Air Pollution and Total Mortality in Cancer Prevention Study Cohort Reanalysis

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November 22, 2017

Text Word Count = 2,950

Key Points

Question: Is fine particulate matter ($PM_{2.5}$) related to total mortality in the 1982 American Cancer Society Cancer Prevention Study (CPS II) Cohort?

Findings: Independent reanalysis found that $PM_{2.5}$ and SO_4^{2-} had no significant relationship with total mortality during 1982-1988 in the CPS II cohort when the best available $PM_{2.5}$ and SO_4^{2-} data were used. Furthermore, this reanalysis found several other null findings that challenge the validity of the positive findings in a seminal 2002 *JAMA* article.

Meaning: There is urgent need for complete reanalysis of the CPS II data used to justify establishment of the 1997 EPA National Ambient Air Quality Standard for $PM_{2.5}$.

Abstract

Importance: The EPA National Ambient Air Quality Standard (NAAQS) was established and tightened for fine particulate matter ($PM_{2.5}$), largely because of its positive long-term relationship to total mortality in one large U.S. cohort, as published in *JAMA* and elsewhere. It is important to independently assess the validity of this relationship.

Objective: To determine whether the relationship between $PM_{2.5}$ and total mortality is positive and robust upon independent reanalysis of the 1982 America Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort.

Design: The CPS II cohort was followed prospectively for all-cause mortality from 1982 to 1988 and this reanalysis is compared with analyses published from 1995 to 2009.

Setting: ACS researchers enrolled volunteer subjects who agreed to participate in a cancer epidemiology study and to be followed.

Participants: Convenience sample of up to 292,277 subjects, mostly white high school graduates aged 30+ years residing in up to 85 U.S. counties with $PM_{2.5}$ data.

Exposures: 1979-1983 EPA Inhalable Particulate Network (IPN) $PM_{2.5}$ data, previously used $PM_{2.5}$ data, and 1980-1981 sulfate (SO_4^{2-}) data.

Main Outcomes and Measures: The CPS II questionnaire data and 1982-1988 mortality follow-up were analyzed using Cox proportional hazards regression to test the validity of published findings.

Results: Among numerous null 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 1.021 (0.984–1.058) for a 10 µg/m³ increase in $PM_{2.5}$ and 1.017 (0.965-1.072) for a 10 µg/m³ increase in SO_4^{2-} in the original 50 counties with IPN $PM_{2.5}$ data. This CPS II reanalysis revealed that the original 1995 analysis, the 2000 reanalysis, and the 2002 and 2009 extended follow-up analyses presented selective positive findings relating $PM_{2.5}$ and SO_4^{2-} to total mortality and omitted essential null findings.

Conclusions and Relevance: $PM_{2.5}$ and SO_4^{2-} had no significant relationship with total mortality in the CPS II cohort when the IPN $PM_{2.5}$ data were used. This independent reanalysis raises serious concerns about the CPS II epidemiologic evidence relating $PM_{2.5}$ and SO_4^{2-} to total mortality. It provides strong justification for objective reassessment of CPS II findings and the $PM_{2.5}$ NAAQS.

Key Words

Epidemiology $PM_{2.5}$ Deaths CPS II Reanalysis

Introduction

Independent reanalysis of the 1982 American Cancer Society (ACS) Cancer Prevention Study (CPS II) cohort recently found no relationship between fine particulate matter ($PM_{2.5}$) and total mortality (Enstrom 2017) (1). This null finding is important because the EPA National Ambient Air Quality Standard (NAAQS) for $PM_{2.5}$was established in 1997 and then tightened in 2012 largely because of its positive relationship to total mortality in the CPS II cohort, as published in 1995 (Pope 1995) (2), in 2000 (HEI 2000) (3), in 2002 (Pope 2002) (4), and in 2009 (HEI 2009) (5). EPA has used this positive relationship to claim that $PM_{2.5}$ *causes* premature deaths in the United States.

However, the validity of this claim has been continuously challenged since 1997 (6-10). No etiologic mechanism has ever been established to prove that $PM_{2.5}$ can *cause* premature deaths, particularly since it involves the lifetime inhalation of only about 1-5 gm of particles that are less than 2.5 μm in diameter (7). The $PM_{2.5}$-mortality relationship has been further criticized because the small increased risk is based on selective and nontransparent analyses that have not properly accounted for well-known epidemiological biases (8). There are now two major national cohorts that show no $PM_{2.5}$-mortality relationship (11). In addition to the null CPS II findings in this manuscript and Enstrom 2017, there are null findings from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Cohort (12).

The $PM_{2.5}$ premature death claim is important because it has been used to provide a public health justification for 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 (8). With the presumed 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 total mortality be independently verified with transparent data and reproducible findings.

Unfortunately, ACS has refused to confirm or refute the peer-reviewed null CPS II evidence in Enstrom 2017. Also, they have refused to address the above criticisms and they continue to oppose independent analysis of the CPS II data. Instead, for almost 25 years, ACS has willingly collaborated with a small group of investigators who have conducted selective and non-transparent epidemiologic analyses based on CPS II subjects who were enrolled in 1982, 35 years ago. ACS ignored numerous 2011-2013 requests for CPS II data and transparency from the U.S. House Science, Space, and Technology Committee (13). Then they ignored the August 1, 2013 subpoena for CPS II data from this same Committee (14). Instead, since August 1, 2003 ACS has collaborated in the publication of eight non-transparent CPS II analyses that did not address the above criticisms of the $PM_{2.5}$-mortality relationship (15).

Furthermore, Enstrom 2017 showed that the Health Effects Institute (HEI) in Boston did not conduct or publish a proper 2000 reanalysis of the original Pope 1995 findings (HEI 2000), particularly regarding the mandated sensitivity analysis, as per their original mandate. The 31-member HEI Reanalysis Team (Team) consisted mainly of Canadian statisticians and geographers, headed by Daniel Krewski, who had no prior expertise in U.S. epidemiologic studies. The Team did not show that the Pope 1995 results were robust to alternative $PM_{2.5}$ data. Enstrom 2017 showed that there is no $PM_{2.5}$-mortality relationship in the CPS II cohort when it is based upon the 1979-1983 EPA Inhalable Particulate Network (IPN) $PM_{2.5}$ data (16,17). The IPN $PM_{2.5}$ data were fully published by EPA as of 1986 and were the best available $PM_{2.5}$ data as of 1995. Furthermore, Frederick Lipfert specifically brought these $PM_{2.5}$ data to the attention of the Team in 1998 (18). The Team did not present meaningful results based on these data and they did not use all the CPS II counties that had IPN $PM_{2.5}$ data. In addition, HEI 2009 did not present null results from the extended mortality follow-up of the CPS II cohort. HEI 2009 continued to ignore the IPN $PM_{2.5}$ data, which was again brought to their attention in 2005 (19). HEI 2009 made no mention of the geographic variation in $PM_{2.5}$ mortality risk shown in HEI 2000 Figure 21, particularly the increased risk in the Ohio Valley states and no risk in California. Enstrom 2017 showed that, when analyzed as separate regions, there was no increased risk in the Ohio Valley states or the remaining states or in California. ACS and its investigators have never addressed the above criticism and they have never cooperated with independent analysis of the CPS II data.

Methods

Computer files containing the original 1982 ACS CPS II de-identified questionnaire data and six-year follow-up on deaths from September 1, 1982 through August 31, 1988, along with detailed documentation, were obtained from a source with appropriate access to these data, as explained in Enstrom 2017 (1). This research is exempt from human subjects or ethics approval because it involved only statistical analysis of existing de-identified data. Human subjects approval was originally obtained by ACS in 1982 from each subject at the time they enrolled in CPS II.

Of the 1.2 million total CPS II subjects, analysis has been done on 292,277 subjects residing in 85 clearly defined counties in the continental U.S. with 1979-1983 EPA IPN $PM_{2.5}$ (IPN $PM_{2.5}$) measurements, as shown in Appendix Table 1. 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. These 292,277 subjects had age at entry of 30-99 years and sex of male [1] or female [2]; 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 unconfirmed deaths were randomly distributed and did not impact relative comparisons of death in a systematic way. The computer codes for the above variables are shown in brackets and they agree with the codes shown in HEI 2000.

This analysis used IPN $PM_{2.5}$ data extracted from the easily accessible EPA Reports (16,17). Close examination of HEI 2000 Appendix D "Alternative Air Pollution Data in the ACS Study" revealed that the $PM_{2.5}$ values in the column labeled '$PM_{2.5}$(DC)' were very similar to the IPN $PM_{2.5}$ data, as shown in Appendix Table 1. For 58 cities with HEI $PM_{2.5}$(DC) values, 46 had $PM_{2.5}$ values identical to the IPN $PM_{2.5}$ values. The correlation coefficient between IPN $PM_{2.5}$ and HEI $PM_{2.5}$(DC) values was 0.957. However, essentially all the 1979-1983 $PM_{2.5}$ calculations in Pope 1995, HEI 2000, Pope 2002, and HEI 2009 were based on the original investigator data in the column labeled '$PM_{2.5}$(OI)' in HEI 2000 Appendix D. Close examination of data for the 50 cities used in Pope 1995 and HEI 2000 revealed that IPN $PM_{2.5}$ data were not measured in three of these cities: Raleigh, NC; Allentown, PA; and Huntington, WV. Huntington, WV was the city with the highest $PM_{2.5}$(OI) value (33.4 $\mu g/m^3$) used in Pope 1995 and HEI 2000. Among the 85 cities with IPN $PM_{2.5}$ data, the city with the highest value was Rubidoux in Riverside County, CA (42.0 $\mu g/m^3$) and the city with the lowest value was Lompoc in Santa Barbara County, CA (10.6 $\mu g/m^3$). Neither of these California cities/counties were used in Pope 1995, HEI 2000, Pope 2002, or HEI 2009.

CPS II subjects were organized in 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 were 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, where the IPN $PM_{2.5}$ measurements were made. Based on indirect CPS II information, at least 90% of the 575 subjects in Unit 041 lived in Jefferson County as of September 1, 1982. This indicates that the ACS Division-Unit number is a good measure of the county of residence of CPS II subjects. All CPS II subjects in Unit 041 were assigned the IPN $PM_{2.5}$ value of 29.6739 $\mu g/m^3$, the weighted average of 191 measurements made in Steubenville as explained in Enstrom 2017. The Unit 041 subjects were also assigned the HEI $PM_{2.5}$(DC) value of 29.7 $\mu g/m^3$ and the HEI $PM_{2.5}$(OI) value of 23.1 $\mu g/m^3$, based on the values shown in HEI 2000 Appendix D. Appendix Table 1 contains the IPN $PM_{2.5}$ values for the

85 counties that included a city with CPS II subjects and IPN $PM_{2.5}$ data. It also contains HEI $PM_{2.5}$(DC) values for 58 of the 85 counties and HEI $PM_{2.5}$(OI) values for 47 of the 85 counties.

Also analyzed were the 1980-81 sulfate (SO_4^{2-}) measurements that were used in Pope 1995, HEI 2000, and Pope 2002 and that are shown in the column labeled 'SO_4(OI)' of HEI 2000 Appendix D. Appendix Table 1 shows the HEI SO_4^{2-} data, which were available for 55 of the 85 cities/counties with IPN $PM_{2.5}$ data and for 44 of the 47 cities/counties with IPN $PM_{2.5}$ and HEI $PM_{2.5}$(OI) data. Pope 1995 and Pope 2002 determined this relationship using 151 cities with HEI SO_4^{2-} data, but 96 of these cities did not have IPN $PM_{2.5}$ data. HEI SO_4^{2-} was used as a confounding variable in the calculation of the $PM_{2.5}$-mortality relationship, something that was not done in Pope 1995 or Pope 2002.

The SAS 9.4 procedure PHREG was used to conduct Cox proportional hazards regression (20). 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 had a strong relationship to total mortality. Race, education, and smoking status were the three adjustment variables that had the greatest impact on the age-sex adjusted RR. Pope 1995, HEI 2000, and Pope 2002 used four additional adjustment variables: body-mass index, alcohol use, exposure to passive cigarette smoke, and occupational exposure. Figure 3 of Pope 2002 shows that these additional adjustment variables had virtually no additional impact on the RR once it was controlled for age, sex, race, education and smoking status.

To test the impact of a co-pollutant, the $PM_{2.5}$-mortality relationship was analyzed including HEI SO_4^{2-} [SO_4(OI)] as an additional confounding variable. Finally, CPS II mortality follow-up results by time period were extracted from HEI 2009 Table 34. These results show the relationship between $PM_{2.5}$ and total mortality during the original follow-up period of 1982-1989 and during the extended follow-up periods of 1990-1998 and 1999-2000.

In the interest of transparency and reproducibility, and depending upon future cooperation with ACS, the goal is to post on the Scientific Integrity Institute website a version of the CPS II data that fully preserves the confidentiality of all the subjects and that contains enough information to verify my findings. Also, the goal is to post the SAS computer programs and outputs that have used in the statistical analyses described below.

Results

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 among the three sources for the adjustment variables of age, sex, race, education, and smoking status. Table 2 shows the RR for total mortality in the CPS II cohort during 1982-1988 based on four measures of air pollution: IPN $PM_{2.5}$, HEI $PM_{2.5}$(DC), HEI $PM_{2.5}$(OI), and HEI SO_4^{2-}. The fully adjusted RR and 95% CI was 1.023 (0.997–1.049) for a 10 $\mu g/m^3$ increase in IPN $PM_{2.5}$ in all 85 counties, 1.025 (0.988–1.062) for a 10 $\mu g/m^3$ increase in HEI $PM_{2.5}$(DC) in 58 counties, and 1.021 (0.984-1.058) for a

10 μg/m^3 increase in IPN $PM_{2.5}$ in 47 counties The RR was 1.017 (0.965-1.072) for a 10 μg/m^3 increase in HEI SO_4^{2-} in 55 counties.

The fully adjusted RR for total mortality during 1982-1988 was 1.081 (1.036-1.128) when based on the HEI $PM_{2.5}$(OI) values in 47 counties with IPN $PM_{2.5}$ data. This RR agrees quite well with the fully adjusted RR of 1.067 (1.037-1.099) for 1982-1989, which is shown in HEI 2009 Table 34 and which is based on the HEI $PM_{2.5}$(OI) values in the 50 Metropolitan Areas (Metro Areas) used in Pope 1995. This was the most important relationship in Pope 1995 and it was confirmed in HEI 2000 and HEI 2009. Table 2 clearly shows that the positive RRs in the CPS II cohort depended upon the use of HEI $PM_{2.5}$(OI) data. The null RRs based on IPN $PM_{2.5}$ and HEI $PM_{2.5}$(DC) were not presented in Pope 1995, HEI 2000, Pope 2002, or HEI 2009. Thus, the $PM_{2.5}$-mortality relationship in the CPS II cohort was not robust.

Table 2 also shows the fully adjusted RR for total mortality was 1.028 (0.979-1.080) when based on HEI SO_4^{2-} data for the 55 CPS II counties with IPN $PM_{2.5}$ data. This null sulfates-mortality relationship is not consistent with the positive relationship found in the 151 CPS II Metro Areas used in Pope 1995, HEI 2000, Pope 2002, and HEI 2009. This finding indicates that the positive relationship of SO_4^{2-} with total mortality was not robust and depended upon the specific CPS II subjects included in the calculation. Finally, Table 2 shows that the small positive fully adjusted RRs based on IPN $PM_{2.5}$ data decline to slightly below 1.0 when controlled for confounding by SO_4^{2-}. This finding indicates the importance of controlling for co-pollutants, which was not done in Pope 1995, HEI 2000, Pope 2002, or HEI 2009.

Table 3 shows that the positive RR between HEI $PM_{2.5}$(OI) and total mortality during 1982-1989 in Pope 1995, became insignificant during 1990-2000, based on the RRs in HEI 2009 Table 34. This finding indicates that many of positive RRs in the CPS II cohort were statistically insignificant after 1989. In particular, the RR of 1.044 (1.011-1.078) during 1982-1998 in Pope 2002 was 1.101 (1.046-1.157) during 1982-1989 and 1.007 (0.966-1.050) during 1990-1998. In any case, even the statistically significant positive RRs were so close to 1.00 that they did not constitute evidence of a causal relationship between $PM_{2.5}$ and total mortality.

Conclusions

This new independent analysis of the CPS II cohort adds significantly to the initial independent analysis in Enstrom 2017. It found that both $PM_{2.5}$ and SO_4^{2-} were not related to mortality from all causes during 1982-1988, when based on IPN $PM_{2.5}$, HEI $PM_{2.5}$(DC), and HEI SO_4(OI) data. A positive $PM_{2.5}$-total mortality relationship was found only when the HEI $PM_{2.5}$(OI) data were used to reproduce the original findings in Pope 1995. The null relationships were found for all 85 CPS II counties with IPN $PM_{2.5}$ data and for the 50 original counties used in Pope 1995, HEI 2000, and HEI 2009. This null evidence demonstrates that the $PM_{2.5}$-mortality relationship is not robust and is indeed sensitive to the $PM_{2.5}$ data and CPS II subjects used in the analysis.

It is important to note that the HEI $PM_{2.5}$(DC) data was published in HEI 2000 Appendix D and is essentially identical to the IPN $PM_{2.5}$ data, but it is not labeled in a way that identifies it as IPN $PM_{2.5}$ data. This observation strongly indicates that the Team was clearly aware of the IPN $PM_{2.5}$

data but never presented null RRs based on IPN $PM_{2.5}$ or HEI $PM_{2.5}$(DC) in either HEI 2000, Pope 2002, or HEI 2009. Furthermore, the statement on page 80 of HEI 2000 that “air quality monitoring data could not be accurately accessed and accurately described” is incorrect because the Team published in HEI 2000 a mislabeled version of the readily available IPN $PM_{2.5}$ data. Thus, the Team did not “evaluate the sensitivity of the original findings to the indicators of exposure to fine particle air pollution used by the Original Investigators.”

Evidence from HEI 2009 Table 34 shows that the positive $PM_{2.5}$-total mortality relationship based on HEI $PM_{2.5}$(OI) values was significant during 1982-89 but not during 1990-2000. It was misleading and inappropriate for all CPS II analyses in Pope 2002 and HEI 2009 to be based on mortality follow-up beginning in 1982. It may well be that there have been no positive $PM_{2.5}$-total mortality relationships in the CPS II cohort since 1989 and the null 1990-1998 and 1990-2000 results were not specifically disclosed in Pope 2002 or HEI 2009.

It is very disturbing that ACS investigators, Pope, HEI officials, and key HEI Reanalysis Team members have all refused to confirm or refute the peer-reviewed evidence of no $PM_{2.5}$-total mortality relationship in the CPS II cohort in Enstrom 2017. Indeed, they have consistently refused to cooperate with anyone in clarifying the $PM_{2.5}$-mortality relationship in the CPS II cohort. Instead they continue to publish selective positive CPS II findings that are not transparent and not reproducible. These investigators need to cooperate with critics and conduct completely transparent epidemiologic analyses of the CPS II cohort.

In summary, the numerous null $PM_{2.5}$-total mortality findings in the CPS II cohort described in this article directly challenge the validity of the original positive Pope 1995 and Pope 2002 findings and they raise serious doubts about the CPS II epidemiologic evidence supporting the $PM_{2.5}$ NAAQS. These findings demonstrate the importance of independent and transparent analysis of underlying data. Finally, these findings provide strong justification for objective independent reanalysis of the CPS II cohort and reassessment of the EPA $PM_{2.5}$ NAAQS.

Acknowledgments

I thank the American Cancer Society for making it possible for me to obtain unique access to the original CPS II cohort data and detailed documentation used in this study. I thank Dr. Frederick W. Lipfert for his assistance since 2002 and for the integrity and scope of his air pollution research. I declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Summary Characteristics of CPS II Subjects in 1) Pope 1995 Table 1 (2), 2) HEI 2000 Table 24 (3), and 3) current analysis based on CPS II subjects in 47 and 85 counties with IPN $PM_{2.5}$ data

Characteristic	Pope 1995	HEI 2000	Current CPS II Analysis		
	Table 1	Table 24	N=47	N=47	N=85
	HEI	HEI	HEI	IPN	IPN
	$PM_{2.5}$(OI)	$PM_{2.5}$(OI)	$PM_{2.5}$(OI)	$PM_{2.5}$	$PM_{2.5}$
Number of metro areas	50	50			
Number of counties	not stated	not stated	47	47	85
Age-Sex Adjusted Subjects			206,379	206,397	292,277
Fully Adjusted Subjects	295,223	298,817	189,676	189,676	269,766
Age-Sex Adjusted Deaths			12,082	12,082	17,231
Fully Adjusted Deaths	20,765	23,093	10,621	10,621	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 (µg/m³)					
Average	18.2	18.2	17.8	21.37	21.16
SD	5.1	4.4	4.5	5.30	5.98
Range	9.0 – 33.5	9.0-33.4	9.0-25.2	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 47, 58, and 85 counties in the continental United States with 1979-1983 IPN $PM_{2.5}$ data. Similar RRs for sulfates (1980-1981 SO_4^{2-}) are shown for 44 and 55 counties with IPN $PM_{2.5}$ data. The RRs indicated with * are for those counties with IPN $PM_{2.5}$ data that are among the original 50 Pope 1995 counties with HEI $PM_{2.5}$(OI) data.

$PM_{2.5}$ Years and Source	Number of Counties	Number of Subjects	Number of Deaths	RR	95% CI Lower – Upper
Age-sex adjusted RR for Both Sexes and All Causes of Death					
1979-1983 $PM_{2.5}$					
IPN $PM_{2.5}$	85	292,277	17,321	1.038	(1.014 – 1.063)
HEI $PM_{2.5}$(DC)	58	229,915	13,654	1.050	(1.015 – 1.087)
IPN $PM_{2.5}$	47	206,379	12,082	1.040	(1.005 – 1.076) *
HEI $PM_{2.5}$(OI)	47	206,379	12,082	1.125	(1.075 – 1.164) *
1980-1981 SO_4^{2-}					
HEI SO_4(OI)	55	211,411	12,466	1.087	(1.038 – 1.138)
HEI SO_4(OI)	44	184,182	10,621	1.077	(1.025 – 1.131) *
Fully adjusted RR for Both Sexes and All Causes of Death					
1979-1983 $PM_{2.5}$					
IPN $PM_{2.5}$	85	269,766	15,593	1.023	(0.997 – 1.049)
HEI $PM_{2.5}$(DC)	58	211,584	12,246	1.025	(0.988 – 1.062)
IPN $PM_{2.5}$	47	189,676	10,836	1.021	(0.984 – 1.058) *
HEI $PM_{2.5}$(OI)	47	189,676	10,836	1.081	(1.036 – 1.128) *
1980-1981 SO_4^{2-}					
HEI SO_4(OI)	55	194,729	11,211	1.028	(0.979 – 1.080)
HEI SO_4(OI)	44	169,405	9,552	1.017	(0.965 – 1.072) *
Fully adjusted RR for Both Sexes and All Causes of Death, controlling for 1980-1981 SO_4^{2-}					
1979-1983 $PM_{2.5}$					
IPN $PM_{2.5}$	55	194,729	11,211	0.990	(0.948 – 1.035)
IPN $PM_{2.5}$	44	169,405	9,552	0.972	(0.909 – 1.040) *

Table 3. Fully adjusted relative risk of death from all causes (RR and 95% CI) from September 1, 1982 through December 31, 2000 associated with change of 10 µg/m³ increase in $PM_{2.5}$ for CPS II subjects residing in 50, 58, or 61 Metro Areas with 1979-1983 HEI $PM_{2.5}$(OI) data. RRs beginning with 1982 deaths were taken from HEI 2009 Table 34. RRs beginning with 1990 or 1999 deaths (indicated with *) were calculated from the Table 34 RRs, using standard formulas for combining RRs with 95% CI. The RR indicated with ** is identical to the RR in Table 2 of Pope 2002.

Follow-up Years	Number of Metro Areas	Number of Subjects	Number of Deaths	RR	95% CI Lower Upper
Fully adjusted RR for Both Sexes and All Causes of Death					
Standard Cox with Different Metro Areas					
1982-1989	50	298,825	23,180	1.067	(1.037 – 1.099)
1990-1998				1.013	(0.995 – 1.031) *
1982-1998	61	360,682	80,819	1.027	(1.012 – 1.043)
Random Effects Cox with Different Metro Areas					
1982-1989	50	298,825	23,180	1.101	(1.046 – 1.157)
1990-1998				1.007	(0.966 – 1.050) *
1982-1998	61	360,682	80,819	1.044	(1.011 – 1.078) **
Standard Cox with Same Metro Areas					
1982-1989	58	342,521		1.048	(1.022 – 1.076)
1990-1998	58			1.021	(1.002 – 1.041) *
1999-2000	58			1.014	(0.980 – 1.049) *
1982-1998	58	342,521		1.031	(1.015 – 1.047)
1982-2000	58	342,521	90,783	1.028	(1.014 – 1.043)
Random Effects Cox with Same Metro Areas					
1982-1989	58	342,521		1.074	(1.028 – 1.122)
1990-1998	58			1.017	(0.971 – 1.064) *
1999-2000	58			1.017	(0.940 – 1.101) *
1982-1998	58	342,521		1.046	(1.014 – 1.080)
1982-2000	58	342,521	90,783	1.042	(1.012 – 1.073)

Appendix Table 1. List of the 85 counties containing 47 of the 50 cities used in Pope 1995, HEI 2000, and HEI 2009, as well as the 38 additional counties used in Enstrom 2017. Each location includes State, primary ACS Division-Unit number and an indication of additional numbers, Federal Information Processing Standards (FIPS) code, IPN/HEI county, IPN/HEI city with $PM_{2.5}$ measurements, 1979-1983 IPN $PM_{2.5}$ (weighted mean), 1979-1983 HEI $PM_{2.5}$(DC) (weighted mean), 1979-1983 HEI $PM_{2.5}$(OI) (median), and 1980-1981 HEI SO_4^{2-} (mean). All 85 counties have IPN $PM_{2.5}$ data, 58 counties have HEI $PM_{2.5}$(DC) data, and 47 counties have HEI $PM_{2.5}$(OI) data. Three of the 50 cities used in Pope 1995 and HEI 2000 (Raleigh NC, Allentown PA, and Huntington WV) were not part of IPN and the origin of the HEI $PM_{2.5}$(OI) data in HEI 2000 Appendix D for these three cities is unknown.

State	ACS Div-Unit	FIPS Code	IPN/HEI County containing IPN/HEI City	IPN/HEI City with $PM_{2.5}$ Measurements	1979-83 IPN $PM_{2.5}$ (μg/m³) (weighted mean)	1979-83 HEI $PM_{2.5}$(DC) (μg/m³) (weighted mean)	1979-83 HEI $PM_{2.5}$(OI) (μg/m³) (median)	1980-81 HEI SO_4^{2-} (μg/m³) (mean)
AL	01037	01073	JEFFERSON	Birmingham	25.6016	28.7	24.5	13.1
AL	01049	01097	MOBILE	Mobile	22.0296	22.0	20.9	12.6
AZ	03700	04013	MARICOPA	Phoenix	15.7790	18.5	15.2	4.3
AR	04071+2	05119	PULASKI	Little Rock	20.5773	20.6	17.8	5.9
CA	06001	06001	ALAMEDA	Livermore	14.3882			
CA	06002	06007	BUTTE	Chico	15.4525			
CA	06003	06013	CONTRA COSTA	Richmond	13.9197			
CA	06004	06019	FRESNO	Fresno	18.3731	10.3	10.3	5.8
CA	06008	06029	KERN	Bakersfield	30.8628			
CA	06051+4	06037	LOS ANGELES	Los Angeles	28.2239	26.8	21.8	14.0
CA	06019	06065	RIVERSIDE	Rubidoux	42.0117			14.6
CA	06020	06073	SAN DIEGO	San Diego	18.9189	18.9		11.2
CA	06021	06075	SAN FRANCISCO	San Francisco	16.3522	16.4	12.2	6.6
CA	06025	06083	SANTA BARBARA	Lompoc	10.6277			
CA	06026	06085	SANTA CLARA	San Jose	17.7884	17.8	12.4	6.2
CO	07004	08031	DENVER	Denver	10.7675	10.8	16.1	5.2
CO	07047	08069	LARIMER	Fort Collins	11.1226			
CO	07008	08101	PUEBLO	Pueblo	10.9155	10.9		6.7
CT	08001	09003	HARTFORD	Hartford	18.3949	18.4	14.8	9.4
CT	08004	09005	LITCHFIELD	Litchfield	11.6502			
DE	09002	10001	KENT	Dover	19.5280			
DE	09004+2	10003	NEW CASTLE	Wilmington	20.3743	20.4		19.4
DC	10001+2	11001	DIST COLUMBIA	Washington	25.9289	25.9	22.5	14.9

FL	11044	12057	HILLSBOROUGH	Tampa	13.7337	13.7	11.4	10.3
GA	12027+4	13051	CHATHAM	Savannah	17.8127	17.8		
GA	12062	13121	FULTON	Atlanta	22.5688	22.6	20.3	12.0
ID	13001	16001	ADA	Boise	18.0052	18.0	12.1	
IL	14089+4	17031	COOK	Chicago	25.1019	23.0	21.0	
IL	14098	17197	WILL	Braidwood	17.1851			
IN	15045	18089	LAKE	Gary	27.4759	27.5	25.2	19.1
IN	15049	18097	MARION	Indianapolis	23.0925	23.1	21.1	12.6
KS	17287	20173	SEDGWICK	Wichita	15.0222	15.0	13.6	4.9
KS	17289	20177	SHAWNEE	Topeka	11.7518	11.8	10.3	6.8
KY	18010	21019	BOYD	Ashland	37.7700			
KY	18055	21111	JEFFERSON	Louisville	24.2134			
MD	21106+1	24510	BALTIMORE CITY	Baltimore	21.6922	21.7		13.0
MD	21101	24031	MONTGOMERY	Rockville	20.2009			
MA	22105+1	25013	HAMPDEN	Springfield	17.5682	17.6		12.8
MA	22136	25027	WORCESTER	Worcester	16.2641	16.3		10.7
MN	25001+2	27053	HENNEPIN	Minneapolis	15.5172	15.5	13.7	8.4
MN	25150+5	27123	RAMSEY	St Paul	15.5823			
MS	26086	28049	HINDS	Jackson	18.1339	18.1	15.7	8.8
MO	27001+3	29095	JACKSON	Kansas City	17.8488	17.8		10.2
MT	28009	30063	MISSOULA	Missoula	17.6212			
MT	28011	30093	SILVER BOW	Butte	16.0405			
NE	30028	31055	DOUGLAS	Omaha	15.2760	15.3	13.1	8.7
NV	31101	32031	WASHOE	Reno	13.1184	13.1	11.8	4.1
NJ	33004	34007	CAMDEN	Camden	20.9523			
NJ	33007	34013	ESSEX	Livingston	16.4775			
NJ	33009	34017	HUDSON	Jersey City	19.9121	19.9	17.3	13.8
NM	34201	35001	BERNALILLO	Albuquerque	12.8865	12.9	9.0	4.5
NY	36014	36029	ERIE	Buffalo	25.1623	26.5	23.5	11.7
NY	35001	36061	NEW YORK	New York City	23.9064	23.9		10.7
NC	37033	37063	DURHAM	Durham	19.4092			11.9
NC	37064	37119	MECKLENBURG	Charlotte	24.1214	24.1	22.6	11.5
OH	39009	39017	BUTLER	Middletown	25.1789			
OH	39018	39035	CUYAHOGA	Cleveland	28.4120	27.9	24.6	13.7
OH	39031	39061	HAMILTON	Cincinnati	24.9979	25.0	23.1	14.3
OH	39041	39081	JEFFERSON	Steubenville	29.6739	29.7	23.1	23.5
OH	39050	39099	MAHONING	Youngstown	22.9404	22.9	20.2	15.7
OH	39057	39113	MONTGOMERY	Dayton	20.8120	20.8	18.8	13.5
OH	39077	39153	SUMMIT	Akron	25.9864	26.0	24.6	14.1
OK	40055	40109	OKLAHOMA	Oklahoma City	14.9767	15.0	15.9	6.3
OR	41019+1	41039	LANE	Eugene	17.1653	17.2		
OR	41026	41051	MULTNOMAH	Portland	16.3537	19.8	14.7	7.7

PA	42101+1	42003	ALLEGHENY	Pittsburgh	29.1043	30.0		15.8
PA	42443	42095	NORTHAMPTON	Bethlehem	19.5265			
PA	43002+11	42101	PHILADELPHIA	Philadelphia	24.0704	24.1	21.4	11.5
RI	45001+6	44007	PROVIDENCE	Providence	14.2341	14.2	12.9	8.7
SC	46016+1	45019	CHARLESTON	Charleston	16.1635			
TN	51019+5	47037	DAVIDSON	Nashville	21.8944	22.6	20.5	8.7
TN	51088	47065	HAMILTON	Chattanooga	18.2433	20.4	16.6	13.9
TX	52811+2	48113	DALLAS	Dallas	18.7594	18.8	16.5	10.0
TX	52859+3	48141	EL PASO	El Paso	16.9021	16.9	15.7	
TX	52882+2	48201	HARRIS	Houston	18.0421	18.0	13.4	10.5
UT	53024	49035	SALT LAKE	Salt Lake City	16.6590	17.5	15.4	4.8
VA	55024	51059	FAIRFAX	Fairfax	19.5425			
VA	55002	51710	NORFOLK CITY	Norfolk	19.5500	19.5	16.9	14.8
WA	56017	53033	KING	Seattle	14.9121	14.9	11.9	7.5
WA	56032	53063	SPOKANE	Spokane	13.5200	13.5	9.4	5.6
WV	58130	54029	HANCOCK	Weirton	25.9181			
WV	58207	54039	KANAWHA	Charleston	21.9511	21.7	20.1	17.8
WV	58117	54069	OHIO	Wheeling	23.9840			
WI	59005	55009	BROWN	Green Bay	20.5462			
WI	59052	55105	ROCK	Beloit	19.8584			

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