 10 ppb in Ozone Exposure, According to Study Subgroups.

Hazard ratios and 95% confidence intervals are shown for an increase of 10 μg per cubic meter in PM₂.₅ and an increase of 10 parts per billion (ppb) in ozone. Subgroup analyses were conducted by first restricting the population (e.g., considering only male enrollees). The same two-pollutant analysis (the main analysis) was then applied to each subgroup. Numeric results are presented in Tables S3 and S4 in the Supplementary Appendix. Dashed lines indicate the estimated hazard ratio for the overall population.

tors, such as smoking and income, which could be important confounders. Still, our analysis of the MCBS subsample (Table S6 in the Supplementary Appendix) increased our level of confidence that the inability to adjust for these individual-level risk factors in the Medicare cohort did not lead to biased results (Section 5 in the Supplementary Appendix). In another study, we analyzed a similar Medicare subsample with detailed individual-level data on smoking, BMI, and many other potential confounders linked to Medicare claims.[23] In that analysis, we found that for mortality and hospitalization, the risks of exposure to PM₂.₅ were not sensitive to the additional control of individual-level variables that were not available in the whole Medicare population.

Figure 3. Concentration–Response Function of the Joint Effects of Exposure to PM₂.₅ and Ozone on All-Cause Mortality.

A log-linear model with a thin-plate spline was fit for both PM₂.₅ and ozone, and the shape of the concentration-response surface was estimated (Fig. S8 in the Supplementary Appendix). The concentration–response curve in Panel A was plotted for an ozone concentration equal to 45 ppb. The concentration–response curve in Panel B was plotted for a PM₂.₅ concentration equal to 10 μg per cubic meter. These estimated curves were plotted at the 5th and 95th percentiles of the concentrations of PM₂.₅ and ozone, respectively. The complete concentration–response three-dimensional surface is plotted in Fig. S8 in the Supplementary Appendix.

We also found that our results were robust when we excluded individual and ecologic covariates from the main analysis (Fig. S2 and Table S2 in the Supplementary Appendix), when we stratified age at entry into 3-year and 4-year categories rather than the 5 years used in the main analysis (Fig. S3 in the Supplementary Appendix), when we varied the estimation procedure (by means of a generalized estimating equation as opposed to mixed effects) (Tables S3 and S4 in the Supplementary Appendix), and when we used different types of statistical software (R, version 3.3.2, vs. SAS, version 9.4). Finally, we found that our results were consistent with others published in the literature (Section 6 in the Supplementary Appendix).[5,17,24-28]

There was a significant association between PM₂.₅ exposure and mortality when the analysis was restricted to concentrations below 12 μg per cubic meter, with a steeper slope below that level. This association indicated that the health-benefit-per-unit decrease in the concentration of PM₂.₅ is larger for PM₂.₅ concentrations that are below the current annual NAAQS than the health benefit of decreases in PM₂.₅ concentrations that are above that level. Similar, steeper concentration-response curves at low concentrations have been observed in previous studies.[29] Moreover, we found no evidence of a threshold value — the concentration at which PM₂.₅ exposure does not affect mortality — at concentrations as low as approximately 5 μg per cubic meter (Fig. 3); this finding is similar to those of other studies.[18,30]

The current ozone standard for daily exposure is 70 ppb; there is no annual or seasonal standard. Our results strengthen the argument for establishing seasonal or annual standards. Moreover, whereas time-series studies have shown the short-term effects of ozone exposure, our results indicate that there are larger effect sizes for longer-term ozone exposure, including in locations where ozone concentrations never exceed 70 ppb. Unlike the American Cancer Society Cancer Prevention Study II,[9,10] our study reported a linear connection between ozone concentration and mortality. This finding is probably the result of the interaction between PM₂.₅ and ozone (Section 7 in the Supplementary Appendix). The significant, linear relationship between seasonal ozone levels and all-cause mortality indicates that current risk assessments,[31-33] which incorporate only the acute effects of ozone exposure on deaths each day from respiratory mortality, may be substantially underestimating the contribution of ozone exposure to the total burden of disease.

The enormous sample size in this study, which includes the entire Medicare cohort, allowed for unprecedented accuracy in the estimation of risks among racial minorities and disadvantaged subgroups. The estimate of effect size for PM₂.₅ expo-

sure was greatest among male, black, and Medicaid-eligible persons. We also estimated risks in subgroups of persons who were eligible for Medicaid and in whites and blacks alone to ascertain whether the effect modifications according to race and Medicaid status were independent. We found that black persons who were not eligible for Medicaid (e.g., because of higher income) continued to have an increased risk of death from exposure to $PM_{2.5}$ (Fig. S4 in the Supplementary Appendix). In addition, we found that there was a difference in the health effects of $PM_{2.5}$ exposure between urban and rural populations, a finding that may be due to compositional differences in the particulates (Table S3 Supplementary Appendix).

Although the Medicare cohort includes only the population of persons 65 years of age or older, two thirds of all deaths in the United States occur in people in that age group. Although our exposure models had excellent out-of-sample predictive power on held-out monitors, they do have limitations. Error in exposure assessment remains an issue in this type of analysis and could attenuate effect estimates for air pollution.[34]

The overall association between air pollution and human health has been well documented since the publication of the landmark Harvard Six Cities Study in 1993.[25] With air pollution declining, it is critical to estimate the health effects of low levels of air pollution — below the current NAAQS — to determine whether these levels are adequate to minimize the risk of death. Since the Clean Air Act requires the EPA to set air-quality standards that protect sensitive populations, it is also important to focus more effort on estimating effect sizes in potentially sensitive populations in order to inform regulatory policy going forward.

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