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Air Pollution and Mortality in the Medicare Population

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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 [$\text{PM}_{2.5}$]) 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ of less than 12 μg per cubic meter and ozone of less than 50 ppb, the same increases in $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$, 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 $\text{PM}_{2.5}$ 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.)

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THE ADVERSE HEALTH EFFECTS ASSOCIATED with long-term exposure to air pollution are well documented.^{1,2} Studies suggest that fine particles (particles with a mass median aerodynamic diameter of less than 2.5 μm [$\text{PM}_{2.5}$]) are a public health concern,³ with exposure 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$).¹⁴⁻¹⁸ However, most of these studies have included populations whose socioeconomic status is higher than the national average and who reside in well-monitored urban areas. Consequently, these studies provide limited information on the health effects of long-term exposure 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 conducted 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 $\text{PM}_{2.5}$ 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 identify populations with a higher or lower level of pollution-associated risk of death from any cause.

METHODS

MORTALITY DATA

We obtained the Medicare beneficiary denominator 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 following 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 $\text{PM}_{2.5}$ were estimated and validated on the basis of previously published prediction models.^{19,20} Briefly, we used an artificial neural network that incorporated satellite-based measurements, simulation outputs from a chemical transport model, land-use terms, meteorologic data, and other data to predict daily concentrations of $\text{PM}_{2.5}$ and ozone at unmonitored 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 stations for $\text{PM}_{2.5}$ and 1877 monitoring stations for ozone). We then predicted daily $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ and ozone were 0.83 and 0.80, respectively; the mean square errors between the target and forecasting values for $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ concentration, a value for average ozone level during the warm season (April 1 through September 30), and values for annual average temperature and humidity according 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 obtained data on $\text{PM}_{2.5}$ and ozone concentrations from the EPA AQS and matched that data with



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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		PM _{2.5} Concentration	
		≥50 ppb*	<50 ppb	≥12 μg/m ³	<12 μg/m ³
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
PM _{2.5} (μg/m ³)	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/km ²)	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

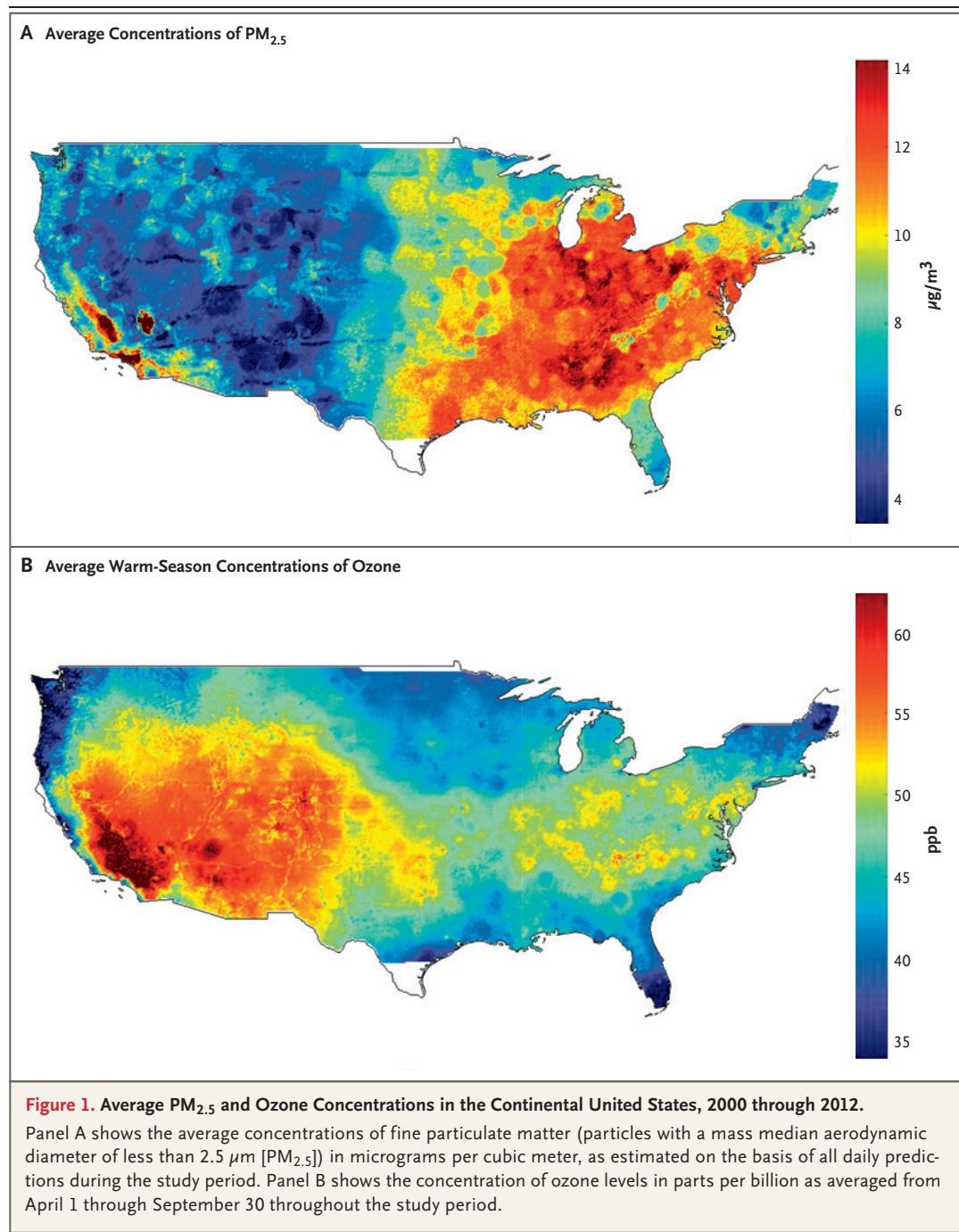
* Summary statistics were calculated separately for persons residing in ZIP Codes where average ozone levels were below or above 50 ppb and where PM_{2.5} levels were below or above 12 μg per cubic meter. The value 12 μg per cubic meter was chosen as the current annual National Ambient Air Quality Standard (NAAQS) (e.g., the “safe” level) for PM_{2.5}. 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.



In a two-pollutant analysis, each increase of 10 μg per cubic meter in annual exposure to PM_{2.5} (estimated independently of ozone) and each increase of 10 ppb in warm-season exposure to ozone (estimated independently of PM_{2.5}) 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 nearest data-monitoring site (Table 2). When we restricted the PM_{2.5} 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 $\text{PM}_{2.5}$ or an Increase of 10 ppb in Ozone Concentration.*

Model	<i>hazard ratio (95% CI)</i>	
	$\text{PM}_{2.5}$	Ozone
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 $\text{PM}_{2.5}$ and an increase of 10 ppb in exposure to ozone.

[†] Daily average monitoring data on $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ was estimated and $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ exposure. We also detected a small but significant interaction between ozone exposure and $\text{PM}_{2.5}$ exposure (Table S8 in the Supplementary Appendix). Our thin-plate-spline fit indicated a relationship between $\text{PM}_{2.5}$, 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 $\text{PM}_{2.5}$ and ozone were associated with an increased risk of death, even at levels below the current annual NAAQS for $\text{PM}_{2.5}$. 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-

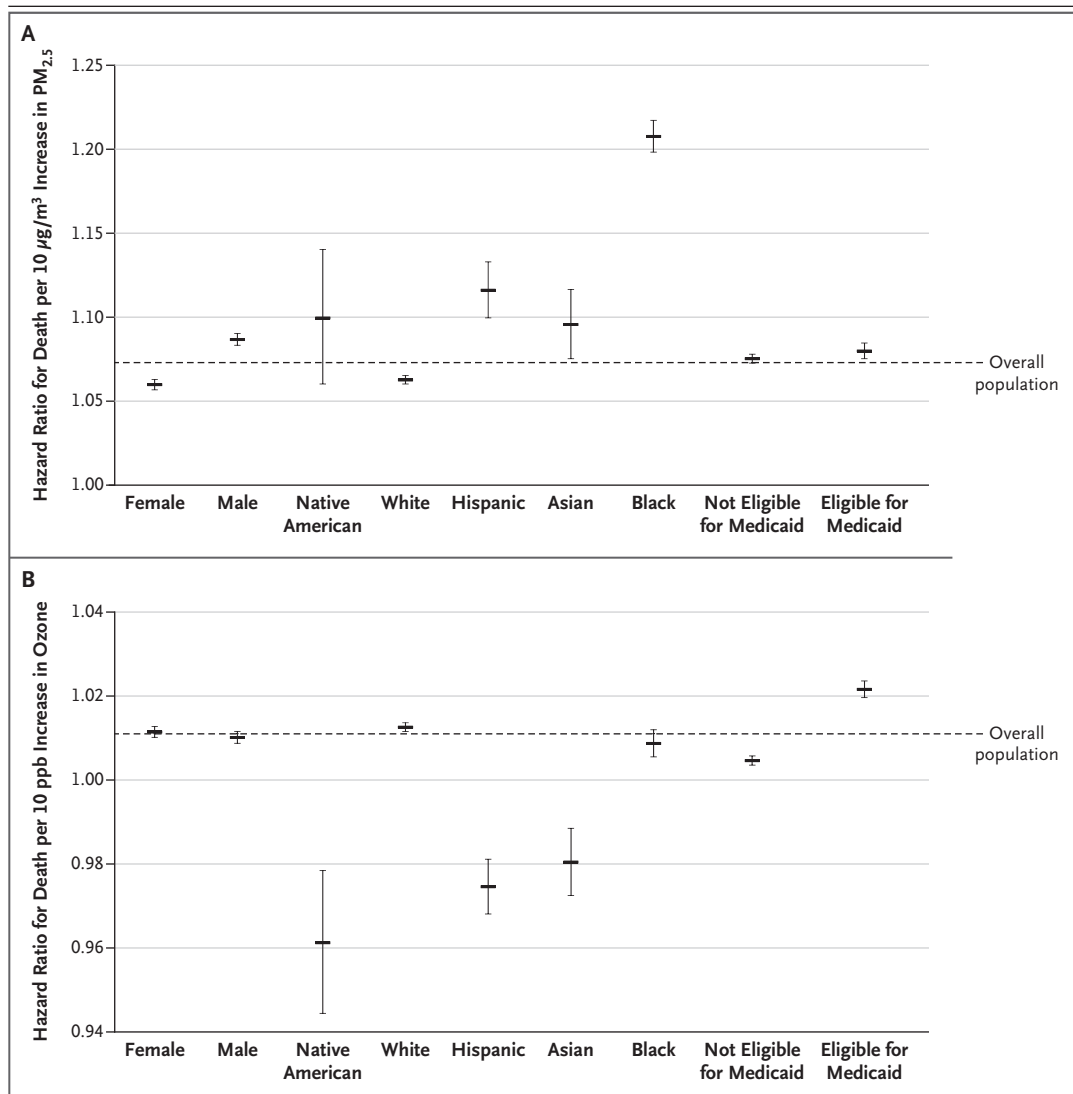
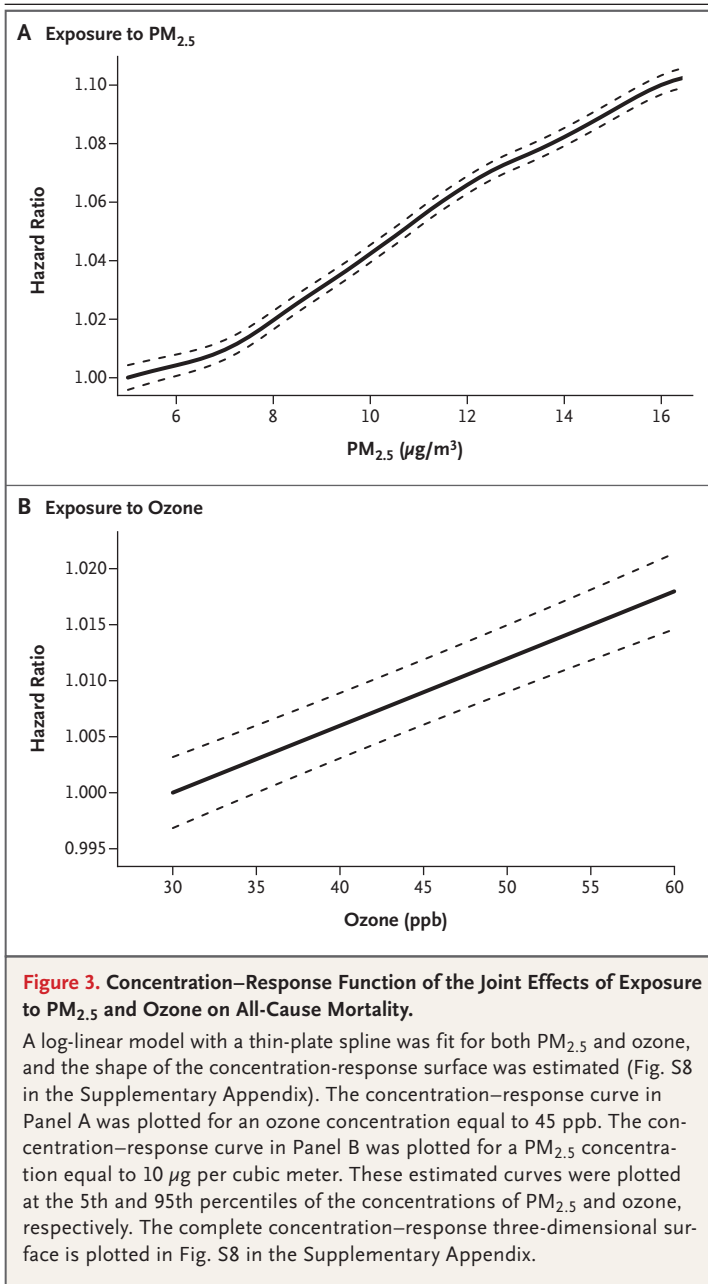


Figure 2. Risk of Death Associated with an Increase of 10 μg per Cubic Meter in $\text{PM}_{2.5}$ Concentrations and an Increase of 10 ppb in Ozone Exposure, According to Study Subgroups.

Hazard ratios and 95% confidence intervals are shown for an increase of 10 μg per cubic meter in $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ were not sensitive to the additional control of individual-level variables that were not available in the whole Medicare population.



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 PM_{2.5} 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 PM_{2.5} is larger for PM_{2.5} concentrations that are below the current annual NAAQS than the health benefit of decreases in PM_{2.5} 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 PM_{2.5} 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 PM_{2.5} 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 PM_{2.5} 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.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the funding agencies. Furthermore, these agencies do not endorse the purchase of any commercial products or services related to this publication.

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Ambient (outdoor) air quality and health. Fact sheet no. 313. Updated March 2014. Geneva: World Health Organization, 2015.
2. Brook RD, Rajagopalan S, Pope CA III, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010; 121:2331-78.
3. Lim SS, Vos T, Flaxman AD, 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;380:2224-60.
4. Crouse DL, Peters PA, Hystad P, et al. Ambient PM_{2.5}, 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;123:1180-6.
5. Wang Y, Kloog I, Coull BA, Kosheleva A, Zanobetti A, Schwartz JD. Estimating causal effects of long-term PM_{2.5} exposure on mortality in New Jersey. *Environ Health Perspect* 2016;124:1182-8.
6. Beelen R, Raaschou-Nielsen O, Stafoglia M, et al. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* 2014;383:785-95.
7. Atkinson RW, Butland BK, Dimitropoulou C, et al. Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies. *BMJ Open* 2016;6(2):e009493.
8. Hao Y, Balluz L, Strosnider H, Wen XJ, Li C, Qualters JR. Ozone, fine particulate matter, and chronic lower respiratory disease mortality in the United States. *Am J Respir Crit Care Med* 2015;192:337-41.
9. Turner MC, Jerrett M, Pope CA III, et al. Long-term ozone exposure and mortality in a large prospective study. *Am J Respir Crit Care Med* 2016;193:1134-42.
10. Jerrett M, Burnett RT, Pope CA III, et al. Long-term ozone exposure and mortality. *N Engl J Med* 2009;360:1085-95.
11. Krewski D, Jerrett M, Burnett RT, et al. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst* 2009;140:5-114, discussion 115-136.
12. Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med* 2013; 187:1226-33.
13. Ostro B, Hu J, Goldberg D, et al. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. *Environ Health Perspect* 2015;123:549-56.
14. Crouse DL, Peters PA, van Donkelaar A, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ Health Perspect* 2012;120:708-14.
15. Wang Y, Shi L, Lee M, et al. Long-term exposure to PM_{2.5} and mortality among older adults in the southeastern US. *Epidemiology* 2017;28:207-14.
16. Thurston GD, Ahn J, Cromar KR, et al. Ambient particulate matter air pollution exposure and mortality in the NIH-AARP Diet and Health cohort. *Environ Health Perspect* 2016;124:484-90.
17. Pinault L, Tjepkema M, Crouse DL, et al.

- Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian Community Health Survey cohort. *Environ Health Perspect* 2016;15:18.
18. Shi L, Zanobetti A, Kloog I, et al. Low-concentration PM_{2.5} and mortality: estimating acute and chronic effects in a population-based study. *Environ Health Perspect* 2016;124:46-52.
 19. Di Q, Kloog I, Koutrakis P, Lyapustin A, Wang Y, Schwartz J. Assessing PM_{2.5} exposures with high spatiotemporal resolution across the continental United States. *Environ Sci Technol* 2016;50:4712-21.
 20. Di Q, Rowland S, Koutrakis P, Schwartz J. A hybrid model for spatially and temporally resolved ozone exposures in the continental United States. *J Air Waste Manag Assoc* 2017;67:39-52.
 21. Kalnay E, Kanamitsu M, Kistler R, et al. The NCEP/NCAR 40-Year Reanalysis Project. *Bull Am Meteorol Soc* 1996;77:437-71.
 22. Lee EW, Wei L, Amato DA, Leurgans S. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein JP, Goel PK, eds. *Survival analysis: state of the art*. Berlin: Springer, 1992:237-47.
 23. Makar M, Antonelli J, Di Q, Cutler D, Schwartz J, Dominici F. Estimating the causal effect of low levels of fine particulate matter on hospitalization. *Epidemiology*, May 25, 2016 (http://journals.lww.com/epidem/Abstract/publishahead/Estimating_the_Causal_Effect_of_Low_Levels_of_Fine.98844.aspx).
 24. Kioumourtzoglou MA, Schwartz J, James P, Dominici F, Zanobetti A. PM_{2.5} and mortality in 207 US cities: modification by temperature and city characteristics. *Epidemiology* 2016;27:221-7.
 25. Dockery DW, Pope CA III, Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 1993;329:1753-9.
 26. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect* 2012;120:965-70.
 27. Pope CA III, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109:71-7.
 28. Eftim SE, Samet JM, Janes H, McDermott A, Dominici F. Fine particulate matter and mortality: a comparison of the six cities and American Cancer Society cohorts with a Medicare cohort. *Epidemiology* 2008;19:209-16.
 29. Pope CA III, Burnett RT, Krewski D, et al. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation* 2009;120:941-8.
 30. Schwartz J, Coull B, Laden F, Ryan L. The effect of dose and timing of dose on the association between airborne particles and survival. *Environ Health Perspect* 2008;116:64-9.
 31. Smith RL, Xu B, Switzer P. Reassessing the relationship between ozone and short-term mortality in U.S. urban communities. *Inhal Toxicol* 2009;21:Suppl 2:37-61.
 32. 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;177:184-9.
 33. Regulatory impact analysis of the final revisions to the National Ambient Air Quality Standards for ground-level ozone. Research Triangle Park, NC: Environmental Protection Agency, 2015 (<https://www.epa.gov/naaqs/regulatory-impact-analysis-final-revisions-national-ambient-air-quality-standards-ground-level>).
 34. Spiegelman D. Evaluating public health interventions. 4. The Nurses' Health Study and methods for eliminating bias attributable to measurement error and misclassification. *Am J Public Health* 2016;106:1563-6.

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