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Via E-mail

January 21, 2018

Dr. Howard Bauchner Editor-in-Chief

Journal of the American Medical Association American Medical Association

Re: Request for review and retraction of a recent article and editorial

Dr. Bauchner,

I am a 45 year physician, emergency medicine specialist and academic, attorney with a special interest in evidence law for 38 years and I am writing to you about the misconduct and evidentiary deception of the authors of the recently published article on air quality lethality in the Journal of the American Medical Association titled, “Association of Short-term Exposure to Air Pollution With Mortality in Older Adults” (JAMA study), and the accompanying editorial, Low-Level Air Pollution Associated With Death: Policy and Clinical Implications” (JAMA editorial), That appeared in the December 26, 2017 issue of JAMA (article is attached). The basis for this request is scientific misconduct on the part of the JAMA study authors. The Authors violated every rule accepted by the scientific community in regards to epidemiological observational studies and the reliability of small associations in such studies. The JAMA should review its editorial policies with regards to small associations studies and withdraw the article. In addition the editors should withdraw the the accompanying laudatory editorial that is manifestly badly informed and also deceptive.

The authors of the study claim that any level of air borne fine particles causes death in a day. That is absolute nonsense and nothing more than an assertion built on data dredging for daily death variations, data torturing or data dredging. The study is of more than 22 million deaths in 12 years and is nothing more than a death certificate location time (temporal spatial) observational study of Medicare age deaths, it isn't a toxicological study at all, just a desk top exercise looking for associations.

[Type text]
The study cannot and does not really study exposures, but merely tracks outdoor and stunningly, they didn’t match for smoking history.

Although the study purports to link inhalation of PM\textsubscript{2.5} to same-day death, the actual causes of death for 22+ million study subjects are not known. Study subject deaths actually include deaths from accidents, violence, cancer, disease and other causes that have absolutely nothing to do with inhalation of outdoor PM\textsubscript{2.5}.

The authors, with no information on exposure, then claim a hazard ratio of 1.05 for death related to small particle inhalation in their review of the 22+ million deaths. Hazard ratio of 1.05 between PM\textsubscript{2.5} inhalation and same-day death. Although their data is obviously extremely imprecise and a Hazard Ratio so small is not proof of anything, the JAMA study authors make their brazen and deceptive claims.

The JAMA study intentionally omits contradictory study information that shows no small particle death effect. That is unethical and unprofessional when a negative study is the measure of the reliability of the claim. The studies that contradict the Di group claims are well known to the Di Authors:

• **Young S et al. Air Quality and Acute Deaths in California. Regul Toxicol Pharmacol.** [https://doi.org/10.1016/j.yrtph.2017.06.003](https://doi.org/10.1016/j.yrtph.2017.06.003). (In press, online June 13, 2017). “Neither PM\textsubscript{2.5} 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.org web site on February 10, 2015 ([https://arxiv.org/abs/1502.03062](https://arxiv.org/abs/1502.03062)) and was presented at a poster session at the 2016 annual meeting of the Health Effects Institute (HEI). Please note that HEI is one of the funders of the JAMA study. This study is particularly relevant in that it, like the JAMA study, also examined the purported association between PM\textsubscript{2.5} and short-term mortality.

• **Enstrom J. Fine Particulate Matter and Total Mortality in Cancer Prevention Study Cohort Reanalysis.** Dose-Response. [http://journals.sagepub.com/doi/10.1177/1559325817693345](http://journals.sagepub.com/doi/10.1177/1559325817693345). (Published March 28, 2017). “No significant relationship between PM\textsubscript{2.5} and total mortality in the CPS II cohort was found when the best available PM\textsubscript{2.5} data were used.”


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The JAMA study authors are aware of these contrary findings yet opted to disregard them so as not to distract from their apparently pre-determined conclusions.

The JAMA study also relies on a statistical precision that simply doesn't exist in epidemiology because of unavoidable uncertainty surrounding the data. This is the “garbage-in, garbage-out” phenomenon. While the JAMA study pretends to condemn PM$_{2.5}$ based on a hazard ratio on the order of 1.05, every professional epidemiologist knows that hazard ratios below the level of 2.0 are unreliable. This is has been a long-held view maintained by the National Academy of Sciences, National Cancer Institute, World Health Organization, Food and Drug Administration and as well as the original Bradford Hill guidelines for interpreting epidemiologic results.

The unreliable data problem is writ large in the JAMA study as it lacks, for example, information on cause of death for any individual in the Medicare population, relies on entirely guesstimated exposure data, and fails to consider confounding factors such as smoking, socioeconomic status and any of the other myriad potential competing risk factors for death.

Dr. Bauchner, I have practiced family and then emergency medicine since 1972 and I know something about making a diagnosis, which is very similar to toxicology in methods and science—the obligation that any physician has is to evaluate the strength of evidence and the known science to assess a causality for a studied end point. If the end point is death, something that comes for many different reasons, proper care must be controlling—and you and I know that desk top epidemiology with small associations has nothing to do with evidence adequate to prove causation. That is my objection to the this junk science and epidemiological deceit and misconduct in the study being considered. It can be said with confidence that these researchers have no evidence that is reliable or dispositive regarding their assertions claimed that they have shown causation. They have shown nothing because their evidence fails to meet the minimal requirements for establishing causation.

The problem is that the run of the mill epidemiologist using small associations with no plausible mechanism for toxicity or lethality is just playing statistical games, without any anchoring to physiological biological reality—and when those games involve small relationships epidemiology fails the basic Bradford Hill reasonable rules for asserting causality. Small associations in uncontrolled population studies mean NOTHING. You know that if you are a serious scientists, and you know that air pollution studies consistently and universally are studies that show such small associations that they would be rejected out of hand if they weren’t jazzed up with environmental political advocacy.

I assert that this study by Di and others is nothing more than another example of their pattern of brazen and pernicious dredging for small
associations in piles of millions of deaths that is well known to bear fruit when the results are in the range of NOISE. Looking for a “trend” or an “association” just cut the data differently and look—gender, age, location, time, reanalyze and teach the computer to look for positive correlations. Then pound the table that the correlations, even if they are small, are reliable and pertinent to the assertions of causation.

The Di group NEJM and JAMA study claims from the same pile of data on deaths conflict, except in the heads of ambitious and unethical air pollution researchers. The findings and claims of both studies intentionally and systematically are deceptive and not consistent with good epidemiology that requires, first and foremost, a robust, not trivial, magnitude of effect and ALSO a reasonable and scientifically well supported plausible mechanism for both the long term and the short term death effects claimed by the researchers.

The DI authors intentionally deceived the public with their extravagant claims and the editors of both journals were apparently intimidated by the fact that the DI group is well financed by government agencies that routinely support such junky epidemiology and invalid and unsupported toxicological claims (in this case deaths) that derive from the epidemiological misconduct.

The reality is that there is no competent and reliable evidence that shows a mechanism for small particles causing death, and no reliable evidence that ambient air pollution levels indoor or outdoor that can kill. The researchers like the DI Group are just torturing death data within the noise range, looking for small associations that they think they can buff up to make claims of lethal effects.

**Small associations in Epidemiological studies is not proof of causation.**

For more than 2 decades the EPA and its sponsored epidemiologists have ignored the most important rule that dominates the Bradford Hill Criteria for proof of causation—the value of a robust effect as expressed in Relative Risks (RR) that are at least 2.0 (100% effect) or more.

The rules on strength of association (Relative Risk) are discussed in depth in the chapter on epidemiology of the Federal Judicial Center’s *Reference Manual on Scientific Evidence*, (National Academy of Sciences Press, 3rd Edition 2011). The
authors of the epidemiology chapter include Leon Gordis, MD, MPH, DrPH, an iconic figure in epidemiology and long-time Chair of Epidemiology at Johns Hopkins University Bloomberg School of Public Health. (Reference Manual on Scientific Evidence https://www.nap.edu/catalog/13163/reference-manual-on-scientific-evidence-third-edition?gclid=COiQovXxpNQCFQElAqOq6H4i6A) All this key information is omitted from the JAMA study discussion section.

Earlier this year, the JAMA study authors published a similar study using the same data in the New England Journal of Medicine (NEJM study). In the NEJM study, the study authors reported that long-term (years) exposure to ambient levels PM$_{2.5}$ was associated with mortality. The JAMA study, in contrast, claims that any exposure (even one molecule) to ambient PM$_{2.5}$ is associated with short-term (same-day) mortality.

Any toxicological analysis of such claims shows them to be contradictory.

The JAMA study authors state:

*The association of mortality and PM2.5 exposure is supported by a large number of published experimental studies in animals [footnotes to three studies] and in humans exposed to traffic air pollution, [footnotes to two studies], diesel particles [footnote to one study] and unfiltered urban air [footnote to one study].*

The three footnoted experimental animal studies are:


But none of these studies report any mortality among animals from their exposures to PM$_{2.5}$. There are no other studies that do so either.

The four footnoted experimental human studies are:

- Hemmingsen JG et al. Controlled exposure to particulate matter from urban street air is associated with decreased vasodilation and heart rate variability in overweight and older adults. *Part Fibre Toxicol.* 2015:12:6.


None of these studies report any clinical health effect, let alone any mortality caused by or associated with PM$_{2.5}$.

All the human exposure small particle clinical research studies (inexplicably not cited by the study authors), including many sponsored by the U.S. Environmental Protection Agency and the U.S. Department of Health and Human Services, fail to associate PM$_{2.5}$ with mortality or even any clinical health effect.

It is worth noting that any human clinical research designed to study whether PM$_{2.5}$ killed people would violate every law and regulation meant to protect humans participating in scientific research from the Nuremberg Code through the federal Common Rule. The fact that humans have often been exposed to exceedingly high levels of PM$_{2.5}$ in human exposure clinical research more reasonably and logically indicates that PM$_{2.5}$ is NOT associated with mortality. This is particularly relevant to the JAMA study, which purports to associate inhalation of PM$_{2.5}$ with same-day/short-term death.

So the JAMA study author claims that experimental evidence supports the reported study results are demonstrably and totally false and their discussion of related research is unethical and dishonest.

The Di authors presented a methodologically flawed and deceitful study for publication that fails the basic test of good science as asserted by Richard Feynman (Nobel Laureate Physics) -- a Scientist should be his own most difficult critic.

There can be little doubt that the methodologically flawed JAMA study, as published, intentionally omits key information that would otherwise place the reported results in accurate context and the authors failed to uphold the standards for scientific integrity. I have declared their perfidy, JAMA editors must consider what is the remedy—I suggest withdrawing the paper, just like the many papers that are withdrawn for scientific error or misconduct. The article and the supportive and flattering editorial should both be stricken since there is no amendment that would repair or revive the study to acceptable standards for publication.

Cordially,

/JDunn MD/
John Dale Dunn MD JD

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

QianDI, MS; Ungzhen Dai, ScD; Yun Wang, PhD; Antonella Zanobetti, PhD; Christine Chorlai, PhD; Joel D. Schwartz, PhD; Francesca Dominici, PhD

OBJECTIVE To estimate the association between short-term exposures to ambient fine particulate matter (PM2.5) and ozone, and all-cause mortality in the continental United States.

DESIGN, SETTING, AND PARTICIPANTS Case-crossover design and conditional logistic regression to estimate the associations between short-term exposures to PM2.5 and ozone (mean of daily exposure on the same day of death and 1 day prior) and mortality in 2-pollutant models. The study included the entire Medicare population from January 1, 2000, to December 31, 2012, residing in 39182 zipcodes.

EXPOSURES Daily PM2.5 and ozone levels in 1-km by 1-km grid cells were estimated using published and validated air pollution prediction models based on land use, chemical tran transport modeling, and satellite remote sensing data. From these gridded exposures, daily exposures were calculated for every zip code in the United States. Warm-season ozone was defined as ozone levels below 100 ppm for the months April to September of each year.

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

RESULTS During the study period, there were 22 433 862 million case days and 761 432 090 control days. Of all case and control days, 93.6% had PM2.5 levels below 25 µg/m³, during which 95.2% of deaths occurred (21 353 817 of 22 433 862), and 91.1% of days had ozone levels below 60 parts per billion, during which 93.4% of deaths occurred (20 955 387 of 22 433 862). The baseline daily mortality rates were 1.37, 1.33, and 1.29, respectively. Each short-term increase of 10 µg/m³ in PM2.5 (adjusted by ozone) and 10 parts per billion (10⁻³) in warm-season ozone (adjusted by PM2.5) were statistically significantly associated with a relative increase of 1.05% (95% CI, 0.95%–1.15%) and 0.51% (95% CI, 0.41%–0.61%) in daily mortality rate, respectively. Absolute risk differences in daily mortality rate were 1.42 (95% CI, 1.29–1.56) and 0.66 (95% CI, 0.53–0.78) per 1 million persons at risk per day. There was no evidence of a threshold or exposure-response relationship.

CONCLUSIONS AND RELEVANCE In the US Medicare population from 2000 to 2012, short-term exposure to PM2.5 and warm-season ozone were statistically significantly associated with increased risk of mortality. This risk occurred at levels below current national air quality standards, suggesting that these standards may need to be reevaluated.
In the United States, the Clean Air Act requires a review of National Ambient Air Quality Standards (NAAQS) for fine particulate matter (PM₂.₅) and ozone every 5 years. In 2012, the annual and 24-hour NAAQS for PM₂.₅ were set to 12 µg/m³ and 35 µg/m³, respectively. With no annual standard for ozone, the 8-hour NAAQS for ozone was set to 70 parts per billion (ppb). Currently, the review of these standards is ongoing, with public comments expected in the fall of 2017.

Several studies have provided evidence that short-term exposures to PM₂.₅ and ozone were associated with mortality, but these studies primarily included large and well-monitored metropolitan areas. While the US Environmental Protection Agency (EPA) in considering more stringent NAAQS, evidence is needed to clarify the association between mortality risk and exposure levels below the daily NAAQS and in rural and unmonitored areas.

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

A case-crossover study was conducted to examine all deaths of Medicare participants in the continental United States from 2000 throughout 2012 and estimate the mortality risk associated with short-term exposures to PM₂.₅ and ozone in the general population as well as in subgroups. The study was designed to estimate the association between daily mortality and air pollution at levels below current daily NAAQS to evaluate the adequacy of the current air quality standards for PM₂.₅ and ozone.

Methods

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

Study Population

Using claims data from the Centers for Medicare & Medicaid Services, all deaths among all Medicare beneficiaries were identified during the period 2000–2012, providing enough power to analyze the risk of mortality associated with PM₂.₅ and ozone concentrations much lower than the current standards (Table 1). For each beneficiary, information was extracted on the date of death, age, sex, race, ethnicity, zip code of residence, and eligibility for Medicaid (a proxy for low income) to assess the associations of mortality with PM₂.₅ and ozone concentrations in potentially vulnerable subgroups. Self-reported information on race and ethnicity was obtained from Medicare beneficiary files.

Outcome

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

Study Design

We estimated the association between short-term exposure to PM₂.₅ (adjusted by ozone) and short-term exposure to ozone (adjusted by PM₂.₅) and all-cause mortality using a case-crossover design. Specifically, “case day” was defined as the date of death. For the same person, we compared daily air pollution exposure on the case day vs daily air pollution exposure on “control days.” Control days were chosen on the same day of the week as the case day to control for potential confounding effect by day of week; (2) before and after the case day (bidirectional sampling) to control for time trend; and (3) only in the same month as the case day to control for seasonal and subseasonal patterns. Individual-level covariates and zip code-level covariates that did not vary day to day (e.g., age, sex, race, ethnicity, socioeconomic status, smoking, and other behavioral risk factors) were not considered to be confounders as they remain constant when comparing case days vs control days.

Environmental Data

Daily ambient levels of PM₂.₅ and ozone were estimated from published and validated air pollution prediction models. Combining monitoring data from the Environmental Protection Agency (EPA), satellite-based measurements, and other data sets, neural networks were used to predict 24-hour PM₂.₅ and 8-hour maximum ozone concentrations at each 1-km × 1-km grid in the continental United States, including locations with no monitoring sites. Cross-validation indicated good agreement between predicted values and monitoring values (R₁ = 0.84 for PM₂.₅ and R₂ = 0.76 for ozone) and at low concentrations (R² = 0.85 when constraining to 24-hour PM₂.₅ <25 µg/m³ and R₂ = 0.75 when constraining to daily 8-hour maximum ozone <60 ppb). Details have been published elsewhere. Warm season was defined to be from April 1 to September 30, which is the specific time window to examine the association between ozone and mortality.

Key Points

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

Finding In a case-crossover study of more than 22 million deaths, each 10-11 g/m³ daily increase in fine particulate matter (PM₂.₅) and ozone exposures were associated with statistically significant increases of 0.42 and 0.66 deaths per million person-years, respectively.

Meaning Day-to-day changes in fine particulate matter and ozone exposures were significantly associated with higher risk of all-cause mortality at levels below current air quality standards, suggesting that those standards may need to be reevaluated.
Meteorological variables, including air and dew point temperatures, were retrieved from North American Regional Reanalysis data and estimated daily mean values were determined for each 32-km x 32-km grid in the continental United States. For each case day (date of death) and its control days, the daily 24-hour PM$_2.5$, 8-hour maximum ozone, and daily air and dew point temperatures were assigned based on zip code of residence of the individual (eAppendix 1 in the Supplement). Because we estimated air pollution levels everywhere in the continental United States, the number of zip codes is indubitable in this study was 39,182, resulting in a 33% increase compared with the number of zip codes with a centroid less than 50 km from a monitor (n = 26,115).

### Statistical Analysis

The relative risk (RR) of all-cause mortality associated with short-term exposures to PM$_2.5$ (adjusted by ozone) and warm-season ozone (adjusted by PM$_2.5$) was estimated by fitting a conditional logistic regression to all pairs of case days and matched control days (eAppendix 2 in the Supplement). The regression model included both pollutant-ant cores, main effects and potential confounder 1. For each case day, daily exposure to air pollution was defined as the mean of the same day of death (lag 0-day) and 1 day prior (lag 1-day), denoted as lag 01-day. Relative risk increase (RRI) was defined as RR - 1. The absolute risk difference (ARD) of all-cause mortality associated with air pollution was defined as ARD = RR - 1/RR, where RR is defined as the mean RR of the baseline daily mortality rate (eAppendix 3 in the Supplement).

The robustness of the analysis was assessed with respect to (1) choosing the duration of the continuous adjustment period, (2) using lag 01-day exposure as the exposure metric, (3) the definition of warm season, and (4) using only air pollution measurements from the nearest 15 monitoring sites. Sensitivity analyses with different exposure metrics and a different model yielded results with a difference of less than 5% of the standard error (eFigure 1 in the Supplement). The main analysis, which used the lag 01-day exposure, yielded the lowest values of the Akaike Information Criteria values, indicating better fit to the data (eTable in the supplement). Different definitions of warm season yielded similar risk estimates (eAppendix 4 in the Supplement), and using exposure measured...
measurements from the nearest monitors resulted in attenuated, but still significant, risk estimates (Table 2).

The subgroup analyses were conducted by sex (male and female), race/ethnicity (white, nonwhite, and others), age (69, 70-74, 75-84, and 85+ years), eligibility for Medicaid, and population density (quartiles). We fit separate conditional logistic regressions to the data for each subgroup and obtained subgroup-specific estimates of RR and ARD. We implemented a 2-sample test for assessing statistically significant differences in the estimated RR and ARD between categories within each subgroup (eg, female vs male), based on the point estimate and standard error (see Appendix 5 in the Supplement):
Figure 1. Daily Mean PM$_{2.5}$ Concentrations in the Continental United States, 2000-2012

Daily mean fine particulate matter (PM$_{2.5}$) concentrations were calculated and plotted by state. The time-series plot at the bottom indicates the national daily mean values across all locations. Boxplots show the di5th to 90th percentiles and the median value. The blue dashed line indicates the daily National Ambient Air Quality Standards (NAAQS) for PM$_{2.5}$ (35 g/m$^3$). The line across the box, upper hinge, and lower hinge represent the median value, 75th percentile (Q3), and 25th percentile (Q1), respectively. The upper whisker is located at the smaller of the maximal value and Q3 + 1.5 x interquartile range; the lower whisker is located at the larger of the minimal value and Q1 - 1.5 x interquartile range. Any values that lie beyond the upper and lower whiskers are outliers.
Daily mean 8-hour maximum ozone concentrations were calculated and plotted by state. The time-series plot at the bottom indicates the national daily mean values across all locations. Boxplots show the distribution of daily ozone levels for each state. The blue dashed line indicates the daily National Ambient Air Quality Standards (NAAQS) for ozone (70 parts per billion [ppb]). The line across the box, upper hinge, and lower hinge represent the median value, 75th percentile (Q3), and 25th percentile (Q1), respectively. The upper whisker is located at the smallest of the maximum value and Q3 + 1.5 "interquartile range; the lower whisker is located at the larger of the minimum value and Q1 - 1.5 "interquartile range. Values that lie beyond the upper and lower whiskers are outliers.
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<th>PValue for Effect Modification</th>
<th>Absolute Risk Difference in Mortality, No. per 1 Million at Risk per Day (95% CI)</th>
<th>PValue for Effect Modification</th>
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<td>Eligible</td>
<td>1.49 (1.29-1.69) .000</td>
<td></td>
<td>1.12 (1.02-1.23) [Reference]</td>
<td></td>
</tr>
<tr>
<td>Medicaid Eligibility</td>
<td></td>
<td></td>
<td>1.09 (1.01-1.23) [Reference]</td>
<td></td>
</tr>
<tr>
<td>Noneligible</td>
<td>1.06 (0.90-1.21) &lt;.001</td>
<td></td>
<td>1.12 (1.02-1.23) [Reference]</td>
<td></td>
</tr>
<tr>
<td>Eligible</td>
<td>1.57 (1.32-1.82) &lt;.001</td>
<td></td>
<td>1.12 (1.02-1.23) [Reference]</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.05 (0.95-1.15)</td>
<td></td>
<td>1.12 (1.02-1.23) [Reference]</td>
<td></td>
</tr>
</tbody>
</table>

The Clean Air Act requires the administrator of the USEPA to set NAAQS at levels that provide protection for at-risk populations, with an adequate margin of safety. In this study, Medicaid-eligible individuals, females, and elderly individuals had

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higher mortality rate increases associated with $PM_{2.5}$ than other groups. Previous studies have found similar results in some subgroups.\textsuperscript{20,21} Poverty, unhealthy lifestyle, poor access to health care, and other factors may make some subgroups more vulnerable to air pollution. The exact mechanism is worth exploring in future studies.
The current NAAQS for daily PM$_2.5$ is 15 μg/m$^3$. When NAAQS for ozone is 70 ppb, when restricting the analysis to daily PM$_2.5$ levels below 25 μg/m$^3$, daily warm-season ozone concentrations below 60 ppb, the association between short-term PM$_2.5$ exposure and excess mortality remained but was elevated. The current daily curves revealed an increased mortality effect size similar to that seen in the association between daily ozone concentration and mortality.
that air pollution is associated with an increase in daily mortality rates, even at levels well below the current standards.

The exposure-response relationship between PMs and exposure and mortality was consistent with findings of previous studies. One study combined exposure-response curves from 22 European cities and reported an almost linear relationship between PMs and mortality. Another multicity study reported a linear relationship down to 2 µg/m³ PMs. The present study found a similarly linear exposure-response relationship below 15-µg/m³ PMs and a less steep slope above this level.

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

Findings from this study are also consistent with the literature regarding the observed effect sizes of both PMs and ozone. This study further demonstrates that in more recent years, during which air pollution concentrations have fallen, statistically significant associations between mortality and exposures to PMs and ozone persist.

The association of mortality and PMs exposure is supported by a large number of published experimental studies in animals and in humans exposed to traffic air pollution, diesel particles, and unfiltered urban air. Similarly, a review of toxicological studies and a recent panel study found that ozone exposure was associated with multiple adverse health outcomes.

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

Limitations
This study also has several limitations. First, the case-crossover design does not allow estimation of mortality rate increase associated with long-term exposure to air pollution. Long-term risks in the same study population have been estimated elsewhere. Second, because this study used residential zip code to ascertain exposure level rather than exact home address or place of death, some measurement error is expected. Third, the Medicare population primarily consists of individuals older than 65 years, which limits the generalizability of findings to younger populations. However, because more than two-thirds of deaths in
the United States occur in people older than 65 years of age, and air pollution-related health risk rises with age. The Medicare population in this study includes most cases of air pollution-induced mortality. Fourth, Medicare files do not report cause-specific mortality. Fifth, the most recent data used in this study are nearly 5 years old, and it is uncertain whether exposures and outcomes would be the same with more current data.

Conclusions

In the US Medicare population from 2000 to 2012, short-term exposures to PM2.5 and warm-season ozone were significantly associated with increased risk of mortality. This risk occurred at levels below current national air quality standards, suggesting that these standards may need to be reevaluated.
Exposure to Air Pollution With Mortality in Older Adults


Low-Level Air Pollution Associated With Death
Policy and Clinical Implications
Juoreng Zhang, PhD

Globally, an estimated 3.3 million annual premature deaths (5.86% of global mortality) are attributable to outdoor air pollution, although ambient air pollution has been regulated under national laws in many countries. In the United States under the Clean Air Act, the primary National Ambient Air Quality Standards (NAAQS) are intended to protect human health, with an adequate margin of safety, including insensitive populations such as children, older adults, and individuals with respiratory diseases. Under the Clean Air Act, the standards are reviewed every 5 years to account for new scientific evidence regarding their appropriateness and adequacy for protecting public health.

Historically, this science-based review process has resulted in continued evolution of the NAAQS. For example, an annual and 24-hour standard for fine particulate matter (PM$_{2.5}$), and an 8-hour standard for ozone were added in 1997. The 24-hour PM$_{2.5}$ standard was lowered from 65 μg/m$^3$ in 1997 to 50 μg/m$^3$ in 2006. The 8-hour ozone standard was lowered from 0.08 parts per million (ppm) in 1997 to 0.075 ppm in 2008 and then to 0.070 ppm in 2015. At the next review of NAAQS for PM$_{2.5}$ and ozone, new scientific evidence will be evaluated in recommending whether the current standards should be revised.

In this issue of JAMA, Di et al report findings that day-to-day changes in PM$_{2.5}$ and ozone ambient concentrations were significantly associated with higher risk of all-cause mortality at levels well below the current daily NAAQS. Using a case-crossover design and conditional logistic regression analysis in a data set involving 22 million deaths among US Medicare participants during 2000–2012, the authors estimated that a 10-μg/m$^3$ increase in PM$_{2.5}$ and a 10-parts-per-billion increase in warm-season (ie, between April 1 and September 30) ozone in the 2 days prior to death were, respectively, associated with a 1.05% (95% CI, 0.95%-1.15%) and 0.51% (95% CI, 0.41%-0.61%) increase in daily mortality rate. The authors also identified susceptible subgroups, reporting that nonwhite individuals, Medicaid-eligible individuals, women, and adults 85 years and older had significantly higher mortality risk associated with increased PM$_{2.5}$ levels and that individuals aged from 75 to 84 years and 85 years and older had higher mortality risk associated with increased ozone levels. Importantly, the authors did not find evidence of a threshold in the exposure-response relationship for either pollutant, suggesting that there is no “absolute” safe level of exposure to PM$_{2.5}$ or ozone.

The Medicare cohort used in this study includes individuals residing in rural areas without nearby air pollution monitors, but the authors were able to estimate exposure to PM$_{2.5}$ and ozone using predictive models of data from remote air monitors, satellite-based measurements, and other datasets. Pollutant concentrations in rural areas are generally lower than in urban areas. The findings from this study add unique evidence, applicable to both rural residents and more vulnerable groups, to raise public awareness concerning health risks associated with low-level PM$_{2.5}$ and ozone pollution. The findings suggest that the current NAAQS for these pollutants should be reevaluated.

The findings from this epidemiological investigation by Di et al are supported by mechanistic insights from recent studies of pathophysiological responses to PM$_{2.5}$ and ozone exposure. It is now well accepted that short-term exposure to PM$_{2.5}$ has cardiorespiratory effects through increased pulmonary and systemic inflammation, increased oxidative stress, enhanced thrombogenesis, and autonomic dysfunction. At relatively high concentrations, ozone impairs lung function and increases the incidence of asthma attacks. As a highly reactive oxidant, ozone has long been considered to mainly affect the respiratory system. However, a recent study showed that at levels below those capable of causing lung function changes, ozone is associated with increases in pulmonary inflammation, blood pressure, and platelet activation (a risk factor for thrombosis). Rodent studies show that ozone compromises immune function against bacterial infection. Not only do these mechanistic studies support the biological plausibility of exposure-mortality associations, such as those found by Di et al, but they also provide insights for potential therapeutic interventions. For instance, a limited number of studies suggested that antioxidant supplementation may reduce the effects of PM$_{2.5}$ or ozone. More intervention trials should be conducted to examine the efficacy of using dietary supplementation, medications, or personal protective equipment in alleviating the adverse health effects of air pollution in the general population and particularly in more susceptible populations.

The findings of Di et al may have implications for forecasting and personal monitoring of exposure to PM$_{2.5}$ and ozone, which could allow individuals at increased risk to reduce cardiometabolic exposure. The study showed that when PM$_{2.5}$ concentration was higher on a particular day, more deaths occurred 2 days later. Predictions of pollutant concentrations for the next few days, such as weather forecasting, can be made readily available to the public. (For example, this has already

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Opinion Editorial

Individuals at increased risk may also wish to avoid places with poor air quality because they are more sensitive to pollution. In the study by Dietzl et al.,2 several subgroups of Medicare recipients, including nonwhite individuals, women, Medicaid-eligible individuals, and older adults (≥70 years) were found to have increased susceptibility to PM2.5 and ozone. These susceptibility factors should be considered in developing personalized protection strategies, such as staying indoors on heavy pollution days and suiting up to avoid respiratory conditions, including asthma and heart disease. Furthermore, with rapid technological advancements, it becomes increasingly feasible to use low-cost, lightweight personal monitors in residences and workplaces or to be worn by individuals. Such exposure data can be integrated into a mobile health platform as part of overall health management plans to achieve maximal risk reductions.

Such individual-level protections, however, are only a complement to the ultimate solution of emission controls. In 2011, 107 million and 23 million people lived in US counties where air quality did not meet the standards for ozone and PM2.5, respectively.9 While efforts are needed to bring these nonattainment counties into compliance with the current NAAQS, regulators should continue to consider emerging scientific evidence such as that reported by Di et al.2 and should further lower the standards to minimize health risks. Some may argue that it would be too costly to make further improvements in air quality when pollution levels are relatively low. However, pollution controls required by the Clean Air Act have been associated with preventing an estimated hundreds of thousands of premature deaths and with estimated economic benefits exceeding the costs.10 It can be assumed that even greater health benefits could result from further emission reductions, which can be achieved through cleaner energy production (eg, by renewable, nonpolluting sources such as wind and solar power) and a cleaner transportation fleet (eg, with electric and hybrid vehicles and low-emission mass transportation).

ARTICLE INFORMATION

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Dr Zhang reported receiving funding from Underwriters Laboratories Inc in the form of a research contract to Duke University to support a study of the health impact of using air purifiers in the bedrooms of children with asthma in Shanghai, China. From 2012 to 2017, he was a member of the Oxides of Nitrogen Primary NAAQS Review Panel on the USEPA Environmental Protection Agency’s advisory board on air pollution from the RB Company in London, England.

REFERENCES