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A Comparative Analysis of the Chronic Effects of Fine Particulate Matter

Sorina E. Eftim, Holly Janes, Aidan McDermott, Jonathan M. Samet, Francesca Dominici

Abstract

The American Cancer Society study (ACS) and the Harvard Six Cities study (SCS) are the two landmark cohort studies for estimating the chronic effects of fine particulate matter (PM_{2.5}) on mortality. To date, no comparative analysis of these studies has been carried out using a different study design, study period, data, and modeling approach. In this paper, we estimate the chronic effects of PM_{2.5} on mortality for the period 2000-2002 by using mortality data from Medicare and PM_{2.5} levels from the National Air Pollution Monitoring Network for the same counties included in the SCS and the ACS. We use a log-linear regression model which controls for individual-level risk factors (age and gender) and area-level covariates (education, income level, poverty and employment). We found that a 10 $\mu\text{g}/\text{m}^3$ increase in the yearly average PM_{2.5} is associated with 10.9% (95% CI: 9.0, 12.8) and with 20.8% (95% CI: 12.3, 30.0) increase in all-cause mortality by using Medicare data for the ACS and SCS counties. The results are similar to those reported by the original SCS and ACS indicating that fine particulate matter is still significantly associated with mortality when more recent air pollution and mortality data are used. Our findings suggest that national government based data, like the Medicare, are useful for advancing our understanding of the chronic effects of ambient air pollution on health.

Introduction

Several epidemiologic studies have provided evidence that longer term exposure to ambient fine particulate matter (PM_{2.5}) is associated with chronic health effects, including cardiovascular and respiratory diseases, and with death (Dockery et al., 1993; Pope et al., 1995, 2002; Krzyzanowski et al., 2002; Laden et al., 2006; Pope and Dockery, 2006). Chronic effects of air pollution potentially encompass cumulative effects of long-term exposures, and persistent effects of acute exposures (Kunzli et al., 2001; Rabl, 2003). Chronic effects of air pollution on human health have been estimated mainly using data from cohort studies.

Cohort studies compare across geographic locations longer term exposure to air pollution and time-to-death adjusted for individual-level risk factors such as age, gender, smoking and body mass index. The two landmark cohort studies, the Harvard Six Cities Study (SCS) (Dockery et al., 1993) and the American Cancer Society (ACS) Study (Pope et al., 1995) and their recent follow up (SCS II) (Laden et al., 2006) (SCS II) and (ACS II) (Pope et al., 2002, 2004) found a significant association between longer term exposure to PM_{2.5} and mortality after adjusting for individual-level risk factors and ecological covariates.

Cohort studies are generally expensive and time consuming because of the need to collect extensive information on individual-level risk factors and to analyze the results after a long follow up. Financial constraints and limited availability of monitoring stations constrain these studies further by including only a limited number of geographical areas.

To date no comparative analysis of the ACS and SCS has been carried using a different approach. Recently we have linked billing claims from Medicare with daily concentrations of PM_{2.5}, by county of residence of the Medicare enrollees, for the period 2000-2002 (Dominici et al., 2006). From this large data set, we have constructed two data sets that include

average exposure to $PM_{2.5}$, mortality, and county-level Census data for the same geographical locations included in the ACS and SCS. These two new data sets differ from the original ACS and SCS with respect to study design, study period, availability of individual and area-level confounders, and modeling approach (see Table 1). Therefore these Medicare data sets provide the opportunity to investigate whether the evidence on the longer term effects of $PM_{2.5}$ on mortality persists, regardless the above differences.

Materials and Methods

From the Medicare enrollment files we have constructed a cohort of roughly 40 million people with individual level information on age, gender and race, and county of residence for the period 2000-2002. First, we link the Medicare data to $PM_{2.5}$ air pollution monitoring data from the U.S EPA National Monitoring Network by county. Second, from this large data set, we have calculated the number of deaths and number of people at risk for the same geographical locations included in the ACS and SCS. We denote these new data sets by Med-ACS and Med-SCS, respectively.

Table 1 compares characteristics of the Medicare study on the chronic effects of $PM_{2.5}$ on mortality versus the ACS and SCS with respect to study design, geographical area, population age, exposure estimation, time scale of exposure and individual and area-level covariates. First, the ACS and SCS are closed to new enrollment, whereas in the Medicare new enrollments are included every month of the study period. Second, unlike the ACS and SCS, the Medicare study population includes only the elderly. Third, the Medicare study relies on measured and concurrent ambient concentrations of $PM_{2.5}$, whereas the ACS and SCS rely on past exposures to $PM_{2.5}$ which are generally estimated from PM_{10} ambient concentrations.

Finally, the ACS and SCS have more extensive information on individual-level risk factors than the Medicare study.

Table 2 summarizes the number of geographical locations, number of deaths and people at risks, average levels of $PM_{2.5}$, and exposure periods of the Med-ACS, ACS II, Med-SCS, and SCS II. For the Med-ACS, we identify the 110 counties corresponding to the the 50 metropolitan areas in the ACS (Pope et al., 1995). These are identified from the list of counties that includes the cities and towns that are within the metropolitan areas' boundaries (Krewski et al., 2000a). For the Med-SCS, we identify the counties that include the cities in the SCS (Dockery et al., 1993). The Med-ACS includes approximately 7.3 million people, while the Med-SCS included 340,000 adults respectively. For comparison, the baseline population sizes in the ACS II and SCS II were 400,000 and 8,000 respectively.

Figure 1 shows the location of the 6 and 110 counties included in the Med-SCS and Med-ACS, respectively. We estimate yearly county-specific averages of $PM_{2.5}$ using only time series data with measurements available for at least ten months per year and four days per month, for the years 2000-2002. Specifically, we compute the 10% trimmed mean of the monitor-specific $PM_{2.5}$ concentrations for each county (source based monitors were excluded) and then we average these concentrations across time.

For the ACS counties, $PM_{2.5}$ concentrations are not available for Chattanooga TN and Omaha NE. We assign to these counties the $PM_{2.5}$ data measured in the neighboring counties: McMinn Co. TN, and Polk Co. IO. For the SCS counties, $PM_{2.5}$ concentrations are not available Roane TN and Columbia WI, which include Harriman and Portage, respectively. We assign to these two counties the $PM_{2.5}$ data measured in the neighboring counties of Knox Co. TN and Dane Co. WI.

As indicators of area-level socioeconomic status (SES), we use: 1) the proportion of women

and men with a college degree or higher; 2) the proportion of women and men with high school degree or higher; 3) proportion of women and men who are unemployed; 4) proportion of individuals below the poverty level in each age-group; and 5) median income in the county, from the 2000 US Census. We select these covariates to maximize comparability with the ACS and SCS.

For each year, county of residence and age-gender stratum, we calculate the number of all-cause deaths and the number of people at risk (Table 2). We stratified the study population in 6 strata by gender and three age groups (65-75 years; 75-85; ≥ 85 years).

Let Y^{sc} and μ^{sc} be the observed and expected number of all cause deaths, and let N^{sc} be the number of people at risk in county c and age-gender stratum s . Let \bar{x}^c be the the average $PM_{2.5}$, for the 2000-2002 period. We fit the following log-linear regression model allowing for age-gender stratum specific intercept and including the SES factors \mathbf{z}^{sc} :

$$\log(\mu^{sc}) = \theta_0^s + \theta \bar{x}^c + \gamma \mathbf{z}^{sc} + \log(N^{sc}) \quad (1)$$

The parameter $10 \times \theta$ denotes the log relative risk of mortality associated with a $10 \mu g/m^3$ increase in longer term average $PM_{2.5}$ adjusted for socioeconomic factors. We fit model (1) to the Med-ACS and Med-SCS data, separately for each year and for all three years combined. Model (1) is fit by assuming a negative binomial variance structure parameterized as $Var(Y^{sc}) = \mu^{sc} + (\mu^{sc})^2/\nu$. We also compute the robust standard errors (Liang and Zeger, 1986), which account for residual autocorrelation in the county-specific mortality rates.

As a sensitivity analysis, we explore the impact of exposure period on the results, separately by year. To explore the sensitivity of the results to the exposure period, we regress county-specific average of $PM_{2.5}$ for the period 1999-2001 on mortality rates for the period 2000-2002.

Data manipulation and analyses are performed using R, version 2.2.1 (R Development Core Team, 2005) and the SAS software package, version 9.1 (SAS Institute Inc., 2000).

Results

Figure 2 shows the averages $PM_{2.5}$ used in the ACS (Pope et al., 1995) for the 1979-1983 period (Krewski et al., 2000b), plotted against the average $PM_{2.5}$ used in the Med-ACS for the 2000-2002 period. As expected, in most counties, average $PM_{2.5}$ was higher in the ACS study than in the Med-ACS. There is a good agreement among these measurements except for the noticeable outlier of Fresno, CA which experienced an increase in $PM_{2.5}$ concentrations (American Lung Association, 2004).

Figure 3 shows age and gender adjusted mortality rates plotted against average $PM_{2.5}$ over the 2000-2002 period for the 6 and 110 counties included in the Med-SCS and Med-ACS, respectively. These adjusted mortality rates are obtained by fitting model (1) without including $PM_{2.5}$ nor the SES covariates in the model.

Table 3 summarizes the results of our comparative analysis of Med-SCS and Med-ACS with the SCS and ACS, (Pope et al., 1995; Dockery et al., 1993), the reanalysis (Krewski et al., 2000c) and the follow up SCS II and ACS II (Laden et al., 2006; Pope et al., 2002). In the Med-SCS, we found that a $10\mu\text{g}/\text{m}^3$ increase in average $PM_{2.5}$ is associated with a 20.8% increase in the mortality rate (95% CI: 12.3, 30.0) adjusted for age and gender. In the Med-ACS, we found that a $10\mu\text{g}/\text{m}^3$ increase in average $PM_{2.5}$ is associated with a 10.8% increase in the mortality rate (95% CI: 8.9, 12.8), adjusted for age and gender. Without adjustment for area-level covariates, the Med-SCS and Med-ACS provide results similar to the ACS and SCS. In the Med-ACS, when we adjust for area-level covariates, we estimate

a 10.9% increase in the mortality rate (95% CI: 9.0, 12.8) which is slightly larger than the ACS results reported by the re-analysis team (Krewski et al., 2000c).

Table 4 summarizes the results of the Med-SCS and Med-ACS by year and for all years combined, with and without adjustment for area-level covariates. Results are similar across years and robust to adjustment with SES variables. Finally, in Table 5, we report results obtained by using as exposure the average $PM_{2.5}$ over the previous year. We find that the results are robust with respect to the time period over which $PM_{2.5}$ is averaged.

Discussion

We have conducted a comparative analysis on the chronic effects of $PM_{2.5}$ on mortality using Medicare and air pollution data for the same geographical locations included in the ACS and SCS. We use mortality data from the Medicare billing records and $PM_{2.5}$ concentrations from the EPA National Monitoring Network for the period 2000-2002 period. We adjust for individual-level covariates (age and gender) and area-level covariates (education, income, poverty level, employment).

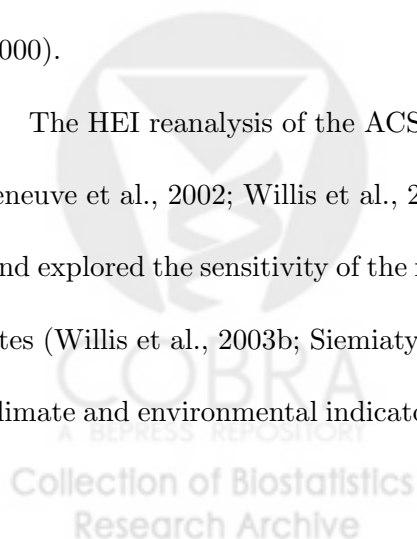
Although the Med-ACS and Med-SCS have a different cohort sampling design, study period, data, and analysis approach than ACS and SCS, our results were qualitatively similar to the findings from these landmark studies. This indicates that valid estimates of the chronic effects of $PM_{2.5}$ on mortality can be obtained from a cohort study based on a different sampling strategy, a large number of locations (50 versus 110 for the ACS) and the most recent $PM_{2.5}$ measurements available.

Without adjustment for area-level covariates, the Med-ACS found results that are almost identical to the ACS. In the Med-ACS we adjusted only for two individual-level covariates

(age and sex), compared to the larger set of individual-level factors considered in the original ACS (age, sex, cigarette smoking, BMI, alcohol consumption, education and occupational exposure). Perhaps fewer individual-level risks factors at baseline are enough for proper adjustment in an older population.

With adjustment for individual-level and area-level covariates, the Med-ACS found results that are slightly larger than reported in the ACS. Several factors might explain the difference. First, this difference could be attributed to aggregation bias resulting from the estimated ambient exposure. The Med-ACS uses smaller geographical areas (110 counties) than ACS (50 metropolitan areas). The Netherlands Cohort study (Hoek et al., 2002) found that risk estimate almost doubled when local sources of pollution were used versus community-wide concentration levels. Therefore chronic effects of $PM_{2.5}$ on mortality might be underestimated when using exposure aggregated at the larger metropolitan area-level (Pope and Dockery, 2006). Second, the study population in Med-ACS is older than the populations of ACS and SCS. The average age at enrollment in the ACS and SCS was 58.6 and 49.7 respectively (Krewski et al., 2003). The Medicare cohort comprises only people over 65 years of age, which is a more sensitive sub-population to the chronic effects of ambient $PM_{2.5}$ on health. Previous studies have shown that when pollution levels are high, senior citizens are more likely to be hospitalized for heart and lung problems, and some may die prematurely (Pope, 2000).

The HEI reanalysis of the ACS and SCS (Krewski et al., 2000c, 2003, 2005a,b, 2004; Villeneuve et al., 2002; Willis et al., 2003a) used the data provided by the original investigators and explored the sensitivity of the results to the adjustment for a large set of ecological covariates (Willis et al., 2003b; Siemiatycki et al., 2003) representing socioeconomic, demographic, climate and environmental indicators and to alternative modeling approaches (Cakmak et al.,



2003; Jerrett et al., 2003a,b). The re-analysis team replicated the original results and found that longer term exposure to $PM_{2.5}$ was modified by individual-level educational attainment (Krewski et al., 2000c; Willis et al., 2003b). Unfortunately because the Medicare data does not contain individual-level information on education, we were not able to verify this finding.

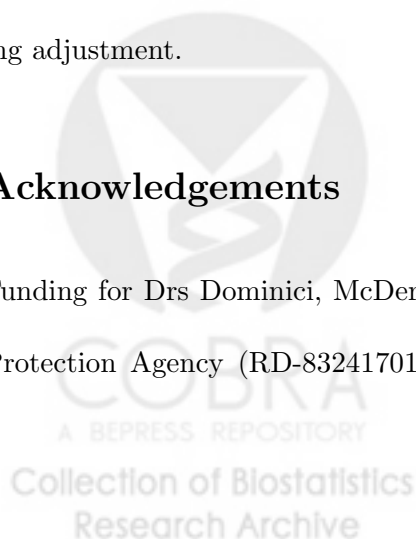
For the SCS data, the HEI reanalysis also investigated the impact of time-dependent risk factors on the risk estimates (Krewski et al., 2000c). The results were robust to the incorporation of time dependency in smoking, BMI and city-specific annual averages of $PM_{2.5}$ (Krewski et al., 2000c, 2003).

An important limitation of this analysis is the lack of adjustment for spatial correlated unmeasured confounders. This is an issue of primary concern in epidemiological studies that compare adjusted mortality rates and longer term air pollution exposure across different locations. The HEI reanalysis (Krewski et al., 2000c, 2003, 2005a,b, 2004) developed statistical methods for analyses of spatially correlated data aimed at minimizing the autocorrelation in the residuals (Jerrett et al., 2003a,b; Burnett et al., 2001; Ma et al., 2003). The original results were confirmed, but the confidence intervals were larger, suggesting that there was significant residual autocorrelation in the data.

The full Medicare cohort study will include $PM_{2.5}$ and mortality data for several hundred U.S. counties, thus increasing our ability to develop statistical methods for spatial confounding adjustment.

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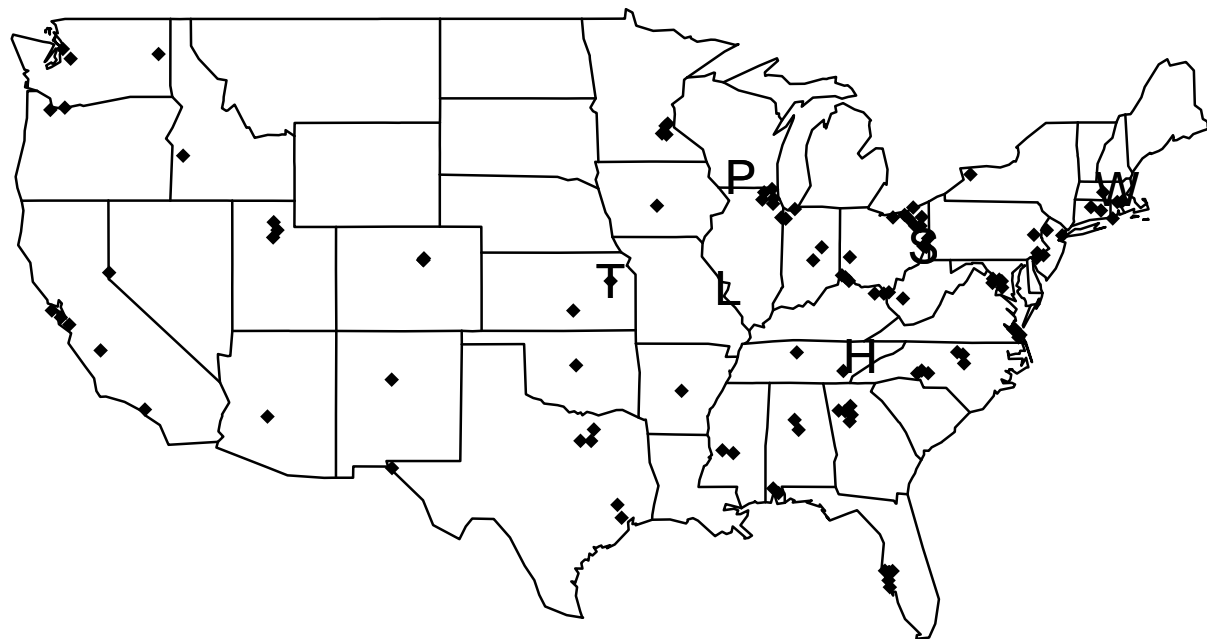


Figure 1: Locations of the counties included in the Med-ACS and Med-SCS. The diamonds represent the 110 locations included in the American Cancer Society study (Pope et al., 1995), and the letters represent the six cities included in the Six Cities Study (Dockery et al., 1993): Topeka KS (T), St. Louis MO (L), Steubenville OH (S), Watertown MA (W), Harriman TN (H), and Portage, WI (P).

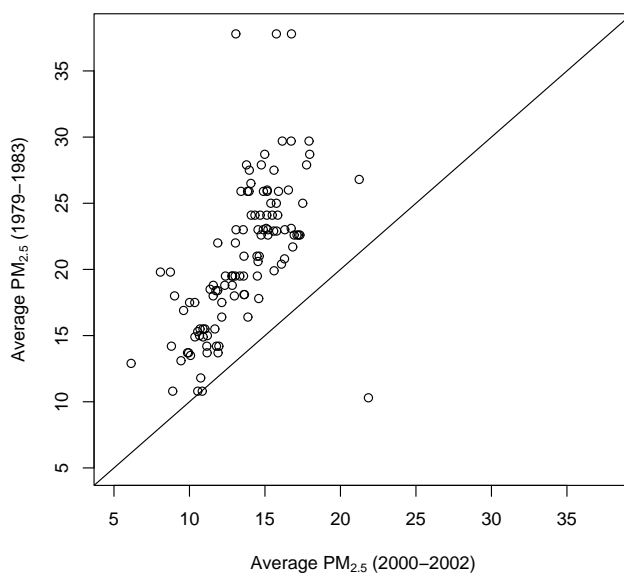


Figure 2: Average PM_{2.5} over the years 1979-1983 (Pope et al., 1995) versus average PM_{2.5} over the years 2000-2002, for 110 U.S. counties.

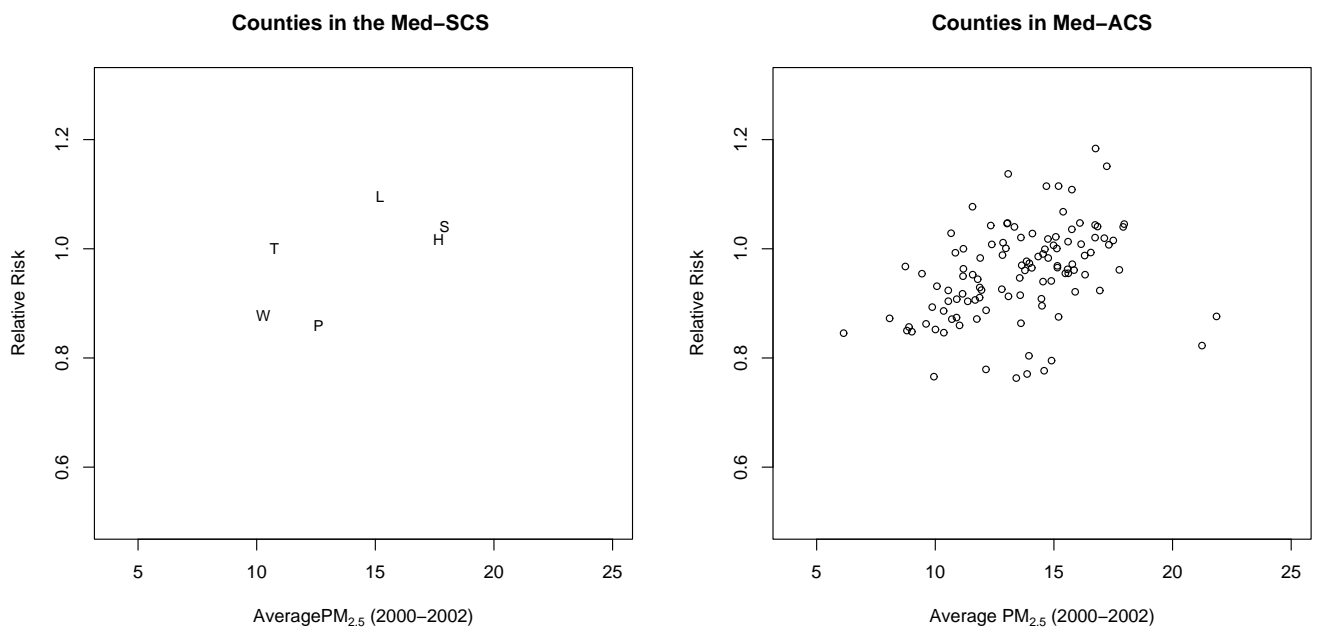


Figure 3: Adjusted mortality relative risk estimates plotted against average PM_{2.5} for the 6 Med-SCS and the 110 Med-ACS counties. T denotes Topeka, KS (the reference city for all plots); W Watertown, MA; L St. Louis, MO; S Steubenville, OH; H Harriman, Tennessee; P Portage, Wisconsin.

Table 1: Comparison of characteristics between the Medicare study versus the ACS and SCS.

	Medicare	ACS and SCS
Study design	open to enrollment	closed to enrollment
Geographical areas	counties	metropolitan areas
Population age	65 and older	25 and older
Exposure	measured PM _{2.5} only	measured PM _{2.5} and estimated PM _{2.5} from PM ₁₀
Time scale of exposure	concurrent with the study period	preceding and concurrent with the study period
Individual-level risk factors	age, gender	age, race, gender, education, smoking, and more
Statistical model	Log-linear regression	Cox proportional hazards regression



Table 2: Study characteristics for Med-ACS, ACS II (Pope et al., 2002), Med-SCS and SCS (Laden et al., 2006).

Characteristics	Med-ACS	ACS II	Med-SCS	SCS II
No. of counties	110 ^a	50 ^b	6 ^{b*}	6
No. of subjects ^c	7,333,040 ^c	295,223	341,099 ^c	8,096
No. of deaths ^d	1,12,311	62,000	54,160	2,732
Average PM _{2.5} , $\mu\text{g}/\text{m}^3$	13.6	17.7	14.1	16.4 ^e
(standard deviation)	(2.8)	(3.7)	(3.1)	(5.6) ^e
range	6.0 - 25.1	9 - 33.5	9.6 - 19.1	9 - 39.0 ^e
Study period	2000-2002	1982-1998	2000-2002	1974-1998
Period of measured exposure	2000-2002	1979-1983, 1999-2000	2000-2002	1979-1988

^a Counties identified by the Reanalysis team (Krewski et al., 2000a) as being within the 50 metropolitan areas included in the ACS (Dockery et al., 1993).

^b These are metropolitan areas.

^{b*} The six counties that include the six cities in the SCS.

^c The number of subject for the Med-ACS and Med-SCS datasets is the number of persons at risk in year 2000. For ACS II and SCS II, it is the number of persons enrolled at the beginning of the study period.

^d Total deaths occurred during the entire study period. For ACS II (Pope et al., 2002), the number of deaths is approximately triple the number of deaths in the original ACS (Pope et al., 1995).

^e Calculated based on Table 1 and Figure 1 from Laden et al. (2006).



Table 3: Comparison of results across studies: estimated % increase in mortality rate per $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ by chronic effects of $\text{PM}_{2.5}$ on mortality for exposure period 2000-2002.

Study	Primary source	Duration of measured exposure ($\text{PM}_{2.5}$)	% Change in mortality risk per $10\mu\text{g}/\text{m}^3$ increase in average $\text{PM}_{2.5}$
SCS ^a	(Dockery et al., 1993)	1979-1988	13.2 (4.2 - 23)
SCS ^b	(Krewski et al., 2000c)	1979-1988	16.6 (7.3 - 26.1)
SCS II ^a	(Laden et al., 2006)	1979-1988	16 (7 - 26)
Med-SCS ^b		2000-2002	20.8 (12.3- 30.0)
ACS ^c	(Pope et al., 1995)	1979-1983	6.6 (3.5 - 9.8)
ACS ^d	(Krewski et al., 2000c)	1979-1983	10.2 (7.0 - 13.7)
ACS ^e	(Krewski et al., 2000c)	1979-1983	7.4 (4.4 - 10.6)
ACS II ^f	(Pope et al., 2002)	1979-1983, 1999-2000	6.2 (1.6 - 11.0)
Med-ACS ^b		2000-2002	10.8 (8.9 - 12.8)
Med-ACS ^g		2000-2002	10.9 (9.0 - 12.8)

^aAdjusted for individual-level age, gender, cigarette smoking, BMI, education.

^b Adjusted for individual-level age and gender.

^cAdjusted for individual-level age, gender, cigarette smoking, BMI, education, race, alcohol consumption and occupational exposure.

^dAdjusted for individual-level age, race, and gender.

^eAdjusted for population change, income, poverty, income disparity, unemployment and education. See Table 47, Part II, (Krewski et al., 2000c).

^fAdjusted for age, gender, race, cigarette smoking, body-mass index, education, alcohol consumption, marital status, diet and occupational exposure.

^gAdjusted for individual-level age and gender, and for area-level education, income, poverty and employment.

Table 4: Estimated % increase in mortality rate per $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ by year and for exposure period 2000-2002.

Model	Years			
	Overall	2000	2001	2002
Med-ACS ^a	10.8 (8.9, 12.8)	10.9 (7.9, 14.0)	9.1 (5.8, 12.1)	10.1(6.3, 13.9)
Med-SCS ^a	20.8 (12.3, 30.0)	17.8 (6.2, 30.7)	16.5 (2.1, 29.0)	33.5 (16.0, 53.5)
Med-ACS ^b	10.9 (9.0, 12.8)	11.4 (8.4, 14.4)	8.7 (5.6, 11.6)	10.4 (6.9, 13.9)

^a Adjusted for individual-level age and gender.

^b Adjusted for individual-level age and gender, and for area-level education, income, poverty and employment.



Table 5: Estimated % increase in mortality rate per $10\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$. The exposure period is 1999-2001.

Model	Years			
	Overall	2000	2001	2002
Med-ACS ^a	9.5 (7.8, 11.3)	8.4 (5.7, 11.1)	8.9 (5.8, 11.6)	11.0 (7.4, 14.7)
Med-SCS ^a	17.9 (10.8, 25.4)	15.2(5.2, 26.2)	17.1 (4.8, 28.3)	21.9 (8.3, 37.1)
Med-ACS ^b	10.0 (8.2, 11.8)	9.3 (6.5, 12.2)	9.1 (6.1, 12.0)	11.2 (7.8, 14.7)

^a Adjusted for individual-level age and gender.

^b Adjusted for individual-level age and gender, and for area-level education, income, poverty and employment.