From: onbehalfof+john.balmes+ucsf.edu@manuscriptcentral.com
john.balmes@ucsf.edu
Sent: Tuesday, December 27, 2016 9:34 AM
To: jenstrom@ucla.edu
Subject: Reject Decision - Blue-201611-2277LE

27-Dec-2016

American Journal of Respiratory and Critical Care Medicine
RE: Blue-201611-2277LE - Reanalysis of CPS II Cohort Finds No Relationship Between PM2.5 and Total Mortality

Dear Dr. Enstrom:

Thank you for allowing us to review your above-referenced manuscript. Your support of the Journal is much appreciated. We have evaluated the reviews of your paper and regret to inform you that it has not been accepted for publication by the American Journal of Respiratory and Critical Care Medicine. Reviewer comments, upon which this decision is based, are attached below for your information. Based on this evaluation we must decline consideration of any subsequent revision.

Due to the volume of submissions, the Journal accepts only a small number of submitted manuscripts. Although we could not offer a favorable decision at this time, we hope you will consider the American Journal of Respiratory and Critical Care Medicine for future submissions.

Thank you again for your submission.

John Balmes, MD
Associate Editor
American Journal of Respiratory and Critical Care Medicine

Jadwiga A. Wedzicha, MD
Editor
American Journal of Respiratory and Critical Care Medicine

Reviewer: 1

Comments to Authors
Comments to authors:

1. This letter briefly presents an analysis of the ACS CPS II cohort data that does not find associations between PM2.5 air pollution and mortality risk as reported in the original 1995 AJRCCM article. In general, this is an important topic and may be of some interest to readers of AJRCCM. However, I have concerns regarding the letter as outlined in comments below.

2. The author indicates that he "obtained computer files containing the original 1982 ACS CPS II de-identified questionnaire data and six-year follow-up data on deaths, along with detailed documentation." The author should document how these data were obtained and provide information regarding the acuity and quality of the death dates and the location of the research subjects. The ACS and their collaboration and contribution should be acknowledged.

3. There are not enough details regarding the proportional hazard regression modeling, controls for age, sex, race, etc. to make judgements regarding how comparable these results are to other analyses of the ACS CPS II cohort.

4. The primary claim of the letter seems to be that the PM2.5-mortality findings in the CPS II cohort are sensitive to PM2.5 data used and that the original investigators and the HEI investigators should confirm the author's findings by redoing their original analysis using alternative PM2.5 data. The biggest flaw of this letter is that it ignores the extent to which extended analysis has been done and the substantial advances that have been made in the last 20 years. The ACS CPS II cohort and extended follow-ups have been explored and reported in many publications (see references 1 – 14). Given the much longer follow-ups of the cohort, the improvements in statistical modeling, and the large advances in modeling pollution exposure, the analysis provided in this letter seems to be naïve and antiquated. For example:

a. In the original 1995 manuscript (ref. 1) there were actually two indices of particulate air pollution (mean sulfate particles for 151 metro areas and median PM2.5 for 50 metro areas). Similar excess mortality risks were observed for both indices.

b. In the HEI reanalysis (ref. 2) multiple alternative pollution data sets were compiled and used with substantial sensitivity analysis. Substantial improvements in modeling and data construction were developed and there was excellent documentation. Similar results were observed.

c. In the 2002 JAMA and 2003 Circulation papers (ref. 3 and 4) mean concentrations of PM2.5 from the IPMN network and AIRS network were compiled for 61 and 116 metro areas. The cohort follow-up was extended by 10 years through 1998 and statistical modeling advances were incorporated. Similar results were observed.

d. The 2005 Epi paper (ref 5) focused on the LA metro area. It used 23 monitoring stations and a hybrid universal kriging, multiquadric model to estimate PM2.5 exposures. The PM2.5-mortality associations were relatively larger than those for the full U.S. analyses.

e. The Krewski et al. 2009 HEI analysis (ref. 7) extended the follow-up for a full 18 years and conducted statistical modeling that also included ecologic covariate data.

f. The Jerrett et al. NEJM 2009 paper (ref. 8) also used extended follow-up and conducted analysis with a focus on ozone exposures, but also including PM2.5.

g. The Jerrett et al. AJRCCM 2013 paper (ref. 10) used land use regression (LUR) to model predicted individualized home-address exposure for cohort participants who lived in California. Pollution was significantly associated with mortality risk similar to estimates observed nationally.

h. Thurston et al. conducted two analyses (ref 11 and 13) that evaluated PM2.5-mortality effects looking at specific components of PM2.5 and/or sources of PM2.5.

i. The most recent Jerrett et al. EHP 2016 paper (ref. 14) provides the most comprehensive analysis using alternative PM2.5 data. It uses the longest available follow-up of the ACS CPS II cohort (22 yrs) and geocodes the baseline residence of 668,698 cohort participants. PM2.5 exposures are assigned to participants sing 7 different exposure models. Significant PM2.5-mortality risks were observed using all of the exposure models. The size of the effect differed across exposure models with the smaller effects observed using remote sensing exposure estimates and generally larger effects observed using exposure models that included ground-based information.

5. This letter also implies that there are no PM2.5-mortality effects outside of "Ohio Valley states"—a claim inconsistent with most of the other analyses of the CPS II cohorts. There have even been studies that have focused on the Los Angeles metropolitan area specifically (see reference 5) and all of California (see reference 10). There have also been other prospective cohort studies that have been conducted (including in the U.S., Canada, Europe, and elsewhere). A recent meta-analysis of these studies indicates that the meta-estimate of the PM2.5-mortality effect is remarkably similar to that reported from studies of the ACS CPS II cohort.

6. As a final note, the letter argues that the "EPA has never established an etiologic mechanism that explains how the inhalation over a lifetime of about 5 gm of PM2.5 causes premature deaths." It is true that the biological mechanisms regarding the health impacts of air pollution are not fully understood. However, analyses of the ACS CPS II cohort data have provided insights and motivation for study of mechanistic pathways (see reference 4) and remarkable progress has been made (see references 16 and 17).

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Reviewer: 2

Comments to Authors
Reference to and Interpretation of Existing Literature

The author cites a nearly 20-year old editorial piece in support of the contention that the validity of the relationship between particulate matter and mortality remains contested. This is a complete misread of the literature and one that is not supported by numerous newer meta-analyses and the EPA's Integrated Science Assessment on PM2.5, which found the evidence sufficiently compelling as to recommend stricter standards to the EPA administrator.

In contrast to the assertions of the author, the etiological mechanisms have been well studied and summarized in a series of AHA statements on the cardiovascular effects of particulate air pollution and in numerous other articles by Dr. R. Brook and Dr. J, Kaufman. The author is encouraged to read the literature more carefully before making such unfounded claims.

Ethical Concerns

I contacted the ACS to determine whether these data were acquired through normal channels and whether the informed consent they obtained would apply to these data. The ACS has no knowledge of these data being used and this raises serious ethical concerns because the author would not have permission from the study subjects or informed consent to use the data. The author should demonstrate that the data have been obtained through legitimate channels and should submit this study to an independent review by the UCLA IRB. The author is likely in violation of protection of human subjects provision of UCLA if he or she is claiming to have an affiliation with that institution but he or she has not put this specific study to the IRB for a determination. If IRB approval has been obtained, it should be noted in the letter.

Methods

The author questions why the Pope and the HEI studies did not use the entire IPN data. The Pope and HEI studies also used 151 cities for which sulfate data was available; from reading the HEI report, the 50 IPN sites represented the maximal overlap with the larger 151 metro study and the smaller IPN study.

The author has not specified which other covariates are used in the model so there is no way for readers to judge the appropriateness of the model specification. Since much of the emphasis is on whether the results differ from Pope et al. or the HEI report, it seems incumbent on the author to show that he or she is using exactly the same covariates and specifying them in the same way. Sensitivity analyses could be completed with different covariate sets as well.

The author refers readers to a submitted publication for a full description of the methods. How are reader to judge the adequacy of the methods if there is no way to access a submitted MS? There was also nothing given in the supplementary material. I would also question why a letter is being submitted giving results that are already being presented elsewhere in the form of a paper.

While the author suggests his or her exposure assessment is superior, there have been numerous advances in exposure modeling since the original Pope study, and studies based on central monitoring data would be considered trailing edge to say the very least. Much larger risks were recently reported in the Blue journal by Turner et al. using a more refined exposure model, which is suggestive that exposure measurement error from using central monitors probably attenuated risks reported by Pope et al and in the HEI report.

Interpretation

To say there is no relationship when the lower confidence bound if rounded to the conventional 2 decimal places would be 1 is a gross misinterpretation of the results.

The author suggests that Pope et al. should replicate his results, but there is insufficient information given in this report to replicate any aspect of the analysis. The lack of clarity in the presentation, the outdated approach to exposure assessment and elevated risks that are mere decimal points off of the conventional significance level do not raise any doubts about the original study results. It is also questionable whether using an analysis using such a dated and inferior method of exposure assessment is worthy any replication by anyone.

American Journal of Respiratory and Critical Care Medicine/AJRCCM

Reanalysis of CPS II Cohort Finds No Relationship Between PM2.5 and Total Mortality

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Keywords:	

Reanalysis of CPS II Cohort Finds No Relationship Between $PM_{2.5}$ and Total Mortality

James E. Enstrom, Ph.D., M.P.H., FACE
UCLA and Scientific Integrity Institute
Los Angeles, CA 90024
jenstrom@ucla.edu

November 14, 2016

The research described in this Research Letter was done with no external funding.

The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter ($PM_{2.5}$), particles no larger than 2.5 μm in diameter, primarily because of its positive relationship to total mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort, as published in March 1995 *AJRCCM* paper by Pope et al. (Pope 1995) (1). However, the validity of this relationship and the EPA NAAQS were immediately questioned (2) and they remain contested. In particular, EPA has never established an etiologic mechanism that explains how the inhalation over a lifetime of about 5 gm of $PM_{2.5}$ *causes* premature deaths.

The Health Effects Institute (HEI) reanalysis of the Pope 1995 findings successfully replicated these findings, but their 2000 Reanalysis Report did not determine how sensitive the relationship was to different $PM_{2.5}$ values (3). I now have strong evidence that the $PM_{2.5}$-mortality relationship is not significant if based on the best available $PM_{2.5}$ data as of 1995.

I have recently obtained computer files containing the original 1982 ACS CPS II de-identified questionnaire data and six-year follow-up data on deaths, along with detailed documentation. Of the 1.2 million total CPS II subjects, I have analyzed the 297,592 subjects residing in 85 counties with 1979-83 EPA Inhalable Particulate Network (IPN) $PM_{2.5}$ measurements (4,5). The IPN PM2.5 measurements are much more detailed and better documented than the 1979-83 IPMN $PM_{2.5}$ measurements in 50 Metropolitan Areas (MA) used in Pope 1995 and HEI 2000. Among these CPS II subjects there were 18,612 total deaths from September 1, 1982 through August 31, 1988; 17,329 of these deaths (93.1%) had a known date of death. Of the 297,592 subjects, 292,277 had age at entry of 30-99 years and known sex. Of the 292,277 subjects, 269,766 had race of white or black, known education level; and known smoking status. Those subjects without a known date of death have been assumed to be alive in this analysis, because this assumption does not impact relative risks.

The Division number and Unit number assigned by ACS to each CPS II subject has been used to define their county of residence. For instance, ACS Division 39 represents the state of Ohio and its Unit 041 represents Jefferson County, which includes the city of Steubenville. In other words, all or most of the 575 subjects in Unit 041 lived in Jefferson County as of September 1, 1982. The IPN $PM_{2.5}$ value of 29.6739 $\mu g/m^3$ assigned to all subjects in Unit 041 is based on measurements made in Steubenville. This $PM_{2.5}$ value is a weighted average of 191 measurements, 84 during 1979-1982 (4) and 107 during 1983 (5). The HEI $PM_{2.5}$ value of 23.1 $\mu g/m^3$ for all CPS II subjects in the Steubenville MA is the median of IPMN $PM_{2.5}$ measurements made in the city of Steubenville and is shown in HEI 2000 Appendix D (3). The median IPMN $PM_{2.5}$ values were taken from a 1998 BNL Report by Lipfert (6) and I have found no explanation as to why Pope and HEI did not use the superior IPN $PM_{2.5}$ data.

Analyses were done for the 50 original counties with IPMN $PM_{2.5}$ values used in Pope 1995 and HEI 2000, as well as for all 85 counties with CPS II subjects and IPN $PM_{2.5}$ data. Without explanation, Pope 1995 and HEI 2000 omitted 35 counties with CPS II subjects and IPN $PM_{2.5}$ data. The SAS 9.4 procedure PHREG was used to conduct Cox proportional hazards regression (7). Relative risks for death from all causes (RR) and 95% confidence intervals (CI) were calculated using age-sex adjustment and full adjustment (age, sex, race, education level, and smoking status).

Table 1 shows basic demographic characteristics for the CPS II subjects, as stated in Pope 1995, HEI 2000, and this current analysis. There is excellent agreement on age, sex, race, education, and smoking status. However, the IPN average $PM_{2.5}$ values are generally about 20% higher than the HEI median $PM_{2.5}$ values, although the differences range from +78% to -28%.

Table 2 shows that during 1982-1988 there was no relationship between IPN $PM_{2.5}$ and total mortality in the entire U.S. The fully adjusted RR and 95% CI was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in all 85 counties and 1.025 (0.990-1.061) in the 50 original counties. Indeed, the fully adjusted RR was not significant in any area of the U.S., such as, the states west of the Mississippi River, the states east of the Mississippi River, the five Ohio Valley states (Indiana, Kentucky, Ohio, Pennsylvania, and West Virginia), and the states other than the Ohio Valley states.

However, the fully adjusted RR for the entire U.S. was 1.082 (1.039-1.128) when based on the HEI $PM_{2.5}$ values in 50 counties. This RR agrees quite well with the fully adjusted RR of 1.067 (1.037-1.099) during 1982-1989, which is the RR shown in Table 34 of the June 2009 HEI Extended Follow-up Research Report (8). Thus, the positive nationwide RRs in the CPS II cohort depend upon the use of HEI IPMN $PM_{2.5}$ values. The nationwide RRs are consistent with no effect when based on IPN $PM_{2.5}$ values. The findings in Table 2 clearly demonstrate the important influence of $PM_{2.5}$ values and geography on the RRs. Further details on the methods and results of this analysis are provided in my full manuscript (9).

The findings presented here raise doubts about prior $PM_{2.5}$-mortality findings based on the CPS II cohort. Because CPS II findings have played a major role in justifying EPA $PM_{2.5}$ regulations, these findings must be transparent, reproducible, and robust (10). This analysis provides evidence that the $PM_{2.5}$-mortality findings in the CPS II cohort are sensitive to the $PM_{2.5}$ data used. The Pope 1995 and HEI 2000 investigators should confirm my findings by redoing their original analysis and my analysis using the EPA IPN data. Furthermore, ACS should make possible independent analyses involving CPS II data, such as the one that I have conducted.

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Table 1. Summary Characteristics of CPS II Subjects in 1) Pope 1995 Table 1 (1), 2) HEI 2000 Table 24 (3), and 3) current analysis based on CPS II subjects in 50 and 85 counties

Characteristic	Pope 1995 Table 1	HEI 2000 Table 24	Current CPS II Analysis N=50 HEI $PM_{2.5}$	N=50 IPN $PM_{2.5}$	N=85 IPN $PM_{2.5}$
Number of metro areas	50	50			
Number of counties	not stated	not stated	50	50	85
Age-Sex Adjusted Subjects			212,370	212,370	292,277
Fully Adjusted Subjects	295,223	298,817	195,215	195,215	269,766
Age-Sex Adjusted Deaths			12,518	12,518	17,231
Fully Adjusted Deaths	20,765	23,093	11,221	11,221	15,593
Values Below are for Subjects in Fully Adjusted Results					
Age at enrollment (mean years)	56.6	56.6	56.66	56.66	56.64
Sex (% females)	55.9	56.4	56.72	56.72	56.61
Race (% white)	94.0	94.0	94.58	94.58	95.09
Less than high school education (%)	11.3	11.3	11.71	11.71	11.71
Never Smoked Regularly (%)			41.69	41.69	41.57
Former smoker (%)			33.25	33.25	33.67
Former cigarette smoker (%)	29.4	30.2	30.43	30.43	30.81
Current smoker (%)			25.06	25.06	24.76
Currrent cigarette smoker (%)	21.6	21.4	21.01	21.01	20.76
Fine particles ($\mu g/m^3$)					
Average	18.2	18.2	17.99	21.37	21.16
SD	5.1	4.4	4.52	5.30	5.98
Range	9.0 – 33.5	9.0- 33.4	9.0- 33.4	10.77- 29.67	10.63- 42.01

Table 2. Age-sex adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through August 31, 1988 associated with change of 10 μg/m³ increase in $PM_{2.5}$ for CPS II subjects residing in 50 and 85 counties in the continental United States with 1979-83 IPN $PM_{2.5}$ measurements. Analysis includes continental United States, five Ohio Valley states, and remainder of the states. The 50 cities and counties with $PM_{2.5}$ measurements are listed in HEI 2000 Appendix D (3) and in full manuscript (9).

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower	95% CI Upper	Average $PM_{2.5}$
Age-sex adjusted RR for the Continental United States							
1979-83 IPN	85	292,277	17,321	1.038	(1.014	– 1.063)	21.16
1979-83 IPN	50	212,370	12,518	1.046	(1.013	– 1.081)	21.36
1979-83 HEI	50	212,370	12,518	1.121	(1.078	– 1.166)	17.99
Fully adjusted RR for the Continental United States							
1979-83 IPN	85	269,766	15,593	1.023	(0.997	– 1.049)	21.15
1979-83 IPN	50	195,215	11,221	1.025	(0.990	– 1.061)	21.36
1979-83 HEI	50	195,215	11,221	1.082	(1.039	– 1.128)	17.99
Age-sex adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-83 IPN	17	56,979	3,649	1.126	(1.011	– 1.255)	25.51
1979-83 IPN	12	45,303	2,942	1.079	(0.951	– 1.225)	25.76
1979-83 HEI	12	45,303	2,942	1.153	(1.027	– 1.296)	22.02
Fully adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-83 IPN	17	53,026	3,293	1.096	(0.978	– 1.228)	25.51
1979-83 IPN	12	42,174	2,652	1.050	(0.918	– 1.201)	25.75
1979-83 HEI	12	42,174	2,652	1.111	(0.983	– 1.256)	22.02
Age-sex adjusted RR for States other than the Ohio Valley States							
1979-83 IPN	68	235,298	13,672	0.999	(0.973	– 1.027)	20.11
1979-83 IPN	38	167,067	9,576	0.983	(0.946	– 1.021)	20.18
1979-83 HEI	38	167,067	9,576	1.045	(0.997	– 1.096)	16.90
Fully adjusted RR for States other than the Ohio Valley States							
1979-83 IPN	68	216,740	12,300	0.994	(0.967	– 1.023)	20.09
1979-83 IPN	38	153,041	8,569	0.975	(0.936	– 1.015)	20.15
1979-83 HEI	38	153,041	8,569	1.025	(0.975	– 1.078)	16.89

*Highly Cited Researcher 2014
**Highly Cited Researcher 2015

De: James E. Enstrom <jenstrom@ucla.edu>
Enviat el: divendres, 4 de novembre de 2016 16:11
Per a: José Luis Domingo Roig
Tema: Request re Reviewers of Manuscript ER_2016_333

November 4, 2016

Dear Editor-in-Chief Domingo,

As you suggest, I will submit my manuscript to another journal. However, please send me the comments of Reviewer 2, which were not included in your November 1 email message. Also, if possible, please let me know if you used any of the reviewers who I suggested.

Thank you very much.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.

From: José Luis Domingo Roig [mailto:joseluis.domingo@urv.cat]
Sent: Wednesday, November 02, 2016 2:40 AM
To: James E. Enstrom <jenstrom@ucla.edu>
Subject: Re: Request for Reconsideration of Manuscript ER_2016_333

Dear Dr Enstrom,

Thanks for your message regarding my recent decision on your submission.

Let me tell you that your manuscript is not in my direct area of expertise. Therefore, I must trust my reviewers. In your case, with their clear recommendations, another decision was not possible.

Please note that we are currently receiving a considerable number of submissions, which surpass notably our capacity of publishing. Only those submissions that are highly recommended by our reviewers are being accepted (20-25%). We are not going to change the decision. I suggest you to submit your manuscript to another journal.

Sincerely,

Jose L Domingo

EiC
Dr Jose L. Domingo
Distinguished Professor, Universitat Rovira i Virgili
Laboratory of Toxicology and Environmental Health
School of Medicine, Sant Llorens 21, 43201 Reus, SPAIN
Editor-in-Chief: ENVIRONMENTAL RESEARCH
Editor-in-Chief: FOOD and CHEMICAL TOXICOLOGY
Tel: 34 977 759380; Fax: 977 759322
e-mail: joseluis.domingo@urv.cat
www.tecnatox.cat

De: James E. Enstrom <jenstrom@ucla.edu>
Enviat el: dimecres, 2 de novembre de 2016 8:12
Per a: José Luis Domingo Roig
Tema: Request for Reconsideration of Manuscript ER_2016_333

November 2, 2016

Dear Editor-in-Chief Domingo,

I appreciate your extensive peer-review of my manuscript, ER_2016_333, and I can understand your decision to reject it, particularly given the strong scientific disagreements that I have had with certain members of your Editorial Board and Reviewer 1. However, Reviewer 3 made very positive comments about my manuscript and Reviewers 1 and 4 provided no specific evidence contesting the validity of my finding of a null relationship between PM2.5 and mortality in the ACS CPS II cohort. Thus, I am requesting addition consideration of my manuscript based on the following comments of Reviewer 3: "The major finding of this review is extremely important, especially given the size and geographic scope of the data brought to bear in seeking effects. The paper is made all the more valuable by the seminal status of the ACS study that it revisits. It is timely in light of the heightened awareness and interest in reproducibility of key studies at present."

Please let me know if you will reconsider my manuscript if it is revised as per the constructive comments of Reviewer 2 and is the "point" of a "point-counterpoint" on PM2.5 and total mortality in the ACS CPS II cohort. The "counterpoint" should be written by Editorial Board

Member Michael Jerrett and his key co-authors on the 2000 and 2009 HEI Reports. These reports analyzed PM2.5 and mortality in the CPS II cohort in detail, as noted in my manuscript. Jerrett can check the validity of my findings because he and his co-authors have access to the same CPS II data that I have. In addition, Jerrett can have the final word on the validity of my findings. If you cannot reconsider my manuscript, I will send it to another journal.

In order to understand the importance to America of the relationship between PM2.5 and mortality in the CPS II cohort, please read the attached June 12, 2013 Congressional letter to the US Environmental Protection Agency, which requests transparency and reproducibility in several papers based on the CPS II cohort, including Pope 1995, HEI 2000, and HEI 2009. This matter also has get importance to Southern California, because selective results by Jerrett showing a positive PM2.5-mortality relationship in the CPS II cohort are being used as public health justification for a $38.2 billion 2016 Air Quality Management Plan that is close to being finalized.

Thank you very much for your timely consideration of my request.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
jenstrom@ucla.edu

From: Jose Domingo (Environmental Research) [mailto:EviseSupport@elsevier.com]
Sent: Tuesday, November 01, 2016 2:18 AM
To: jenstrom@ucla.edu
Subject: Your manuscript, ER_2016_333, has not been accepted

Ref: ER_2016_333
Title: James E. Enstrom, Ph.D., M.P.H.
Journal: Environmental Research

Dear Dr. Enstrom,

Thank you for submitting your manuscript to Environmental Research. I regret to inform you that reviewers have advised against publishing your manuscript, and we must therefore reject it.

Please refer to the comments listed at the end of this letter for details of why I reached this decision.

We appreciate your submitting your manuscript to this journal and for giving us the opportunity to consider your work.

Kind regards,

Jose Domingo
Editor-in-Chief
Environmental Research

Comments from the editors and reviewers:

-Reviewer 1

I previously reviewed this paper for N Engl J Med. It is not publishable and the data were obtained through questionable means. Editor: I suggest you send it back and do not publish this. The author has some issue with the ACS study and completely ignores years of evidence from other studies that support a relationship between air pollution and adverse health effects.

-**Reviewer 3**

- The major finding of this review is extremely important, especially given the size and geographic scope of the data brought to bear in seeking effects. The paper is made all the more valuable by the seminal status of the ACS study that it revisits. It is timely in light of the heightened awareness and interest in reproducibility of key studies at present.

The technical analysis and exposition seem straight-forward and the conclusion of no clear effect appears to follow from the data and analyses presented. While I can readily imagine more in-depth investigation of the data using nonparametric multivariate methods, I believe that the relatively simple approach adopted is probably more useful at present, and is in line with previous analyses by EPA.

Despite these strengths, there is a nuanced but important matter of style and tone that I hope the author will take under advisement. To me, suggesting that previous researchers were nefarious in exaggerating effects and selectively dropping data -- even if true -- undermines the credibility of the work as a dispassionate inquiry into truth based on data. I urge the author, unfair as this may be, to scrub the manuscript to remove any hint of "I was right all along," "Those guys lied or misled," and "Gotcha!" messages. Let the data and analyses speak for themselves. This is a much more credible way to communicate an important data-driven finding than mixing it in with opinions on the history of the field, however well-justified they may be. I think that pointing out that a fuller analysis of all the data leads to a finding opposite to that previously published is sufficiently sensational news by itself that there is no need (and indeed some loss) for commenting negatively on the work of others.

If the author's personal passion, interest, and history in this field are minimized and the analysis and finding are presented as neutrally and factually as possible, I believe this will be a tremendous -- and possibly even game-changing -- contributon to the field.

-**Reviewer 4**

- This paper opens with a loaded abstract that cites "implausible" relationships and the need for "truly independent examination". The second statement implies that the original analyses were biased, and there are later serious accusations of "evasion, obfuscation and falsification". This requires multiple scientists to break their codes of conduct for their institutes and professional societies. It would also need a large and well coordinated cover up, which is hard to believe given the number of people involved in the HEI analysis (see Grimes DR (2016) On the Viability of Conspiratorial Beliefs. doi: info:doi/10.1371/journal.pone.0151003).

I don't agree that the relationship is "implausible" given the many studies that have repeated the association using detailed spatial data (e.g, 10.1097/EDE.0b013e318294beaa, *10.1136/bmj.f7412*) and the animal studies (reviewed here http://circ.ahajournals.org/content/121/21/2331).

The style and content of the paper are very unusual. It reads like the author has an axe to grind rather than a sober re-analysis of a landmark study.

Manuscript Details

Manuscript number	ER_2016_333
Title	James E. Enstrom, Ph.D., M.P.H.
Article type	Research Paper

Abstract

Background. The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter (PM2.5), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort. This implausible and contested relationship has been used to justify many costly EPA regulations, most recently the Clean Power Plan. This paper presents the first truly independent examination of the CPS II data in order to test the validity of this relationship. Methods. The original CPS II questionnaire data, including 1982-1988 mortality follow-up, was analyzed using Cox proportional hazards regression. Results were obtained for 292,277 subjects in 85 counties with 1979-1983 EPA Inhalable Particulate Network (IPN) PM2.5 measurements, as well as for 212,370 subjects in the 50 counties used in the original 1995 analysis. Results. The 1982-1988 relative risk of death from all causes (RR) and 95% confidence interval (CI) adjusted for age, sex, race, education, and smoking status was 1.023 (0.997–1.049) for a 10 μg/m³ increase in PM2.5 in 85 counties and 1.025 (0.990-1.061) in the 50 original counties. The fully adjusted RR was null in the western and eastern portions of the US, including in areas with somewhat higher PM2.5 levels, particularly five Ohio Valley states and California. Conclusions. No significant relationship between PM2.5 and total mortality in the CPS II cohort was found when the best available PM2.5 data was used. The 1995 analysis misrepresented and exaggerated this relationship by selective use of CPS II and PM2.5 data. This independent analysis of underlying data raises serious doubts about the CPS II epidemiologic evidence supporting the PM2.5 NAAQS. These findings have direct relevance to regulations that are being justified by positive CPS II relationships.

Keywords	epidemiology; PM2.5; deaths; CPS II; reanalysis
Manuscript category	Risk, Policy & Social Sciences

Corresponding Author	James Enstrom
Corresponding Author's Institution	UCLA and Scientific Integrity Institute
Order of Authors	James Enstrom
Suggested reviewers	

Submission Files Included in this PDF

File Name [File Type]

Enviro Res Cover Letter re PM2.5 & Mortality in CPS II 100416.docx [Cover Letter]

Enviro Res Manuscript PM2.5 Mortality in CPS II 100416.pdf [Manuscript File]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

October 4, 2016

Environmental Research Cover Letter

This manuscript represents the first truly independent analysis of the ACS CPS II cohort with regard to the relationship of fine particulate matter (PM2.5) and total mortality. This analysis is based on an original version of the 1982 CPS II data with 1982-1988 mortality follow-up. These data and detailed documentation were obtained from a source that has officially possessed this material for many years. This manuscript contains only the most essential initial statistical calculations that I have made. Additional calculations are currently being made and will be incorporated into an updated version of the manuscript. To fully understand the significance of this manuscript you need to examine the text, tables, and references in detail. The URLs provide direct access to all of the key references.

My null findings on PM2.5 and total mortality raise serious concerns about the integrity and validity of the existing analyses of CPS II data, dating back to 1995. This is an important matter because the CPS II results have played a key role in the establishment and refinement of the US EPA National Ambient Air Quality Standard for PM2.5. The CPS II results have been used as the primary public health justification for EPA's most important and most costly air pollution regulations, such as, the Clean Power Plan. In addition, selected CPS II results are currently being used to provide the primary public health justification for the South Coast Air Quality Management District Draft 2016 Air Quality Management Plan, which will impose $38.2 billion in new regulatory costs on the Southern California economy.

I have read and approved this paper and it has not been published previously nor is it being considered by any other peer-reviewed journal. None of this material has been published or is under consideration elsewhere. This research is exempt from human subjects review because only involves statistical analysis of existing de-identified data. The CPS II subjects were originally enrolled by ACS in 1982 and their informed consent was obtained at that time. There has been no external funding for the research described in this manuscript.

Thank you very much for our consideration.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
907 Westwood Boulevard #200
Los Angeles, CA 90024
jenstrom@ucla.edu
(310) 472-4274
(310) 476-9110 FAX

Fine Particulate Matter and Mortality in Cancer Prevention Study Cohort Reanalysis

James E. Enstrom, Ph.D., M.P.H., FACE
UCLA and Scientific Integrity Institute
907 Westwood Boulevard #200
Los Angeles, CA 90024
jenstrom@ucla.edu
(310) 472-4274
(310) 476-9110 FAX

October 4, 2016

Abstract

Background. The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort. This implausible and contested relationship has been used to justify many costly EPA regulations, most recently the Clean Power Plan. This paper presents the first truly independent examination of the CPS II data in order to test the validity of this relationship.

Methods. The original CPS II questionnaire data, including 1982-1988 mortality follow-up, was analyzed using Cox proportional hazards regression. Results were obtained for 292,277 subjects in 85 counties with 1979-1983 EPA Inhalable Particulate Network (IPN) $PM_{2.5}$ measurements, as well as for 212,370 subjects in the 50 counties used in the original 1995 analysis.

Results: The 1982-1988 relative risk of death from all causes (RR) and 95% confidence interval (CI) adjusted for age, sex, race, education, and smoking status was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in 85 counties and 1.025 (0.990-1.061) in the 50 original counties. The fully adjusted RR was null in the western and eastern portions of the US, including in areas with somewhat higher $PM_{2.5}$ levels, particularly five Ohio Valley states and California.

Conclusions: 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 was used. The 1995 analysis misrepresented and exaggerated this relationship by selective use of CPS II and $PM_{2.5}$ data. This independent analysis of underlying data raises serious doubts about the CPS II epidemiologic evidence supporting the $PM_{2.5}$ NAAQS. These findings have direct relevance to regulations that are being justified by positive CPS II relationships.

Highlights

- This is the first truly independent analysis of the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort with regard to the relationship between fine particulate matter ($PM_{2.5}$) and total mortality.
- This analysis found no consistent relation in this cohort during 1982-1988, contradicting the 1995 findings of a positive relationship, which were the primary justification for the 1997 US EPA National Ambient Air Quality Standard (NAAQS) for $PM_{2.5}$.
- This analysis demonstrates the weak and inconclusive nature of $PM_{2.5}$ mortality studies that rely on selected ecological data rather than on actual human exposure data.
- This failure to support original findings reinforces the importance of access to underlying data and independent analysis, particularly for studies that have regulatory implications.

Key Words

Epidemiology $PM_{2.5}$ Deaths CPS II Reanalysis

Manuscript Disclosures

The author is responsible for all aspects of the study and is the guarantor for the study.

The research described in this manuscript did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. ACS provided the funding for the establishment of the CPS II cohort in 1982, the mortality follow-up from 1982 through 1988, and preparation of the computerized files and documentation used for this research.

The research described in this manuscript is exempt from human subjects or ethics approval because it involved only statistical analysis of existing de-identified data. Full human subjects approval was obtained by ACS in 1982 when individuals enrolled in CPS II (http://www.cancer.org/research/researchtopreventcancer/currentcancerpreventionstudies/cancer-prevention-study).

Because of the importance of the CPS II data in establishing and reinforcing the relationship between fine particulate matter and mortality, an effort will be made to share some version of anonymized CPS II data in a way that individual subjects cannot be identified and the findings in this manuscript can be independently confirmed.

Introduction

The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort, as published in 1995 by Pope et al. (Pope 1995) (1). However, the validity of this finding was immediately challenged (2,3) and it still remains intensely contested. The EPA claim that $PM_{2.5}$ *causes* premature deaths is implausible because no etiologic mechanism has ever been established, because it is based on inhaling over a lifetime only about 5 gm of particles that are less than 2.5 μm in diameter, and because the underlying CPS II data have never been independently analyzed. The $PM_{2.5}$-mortality relationship has been further challenged because the small increased risk could be due to well-known epidemiological biases, such as, the ecological fallacy, inaccurate exposure measurements, and confounding variables like co-pollutants. In addition, there is extensive evidence of spatial and temporal variation in $PM_{2.5}$ mortality risk that does not support one national standard for $PM_{2.5}$.

In spite of these serious problems, EPA and the major $PM_{2.5}$ investigators continue to assert that their selected positive findings are sufficient proof that that $PM_{2.5}$ *causes* premature deaths. This premature death claim has been used to justify many costly EPA regulations, most recently the Clean Power Plan. Indeed, 85% of the total estimated benefits of all EPA regulations have been attributed to reductions in $PM_{2.5}$-related premature deaths. With the assumed benefits of $PM_{2.5}$ reductions playing such a major role in EPA regulatory policy, it is essential that the relationship of $PM_{2.5}$ to mortality be independently verified with transparent data and reproducible findings.

In 1998 the Health Effects Institute (HEI) in Boston was commissioned to conduct a detailed reanalysis of the original Pope 1995 findings. The July 2000 HEI Reanalysis Report (HEI 2000) included "PART I: REPLICATION AND VALIDATION" and "PART II: SENSITIVITY ANALYSES" (4). The HEI Reanalysis Team lead by Krewski successfully replicated and validated the 1995 CPS II findings, but they did not analyze the CPS II data in ways that would determine whether the original results remained robust to different analytic assumptions. For instance, none of their models used the best available $PM_{2.5}$ measurements as of 1995.

Particularly troubling is the fact that EPA, Pope, and other investigators have ignored multiple null findings on the relationship between $PM_{2.5}$ and mortality in California. These findings have been pointed out to them repeatedly in my 2005 paper (5), my 2006 clarification (6), my 2012 American Statistical Society Joint Statistical Meeting Proceedings (7), and my 2015 presentation on the Clean Power Plan and $PM_{2.5}$-related co-benefits (8). There is other published evidence of a null relationship, particularly in the western U.S. (9). This is now overwhelming evidence of misrepresentation and exaggeration of the $PM_{2.5}$-mortality relationship dating back to 2000. These continual problems with the $PM_{2.5}$-mortality relationship have generated substantial media and political concern.

Since 2011 the U.S. House Science, Space, and Technology Committee (HSSTC) has requested that EPA provide access to the underlying CPS II data, particularly since substantial Federal funding has been used for the major $PM_{2.5}$-mortality research and publications. On July 22, 2013 the HSSTC made a particularly detailed request to EPA that included 49 pages of letters dating

back to September 22, 2011 (10). When EPA failed to provide the requested data, the HSSTC issued an August 1, 2013 subpoena to EPA for the CPS II data (11). The ACS refused to comply with the HSSTC subpoena in any way, as explained in an August 19, 2013 letter to EPA by Chief Medical Officer Otis W. Brawley (12). Also, ACS has refused to work with me and other highly qualified investigators regarding collaborative analysis of the CPS II data. Finally, HEI has refused to conduct my proposed CPS II analyses, as explained in an October 4, 2013 HEI letter (13). However, my recent acquisition of an original version of the CPS II data makes possible this first truly independent analysis.

Methods

Computer files containing the original 1982 ACS CPS II de-identified questionnaire data and six-year follow-up data on deaths from September 1, 1982 through August 31, 1988, along with detailed documentation, have been obtained from a source with access to these data. Of the 1.2 million total CPS II subjects, analysis has been done on 297,592 subjects residing in 85 counties in the continental U.S. with 1979-83 EPA IPN PM2.5 measurements (14,15). Among these subjects there were 18,612 total deaths from September 1, 1982 through August 31, 1988; 17,329 of these deaths (93.1%) had a known date of death. Of the 297,592 subjects, 292,277 had age at entry of 30-99 years and sex of male [1] or female [2]. Of the 292,277 subjects, 269,766 had race of white [1,2,5] or black [3,4]; education level of no or some high school [1,2], high school graduate [3], some college [4,5], college graduate [6], or graduate school [7]; and smoking status of never [1], former [5-8 for males and 3 for females], or current [2-4 for males and 2 for females]. Those subjects reported to be dead [D,G,K] but without an exact date of death have been assumed to be alive in this analysis. These unconfirmed deaths are randomly distributed and do not impact relative comparisons of death in a systematic way. The computer codes for the above variables are shown in brackets.

CPS II subjects were entered into the master data file geographically. Since this de-identified data file does not contain home addresses, the Division number and Unit number assigned by ACS to each CPS II subject has been used to define their county of residence. For instance, ACS Division 39 represents the state of Ohio and its Unit 041 represents Jefferson County, which includes the city of Steubenville. In other words, most of the 575 subjects in Unit 041 lived in Jefferson County as of September 1, 1982. The IPN $PM_{2.5}$ value of 29.6739 $\mu g/m^3$ assigned to all subjects in Unit 041 is based on measurements made in Steubenville. This $PM_{2.5}$ value is a weighted average of 53 measurements (mean of 33.9260 $\mu g/m^3$) and 31 measurements (mean of 29.4884 $\mu g/m^3$) made during 1979-1982 (14) and 53 measurements (mean of 27.2473 $\mu g/m^3$) and 54 measurements (mean of 28.0676 $\mu g/m^3$) made during 1983 (15). The HEI $PM_{2.5}$ value of 23.1 $\mu g/m^3$ assigned to all subjects in Unit 041 is the median of $PM_{2.5}$ measurements made in Steubenville and is shown in HEI 2000 Appendix D "Alternative Air Pollution Data in the ACS Study" (4). Although the IPN collected some data through 1984, the $PM_{2.5}$ data was collected only during 1979-1983.

Analyses were done for the 50 original counties with HEI $PM_{2.5}$ values used in Pope 1995 and HEI 2000, as well as for all 85 counties with CPS II subjects and IPN $PM_{2.5}$ data. Without explanation, Pope 1995 and HEI 2000 omitted 35 counties with CPS II subjects and IPN $PM_{2.5}$

data. The SAS 9.4 procedure PHREG was used to conduct Cox proportional hazards regression (17). Relative risks for death from all causes (RR) and 95% confidence intervals (CI) were calculated using age-sex adjustment and full adjustment (age, sex, race, education, and smoking status, as defined above). Each of the five adjustment variables has a strong relationship to mortality.

In addition, county-level ecological analyses were done by comparing IPN $PM_{2.5}$ and HEI $PM_{2.5}$ values with 1980 age-adjusted white total death rates (DR) determined by CDC WONDER (16) and mortality risks (MR) as shown in Figures 5 and 21 of HEI 2000 (4). The death rates are age-adjusted to the 2000 US Standard Population and are expressed as annual deaths per 100,000 persons. The SAS 9.4 procedure REGRESSION was used to conduct linear regression of $PM_{2.5}$ values with death rates (DR) and mortality risks (MR). Appendix Table 1 lists the 50 original counties used in Pope 1995 and HEI 2000 and includes city, county, state, FIPS code, IPN average $PM_{2.5}$ level, HEI median $PM_{2.5}$ level, 1980 DR, and HEI MR. Similar information is available for the 35 additional counties with CPS II subjects and IPN $PM_{2.5}$ data.

Results

Table 1 shows basic demographic characteristics for the CPS II subjects, as stated in Pope 1995 (1), HEI 2000 (4), and this current analysis. There is excellent agreement on age, sex, race, education, and smoking status. However, the IPN average $PM_{2.5}$ values are generally about 20% higher than the HEI median $PM_{2.5}$ values, although the differences range from +78% to -28%.

Table 2 shows that during 1982-1988 there was no relationship between IPN $PM_{2.5}$ and total mortality in the entire U.S. The fully adjusted RR and 95% CI was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in all 85 counties and 1.025 (0.990-1.061) in the 50 original counties. Indeed, the fully adjusted RR was not significant in any area of the U.S., such as, the states west of the Mississippi River, the states east of the Mississippi River, the five Ohio Valley states (Indiana, Kentucky, Ohio, Pennsylvania, and West Virginia), and the states other than the Ohio Valley states. The age-sex adjusted and fully adjusted RRs in the states other than the Ohio Valley states are all consistent with no relationship and most are very close to 1.00. The positive age-sex adjusted RRs for the entire U.S. and the Ohio Valley states became statistically insignificant after controlling for the three confounding variables of race, education, and smoking status.

However, the fully adjusted RR for the entire U.S. was 1.082 (1.039-1.128) when based on the HEI $PM_{2.5}$ values in 50 counties. This RR agrees quite well with the fully adjusted RR of 1.067 (1.037-1.099) for 1982-1989, which is shown in Table 34 of the June 2009 HEI Extended Follow-up Research Report (HEI 2009) (18). Thus, the positive nationwide RRs in the CPS II cohort depend upon the use of HEI $PM_{2.5}$ values. The nationwide RRs are consistent with no effect when based on IPN $PM_{2.5}$ values. The findings in Table 2 clearly demonstrate the large influence of $PM_{2.5}$ values and geography on the RRs.

Table 3 shows that the fully adjusted RR in California was 0.992 (0.954–1.032) when based on IPN $PM_{2.5}$ values in all 11 California counties. This null finding is consistent with the 15 other

findings of a null relationship in California, all of which are shown in Appendix Table 2. However, when the RR is based on the 4 California counties used in Pope 1995 and HEI 2000, there is a significant inverse relationship. The fully adjusted RR is 0.879 (0.805-0.960) when based on the IPN $PM_{2.5}$ values and is 0.870 (0.788–0.960) when based on the HEI $PM_{2.5}$ values. This significant inverse relationship is in exact agreement with the finding of a special analysis of the CPS II cohort done by Krewski in 2010, which yielded a fully adjusted RR of 0.872 (0.805– 0.944) during 1982-89 in California when based on HEI $PM_{2.5}$ values (19). In this instance, the California RRs are dependent upon the number of counties used.

Table 4 shows that the ecological analysis based on linear regression is quite consistent with the proportional hazard regression results in Tables 2 and 3, in spite of the fact that the regression results are not fully adjusted. Using 1980 age-adjusted white total death rates versus HEI $PM_{2.5}$ values in 50 counties, linear regression yielded a regression coefficient of 6.96 (SE = 1.85) that was statistically significant at the 95% confidence level. Pope 1995 reported a significant regression coefficient for 50 cities of 8.0 (SE = 1.4). However, this positive coefficient is misleading because both the death rates and $PM_{2.5}$ levels are higher in the East than in the West. Regional regression analyses did not generally yield significant regression coefficients. Specifically, there were no significant regression coefficients for California, the five Ohio Valley states, or all the states west of the Mississippi River. These findings reinforce the CPS II cohort evidence of statistically insignificant $PM_{2.5}$ mortality risk throughout the U.S.

Discussion

This independent analysis of the CPS II cohort reveals that there was no significant relationship between $PM_{2.5}$ and death from all causes during 1982-1988, when the best available $PM_{2.5}$ measurements were used for the 50 original counties or for all 85 counties with $PM_{2.5}$ data and CPS II subjects. However, a positive relationship was found when the HEI $PM_{2.5}$ measurements were used for the 50 original counties, consistent with the findings in Pope 1995 and HEI 2000. This null and positive evidence demonstrates that the $PM_{2.5}$-mortality relationship is not robust and is quite sensitive to the $PM_{2.5}$ data and CPS II subjects used in the analysis.

Furthermore, the following statement on page 80 of HEI 2000 raises serious doubts about the quality of the air pollution data used in Pope 1995 and HEI 2000: "AUDIT OF AIR QUALITY DATA The ACS Study was not originally designed as an air pollution study. The air quality monitoring data used for the ACS analyses came from various sources, some of which are now technologically difficult to access. Documentation of the statistical reduction procedures has been lost. Summary statistics for different groups of standard metropolitan statistical areas had been derived by different investigators. These data sources do not indicate whether the tabulated values refer to all or a subset of monitors in a region or whether they represent means or medians." (4)

The Pope 1995, HEI 2000, and HEI 2009 analyses did not cite or use the high quality and widely known EPA IPN $PM_{2.5}$ data in spite of the fact that these data have been available in two detailed EPA reports since 1986 (14,15). These investigators did not use the EPA IPN reports even after I cited them in 2005 (5) and personally discussed these data with Pope in 2008 (8). Instead they

repeatedly used 50 median $PM_{2.5}$ values shown in Appendix A of the 1988 Brookhaven National Laboratory Report 52122 by Lipfert et al. (20). HEI 2000 acknowledged that $PM_{2.5}$ data was located for 63 cities, but they analyzed only 50 cities (metropolitan areas). HEI 2009 did analyses for 50 and 58 cities, but did not acknowledge or analyze that IPN $PM_{2.5}$ data was available for 85 cities (counties) with CPS II subjects.

Thus, the HEI Reanalysis Team failed to properly "evaluate the sensitivity of the original findings to the indicators of exposure to fine particle air pollution used by the Original Investigators" and failed to select "all participants who lived within each MA (metropolitan area) for which data on sulfate or fine particle pollution were available" (4). HEI 2009 did not cite my 2005 null PM2.5-mortality findings in California (5), which were based on the IPN data for 11 California counties, instead of the 4 California counties used in Pope 1995, HEI 2000, and HEI 2009. Furthermore, HEI 2009 did not acknowledge or address my 2006 concerns about the geographic variation in PM2.5 mortality risk clearly shown in HEI 2000 Figure 21 (6), which is included here as Appendix Figure 1.

Since 2002, HEI has repeatedly refused to provide the $PM_{2.5}$-related "mortality risk" (MR) for the 50 cities included in Figures 5 and 21 of HEI 2000 (18). I estimated these mortality risks in 2010 based on visual measurements of Figure 5 and these estimates are shown in Appendix Table 1. However, these estimates need to be confirmed by HEI, especially given the findings in this paper. The pattern of evasion, obfuscation, and falsification by the authors of CPS II $PM_{2.5}$ epidemiology publications began in 1997 in response to the original critics (2,3), begin in 2005 in response to me (5-8,13), and began in 2011 in response to the HSSTC (10-12). This misrepresentation and exaggeration has been deliberate in order to continue the EPA claim that $PM_{2.5}$ has a *causal* relationship to total mortality, in spite of massive evidence to the contrary.

The claim of excess $PM_{2.5}$ mortality risk in Southern California has been made again, in spite of the overwhelming evidence in Appendix Table 2 that there is no such risk in California. The 2016 Draft Air Quality Management Plan (AQMP) of the South Coast Air Quality Management District is using three positive RRs found within the CPS II cohort in order to show that 2111 annual deaths in Southern California are caused by current levels of $PM_{2.5}$ (21). This claim is not justified given all the existing null California evidence and the new null CPS II evidence presented in this paper.

In conclusion, the findings in this paper raise serious doubts about the validity of the $PM_{2.5}$ epidemiology findings based on the CPS II cohort. Thus, there is an immediate need for ACS and HEI to cooperate in the independent analysis of the CPS II data. Finally, these findings demonstrate the importance of independent analysis of underlying data and raise concerns about the epidemiologic basis for the current $PM_{2.5}$ NAAQS.

References

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Table 1. Summary Characteristics of CPS II Subjects in 1) Pope 1995 Table 1 (1), 2) HEI 2000 Table 24 (4), and 3) current analysis based on CPS II subjects in 50 and 85 counties

Characteristic	Pope 1995 Table 1	HEI 2000 Table 24	Current CPS II Analysis N=50 HEI $PM_{2.5}$	N=50 IPN $PM_{2.5}$	N=85 IPN $PM_{2.5}$
Number of metro areas	50	50			
Number of counties	not stated	not stated	50	50	85
Age-Sex Adjusted Subjects			212,370	212,370	292,277
Fully Adjusted Subjects	295,223	298,817	195,215	195,215	269,766
Age-Sex Adjusted Deaths			12,518	12,518	17,231
Fully Adjusted Deaths	20,765	23,093	11,221	11,221	15,593
Values Below are for Subjects in Fully Adjusted Results					
Age at enrollment (mean years)	56.6	56.6	56.66	56.66	56.64
Sex (% females)	55.9	56.4	56.72	56.72	56.61
Race (% white)	94.0	94.0	94.58	94.58	95.09
Less than high school education (%)	11.3	11.3	11.71	11.71	11.71
Never Smoked Regularly (%)			41.69	41.69	41.57
Former smoker (%)			33.25	33.25	33.67
Former cigarette smoker (%)	29.4	30.2	30.43	30.43	30.81
Current smoker (%)			25.06	25.06	24.76
Currrent cigarette smoker (%)	21.6	21.4	21.01	21.01	20.76
Fine particles ($\mu g/m^3$)					
Average	18.2	18.2	17.99	21.37	21.16
SD	5.1	4.4	4.52	5.30	5.98
Range	9.0 – 33.5	9.0- 33.4	9.0- 33.4	10.77- 29.67	10.63- 42.01

Table 2. Age-sex adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through August 31, 1988 associated with change of 10 μg/m³ increase in $PM_{2.5}$ for CPS II subjects residing in 50 and 85 counties in the continental United States with 1979-83 IPN $PM_{2.5}$ measurements. Analysis includes continental United States, five Ohio Valley states, and remainder of the states. Appendix Table 1 lists the 50 cities and counties with $PM_{2.5}$ measurements.

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower	95% CI Upper	Average $PM_{2.5}$
Age-sex adjusted RR for the Continental United States							
1979-83 IPN	85	292,277	17,321	1.038	(1.014	– 1.063)	21.16
1979-83 IPN	50	212,370	12,518	1.046	(1.013	– 1.081)	21.36
1979-83 HEI	50	212,370	12,518	1.121	(1.078	– 1.166)	17.99
Fully adjusted RR for the Continental United States							
1979-83 IPN	85	269,766	15,593	1.023	(0.997	– 1.049)	21.15
1979-83 IPN	50	195,215	11,221	1.025	(0.990	– 1.061)	21.36
1979-83 HEI	50	195,215	11,221	1.082	(1.039	– 1.128)	17.99
Age-sex adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-83 IPN	17	56,979	3,649	1.126	(1.011	– 1.255)	25.51
1979-83 IPN	12	45,303	2,942	1.079	(0.951	– 1.225)	25.76
1979-83 HEI	12	45,303	2,942	1.153	(1.027	– 1.296)	22.02
Fully adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-83 IPN	17	53,026	3,293	1.096	(0.978	– 1.228)	25.51
1979-83 IPN	12	42,174	2,652	1.050	(0.918	– 1.201)	25.75
1979-83 HEI	12	42,174	2,652	1.111	(0.983	– 1.256)	22.02
Age-sex adjusted RR for States other than the Ohio Valley States							
1979-83 IPN	68	235,298	13,672	0.999	(0.973	– 1.027)	20.11
1979-83 IPN	38	167,067	9,576	0.983	(0.946	– 1.021)	20.18
1979-83 HEI	38	167,067	9,576	1.045	(0.997	– 1.096)	16.90
Fully adjusted RR for States other than the Ohio Valley States							
1979-83 IPN	68	216,740	12,300	0.994	(0.967	– 1.023)	20.09
1979-83 IPN	38	153,041	8,569	0.975	(0.936	– 1.015)	20.15
1979-83 HEI	38	153,041	8,569	1.025	(0.975	– 1.078)	16.89

Table 3. Age-sex adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through August 31, 1988 associated with 10 μg/m³ increase in $PM_{2.5}$ for California CPS II subjects living in 4 and 11 counties with 1979-83 IPN $PM_{2.5}$ measurements. Also, fully adjusted RR for California subjects in 4 counties from September 1, 1982 through December 31, 1989 as calculated by Krewski (19).

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower	95% CI Upper	Average $PM_{2.5}$
Age-sex adjusted RR for California during 1982-1988							
1979-83 IPN	11	66,615	3,856	1.005	(0.968 – 1.043)		24.08
1979-83 IPN	4	40,527	2,146	0.904	(0.831 – 0.983)		24.90
1979-83 HEI	4	40,527	2,146	0.894	(0.817 – 0.986)		18.83
Fully adjusted (age, sex, race, education, smoking status) RR for California during 1982-1988							
1979-83 IPN	11	60,521	3,512	0.992	(0.954 – 1.032)		24.11
1979-83 IPN	4	36,201	1,939	0.879	(0.805 – 0.960)		25.01
1979-83 HEI	4	36,201	1,939	0.870	(0.788 – 0.960)		18.91
Fully adjusted (44 confounders) RR for California during 1982-1989 as per Krewski (19)							
'Same' Standard Cox Model							
1979-83 HEI	4	40,408		0.872	(0.805 – 0.944)		
'Different' Standard Cox Model							
1979-83 HEI	4	38,925		0.893	(0.823 – 0.969)		

Table 4: Linear regression results for 1979-83 IPN $PM_{2.5}$ and 1979-83 HEI $PM_{2.5}$ versus 1980 Age-adjusted White Total Death Rate (DR) for 85 counties with IPN data and for 50 HEI 2000 counties with IPN data. Linear regression results are also shown for 1979-83 IPN $PM_{2.5}$ and 1979-83 HEI $PM_{2.5}$ versus Mortality Risk (MR) for the 50 'cities' (metropolitan areas) in Figure 5 and Figure 21 in HEI 2000.

DR or MR, $PM_{2.5}$ Years and Source	Number of Counties	DR or MR Intercept	DR or MR Slope	95% CI Lower	DR/MR Slope Upper	P-value
Entire Continental United States						
DR & 1979-83 IPN	85	892.68	6.8331	3.8483	9.8180	0.0000
DR & 1979-83 HEI	50	910.92	6.9557	3.2452	10.6662	0.0004
MR & 1979-83 IPN	50	0.6821	0.0102	0.0044	0.0160	0.0009
MR & 1979-83 HEI	50	0.6754	0.0121	0.0068	0.0173	0.0000
Ohio Valley States (IN, KY, OH, PA, WV)						
DR & 1979-83 IPN	17	941.770	6.0705	-0.0730	12.2139	0.0524
DR & 1979-83 HEI	12	1067.285	1.3235	-7.3460	9.9930	0.7408
MR & 1979-83 IPN	12	0.8153	0.0077	-0.0054	0.0208	0.2202
MR & 1979-83 HEI	12	0.9628	0.0020	-0.0080	0.0121	0.6608
States Other Than the Ohio Valley States						
DR & 1979-83 IPN	68	921.452	4.8639	0.9093	8.8186	0.0167
DR & 1979-83 HEI	38	934.659	4.8940	-0.4337	10.2218	0.0706
MR & 1979-83 IPN	38	0.8111	0.0020	-0.0054	0.0094	0.5891
MR & 1979-83 HEI	38	0.7334	0.0072	0.0000	0.0144	0.0491
States West of the Mississippi River						
DR & 1979-83 IPN	36	920.099	4.0155	-0.9396	8.9706	0.1088
DR & 1979-83 HEI	22	930.110	4.1726	-5.2015	13.5468	0.3642
MR & 1979-83 IPN	22	0.8663	-0.0025	-0.0162	0.0112	0.7067
MR & 1979-83 HEI	22	0.6413	0.0134	-0.0018	0.0285	0.0807
California						
DR & 1979-83 IPN	11	921.708	3.6516	-1.8230	9.1262	0.1656
DR & 1979-83 HEI	4	992.502	1.9664	-46.6929	50.6256	0.8780
MR & 1979-83 IPN	4	0.9529	-0.0074	-0.0600	0.0453	0.6072
MR & 1979-83 HEI	4	0.8336	-0.0021	-0.0618	0.0576	0.8935

Appendix Table 1. List of the 50 original counties used in Pope 1995, HEI 2000, and this analysis, including Federal Information Processing Standards (FIPS) code, state, county, city with IPN/HEI $PM_{2.5}$ measurements, 1979-1983 IPN average $PM_{2.5}$ level, 1979-1983 HEI median $PM_{2.5}$ level, 1980 age-adjusted white county total death rate (annual deaths per 100,000), and HEI 2000 Figure 5 mortality risk for HEI city (metropolitan area).

FIPS Code	State	IPN/HEI County containing IPN/HEI City	IPN/HEI City with $PM_{2.5}$ Measurements	1979-83 IPN $PM_{2.5}$ ($\mu g/m^3$) (weighted average)	1979-83 HEI $PM_{2.5}$ ($\mu g/m^3$) (median)	1980 Age-Adj White Death Rate (DR)	HEI 2000 Figure 5 Mortality Risk (MR)
01073	AL	JEFFERSON	Birmingham	25.6016	24.5	1025.3	0.760
01097	AL	MOBILE	Mobile	22.0296	20.9	1067.2	0.950
04013	AZ	MARICOPA	Phoenix	15.7790	15.2	953.0	0.855
05119	AR	PULASKI	Little Rock	20.5773	17.8	1059.4	0.870
06019	CA	FRESNO	Fresno	18.3731	10.3	1001.4	0.680
06037	CA	LOS ANGELES	Los Angeles	28.2239	21.8	1035.1	0.760
06081	CA	SAN FRANCISCO	San Francisco	16.3522	12.2	1123.1	0.890
06085	CA	SANTA CLARA	San Jose	17.7884	12.4	921.9	0.885
08031	CO	DENVER	Denver	10.7675	16.1	967.3	0.925
09003	CT	HARTFORD	Hartford	18.3949	14.8	952.0	0.845
11001	DC	DISTRIC COLUMBIA	Washington	25.9289	22.5	993.2	0.850
12057	FL	HILLSBOROUGH	Tampa	13.7337	11.4	1021.8	0.845
13121	GA	FULTON	Atlanta	22.5688	20.3	1063.5	0.840
16001	ID	ADA	Boise	18.0052	12.1	892.6	0.600
17031	IL	COOK	Chicago	25.1019	21.0	1076.3	0.945
18089	IN	LAKE	Gary	27.4759	25.2	1129.8	0.995
18097	IN	MARION	Indianapolis	23.0925	21.1	1041.2	0.970
20173	KS	SEDGWICK	Wichita	15.0222	13.6	953.4	0.890
20177	KS	SHAWNEE	Topeka	11.7518	10.3	933.7	0.830
27053	MN	HENNEPIN	Minneapolis	15.5172	13.7	905.3	0.815
28049	MS	HINDS	Jackson	18.1339	15.7	1087.4	0.930
31055	NE	DOUGLAS	Omaha	15.2760	13.1	991.0	0.880
32031	NV	WASHOE	Reno	13.1184	11.8	1049.5	0.670
34017	NJ	HUDSON	Jersey City	19.9121	17.3	1172.6	0.810
35001	NM	BERNALILLO	Albuquerque	12.8865	9.0	1014.7	0.710
36029	NY	ERIE	Buffalo	25.1623	23.5	1085.6	0.960
37063	NC	DURHAM	Durham/Raleigh	19.4092	16.8	1039.2	1.000
37119	NC	MECKLENBURG	Charlotte	24.1214	22.6	932.8	0.835

39035	OH	CUYAHOGA	Cleveland	28.4120	24.6	1089.1	0.980
39061	OH	HAMILTON	Cincinnati	24.9979	23.1	1095.2	0.980
39081	OH	JEFFERSON	Steubenville	29.6739	23.1	1058.6	1.145
39099	OH	MAHONING	Youngstown	22.9404	20.2	1058.4	1.060
39113	OH	MONTGOMERY	Dayton	20.8120	18.8	1039.5	0.980
39153	OH	SUMMIT	Akron	25.9864	24.6	1064.0	1.060
40109	OK	OKLAHOMA	Oklahoma City	14.9767	15.9	1050.4	0.985
41051	OR	MULTNOMAH	Portland	16.3537	14.7	1060.8	0.830
42003	PA	ALLEGHENY	Pittsburgh/Allentown	29.1043	17.9	1115.6	1.005
42101	PA	PHILADELPHIA	Philadelphia	24.0704	21.4	1211.0	0.910
44007	RI	PROVIDENCE	Providence	14.2341	12.9	1006.1	0.890
47037	TN	DAVIDSON	Nashville	21.8944	20.5	981.9	0.845
47065	TN	HAMILTON	Chattanooga	18.2433	16.6	1087.9	0.840
48113	TX	DALLAS	Dallas	18.7594	16.5	1024.9	0.850
48141	TX	EL PASO	El Paso	16.9021	15.7	903.5	0.910
48201	TX	HARRIS	Houston	18.0421	13.4	1025.7	0.700
49035	UT	SALT LAKE	Salt Lake City	16.6590	15.4	954.3	1.025
51710	VA	NORFOLK CITY	Norfolk	19.5500	16.9	1139.3	0.910
53033	WA	KING	Seattle	14.9121	11.9	943.6	0.780
53063	WA	SPOKANE	Spokane	13.5200	9.4	959.2	0.810
54039	WV	KANAWHA	Charleston	21.9511	20.1	1149.5	1.005
54069	WV	OHIO	Wheeling/Huntington	23.9840	33.4	1117.5	1.020

Appendix Figure 1. 1982-1989 $PM_{2.5}$ mortality risk in 50 cities (metropolitan areas) shown in Figure 21 on page 197 of HEI 2000 (4,6) and listed in Appendix Table 1.

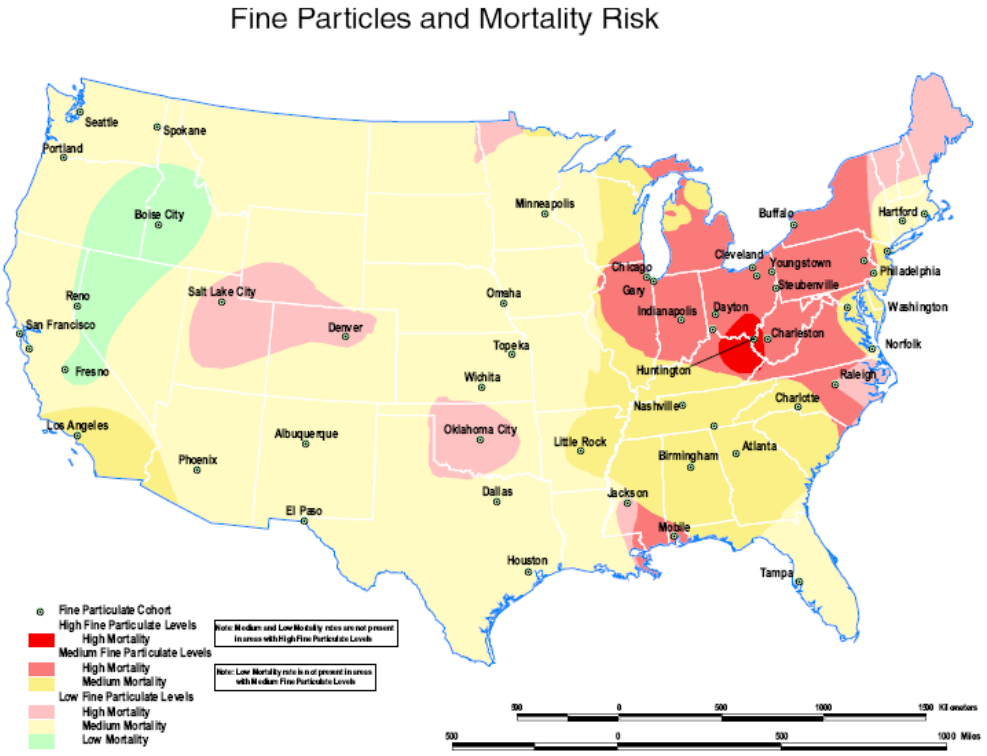

Figure 21. Spatial overlay of fine particle levels and relative risk of mortality. Interval classifications for fine particles (in $\mu g/m^3$): low 8.99–17.03; medium 17.03–25.07; high 25.07–33 Interval classifications for relative risks of mortality: low 0.502–0.711; medium 0.711–0.919; high 0.919–1.128.

Appendix Table 2. Epidemiologic cohort studies of $PM_{2.5}$ and total mortality in California, 2000-2016
Relative risk of death from all causes (RR and 95% CI) associated with increase of 10 µg/m³ in PM2.5
(http://scientificintegrityinstitute.org/NoPMDeaths112215.pdf)

Krewski 2000 & 2010 CA CPS II Cohort N=40,408 RR = 0.872 (0.805-0.944) 1982-1989
(N=[18,000 M + 22,408 F]; 4 MSAs; 1979-1983 PM2.5; 44 covariates)

McDonnell 2000 CA AHSMOG Cohort N~3,800 RR ~ 1.00 (0.95 – 1.05) 1977-1992
(N~[1,347 M + 2,422 F]; SC&SD&SF AB; M RR=1.09(0.98-1.21) & F RR~0.98(0.92-1.03))

Jerrett 2005 CPS II Cohort in LA Basin N=22,905 RR = 1.11 (0.99 - 1.25) 1982-2000
(N=22,905 M & F; 267 zip code areas; 1999-2000 PM2.5; 44 cov + max confounders)

Enstrom 2005 CA CPS I Cohort N=35,783 RR = 1.039 (1.010-1.069) 1973-1982
(N=[15,573 M + 20,210 F]; 11 counties; 1979-1983 PM2.5) RR = 0.997 (0.978-1.016) 1983-2002

Enstrom 2006 CA CPS I Cohort N=35,783 RR = 1.061 (1.017-1.106) 1973-1982
(11 counties; 1979-1983 & 1999-2001 PM2.5) RR = 0.995 (0.968-1.024) 1983-2002

Zeger 2008 MCAPS Cohort "West" N=3,100,000 RR = 0.989 (0.970-1.008) 2000-2005
(N=[1.5 M M + 1.6 M F]; Medicare enrollees in CA+OR+WA (CA=73%); 2000-2005 PM2.5)

Jerrett 2010 CA CPS II Cohort N=77,767 RR ~ 0.994 (0.965-1.025) 1982-2000
(N=[34,367 M + 43,400 F]; 54 counties; 2000 PM2.5; KRG ZIP; 20 ind cov+7 eco var; Slide 12)

Krewski 2010 (2009) CA CPS II Cohort
(4 MSAs; 1979-1983 PM2.5; 44 cov) N=40,408 RR = 0.960 (0.920-1.002) 1982-2000
(7 MSAs; 1999-2000 PM2.5; 44 cov) N=50,930 RR = 0.968 (0.916-1.022) 1982-2000

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 0.994 (0.965-1.024) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; KRG ZIP Model; 20 ind cov+7 eco var; Table 28)

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 1.002 (0.992-1.012) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; Nine Model Ave; 20 ic+7 ev; Fig 22 & Tab 27-32)

Lipsett 2011 CA Teachers Cohort N=73,489 RR = 1.01 (0.95 – 1.09) 2000-2005
(N=[73,489 F]; 2000-2005 PM2.5)

Ostro 2011 CA Teachers Cohort N=43,220 RR = 1.06 (0.96 – 1.16) 2002-2007
(N=[43,220 F]; 2002-2007 PM2.5)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.060 (1.003–1.120) 1982-2000
(N=[~32,550 M + ~41,161 F]; 54 counties; 2000 PM2.5; LUR Conurb Model; 42 ind cov+7 eco var+5 metro; Table 6)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.028 (0.957-1.104) 1982-2000
(same parameters and model as above, except including co-pollutants NO2 and Ozone; Table 5)

Ostro 2015 CA Teachers Cohort N=101,884 RR = 1.01 (0.98 -1.05) 2001-2007
(N=[101,881 F]; 2002-2007 PM2.5) (all natural causes of death)

Thurston 2016 CA NIH-AARP Cohort N=160,209 RR = 1.02 (0.99 -1.04) 2000-2009
(N=[~95,965 M + ~64,245 F]; full baseline model: PM2.5 by zip code; Table 3) (all natural causes of death)

Enstrom 2016 unpub CA NIH-AARP Cohort N=160,368 RR = 1.001 (0.949-1.055) 2000-2009
(N=[~96,059 M + ~64,309 F]; full baseline model: 2000 PM2.5 by county)

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From: Emma Gray [mailto:egray@bmj.com]
Sent: Tuesday, September 27, 2016 6:47 AM
To: James E. Enstrom <jenstrom@ucla.edu>
Cc: Adrian Aldcroft <aaldcroft@bmj.com>
Subject: Status of manuscript bmjopen-2016-013986

Dear Dr Enstrom,

I am writing to you regarding your submission to BMJ Open which was rejected earlier this month.

The editorial team at BMJ Open has looked over your manuscript, and we concluded that we are unable to reconsider the decision on your manuscript. While we appreciate that the issues involved are highly complicated, BMJ Open is guided by principles of openness and transparency, and we reserve the right to reject papers that we don't feel meet our high standards. In light of these principles, the data in your paper are problematic and not suitable for further consideration in BMJ Open. As such, we recommend seeking an alternative venue for your manuscript.

Please note that both the Editor of the journal and an Associate Editor were consulted for this decision, and all parties agree with the rejection. This is our final decision on your paper, and we will not be reconsidering.

I appreciate that this decision will be disappointing. We wish you the best of luck finding an appropriate means of publishing your work.

Sincerely,

Emma Gray, Assistant Editor, BMJ Open, and

Adrian Aldcroft, Editor, BMJ Open

--

Emma Gray
Assistant Editor
BMJ Open

BMJ, BMA House, Tavistock Square, London, WC1H 9JR
T: 020 7874 0783
E: egray@bmj.com
W: http://bmjopen.bmj.com/

From: Emma Gray [mailto:egray@bmj.com]
Sent: Thursday, September 15, 2016 8:41 AM
To: James E. Enstrom <jenstrom@ucla.edu>
Subject: Re: Please Update Status of bmjopen-2016-013986 Manuscript

Dear Dr Enstrom,

Thank you for your email. This is currently with the Editor and I am waiting to hear back from him. He is on leave today and tomorrow, so I hope to be in touch with you next week.

Kind regards,

Emma

On 14 September 2016 at 16:24, James E. Enstrom <jenstrom@ucla.edu> wrote:

Please provide me with an update on the status of bmjopen-2016-013986 Manuscript. Has the Associate Editor made an assessment? Thank you very much.

From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: Thursday, September 08, 2016 8:46 AM
To: 'Emma Gray' <egray@bmj.com>
Cc: 'BMJ Open Editorial Office' <editorial.bmjopen@bmjgroup.com>; 'editorial journals.spi' <info.bmjopen@bmj.com>
Subject: Information Relevant to bmjopen-2016-013986 Manuscript

Dear Editor Gray,

I appreciate your September 6 response. I want to bring to your attention the fact that my bmjopen-2016-013986 Manuscript has a direct relationship to the *BMJ Open 2016;6:e009493* Epidemiology Paper "Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies". Indeed, references 15 and 29 in this paper play a prominent role in my paper. Both papers present strong evidence that air pollution (PM2.5 and ozone) is NOT related to total mortality in the ACS CPS II cohort. However, the authors of references 15 and 29 claim that significant relationships exist. BMJ Open can play an important role in resolving this scientific dispute, which is quite important to US EPA air pollution regulatory policy.

Thank you very much for your consideration.

James E. Enstrom, Ph.D., M.P.H.

From: Emma Gray [mailto:egray@bmj.com]
Sent: Tuesday, September 06, 2016 7:08 AM
To: James E. Enstrom <jenstrom@ucla.edu>
Cc: BMJ Open Editorial Office <editorial.bmjopen@bmjgroup.com>; editorial journals.spi <info.bmjopen@bmj.com>
Subject: Re: FW: Request to Discuss: bmjopen-2016-013986 Manuscript

Dear Dr Enstrom,

Thank you for your email. I did receive your request, and I have sent this, along with your manuscript and our previous feedback, across to one of our Associate Editors for further assessment. I expect to hear back from them shortly, and will be in touch to give you an update soon.

Kind regards,

Emma

On 6 September 2016 at 15:04, James E. Enstrom <jenstrom@ucla.edu> wrote:

September 6, 2016

Dear BMJ Open Editorial Office,

Editor Emma Gray has not yet responded to my email message below. Please let me know as soon as possible if I will be able to speak with anyone in your office about my bmjopen-2016-013986 Manuscript. I would to be given an opportunity to address your reasons for rejection in a way that will allow further consideration of my manuscript. The best way for me to do this is by personal conversation. This is a very important request.

Thank you very much for your assistance.

James E. Enstrom, Ph.D., M.P.H.

-----Original Message-----
From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: Friday, September 02, 2016 7:45 AM
To: 'Emma Gray' <egray@bmj.com>
Subject: Request to Discuss: bmjopen-2016-013986 Manuscript

September 2, 2016

Dear Editor Gray,

I understand the reasons for your decision to reject my bmjopen-2016-013986 Manuscript, but they involve extremely complex issues that are not fully explained in the manuscript. Thus, I request an opportunity to address your concerns about both the confidential nature of the data and the historical nature of the data. This is an important matter in the US because existing published results from these thirty-year old ACS CPS II data are currently being used to justify multi-billion dollar US EPA regulations. Please allow me to speak with you via telephone in order to determine if I can address your concerns well enough to allow further evaluation of my manuscript.

Thank you very much for your consideration.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
(310) 472-4274

-----Original Message-----
From: onbehalfof+info.bmjopen+bmj.com@manuscriptcentral.com
[mailto:onbehalfof+info.bmjopen+bmj.com@manuscriptcentral.com]
Sent: Friday, September 02, 2016 6:03 AM
To: jenstrom@ucla.edu
Cc: jenstrom@ucla.edu
Subject: bmjopen-2016-013986 Manuscript Decision Research: reject

02-Sep-2016

Dear Dr. Enstrom:

I am writing to you in regard to manuscript # bmjopen-2016-013986, "Fine Particulate Matter and Mortality in Cancer Prevention Study Cohort Reanalysis", which you submitted to BMJ Open. Your manuscript has been evaluated and has been declined for publication in BMJ Open.

We have looked over your submission in detail, and I'm sorry to say that we have a number of concerns that preclude further consideration of your article in BMJ Open.

Primarily we are concerned with the source of your data, which you state is "confidential". As the data are not public, and as you state the "subjects never gave informed consent for data sharing", we would have expected authorization to use the data to have gone through an ethics committee or a data protection committee. As this does not appear to be the case, your manuscript does not meet the journal's ethical standards.

Secondly, we feel that the study takes more of a historical approach and is not directly relevant to health practitioners today. As such, the submission is out of scope for BMJ Open.

I am sorry that we cannot be more positive on this occasion, but I hope you appreciate the reasons for the decision.

Sincerely,
Emma Gray
Assistant Editor, BMJ Open
egray@bmj.com

If you elected during submission to send your article on to another journal the article will be transferred in 5 working days. If you intend to rebut this decision please notify us before then.
The journal(s) (if any) you have selected at submission are:
If you want to speed up or stop this onward transmission please email the editorial office:
info.bmjopen@bmj.com

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Emma Gray
Assistant Editor
BMJ Open

BMJ, BMA House, Tavistock Square, London, WC1H 9JR
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-----Original Message-----
From: onbehalfof+info.bmjopen+bmj.com@manuscriptcentral.com
[mailto:onbehalfof+info.bmjopen+bmj.com@manuscriptcentral.com]
Sent: Monday, August 22, 2016 3:15 PM
To: jenstrom@ucla.edu
Subject: BMJ Open - Manuscript ID bmjopen-2016-013986

22-Aug-2016

Dear Dr. Enstrom:

Your manuscript entitled "Fine Particulate Matter and Mortality in Cancer Prevention Study Cohort Reanalysis" has been successfully submitted online and is presently being given full consideration for publication in BMJ Open.

Your manuscript ID is bmjopen-2016-013986.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://mc.manuscriptcentral.com/bmjopen and edit your user information as appropriate.

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We are constantly trying to find ways of improving the peer review system and continually monitor processes and methods by including article submissions and reviews in our research. If you do not wish your paper or review entered into our peer review research programme, please let us know by emailing editorial.bmjopen@bmjgroup.com as soon as possible.

Any individuals listed as co-authors on this manuscript are copied into this submission confirmation email. If you believe that you have received this email in error, please contact the Editorial Office.

Thank you for submitting your manuscript to BMJ Open.

Sincerely,
BMJ Open Editorial Office

P.s. What did you think of the article submission process?
At BMJ, we constantly strive to improve our services for authors and value your feedback. We'd really like to hear your opinions as part of our on-going efforts, and we'd be grateful if could take a few minutes to fill out our short survey. Your responses will, of course, remain confidential and you won't be identified in any results.

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https://bmj.az1.qualtrics.com/SE/?SID=SV_6rNsVdbXkXH2WmV

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From: onbehalfof+info.bmjopen+bmj.com@manuscriptcentral.com
[mailto:onbehalfof+info.bmjopen+bmj.com@manuscriptcentral.com]
Sent: Monday, August 15, 2016 1:29 AM
To: jenstrom@ucla.edu
Cc: jenstrom@ucla.edu
Subject: Manuscript transferred to BMJ Open

15-Aug-2016

draft - Fine Particulate Matter and Mortality in Cancer Prevention Study Cohort Reanalysis

Dear Dr. Enstrom,

As requested, your manuscript entitled: 'Fine Particulate Matter and Mortality in Cancer Prevention Study Cohort Reanalysis' has been transferred to BMJ Open.

The editorial criteria for BMJ Open are slightly different to those of other journals. Therefore please make the following changes to the manuscript before submitting it for consideration:

- Please write a contributorship statement which outlines how each author contributed to the research and the final document.

- Please provide an 'Article summary' section consisting of the heading: 'Strengths and limitations of this study', and containing up to five bullet points that relate specifically to the study reported. This should be placed after the abstract.

- Please include a data sharing statement which either says where extra data can be accessed (e.g. "Extra data is available by emailing XYZ") or simply "No additional data available".

- It is a good idea to include statements relating to ethics, funding, data sharing, etc within the main document file so that they are easily accessible to peer reviewers.

Your login details and a link to create a password are below:

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If you require any assistance, please do not hesitate to contact the Editorial Office, info.bmjopen@bmj.com.

Kind Regards,

BMJ Open Editorial Office

From: Elizabeth Loder [mailto:eloder@bmj.com]
Sent: Sunday, August 14, 2016 3:09 PM
To: James E. Enstrom <jenstrom@ucla.edu>
Cc: BMJ Editorial Office <papersadmin@bmj.com>; BMJ Open Editorial Office <editorial.bmjopen@bmjgroup.com>
Subject: Re: Request for BMJ Open to Consider BMJ.2016.035002 Manuscript

You have correctly copies our manuscript administrator on this and I am sure she will transfer this promptly to BMJ Open. Good luck!

On Sun, Aug 14, 2016 at 5:43 PM, James E. Enstrom <jenstrom@ucla.edu> wrote:

August 14, 2016

Dear Editor Loder and BMJ Editorial Office,

Although I wish it was different, I understand your decision below regarding BMJ.2016.035002 Manuscript. Please assist me in immediately transferring this manuscript to BMJ Open for their consideration. I have copied BMJ Open on this message, as per your instructions below.

Thank you very much.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
jenstrom@ucla.edu

-----Original Message-----
From: onbehalfof+eloder+bmj.com@manuscriptcentral.com
[mailto:onbehalfof+eloder+bmj.com@manuscriptcentral.com]
Sent: Sunday, August 14, 2016 2:18 PM
To: jenstrom@ucla.edu
Cc: jenstrom@ucla.edu
Subject: BMJ.2016.035002 Manuscript Decision Research

14-Aug-2016

Dear Prof. Enstrom,

BMJ.2016.035002 entitled "Fine Particulate Matter and Mortality in Cancer Prevention Study Cohort Reanalysis"

Thank you for sending us your paper. We read it with interest but I am sorry to say that we do not think it is right for the BMJ. In comparison with the many other papers we have to consider, this one is a lower priority for us.

We receive over 3600 research papers each year and accept less than 5%. We have to make hard decisions on just how interesting an article will be to our general clinical readers and how much it adds to what is already known. We do not send out for external peer review manuscripts whose subject matter, design or topic do not meet our current priorities and are unlikely to make it through our process. We hope that this will allow you to promptly submit this manuscript elsewhere.

You may want to consider sending this paper to BMJ Open. BMJ Open (http://bmjopen.bmj.com) is an open access, open peer-reviewed, online journal from BMJ dedicated to publishing high quality, methodologically sound medical research from all disciplines, therapeutic areas, and regions of the world. All types of research article are welcome, from pilot studies to meta-analyses.

If you would like your article to be considered by BMJ Open please submit it via http://mc.manuscriptcentral.com/bmjopen, or contact the editorial office editorial.bmjopen@bmjgroup.com with your BMJ manuscript number for more information. Papers accepted for publication will be subject to an article processing charge, as they are at The BMJ (for details please see http://journals.bmj.com/site/authors/openaccess.xhtml).

Thank you for considering The BMJ for the publication of your research. I hope the outcome of this specific submission will not discourage you from the submission of future manuscripts.

Yours sincerely

Elisabeth Loder
eloder@bmj.com

If you elected during submission to send your article on to another journal the article will be transferred in 5 working days. If you intend to rebut this decision please notify us before then.
The journal(s) (if any) you have selected at submission are: BMJ Open

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Dr. Elizabeth Loder
Acting Head of Research

BMJ

BMJ, BMA House, Tavistock Square

London, WC1H 9JR
T: 020 7383 6950 (UK) or 617-983-7580 (US)
E: eloder@bmj.com
W: bmj.com/company

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-----Original Message-----
From: onbehalfof+papersadmin+bmj.com@manuscriptcentral.com
[mailto:onbehalfof+papersadmin+bmj.com@manuscriptcentral.com]
Sent: Thursday, August 11, 2016 1:03 PM
To: jenstrom@ucla.edu
Cc: jenstrom@ucla.edu
Subject: BMJ - Manuscript ID BMJ.2016.035002

11-Aug-2016

Dear Prof. Enstrom:

Your manuscript entitled "Fine Particulate Matter and Mortality in Cancer Prevention Study Cohort Reanalysis" has been successfully submitted online and is presently being given full consideration for publication in BMJ.

Your manuscript ID is BMJ.2016.035002.

Thank you for considering The BMJ as the right place for your article. All material submitted for publication must be submitted exclusively to The BMJ. We expect that all authors included on a paper fulfil the ICMJE criteria for authorship http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html
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All research papers should include declarations of competing interests, study funding, and ethics approval. In addition, the BMJ requires a transparency declaration for each research paper [see BMJ 2013;347:f4796]: a statement that the lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies are disclosed.

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Yours sincerely

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The BMJ

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Please click on this link to access the survey:
https://bmj.az1.qualtrics.com/SE/?SID=SV_6rNsVdbXkXH2WmV

From: Tiago Villanueva [mailto:tvillanueva@bmj.com]
Sent: Monday, August 08, 2016 3:23 PM
To: James E. Enstrom <jenstrom@ucla.edu>
Cc: Sue Minns <sminns@bmj.com>
Subject: Re: BMJ Presubmission Inquiry

Dear Dr Enstrom,

many thanks for your email.

We would be pleased to consider this.

Could I please ask you to submit the manuscript via our website at http://mc.manuscriptcentral.com/bmj. We will endeavour to give you a quick decision although I can guarantee no promises of publication.

Do you think this falls within the realm of a RIAT paper?

http://www.bmj.com/content/346/bmj.f2865

Thanks.

best wishes,

Tiago

From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: Monday, August 08, 2016 12:11 AM
To: 'Tiago Villanueva' <tvillanueva@bmj.com>
Cc: 'Sue Minns' <sminns@bmj.com>
Subject: BMJ Presubmission Inquiry

August 8, 2016

BMJ Presubmission Inquiry
c/o Tiago Villanueva <tvillanueva@bmj.com>

Dear Editor Villanueva,

Please let me know if The BMJ will consider for publication the first truly independent analysis of the American Cancer Society (ACS) 1982 Cancer Prevention Study (CPS II) cohort with regard to the relationship of fine particulate matter (PM2.5) and total mortality. My analysis is based on the original version of the 1982 CPS II data with 1982-1988 mortality follow-up. These data and detailed documentation were recently sent to me confidentially by a source that has legally possessed them for many years. Until now the CPS II data have never been analyzed without direct ACS involvement, in spite of a 20-year effort for independent analysis of the data, including a 2013 Congressional subpoena for the data.

My null findings on PM2.5 and total mortality are summarized in the Draft Abstract below. They raise serious concerns about the integrity and validity of the existing analyses of CPS II data, dating back to 1995. This is an important matter because the CPS II results have played a key role in establishing the 1997 EPA National Ambient Air Quality Standard (NAAQS) for PM2.5, which has been used to justify multi-billion dollar state and national air pollution regulations in the US. These data are currently being used as the primary public health justification for a proposed $38.2 billion Air Quality Management Plan in Southern California.

key aspects of my epidemiologic research and with the ACS. Furthermore, you could request independent verification of my null findings by sending the EPA PM2.5 data that I used to the Health Effects Institute. HEI could easily recalculate the key PM2.5-mortality relative risks in the 2000 HEI Reanalysis Report and the 2009 HEI Extended Followup Report and determine if the recalculated relative risks are null, in agreement with my findings, or positive, in agreement with the findings in their reports.

Because The BMJ has been willing to consider and publish null epidemiologic findings, you could play an important role in resolving a 20-year scientific controversy regarding PM2.5 and mortality. The controversy, both current and former, is summarized quite well in the July 25, 1997 *Science* news article "Showdown over clean air science" (http://science.sciencemag.org/content/277/5325/466).

Thank you very much for our consideration.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu
(310) 472-4274

Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

James E. Enstrom, Ph.D., M.P.H., FACE

Draft Abstract

Background. The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter (PM2.5), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort. This implausible and contested relationship has been used to justify many costly EPA regulations, most recently the Clean Power Plan. This paper presents the first truly independent examination of the CPS II data.

Methods. The original CPS II questionnaire data, including 1982-1988 mortality follow-up, was analyzed using Cox proportional hazards regression. Results were obtained for 292,277 subjects in 85 counties with 1979-1984 EPA Inhalable Particulate Network (IPN) PM2.5 measurements, as well as for 212,370 subjects in the 50 counties used in the original 1995 analysis.

Results. The 1982-1988 relative risk of death from all causes (RR) and 95% confidence interval (CI) adjusted for age, sex, race, education, and smoking status was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in PM2.5 in 85 counties and 1.025 (0.990-1.061) in the 50 original counties. The relationship between PM2.5 and total mortality depended upon the CSP II subjects selected and the PM2.5 values assigned to these subjects.

Conclusions. No significant relationship between PM2.5 and total mortality in the CPS II cohort was found when the best available PM2.5 data was properly included. The 1995 analysis and 2000 reanalysis misrepresented and exaggerated this relationship by selective use of CPS II and PM2.5 data. These findings demonstrate the importance of independent analysis of underlying data and raise serious doubts about the CPS II epidemiologic evidence supporting the PM2.5 NAAQS.

From: em.scienceadvances.0.4cdca0.568db7e3@editorialmanager.com
[em.scienceadvances.0.4cdca0.568db7e3@editorialmanager.com] On Behalf Of Science Advances
Sent: Saturday, July 30, 2016 8:06 AM
To: James E Enstrom <jenstrom@ucla.edu>
Subject: Decision on ScienceAdvances-D-16-01615

Ref.: Ms. No. ScienceAdvances-D-16-01615 Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

Dear Dr. Enstrom,

Thank you for submitting your manuscript "Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis" to Science Advances. Because your manuscript was not given a high priority rating during the initial screening process, we have decided not to send your paper for further in-depth review. The overall view is that the scope and focus of your manuscript make it more appropriate for a more specialized journal. We are therefore notifying you so that you can seek publication elsewhere.

Please note that Science Advances receives many more interesting submissions than we can send out for in-depth review or can publish. Therefore, our decision is not necessarily a reflection of the quality of your research but rather of our goals to publish highly novel results across a broad and balanced array of disciplines.

Yours sincerely,

Dr. Ali Shilatifard
Deputy Editor
on behalf of the
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[em.scienceadvances.0.4c7e8d.9b0dcf16@editorialmanager.com] On Behalf Of Science Advances
Sent: Wednesday, July 13, 2016 2:43 PM
To: James E Enstrom <jenstrom@ucla.edu>
Subject: A manuscript number has been assigned to Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

Dear Dr. Enstrom,
Your submission entitled "Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis" has been been assigned the following Science Advances manuscript number: ScienceAdvances-D-16-01615.

You can check on the progress of your paper by logging on as an author to our submission site at http://scienceadvances.edmgr.com/.

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Sent: Wednesday, July 13, 2016 2:43 PM
To: James E Enstrom <jenstrom@ucla.edu>
Subject: Submission Confirmation for Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

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We have received your submission entitled "Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis".

You can check on the progress of your paper by logging on to our site as an author at http://scienceadvances.edmgr.com/.

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Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

--Manuscript Draft--

Manuscript Number:	
Full Title:	Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis
Short Title:	PM2.5 and Mortality in CPS II Reanalysis
Abstract:	Background. The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter (PM2.5), largely because of its positive relationship to mortality in the 1982 ACS Cancer Prevention Study (CPS II) cohort. This contested relationship has been used to justify many costly EPA regulations. This paper presents the first truly independent examination of CPS II data. Methods. The original CPS II questionnaire data, including 1982-1988 mortality follow-up, was analyzed using Cox proportional hazards regression. Results were obtained for 292,277 subjects in 85 counties with 1979-1984 EPA Inhalable Particulate Network (IPN) PM2.5 measurements, as well as for 212,370 subjects in the 50 counties used in the original 1995 analysis. Results. The 1982-1988 relative risk of death from all causes (RR) and 95% confidence interval (CI) adjusted for age, sex, race, education, and smoking status was 1.023 (0.997-1.049) for a 10 μg/m³ increase in PM2.5 in 85 counties and 1.025 (0.990-1.061) in the 50 original counties. The relationship between PM2.5 and total mortality depended upon the CSP II subjects selected and the PM2.5 values assigned to these subjects. Conclusions. No significant relationship between PM2.5 and total mortality in the CPS II cohort was found when the best available PM2.5 data was properly included. The 1995 analysis and 2000 reanalysis misrepresented and exaggerated this relationship by selective use of CPS II and PM2.5 data. These findings demonstrate the importance of independent analysis of underlying data and raise serious doubts about the CPS II epidemiologic evidence supporting the PM2.5 NAAQS.
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Section/Category:	Environmental Studies
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Keywords:	fine particulate matter; mortality; Cancer Prevention Study; reanalysis; epidemiology; cohort; relative risk; EPA; National Ambient Air Quality Standard; transparent data.
First Author:	James E Enstrom, Ph.D.
Corresponding Author:	James E Enstrom, Ph.D. University of California Los Angeles UNITED STATES
Corresponding Author E-Mail:	jenstrom@ucla.edu
Corresponding Author's Institution:	University of California Los Angeles
Corresponding Author's Secondary Institution:	
Order of Authors:	James E Enstrom, Ph.D.
Order of Authors Secondary Information:	
Corresponding Author Secondary Information:	
Suggested Reviewers:	

Opposed Reviewers:

July 13, 2016

ScienceAdvances Cover Letter

I have submitted for your consideration the first truly independent analysis of the ACS CPS II cohort with regard to the relationship of fine particulate matter (PM2.5) and total mortality. This analysis is based on an original version of the 1982 CPS II data with 1982-1988 mortality follow-up. These data and detailed documentation were recently sent to me confidentially by a key individual who has legally possessed this material for many years.

To fully understand the significance of this manuscript you need to examine the text, tables, and references in detail. The URLs provide direct access to all of the key references. I have also uploaded a twelve-page Supplement that provides background relevant to the significance this manuscript and includes references 2 and 10.

My null findings on PM2.5 and total mortality raise serious concerns about the integrity and validity of the existing analyses of CPS II data, dating back to 1995. This is an important matter because the CPS II results have played a key role in the establishment and continuation of the EPA PM2.5 NAAQS. This manuscript contains only the most essential initial calculations that I have made. Confirmation of these findings and additional calculations are currently being made.

None of the material has been published or is under consideration elsewhere. This research is exempt from human subjects review because involves secondary analysis of existing de-identified data on human subjects. These subjects were originally enrolled in CPS II by ACS in 1982 and their informed consent was obtained at that time. There has been no external funding for the analysis described in this manuscript. It has been conducted entirely by using my personal assets.

If helpful in making a final decision on my manuscript, you can request independent verification of my key findings by sending only Appendix Table 1 to Health Effects Institute President Daniel Greenbaum. Ask HEI to recalculate the relative risks for all deaths during 1982-1989 shown in Table 34 of HEI 2009, using both the 1979-1984 IPN PM2.5 and 1979-1983 HEI PM2.5 values for the 50 counties shown in Appendix Table 1. If HEI cooperates, it can make these calculations within 10 days using the SAS computer programs and CPS II data that it has possessed since 2000. HEI can also be asked to submit a manuscript in response to my manuscript. If HEI does not make these calculations, their refusal will reinforce the importance of my findings. If you make a request to HEI, please do not identify me in any way.

Thank you very much for our consideration.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu
(310) 472-4274

Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

James E. Enstrom, Ph.D., M.P.H., FACE
UCLA and Scientific Integrity Institute
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July 13, 2016

Abstract

Background. The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort. This implausible and contested relationship has been used to justify many costly EPA regulations, most recently the Clean Power Plan. This paper presents the first truly independent examination of the CPS II data.

Methods. The original CPS II questionnaire data, including 1982-1988 mortality follow-up, was analyzed using Cox proportional hazards regression. Results were obtained for 292,277 subjects in 85 counties with 1979-1984 EPA Inhalable Particulate Network (IPN) $PM_{2.5}$ measurements, as well as for 212,370 subjects in the 50 counties used in the original 1995 analysis.

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Conclusions. 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 was properly included. The 1995 analysis and 2000 reanalysis misrepresented and exaggerated this relationship by selective use of CPS II and $PM_{2.5}$ data. These findings demonstrate the importance of independent analysis of underlying data and raise serious doubts about the CPS II epidemiologic evidence supporting the $PM_{2.5}$ NAAQS.

Background

The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort, as published in 1995 by Pope et al. (Pope 1995) (1). However, the validity of this finding was immediately challenged (2,3) and it still remains intensely contested. The EPA claim that $PM_{2.5}$ *causes* premature deaths is implausible because no etiologic mechanism has ever been established, because it is based on inhaling over a lifetime only about 5 gm of particles that are less than 2.5 µm in diameter, and because the underlying CPS II data have never been independently analyzed. The $PM_{2.5}$-mortality relationship has been further challenged because the small increased risk could be due to well-known epidemiological biases, such as, the ecological fallacy, inaccurate exposure measurements, and confounding variables like co-pollutants. In addition, there is extensive evidence of spatial and temporal variation in $PM_{2.5}$ mortality risk that does not support one national standard for $PM_{2.5}$.

In spite of these serious problems, EPA and the major $PM_{2.5}$ investigators continue to assert that their selected positive findings are sufficient proof that that $PM_{2.5}$ *causes* premature deaths. This premature death claim has been used to justify many costly EPA regulations, most recently the Clean Power Plan. Indeed, 85% of the total estimated benefits of all EPA regulations have been attributed to reductions in $PM_{2.5}$-related premature deaths. With the assumed benefits of $PM_{2.5}$ reductions playing such a major role in EPA regulatory policy, it is essential that the relationship of $PM_{2.5}$ to mortality be independently verified with transparent data and reproducible findings.

In 1998 the Health Effects Institute (HEI) in Boston was commissioned to conduct a detailed reanalysis of the original Pope 1995 findings. The July 2000 HEI Reanalysis Report (HEI 2000) included "PART I: REPLICATION AND VALIDATION" and "PART II: SENSITIVITY ANALYSES" (4). The HEI Reanalysis Team lead by Krewski successfully replicated and validated the 1995 CPS II findings, but they did not analyze the CPS II data in ways that would determine whether the original results remained robust to different analytic assumptions. For instance, none of their models used the best available $PM_{2.5}$ measurements as of 1995.

Particularly troubling is the fact that EPA, Pope, and other investigators have ignored multiple null findings on the relationship between $PM_{2.5}$ and mortality in California. These findings have been pointed out to them repeatedly in my 2005 paper (5), my 2006 clarification (6), my 2012 American Statistical Society Joint Statistical Meeting Proceedings (7), and my 2015 presentation on the Clean Power Plan and $PM_{2.5}$-related co-benefits (8). There is other published evidence of a null relationship, particularly in the western U.S. (9). This is now overwhelming evidence of misrepresentation and exaggeration of the $PM_{2.5}$-mortality relationship dating back to 2000. These continual problems with the $PM_{2.5}$-mortality relationship have generated substantial media and political concern.

Since 2011 the U.S. House Science, Space, and Technology Committee (HSSTC) has requested that EPA provide access to the underlying CPS II data, particularly since substantial Federal funding has been used for the major $PM_{2.5}$-mortality research and publications. On July 22, 2013 the HSSTC made a particularly detailed request to EPA that included 49 pages of letters dating

back to September 22, 2011 (10). When EPA failed to provide the requested data, the HSSTC issued an August 1, 2013 subpoena to EPA for the CPS II data (11). The ACS refused to comply with the HSSTC subpoena in any way, as explained in an August 19, 2013 letter to EPA by Chief Medical Officer Otis W. Brawley (12). Also, ACS has refused to work with me and other highly qualified investigators regarding collaborative analysis of the CPS II data. Finally, HEI has refused to conduct my proposed CPS II analyses, as explained in an October 4, 2013 HEI letter (13). However, my recent acquisition of an original version of the CPS II data makes possible this first truly independent analysis.

Methods

Computer files containing the original 1982 ACS CPS II de-identified questionnaire data and six-year follow-up data on deaths from September 1, 1982 through August 31, 1988 have been recently obtained from a confidential source. Of the 1.2 million total CPS II subjects, analysis has been done on 297,592 subjects residing in 85 counties in the continental U.S. with 1979-84 EPA IPN PM2.5 measurements (14,15). Among these subjects there were 18,612 total deaths from September 1, 1982 through August 31, 1988; 17,329 of these deaths (93.1%) had a known date of death. Of the 297,592 subjects, 292,277 had age at entry of 30-99 years and sex of male [1] or female [2]. Of the 292,277 subjects, 269,766 had race of white [1,2,5] or black [3,4]; education level of no or some high school [1,2], high school graduate [3], some college [4,5], college graduate [6], or graduate school [7]; and smoking status of never [1], former [5-8 for males and 3 for females], or current [2-4 for males and 2 for females]. Those subjects reported to be dead [D,G,K] but without an exact date of death have been assumed to be alive in this analysis. These unconfirmed deaths are randomly distributed and do not impact relative comparisons of death. The computer codes for the above variables are shown in brackets.

CPS II subjects were entered into the master data file geographically. Since this de-identified data file does not contain home addresses, the Division number and Unit number assigned by ACS to each CPS II subject has been used to define their county of residence. For instance, ACS Division 39 represents the state of Ohio and its Unit 041 represents Jefferson County, which includes the city of Steubenville. In other words, most of the 575 subjects in Unit 041 lived in Jefferson County as of September 1, 1982. The IPN $PM_{2.5}$ value of 29.6739 $\mu g/m^3$ assigned to all subjects in Unit 041 is based on measurements made in Steubenville. This $PM_{2.5}$ value is a weighted average of 53 measurements (mean of 33.9260 $\mu g/m^3$) and 31 measurements (mean of 29.4884 $\mu g/m^3$) made during 1979-1982 (14) and 53 measurements (mean of 27.2473 $\mu g/m^3$) and 54 measurements (mean of 28.0676 $\mu g/m^3$) made during 1983-1984 (15). The HEI $PM_{2.5}$ value of 23.1 $\mu g/m^3$ assigned to all subjects in Unit 041 is the median of $PM_{2.5}$ measurements made in Steubenville and is shown in HEI 2000 Appendix D "Alternative Air Pollution Data in the ACS Study" (4).

Analyses were done for the 50 original counties with HEI $PM_{2.5}$ values used in Pope 1995 and HEI 2000, as well as for all 85 counties with CPS II subjects and IPN $PM_{2.5}$ data. Without explanation, Pope 1995 and HEI 2000 omitted 35 counties with CPS II subjects and IPN $PM_{2.5}$ data. The SAS 9.4 procedure PHREG was used to conduct Cox proportional hazards regression (17). Relative risks for death from all causes (RR) and 95% confidence intervals (CI) were

calculated using age-sex adjustment and full adjustment (age, sex, race, education, and smoking status, as defined above). Each of the five adjustment variables has a strong relationship to mortality.

In addition, county-level ecological analyses were done by comparing IPN $PM_{2.5}$ and HEI $PM_{2.5}$ values with 1980 age-adjusted white total death rates (DR) determined by CDC WONDER (16) and mortality risks (MR) as shown in Figures 5 and 21 of HEI 2000 (4). The death rates are age-adjusted to the 2000 US Standard Population and are expressed as annual deaths per 100,000 persons. The SAS 9.4 procedure REGRESSION was used to conduct linear regression of $PM_{2.5}$ values with death rates (DR) and mortality risks (MR). Appendix Table 1 lists the 50 original counties used in Pope 1995 and HEI 2000 and includes city, county, state, FIPS code, IPN average $PM_{2.5}$ level, HEI median $PM_{2.5}$ level, 1980 DR, and HEI MR. Similar information is available for the 35 additional counties with CPS II subjects and IPN $PM_{2.5}$ data.

Results

Table 1 shows basic demographic characteristics for the CPS II subjects, as stated in Pope 1995 (1), HEI 2000 (4), and this current analysis. There is excellent agreement on age, sex, race, education, and smoking status. However, the IPN average $PM_{2.5}$ values are generally about 20% higher than the HEI median $PM_{2.5}$ values, although the differences range from +78% to -28%.

Table 2 shows that during 1982-1988 there was no relationship between IPN $PM_{2.5}$ and total mortality in the entire U.S. The fully adjusted RR and 95% CI was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in all 85 counties and 1.025 (0.990-1.061) in the 50 original counties. Indeed, the fully adjusted RR was not significant in any area of the U.S., such as, the states west of the Mississippi River, the states east of the Mississippi River, the five Ohio Valley states (Indiana, Kentucky, Ohio, Pennsylvania, and West Virginia), and the states other than the Ohio Valley states. The age-sex adjusted and fully adjusted RRs in the states other than the Ohio Valley states are all consistent with no relationship and most are very close to 1.00. The positive age-sex adjusted RRs for the entire U.S. and the Ohio Valley states became statistically insignificant after controlling for the three confounding variables of race, education, and smoking status.

However, the fully adjusted RR for the entire U.S. was 1.082 (1.039-1.128) when based on the HEI $PM_{2.5}$ values in 50 counties. This RR agrees quite well with the fully adjusted RR of 1.067 (1.037-1.099) for 1982-1989, which is shown in Table 34 of the June 2009 HEI Extended Follow-up Research Report (HEI 2009) (18). Thus, the positive nationwide RRs in the CPS II cohort depend upon the use of HEI $PM_{2.5}$ values. The nationwide RRs are consistent with no effect when based on IPN $PM_{2.5}$ values. The findings in Table 2 clearly demonstrate the large influence of $PM_{2.5}$ values and geography on the RRs.

Table 3 shows that the fully adjusted RR in California was 0.992 (0.954–1.032) when based on IPN $PM_{2.5}$ values in all 11 California counties. This null finding is consistent with the 15 other findings of a null relationship in California, all of which are shown in Appendix Table 2. However, when the RR is based on the 4 California counties used in Pope 1995 and HEI 2000,

there is a significant inverse relationship. The fully adjusted RR is 0.879 (0.805-0.960) when based on the IPN $PM_{2.5}$ values and is 0.870 (0.788–0.960) when based on the HEI $PM_{2.5}$ values. This significant inverse relationship is in exact agreement with the finding of a special analysis of the CPS II cohort done by Krewski in 2010, which yielded a fully adjusted RR of 0.872 (0.805– 0.944) during 1982-89 in California when based on HEI $PM_{2.5}$ values (19). In this instance, the California RRs are dependent upon the number of counties used.

Table 4 shows that the ecological analysis based on linear regression is quite consistent with the proportional hazard regression results in Tables 2 and 3, in spite of the fact that the regression results are not fully adjusted. Using 1980 age-adjusted white total death rates versus HEI $PM_{2.5}$ values in 50 counties, linear regression yielded a regression coefficient of 6.96 (SE = 1.85) that was statistically significant at the 95% confidence level. Pope 1995 reported a significant regression coefficient for 50 cities of 8.0 (SE = 1.4). However, this positive coefficient is misleading because both the death rates and $PM_{2.5}$ levels are higher in the East than in the West. Regional regression analyses did not generally yield significant regression coefficients. Specifically, there were no significant regression coefficients for California, the five Ohio Valley states, or all the states west of the Mississippi River. These findings reinforce the CPS II cohort evidence of statistically insignificant $PM_{2.5}$ mortality risk throughout the U.S.

Discussion and Conclusions

This independent analysis of the CPS II cohort reveals that there was no significant relationship between $PM_{2.5}$ and death from all causes during 1982-1988, when the best available $PM_{2.5}$ measurements were used for the 50 original counties or for all 85 counties with $PM_{2.5}$ data and CPS II subjects. However, a positive relationship was found when the HEI $PM_{2.5}$ measurements were used for the 50 original counties, consistent with the findings in Pope 1995 and HEI 2000. This null and positive evidence demonstrates that the $PM_{2.5}$-mortality relationship is not robust and is quite sensitive to the $PM_{2.5}$ data and CPS II subjects used in the analysis.

Furthermore, the following statement on page 80 of HEI 2000 raises serious doubts about the quality of the air pollution data used in Pope 1995 and HEI 2000: "AUDIT OF AIR QUALITY DATA The ACS Study was not originally designed as an air pollution study. The air quality monitoring data used for the ACS analyses came from various sources, some of which are now technologically difficult to access. Documentation of the statistical reduction procedures has been lost. Summary statistics for different groups of standard metropolitan statistical areas had been derived by different investigators. These data sources do not indicate whether the tabulated values refer to all or a subset of monitors in a region or whether they represent means or medians." (4)

The Pope 1995, HEI 2000, and HEI 2009 analyses did not cite or use the high quality and widely known EPA IPN $PM_{2.5}$ data in spite of the fact that these data have been available in two detailed EPA reports since 1986 (14,15). These investigators did not use the EPA IPN reports even after I cited them in 2005 (5) and personally discussed these data with Pope in 2008 (8). Instead they repeatedly used 50 median $PM_{2.5}$ values shown in Appendix A of the 1988 Brookhaven National Laboratory Report 52122 by Lipfert et al. (20). HEI 2000 acknowledged that $PM_{2.5}$ data was

located for 63 cities, but they analyzed only 50 cities (metropolitan areas). HEI 2009 did analyses for 50 and 58 cities, but did not acknowledge or analyze that IPN $PM_{2.5}$ data was available for 85 cities (counties) with CPS II subjects.

Thus, the HEI Reanalysis Team failed to properly "evaluate the sensitivity of the original findings to the indicators of exposure to fine particle air pollution used by the Original Investigators" and failed to select "all participants who lived within each MA (metropolitan area) for which data on sulfate or fine particle pollution were available" (4). HEI 2009 did not cite my 2005 null PM2.5-mortality findings in California (5), which were based on the IPN data for 11 California counties, instead of the 4 California counties used in Pope 1995, HEI 2000, and HEI 2009. Furthermore, HEI 2009 did not acknowledge or address my 2006 concerns about the geographic variation in PM2.5 mortality risk clearly shown in HEI 2000 Figure 21 (6), which is included here as Appendix Figure 1.

Since 2002, HEI has repeatedly refused to provide the $PM_{2.5}$-related "mortality risk" (MR) for the 50 cities included in Figures 5 and 21 of HEI 2000 (18). I estimated these mortality risks in 2010 based on visual measurements of Figure 5 and these estimates are shown in Appendix Table 1. However, these estimates need to be confirmed by HEI, especially given the findings in this paper. The pattern of evasion, obfuscation, and falsification by the authors of CPS II $PM_{2.5}$ epidemiology publications began in 1997 with the original critics (2,3), begin in 2005 with me (5-8,13), and began in 2011 with the HSSTC (10-12). The massive documented evidence in these references supports that notion that the misrepresentation and exaggeration has been deliberate in order to promote the notion that $PM_{2.5}$ has a positive relationship to total mortality.

In conclusion, these findings raise serious doubts about the validity of the $PM_{2.5}$ epidemiology findings based on the CPS II cohort. Thus, there is an immediate need for ACS and HEI to cooperate in the independent analysis of the CPS II data. Finally, these findings demonstrate the importance of independent analysis of underlying data and raise concerns about the epidemiologic basis for the current $PM_{2.5}$ NAAQS.

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Table 1. Summary Characteristics of CPS II Subjects in 1) Pope 1995 Table 1 (1), 2) HEI 2000 Table 24 (4), and 3) current analysis based on CPS II subjects in 50 and 85 counties

Characteristic	Pope 1995 Table 1	HEI 2000 Table 24	Current CPS II Analysis N=50 HEI $PM_{2.5}$	N=50 IPN $PM_{2.5}$	N=85 IPN $PM_{2.5}$
Number of metro areas	50	50			
Number of counties	not stated	not stated	50	50	85
Age-Sex Adjusted Subjects			212,370	212,370	292,277
Fully Adjusted Subjects	295,223	298,817	195,215	195,215	269,766
Age-Sex Adjusted Deaths			12,518	12,518	17,231
Fully Adjusted Deaths	20,765	23,093	11,221	11,221	15,593
Values Below are for Subjects in Fully Adjusted Results					
Age at enrollment (mean years)	56.6	56.6	56.66	56.66	56.64
Sex (% females)	55.9	56.4	56.72	56.72	56.61
Race (% white)	94.0	94.0	94.58	94.58	95.09
Less than high school education (%)	11.3	11.3	11.71	11.71	11.71
Never Smoked Regularly (%)			41.69	41.69	41.57
Former smoker (%)			33.25	33.25	33.67
Former cigarette smoker (%)	29.4	30.2	30.43	30.43	30.81
Current smoker (%)			25.06	25.06	24.76
Currrent cigarette smoker (%)	21.6	21.4	21.01	21.01	20.76
Fine particles ($\mu g/m^3$)					
Average	18.2	18.2	17.99	21.37	21.16
SD	5.1	4.4	4.52	5.30	5.98
Range	9.0 – 33.5	9.0- 33.4	9.0- 33.4	10.77- 29.67	10.63- 42.01

Table 2: Age-sex adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through August 31, 1988 associated with change of 10 μg/m³ increase in $PM_{2.5}$ for CPS II subjects residing in 50 and 85 counties in the continental United States with 1979-84 IPN $PM_{2.5}$ measurements. Analysis includes continental United States, five Ohio Valley states, and remainder of the states. Appendix Table 1 lists the 50 cities and counties with $PM_{2.5}$ measurements.

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower	95% CI Upper	Average $PM_{2.5}$
Age-sex adjusted RR for the Continental United States							
1979-84 IPN	85	292,277	17,321	1.038	(1.014	– 1.063)	21.16
1979-84 IPN	50	212,370	12,518	1.046	(1.013	– 1.081)	21.36
1979-83 HEI	50	212,370	12,518	1.121	(1.078	– 1.166)	17.99
Fully adjusted RR for the Continental United States							
1979-84 IPN	85	269,766	15,593	1.023	(0.997	– 1.049)	21.15
1979-84 IPN	50	195,215	11,221	1.025	(0.990	– 1.061)	21.36
1979-83 HEI	50	195,215	11,221	1.082	(1.039	– 1.128)	17.99
Age-sex adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-84 IPN	17	56,979	3,649	1.126	(1.011	– 1.255)	25.51
1979-84 IPN	12	45,303	2,942	1.079	(0.951	– 1.225)	25.76
1979-83 HEI	12	45,303	2,942	1.153	(1.027	– 1.296)	22.02
Fully adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-84 IPN	17	53,026	3,293	1.096	(0.978	– 1.228)	25.51
1979-84 IPN	12	42,174	2,652	1.050	(0.918	– 1.201)	25.75
1979-83 HEI	12	42,174	2,652	1.111	(0.983	– 1.256)	22.02
Age-sex adjusted RR for States other than the Ohio Valley States							
1979-84 IPN	68	235,298	13,672	0.999	(0.973	– 1.027)	20.11
1979-84 IPN	38	167,067	9,576	0.983	(0.946	– 1.021)	20.18
1979-83 HEI	38	167,067	9,576	1.045	(0.997	– 1.096)	16.90
Fully adjusted RR for States other than the Ohio Valley States							
1979-84 IPN	68	216,740	12,300	0.994	(0.967	– 1.023)	20.09
1979-84 IPN	38	153,041	8,569	0.975	(0.936	– 1.015)	20.15
1979-83 HEI	38	153,041	8,569	1.025	(0.975	– 1.078)	16.89

Table 3. Age-sex adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through August 31, 1988 associated with 10 µg/m³ increase in $PM_{2.5}$ for California CPS II subjects living in 4 and 11 counties with 1979-84 IPN $PM_{2.5}$ measurements. Also, fully adjusted RR for California subjects in 4 counties from September 1, 1982 through December 31, 1989 as calculated by Krewski (19).

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower	95% CI Upper	Average $PM_{2.5}$
Age-sex adjusted RR for California during 1982-1988							
1979-84 IPN	11	66,615	3,856	1.005	(0.968 – 1.043)		24.08
1979-84 IPN	4	40,527	2,146	0.904	(0.831 – 0.983)		24.90
1979-83 HEI	4	40,527	2,146	0.894	(0.817 – 0.986)		18.83
Fully adjusted (age, sex, race, education, smoking status) RR for California during 1982-1988							
1979-84 IPN	11	60,521	3,512	0.992	(0.954 – 1.032)		24.11
1979-84 IPN	4	36,201	1,939	0.879	(0.805 – 0.960)		25.01
1979-83 HEI	4	36,201	1,939	0.870	(0.788 – 0.960)		18.91
Fully adjusted (44 confounders) RR for California during 1982-1989 as per Krewski (19)							
'Same' Standard Cox Model							
1979-84 HEI	4	40,408		0.872	(0.805 – 0.944)		
'Different' Standard Cox Model							
1979-84 HEI	4	38,925		0.893	(0.823 – 0.969)		

Table 4: Linear regression results for 1979-84 IPN $PM_{2.5}$ and 1979-83 HEI $PM_{2.5}$ versus 1980 Age-adjusted White Total Death Rate (DR) for 85 counties with IPN data and for 50 HEI 2000 counties with IPN data. Linear regression results are also shown for 1979-84 IPN $PM_{2.5}$ and 1979-83 HEI $PM_{2.5}$ versus Mortality Risk (MR) for the 50 'cities' (metropolitan areas) in Figure 5 and Figure 21 in HEI 2000.

DR or MR, $PM_{2.5}$ Years and Source	Number of Counties	DR or MR Intercept	DR or MR Slope	95% CI Lower	DR/MR Slope Upper	P-value
Entire Continental United States						
DR & 1979-84 IPN	85	892.68	6.8331	3.8483	9.8180	0.0000
DR & 1979-83 HEI	50	910.92	6.9557	3.2452	10.6662	0.0004
MR & 1979-84 IPN	50	0.6821	0.0102	0.0044	0.0160	0.0009
MR & 1979-83 HEI	50	0.6754	0.0121	0.0068	0.0173	0.0000
Ohio Valley States (IN, KY, OH, PA, WV)						
DR & 1979-84 IPN	17	941.770	6.0705	-0.0730	12.2139	0.0524
DR & 1979-83 HEI	12	1067.285	1.3235	-7.3460	9.9930	0.7408
MR & 1979-84 IPN	12	0.8153	0.0077	-0.0054	0.0208	0.2202
MR & 1979-83 HEI	12	0.9628	0.0020	-0.0080	0.0121	0.6608
States Other Than the Ohio Valley States						
DR & 1979-84 IPN	68	921.452	4.8639	0.9093	8.8186	0.0167
DR & 1979-83 HEI	38	934.659	4.8940	-0.4337	10.2218	0.0706
MR & 1979-84 IPN	38	0.8111	0.0020	-0.0054	0.0094	0.5891
MR & 1979-83 HEI	38	0.7334	0.0072	0.0000	0.0144	0.0491
States West of the Mississippi River						
DR & 1979-84 IPN	36	920.099	4.0155	-0.9396	8.9706	0.1088
DR & 1979-83 HEI	22	930.110	4.1726	-5.2015	13.5468	0.3642
MR & 1979-84 IPN	22	0.8663	-0.0025	-0.0162	0.0112	0.7067
MR & 1979-83 HEI	22	0.6413	0.0134	-0.0018	0.0285	0.0807
California						
DR & 1979-84 IPN	11	921.708	3.6516	-1.8230	9.1262	0.1656
DR & 1979-83 HEI	4	992.502	1.9664	-46.6929	50.6256	0.8780
MR & 1979-84 IPN	4	0.9529	-0.0074	-0.0600	0.0453	0.6072
MR & 1979-83 HEI	4	0.8336	-0.0021	-0.0618	0.0576	0.8935

Appendix Table 1. List of the 50 original counties used in Pope 1995, HEI 2000, and this analysis, including Federal Information Processing Standards (FIPS) code, state, county, city with IPN/HEI $PM_{2.5}$ measurements, 1979-1984 IPN average $PM_{2.5}$ level, 1979-1983 HEI median $PM_{2.5}$ level, 1980 age-adjusted white county total death rate (annual deaths per 100,000), and HEI 2000 Figure 5 mortality risk for HEI city (metropolitan area).

FIPS Code	State	IPN/HEI County containing IPN/HEI City	IPN/HEI City with $PM_{2.5}$ Measurements	1979-84 IPN $PM_{2.5}$ ($\mu g/m^3$) (weighted average)	1979-83 HEI $PM_{2.5}$ ($\mu g/m^3$) (median)	1980 Age-Adj White Death Rate (DR)	HEI 2000 Figure 5 Mortality Risk (MR)
01073	AL	JEFFERSON	Birmingham	25.6016	24.5	1025.3	0.760
01097	AL	MOBILE	Mobile	22.0296	20.9	1067.2	0.950
04013	AZ	MARICOPA	Phoenix	15.7790	15.2	953.0	0.855
05119	AR	PULASKI	Little Rock	20.5773	17.8	1059.4	0.870
06019	CA	FRESNO	Fresno	18.3731	10.3	1001.4	0.680
06037	CA	LOS ANGELES	Los Angeles	28.2239	21.8	1035.1	0.760
06081	CA	SAN FRANCISCO	San Francisco	16.3522	12.2	1123.1	0.890
06085	CA	SANTA CLARA	San Jose	17.7884	12.4	921.9	0.885
08031	CO	DENVER	Denver	10.7675	16.1	967.3	0.925
09003	CT	HARTFORD	Hartford	18.3949	14.8	952.0	0.845
11001	DC	DISTRIC COLUMBIA	Washington	25.9289	22.5	993.2	0.850
12057	FL	HILLSBOROUGH	Tampa	13.7337	11.4	1021.8	0.845
13121	GA	FULTON	Atlanta	22.5688	20.3	1063.5	0.840
16001	ID	ADA	Boise	18.0052	12.1	892.6	0.600
17031	IL	COOK	Chicago	25.1019	21.0	1076.3	0.945
18089	IN	LAKE	Gary	27.4759	25.2	1129.8	0.995
18097	IN	MARION	Indianapolis	23.0925	21.1	1041.2	0.970
20173	KS	SEDGWICK	Wichita	15.0222	13.6	953.4	0.890
20177	KS	SHAWNEE	Topeka	11.7518	10.3	933.7	0.830
27053	MN	HENNEPIN	Minneapolis	15.5172	13.7	905.3	0.815
28049	MS	HINDS	Jackson	18.1339	15.7	1087.4	0.930
31055	NE	DOUGLAS	Omaha	15.2760	13.1	991.0	0.880
32031	NV	WASHOE	Reno	13.1184	11.8	1049.5	0.670
34017	NJ	HUDSON	Jersey City	19.9121	17.3	1172.6	0.810
35001	NM	BERNALILLO	Albuquerque	12.8865	9.0	1014.7	0.710
36029	NY	ERIE	Buffalo	25.1623	23.5	1085.6	0.960
37063	NC	DURHAM	Durham/Raleigh	19.4092	16.8	1039.2	1.000
37119	NC	MECKLENBURG	Charlotte	24.1214	22.6	932.8	0.835

39035	OH	CUYAHOGA	Cleveland	28.4120	24.6	1089.1	0.980
39061	OH	HAMILTON	Cincinnati	24.9979	23.1	1095.2	0.980
39081	OH	JEFFERSON	Steubenville	29.6739	23.1	1058.6	1.145
39099	OH	MAHONING	Youngstown	22.9404	20.2	1058.4	1.060
39113	OH	MONTGOMERY	Dayton	20.8120	18.8	1039.5	0.980
39153	OH	SUMMIT	Akron	25.9864	24.6	1064.0	1.060
40109	OK	OKLAHOMA	Oklahoma City	14.9767	15.9	1050.4	0.985
41051	OR	MULTNOMAH	Portland	16.3537	14.7	1060.8	0.830
42003	PA	ALLEGHENY	Pittsburgh/Allentown	29.1043	17.9	1115.6	1.005
42101	PA	PHILADELPHIA	Philadelphia	24.0704	21.4	1211.0	0.910
44007	RI	PROVIDENCE	Providence	14.2341	12.9	1006.1	0.890
47037	TN	DAVIDSON	Nashville	21.8944	20.5	981.9	0.845
47065	TN	HAMILTON	Chattanooga	18.2433	16.6	1087.9	0.840
48113	TX	DALLAS	Dallas	18.7594	16.5	1024.9	0.850
48141	TX	EL PASO	El Paso	16.9021	15.7	903.5	0.910
48201	TX	HARRIS	Houston	18.0421	13.4	1025.7	0.700
49035	UT	SALT LAKE	Salt Lake City	16.6590	15.4	954.3	1.025
51710	VA	NORFOLK CITY	Norfolk	19.5500	16.9	1139.3	0.910
53033	WA	KING	Seattle	14.9121	11.9	943.6	0.780
53063	WA	SPOKANE	Spokane	13.5200	9.4	959.2	0.810
54039	WV	KANAWHA	Charleston	21.9511	20.1	1149.5	1.005
54069	WV	OHIO	Wheeling/Huntington	23.9840	33.4	1117.5	1.020

Appendix Figure 1. 1982-1989 $PM_{2.5}$ mortality risk in 50 cities (metropolitan areas) shown in Figure 21 on page 197 of HEI 2000 (4,6) and listed in Appendix Table 1.

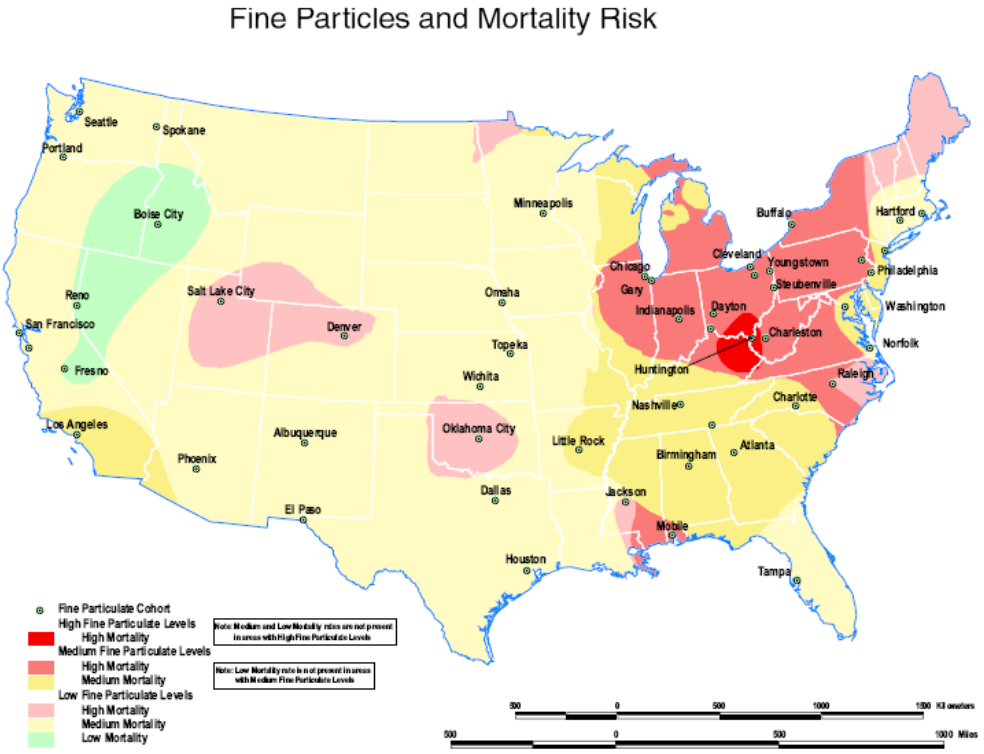

Figure 21. Spatial overlay of fine particle levels and relative risk of mortality. Interval classifications for fine particles (in $\mu g/m^3$): low 8.99–17.03; medium 17.03–25.07; high 25.07–33 Interval classifications for relative risks of mortality: low 0.502–0.711; medium 0.711–0.919; high 0.919–1.128.

Appendix Table 2. Epidemiologic cohort studies of $PM_{2.5}$ and total mortality in California, 2000-2016
Relative risk of death from all causes (RR and 95% CI) associated with increase of 10 µg/m³ in PM2.5

Krewski 2000 & 2010 CA CPS II Cohort N=40,408 RR = 0.872 (0.805-0.944) 1982-1989
(N=[18,000 M + 22,408 F]; 4 MSAs; 1979-1983 PM2.5; 44 covariates)

McDonnell 2000 CA AHSMOG Cohort N~3,800 RR ~ 1.00 (0.95 – 1.05) 1977-1992
(N~[1,347 M + 2,422 F]; SC&SD&SF AB; M RR=1.09(0.98-1.21) & F RR~0.98(0.92-1.03))

Jerrett 2005 CPS II Cohort in LA Basin N=22,905 RR = 1.11 (0.99 - 1.25) 1982-2000
(N=22,905 M & F; 267 zip code areas; 1999-2000 PM2.5; 44 cov + max confounders)

Enstrom 2005 CA CPS I Cohort N=35,783 RR = 1.039 (1.010-1.069) 1973-1982
(N=[15,573 M + 20,210 F]; 11 counties; 1979-1983 PM2.5) RR = 0.997 (0.978-1.016) 1983-2002

Enstrom 2006 CA CPS I Cohort N=35,783 RR = 1.061 (1.017-1.106) 1973-1982
(11 counties; 1979-1983 & 1999-2001 PM2.5) RR = 0.995 (0.968-1.024) 1983-2002

Zeger 2008 MCAPS Cohort "West" N=3,100,000 RR = 0.989 (0.970-1.008) 2000-2005
(N=[1.5 M M + 1.6 M F]; Medicare enrollees in CA+OR+WA (CA=73%); 2000-2005 PM2.5)

Jerrett 2010 CA CPS II Cohort N=77,767 RR ~ 0.994 (0.965-1.025) 1982-2000
(N=[34,367 M + 43,400 F]; 54 counties; 2000 PM2.5; KRG ZIP; 20 ind cov+7 eco var; Slide 12)

Krewski 2010 CA CPS II Cohort
(4 MSAs; 1979-1983 PM2.5; 44 cov) N=40,408 RR = 0.960 (0.920-1.002) 1982-2000
(7 MSAs; 1999-2000 PM2.5; 44 cov) N=50,930 RR = 0.968 (0.916-1.022) 1982-2000

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 0.994 (0.965-1.024) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; KRG ZIP Model; 20 ind cov+7 eco var; Table 28)

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 1.002 (0.992-1.012) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; Nine Model Ave; 20 ic+7 ev; Fig 22 & Tab 27-32)

Lipsett 2011 CA Teachers Cohort N=73,489 RR = 1.01 (0.95 – 1.09) 2000-2005
(N=[73,489 F]; 2000-2005 PM2.5)

Ostro 2011 CA Teachers Cohort N=43,220 RR = 1.06 (0.96 – 1.16) 2002-2007
(N=[43,220 F]; 2002-2007 PM2.5)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.060 (1.003–1.120) 1982-2000
(N=[~32,550 M + ~41,161 F]; 54 counties; 2000 PM2.5; LUR Conurb Model; 42 ind cov+7 eco var+5 metro; Table 6)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.028 (0.957-1.104) 1982-2000
(same parameters and model as above, except including co-pollutants NO2 and Ozone; Table 5)

Thurston 2016 CA NIH-AARP Cohort N=160,209 RR = 1.02 (0.99 -1.04) 2000-2009
(N=[~95,965 M + ~64,245 F]; full baseline model: PM2.5 by zip code; Table 3)

Enstrom 2016 unpub CA NIH-AARP Cohort N=160,368 RR = 1.001 (0.949-1.055) 2000-2009
(N=[~96,059 M + ~64,309 F]; full baseline model: 2000 PM2.5 by county)

References for Appendix Table 2

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(http://www.scientificintegrityinstitute.org/CARBJerrett022610.pdf)

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(http://www.arb.ca.gov/research/rsc/10-28-11/item1dfr06-332.pdf) and
(http://www.scientificintegrityinstitute.org/Jerrett012510.pdf) and
(http://www.scientificintegrityinstitute.org/JerrettCriticism102811.pdf)

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Pope CA III, Dockery DW. (2006). Health Effects of Fine Particulate Air Pollution: Lines that Connect. *JAWMA*, Critical Review. 56(6):709-742 (http://www.scientificintegrityinstitute.org/PopeDockery2006.pdf) and (http://www.scientificintegrityinstitute.org/PopePPT2006.pdf)

Thurston GD, Ahn J, Cromar KR, Shao Y, Reynolds HR, Jerrett M, Lim CC, Shanley R, Park Y, Hayes RB (2016). Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort. *Environ Health Perspect* 2016;124:484-490 (http://ehp.niehs.nih.gov/1509676/)

U.S. EPA (2012). Regulatory Impact Analysis related to the Proposed Revisions to the National Ambient Air Quality Standards for Particulate Matter EPA-452/R-12-003 (http://www.epa.gov/ttn/ecas/regdata/RIAs/PMRIACombinedFile_Bookmarked.pdf)

Zeger SL, Dominici F, McDermott A, Samet JM (2008). Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000-2005). *Environ Health Perspect* 2008;116:1614-1619 (http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.11449)

From: Andrew Sugden [mailto:asugden@science-int.co.uk]
Sent: Monday, July 11, 2016 8:19 AM
To: James E. Enstrom <jenstrom@ucla.edu>
Cc: 'Jake Yeston' <jyeston@aaas.org>
Subject: RE: Call re Decision on your Science Manuscript aah4744

Dear Dr Enstrom

Thank you for your message. I'm sorry to say that I shall have to decline your request for another phone conversation. We have already devoted time to considering your submitted manuscript (and to a previous conversation), and our conclusion was that the paper did not meet the standards of the 20% of Science submissions that are sent for in-depth peer review. I am sorry to disappoint you, but we will not be able to consider a resubmission in this case.

Yours sincerely

Andrew Sugden

Dr Andrew Sugden
Deputy Editor & International Managing Editor, Science
AAAS Science International Inc
Clarendon House
Clarendon Road
Cambridge
UK CB2 8FH
+44 (0)1223 326500
asugden@science-int.co.uk

From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: 08 July 2016 18:27
To: Andrew Sugden
Cc: 'Jake Yeston'
Subject: Call re Decision on your Science Manuscript aah4744

July 8, 2016

Dear Dr. Sugden,

I am writing to ask if you and/or Dr. Yeston will speak with me over the phone about your decision below. Since you were willing to have a presubmission conversation with me, I would greatly appreciate the opportunity to have a post-decision conversation that I believe will be mutually beneficial.

Thank you very much for your consideration.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
jenstrom@ucla.edu
(310) 472-4274

From: Andrew Sugden [mailto:science_editors@aaas.org]
Sent: Friday, July 08, 2016 9:13 AM
To: jenstrom@ucla.edu
Cc: jyeston@aaas.org
Subject: Decision on your Science Manuscript aah4744

08-Jul-2016
Retired Research Faculty
University of California Los Angeles Jonathan and Karin Fielding School of Public Health
Los Angeles CA 90024-2905

Dear Dr. Enstrom,

Manuscript number: aah4744

Thank you for submitting your manuscript "Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis" to Science. Because your manuscript was not given a high priority rating during the initial screening process, we have decided not to proceed to in-depth review. The overall view is that the scope and focus of your paper make it more appropriate for a more specialized journal.

I'm sorry to disappoint you, but we now receive many more papers than we can publish. We therefore send for in-depth review only those papers most likely to be ultimately published in Science. Papers are selected on the basis of discipline, novelty, and general significance, in addition to the usual criteria for publication in specialized journals. The editors took the view that your paper would not be appropriate for publication in Science on those grounds, and therefore our recommendation is that you seek publication elsewhere.

Sincerely,

Andrew Sugden, Ph.D.
Deputy Editor
Science

-----Original Message-----
From: science_editors@aaas.org [mailto:science_editors@aaas.org]
Sent: Tuesday, July 05, 2016 10:28 AM
To: jenstrom@ucla.edu
Subject: Successful Submission of a Manuscript to Science

Manuscript Title: Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis
Author: Enstrom
Manuscript Number: aah4744

Dear Dr. Enstrom:

Thank you for your submission to Science. We have successfully received your Report.

You can see the status of your manuscript at any time by logging into your account at the Science Journals Submission and Information Portal at https://cts.sciencemag.org. Your manuscript number is noted above. Your manuscript is now undergoing an initial screening to determine whether it will be sent for in-depth review. If the manuscript is sent to review, its status will change to "To Review".

We encourage you to login and link your account to your ORCID ID, an identifier that facilitates correct attribution of your publications. To learn more about ORCID or to obtain an ORCID ID, visit their site at: http://orcid.org.

Sincerely,
The Editors
Science

From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: Wednesday, June 29, 2016 10:39 AM
To: 'Jake Yeston' <jyeston@aaas.org>
Cc: 'Andrew Sugden' <asugden@science-int.co.uk>
Subject: RE: Request re Science Editorial Procedures: June 29 @ 11:30 AM PDT

A conference call at or about 11:30 AM PDT today is fine with me: (310) 472-4274. Let me know if you need to change the time.

From: Andrew Sugden [mailto:asugden@science-int.co.uk]
Sent: Wednesday, June 29, 2016 10:20 AM
To: Jake Yeston <jyeston@aaas.org>; 'James E. Enstrom' <jenstrom@ucla.edu>
Subject: RE: Request re Science Editorial Procedures for Research Report

I have a short meeting scheduled for that time – I could probably manage 11.30 California time, though.

Andrew

From: Jake Yeston [mailto:jyeston@aaas.org]
Sent: 29 June 2016 18:04
To: 'James E. Enstrom'
Cc: Andrew Sugden
Subject: RE: Request re Science Editorial Procedures for Research Report

I'd like for my colleague Andrew Sugden (another deputy editor) to sit in as well. Are you available in an hour (11 am California time)?

From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: Wednesday, June 29, 2016 12:47 PM
To: Jake Yeston
Subject: RE: Request re Science Editorial Procedures for Research Report

It involves environmental epidemiology and atmospheric chemistry that is directly related to Kaiser J. Showdown over clean air science. *Science* 1997;277:466-469. I believe your background is appropriate to answer my questions, but I will talk with the Editor you recommend.

From: Jake Yeston [mailto:jyeston@aaas.org]
Sent: Wednesday, June 29, 2016 9:19 AM
To: 'James E. Enstrom' <jenstrom@ucla.edu>
Subject: RE: Request re Science Editorial Procedures for Research Report

Could you please let me know the subject matter first? I want to be sure I'm the best editor to talk with you—I oversee the physical sciences.

From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: Wednesday, June 29, 2016 12:15 PM
To: Jake Yeston
Subject: Request re Science Editorial Procedures for Research Report

June 29, 2016

Jake S. Yeston, Ph.D.
Deputy Editor, Research
Science
jyeston@aaas.org
(202) 326-6550

Dear Editor Yeston,

I understand from the Science website that you respond to general inquiries about editorial procedures and policies. I would like to discuss with you how *Science* would handle my Research Report manuscript, which is ready for submission. Please call me as soon as you can or let me know how I can call you.

Thank you very much for your assistance.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H.
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu
(310) 472-4274

-----Original Message-----
From: onbehalfof+editorial+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com]
Sent: Tuesday, June 28, 2016 1:50 PM
To: jenstrom@ucla.edu
Subject: New England Journal of Medicine - 16-07588

Dear Dr. Enstrom,

Thank you for your response letter regarding 16-07588 entitled "Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis." We respect your work, but are unable to reconsider your manuscript. Due to the volume of submissions, we must decline over 95 percent of the manuscripts that we receive. Please consider this our final decision.

We appreciate your interest in the Journal and wish you well in finding another venue for the article.

Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
http://www.nejm.org

From: Sandrew, Caryn [mailto:csandrew@nejm.org]
Sent: Monday, June 27, 2016 10:33 AM
To: 'James E. Enstrom' <jenstrom@ucla.edu>
Subject: RE: Request for Reconsideration of NEJM Manuscript 16-07588

Dear Dr. Enstrom,

Your appeal has been received and posted for consideration by Dr. Drazen and the editors.

Kind regards,
Caryn Sandrew

Caryn Sandrew | ***Executive Assistant to the Editor-in-Chief***
The New England Journal of Medicine | **NEJM Group**
10 Shattuck Street, Boston, MA 02115
Tel: 617-487-6514 | Fax: 781-207-6529 | csandrew@nejm.org

-----Original Message-----
From: James E. Enstrom [mailto:jenstrom@ucla.edu]
Sent: Monday, June 27, 2016 1:20 PM
To: Sandrew, Caryn
Subject: Request for Reconsideration of NEJM Manuscript 16-07588

June 27, 2016

Editor-in-Chief Jeffrey M. Drazen, M.D.
New England Journal of Medicine
c/o Caryn Sandrew
csandrew@nejm.org

Re: Request for Reconsideration of NEJM Manuscript 16-07588

Dear Editor-in-Chief Drazen,

I request reconsideration of my Manuscript 16-07588, "Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis." I am making this request because of the very positive, constructive review from Reviewer 2 and because this first ever independent reanalysis of ACS CPS II data reveals that the original Pope 1995 finding of a positive relationship between PM2.5 and mortality is quite sensitive to the PM2.5 values used. Furthermore, Reviewer 1 did not understand the significance of my findings challenging the PM2.5-mortality relationship, repeatedly and unprofessionally impugned my scientific integrity, and focused on PM2.5 evidence that was not part of my paper. Because of these points and because of the importance of the PM2.5-mortality relationship to the 1997 EPA PM2.5 NAAQS and subsequent national and state PM2.5 regulations, I request that my manuscript be assessed by a third reviewer and/or by a NEJM statistical consultant who is not directly involved with PM2.5 epidemiology like Reviewer 1.

Reviewer 2 stated "The author [Enstrom] points out [to] a significant limitation and shortcoming of the HEI 2000 report (i.e., potentially unreliable air quality data). . . . Therefore, it appears that the original analyses and subsequent re-analyses could be impacted consistently and systematically by the same problem of potentially unreliable population exposure to fine particulate matter air pollution (PM2.5)."

Indeed, the 2000 HEI Reanalysis Report Executive Summary and Commentary states on page 20: "Because the Original Investigators in the ACS Study [Pope 1995] had derived their air pollution data from secondary sources, the original records of air pollution data from secondary sources, the original records of air pollution data they used were not available for audit. In order to evaluate the sensitivity of the risk estimates obtained in the ACS Study, the Reanalysis Team . . . obtained data from both IPMN and AIRS databases maintained by the EPA. Whereas the Original Investigators had reported fine particle data for 50 of the 154 cities they considered in the ACS Study, we were able to locate fine particle measurements within the IPMN for 63 of the 154 cities."

However, HEI 2000 used the same 50 cities used in Pope 1995 and apparently used the same median PM2.5 values that are in Lipfert 1988, the source cited in Pope 1995. These median PM2.5 values are shown in HEI 2000 Appendix D. HEI 2000 published NO results based on the mean IPMN PM2.5 values for 50 or 63 cities and HEI 2000 published NO results based on mean IPN PM2.5 values for 50 or 85 cities/counties that I used in my reanalysis. In other words, HEI 2000 DID NOT "evaluate the sensitivity of the risk estimates obtained in the ACS study," which was one of their primary tasks. Furthermore, nine years later, HEI 2009 did not evaluate the PM2.5 risk estimate sensitivity even after I specifically identified the 1979-1984 EPA IPN PM2.5 data (Hinton 1984 and Hinton 1986) and used these data to produce a null PM2.5-mortality relationship in 11 California cities/counties (Enstrom 2005).

The Pope 1995, HEI 2000, and HEI 2009 investigators have continuously refused to do their own sensitivity analyses on the CPS II data and have continuously refused to allow independent reanalysis of the CPS II data. As a potential way to resolve this impasse, I propose that you test whether the HEI investigators will do a PM2.5-mortality sensitivity analysis now. Simply, send HEI President Daniel Greenbaum my Appendix Table 1 (without identifying me as the source) and request that HEI reproduce the hazard ratio (RR) findings in HEI 2009 Table 34 for 1982-1989 mortality follow-up in 50 cities/MSAs using the 1979-1984 EPA IPN PM2.5 data. The HEI investigators simply have to replace the PM2.5 data

they used with the 1979-1984 EPA IPN PM2.5 data in Appendix Table 1 and rerun the regression analyses with the SAS programs that they used for HEI 2009 Table 34.

Finally, I am willing to consider any other suggestions that you might have, such as, having this manuscript treated as a commentary or perspective instead of as original research.

Thank you very much for your reconsideration.

Sincerely yours,

James E. Enstrom, Ph.D., M.P.H., FACE
UCLA and Scientific Integrity Institute
jenstrom@ucla.edu
(310) 472-4274

-----Original Message-----
From: onbehalfof+editorial+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com]
Sent: Friday, June 17, 2016 4:41 PM
To: jenstrom@ucla.edu
Subject: New England Journal of Medicine 16-07588

Dear Dr. Enstrom,

Your manuscript, "Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis," was evaluated by external reviewers and was discussed among the editors. Although it is interesting, I am sorry to say it was not accepted for publication. This was an editorial decision and reflects an assessment of the merits of your manuscript as compared with the many others we receive. Unfortunately, many manuscripts must be declined for lack of space.

Thank you very much for the opportunity to review this manuscript.

Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
http://www.nejm.org

Reviewer: 1
Comments for the Author

I have never read a paper that so willfully ignored the breadth of scientific evidence and attacked a specific study/group of investigators. This should not be published. I find the way in which the data were obtained to be highly suspect if not unethical.

General Comments

Numerous cohorts around the world have document the long-term health effects of exposure to ambient fine particulate air pollution including cardiorespiratory mortality and lung cancer. These relationships have been demonstrated using both ground monitoring data, land use regression models, and more recently, remote-sensing based estimates of exposure assessment combined with chemical transport models. In particular, two recent studies (Pope et al. 2015 in Circulation Research and Turner et al. 2016 in Am J Respir Crit Care Med) in the ACS CPS II cohort including more than 600,000 people followed for more than 20 years demonstrated significant associations with mortality as have other recent studies in Canada and elsewhere. Epidemiological evidence is also supported by toxicological/human panel studies that support the biological plausibility of these relationships (e.g. for cardiovascular disease: changes in heart rate variability, endothelial function, coronary artery calcification, etc.).

The author's central thesis that there should be no PM2.5 NAAQS because of results he obtained over a short follow-up period in the 1980s using data that were obtained under questionable circumstances is not believable or scientifically sound. This paper should not be published.

Specific Comments

Ethics: The ethics of receiving ACS data from a "confidential source" seems highly inappropriate boarding on misconduct. Was there any ethics approval for this analyses? How can the reader judge the quality of the data or the analyses if we cannot be sure of the source of the data? Should we just believe the author given his clear bias with respect to the findings? I actually find it surprising that this issue didn't stop the paper's progress through the review process immediately at the editorial stage. The author is clearly contravening procedures put in place to protect the integrity of the ACS data if he had to obtain the data secretly.

Of what relevance is 6 years of follow-up in the 1980s given the bulk of scientific evidence currently available supporting the association between PM2.5 and mortality? This seems like more of a crusade than an honest scientific pursuit. Even if the ACS study didn't exist, others are currently available to take its place.

Page 3, Methods (first paragraph): Why did the author assume that dead people were alive in the analyses? Clearly this could bias the results downward. Why not just remove these people if a date of death wasn't known (rather than just pretending they are still alive?). This is not an appropriate approach.

While the author totes the use of "best available PM2.5" data, he did not have access to participants' home addresses? More recent analyses in the CPS II assigned exposure to the home addresses of more than 600,000 subjects and noted significant associations with mortality. Should these results based on fewer people, over a shorter time period, with less precise exposure assignment supersede these results? This is just ridiculous.

It is not surprising that HRs would move around when you include/remove different counties given the short follow-up time and small number of deaths. The 95% CIs overlap for all of the estimates, they are basically the same. Focusing on "significant" vs. "insignificant" in interpreting the findings is not meaningful way to interpret statistics- the magnitude and precision of effect estimates is what is important.

The fact that PM2.5 relationships differ geographically also isn't surprising. PM2.5 is a mixture- if the composition differs geographically then the health effects will as well. There is no currently accepted way to deal with this heterogeneity; oxidative potential is currently being evaluated as a means of dealing with geographical differences in PM2.5 toxicity but this research is still in the early stages. Right now the mass based measure is the best we have but someday we may be able to do better.

How much variance was there in PM2.5 exposures within states? Little variance means little power to detect an effect.

Reviewer: 2
Comments for the Author

General Comments:

This paper re-examines the relationship between exposure to fine airborne particulate matter (PM2.5) and total mortality in the US population. The conclusions appear to be supported by the results of presented statistical analyses (i.e., 95% CIs for fully adjusted relative risk estimates show absence of statistical significance).

The author may decide to modify writing style and focus primarily on the findings and results of the presented comparative re-analyses with relevant historical background and only limited reference to personal communication.

The pros and cons, including key differences in the analytical method(s) applied in this paper vs. earlier published papers on the basis of the same data-set, may be useful to explain for the reader in a comparative Table (e.g., a) original 1995 analysis vs. b) 2000 re-analysis vs. c) current re-analysis; with emphasis on the most important pros and cons for each). As presented in Table 1, it appears that some of the earlier published studies may have underestimated population exposure to PM2.5 and the prevalence of current/former smokers.

The presented re-analyses illustrate the importance and the need to distinguish practical/clinical significance from a mere statistical significance. A large enough study population/sample is expected to yield statistically significant analytical results even if the actual difference between the study groups is so small that it could be considered essentially negligible and unimportant (e.g., not significant from a public health policy perspective).

A separate section titled “Study Limitations and Uncertainties” should be included in the paper to inform the reader on all reasonably foreseeable limitations of the study design, quality of obtained data, applied vs. alternative analytical methods, validity of the applied model assumptions, and uncertainties in the interpretation of the results.

Specific Comments:

Conclusion: the statement “No significant relationship…” should be changed to “No [statistically] significant relationship…”. This should be applied consistently in other parts of the paper as well.

Present all numbers in a consistent format (e.g., Table 1: numbers with or without [,] to separate thousands).

Table 1 (line 24): no numbers are provided for “Fully Adjusted Values”…(check the alignment)

Appendix Table 1 should include additional columns with 95% CIs and p-values for the reported HEI 2000 mortality risks (MR), if available, to inform the reader on statistical significance of the presented results.

Page 5 (lines 37 – 48): The author points out to a significant limitation and shortcoming of the HEI 2000 report (i.e., potentially unreliable air quality data). It has been acknowledged also in the HEI 2000 special report (page 20): “Because the Original Investigators in the ACS Study had derived their air pollution data from secondary sources, the original records of air pollution data they used were not available for audit” (HEI, 2000). Therefore, it appears that the original analyses and subsequent re-analyses could be impacted consistently and systematically by the same problem of potentially unreliable population exposure to fine particulate matter air pollution (PM2.5). This may render the analytical results, conclusions, recommendations and the derived health policy decisions on the basis of Pope et al. (1995) and HEI (2000) study reports as reliable as the quality of available data and model input parameters.

Two numbers in Appendix (Table 1) are presented in red (check line 39 on page 13; and line 31 on page 14).

Some relevant published papers on statistical vs. practical (clinical) significance:

Friedman, L. M. 2005. Clinical Significance versus Statistical Significance. Encyclopedia of Biostatistics. 2.
http://onlinelibrary.wiley.com/doi/10.1002/0470011815.b2a01006/abstract ;

Gelman and Stern, 2006: The Difference Between "Significant" and "Not Significant" is not Itself Statistically Significant. The American Statistician, Vol. 60, No. 4.
http://www.stat.columbia.edu/~gelman/research/published/signif4.pdf ;

McCluskey and Lalkhen, 2007. Statistics IV: Interpreting the results of statistical tests. Contin Educ Anaesth Crit Care Pain, 7 (6): 208-212. http://ceaccp.oxfordjournals.org/content/7/6/208.full .

In their section on statistical vs. clinical significance, McCluskey and Lalkhen (2007) indicate: "Statistical significance should not be confused with clinical significance. Suppose two hypotensive agents are compared and the mean arterial blood pressure after treatment with drug A is 2 mm Hg lower than after treatment with drug B. If the study sample sizes are large enough, even such a small difference between the two groups may be statistically significant with a P-value of <0.05. However, the clinical advantage of an additional 2 mm Hg reduction in mean arterial blood pressure is small and not clinically significant". The same concept is applicable to large epidemiological studies on population health vs. small regional differences in exposure to low levels of ambient air pollution.

In conclusion, it needs to be emphasized for the reader that the observed association between fine particulate matter (PM2.5) air pollution exposure and population mortality in the studied cohort is very weak (i.e., the estimated relative risks appear close to 1.0, with lower 95% CIs in most analyses less than 1.0), and that these could be affected further by other air pollutants, seasonal weather/temperature/insolation variation, or potentially significant socio-economic, behavioural, biological, and environmental confounding factors not included or adequately controlled for in the original analysis and/or in the subsequent re-analyses.

The NEW ENGLAND JOURNAL of MEDICINE

Please review the Supplemental Files folder to review documents not compiled in the PDF.

Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

Journal:	*New England Journal of Medicine*
Manuscript ID	Draft
Article Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Enstrom, James; University of California, Los Angeles,
Abstract:	Background. The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter (PM2.5), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort. This implausible and contested relationship justifies many costly EPA regulations. This paper presents the first truly independent examination of the CPS II data. Methods. The original CPS II questionnaire data, including 1982-1988 mortality follow-up, was analyzed using Cox proportional hazards regression. Results were obtained for 292,277 subjects in 85 counties with 1979-1984 EPA Inhalable Particulate Network (IPN) PM2.5 measurements, as well as for 212,370 subjects in the 50 counties used in the original 1995 analysis. Results. The 1982-1988 relative risk of death from all causes (RR) and 95% confidence interval (CI) adjusted for age, sex, race, education, and smoking status was 1.023 (0.997–1.049) for a 10 μg/m³ increase in PM2.5 in 85 counties and 1.025 (0.990-1.061) in the 50 original counties. The relationship between PM2.5 and total mortality depended upon the CSP II subjects selected and the PM2.5 values assigned to these subjects. Conclusions. No significant relationship between PM2.5 and total mortality in the CPS II cohort was found when the best available PM2.5 data was properly included. The 1995 analys and 2000 reanalysis misrepresented and exaggerated this relationship by selective use of CPS II and PM2.5 data. These findings demonstrate the importance of independent analysis of underlying data and raise serious doubts about the epidemiologic evidence supporting the PM2.5 NAAQS.

Fine Particulate Matter and Mortality in Cancer Prevention Study Reanalysis

James E. Enstrom, Ph.D., M.P.H., FACE
UCLA and Scientific Integrity Institute
907 Westwood Blvd. #200
Los Angeles, CA 90024
jenstrom@ucla.edu

June 7, 2016

Abstract

Background. The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort. This implausible and contested relationship has been used to justify many costly EPA regulations, most recently the Clean Power Plan. This paper presents the first truly independent examination of the CPS II data.

Methods. The original CPS II questionnaire data, including 1982-1988 mortality follow-up, was analyzed using Cox proportional hazards regression. Results were obtained for 292,277 subjects in 85 counties with 1979-1984 EPA Inhalable Particulate Network (IPN) $PM_{2.5}$ measurements, as well as for 212,370 subjects in the 50 counties used in the original 1995 analysis.

Results. The 1982-1988 relative risk of death from all causes (RR) and 95% confidence interval (CI) adjusted for age, sex, race, education, and smoking status was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in 85 counties and 1.025 (0.990-1.061) in the 50 original counties. The relationship between $PM_{2.5}$ and total mortality depended upon the CSP II subjects selected and the $PM_{2.5}$ values assigned to these subjects.

Conclusions. 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 was properly included. The 1995 analysis and 2000 reanalysis misrepresented and exaggerated this relationship by selective use of CPS II and $PM_{2.5}$ data. These findings demonstrate the importance of independent analysis of underlying data and raise serious doubts about the epidemiologic evidence supporting the $PM_{2.5}$ NAAQS.

Background

The EPA National Ambient Air Quality Standard (NAAQS) was established in 1997 for fine particulate matter ($PM_{2.5}$), largely because of its positive relationship to mortality in the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort, as published in 1995 by Pope et al. (Pope 1995) (1). However, the validity of this finding was immediately challenged (2,3) and it still remains intensely contested. The EPA claim that $PM_{2.5}$ *causes* premature deaths is implausible because no etiologic mechanism has ever been established, because it is based on inhaling over a lifetime only about 5 gm of particles that are less than 2.5 µm in diameter, and because the underlying CPS II data have never been independently analyzed. The $PM_{2.5}$-mortality relationship has been further challenged because the small increased risk could be due to well-known epidemiological biases, such as, the ecological fallacy, inaccurate exposure measurements, and confounding variables like co-pollutants. In addition, there is extensive evidence of spatial and temporal variation in $PM_{2.5}$ mortality risk that does not support one national standard for $PM_{2.5}$.

In spite of these serious problems, EPA and the major $PM_{2.5}$ investigators continue to assert that their selected positive findings are sufficient proof that that $PM_{2.5}$ *causes* premature deaths. This premature death claim has been used to justify many costly EPA regulations, most recently the Clean Power Plan. Indeed, 85% of the total estimated benefits of all EPA regulations have been attributed to reductions in $PM_{2.5}$-related premature deaths. With the assumed benefits of $PM_{2.5}$ reductions playing such a major role in EPA regulatory policy, it is essential that the relationship of $PM_{2.5}$ to mortality be independently verified with transparent data and reproducible findings.

In 1998 the Health Effects Institute (HEI) in Boston was commissioned to conduct a detailed reanalysis of the original Pope 1995 findings. The July 2000 HEI Reanalysis Report (HEI 2000) included "PART I: REPLICATION AND VALIDATION" and "PART II: SENSITIVITY ANALYSES" (4). The HEI Reanalysis Team lead by Krewski successfully replicated and validated the 1995 CPS II findings, but they did not analyze the CPS II data in ways that would determine whether the original results remained robust to different analytic assumptions. For instance, none of their models used the best available $PM_{2.5}$ measurements as of 1995.

Particularly troubling is the fact that EPA, Pope, and other investigators have ignored multiple null findings on the relationship between $PM_{2.5}$ and mortality in California. These findings have been pointed out to them repeatedly in my 2005 paper (5), my 2006 clarification (6), my 2012 American Statistical Society Joint Statistical Meeting Proceedings (7), and my three 2015 submissions to *Science* (8). The submissions to *Science* contain detailed evidence of falsification and exaggeration of the $PM_{2.5}$-mortality relationship (8). EPA has also ignored evidence of a null relationship in the western U.S. (9). These continual problems with the $PM_{2.5}$-mortality relationship have generated substantial media and political concern.

Since 2011 the U.S. House Science, Space, and Technology Committee (HSSTC) has requested that EPA provide access to the underlying CPS II data, particularly since substantial Federal funding has been used for the major $PM_{2.5}$-mortality research and publications. On July 22, 2013 the HSSTC made a particularly detailed request to EPA that included 49 pages of letters dating back to September 22, 2011 (10). When EPA failed to provide the requested data, the HSSTC

issued an August 1, 2013 subpoena to EPA for the CPS II data (11). The ACS refused to comply with the HSSTC subpoena in any way, as explained in an August 19, 2013 letter to EPA by Chief Medical Officer Otis W. Brawley (12). Also, ACS has refused to work with me and other highly qualified investigators regarding collaborative analysis of the CPS II data. Finally, HEI has refused to conduct my proposed CPS II analyses, as explained in an October 4, 2013 HEI letter (13). However, my recent acquisition of an original version of the CPS II data makes possible this first truly independent analysis.

Methods

Computer files containing the original 1982 ACS CPS II de-identified questionnaire data and six-year follow-up data on deaths from September 1, 1982 through August 31, 1988 have been recently obtained from a confidential source. Of the 1.2 million total CPS II subjects, analysis has been done on 297,592 subjects residing in 85 counties in the continental U.S. with 1979-84 EPA IPN PM2.5 measurements (14,15). Among these subjects there were 18,612 total deaths from September 1, 1982 through August 31, 1988; 17,329 of these deaths (93.1%) had a known date of death. Of the 297,592 subjects, 292,277 had age at entry of 30-99 years and sex of male [1] or female [2]. Of the 292,277 subjects, 269,766 had race of white [1,2,5] or black [3,4]; education level of no or some high school [1,2], high school graduate [3], some college [4,5], college graduate [6], or graduate school [7]; and smoking status of never [1], former [5-8 for males and 3 for females], or current [2-4 for males and 2 for females]. Those subjects reported to be dead [D,G,K] but without an exact date of death have been assumed to be alive in this analysis. The computer codes for the above variables are shown in brackets.

CPS II subjects were entered into the master data file geographically. Since this de-identified data file does not contain home addresses, the Division number and Unit number assigned by ACS to each CPS II subject has been used to define their county of residence. For instance, ACS Division 39 represents the state of Ohio and its Unit 041 represents Jefferson County, which includes the city of Steubenville. In other words, most of the 575 subjects in Unit 041 lived in Jefferson County as of September 1, 1982. The IPN $PM_{2.5}$ value of 29.6739 $\mu g/m^3$ assigned to all subjects in Unit 041 is based on measurements made in Steubenville. This $PM_{2.5}$ value is a weighted average of 53 measurements (mean of 33.9260 $\mu g/m^3$) and 31 measurements (mean of 29.4884 $\mu g/m^3$) made during 1979-1982 (14) and 53 measurements (mean of 27.2473 $\mu g/m^3$) and 54 measurements (mean of 28.0676 $\mu g/m^3$) made during 1983-1984 (15). The HEI $PM_{2.5}$ value of 23.1 $\mu g/m^3$ assigned to all subjects in Unit 041 is the median of $PM_{2.5}$ measurements made in Steubenville and is shown in HEI 2000 Appendix D "Alternative Air Pollution Data in the ACS Study" (4).

Analyses were done for the 50 original counties with HEI $PM_{2.5}$ values used in Pope 1995 and HEI 2000, as well as for all 85 counties with CPS II subjects and IPN $PM_{2.5}$ data. Without explanation, Pope 1995 and HEI 2000 omitted 35 counties with CPS II subjects and IPN $PM_{2.5}$ data. The SAS 9.4 procedure PHREG was used to conduct Cox proportional hazards regression (17). Relative risks for death from all causes (RR) and 95% confidence intervals (CI) were calculated using age-sex adjustment and full adjustment (age, sex, race, education, and smoking

status, as defined above). Each of the five adjustment variables has a strong relationship to mortality.

In addition, county-level ecological analyses were done by comparing IPN $PM_{2.5}$ and HEI $PM_{2.5}$ values with 1980 age-adjusted white total death rates (DR) determined by CDC WONDER (16) and mortality risks (MR) as shown in Figures 5 and 21 of HEI 2000 (4). The death rates are age-adjusted to the 2000 US Standard Population and are expressed as annual deaths per 100,000 persons. The SAS 9.4 procedure REGRESSION was used to conduct linear regression of $PM_{2.5}$ values with death rates (DR) and mortality risks (MR). Appendix Table 1 lists the 50 original counties used in Pope 1995 and HEI 2000 and includes city, county, state, FIPS code, IPN average $PM_{2.5}$ level, HEI median $PM_{2.5}$ level, 1980 DR, and HEI MR. Similar information is available for the 35 additional counties with CPS II subjects and IPN $PM_{2.5}$ data.

Results

Table 1 shows basic demographic characteristics for the CPS II subjects, as stated in Pope 1995 (1), HEI 2000 (4), and this current analysis. There is excellent agreement on age, sex, race, education, and smoking status. However, the IPN average $PM_{2.5}$ values are generally about 20% higher than the HEI median $PM_{2.5}$ values, although the differences range from +78% to -28%.

Table 2 shows that during 1982-1988 there was no relationship between IPN $PM_{2.5}$ and total mortality in the entire U.S. The fully adjusted RR and 95% CI was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in all 85 counties and 1.025 (0.990-1.061) in the 50 original counties. Indeed, the fully adjusted RR was not significant in any area of the U.S., such as, the states west of the Mississippi River, the states east of the Mississippi River, the five Ohio Valley states (Indiana, Kentucky, Ohio, Pennsylvania, and West Virginia), and the states other than the Ohio Valley states. The age-sex adjusted and fully adjusted RRs in the states other than the Ohio Valley states are all consistent with no relationship and most are very close to 1.00. The positive age-sex adjusted RRs for the entire U.S. and the Ohio Valley states became statistically insignificant after controlling for the three confounding variables of race, education, and smoking status.

However, the fully adjusted RR for the entire U.S. was 1.082 (1.039-1.128) when based on the HEI $PM_{2.5}$ values in 50 counties. This RR agrees quite well with the fully adjusted RR of 1.067 (1.037-1.099) for 1982-1989, which is shown in Table 34 of the June 2009 HEI Extended Follow-up Research Report (HEI 2009) (18). Thus, the positive nationwide RRs in the CPS II cohort depend upon the use of HEI $PM_{2.5}$ values. The nationwide RRs are consistent with no effect when based on IPN $PM_{2.5}$ values. The findings in Table 2 clearly demonstrate the large influence of $PM_{2.5}$ values and geography on the RRs.

Table 3 shows that the fully adjusted RR in California was 0.992 (0.954–1.032) when based on IPN $PM_{2.5}$ values in all 11 California counties. This null finding is consistent with the 15 other findings of a null relationship in California, all of which are shown in Appendix Table 2. However, when the RR is based on the 4 California counties used in Pope 1995 and HEI 2000, there is a significant inverse relationship. The fully adjusted RR is 0.879 (0.805-0.960) when

based on the IPN $PM_{2.5}$ values and is 0.870 (0.788–0.960) when based on the HEI $PM_{2.5}$ values. This significant inverse relationship is in exact agreement with the finding of special analysis of the CPS II cohort done by Krewski in 2010, which yielded a fully adjusted RR of 0.872 (0.805–0.944) during 1982-89 in California when based on HEI $PM_{2.5}$ values (19). In this instance, the California RRs are dependent upon the number of counties used.

Table 4 shows that the ecological analysis based on linear regression is quite consistent with the proportional hazard regression results in Tables 2 and 3, in spite of the fact that the regression results are not fully adjusted. Using 1980 age-adjusted white total death rates versus HEI $PM_{2.5}$ values in 50 counties, linear regression yielded a regression coefficient of 6.96 (SE = 1.85) that was statistically significant at the 95% confidence level. Pope 1995 reported a significant regression coefficient for 50 cities of 8.0 (SE = 1.4). However, this positive coefficient is misleading because both the death rates and $PM_{2.5}$ levels are higher in the East than in the West. Regional regression analyses did not generally yield significant regression coefficients. Specifically, there were no significant regression coefficients for California, the five Ohio Valley states, or all the states west of the Mississippi River. These findings reinforce the CPS II cohort evidence of statistically insignificant $PM_{2.5}$ mortality risk throughout the U.S.

Discussion and Conclusions

This independent analysis of the CPS II cohort reveals that there was no significant relationship between $PM_{2.5}$ and death from all causes during 1982-1988, when the best available $PM_{2.5}$ measurements were used for the 50 original counties or for all 85 counties with $PM_{2.5}$ data and CPS II subjects. However, a positive relationship was found when the HEI $PM_{2.5}$ measurements were used for the 50 original counties, consistent with the findings in Pope 1995 and HEI 2000. This null and positive evidence demonstrates that the $PM_{2.5}$-mortality relationship is quite sensitive to the $PM_{2.5}$ data and CPS II subjects used in the analysis.

However, the following statement on page 80 of HEI 2000 raises serious doubts about the quality of the air pollution data used in Pope 1995 and HEI 2000: "AUDIT OF AIR QUALITY DATA The ACS Study was not originally designed as an air pollution study. The air quality monitoring data used for the ACS analyses came from various sources, some of which are now technologically difficult to access. Documentation of the statistical reduction procedures has been lost. Summary statistics for different groups of standard metropolitan statistical areas had been derived by different investigators. These data sources do not indicate whether the tabulated values refer to all or a subset of monitors in a region or whether they represent means or medians." (4)

The Pope 1995, HEI 2000, and HEI 2009 analyses did not cite or use the high quality and widely known EPA IPN $PM_{2.5}$ data in spite of the fact that these data have been available in two detailed EPA reports since 1986 (14,15). These investigators did not use the EPA IPN reports even after I cited them in 2005 (5). Instead they repeatedly used most, but not all, of the median $PM_{2.5}$ values shown in Appendix A of the 1988 Brookhaven National Laboratory Report 52122 by Lipfert et al. (20). They have never acknowledged that IPN data has been fully available for 85

counties with CPS II subjects, not just the 50 cities (metropolitan areas) that they chose to analyze.

Thus, the HEI Reanalysis Team failed to properly "evaluate the sensitivity of the original findings to the indicators of exposure to fine particle air pollution used by the Original Investigators" and failed to select "all participants who lived within each MA (metropolitan area) for which data on sulfate or fine particle pollution were available" (4). HEI 2009 did not cite my 2005 null $PM_{2.5}$-mortality findings in California (5), which were based on the IPN data for 11 California counties, instead of the 4 California counties used in Pope 1995, HEI 2000, and HEI 2009. Furthermore, HEI 2009 did not acknowledge or address my 2006 concerns about the geographic variation in $PM_{2.5}$ mortality risk clearly shown in HEI 2000 Figure 21 (6).

Since 2002, HEI has repeatedly refused to provide the $PM_{2.5}$-related "mortality risk" (MR) for the 50 cities included in Figures 5 and 21 of HEI 2000 (18). I estimated these mortality risks in 2010 based on visual measurements of Figure 5 and these estimates are shown in Appendix Table 1. However, these estimates need to be confirmed by HEI, especially given the findings in this paper. The pattern of evasion, obfuscation, and falsification by the authors of CPS II $PM_{2.5}$ epidemiology publications began in 1997 with the original critics (2,3), begin in 2005 with me (5-8,13), and began in 2011 with the HSSTC (10-12). The massive documented evidence in these references supports that notion that the misrepresentation and exaggeration has been deliberate in order to promote the notion that $PM_{2.5}$ has a positive relationship to total mortality.

In conclusion, these findings raise serious doubts about the validity of the $PM_{2.5}$ epidemiology findings based on the CPS II cohort. Thus, there is an immediate need for ACS and HEI to cooperate in the independent analysis of the CPS II data. Finally, these findings raise serious doubts about the epidemiologic basis for the current $PM_{2.5}$ NAAQS.

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Table 1. Summary Characteristics of CPS II Subjects in 1) Pope 1995 Table 1 (1), 2) HEI 2000 Table 24 (4), and 3) current analysis based on CPS II subjects in 50 and 85 counties

Characteristic	Pope 1995 Table 1	HEI 2000 Table 24	Current CPS II Analysis N=50 HEI $PM_{2.5}$	N=50 IPN $PM_{2.5}$	N=85 IPN $PM_{2.5}$
Number of metro areas	50	50			
Number of counties	not stated	not stated	50	50	85
Age-Sex Adjusted Subjects			212,370	212,370	292277
Fully Adjusted Subjects	295,223	298,817	195,215	195,215	269766
Age-Sex Adjusted Deaths			12,518	12,518	17,231
Fully Adjusted Deaths	20,765	23,093	11,221	11,221	15,593
Fully Adjusted Values					
Age at enrollment (mean years)	56.6	56.6	56.66	56.66	56.64
Sex (% females)	55.9	56.4	56.72	56.72	56.61
Race (% white)	94.0	94.0	94.58	94.58	95.09
Less than high school education (%)	11.3	11.3	11.71	11.71	11.71
Never Smoked Regularly (%)			41.69	41.69	41.57
Former smoker (%)			33.25	33.25	33.67
Former cigarette smoker (%)	29.4	30.2			
Current smoker (%)			25.06	25.06	24.76
Currrent cigarette smoker (%)	21.6	21.4			
Fine particles ($\mu g/m^3$)					
Average	18.2	18.2	17.99	21.37	21.16
SD	5.1	4.4	4.52	5.30	5.98
Range	9.0 – 33.5	9.0- 33.4	9.0- 33.4	10.77- 29.67	10.63- 42.01

Table 2: Age-sex adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through August 31, 1988 associated with change of 10 μg/m³ increase in $PM_{2.5}$ for CPS II subjects residing in 50 and 85 counties in the continental United States with 1979-84 IPN $PM_{2.5}$ measurements. Analysis includes continental United States, five Ohio Valley states, and remainder of the states. Appendix Table 1 lists the 50 cities and counties with $PM_{2.5}$ measurements.

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower	95% CI Upper	Average $PM_{2.5}$
Age-sex adjusted RR for the Continental United States							
1979-84 IPN	85	292,277	17,321	1.038	(1.016	– 1.064)	21.16
1979-84 IPN	50	212,370	12,518	1.046	(1.013	– 1.081)	21.36
1979-83 HEI	50	212,370	12,518	1.121	(1.078	– 1.166)	17.99
Fully adjusted RR for the Continental United States							
1979-84 IPN	85	269,766	15,593	1.023	(0.997	– 1.049)	21.15
1979-84 IPN	50	195,215	11,221	1.025	(0.990	– 1.061)	21.36
1979-83 HEI	50	195,215	11,221	1.082	(1.039	– 1.128)	17.99
Age-sex adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-84 IPN	17	56,979	3,649	1.126	(1.011	– 1.255)	25.51
1979-84 IPN	12	45,303	2,942	1.079	(0.951	– 1.225)	25.76
1979-83 HEI	12	45,303	2,942	1.153	(1.027	– 1.296)	22.02
Fully adjusted RR for Ohio Valley States (IN, KY, OH, PA, WV)							
1979-84 IPN	17	53,026	3,293	1.096	(0.978	– 1.228)	25.51
1979-84 IPN	12	42,174	2,652	1.050	(0.918	– 1.201)	25.75
1979-83 HEI	12	42,174	2,652	1.111	(0.983	– 1.256)	22.02
Age-sex adjusted RR for States other than the Ohio Valley States							
1979-84 IPN	68	235,298	13,672	0.999	(0.973	– 1.027)	20.11
1979-84 IPN	38	167,067	9,576	0.983	(0.946	– 1.021)	20.18
1979-83 HEI	38	167,067	9,576	1.045	(0.997	– 1.096)	16.90
Fully adjusted RR for States other than the Ohio Valley States							
1979-84 IPN	68	216,740	12,300	0.994	(0.967	– 1.023)	20.09
1979-84 IPN	38	153,041	8,569	0.975	(0.936	– 1.015)	20.15
1979-83 HEI	38	153,041	8,569	1.025	(0.975	– 1.078)	16.89

Table 3. Age-sex adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through August 31, 1988 associated with 10 μg/m³ increase in $PM_{2.5}$ for California CPS II subjects living in 4 and 11 counties with 1979-84 IPN $PM_{2.5}$ measurements. Also, fully adjusted RR for California subjects in 4 counties from September 1, 1982 through December 31, 1989 as calculated by Krewski (19).

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower	95% CI Upper	Average $PM_{2.5}$
Age-sex adjusted RR for California during 1982-1988							
1979-84 IPN	11	66,615	3,856	1.005	(0.968 – 1.043)		24.08
1979-84 IPN	4	40,527	2,146	0.904	(0.831 – 0.983)		24.90
1979-83 HEI	4	40,527	2,146	0.894	(0.817 – 0.986)		18.83
Fully adjusted (age, sex, race, education, smoking status) RR for California during 1982-1988							
1979-84 IPN	11	60,521	3,512	0.992	(0.954 – 1.032)		24.11
1979-84 IPN	4	36,201	1,939	0.879	(0.805 – 0.960)		25.01
1979-83 HEI	4	36,201	1,939	0.870	(0.788 – 0.960)		18.91
Fully adjusted (44 confounders) RR for California during 1982-1989 as per Krewski (19)							
'Same' Standard Cox Model							
1979-84 HEI	4	40,408		0.872	(0.805 – 0.944)		
'Different' Standard Cox Model							
1979-84 HEI	4	38,925		0.893	(0.823 – 0.969)		

Table 4: Linear regression results for 1979-84 IPN $PM_{2.5}$ and 1979-83 HEI $PM_{2.5}$ versus 1980 Age-adjusted White Total Death Rate (DR) for 85 counties with IPN data and for 50 HEI 2000 counties with IPN data. Linear regression results are also shown for 1979-84 IPN $PM_{2.5}$ and 1979-83 HEI $PM_{2.5}$ versus Mortality Risk (MR) for the 50 'cities' (metropolitan areas) in Figure 5 and Figure 21 in HEI 2000.

DR or MR, $PM_{2.5}$ Years and Source	Number of Counties	DR or MR Intercept	DR or MR Slope	95% CI Lower	DR/MR Slope Upper	P-value
Entire Continental United States						
DR & 1979-84 IPN	85	892.68	6.8331	3.8483	9.8180	0.0000
DR & 1979-83 HEI	50	910.92	6.9557	3.2452	10.6662	0.0004
MR & 1979-84 IPN	50	0.6821	0.0102	0.0044	0.0160	0.0009
MR & 1979-83 HEI	50	0.6754	0.0121	0.0068	0.0173	0.0000
Ohio Valley States (IN, KY, OH, PA, WV)						
DR & 1979-84 IPN	17	941.770	6.0705	-0.0730	12.2139	0.0524
DR & 1979-83 HEI	12	1067.285	1.3235	-7.3460	9.9930	0.7408
MR & 1979-84 IPN	12	0.8153	0.0077	-0.0054	0.0208	0.2202
MR & 1979-83 HEI	12	0.9628	0.0020	-0.0080	0.0121	0.6608
States Other Than the Ohio Valley States						
DR & 1979-84 IPN	68	921.452	4.8639	0.9093	8.8186	0.0167
DR & 1979-83 HEI	38	934.659	4.8940	-0.4337	10.2218	0.0706
MR & 1979-84 IPN	38	0.8111	0.0020	-0.0054	0.0094	0.5891
MR & 1979-83 HEI	38	0.7334	0.0072	0.0000	0.0144	0.0491
States West of the Mississippi River						
DR & 1979-84 IPN	36	920.099	4.0155	-0.9396	8.9706	0.1088
DR & 1979-83 HEI	22	930.110	4.1726	-5.2015	13.5468	0.3642
MR & 1979-84 IPN	22	0.8663	-0.0025	-0.0162	0.0112	0.7067
MR & 1979-83 HEI	22	0.6413	0.0134	-0.0018	0.0285	0.0807
California						
DR & 1979-84 IPN	11	921.708	3.6516	-1.8230	9.1262	0.1656
DR & 1979-83 HEI	4	992.502	1.9664	-46.6929	50.6256	0.8780
MR & 1979-84 IPN	4	0.9529	-0.0074	-0.0600	0.0453	0.6072
MR & 1979-83 HEI	4	0.8336	-0.0021	-0.0618	0.0576	0.8935

Appendix Table 1. List of the 50 original counties used in Pope 1995, HEI 2000, and this analysis, including Federal Information Processing Standards (FIPS) code, state, county, city with IPN/HEI $PM_{2.5}$ measurements, 1979-1984 IPN average $PM_{2.5}$ level, 1979-1983 HEI median $PM_{2.5}$ level, 1980 age-adjusted white county total death rate (annual deaths per 100,000), and HEI 2000 Figure 5 mortality risk for HEI city (metropolitan area).

FIPS Code	State	IPN/HEI County containing IPN/HEI City	IPN/HEI City with $PM_{2.5}$ Measurements	1979-84 IPN $PM_{2.5}$ ($\mu g/m^3$) (weighted average)	1979-83 HEI $PM_{2.5}$ ($\mu g/m^3$) (median)	1980 Age-Adj White Death Rate (DR)	HEI 2000 Figure 5 Mortality Risk (MR)
01073	AL	JEFFERSON	Birmingham	25.6016	24.5	1025.3	0.760
01097	AL	MOBILE	Mobile	22.0296	20.9	1067.2	0.950
04013	AZ	MARICOPA	Phoenix	15.7790	15.2	953.0	0.855
05119	AR	PULASKI	Little Rock	20.5773	17.8	1059.4	0.870
06019	CA	FRESNO	Fresno	18.3731	10.3	1001.4	0.680
06037	CA	LOS ANGELES	Los Angeles	28.2239	21.8	1035.1	0.760
06081	CA	SAN FRANCISCO	San Francisco	16.3522	12.2	1123.1	0.890
06085	CA	SANTA CLARA	San Jose	17.7884	12.4	921.9	0.885
08031	CO	DENVER	Denver	10.7675	16.1	967.3	0.925
09003	CT	HARTFORD	Hartford	18.3949	14.8	952.0	0.845
11001	DC	DISTRIC COLUMBIA	Washington	25.9289	22.5	993.2	0.850
12057	FL	HILLSBOROUGH	Tampa	13.7337	11.4	1021.8	0.845
13121	GA	FULTON	Atlanta	22.5688	20.3	1063.5	0.840
16001	ID	ADA	Boise	18.0052	12.1	892.6	0.600
17031	IL	COOK	Chicago	25.1019	21.0	1076.3	0.945
18089	IN	LAKE	Gary	27.4759	25.2	1129.8	0.995
18097	IN	MARION	Indianapolis	23.0925	21.1	1041.2	0.970
20173	KS	SEDGWICK	Wichita	15.0222	13.6	953.4	0.890
20177	KS	SHAWNEE	Topeka	11.7518	10.3	933.7	0.830
27053	MN	HENNEPIN	Minneapolis	15.5172	13.7	905.3	0.815
28049	MS	HINDS	Jackson	18.1339	15.7	1087.4	0.930
31055	NE	DOUGLAS	Omaha	15.2760	13.1	991.0	0.880
32031	NV	WASHOE	Reno	13.1184	11.8	1049.5	0.670
34017	NJ	HUDSON	Jersey City	19.9121	17.3	1172.6	0.810
35001	NM	BERNALILLO	Albuquerque	12.8865	9.0	1014.7	0.710
36029	NY	ERIE	Buffalo	25.1623	23.5	1085.6	0.960
37063	NC	DURHAM	Durham/Raleigh	19.4092	16.8	1039.2	1.000
37119	NC	MECKLENBURG	Charlotte	24.1214	22.6	932.8	0.835

39035	OH	CUYAHOGA	Cleveland	28.4120	24.6	1089.1	0.980
39061	OH	HAMILTON	Cincinnati	24.9979	23.1	1095.2	0.980
39081	OH	JEFFERSON	Steubenville	29.6739	23.1	1058.6	1.145
39099	OH	MAHONING	Youngstown	22.9404	20.2	1058.4	1.060
39113	OH	MONTGOMERY	Dayton	20.8120	18.8	1039.5	0.980
39153	OH	SUMMIT	Akron	25.9864	24.6	1064.0	1.060
40109	OK	OKLAHOMA	Oklahoma City	14.9767	15.9	1050.4	0.985
41051	OR	MULTNOMAH	Portland	16.3537	14.7	1060.8	0.830
42003	PA	ALLEGHENY	Pittsburgh/Allentown	29.1043	17.9	1115.6	1.005
42101	PA	PHILADELPHIA	Philadelphia	24.0704	21.4	1211.0	0.910
44007	RI	PROVIDENCE	Providence	14.2341	12.9	1006.1	0.890
47037	TN	DAVIDSON	Nashville	21.8944	20.5	981.9	0.845
47065	TN	HAMILTON	Chattanooga	18.2433	16.6	1087.9	0.840
48113	TX	DALLAS	Dallas	18.7594	16.5	1024.9	0.850
48141	TX	EL PASO	El Paso	16.9021	15.7	903.5	0.910
48201	TX	HARRIS	Houston	18.0421	13.4	1025.7	0.700
49035	UT	SALT LAKE	Salt Lake City	16.6590	15.4	954.3	1.025
51710	VA	NORFOLK CITY	Norfolk	19.5500	16.9	1139.3	0.910
53033	WA	KING	Seattle	14.9121	11.9	943.6	0.780
53063	WA	SPOKANE	Spokane	13.5200	9.4	959.2	0.810
54039	WV	KANAWHA	Charleston	21.9511	20.1	1149.5	1.005
54069	WV	OHIO	Wheeling/Huntington	23.9840	33.4	1117.5	1.020

Appendix Table 2. Epidemiologic cohort studies of PM2.5 and total mortality in California, 2000-2016
Relative risk of death from all causes (RR and 95% CI) associated with increase of 10 µg/m³ in PM2.5

Krewski 2000 & 2010 CA CPS II Cohort N=40,408 RR = 0.872 (0.805-0.944) 1982-1989
(N=[18,000 M + 22,408 F]; 4 MSAs; 1979-1983 PM2.5; 44 covariates)

McDonnell 2000 CA AHSMOG Cohort N~3,800 RR ~ 1.00 (0.95 – 1.05) 1977-1992
(N~[1,347 M + 2,422 F]; SC&SD&SF AB; M RR=1.09(0.98-1.21) & F RR~0.98(0.92-1.03))

Jerrett 2005 CPS II Cohort in LA Basin N=22,905 RR = 1.11 (0.99 - 1.25) 1982-2000
(N=22,905 M & F; 267 zip code areas; 1999-2000 PM2.5; 44 cov + max confounders)

Enstrom 2005 CA CPS I Cohort N=35,783 RR = 1.039 (1.010-1.069) 1973-1982
(N=[15,573 M + 20,210 F]; 11 counties; 1979-1983 PM2.5) RR = 0.997 (0.978-1.016) 1983-2002

Enstrom 2006 CA CPS I Cohort N=35,783 RR = 1.061 (1.017-1.106) 1973-1982
(11 counties; 1979-1983 & 1999-2001 PM2.5) RR = 0.995 (0.968-1.024) 1983-2002

Zeger 2008 MCAPS Cohort "West" N=3,100,000 RR = 0.989 (0.970-1.008) 2000-2005
(N=[1.5 M M + 1.6 M F]; Medicare enrollees in CA+OR+WA (CA=73%); 2000-2005 PM2.5)

Jerrett 2010 CA CPS II Cohort N=77,767 RR ~ 0.994 (0.965-1.025) 1982-2000
(N=[34,367 M + 43,400 F]; 54 counties; 2000 PM2.5; KRG ZIP; 20 ind cov+7 eco var; Slide 12)

Krewski 2010 CA CPS II Cohort
(4 MSAs; 1979-1983 PM2.5; 44 cov) N=40,408 RR = 0.960 (0.920-1.002) 1982-2000
(7 MSAs; 1999-2000 PM2.5; 44 cov) N=50,930 RR = 0.968 (0.916-1.022) 1982-2000

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 0.994 (0.965-1.024) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; KRG ZIP Model; 20 ind cov+7 eco var; Table 28)

Jerrett 2011 CA CPS II Cohort N=73,609 RR = 1.002 (0.992-1.012) 1982-2000
(N=[32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; Nine Model Ave; 20 ic+7 ev; Fig 22 & Tab 27-32)

Lipsett 2011 CA Teachers Cohort N=73,489 RR = 1.01 (0.95 – 1.09) 2000-2005
(N=[73,489 F]; 2000-2005 PM2.5)

Ostro 2011 CA Teachers Cohort N=43,220 RR = 1.06 (0.96 – 1.16) 2002-2007
(N=[43,220 F]; 2002-2007 PM2.5)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.060 (1.003–1.120) 1982-2000
(N=[~32,550 M + ~41,161 F]; 54 counties; 2000 PM2.5; LUR Conurb Model; 42 ind cov+7 eco var+5 metro; Table 6)

Jerrett 2013 CA CPS II Cohort N=73,711 RR = 1.028 (0.957-1.104) 1982-2000
(same parameters and model as above, except including co-pollutants NO2 and Ozone; Table 5)

Thurston 2016 CA NIH-AARP Cohort N=160,209 RR = 1.02 (0.99 -1.04) 2000-2009
(N=[~95,965 M + ~64,245 F]; full baseline model: PM2.5 by zip code; Table 3)

Enstrom 2016 unpub CA NIH-AARP Cohort N=160,368 RR = 1.001 (0.949-1.055) 2000-2009
(N=[~96,059 M + ~64,309 F]; full baseline model: 2000 PM2.5 by county)

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Dear Dr. Enstrom,

I am sorry to inform you that your submission, "Particulate Matter Does Not Cause Premature Deaths," has not been accepted for publication in the Journal. It was evaluated by members of our editorial staff. After considering its focus, content, and interest, it was our editorial decision not to consider your submission further. We are informing you of this promptly so that you can submit it elsewhere.

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Particulate Matter Does Not *Cause* Premature Deaths

James E. Enstrom, Ph.D., M.P.H., FACE
UCLA and Scientific Integrity Institute
914 Westwood Blvd. #577
Los Angeles, CA 90024-2905
http://www.scientificintegrityinstitute.org/
jenstrom@ucla.edu
(310) 472-4274

September 8, 2015

An extensive 2011 U.S. Environmental Protection Agency (EPA) cost-benefit report estimates the annual costs required to meet 1990 Clean Air Act (CAA) Amendment regulations to be about $65 billion in 2020. The annual economic benefits of these regulations are estimated to be about $2 trillion in 2020, based primarily on EPA-projected reductions in air pollution-related premature deaths and illness (1). This report has been challenged because the benefits are unproven and depend upon several questionable and unverified assumptions. Among these are assumptions that a linear, no-threshold, *causal* relation exists between fine particulate air pollution ($PM_{2.5}$) and total mortality and that additional life expectancy gained at a median age of about 80 years should be valued at about $80,000 per month. These assumptions are essential because $1.7 trillion (85%) of the $2.0 trillion total benefit estimate is attributable to reductions in premature deaths due to reductions in $PM_{2.5}$. Using discrete uncertainty analysis with plausible alternative assumptions, Cox found that the costs of CAA amendments actually exceed their benefits (2).

With the assumed benefits of $PM_{2.5}$ reductions playing such a major role in regulatory policy, it is critical that the estimated health benefits of EPA regulations be verified by transparent and reproducible data. Since 2011 Congress has been leading an effort to do this verification, particularly regarding the science and data that underlie the $PM_{2.5}$ regulations (3). This investigation has led to the current effort by Congress to enact the Secret Science Reform Act of 2015 (SSRA) (4). The SSRA would "prohibit the Environmental Protection Agency from proposing, finalizing, or disseminating regulations or assessments based upon science that is not transparent or reproducible."

Based on the data and research findings that are currently available without the SSRA, we challenge the validity of the annual $1.7 trillion health benefit attributed to reductions in $PM_{2.5}$. Specifically, we present four types of evidence that $PM_{2.5}$ does not *cause* premature deaths.

1) The major increase in U.S. life expectancy since 1970 is not due to reduction in $PM_{2.5}$. In 2009 Pope claimed that from 1980 to 2000 a decrease of 10 µg/m³ of $PM_{2.5}$ was associated nationally with a 0.61 year increase in life expectancy based on a correlation involving 51 U.S. metropolitan areas (USMAs) (5). This association was vigorously contested by four independent analyses because the underlying data was available, as would be required by the SSRA. Enstrom found no association whatsoever in 11 California counties (6). Krstic found that the national association claimed by Pope lost statistical significance with the removal of one USMA (Topeka, KS) and that the correlation between changes in $PM_{2.5}$ and life expectancy had so much scatter that it explained almost none of the association (7). Young showed that there was no association in the Western U.S., thereby supporting Enstrom, and showed that the national association was much stronger with income than with $PM_{2.5}$ (8). Cox found no significant association between reductions in $PM_{2.5}$ and total mortality rate between 2000 and 2010 in 483 counties in the 15 most populated states, including California (9). The inconsistencies and weaknesses found in the association means that Pope did not prove the hypothesis that a reduction in $PM_{2.5}$ *causes* an increase in life expectancy. However, since 1970, the year that EPA was established, health-related factors other than air pollution have had a major impact on increasing the longevity of Americans. The total annual age-adjusted death rate in the U.S. has declined by 40% from 12.226 deaths/1000 in 1970 to 7.319 deaths/1000 in 2013. The death rate in California has declined by 45% from 11.370 deaths/1000 in 1970 to 6.301 deaths/1000 in 2013. Life expectancy from birth has increased from 70.8 years in 1970 to 78.8 years in 2013 in the U.S. and from 71.7 years in 1970 to 80.8 years in 2013 in California (10).

2) No plausible etiologic mechanism by which $PM_{2.5}$ *causes* premature death is established. It is implausible that a never-smoker's death could be *caused* by inhalation over an 80 year lifespan of about one teaspoon (~5 grams) of invisible fine particles as a result of daily exposure to 15 µg/m³. This level of exposure is equivalent to smoking about 100 cigarettes over a lifetime or 0.004 cigarettes per day, which is the level often used to define a never-smoker. The notion that $PM_{2.5}$ *causes* premature death becomes even more implausible when one realizes that a person who smokes 0.2 cigarettes/day has a daily exposure of about 750 µg/m³. If a 10 µg/m³ increase in $PM_{2.5}$ actually *caused* a 0.61 year reduction in life expectancy, equivalent to the claim of Pope (5), then a 0.2 cigarettes/day smoker would experience about a 45-year reduction in life expectancy, assuming a linear relationship between changes in $PM_{2.5}$ and life expectancy. In actuality, never-smokers and smokers of 0.2 cigarettes/day do not experience any increase in total death rate or decrease in life expectancy, in spite of a 50-fold greater exposure to $PM_{2.5}$ (11). Furthermore, hundreds of toxicology experiments on both animals and humans have not proven that $PM_{2.5}$ at levels up to 750 µg/m³ *causes* death. Finally, the small relative risks of death and other biases and weaknesses of the $PM_{2.5}$ epidemiologic studies do not meet the standards of causality set by the 2011 Federal Judicial Center Reference Manual on Scientific Evidence (12). The legal standard for causality in epidemiologic studies is a large relative risk ($RR \geq 2.0$), not the small relative risk ($RR \sim 1.1$) typically found in $PM_{2.5}$-mortality studies.

3) Misrepresentation of $PM_{2.5}$–death findings has harmed the credibility of epidemiology. The $PM_{2.5}$-mortality relationship has been contested since 1993 because this small risk could be due to well-known biases, such as, confounding variables and the ecological fallacy. In spite of these biases, several major $PM_{2.5}$ investigators continue to assert that selected positive findings prove that $PM_{2.5}$ *causes* death and they continue to ignore or dismiss null $PM_{2.5}$ results. Enstrom prepared a detailed November 15, 2013 document (5000 words of text with 77 URLs) which

describes many misrepresentations and exaggerations (13). In particular, Pope and others have ignored null $PM_{2.5}$ findings in California. Serious concerns about the $PM_{2.5}$-mortality relationship in California were expressed at a February 26, 2010 Symposium on "Estimating Premature Deaths from Long-term Exposure to PM2.5" by the California Air Resources Board (CARB). Vastly different viewpoints were expressed by scientists like Enstrom and Pope. Although this Symposium could have led to better understanding and cooperation among $PM_{2.5}$ investigators, it did not. For instance, three Symposium attendees (Pope, Jerrett, and Krewski), published extensive findings in their October 28, 2011 CARB report showing that there was an overall null relationship between $PM_{2.5}$ and mortality in California, if one averaged the results from all nine of their models. This null finding agrees exactly with the null findings of Enstrom and others. However, in their subsequent September 1, 2013 *AJRCCM* paper, "Air Pollution and Mortality in California," (14) they selectively published the positive findings found in one model, but omitted the null findings of the eight other models in their 2011 report (13).

4) The American Cancer Society actively supports "secret science" $PM_{2.5}$ epidemiology. Since 1995 ACS has repeatedly allowed its 1982 Cancer Prevention Study (CPS II) data to be selectively used for $PM_{2.5}$ epidemiology research. However, ACS has refused to release the CPS II data or allow analysis that addresses the legitimate concerns raised by qualified critics of this "secret science" research. ACS is well aware of the scientific controversy generated by the original 1995 Pope *AJRCCM* paper and subsequent papers that have been used by EPA as a primary justification for its $PM_{2.5}$ regulations. The demand for CPS II data access has increased as $PM_{2.5}$–related regulations have gotten stricter, more expensive, and more implausible. While ACS refuses any independent access to its CPS II data, because of alleged concerns about subject confidentiality, it has repeatedly allowed Pope and his collaborators to violate a confidentiality pledge made to CPS II subjects. When personal questionnaire data was collected from CPS II subjects upon enrollment in late 1982, ACS informed them with this exact sentence: "We will **never** release information about any particular person and will not release addresses to any agency for any purpose, whatsoever" (15). Both the September 1, 2013 *AJRCCM* paper (14) and the new January 2, 2015 *Circulation Research* paper by Pope (16) include findings based on linking the home address of each study subject to a geographically estimated $PM_{2.5}$ concentration, in violation of the 1982 agreement.

Our strong evidence that $PM_{2.5}$ does not *cause* premature deaths invalidates the $1.7 trillion annual benefit that EPA attributes to reductions in $PM_{2.5}$ and supports Cox's findings that the economic costs of EPA CAA Amendment regulations exceed the resulting health benefits. Because the scientific and economic stakes are high for America, there is an urgent need for transparency and reproducibility in the science and data underlying EPA regulations, as required by the SSRA. The data access requirement in the SSRA is very similar to the one *Science* has for its research papers and to the one recently recommended by the editors of 30 major journals, including *Science* (17). However, recent attempts to get *Science* to publish our evidence that $PM_{2.5}$ does not *cause* premature deaths have been unsuccessful (18).

The *New England Journal of Medicine (NEJM)* has published important evidence showing a positive epidemiological relationship between $PM_{2.5}$ and mortality in the U.S., including the seminal 1993 Dockery paper based on Harvard Six Cities (H6CS) data (19), the 2009 Pope paper based on EPA/CDC public data (5), and the 2009 Jerrett paper based on 1982 ACS Cancer Prevention Study (CPS II) data (20). Because of the great prestige of *NEJM*, these publications

have been given extraordinary weight by EPA and CARB. The positive findings in these and a few related papers have been used by EPA and CARB as the primary justification for aggressive $PM_{2.5}$ regulations. However, there is much null evidence, including the four types of evidence described above. Because of the serious questions that have been raised about these key studies, on August 1, 2013 the US House Committee on Science, Space, and Technology subpoenaed the H6CS data, the ACS CPS II data, as well as the EPA/CDC public data (3). As explained above, Enstrom, Krstic,Young, and Cox have done four independent PhD-level analyses of the EPA/CDC public data that invalidate claims made in the 2009 Pope article (5). Additional indirect analyses by us and others appear to invalidate claims based on the still "secret" ACS CPS II and H6CS data, reinforcing the need for independent examination of these two data sets.

Also, upon reviewing *NEJM* publications since 1993, it is clear that *NEJM* has never published evidence about a null and noncausal relationship between PM2.5 and total mortality. There is clear geographic variation in $PM_{2.5}$ mortality risk within the US that was first published in the 2000 HEI Reanalysis Report by Krewski and there is overwhelming evidence of NO mortality risk in California (13). This null evidence has NEVER been published or cited in the *NEJM* articles or editorials related to air pollution, but it has been published in other journals or on Internet websites. The *NEJM* has rejected for publication the null evidence contained in a 2004 paper and 2009 letter by Enstrom and in a 2009 letter and 2015 perspective by Young. Furthermore, *NEJM* selected CARB member and non-epidemiologist John R. Balmes to peer review the 2009 Pope epidemiological article (5) and also selected Krewski to write the Editorial for this article. Pope, Krewski, and Balmes have known for up to 15 years about the clear geographic variation in $PM_{2.5}$ mortality risk within the US and the null risk in California. This geographic variation was NOT mentioned in the 2009 Pope article or the 2009 Krewski editorial. This failure adds to the evidence of misrepresentation and falsification described above (13).

Table 1 shows a Time Line with strong evidence of falsification of $PM_{2.5}$–death findings since 2000. This falsification involves Pope, Dockery, Krewski, Balmes, and *NEJM* Editor-in-Chief Jeffrey M. Drazen. Particularly troubling is the period from June 2008 through May 2009, when Enstrom personally informed Drazen, Pope, and Balmes of the extensive evidence of a null relationship in California and this null evidence was totally suppressed by Drazen, Pope, Balmes, and Krewski. The pattern of falsification since 2000 has made it possible for EPA and CARB to implement particularly draconian $PM_{2.5}$ regulations in California, where there is overwhelming evidence of NO relationship between $PM_{2.5}$ and mortality. The evidence presented above represents a very strong case for immediate reassessment of all EPA and CARB regulations that are based on the supposed causal relationship between $PM_{2.5}$ and premature deaths.

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Table 1. Time Line documenting the *NEJM* role in falsifying the relationship between $PM_{2.5}$ and mortality, with particular focus on Lead Author and Editorial Writer C. Arden Pope III, Lead Author and Editorial Writer Douglas W. Dockery, Co-author and Editorial Writer Daniel Krewski, Peer Reviewer John R. Balmes, and Editor-in-Chief Jeffrey M. Drazen.

Major *NEJM* Individuals in Time Line

BYU Professor C. Arden Pope III has long-term ties to Dockery, Krewski, ACS, CARB, EPA, and others that represent conflicts of interest and that compromise his objectivity on air pollution health effects. Also, he has directly defied an August 1, 2013 House Science Committee subpoena regarding his air pollution health effects research.

HSPH DEH Chairman Douglas W. Dockery has long-term ties to Pope, Krewski, Drazen, ACS, EPA, and others that represent conflicts of interest and that compromise his objectivity on the air pollution health effects. Also, he has directly defied an August 1, 2013 House Science Committee subpoena regarding his air pollution health effects research.

U Ottawa Professor Daniel Krewski has long-term ties to Pope, Dockery, ACS, EPA, and others that represent conflicts of interest and that compromise his objectivity on the air pollution health effects. Also, he has indirectly defied an August 1, 2013 House Science Committee subpoena regarding his air pollution health effects research.

UCSF/UCB Professor John R. Balmes is a CARB Physician Member who has ties to CARB Research Screening Committee, CARB Scientific Review Panel on Toxic Air Contaminants, UC Center for Occupational and Environmental Health, and the American Lung Association. All of these affiliations represent extreme conflicts of interest and severely compromise his objectivity regarding air pollution health effects, particularly in California.

Jeffrey M. Drazen, M.D. (http://www.nejm.org/page/media-center/editor-in-chief), has been *NEJM* Editor-in-Chief since July 2000 and his "responsibilities include oversight of all editorial content and policies." Since July 2000 he has made the ultimate decision on those articles and editorials on air pollution health effects that have and have not been peer-reviewed and published in *NEJM*. The 15-year pattern of his decisions is clear.

Time Line from 1993 to 2015: Key Events Involving Major *NEJM* Individuals re $PM_{2.5}$ and Mortality

December 9, 1993 SEMINAL *NEJM* PAPER on $PM_{2.5}$ and Mortality: **Dockery DW**, **Pope CA III**, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An Association between Air Pollution and Mortality in Six U.S. Cities. *N Engl J Med* 9 Dec 1993;329:1753-1759 DOI: 10.1056/NEJM199312093292401 (http://www.nejm.org/doi/full/10.1056/NEJM199312093292401).

July 2000 HEI Reanalysis Report by **Krewski** re **Dockery 1993** and **Pope 1995** (http://pubs.healtheffects.org/view.php?id=6), including Figures 18 and 21 Maps of Fine Particle Spatial Distribution & Mortality Risk, clearly showing geographic variation in US and low risk in California (http://www.scientificintegrityinstitute.org/HEIPM25Maps2000.pdf).

August 9, 2002 Cohen Email Response to Enstrom re 2000 HEI Reanalysis Report Figure 21. **Krewski** has NEVER provided the requested $PM_{2.5}$ mortality risk by city as shown in Figure 21 (http://www.scientificintegrityinstitute.org/Cohen080902.pdf).

September 9, 2004 *NEJM* Editorial by **Pope**: "Air Pollution and Health — Good News and Bad" *NEJM* 9 Sep 2004;351:1132-1134, focusing on USC Children's Health Study in California, with arrogant claims about LNT $PM_{2.5}$ mortality risk and no mention of the low $PM_{2.5}$ mortality risk in California shown in **Krewski 2000** (http://www.nejm.org/doi/full/10.1056/NEJMe048182).

October 12, 2004 *NEJM* Enstrom Manuscript #04-3494 "Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1980-98" submitted to and rejected by **Drazen** on November 10, 2004 (via Caryn Sandrew).

December 15, 2005 Enstrom paper "Fine particulate air pollution and total mortality among elderly Californians, 1973-2002" *Inhalation Toxicology* 2005;17:803-816 submitted to CARB on January 9, 2006 and ignored by CARB, **Balmes, Pope,** and **Krewski** re 2007-2013 CARB Research Proposal/Funded Project and 2008 CARB 'Tran' Report on $PM_{2.5}$ Premature Deaths in California (http://www.arb.ca.gov/planning/gmerp/dec1plan/gmerp_comments/enstrom.pdf).

April 22, 2008 Enstrom CARB Comments Regarding CARB GMERP—ignored by **Pope** and **Balmes** in May 2008 Draft CARB 'Tran' Report on $PM_{2.5}$ Premature Deaths in California (http://www.arb.ca.gov/lists/erplan08/2-carb_enstrom_comments_on_gmerp_042208.pdf).

June 4, 2008 Enstrom Comments about low PM2.5 mortality risk in California at California Senate Rules Committee Confirmation Hearing for CARB Members Mary D. Nichols and **John R. Balmes. Balmes** met with Enstrom for about thirty minutes after hearing to discuss $PM_{2.5}$ mortality risk in California and the flawed process used for justifying CARB $PM_{2.5}$ regulations (http://www.scientificintegrityinstitute.org/Nichols060408.mp3) (http://www.scientificintegrityinstitute.org/Nichols060408.pdf).

July 11, 2008 CARB Teleconference and Transcript on $PM_{2.5}$ Premature Deaths in California, including Enstrom and CARB Scientific Advisor **Pope,** who then ignored Enstrom concerns (http://www.scientificintegrityinstitute.org/CARBTeleconference071108.wav) (http://www.scientificintegrityinstitute.org/CARB071108.pdf).

August 12, 2008 *Environmental Health Perspectives* online paper by SL Zeger, F Dominici, A McDermott, and JM Samet, "Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000-2005)." Paper published in December 1, 2008 *EHP* 2008;116(12):1614–1619 (http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.11449). Paper states: "A provocative finding is that the MCAPS data show **no** evidence of a positive association between zip-level PM2.5 and mortality rates for the 640 urban zip counties in the West. This lack of association is largely because the *Los Angeles basin counties have higher PM2.5 levels than other West Coast urban centers but not higher adjusted mortality rates*."

October 1, 2008 Enstrom Comments on CARB Diesel PM2.5 Issues -- ignored by **Balmes** (http://www.arb.ca.gov/lists/verdev2008/33-32-carb_enstrom.pdf).

October 24, 2008 Enstrom CARB Public Comments on Fine PM and Premature Deaths in California. Enstrom comments ignored by **Pope** and **Balmes** in preparation of October 2008 Final CARB 'Tran' Report (http://www.arb.ca.gov/research/health/pm-mort/pm-mort_supp.pdf).

November 2008 *NEJM* manuscript "Fine-Particulate Air Pollution and Life Expectancy in the United States" was submitted by **Pope** and **Dockery**. It ignored major existing evidence of geographic variation in $PM_{2.5}$ mortality risk (**Krewski 2000**, Enstrom 2005, Zeger 2008). **Drazen** selected CARB Member **Balmes**, California regulatory activist and non-epidemiologist, as peer reviewer for manuscript (http://www.nejm.org/doi/pdf/10.1056/NEJMe0901597). In his obviously glowing assessment of this crude observational epidemiology study, **Balmes** ignored geographic variation of $PM_{2.5}$ mortality risk, particularly NO risk in California, as explained to him by Enstrom in several ways during 2008.

December 3, 2008 Enstrom-Fucaloro-Malkan-Phalen "Request to Postpone and Reassess CARB Diesel Regulations" ignored by CARB and **Balmes** (http://www.arb.ca.gov/lists/truckbus08/902-request_to_postpone_and_reassess_carb_diesel_regulations_120308.pdf).

December 10, 2008 Enstrom public comments regarding proposed CARB Statewide Truck and Bus Regulations ignored by **Pope** and **Balmes** (http://www.arb.ca.gov/lists/truckbus08/897-carb_enstrom_comments_on_statewide_truck_regulations_121008.pdf).

January 22, 2009 *NEJM* Paper "Fine-Particulate Air Pollution and Life Expectancy in the United States" by CA **Pope** III, M Ezzati, DW **Dockery** *N Engl J Med* 2009;360:376-386 was published and widely publicized (http://www.nejm.org/doi/full/10.1056/NEJMsa0805646).

January 22, 2009 *NEJM* Editorial "Evaluating the Effects of Ambient Air Pollution on Life Expectancy" by D Krewski *N Engl J Med* 2009;360:413-415 was published and publicized (http://www.nejm.org/doi/full/10.1056/NEJMe0809178). **Drazen** selected **Krewski** to write Editorial, which contains NO mention of geographic variation of $PM_{2.5}$ mortality risk, which was initially found by Krewski (**Krewski 2000**, Enstrom 2005, Zeger 2008). During 2007-2013 Krewski was co-investigator on CARB-funded Project to examine $PM_{2.5}$ mortality risk in California. At the time he wrote the Editorial, **Krewski** knew there is geographic variation in $PM_{2.5}$ mortality risk and NO risk in California and he exaggerated the importance of this study.

January 22, 2009 CARB Meeting in Sacramento, CA discusses *NEJM* **Pope** and **Dockery** paper, which coincided exactly with meeting (http://www.arb.ca.gov/board/ma/2009/ma012209.htm). **Balmes** promotes the *NEJM* paper that he peer reviewed, as stated on page 34 of CARB Meeting Transcript (http://www.arb.ca.gov/board/mt/2009/mt012209.pdf).

February 11, 2009 Enstrom Letter Showing No Relationship between $PM_{2.5}$ and Life Expectancy in California was submitted in response to **Pope** and **Dockery** paper submitted to *NEJM*. Reference 5 in my letter is my December 10, 2008 CARB comments above. Reference 9 alerts *NEJM* to severe problems with $PM_{2.5}$ science and regulations in California. **Drazen** rejects my letter on March 16, 2009 (http://www.scientificintegrityinstitute.org/NEJM031609.pdf).

March 12, 2009 *NEJM* "Long-Term Ozone Exposure and Mortality" by M Jerrett, CA **Pope** III, D **Krewski**, and others. *N Engl J Med* 2009;360:1085-1095 DOI: 10.1056/NEJMoa0803894 (http://www.nejm.org/doi/full/10.1056/NEJMoa0803894). This paper repeats the evidence on $PM_{2.5}$ and mortality without addressing any of the problems described above.

March 15, 2009 S. Stanley Young Letter criticizing the March 12, 2009 *NEJM* paper was submitted to *NEJM* and rejected by **Drazen**.

May 27, 2009 Enstrom Comments to CARB members, including **Balmes**, made clear that there is NO relationship between $PM_{2.5}$ and mortality or life expectancy in California, even using the California data in the *NEJM* **Pope** and **Dockery** paper (http://www.arb.ca.gov/lists/gmove09/1-carb_enstrom_comments_re_pm2.5_and_life_expectancy_052709.pdf).

May 28, 2009 CARB Meeting includes a special presentation of *NEJM* **Pope** and **Dockery** paper (http://www.arb.ca.gov/board/ma/2009/ma052809.htm). My May 27, 2009 and earlier comments were entirely ignored by the CARB Board, including **Balmes**, and the CARB staff. During the presentation, Balmes reveals that he was a peer-reviewer of this very paper (see page 8 of the CARB Meeting Transcript) (http://www.arb.ca.gov/board/mt/2009/mt052809.pdf).

November 16, 2009 CARB Member John B. Telles Letter and Attachments to Ellen Peter Regarding 2008 CARB 'Tran' Report Fraud by Lead Author Hien T. Tran, which involved **Pope, Balmes,** CARB Chair Mary Nichols, and others, as explained by CARB Member John G. Telles (http://www.scientificintegrityinstitute.org/Telles111609.pdf).

February 26, 2010 CARB Symposium "Estimating Premature Deaths from Long-term Exposure to $PM_{2.5}$", a direct result of the November 16, 2009 Telles Letter, was a major one-day effort to discuss and analyze the evidence on $PM_{2.5}$ and mortality, particularly in California. Enstrom, **Pope**, **Krewski**, and other key $PM_{2.5}$ scientists participated, but **Pope** and **Krewski** did not change positions (http://www.arb.ca.gov/research/health/pm-mort/pm-mort-ws_02-26-10.htm).

August 1, 2013 US House Committee on Science, Space, and Technology Subpoena of the H6CS data underlying the 1993 **Dockery** and **Pope** paper (19), the ACS CPS II data underlying the 2009 Jerrett paper (20), and EPA/CDC data underlying the 2009 **Pope** and **Dockery** paper (5) (https://science.house.gov/issues/committee-investigation-epas-secret-science).

August 1, 2013 five-page Subpoena response letter by **Pope** claimed no access to H6CS and ACS CPS II data, but made clear that the EPA/CDC data is public. Public assess has lead to four Ph.D.-level analyses that refute the $PM_{2.5}$ and life expectancy findings of **Pope** and **Dockery**.

September 6, 2013 twelve-page Subpoena response letter by **Dockery** used Orwellian New Speak to refuse access to H6CS data. **Dockery** even refused to clarify published findings based on H6CS data, but he acknowledged the concerns at the February 26, 2010 CARB Symposium.

August 7, 2015 Rejection by Debra Malina of S. Stanley Young *NEJM* Perspective manuscript "A Cautionary Tale of Two Air Pollution Papers" demonstates continuing refusal of *NEJM* and **Drazen** to publish null evidence and valid criticism on the $PM_{2.5}$ and mortality relationship.