September 5, 2017

Dr. Kathy Partin
Director
Office of Research Integrity
U.S. Department of Health and Human Services
Office of Research Integrity
1101 Wootton Parkway, Suite 750
Rockville, Maryland 20852

Re; Request for Investigation of Research Misconduct

Dear Dr. Partin,

I am requesting that the Office of Research Integrity (ORI) commence an investigation regarding research misconduct committed by the authors of the following study ("NEJM study"):

> *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. N Engl J Med 2017; 376:2513-2522 June 29, 2017DOI: 10.1056/NEJMoa1702747.*

A copy of the study is attached. The reasons for the request are set out below.

I. ORI has jurisdiction in this matter as the NEJM study was funded by multiple grants from the Department of Health and Human Services.

The NEJM study was funded by the National Institutes of Health (Grant Nos. R01 ES024332-01A1, ES-000002, ES024012, R01ES026217) and the National Cancer Institute (Grant No. R35CA197449).

II. Misrepresenting research so it is not accurately represented in the research record is misconduct.

As the National Institutes of Health and the National Cancer Institute are parts of the Department of Health and Human Services, this matter is governed by the standards established in 42 CFR Part 93 — Public Health Service Policies On Research Misconduct. Thereunder, "research misconduct" means:

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... fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

(b) Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record...

(d) Research misconduct does not include honest error or differences of opinion. [Emphasis added]

The case is made below that the omissions in the case of the NEJM study not only misrepresent the research record but also are not the product of mere honest error or differences of opinion.

III. Facts: The NEJM study reports in no uncertain terms that $PM_{2.5}$ causes premature mortality.

The NEJM study concludes in main part:[1]

This study... showed that long-term exposures to $PM_{2.5}$... were associated with an increased risk of death, even at levels below the current [regulatory standard]...

The overall association between air pollution and [premature mortality] has been well-documented since the publication of the landmark Harvard Six Cities Study in 1993.

The absolute certainty of these statements, made without qualification, inspired an editorial (attached) by the *New England Journal of Medicine* entitled, "Air Pollution Still Kills." The editorial concludes with the sentence: "Do we really want to breathe air that kills us?"[2]

Although the NEJM study authors carefully, if not cynically, used the term "associated with" rather than "causes," there can be no doubt as to their intent to convey a false certainty that $PM_{2.5}$ causes death.

IV. The researchers have committed misconduct by knowingly misrepresenting the research record.

A. No mention made of contradictory research.

The NEJM study authors failed to mention the existence of the contradictory findings of numerous other $PM_{2.5}$-mortality epidemiologic studies despite

[1] NEJM study, at 2518.
[2] "Air Pollution Still Kills", at 2592.

knowledge by the authors/editors of their existence. Just some examples of recent significant contradictory findings include the following (Citation/Excerpt from Abstract/Comment):

- **Young S et al. Air Quality and Acute Deaths in California. *Regul Toxicol Pharmacol*. https://doi.org/10.1016/j.yrtph.2017.06.003.** (In press, online June 13, 2017). "Neither PM2.5 nor ozone added appreciably to the prediction of daily deaths. These results call into question the widespread belief that association between air quality and acute deaths is causal/near-universal." Although this study became available at *Regulatory Toxicology and Pharmacology* in June 2017, it was first made available on Cornell University's arXiv.orgweb site on February 10, 2015 (https://arxiv.org/abs/1502.03062). The study was also presented at a poster session at the 2016 annual meeting of the Health Effects Institute (HEI), one of the funders of the NEJM study.

- **Enstrom J. Fine Particulate Matter and Total Mortality in Cancer Prevention Study Cohort Reanalysis. *Dose-Response*. http://journals.sagepub.com/doi/10.1177/1559325817693345.** "No significant relationship between $PM_{2.5}$ and total mortality in the CPS II cohort was found when the best available $PM_{2.5}$ data were used." Not only was this study published three months ahead of the NEJM study The editor-in-chief of the *New England Journal of Medicine*, Jeffrey M. Drazen, personally rejected the study for publication in the NEJM on June 28, 2016.

- **Greven S et al. An Approach to the Estimation of Chronic Air Pollution Effects Using Spatio-Temporal Information. *J. American Statistical Association*. http://amstat.tandfonline.com/doi/abs/10.1198/jasa.2011.ap09392 (Published January 12, 2012).**"[W]e are not able to demonstrate any change in life expectancy for a reduction in $PM_{2.5}$." One of the co-authors of this study, Francesca Dominici, is also a co-author on the NEJM study.

There are many other studies in the published literature that dispute the purported link between $PM_{2.5}$ and premature morality. But the above-cited studies, in particular, were well known to those involved with the NEJM study. NEJM study funder HEI, NEJM study author Dominici and the NEJM study editor-in-chief Drazen all knew of these contradictory findings, yet there is still no mention or allusion to these or other studies in the NEJM study. This can only have occurred by design. The omissions cannot be viewed as inadvertent or honest error.

The NEJM study authors also omitted other key information that would have more accurately placed their results in the context of the research record.

B. The NEJM study authors omitted mentioning the limitations of epidemiology, including that there is no biological plausibility for the notion that $PM_{2.5}$ kills.

Like all epidemiologic studies, the NEJM study is purely statistical in nature and cannot by itself establish a causal relationship between $PM_{2.5}$ and premature death. As the U.S. Environmental Protection Agency (EPA), which is responsible for regulating $PM_{2.5}$ in outdoor air, acknowledged to a federal court in litigation involving $PM_{2.5}$:[3]

> *[E]pidemiological studies do not generally provide direct evidence of causation; instead they indicate the existence or absence of a statistical relationship. Large population studies cannot assess the biological mechanisms that could explain how inhaling [PM2.5] can cause illness or death in susceptible individuals.*

To assess the "biological mechanisms" that could explain how inhaling $PM_{2.5}$ could cause death, animal toxicology or human clinical research is necessary. But none of the extant $PM_{2.5}$ animal toxicology, human medical research or human clinical research studies supports the hypothesis that $PM_{2.5}$ kills. In short, there is absolutely no physical evidence that supports the claim that $PM_{2.5}$ kills.

In addition to the absence of biological, medical, or other physical evidence supporting the notion that $PM_{2.5}$ in outdoor air kills, there is a host of real-world evidence ranging from the tobacco epidemiology to the epidemiology of workers with high exposure to $PM_{2.5}$ (e.g., coal miners and diesel workers) to other high, real-world $PM_{2.5}$ exposures (e.g., prior lethal air pollution incidents, ongoing high $PM_{2.5}$ exposures in China and India, and forest fires) that plainly contradict the $PM_{2.5}$-kills hypothesis. [4]

The absence of physical evidence that $PM_{2.5}$ kills has been admitted by the EPA in its explanation for conducting human experiments involving $PM_{2.5}$. In explaining to a federal court why EPA researchers wanted to expose elderly human subjects to exceedingly high doses of $PM_{2.5}$, EPA stated:[5]

> *[Controlled human experiments] help to determine whether the mathematical associations between ambient (outdoor) levels of air pollutants and health effects seen in large-scale epidemiologic studies are biologically plausible (or not).*

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[3] *See* https://junkscience.com/wp-content/uploads/2016/05/EPA's -Memo-in-opp-to-TRO-1.pdf, at 6.
[4] *See* Milloy, Steve. *Scare Pollution: Why and How to Fix the EPA*. Bench Press (2016). https://www.amazon.com/Scare-Pollution-Why-How-Fix/dp/0998259713.
[5] *Id.*, at 5.

But none of the hundreds of EPA human study subjects exposed to $PM_{2.5}$ has ever been harmed in the slightest by $PM_{2.5}$.

In short, if $PM_{2.5}$ kills anyone as the NEJM study authors claim to have demonstrated, no physical evidence of this phenomenon has ever been produced by anyone at anytime. The NEJM study authors failed to acknowledge this reality and its consequences for their dubious statistical results (discussed below).

C. The NEJM study authors misrepresented the interpretation of their statistical analysis.

The NEJM study relies on a statistical precision that simply doesn't exist in real-world epidemiology because of unavoidable uncertainty surrounding the data. The NEJM study is a great example of the "garbage-in, garbage-out" phenomenon.

While the NEJM study purports to causally associate $PM_{2.5}$ with premature mortality based on a hazard ratio on the order of 1.08, every epidemiologist knows that hazard ratios below the level of 2.0 are unreliable.

This is has been a long-held view maintained by bodies such as the National Academy of Sciences[6] and National Cancer Institute, which stated in a media release on October 26, 1994:

> *In epidemiologic research, relative risks of less than 2 are considered small and usually difficult to interpret. Such increases may be due to chance, statistical bias or effects of confounding factors that are sometimes not evident.*

In his highly-valued 1965 essay in the *Proceedings of the Royal Society of Medicine*, entitled "The Environment and Disease: Association or Causation," Sir Austin Bradford Hill described the criteria for evaluating epidemiologic studies and discounted hazard ratios below 2.0:[7]

> *First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the enormous increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'*

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[6] *See* https://www.fjc.gov/sites/default/files/2015/SciMan3D01.pdf, at 612.
[7] *See* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1898525/

> *To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times as great. On the other hand the death rate from coronary thrombosis in smokers is no more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some feature of life that may go hand-in-hand with smoking – features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess of cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic 'you can't prove it, there may be such a feature'.*

The reason hazard rations below 2.0 are unreliable is because much epidemiologic data are incomplete, guesstimated and/or otherwise of dubious validity. The unreliable data problem is writ large in the NEJM study:

- **No information on cause of death.** The NEJM study data lacks information on the cause of death for any individual in the Medicare population — so deaths not possibly caused by $PM_{2.5}$ (e.g., those resulting from accidents, homicide/suicide, cancer, etc.) are included in the study population.

- **Guesstimated exposure data.** The NEJM study relies entirely on guesstimated exposure data extrapolated from relatively few air monitor measurements. These guesstimated data have no relationship to actual $PM_{2.5}$ exposures among the study subjects which are affected in the short-term and long-term by occupational, residential and lifestyle $PM_{2.5}$ exposures that are not measured by outdoor air monitors. Smokers in particular inhale thousands of time more $PM_{2.5}$ from tobacco than they inhale from outdoor air. In studies like the NEJM study-touted Harvard Six City Study, about 50% of the study population are either current or former smokers. In these cases, $PM_{2.5}$ exposures from outdoor air pale in comparison and are insignificant to $PM_{2.5}$ exposures from smoking. Attribution of death to $PM_{2.5}$ in outdoor air is an exercise in statistical absurdity.

- **Confounding risk factors ignored.** The NEJM study fails to consider confounding factors such as smoking, socioeconomic status and any of the other myriad potential competing risk factors for death. In essence, the NEJM study assumes all "excess" deaths are $PM_{2.5}$-related.

> A particularly egregious example of the NEJM study authors' failure to consider confounding risk factors occurred a mere two weeks after the NEJM study was published. On July 13, 2017, the NEJM published another study from Harvard School of Public Health researchers reporting that poor diet was associated with premature mortality.[8] Despite the near simultaneity of this study with the NEJM study, the authors of the NEJM study did not consider diet as a potential confounding factor for mortality. Both studies involve Harvard School of Public Health researchers studying the same health endpoint (premature mortality) and published by the same journal (*New England Journal of Medicine*), but neither study considers other study's exposure of concern as a confounding factor in its own results. Are we really to believe this failure was inadvertent?

Also, the NEJM study authors repeatedly present their hazard ratio estimates as "risk" estimates. It is "Epidemiology 101" that, despite terminology like "relative risk," hazard ratios are not estimates of risk. Hazard ratios are merely measures of the statistical correlation between exposure and health endpoints in specific study populations. This "strength of association" measurement may then be used along with all the (Bradford Hill) criteria in determining whether actual cause-and-effect can be identified. But hazard ratio estimates have nothing to do with risk per se. Communicating hazard ratios as risk is deceptive.

D. NEJM study authors misrepresent the Harvard Six Cities Study.

As cited above, the NEJM study authors base the credibility of their results on the allegedly "landmark Harvard Six Cities Study of 1993." In addition to the fact that the Harvard Six Cities Study is yet another dubious piece of statistics-only work, the co-authors of that study have hidden their data from outside/independent scrutiny for about 23 years.

The EPA's Clean Air Act Scientific Advisory Committee, Congress and qualified researchers have made multiple requests for the raw data underlying the Harvard Six Cities Study. All requests have been refused by the study authors.

One of the Harvard Six Cities Study researchers refusing to make this data available for independent replication is NEJM study co-author Joel Schwartz.

Between its secret data and dubious epidemiologic analysis, the only things "landmark" about the Harvard Six Cities Study is the study authors' ability to hide

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[8] Association of Changes in Diet Quality with Total and Cause-Specific Mortality Mercedes Sotos-Prieto, Ph.D., Shilpa N. Bhupathiraju, Ph.D., Josiemer Mattei, Ph.D., M.P.H., Teresa T. Fung, Sc.D., Yanping Li, Ph.D., An Pan, Ph.D., Walter C. Willett, M.D., Dr.P.H., Eric B. Rimm, Sc.D., and Frank B. Hu, M.D., Ph.D. *N Engl J Med* 2017; 377:143-153 July 13, 2017DOI: 10.1056/NEJMoa1613502

their data for more than 20 years and their sheer arrogance in then offering it up as validation of the NEJM study claims.

It is also worth mentioning that NEJM study co-author Antonella Zanobetti is also a data-hider. She has also refused to provide $PM_{2.5}$-related study data to qualified researchers for purposes of study replication.

E. EPA compelled NEJM study author forced to recant negative $PM_{2.5}$ study results.

EPA once compelled NEJM study author Francesca Dominici to recant negative $PM_{2.5}$ study findings. Unhappy with the EPA-funded 2011 Greven et al study contradicting EPA's $PM_{2.5}$-kills claims on which Dominici was a co-author, EPA pressured Dominici to explain them away. Dominici complied in writing (letter attached and highlighted in relevant part) by nonsensically stating that while her study showed $PM_{2.5}$ did not kill on a local level, her study showed that $PM_{2.5}$ killed on a broader national level. This is patently absurd. If $PM_{2.5}$ causes death as hypothesized, then it causes death everywhere.

F. Peer review or "pal" review?

There is no doubt that the NEJM study authors will raise peer review as a defense to these charges. This is an entirely bogus defense. I have attached a copy of a recent *Wall Street Journal* op-ed explaining how the $PM_{2.5}$ "peer" review process is more like "pal" review.

As an example, Harvard University's Doug Dockery sits on the EPA scientific advisory committee responsible for "peer" reviewing the EPA-funded Harvard Six City study, for which he was also the lead author. Reviewing your own work is not "peer" review. It is likely that the "peer" reviewers of the NEJM study are either:

- Fellow $PM_{2.5}$ cronies of the study authors; or
- Lack familiarity with the $PM_{2.5}$ epidemiology and controversy.

So there was no legitimate peer review of this study.

G. Political nature of the HSPH/NEJM study.

Given the current political situation — a new administration reportedly looking to cut EPA's budget (including for university-conducted research into $PM_{2.5}$) and cut EPA's regulatory overreach — the political nature and timing of the HSPH/NEJM study and editorial cannot be overlooked.

The study result is not novel. The editorial drives home a wild political attack on President Trump, concluding with the irresponsible implication that President Trump's administration is going to cause U.S. air to be polluted to lethal levels — i.e., "Do we really want to breath air that kills us?"

It is worth noting that while air pollution did kill people on several occasions during the 20th century, these deaths were NOT caused by particulate matter but by temperature inversions that trapped and concentrated emissions of caustic gases.[9]

V. Conclusion

In an interview about the NEJM study, NEJM study author Francesca Dominici told the media that:[10]

We are now providing bullet-proof evidence that we are breathing harmful air.

So the intent of the NEJM study authors is clear — to present their study as incontrovertible evidence that $PM_{2.5}$ kills. They attempted to accomplish this by intentionally omitting from their study key information that entirely contradicts and deflates their claim. Theirs is a deliberate attempt to misrepresent the research record. This is a fraud on the government and taxpayers who have funded this "research." These researchers should be appropriately sanctioned.

Finally, in the event that you disagree with any or all of these allegations, I request a detailed response explaining your specific points of disagreement.

Please let me know if you require further information.

Sincerely,

Steven Milloy

Digitally signed by Steven Milloy
DN: cn=Steven Milloy, o, ou, email=milloy@me.com, c=US
Date: 2017.09.05 10:23:55 -04'00'

Steven J. Milloy
Publisher

Attachments

[9] *See* Milloy, Steve. *Scare Pollution: Why and How to Fix the EPA*. Bench Press (2016). https://www.amazon.com/Scare-Pollution-Why-How-Fix/dp/0998259713.

[10] *See* http://www.npr.org/sections/health-shots/2017/06/28/534594373/u-s-air-pollution-still-kills-thousands-every-year-study-concludes.

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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.

N Engl J Med 2017;376:2513-22.
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A Quick Take is available at NEJM.org

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 [$PM_{2.5}$]) 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 $PM_{2.5}$ 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 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 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 $PM_{2.5}$ 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 cohort, 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 $\mu g/m^3$	<12 $\mu g/m^3$
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
$PM_{2.5}$ ($\mu g/m^3$)	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.

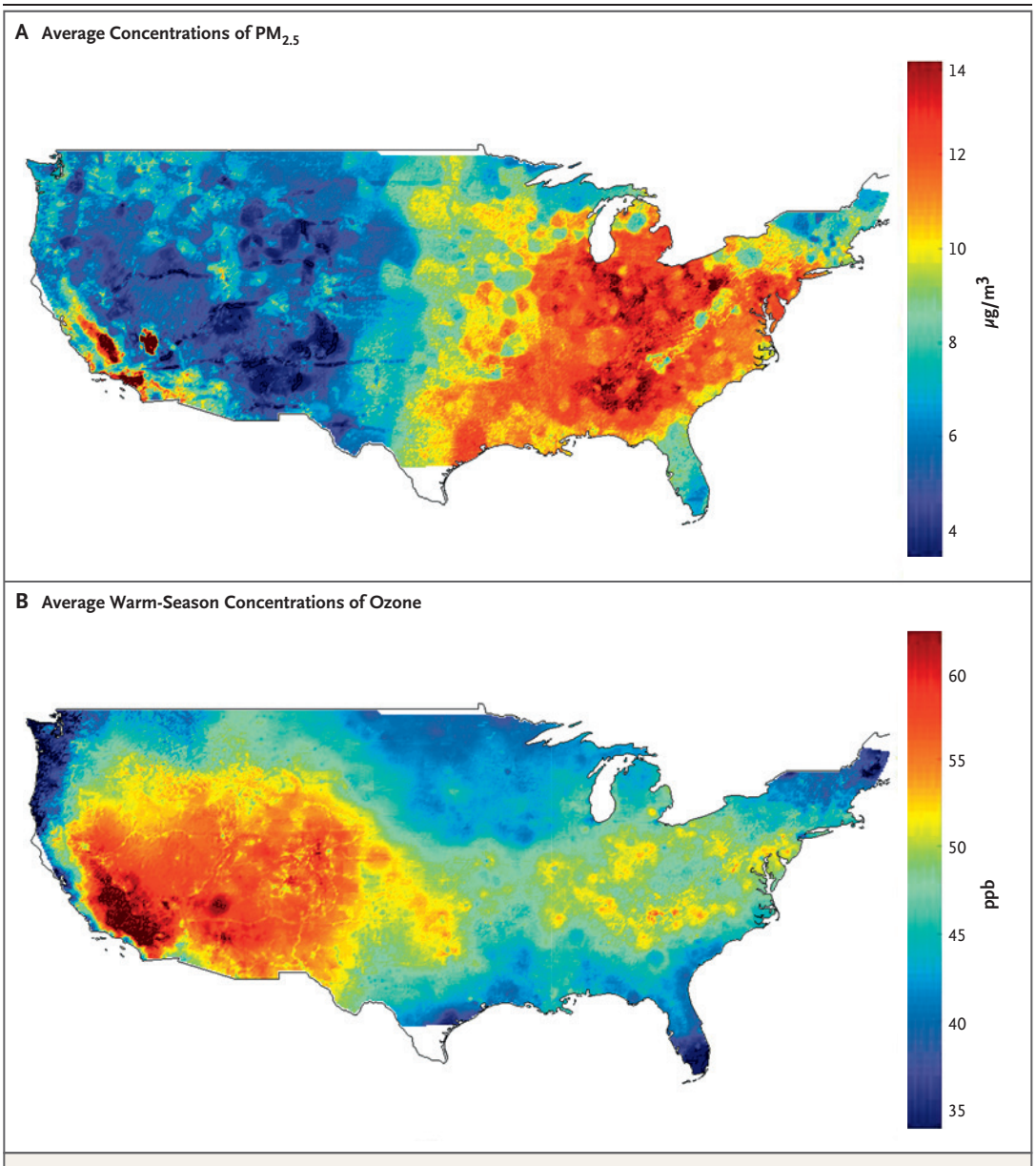

Figure 1. Average $PM_{2.5}$ and Ozone Concentrations in the Continental United States, 2000 through 2012.

Panel A shows the average concentrations of fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [$PM_{2.5}$]) 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 $PM_{2.5}$ (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), respectively. 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 $PM_{2.5}$ 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-

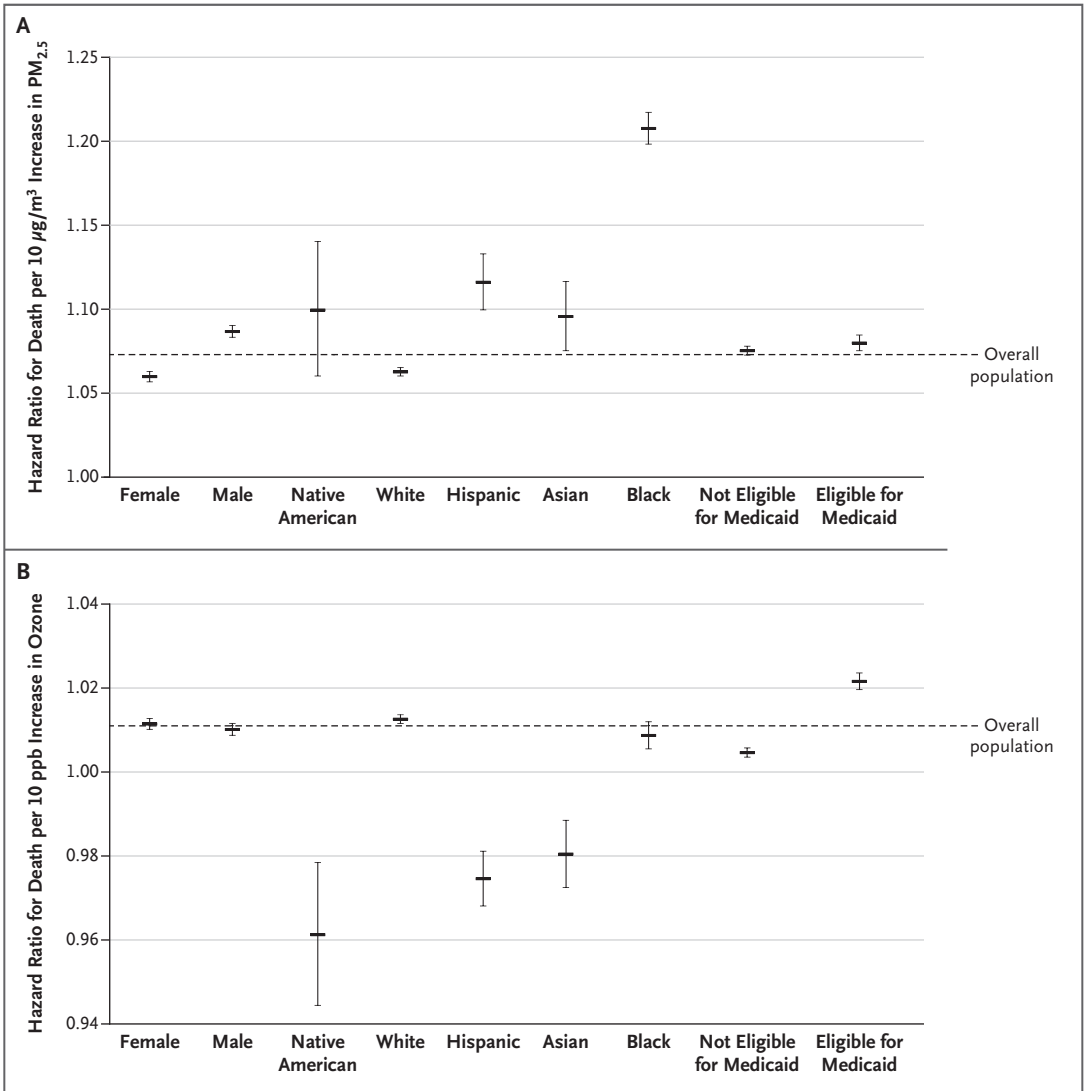

Figure 2. Risk of Death Associated with an Increase of 10 μg per Cubic Meter in $PM_{2.5}$ Concentrations and an Increase of 10 ppb in Ozone Exposure, According to Study Subgroups.

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

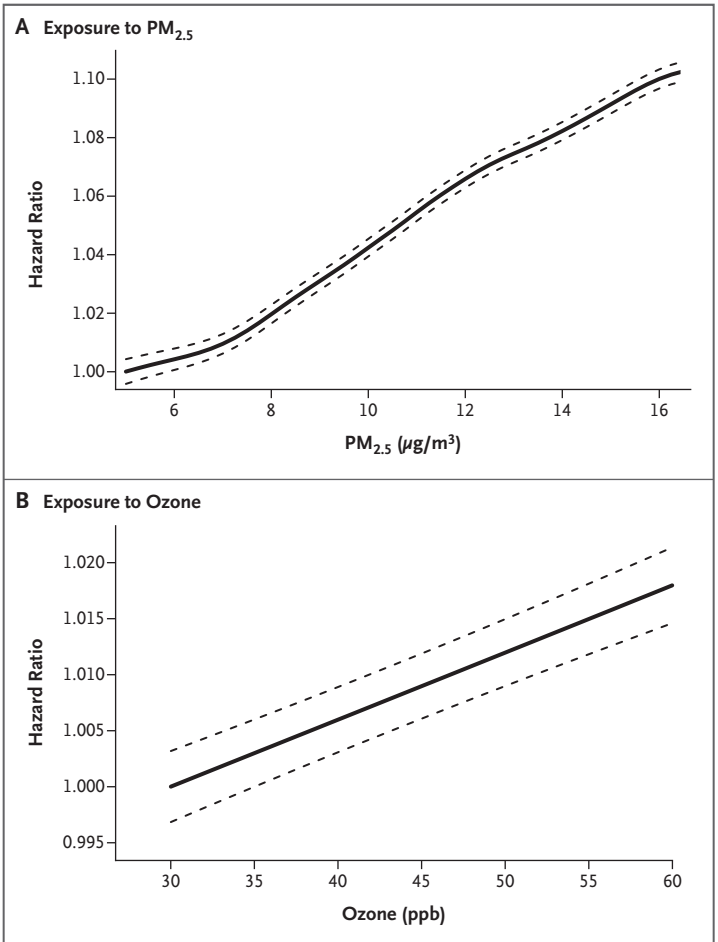

Figure 3. Concentration–Response Function of the Joint Effects of Exposure to $PM_{2.5}$ and Ozone on All-Cause Mortality.

A log-linear model with a thin-plate spline was fit for both $PM_{2.5}$ 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 $PM_{2.5}$ concentration equal to 10 μg per cubic meter. These estimated curves were plotted at the 5th and 95th percentiles of the concentrations of $PM_{2.5}$ 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 $PM_{2.5}$ 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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EDITORIALS

Air Pollution Still Kills

Rebecca E. Berger, M.D., Ramya Ramaswami, M.B., B.S., M.P.H., Caren G. Solomon, M.D., M.P.H., and Jeffrey M. Drazen, M.D.

In late October 1948, a dense smog descended over the town of Donora, Pennsylvania. The town was home to a zinc plant and a steel mill, both run by the United States Steel Corporation. Susan Gnora, a 62-year-old resident of Donora, started to gasp and cough as the smog descended.[1] She died the next day. Dr. William Rongaus, a physician and a member of the board of health, went door to door, treating patients for their respiratory symptoms and encouraging them to leave town if they could. Many thousands were ill, and at least 20 people died in one of the worst air-pollution disasters in U.S. history. The Donora tragedy transformed our perception of smog from a nuisance to a potential killer.

We started to improve air quality with the Clean Air Act of 1963. In 1970, Richard Nixon established the Environmental Protection Agency (EPA) by executive order, and the Clean Air Act was amended to institute National Ambient Air Quality Standards (NAAQS), which set exposure limits for six major air pollutants.[2] Among the pollutants regulated by the EPA is fine particulate matter — inhalable particles with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$). Major contributors to $PM_{2.5}$ in the United States include various types of transportation and the coal-fired generation of electricity.[3,4] Since the 1970s, hundreds of articles have been written establishing an association between $PM_{2.5}$ and poor health outcomes, including asthma, ischemic heart disease, and all-cause mortality in urban populations.[5,6] In response to these findings, regulators have lowered NAAQS for the allowable amount of $PM_{2.5}$ in the air.[7] Current NAAQS, last updated in 2012, set an annual mean $PM_{2.5}$ level of 12 μg per cubic meter. This standard, which is to be reviewed every 5 years, aims to protect the population, especially those who are particularly sensitive to the adverse effects of air pollution, including children, elderly persons, and persons with cardiopulmonary disease.[2] As communities meet these stricter standards, fewer people will become sick and die as a result of air pollution. A 2011 report from the EPA projected that by 2020, amendments to the Clean Air Act would prevent more than 230,000 premature deaths, largely as a result of reductions in $PM_{2.5}$ levels.[8] But are current standards sufficient to protect public health?

Di et al. now report in the *Journal* the results of a large study, including more than 60 million Medicare beneficiaries from the years 2000 through 2012, that addresses the association between annual average levels of $PM_{2.5}$ and ozone,[9] as measured at the ZIP Code level, and mortality. For every increase of 10 μg per cubic meter in $PM_{2.5}$, there was an associated 7.3% increase in all-cause mortality (95% confidence interval [CI], 7.1 to 7.5), after adjustment for demographic characteristics, Medicaid eligibility, and area-level covariates. Below the current NAAQS for $PM_{2.5}$ of 12 μg per cubic meter, the data showed that each increase in $PM_{2.5}$ of 10 μg per cubic meter was associated with an even greater increase (13.6%) in mortality (95% CI, 13.1 to 14.1). There was no appreciable level below which the risk of death tapered off — and thus no "safe" level of $PM_{2.5}$. Owing to the large size of the cohort, Di et al. were able to perform robust sub-

group analyses and identified greater risks of death associated with air pollutants among blacks and Medicaid-eligible populations; moreover, these groups were more likely to be exposed to higher pollutant levels.

The findings of Di et al. stress the need for tighter regulation of air-pollutant levels, including the imposition of stricter limits on levels of $PM_{2.5}$. Despite compelling data, the Trump administration is moving headlong in the opposite direction. In March, Trump signed an executive order that lifted a moratorium on new leases for coal mined on public and tribal lands and began a process to dismantle guidelines intended to reduce emissions from coal-fired electricity plants.[10] Earlier this month, he announced his intention to withdraw the United States from the Paris climate agreement. Although these actions were primarily intended to undo efforts made by the Obama administration to address climate change, the potentially dire consequences also include increasing people's exposure to particulate matter. In addition, EPA Administrator Scott Pruitt has not ruled out the possibility of revoking a waiver included in the 1970 Clean Air Act that allows California to set limits on automotive tailpipe emissions that are more stringent than national standards[11]; 15 states have adopted California's standards. Revoking this waiver could have the effect of exposing more than 100 million Americans to higher levels of automobile emissions. Trump's proposed budget includes crippling cuts to the EPA, including cuts in funding for both federal and state enforcement of regulations. The increased air pollution that would result from loosening current restrictions would have devastating effects on public health.

In explaining his withdrawal from the Paris climate agreement, Trump stated, "I was elected to represent the citizens of Pittsburgh, not Paris." Ironically, Pittsburgh is less than 30 miles from the Donora Smog Museum, where a sign reads, "Clean Air Started Here." With the report by Di et al. adding to the large body of evidence indicating the risks of air pollution, even at current standards, we must redouble our commitment to clean air. If such protections lapse, Americans will suffer and we are doomed to repeat history. Do we really want to breathe air that kills us?

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

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From: Francesca Dominici, Scott L Zeger, Holly Janes, Sonja Greven
To: Bryan Hubbell, Jason Sack, EPA

Reply to: *additional information to EPA for these two studies*

1) Janes H, Dominici**,** Zeger SL (2007) Trends in Particulate Matter and Mortality in 113 U.S. Counties, 2000-2002: Evidence on the Long Term Effects of Air Pollution. *Epidemiology,* 18: 416-423 (with discussion)
2) Greven S, Dominici F, Zeger SL (2011): An Approach to the Estimation of Chronic Air Pollution Effects Using Spatio-Temporal Information. *Journal of the American Statistical Association,* 106(494): 396–406.

These two studies targeted a very specific question: whether there is an association between month-to-month variations in mortality rates and month to month variations in the average PM2.5 for the previous 12 months (**global effect**) in the Medicare population. The fact that this particular study does not find an association at this specific time scale of variation of exposure to air pollution and for the study population considered cannot lead to a conclusion that all the other epidemiological studies are confounded and that air pollution is not causally linked to mortality. In this document we summarize our rationale for making this statement.

In these studies we decompose the **global effects** into two parts: 1) the association between the national average trend (NAT) in the monthly PM2.5 levels averaged over the previous 12 months and the national average trend (NAT) in monthly mortality rates (**national effect**); and 2) the association between the deviation of the community-specific trend from the NAT of PM2.5 and the deviation of the community-specific trend from the (NAT) of mortality rates (**local effect**). We decompose the global effect into a national effect plus a local effect because we hypothesize that the national effect is more likely to be affected by unmeasured confounding than the local effect. We also argue that if there are large differences between the local and the national effects then the global effect should not be reported without a more in depth investigation of confounding. We also acknowledge in the papers that differences between the local and national effects might be due to measurement error and not necessarily unmeasured confounding.

Our results do not invalidate previous epidemiological studies: In Janes et al and Greven et al, both using Medicare data, we did not find evidence of a local effect and we instead found evidence of a national effect. Although these results call for additional investigation of why we found these differences between the local and the national effects, these results do not invalidate results of the other cohort and multi-site time series studies. We summarize below why:

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1. We eliminate spatial information, purposely. Our studies, on purpose, discard all the spatial variation in air pollution and mortality that is available in the data. This is the main and only information used in the cohort studies. Also, our studies cannot invalidate the time series studies, because they also do not rely on the day-to-day information. Again, our studies only focus on associations at monthly temporal scales and include a fixed effect for county in the regression model which purposely eliminate the spatial information when estimating the global effect. At the other end, the cohort studies by Pope et al 2009 NEJM, rely almost entirely on spatial information and they have developed approaches to adjust for measured and unmeasured confounding. In Table 1 of Janes et al, the percentage of the variability in their $PM_{2.5}$ variable is broken down by space, time, and space by time components. We found that over 90% of the variance in this data is attributable to spatial variation (which we ignore), and roughly only 5% attributable to the space by time component (which is what we used in our papers). Thus, when one considers that this wealth of information is not accounted for in that study, it is not as surprising that we see vastly different estimates of the $PM_{2.5}$/mortality relationship than in other studies that do exploit that variability.

2. Both the local and the national effects can be affected by unmeasured confounding. We do hypothesize that the national effect is more likely to be affected by unmeasured confounding than the local effect. However the unmeasured confounding for the local scale cannot be excluded either. For example, the national association can be confounded by a national downward trend in smoking that causes a reduction in mortality. As PM2.5 and mortality are both trending downwards nationally, not having a good measure of the effect of smoking in the model would cause an upward bias in the national association. An example that would cause the local association to be biased upwards would be if communities that were very 'health conscious and environmentally friendly' and thus reduced their air pollution more than the average community would also improve on other health-related measures such as smoking and obesity, causing drops in mortality larger than in the average community, even without the effects of the reduce in air pollution. On the other hand, an example that would cause a downward bias in the local association would be local manufacturing activity. For example, suppose a new plant is built that employs 3,000 workers and has a positive influence on the economic productivity of its local area. The improved economy causes reduced mortality relative to the regional trend, but also increases pollution relative to the regional trend. Such a phenomena would shift the local association toward zero. As individual- and location-level information, in contrast to cohort studies, is very limited for the Medicare data, we cannot exclude any of these potential sources of confounding in our studies.

3. Another important driver of the potential differences between the local and the national effects could be measurement error. We expect that measurement error could affect both these associations but it is hard to anticipate which one is more biased. If the exposure is measured with error, as we know is the case, one of the two components might be more precise than the other. Because the national scale component is an average of more independent monitors across a broader geographic extent, its "measurement error" (including local geographic variations and pure device measurement error) might be expected to be smaller, relative to the size of the PM signal. The local component might have greater measurement error as a proportion of its signal, and this might bias its coefficients, probably toward the null. More work is needed in this area.

4. <u>There might not be an association at the time scale and lag investigated in our studies.</u> Further, it is an open question as to what lag the "monthly" $PM_{2.5}$ levels should be calculated at. In the Janes paper this is calculated as the 12 and 24-month averages of $PM_{2.5}$ up to and including the current month. It is then assumed that that calculated exposure is associated with the current month's observed deaths. It may be the case that the exposure period does not stretch that far back, and is in fact over a shorter window. In Janes et al, the authors acknowledge that this is a question that warrants further research (see also Schwartz et al EHP 2008). Thus, it is entirely possible that these papers are looking for an association at a timescale for which no association truly exists.

In summary, in Janes et al 2007 and Greven et al 2011, we examined in unbiased fashion, the epidemiologic evidence relevant to estimating the effect of chronic air pollution exposure on survival. We have published all of our findings without regard to the outcome. None of the investigators have a financial conflict of interest.

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OPINION | COMMENTARY

A Step Toward Scientific Integrity at the EPA

Scott Pruitt sweeps out Obama-era science advisers. The agency needs truly independent ones.

PHOTO: GETTY IMAGES/ISTOCKPHOTO

By Steve Milloy
July 17, 2017 5:14 p.m. ET

The Trump administration in May began the process of replacing the small army of outside science advisers at the Environmental Protection Agency. In June, 38 additional EPA advisers were notified that their appointments would not be renewed in August. To Mr. Trump's critics, this is another manifestation of his administration's "war on science." Histrionics aside, the administration's actions are long overdue.

The most prominent of the EPA's myriad boards of outside advisers are the Science Advisory Board and the Clean Air Scientific Advisory Committee, or CASAC. Mostly made up of university professors, these boards also frequently draw members from consulting firms and activist groups. Only rarely do members have backgrounds in industry. All EPA boards are governed by the Federal Advisory Committee Act, which requires that they be balanced and unbiased. While the EPA is required by law to convene the SAB and CASAC, the agency is not bound by law to heed their advice.

The EPA's Obama -era "war on coal" rules and its standards for ground-level ozone—possibly the most expensive EPA rule ever issued—depend on the same scientifically unsupported notion that the fine particles of soot emitted by smokestacks and tailpipes are lethal. The EPA claims that such particles kill hundreds of thousands of Americans annually.

The EPA first considered regulating fine particles in the mid-1990s. But when the agency ran its claims past CASAC in 1996, the board concluded that the scientific evidence did not support the agency's regulatory conclusion. Ignoring the panel's advice, the EPA's leadership chose to regulate fine particles anyway, and resolved to figure out a way to avoid future troublesome opposition from CASAC.

In 1996 two-thirds of the CASAC panel had no financial connection to the EPA. By the mid-2000s, the agency had entirely flipped the composition of the advisory board so two-thirds of its members were agency grantees. Lo and behold, CASAC suddenly agreed with the EPA's leadership that fine particulates in outdoor air kill. During the Obama years, the EPA packed the CASAC panel. Twenty-four of its 26 members are now agency grantees, with some listed as principal investigators on EPA research grants worth more

than $220 million.

Although the scientific case against particulate matter hasn't improved since the 1990s, the EPA has tightened its grip on CASAC. In effect, EPA-funded researchers are empowered to review and approve their own work in order to rubber-stamp the EPA's regulatory agenda. This is all done under the guise of "independence."

Another "independent" CASAC committee conducted the most recent review of the Obama EPA's ground-level ozone standards. Of that panel's 20 members, 70% were EPA grantees who'd hauled in more than $192 million from the agency over the years. These EPA panels make decisions by consensus, which has lately been easy enough to achieve considering they are usually chaired by an EPA grantee.

Would-be reformers have so far had no luck changing the culture at these EPA advisory committees. In 2016 the Energy and Environment Legal Institute, where I am a senior fellow, sued the agency. We alleged that the CASAC fine-particulate subcommittee was biased—a clear violation of the Federal Advisory Committee Act. We found a plaintiff who had been refused CASAC membership because of his beliefs about fine particles. Unfortunately, that individual was not willing to take a hostile public stand against the EPA for fear of professional retribution. We ultimately withdrew the suit.

The EPA's opaque selection process for membership on its advisory boards has opened the agency to charges of bias. In 2016 Michael Honeycutt, chief toxicologist of the Texas Commission on Environmental Quality, was recommended in 60 of the 83 nominations to the EPA for CASAC membership. The EPA instead selected Donna Kenski of the Lake Michigan Air Directors Consortium. Ms. Kenski received only one of the 83 recommendations. While no one objected to Mr. Honeycutt's nomination, Sen. James Inhofe (R., Okla.) lodged an objection to Ms. Kenski's nomination, claiming she had exhibited partisanship during an earlier term on the committee.

Congress has also tried to reform the EPA's science advisory process. During the three most recent Congresses, the House has passed bills to provide explicit conflict-of-interest rules for EPA science advisers, including bans on receiving EPA grants for three years before and after service on an advisory panel. The bills went nowhere in the Senate, where the threat of a Democrat-led filibuster loomed. Had they passed, President Obama surely would have vetoed them.

President Trump and his EPA administrator have ample statutory authority to rectify the problem. As Oklahoma's attorney general, Scott Pruitt spent years familiarizing himself with the EPA's unlawful ways. He is in the process of reaffirming the independence of the agency's science advisory committees. This won't mean that committee members can't have a point of view. But a committee as a whole must be balanced and unbiased. Mr. Pruitt's goal is the one intended by Congress—peer review, not pal review.

Mr. Milloy served on the Trump EPA transition team and is the author of "Scare Pollution: Why and How to Fix the EPA."

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