

## **Preliminary Analysis of 2012 EHS Lepeule Paper on PM2.5 and Mortality in H6CS**

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**Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009.**

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### **Abstract**

#### **BACKGROUND:**

Epidemiologic studies have reported associations between fine particles (aerodynamic diameter 2.5  $\mu\text{m}$ ; PM2.5) and mortality. However, concerns have been raised regarding the sensitivity of the results to model specifications, lower exposures, and averaging time.

#### **OBJECTIVE:**

We addressed these issues using 11 additional years of follow-up of the Harvard Six Cities study, incorporating recent lower exposures.

#### **METHODS:**

We replicated the previously applied Cox regression, and examined different time lags, the shape of the concentration-response relationship using penalized splines, and changes in the slope of the relation over time. We then conducted Poisson survival analysis with time-varying effects for smoking, sex, and education.

#### **RESULTS:**

Since 2001, average PM2.5 levels, for all six cities, were  $< 18 \mu\text{g}/\text{m}^3$ . Each increase in PM2.5 (10  $\mu\text{g}/\text{m}^3$ ) was associated with an adjusted increased risk of all-cause mortality (PM2.5 average on previous year) of 14% [95% confidence interval (CI): 7, 22], and with 26% (95% CI: 14, 40) and 37% (95% CI: 7, 75) increases in cardiovascular and lung-cancer mortality (PM2.5 average of three previous years), respectively. The concentration-response relationship was linear down to PM2.5 concentrations of 8  $\mu\text{g}/\text{m}^3$ . Mortality rate ratios for PM2.5 fluctuated over time, but without clear trends despite a substantial drop in the sulfate fraction. Poisson models produced similar results.

#### **CONCLUSIONS:**

These results suggest that further public policy efforts that reduce fine particulate matter air pollution are likely to have continuing public health benefits.

# Chronic Exposure to Fine Particles and Mortality: An Extended Follow-up of the Harvard Six Cities Study from 1974 to 2009

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**Table 1.** Number of participants, mortality, and average PM<sub>2.5</sub> levels in the Harvard Six Cities study, 1974–2009.

Characteristic	Six cities (combined)	Steubenville	Kingston–Harriman	St. Louis	Watertown	Topeka	Portage–Wycena–Pardeeville
Participants ( <i>n</i> )	8,096	1,346	1,258	1,292	1,332	1,238	1,630
Person-years ( <i>n</i> )	212,067	33,276	33,067	32,225	36,818	32,877	43,804
Cause of death							
All causes [ <i>n</i> (%)]	4,495 (55.5)	822 (61.1)	733 (58.3)	827 (64.0)	700 (52.6)	617 (49.8)	796 (48.8)
Cardiovascular (%)	40.8	45.3	41.1	42.2	39.3	37.4	38.6
Lung cancer (%)	7.8	9.0	8.0	8.7	6.6	7.3	6.8
COPD (%)	5.5	4.9	7.0	5.1	4.9	7.3	4.6
1974–2009 average of individual PM <sub>2.5</sub> concentrations	15.9	23.6	19.1	16.7	14.0	12.2	11.4

**Table 2.** Adjusted<sup>a</sup> association between PM<sub>2.5</sub> and mortality, for the 8,096 participants and certain sub-populations of the Harvard Six Cities study, 1974–2009.

Cause of death/stratum-specific estimates according to characteristics at enrollment

*n* participants  
(*n* person-years)

RR (95% CI) for 10-μg/m<sup>3</sup>  
increase in PM<sub>2.5</sub>

All-cause	8,096 (212,067)	1.14 (1.07, 1.22)
Chronic conditions <sup>c</sup>		
Hypertension	1,439 (30,540)	1.17 (1.03, 1.32)
COPD	942 (17,723)	1.09 (0.95, 1.26)
Diabetes	563 (11,473)	1.04 (0.85, 1.27)
Smoking status ( <i>p</i> -interaction = 0.58)		
Never smoker	3,265 (90,372)	1.09 (0.98, 1.21)
Former smoker	1,934 (48,049)	1.17 (1.04, 1.30)
Current smoker	2,897 (73,646)	1.17 (1.06, 1.28)
Follow-up period ( <i>p</i> -interaction = 0.06)		
1974–1982	8,096 (58,798)	1.06 (0.96, 1.17)
1983–1991	7,478 (63,129)	1.32 (1.16, 1.50)
1992–2000	6,391 (51,800)	1.11 (0.98, 1.27)
2001–2009	4,910 (38,340)	1.19 (0.91, 1.55)

Table 1. Characteristics of the Study Population and Mean Air-Pollution Levels in Six Cities.\*

CHARACTERISTIC	PORTAGE, WIS.	TOPEKA, KANS.	WATERTOWN, MASS.	HARRIMAN, TENN.	ST. LOUIS	STEUBENVILLE, OHIO
No. of participants	1,631	1,239	1,336	1,258	1,296	1,351
Person-years of follow-up	21,618	16,111	19,882	17,836	17,715	17,914
No. of deaths	232	156	248	222	281	291
Deaths/1000 person-years	10.73	9.68	12.47	12.45	15.86	16.24
Female sex (%)	52	56	56	54	55	56
Smokers (%)	36	33	40	37	35	35
Former smokers (%)	24	25	25	21	24	23
Average pack-years of smoking						
Current smokers	24.0	25.6	25.2	24.5	30.9	28.0
Former smokers	18.0	19.7	21.8	21.1	22.0	25.0
Less than high-school education (%)	25	12	22	35	45	30
Average age (yr)	48.4	48.3	48.5	49.4	51.8	51.6
Average body-mass index	26.3	25.3	25.5	25.1	26.0	26.4
Job exposure to dust or fumes (%)	53	28	38	50	40	48
Total particles ( $\mu\text{g}/\text{m}^3$ )	34.1	56.6	49.2	49.4	72.5	89.9
Inhalable particles ( $\mu\text{g}/\text{m}^3$ )	18.2	26.4	24.2	32.5	31.4	46.5
Fine particles ( $\mu\text{g}/\text{m}^3$ )	11.0	12.5	14.9	20.8	19.0	29.6
Sulfate particles ( $\mu\text{g}/\text{m}^3$ )	5.3	4.8	6.5	8.1	8.1	12.8
Aerosol acidity ( $\text{nmol}/\text{m}^3$ )	10.5	11.6	20.3	36.1	10.3	25.2
Sulfur dioxide (ppb)	4.2	1.6	9.3	4.8	14.1	24.0
Nitrogen dioxide (ppb)	6.1	10.6	18.1	14.1	19.7	21.9
Ozone (ppb)	28.0	27.6	19.7	20.7	20.9	22.3

\*Air-pollution values were measured in the following years: total particles, sulfur dioxide, nitrogen dioxide, and ozone, 1977 through 1985; inhalable and fine particles, 1979 through 1985; sulfate particles, 1979 through 1984; and aerosol acidity, 1985 through 1988.

## Laden 2006

TABLE 1. NUMBER OF PERSON-YEARS OF FOLLOW-UP AND TOTAL DEATHS IN SIX CITIES: PERIOD 1 (1974–1989 FOLLOW-UP) AND PERIOD 2 (1990–1998 FOLLOW-UP)

Characteristics	Portage	Topeka	Watertown	Harriman	St. Louis	Steubenville
No. participants	1,630	1,238	1,332	1,258	1,292	1,346
Period 1* (1,364 deaths; 104,243 person-yr)						
Person-yr	20,224	14,967	18,640	16,991	16,572	16,849
No. deaths	212	149	238	219	267	279
Deaths/1,000 person-yr	10.5	10.0	12.8	12.9	16.1	16.6
Average PM <sub>2.5</sub> (µg/m <sup>3</sup> )	11.4	12.4	15.4	20.9	19.2	29.0
Period 2 (1,368 deaths; 54,735 person-yr)						
Person-yr	11,658	9,062	8,979	8,363	8,172	8,501
No. deaths	264	184	194	229	251	246
Deaths/1,000 person-yr	22.6	20.3	21.6	27.4	30.7	28.9
Average PM <sub>2.5</sub> (µg/m <sup>3</sup> )	10.2	13.1	12.1	18.1	13.4	22.0

\* Period 1 is restricted to 1,974 through 1989, whereas the original Dockery and colleagues (7) analysis included person-years of follow-up through June 1991 for a total of 111,076 person-years and 1,430 deaths. In Period 1, average PM<sub>2.5</sub> (µg/m<sup>3</sup>) is the mean concentration in 1980–1985, the years when there are monitoring data for all cities (18). In Period 2, average PM<sub>2.5</sub> is the mean concentrations of the estimated PM<sub>2.5</sub> in 1990–1998.

## Laden 2006

TABLE 2. ADJUSTED TOTAL MORTALITY RATE RATIOS AND 95% CONFIDENCE INTERVALS ESTIMATED FROM COX PROPORTIONAL HAZARDS MODEL FOR EACH FOLLOW-UP PERIOD (1974–1989 AND 1990–1998) AND THE COMPLETE FOLLOW-UP (1974–1998)

	Period 1	Period 2	Complete
Person-Yr of Follow-up	104,243	54,735	158,978
Deaths	1,364	1,368	2,732
	RR (95% CI)	RR (95% CI)	RR (95% CI)
City-specific model*			
Portage	1.00		1.00
Topeka	1.06 (0.86–1.31)	1.01 (0.83–1.22)	1.03 (0.89–1.19)
Watertown	1.06 (0.87–1.28)	0.82 (0.67–1.00)	0.95 (0.83–1.08)
Harriman St.	1.19 (0.98–1.44)	1.10 (0.91–1.33)	1.15 (1.01–1.32)
Louis	1.15 (0.96–1.38)	0.96 (0.80–1.15)	1.05 (0.93–1.20)
Steubenville	1.31 (1.10–1.57)	1.06 (0.89–1.27)	1.18 (1.04–1.34)
Period	1.00	0.97 (0.70–1.35)	

Definition of abbreviations: CI = confidence interval; RR = rate ratio.

Rate ratios have been adjusted for age in 1-yr categories, sex, current smoker, current pack-years of smoking, former smoker, former pack-years of smoking, less than high school education, and linear and quadratic terms for body mass index.

\* City-specific rate ratios are all expressed in relation to Portage.

## Lepeule 2012

Table 1. Number of participants, mortality, and average PM<sub>2.5</sub> levels in the Harvard Six Cities study, 1974–2009.

Characteristic	Six cities (combined)	Steubenville	Kingston–Harriman	St. Louis	Watertown	Topeka	Portage–Wycocena–Pardeeville
Participants (n)	8,096	1,346	1,258	1,292	1,332	1,238	1,630
Person-years (n)	212,067	33,276	33,067	32,225	36,818	32,877	43,804
Cause of death							
All causes [n (%)]	4,495 (55.5)	822 (61.1)	733 (58.3)	827 (64.0)	700 (52.6)	617 (49.8)	796 (48.8)
Cardiovascular (%)	40.8	45.3	41.1	42.2	39.3	37.4	38.6
Lung cancer (%)	7.8	9.0	8.0	8.7	6.6	7.3	6.8
COPD (%)	5.5	4.9	7.0	5.1	4.9	7.3	4.6
1974–2009 average of individual PM <sub>2.5</sub> concentrations	15.9	23.6	19.1	16.7	14.0	12.2	11.4

<b>Characteristic</b>	<b>Six cities (combined)</b>	<b>Steubenville</b>	<b>Kingston-Harriman</b>	<b>St. Louis</b>	<b>Watertown</b>	<b>Topeka</b>	<b>Portage-Wyocena Pardeeville</b>
Participants (n)	8096	1346	1258	1292	1332	1238	1630
Person-years (n)	212067	33276	33067	32225	36818	32877	43804
All causes	3184 (39.3%)	566 (42.1%)	526 (41.8%)	561 (43.4%)	467 (35.1%)	480 (38.8%)	584 (35.8%)
Cardiovascular	1237 (15.3%)	247 (18.4%)	204 (16.2%)	229 (17.7%)	165 (12.4%)	178 (14.4%)	214 (13.1%)
Lung cancer	246 (3.0%)	53 (3.9%)	41 (3.3%)	44 (3.4%)	34 (2.6%)	33 (2.7%)	41 (2.5%)
COPD	188 (2.3%)	28 (2.1%)	38 (3.0%)	28 (2.2%)	26 (2.0%)	41 (3.3%)	27 (1.7%)
mean PM2.5 person-year	16.3	23.9	19.4	16.9	14.1	12.3	11.3

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SAS Analysis of Lepeule EHP 1974-2009 PM2.5 & Mortality 0712 FinalData0713.xlsx (H6CS file submitted to EPA by Harvard in response to August 1, 2013 US House Science Subpoena)

SAS Frequency of Participants in H6CS by City Agrees Exactly with 2012 Lepeule Table 1:

<b>city</b>	<b>City c</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
<b>1</b>	<b>STU</b>	1346	16.63	1346	16.63
<b>2</b>	<b>KH</b>	1258	15.54	2604	32.16
<b>3</b>	<b>STL</b>	1292	15.96	3896	48.12
<b>4</b>	<b>WAT</b>	1332	16.45	5228	64.58
<b>5</b>	<b>TOP</b>	1238	15.29	6466	79.87
<b>6</b>	<b>POR</b>	1630	20.13	8096	100.00

SAS Frequency of Person-years in H6CS by City Agrees Exactly with 2012 Lepeule Table 1:

	<b>City c</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
<b>1</b>	<b>STU</b>	33276	15.69	33276	15.69
<b>2</b>	<b>KH</b>	33067	15.59	66343	31.28
<b>3</b>	<b>STL</b>	32225	15.20	98568	46.48
<b>4</b>	<b>WAT</b>	36818	17.36	135386	63.84
<b>5</b>	<b>TOP</b>	32877	15.50	168263	79.34
<b>6</b>	<b>POR</b>	43804	20.66	212067	100.00

SAS Tabulations of 1989-2009 H6CS Deaths Follows Pattern of 1974-2009 Deaths in 2012 Lepeule Table 1, but no exact comparisons because 1974-1988 Deaths Omitted from xlsx file:

<b>deadt</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
<b>0</b>	4912	60.67	4912	60.67
<b>1</b>	3184	39.33	8096	100.00

  

<b>deadt</b>	<b>cvddeadt</b>	<b>lungcat</b>	<b>copddeadt</b>	<b>nexdeadt</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	4912	60.67	4912	60.67
<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	89	1.10	5001	61.77
<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	1424	17.59	6425	79.36
<b>1</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>1</b>	188	2.32	6613	81.68
<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	246	3.04	6859	84.72
<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>1</b>	1237	15.28	8096	100.00

**Harvard Six Cities Study Results: Comparison of Dockery 1993 & Lepeule 2012 & EPA Excel 2013 Preliminary**

James E. Enstrom, Ph.D., M.P.H. and Lingqi Tang, Ph.D.

October 10, 2013

Characteristic			Portage, WI	Topeka, KS	Watertown, MA	Harriman, TN	St Louis, MO	Steubenville, OH
City								
Participants 1974	Dockery T1		1631	1239	1336	1258	1296	1351
Participants 1974	Lepeule T1		1630	1238	1332	1258	1292	1346
Participants 1974	Excel		1630	1238	1332	1258	1292	1346
Person-years FU 1974-1988	Dockery T1		21618	16111	19882	17836	17715	17914
Person-years FU 1974-2009	Lepeule T1		43804	32877	36818	33067	32225	33276
Person-years FU 1974-2009	Excel		43804	32877	36818	33067	32225	33276
Deaths 1974-1988	Dockery T1		232	156	248	222	281	291
Deaths 1974-2009	Lepeule T1		796	617	700	733	827	822
Deaths 1989-2009	Excel		584	480	467	526	561	566
Deaths 1974-2009	Dockery T1 + Excel		816	636	715	748	842	857
Deaths / 1000 P-Y 1974-1988	Dockery T1		10.73	9.68	12.47	12.45	15.86	16.24
Deaths / 1000 P-Y 1974-2009	Lepeule		18.17	18.77	19.01	22.17	25.66	24.70
Deaths / 1000 P-Y 1989-2009	Excel		13.33	14.60	12.68	15.91	17.41	17.01
Crude Mortality Ratio 1974-1988	Dockery		1.00	0.902	1.162	1.160	1.478	1.514
Adjusted Mortality Ratio 1974-1988	Dockery T2		1.00	1.01	1.07	1.17	1.14	1.26
Ratio Adjusted MR / Crude MR 1974-1988 [= R]			1.000	1.119	0.921	1.009	0.771	0.832
Crude Mortality Ratio 1974-2009	Lepeule		1.00	1.033	1.046	1.220	1.412	1.359
"Adjusted" MR 1974-2009 = Crude MR * R			1.00	1.156	0.963	1.231	1.089	1.132
Crude Mortality Ratio 1989-2009	Excel		1.00	1.095	0.951	1.193	1.306	1.276
"Adjusted" MR 1989-2009 = Crude MR * R			1.00	1.226	0.876	1.204	1.007	1.062
Average Age (Years) 1974	Dockery T1		48.4	48.3	48.5	49.4	51.8	51.6
Fine Particles PM2.5 (ug/m3)	Dockery T1		11.0	12.5	14.9	20.8	19.0	29.6
Fine Particles PM2.5 (ug/m3)	Lepeule T1		11.4	12.2	14.0	19.1	16.7	23.6
Fine Particles PM2.5 (ug/m3)	Excel		11.3	12.3	14.1	19.4	16.9	23.9