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January 30, 2018

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 for paper published in Journal of the American Medical Association December 26, 2017 and Editorial misconduct writing a supportive editorial.

Dr. Partin,

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. The JAMA editors should withdraw the accompanying laudatory editorial that is manifestly badly informed and also deceptive, since it promotes malpractice and deception in epidemiological research.

I am aware of a complaint made by Steve Milloy (copy attached) in regards to the NEJM article (cite below) by Di and others that claimed the long term death effects, but now the same group, with the same data are changing their claims from long term death effects to acute death effects that the Di group scammers

cobbled together for their new article in JAMA:

> *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.*

I object to the author's claims of deaths, long term (*NEJM*) or short term (*JAMA*) death effects—since they are based on small associations in an uncontrolled observational study that mean nothing, but after their scandalous publication of those small association claims for long term effects at NEJM they now claim that they can find short term death effects and publish another paper at *JAMA*? [1]

The information presented here relates primarily to the *JAMA* article claiming short term acute deaths study published on December 26, 2017 by the same authors (save one, Petros Koutrakis) in the *Journal of the American Medical Association* ("JAMA study"):[1]

> *Qian Di, Lingzhen Dai, Yun Wang, Antonella Zanobetti, Christine Choirat, Joel D. Schwartz, Francesca Dominici. Association of Short-term Exposure to AirPollution with Mortality in Older Adults. JAMA.2017;318(24):2446–2456. doi:10.1001/jama.2017.17923*
> (https://jamanetwork.com/journals/jama/article-abstract/2667069?redirect=true. A copy of the study is also attached.)

In summary of the JAMA study, the Di authors claim to report that $PM_{2.5}$ is associated with an increased risk of mortality from ***short-term (i.e., same-day) exposure*** to $PM_{2.5}$ at levels below current air quality standards less than a year after they announced a long term and chronic death effect discovered in the same pile of death certificates.

Dr. Partin, I have practiced private and academic family practice, and then emergency medicine in private practice and academics settings for 45 years and I know something about making a diagnosis, or establishing a likely medical cause of an effect, including death, closely related to methods in epidemiology and toxicology and the obligation that any physician scientist 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 prevail--and you and I know that desk top epidemiology with small associations cannot make evidence that is adequate to prove causation, or even a hypothesis generator. A small effect is, in fact evidence that argues for no effect, yet persistently and repeatedly air quality research claims are founded on small Relative Risks, less than 1.1 and similarly small Hazard Ratios.

That is my objection to the this junk science epidemiological deceit and misconduct in the studies written by the DI group and then published in *NEJM*

and *JAMA*. 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 for long term chronic exposure deaths in the *NEJM* study or short term acute deaths in the *JAMA* study. Their evidence fails to meet the minimal requirements for establishing causation in observational population studies.

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 studies like the Di studies would be rejected out of hand if they weren't jazzed up by environmental political advocacy.

Brazen and perfidious dredging for small associations in piles of millions of deaths that is well known to bear fruit that can be labeled "statistically significant" even though the results are in the range of NOISE. The small associations could easily be generated by computer and data dredging methods, looking for a "trend" or an "association" that is created by slicing and dicing the data differently—gender, age, location, time, reanalyze and teach the computer to look for positive correlations, *voila*! Then pound the table that the correlations, even if they are small, are reliable and pertinent to the assertions of causation and projections to much larger populations for a media splash.

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.

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=COiQovXxpNQCFQEIaQod6H4I6A)

I ask that your office review the rules on epidemiological proof of causation, see if you don't agree that the articles complained about exemplify a deception that rises to a level of professional misconduct and deception and the Journal Editors, who know the rules too, are complicit and should be admonished for their complicity. Your interest in this is certainly worthwhile to protect the interests of the taxpayers in scientific integrity, and an argument can be made that deceitful research and support deceitful research resides very closely to false claims for federal money.

Thank you for your consideration of this complaint.

Cordially,

/JDunn MD /
John Dale Dunn MD JD

JAMA | Original Investigation

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

Qian Di, MS; Ungzhen Dai, ScD: Yun Wang, PhD; Antonella Zanobetti. PhD: Christine Cholrat, PhD; Joel D. Schwartz, PhD; Francesca Dominici, PhD

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

OBJECTIVE To estimate the associliltion between short-term exposures to ambient fine particulate matter (PM_{25}) and ozone, and at levels below the current daily NAAQS. and mortality in the continental United States.

DESIGN, SETTING, AND PARTICIPANTS Case-crossover deslgn and conditionallogistic regression to estimate the association between shorHerm exposures to PM_2.s and ozone (mean of daily exposure on the same day of death and 1 day prior) and mortality In 2-pollutant models. The study inducled the entire Medicare population from January 1, 2000, to December 31, 2012, residing In 39182 zip codes.

EXPOSURES Daily PMi.s and ozone levels ina 1-km 1-km gTid were estimated using published and validated air pollution prediction models based. on land use. chemical tran port modeling, and satellite remote sensing data. From these gridded exposures, daily exposures were calculated for every zipcode in the United States. Wanm-season ozone was defined as ozone le1.1!ls for the months April-to September of each year.

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

RESULTS During the study period, there were 22 433862 million case days and 76143209 control days. Of all case and control days, 93.6% had $PM_{2.5}$ levels below 25 μg/m^3, during which 95.2"/4 of deaths occurred (21353817 of 22433862). and 91.1% of days had ozone levels below 60 parts per billion, during which 93.4% of deaths occurred (20955387 of 22433862). The baseline daily mortality rates were 137.33 and 129.44 (per 1 million persons atrlsl< per day) for the entire year and for the warm season, respectively. Each short-term increase of IO μg/m^3 In PM2.5 (adjusted by ozone) and 10 parts per billion (10^{-9}) in wanm, season ozone (adjusted by PM_{25}) were statistically significantly associated with a relatlve increase of 1.05% (95% Cl, 0.95%-1.15%) and 0.51% (95% Cl, 0.41%·0.61%) in daily mortal;ty rate, respectively. Absolute rtsk differences in daily mortality rate were 1.42 (95% Cl, 1.29·156) and 0.66 (95% Cl, 0.53·0.78) per 1 million persons at risk per day. Ther was no evidence of a thresholdin the exposure-response relationship.

CONCLUSIONS ANO RELEVANCE In the US Medic.are population from 2000 to 201,2 short-term exposures to $PM_{2.5}$ and wanm-season ozone were significantly associated with increased risk of morta lity. This risk occurred at levels below current national air quallty standards, suggesting that these standards may need to bereevaluated.

Author Affilllatlons: Department or Environmental Health, Harvard T.H. Chan School of Public Health. Boston. Massachusetts (Di, Dai, zanobetti, Schwartz}; Department of Biostatistic;, Harvard T.H. Chan School of Public Health. Bosron. Massachusetts (Wang, Cholrat, Dominici).

COfl'espondlng Author$: Joel D. Schwartz. PhD, Department of Environmental Health, Harvard T.H. Chan School of Publlc Health, Landmarl< Center West 404H, Boston, MA 02215 Oschwrtz@hsph .harvard.edu).

JAMA. 2017:318(24):2446·2456. doi:10.IDDl/Jama.2017.17923

n the United States, the Clean Air Act[1] requires a review of National Ambient Afr Quality Standards (NAAQS) for fine particulate matter ($PM_{2.5}$) and ozone every 5 years.[2] In 2012, the annual and 24-hour NAAQS for $PM_{2.5}$ were set to 12 μg/m3 and 35 μg/m ^{3}, respectively. With no annual standard for ozone, the 8-hour NAAQS for ozone was set to 70 parts per billion (ppb). Currently, the review of these standards is ongoing, with public comments expected in the fall of 2017[3]

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

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

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

Key Points

Question What!s the association between short·tenn exposure to air pollution below current air quality standard$ and all-cause mortality?

Finding In a case-crossover study of more than 22 million deaths, each 10·11g/ m^3 dally Increase In fine p.irticulc!te matter and 10-p.irts-per-billion daily increase in warm-season ozone exposures were associated with statistically significant Increase of l.42 and 0.66 deaths per 1 mllllon pe1S011Satrisk **per** day. respectively,

Meaning Day-to-day.changes In fine partigilate matter and ozone exposures were significantly associated with higher risk of all-cause mortafity at **levels below** eurrental rq uallty standads, suggesting that those standards may need to be reevaluated.

Methods

This study was approved by the institutional review boa:id at the Harvard T.H. Chan School of Public Health. As a study of previously collectec;I administrative data, it was exempt from informed consent requirements.

Study Population

Using claims data from the Centers for Medicare & Medicaid Services, all deaths among all Medicare beneficiaries were identified during the period 2000 to 2012, providing enough power to analyze the risk of mortality associated with PM_{25} and ozone concentrations much lower than the current standards (Table 1). For each beneficiary, information was extracted on the date of death, age, sex, race, ethnicity, zip code of residence, and eligibility for Medicaid (a proxy for low income) to assess the associations of mortality with $PM_{2.5}$ and ozone concentrations in potentially vulnerable subgroups. Self-repcrted 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 exduded.

Study Design

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

Environmental Data

Daily ambient levels of $PM_{2.5}$ and ozone were estimated from published and validated **air** pollution prediction models.[13,14] Combining monitoring data from the **EPA,** satellite-based measurements, and other data sets, neural networks were used to predict 24-hour $PM_{2.5}$ and 8-hour maximum ozone concentrations at each 1-km x1-km grid in the continental United States, including locations with no monitoring sites. Cross-validation indicated good agreement between predicted values and monitoring values (R^2 = 0.84 for $PM_{2.5}$ and R^2 = 0.76 for ozone) and at low concentrations (R^2 = 0.85 when constraining to 24-hour $PM_{2.5}$ <25 μg/m^3 and R^2 = 0.75 when constraining to daily 8-hour maximum ozone <60 ppb). Details have been published elsewhere.[13,14] Warm season was defined to be from April 1 to September 30, which is the specific time window to examine the association between ozone and mortality.

Meteorological variables, inducting air and dew point tern· peratures, 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.[15]

For each case day (date of death) and its control days, the daily24·hour $PM_{2.5}$,8-hourmaximum ozone,and dailyairand dew point temperatures were assigned based on zip code of residence of the individual (eAppendix l in the Supplement). Because we estimated air pollution levels everywhere in the continental United States, the number of zip codes induded in this study was 39182, resulting in a 33% increase com· pared with the number of zip codes with a centroid less than 50 km froma monitor (n = 26115).

Table 1. Ba5elineCharacteristicsof StudyPopulati0r1(2000-2012)

Base!fne Characteristic	Vallie
Case days, No.	22433 862
Controlday,;, No.	76143209
Among AllCases (n a 22433862),%	
Ageat deatti, y	
69	1 0.38
70-74	1 .37
75-84	39.4
l:85	37.78
sex	
Mall!	44.73
Female	SS.27
Race/ethnicity	
White	87 .34
81.ick	8.87
Asian	1.01
H i*	1.51
Native American	0.31
Medlcald Etivibllity (n = 22433 861).%	
Ineligible	77.36
EUglble	22.64

Statistical Analysis

The relative risk (RR) of all-cause mortality associated with short-term exposures to $PM_{2.5}$ (adjusted by ozone) and warm-season ozone (adjusted by $PM_{2.5}$) was estimated by fitting a conditional logistic regression to all pairs of case days and matched control days (eAppendix 2 in the Supplement)[9]. The regression model induded both pollut· antsas main effects and natural splines of air and dew point temperatures **with** 3 *elf* to control for potential residual con- founding by weather. For each case day, daily exposure to air pollution *was* defined as the mean of the same day of death (lag 0-day) and **1** day prior (lag l·day), denoted as lag Ol-day.s, [16 17] Relative **risk** increase (RRI) was defined as RR-1. Theabsolute risk difference (ARD) of all-cause mor- tality associated with air pollution was defined as ARD = a >< (RR - 1)/RR, where a denotes the baseline daily mortality rate(eAppendix 3 in the Supplement).

The robustness of the analysis results was assessed with respect to (1)choosing the dfused for the conto W ldingadjust- mentfortemperature, (2) usinglag01-dayexposure as theex- posure metric,(3) the definition of warmseason,and (4)using only airpollution measurements fromthenearest EPA monitoring sites. Splineson meteorological variables with 6 and 9 *elf* yielded results with a difference of less than 5% of the standard error (eFigure 1 in the Supplement). The main analysis, which used the lag01-day exposure, yielded the lowest values of the Akaike Information Criteria values, indicating better flt to the data (eTable in the supplement). Different definitions of warm season yielded similar risk estimates (eAppendix 4 in the Supplement), and using exposure mea·

Table2. Relative Risk Increase and Absolute RiskDifference of Daily Mortality Associated With Each10- g/m'Increasein $PM_{2.5}$ and Each10-ppbIncreasein Ozone

	Relilti ve R]sk Increase," (95% Ct)		Al>SOlute RiSk Difference in DailyMortality Rates, No. per l Miltion Persons at lilskperDay (95% Cl)•	
AirPollutant Analysis	$PM_{2.5}$	Ozone•	**$PM_{2.5}$**	Ozone•
Main analysiS"	1.05 (0.95-1.15)	0.51(0.41-0.61)	1.42 (l.29-1.56)	0.66 (0,53-0.78)
""Qw: expo anatysl,"	1.61 (1.48-1.74)	**0.58** (0,46-0.70)	**2-1 1-c-2. oo2.·34)**	0.74 (0.59-0.90)
Single-pollutant anafy$ls"	1.1,8 (1.09-1.28)	0.55 (0.48-0.62)	1.61(1.48-1.73)	0.71 {0.62•0.79)
Nearest monitors ana1y;1s r--	0,s3 co.n-0.93J	0.35 (0.28-0.41)	1.13 {0.99'1.26)	0,45 (0.37-0.53)

Abbreviations: $PM_{2.5}$, finepartiwlatematter:ppb,partsperbillion.

' Tliedaily baseline mortality ratewas137.33per1millionpersonsat riskper day:thewarm-season dailybaseline mortality rate was129.44per1million personsat riskper day.

bOzone analyses indudeddays f-romthe warm seasonon ly(Aprll1 to September30).

< Tliemalnanalysisusedthemean of dally exposure onthesameday of death and1dayprior (lag01-day) asthe exposuremetric forbothPM_{25} andozone. andcontrolled for natural splines of air anddewpoint temperatures with *3df.* Themainanalysis considered the2pollutants jointly Indudedintothe regression modeland estimated thepercentage increaseIn the dally mortality rateassodated witha10- g/m'IncreaseIn PM_{25} exposureadjusted fa, ozone andthepercentageIncrease in dallymortality rateassociated witha10-ppb increase In warm-season ozone exposure adjustedrorPM2·5

dThelow-exposure analysis had thesamemodel specificationsas the 2-pollutant analysiS and was constrained for days when$PM_{2.5}$ was below 25µg/m' or ozone below 60 ppb.

"Thesingle-pollutantanalysis estimated thepercentage increase!n thedally mortality rateassociated With a10-µg/m• Increase In $PM_{2.5}$ exposure without adjusting for ozoneandthe percentageincrease in thedaily mortality rateassociated witha10-pbincrease in ozoneexposure without adjusting *IOI* PM25.

' $PM_{2.5}$ and ozonemonitoring data wereretrieved from theUSEnvironmental Protection Agency Air Quality System, whichprovides thedaily mean of PM_{25} anddaily a-hour maximum ozone levelsat eachmonitoringsite,Daily ozone concentrationswere averaged from Apr1l1to September 30. Indwidualswere assignedto thePM_{25} andozonelevels from thenearest monitor sIte within 50 km. Those llving50 km from any monitoring site were excluded.

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

The subgroup analyses were conducted by sex (male and female), race/ethnicity (white, nonwhite, and others), age (s69, 70-74, 75-84, and 2:85 years), eligibility for Medlc-aid, and population density (quartiles). we fitted separate conditional logistic regressions to the data for each sub-group and obtained subgroup-specific estimates of RR and ARD. We implemented a 2-sample test **for** assessing statistically significant differences in the estimated RR and ARD between categories within each subgroup (eg, female vs male), based on the point estimate and standard error (se) (eAppendix 5 in the Supplement):

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

Thegoalwas to estimate mortality rateincreases (both RRI and ARD) at air pollution levels well below the current daily NAAQS. The analysis was restricted to days with daily air pollution concentrationsbelow 25 μg/m^3 for$\mathbf{PM_{2.5}}$ and 60 ppb for ozone. We chose 25μg/m^3 and 60 ppbinstead of the current daily NAAQS (35 μg/m^3 for daily $\mathbf{PM_{2-5}}$ and 70 ppb for 8-hour maximwn ozone) because levels of $\mathbf{PM_{2.5}}$ and ozone on most of the daysincluded in the analysis werealready below the current safety standards.

Exposure-responsecurves wereestimated between $PM_{2.5}$ or ozoneand mortality by replacing linear termsfor the 2 pollutants with penalized splines for both $\mathbf{PM_{2.5}}$ and ozone.

All analyses were performed in R software version 3.3.2 (RFoundation).Computations wererun on (1) the Odyssey cluster supported by the Faculty of Arts and Sciences Division of Science, Research Computing Group at Harvard Universityand (2)the Research Computing Environment supported bythe InstituteforQuantitativeSocialSciencein the Faculty of Artsand SciencesatHarvard University.

Results

During the studyperiod, therewere morethan22million case days(deaths) and more than 76million control days(Table1). Of all case and control days, 93.6% had $PM_{2.5}$ levels below 25μg/m3, during which 95.2% of deaths occurred (21353817 of 22 433 862), and 91.1% of days had ozone levels below 60 ppb, duringwhich 93.4% of deaths occurred (20 955387of 22433862).The baseline dailymortality rateswere137.33and 129.44{per **1** million persons at risk per day [per lM per dayJ) for the entire year and for the warm season, respectively. The mean time between caseand control days was12.55 days (range 7-28 days), with minimal differences in airand dew point temperatures between case and control days (0.003°C and 0.01°c, respectively). During the study period, the meanconcentrations of $PM_{2.5}$ and ozone were 11.6 μg/m^3 and 37.8 ppb, respectively. Figure 1 and Figure 2 show the daily $PM_{2.5}$ and ozone time series bystate, respectively.

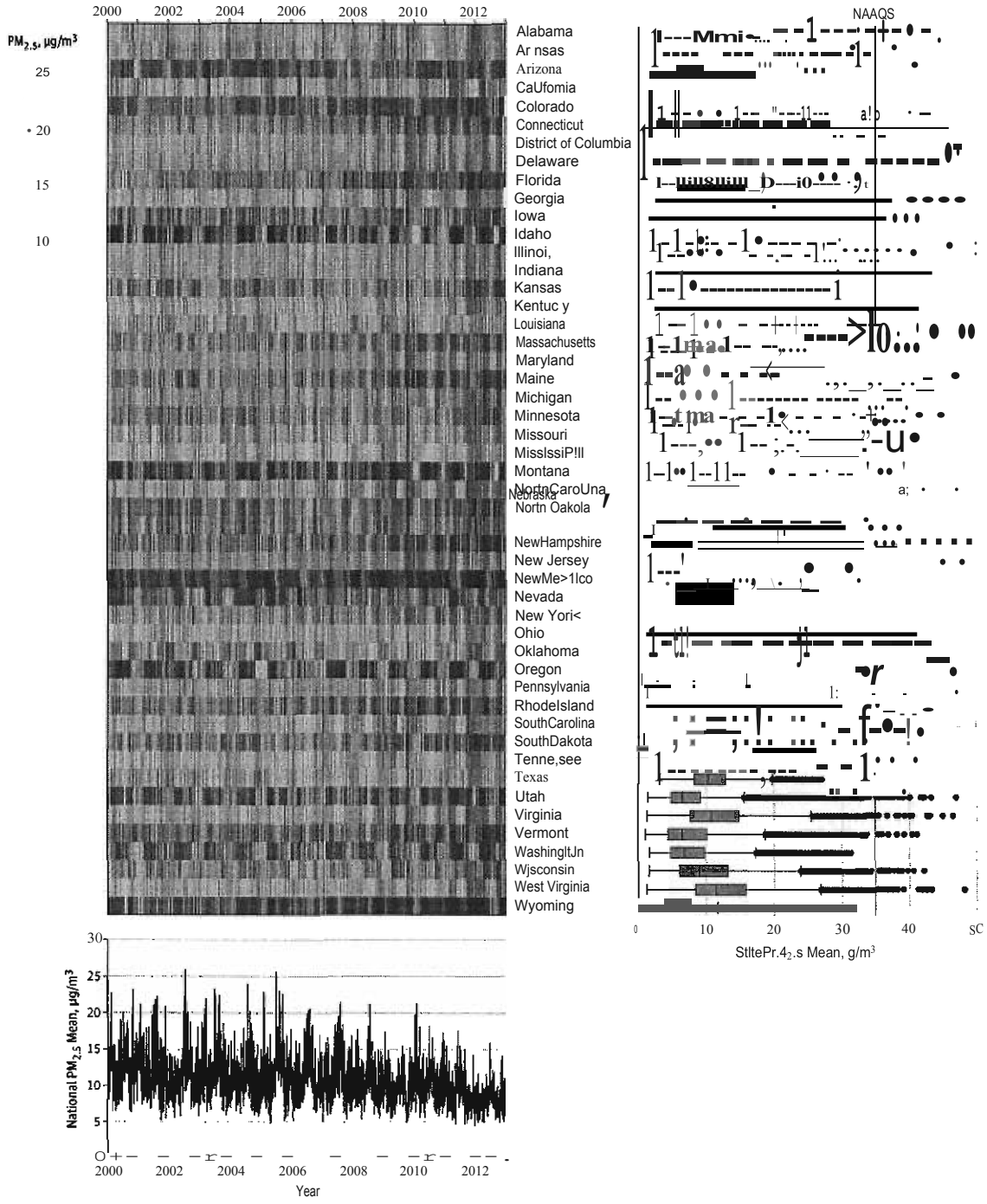
Each 10-l,lg/m^3 and 10-ppb increase in the lag 01-day exposure for PM_{2}.s and warm-season ozone was associated with an RRI of 1.05% (95% CI, Q.95%-1.15%) and 0.51% (95% CI, 0.41 %-0.61%) in the dally mortality rate. TheARDswere1.42 (95%CI,1.29-1.56) and 0.66(95%Cl,0,53-0,78) per 1M per day. These associations remainedsignificant when examining days below 25 μg/m^3 for PM2.5 and below 60 ppb for ozone, with larger effectsize estimates for both $\mathbf{PM_{2.5}}$ and ozone(RRI:1.61% [95% CI,1.48%-l.74%J and 0.58%[95%Cl,0.46%-0.70%]; ARD: 2.17 [95% Cl, 2.00-2.34] and 0.74 [95% Cl, 0.59-0.90] per lM per day, respectively) (Table 2). $\mathbf{PM_{2.5}}$ was associated with higher mortality ratein somesubgroups, including Medicaid-eligible individuals {RRI: 1.49% [95% CI, 1.29%-l.70%J; ARD: 3,59[95% CI, 3.11-4.08) per lM per day; interaction: $P < .001$), individuals older than 70 years (eg, for 85 years, RRI: 1.38% [95%CI,1.23%-1.543/oJ; ARD: 5.35[95%Cl,4.75-5.95] per 1M per day;interaction: P < .001), and females (RRl:1.20%[95% Cl,l.07"/4-1.33%];ARD: 1.56[95% CI,1.39-1.721 per lM per day; interaction: $P = .02$) (Figure 3 and Figure **4).** The effect estimates for $\mathbf{PM_{25}}$ increased withage.Theeffectestimateforblack individualswashigherthanthatforwhiteindividuals(P= .001; eFigure 2in the Supplement). For ozone,similar patterns were observed, but with less contrast between groups. No significantdifferences were found in the shon-term associations between air pollution exposure ($PM_{2..5}$ and ozone) and mortality across areas with different population density levels (Figure 3 and Figure 4). Effect estimates using different lags of exposure are shown in eFigure 3in the Supplement.

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

Discussion

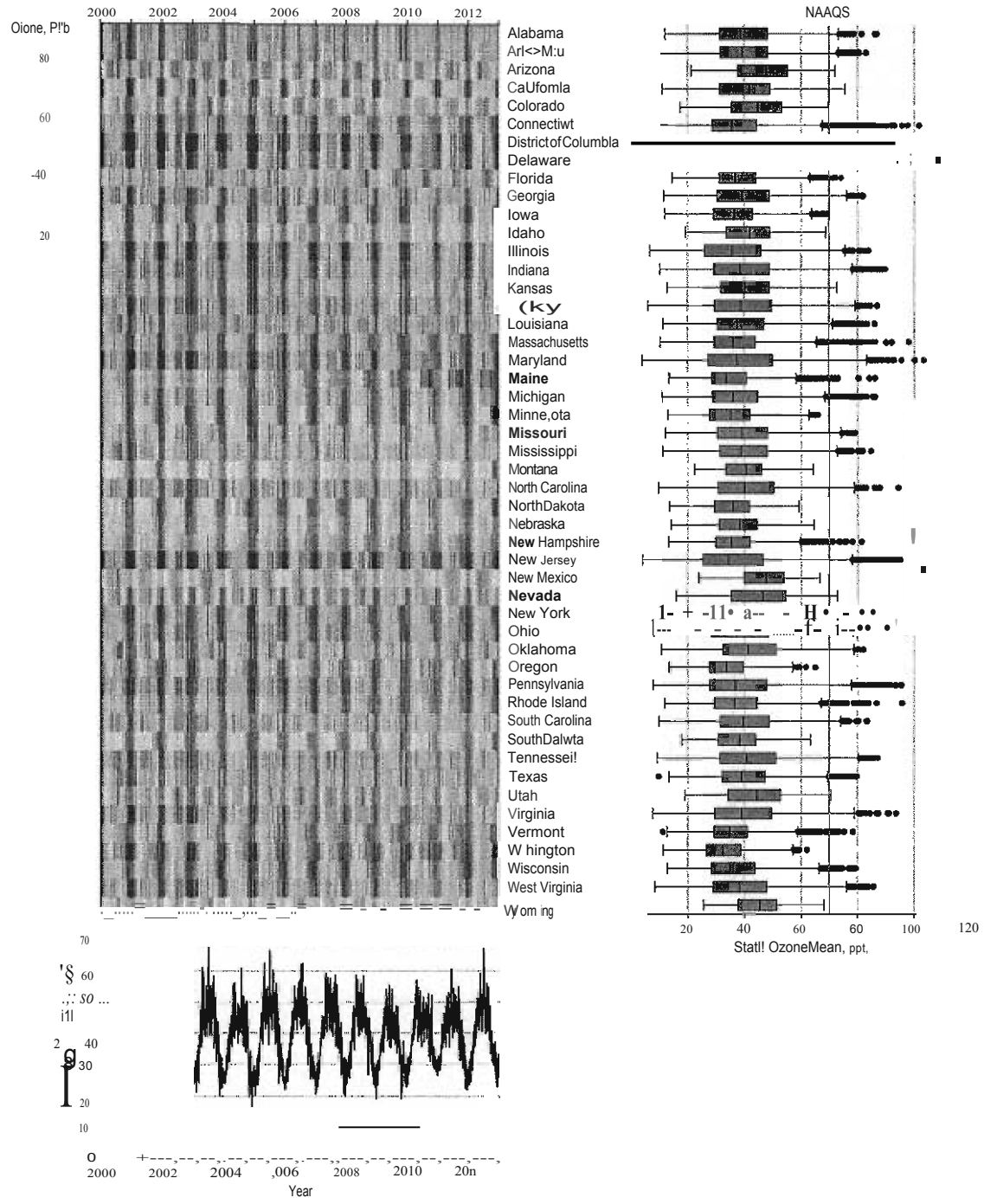
In this large case-crossover study of all Medicare deaths in the continental United States from 2000 to 2012, a 10-μg/m^3 daily increase in PM2..s and a 10-ppb daily increase in warm-season ozone exposures were associated with a statistically significant increase of 1.42 and 0.66 deaths per lM per day, respectively. The risk of mortality remained statistically significant when restricting the analysis to days with PM2.s and ozone levels much lower than the current dally NAAQSY This study included individuals living in smaller cities, towns, and rural areas that were unmonitored and thus excluded from previous time series studies. There were no significant differences in the mortality risk associated with air pollution among individuals living in urban vs rural areas. Taken together, these results provide evidence that short-term exposures to $PM_{2.5}$ and 0<1one, even **at** levels much lower than the current daily standards, are associated with increased mortality, particularly for susceptible populations.

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



Oallymeanfinepartlculatematter(PM";)concentrationswerec;ilrulatedand plotted*by*stare. Thetlme-seliesplot atthebottom Indicatesthenational daily mean valuesacrossalllocations. Boxplots show the di5U-ibu on or dally $PM_{2.5}$ levels for each State. The blue dashed lineindicates the daily National Ambient AirQualltyStandards(NAAQS)for$PM_{2.5}$(35 g/m^3). Thelineacrossthebox, upper hinge, andlower hinge represent the median value, 75th percentlle (Q3), and25thpercenijle (Ql),respectively. Theupper whisker islocated at the smaller or themaximal value andQ3 .. 1.5 • interquartile range; thelower whisker is located at thelarger of themlnimal valueandQl - 1.5x interquartile range. Any values that liebeyond theupper and lower whiskers are outliers.

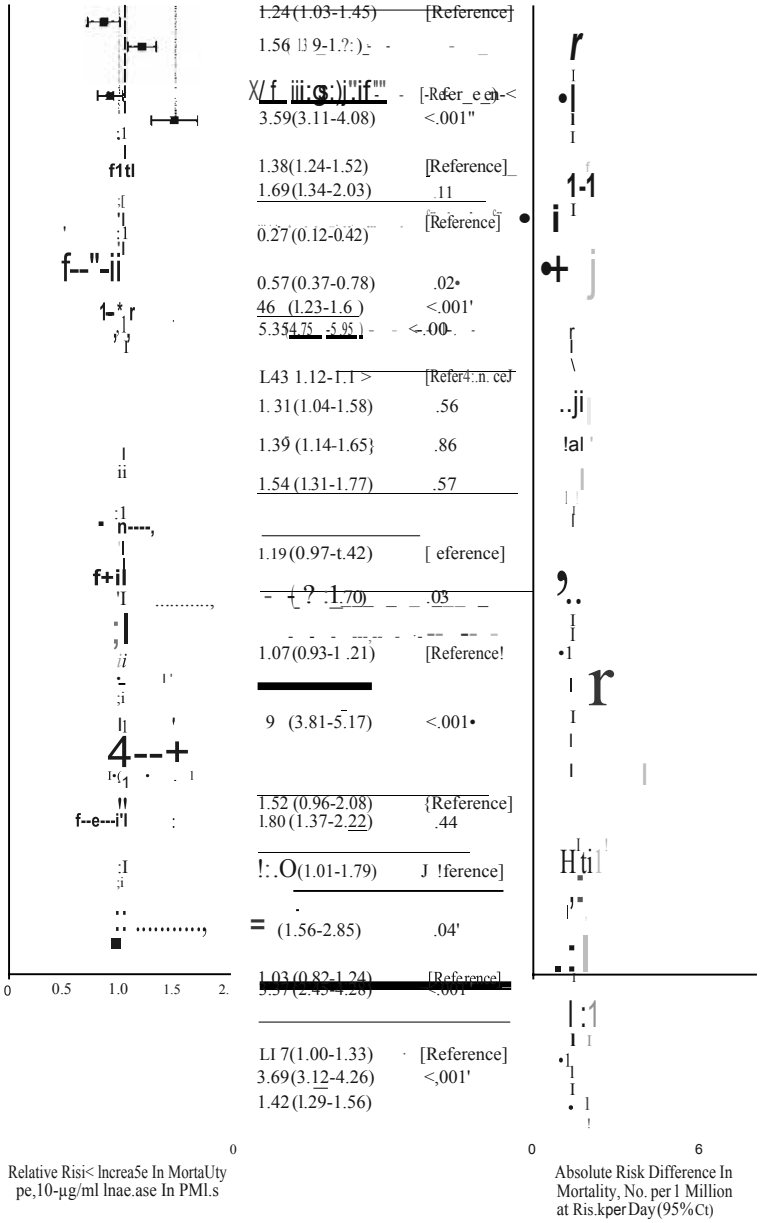
FIgure 2.Dally 8-Hour Maximum OzoneConcentrationsIn theContinental United States. 2000-2012



Dally mean 8-hour maximum ozoneconcentratlons**wefe** calculated andplotted bystate. Thetlme-serles plot atthebottom Indlcates thenatlonal dally mean values across all locations. Boxplots show the dlStribution of dally ozone levels foreachstate. Theblue dashed line indicates the daily National Ambient Air Quality Standards (NAAQS) for ozone (70 partsper billion [ppb]). The line across thebox, upper hinge, and lower hinge represent themedian value, 75thpercentile (Q3), and25thpercentile (QI), respectively. Theupper whisker islocated at thesmallef of themaximal value andQ3 • 1.5"Interquartilerange: the lower whisker Islocated at thelarger of tileminimal value andQI-1.5" Interquartile range./viy values thatlie beyondthe upper and lowet whiskers are outliers.

Figull!3. Relative Risk Increase and Absolute Risk Difference of Daily Mortality Associated With 10-µg/m' Increase In Fine Particulate Matter (PM_2 J

Model	Relillive Risk Increase in Mortality per 10- g/m3 Increase lo PM 5.% (95% Cl)	P Value for Effect Modlficillion	Absolute Risk Difference in Mortality. No. per 1 Million at Risk per Oay (95% Cl)	PValue for Effect Modification
Sex				
Male	0.86(0.72-1.00)	[Reference]	1.24 (1.03-1.45)	[Reference]
Female	1.20 (1.07-1.33)	< .OOP	1.56 (1.39-1.73)	
Medicaid eUgibility				
Nonellglble	0.92 (0.81-1.03)	[Reference]	3.59(3.11-4.08)	[Reference]
EUglble	1.49 (1.29-1.70)	<.001•	1.38(1.24-1.52)	<.001"
Race/ethnicity				
Whl te	1.01(0.91-1.12)	[Reference]	1.69(1.34-2.03)	[Reference]
Non	1.27 (J.01-1.53)	.07	0.27(0.12-0.42)	.11
Age,y				
69	0.55_(0.25-0.86)	[Reference]	0.57(0.37-0.78)	[Reference]
70-74	0.75(0.48-1.01)	.35	46 (1.23-1.6)	.02•
75-84	0.96(0.80-1.11)	.02•	5.354.75 .5.95	<.001'
Population density			L43 1.12-1.1 >	<.00
Low	1.04 (0.8!-1.27)	[Reference]	1. 31(1.04-1.58)	[Reference]
Medium low	o 97 (0 1767)	.9s .64	1.39 (1.14-1.65}	.56
Mediu mhigh	1.03 (0.8 : !2)2	.86	1.54 (1.31-1.77)	.57
High	1l 0.97-1.30)	.52		
Whites				
Sex				
Male	0.83 (0.67-0.99)	[Reference]	1.19 (0.97-t.42)	[eference]
Female	l. 1 6-'-(l.O:i:Jjoj 2		- (? 1.70)	.05
Medicald e ligiblUty				
Noneligible	0.88(0.77-1.00)	[RewenceJ	1.07(0.93-1 .21)	[Reference!
g b-l	1.58(l.34-1.83)	<.001[1]	9 (3.81-5.17)	<.001•
Nonwhites				
Sex				
	1.03(0.65-1.42)	[Referetice]	1.52 (0.96-2.08)	{Reference]
	1.47.(1.12-1.82)	.Ol	1.80 (1.37-2.22)	.44
Medic•Idellglblllty				
NoneUgible	L26 (0.91-1.62)	[Reference]	!:.O(1.01-1.79)	J !ference]
Eligible	:2 (0.90:1·6.6.l	.94	(1.56-2.85)	.04'
Medicaid eUgiblUty, males				
one_li ibll!	0.77(0.61--0.93)	[Reference]	1.03 (0.82-1.24)	[Reference]
Eligible	1.32 (0.96·169)	.006	3.57 (2.45-4.26)	<.001
Medicaid eligibility, fm- le s				
None glble	1.06(0.90-1.21)	[Reference]	LI 7(1.00-1.33)	[Reference]
Eligible	1.57(1.32-1.82)	<.001'	3.69(3.12-4.26)	<,001'
Overall	1.05(0.95-1.15)		1.42 (l.29-1.56)	



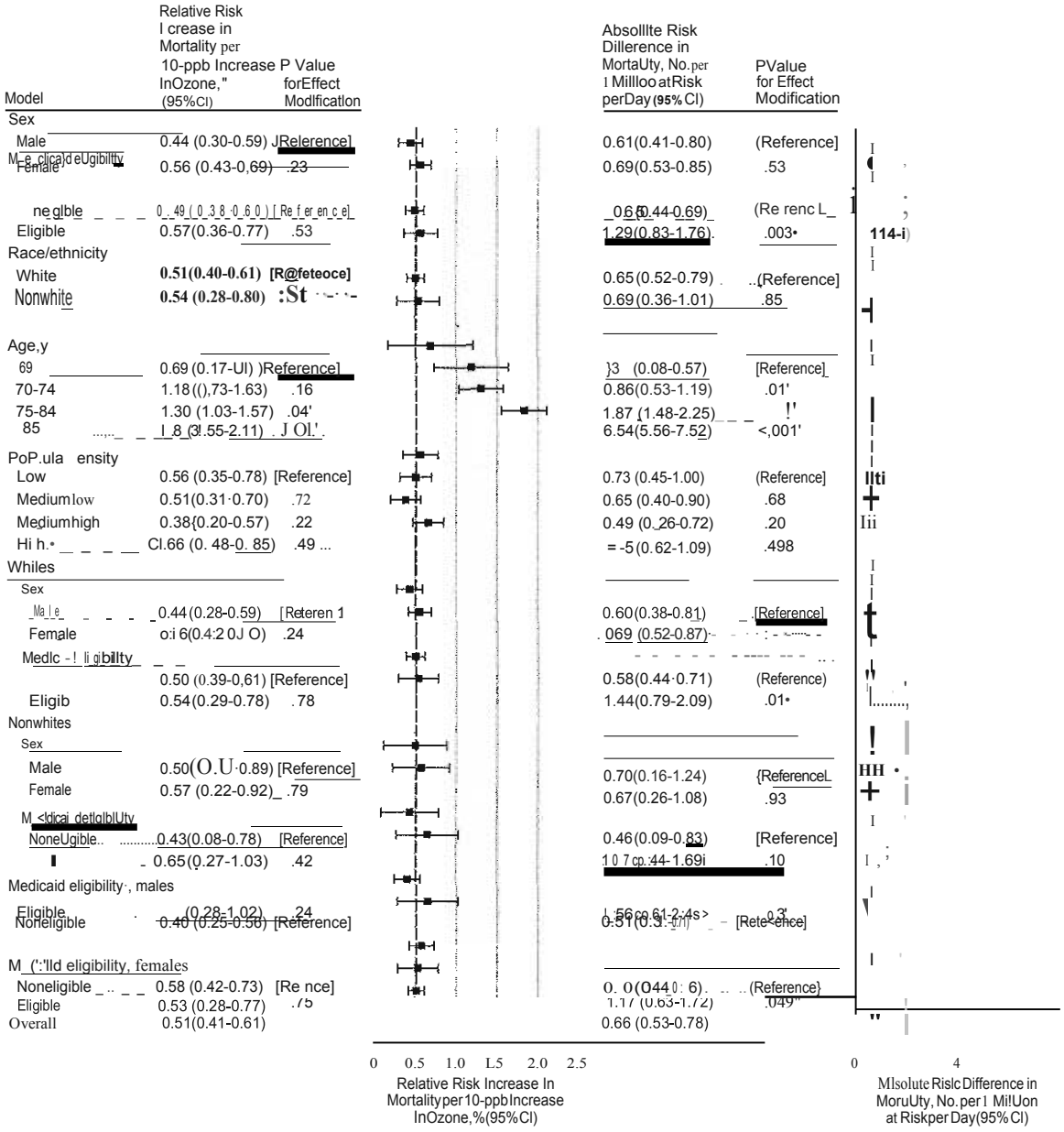
For the main analysis. subgroop analyses used a 2-poUutant analysis (with both $PM_{2.5}$ and ozone), based on tile mean of daily expOS1Jre on the same day of death and 1 day plier (lag01-day) as the exposure metric for PM_{25}, and controlled for natural splines or air and dew point temperatures (each with 3 *df*). Vertical lines Indicate effects for the entlrestudy populaijon. Subgroup analyses were conducted for each subgroup (eg, male or female, white or nonwhite, Medicare ellgfble or Medic.ire lnelligible, agegroups. and quartiles of population density). For the main analysis and each subgroup, conditional logistlc regressions were run to obtain relative risk increases and c.ilrulated absolute risk difference based on baserJne mortanty rates (eAppendix 2 in the Supplement). Numbers Jn **the** f,gure represent point estimates, 9S% Gs. and *P* values for effect modlnca ons. The reference groups were used wllen assessing effect modifiCatloo.

'Statistrcally significant effect estimate (atS% level) compared with the reference group.

The Clean Air Act'requires the administrator of the USEPA to set NAAQSat levels that provide "protection for at-risk populations, with an adequate margin of safety."[19] In this study,

Medicaid-eligible individuals, females, and elderly individuals had higher mortality rate increases associated with PM_{25} than other groups. Previous studies have found similar results in some subgroups.[20,21] Poverty, unhealthy lifestyle, poor access to health care, and other factors may make some subgroups more vulnerable to air pollution. The exact mechanism is worth exploring in future studies.

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

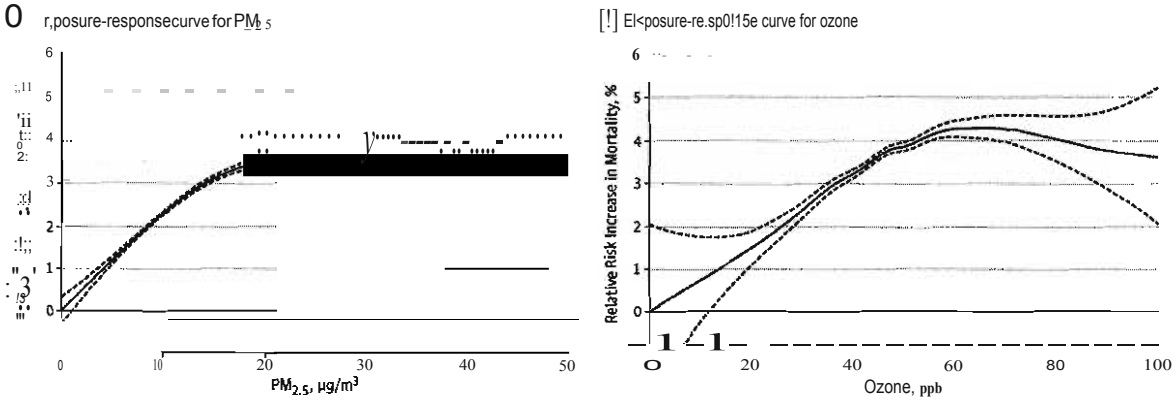


For the main analysis. subgroup analyses used a 2-pollutant analysis (with both PM,.. and 020ne), based on the mean of daily exposure on the same day of death and 1 day prior Oag 01-day) as the exposure metric for ozone, and controlled for nall Jral splines of air and dew point tempefatures (eadi with 3 *df*). Vertlcal fines indicate effects for the entire study populatfon. Subgroup analyses were conducted for each subgroup (eg. male or female, white or nonwhite. Medicare eligible or Medicare ineligible, age groops. and quartiles of population density). For the main analysis and each subgroup, conditional log lstlc regressions were run to obtain relative risk Increases, and calculated absolute risk difference based on baseline mortalil Y rates (eAppendlx 2 in the Supplement). For 020ne, analyses were restricted to the warm season (April ro September). Number; In the flgure represent point estimates, 95% Cls, and P values for effect modifications. The reference groups were used when assessing effect modification.

• Statistically slgnlflcam effect estimate (at 5% level) compared with the refefence group.

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

Agure5.Estimate<! Exposure-Resp0nsecurves for Short-tenn Exposures to FineParticulate Matter (PM._.) andOzone



A2-pollutant analysis withseparate penalized splines onPM2.s (A)andozone (B) wasconducted to a55e55 thepercentage increaseIndailymortality at variouspollution levels. Dashed linesIndicate 95%Cls. Themeanofdally exposure onthesame dayofdeath and1dayplior 0agOl-day) wasused as metricsofexposure to **PM..5** andozone. Analysis for ozone wasrestricted to thewarmseason (Aprilto September). PpbIndicates partsperbllllon.

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

The exposure·response relationship between PM•.s exposure and mortality was consistent with findings of pre·vlous studies. One study combined exposure-response curves from 22 European cities and reported an almost linear relationship between PMJ.s and mortality. [2] iAnother multicity study reported a linear relationship down to 2·µg/m³ $PM_{2.5}$,[03] The present study found a similarly linear exposure-response relationship below 15-µg/m³ *PMi.s* and a less steep slope above thislevel.

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

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

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

Strengths

This study has several strengths. First, to our knowledge, this is the largest analysis of daily air pollution exposure and mortality to date, **with** approximately 4 times the number of deaths included in a previous large s tudy.[5] Second, this study assessed daily exposures using air pollution prediction models that provide accurate estimates of daily levels of $PM_{1.5}$ and ozone for most of the United States, including previously unmonitored areas. An analysis that relied only on exposure data from monitoring stations was found to result in a downward bias in estimates (Table 2). Third, the inclusion of more than 22 million deaths from 2000 to 2012 from the entire Medicare population provided large statistical power to detect differences in mortality rates in potentially vulnerable populations and to estimate mortality rates at very low $PM_{2.5}$ and ozone concentrations. Fourth, this study estimated the air pollution-mortalityassociation well below the current daily NAAQS and in unmonitored areas, and it did not identify significant differences *in* the mortality rate increase between urban and rural areas. Fifth, this study used a case-crossover design that individually matched potential confounding factors by month, year, and other time-invariant variables and controlled for time-varying patterns, as demonstrated by the minimal differences in meteorological variables between *case* and control days.

Limitations

This study also has several limitations. First, the case-crossover design does not allow estimation of mortality rate increase associated with long-term exposure to air pollution. Long-term risks in the same study population have been estimated elsewhere.[40] Second, because this study used residential zip code to ascertain exposure level rather than exact home address or place of death, some measurement error is expected. Third, the Medicare population primarily consis ts 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 exposUies and outcomes would be the same with more current data.

Conclusions

In the US Medicare population from 2000 to 2012, short-term exposUies to PM_2.sand 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.

ARTICL.f INFORMATION

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AuthorContributions;MrDihad full a=ss tO all of the data Inthestudy and takes responslbllity for the Integrity of the data and the accuracy of the data analysis. Mr Oland Dr Daicontributed equally to thisstudy.

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*Acqulslrlan. analysis. or Interp11?tationof data,*All authors.

Dra{ring af the manuscript: Di.Oai, Cholrat. Dominici.

Oiriai/*revisionofthemanuscript{orImportant intellectual content:* AU authors.

Statistical analys , DI, Dai, Choirat. **Schwaru.** Dominici.

Obtained {\Jnrilng: Zanobettl. Schwam.Dominici.

Adm/nistrotive, technicnl. a, material support: Wang, Choir-at.

Supervision: Zanobettl, Schwartz, Dominici.

Conflict or **Interest Di5closures:** All authors have completed and submitted the 1CMJE FOTTTI for Disdosure of Potential uinflict 5 of Imerest. Mr DI reported r Mng grants from the National Institutes of Health (NIH), Environmental Protection Agency (EPA), Health Effects Institute (HEI). and the National Cancer Institute. Dr Zanobettl reported receiving grants from the NIH. HEI, and EPA Dr Choirat reported receiving grants from the NIH *and* EPA Dr Schwartz rl!PQrted receiving !undlng from the US Department of Justice, NIH, EPA. and HEI. Dr Schwartz is an expert consultant of the US Department of Justia. regarding health Impacts of Oean Air Act v!olatlons. Noother disclosures were reported.

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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. <u>On the other hand the death rate from coronary thrombosis in smokers is no more than twice</u>, 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 J. Milloy
Publisher

Attachments

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[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.