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Dear Dr. Enstrom,

I am sorry to inform you that your manuscript, "Fine Particulate Air Pollution and Total Mortality among Elderly Californians, 1980-98," has not been accepted for publication in the Journal. This decision was based not only on the reviewers' comments, but also on the editors' evaluation of the manuscript's focus, content, and interest to our diverse readership. While we found your work interesting, we feel it is more appropriate for a specialty journal.

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

Sincerely yours,

Jeffrey M. Drazen, M.D.
Editor-in-Chief

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spoke with Jeffrey Drazen: 11-12-04 2PM

Took reviewers I suggested under consideration & some of comments were from them.
NEJM editors made decision they do not want to deal with this issue (AP) anymore. No rejected on scientific criticisms primarily.
May consider Commentary after published elsewhere

Reviewer A

The authors find no association between fine particles and mortality in elderly Californians. The critical questions are, how does the strength of this evidence match that of the many other, mostly positive, studies, and if the findings here hold up, what are the reasons for the differences in results? Overall this study appears to be well done, but these questions are not adequately addressed and it is not clear how much it adds to present knowledge.

This study is rather weak (as noted by the authors) because of its ecologic design. Of course, most of the other studies are also weak, but not all of them. Additional problems here include:

The substantial number of subjects lost to follow-up
Insensitivity of changes in total mortality to changes in specific causes of death
Lack of match on time for the residence data, the air pollution data, and death, especially the lack of smoking status since 1972
Adjustment for confounders at the personal level, but not at the county level (which would be difficult)
The puzzling (to me) lack of negative interaction between ambient PM and the PM (and a lot of other junk) in tobacco smoke

The failure to demonstrate an effect of cigarette smoking (basically an interaction of ambient PM with the PM and other pollutants in tobacco smoke, see Table 4) is a bit unexpected, and may indicate an unidentified problem with the data. This should be further explored in the present text.

I was very glad to see the final two sentences of this paper, which have a lesson that needs to be more widely understood. However, I am not convinced that the differences among study results are entirely a result of differences among the cohorts. This should be either deleted or strengthened.

Reviewer B

REVIEW OF
"Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1980-1998

In page order.

1. The references have some glaring omissions, particularly EPA's final version of the Air Quality Criteria for Particulate Matter document (AQCD) released on October 28, 2004. However, this has been available to the public in draft form since July, 2004. To be sure, a draft report was "gray literature" then, but is now a published document as is the CARB report (ref. 13). The existence of the most recent drafts should have been acknowledged, as the AQCD is generally regarded as the most comprehensive and encyclopedic source of current information on particulate matter (PM) in the U.S. and probably in many other countries. Even if the authors disagree with many of the AQCD conclusions, omitting this reference is like failing to mention the elephant is a serious omission. Several other critical references are missing and were published well before this paper was submitted, notably Villeneuve et al. (2002) and Burnett et al. (2001c) in the AQCD.

2. In the last paragraph on page 3, the authors present a good case that all particles are not created equal, then lose this insight in subsequent analyses.
3. Page 4, line 3. Because these cohort data have individual outcomes and covariates but aggregate air pollution measurements, they might be more accurately characterized as semi-ecological studies (Kunzli et al.).
4. The statement on page 4 line "… one … study has not found fine particles associated with mortality … " is overly broad. Many epidemiologic studies have found short-term effects that are increasingly buttressed by toxicology evidence. There is less known about effects of long-term PM exposure in long-term experimental toxicology studies.
5. Plausible mechanisms for short-term effects are being published.
6. Page 5, 4 lines from bottom. Most of the decedents were probably elderly and no longer driving. Were the drivers' license searches current or historical as well?
7. Page 6, lines 2 and 3. Was any attempt made to obtain primary cause of death information from the California death file or the Social Security Death index? Other prospective cohort studies have found much higher mortality rates for lung cancer and cardiopulmonary diseases.
8. Page 6. I'm really concerned about the use of county-wide averages to characterize PM exposure. Some of these counties are very large, e.g. San Bernardino, Riverside, and San Diego which reaches the Arizona border. I'm concerned about the exposure measurement error issue, although of course other authors have had to do the same thing. The spatial scale of averaging may be important, see (Burnett et al., 2001c).
9. The Harvard Six City (H6C) and American (ACS) studies made use of "interaction" terms as well as stratification, which allows the PM metric to entered linearly or otherwise in the model, and qualitative measurements such as education level to be entered as coded factors. Were any such analyses done here? This approach allowed the reanalyses done by the Health Effects Institiute (HEI) investigators to determine that education level and smoking status were significant modifiers of PM effects with relatively few parameters to estimate.
10. Page 7. Here is where the authors' insights that different particles may have different toxicity could have been made more useful. The counties listed in Table 1 with the highest PM2.5 levels (Kern and Riverside) might be reasonably assumed to have mostly ground-up crustal material. For the counties with the lowest PM2.5 levels (Santa Barbara and Contra Costa) this seems less likely, and the possibility that (depending where the air monitors are located) more likely to have urban-source PM2.5 particles. Were any sensitivity analyses done to look at discriminating among counties with likely fine/coarse or urban/crustal sources?
11. Table 2 is topsy-turvy from every similar table I've seen of this sort. I'm not an epidemiologist, but I believe most epidemiologists would have used the county with the lowest PM2.5 level as the baseline (Santa Barbara in this list, at 10.6) and the county that has almost always been identified as a potential urban source problem, Los Angeles (3rd highest at 28.2) as the upper baseline for determining an increment suitable for dirty-vs.-clean city comparisons, 28.2 - 10.6 = 17.6 mcg/cu.m, pretty similar to the H6C and ACS increments. Likewise, instead of a RR relative to L.A., most of the RRs in the Table (15/24) would be greater than 1 and some rather far above 1, even if non-significant, relative to Santa Barbara. This suggests that a population-weighted or standard-error-weighted meta-analyses might have found a positive effect. Worth trying, if only to compare with other studies.
12. On the other analyses, a surrogate indicator of the general health of the county (as opposed to the cohort) might be a useful covariate in a semi-ecological study, e.g. county-wide total mortality or by-cause mortality.
13. Table 5: Why isn't the largest cohort study, the ACS study, listed here?
14. Time-varying covariates can be used in PHREG models, see (Villeneuve et al. 2002.)

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Dear Dr. Enstrom:

Thank you for submitting your manuscript, "Fine Particulate Air Pollution and Total Mortality among Elderly Californians, 1980-98," to the New England Journal of Medicine.

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Jeffrey M. Drazen, M.D.
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The NEW ENGLAND JOURNAL of MEDICINE

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Title:
FINE PARTICULATE AIR POLLUTION AND TOTAL MORTALITY AMONG ELDERLY CALIFORNIANS, 1980-98

Authors:

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

2 Dr. Frederick W Lipfert Ph.D.

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Sources of Funding for This Study:

All analyses presented in this manuscript have been funded by EPRI. The entire funding history of the underlying data used for the analyses has been described in detail in my prior publications (see references 20 and 21).

Manuscript Words	2800
Number of References	24
Number of Tables	5
Number of Figures	0

Abstract:

BACKGROUND Fine particulate air pollution has been associated with significant long-term mortality effects, but this epidemiologic evidence is still controversial because of methodological issues, lack of support from toxicology studies and some epidemiology studies, and lack of a plausible causal mechanism. METHODS The long-term relation between fine particulate air pollution and total mortality was evaluated in a cohort of 30,977 elderly Californians defined in 1959 and 1972 and followed through 1998. Exposure to fine particles (PM2.5, median diameter <2.5 um) was estimated from sample outdoor ambient concentrations measured in 11 counties during 1979-84. Proportional hazards regression was used to determine the relative risk of death (RR) and 95% confidence interval (CI) during 1980-98 among cohort members as a function of PM2.5 level. Also, RRs by county of residence were calculated for 43,209 cohort members in 25 California counties. RESULTS After controlling for age, sex, and eight confounding variables, all RRs by county of residence were statistically the same. Subjects in the highest-PM2.5 counties had no greater risk of death than those in the lowest-PM2.5 counties. The overall relationship was RR = 1.00 (0.98-1.02) per 10 ug/m3 increase in PM2.5, before or after adjusting for confounding variables. The RRs varied somewhat among subgroups defined by sex, age, education, smoking status, and health status, but none was statistically different from 1.0. CONCLUSIONS These epidemiologic results do not support a causal relationship between fine particulate pollution and total mortality in elderly Californians, but they do not rule out a small effect.

Dear Editor:

Dr. Fred W. Lipfert and I are submitting a manuscript entitled "Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1980-98." We feel this manuscript should be given serious consideration because the New England Journal of Medicine has published two other important papers on fine particulate air pollution and mortality (references 4 and 5), as well as the September 9, 2004 paper on air pollution and lung development and the January 8, 2004 perspective on air pollution and federal regulations by Dr. Robert Steinbrook ("Peer Review and Federal Regulations"). Our epidemiologic study involves one of largest cohorts ever examined with respect to fine particulate air pollution and long-term mortality. It deals with a susceptible population of elderly Californians, who have lived in a state that is very concerned about air pollution. Furthermore, the relative risks in this study are more precise (have smaller 95% confidence intervals) than those in than any previous cohort study. The cohort is well defined and relatively few subjects have been lost to follow-up. If you decide to send our manuscript out for review, I assume that it will be treated as a strictly confidential document by the reviewers. If this is not the case, I would like to know your current review policy before you send out the manuscript. Because our findings may be considered controversial by some, we hope that you will select reviewers who have not taken a strong position on air pollution and mortality and who can provide an objective evaluation. We would like you to consider using the experienced reviewers suggested below, each of whom has expertise in air pollution epidemiology. In the spirit of the Data Quality Act, discussed in Dr. Steinbrook's perspective, we would be willing to work out a way to have our underlying data independently examined and analyzed, if this is deemed necessary by the reviewers in order to confirm the accuracy of our findings. Thank you very much for your consideration.

Sincerely yours,
James Enstrom, Ph.D., M.P.H.

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FINE PARTICULATE AIR POLLUTION AND TOTAL MORTALITY AMONG ELDERLY CALIFORNIANS, 1980-98

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ABSTRACT

Background Fine particulate air pollution has been associated with significant long-term mortality effects, but this epidemiologic evidence is still controversial because of methodological issues, lack of support from toxicology studies and some epidemiology studies, and lack of a plausible causal mechanism.

Methods The long-term relation between fine particulate air pollution and total mortality was evaluated in a cohort of 30,977 elderly Californians defined in 1959 and 1972 and followed through 1998. Exposure to fine particles ($PM_{2.5}$, median diameter <2.5 μm) was estimated from sample outdoor ambient concentrations measured in 11 counties during 1979-84. Proportional hazards regression was used to determine the relative risk of death (RR) and 95% confidence interval (CI) during 1980-98 among cohort members as a function of $PM_{2.5}$ level. Also, RRs by county of residence were calculated for 43,209 cohort members in 25 California counties.

Results After controlling for age, sex, and eight confounding variables, all RRs by county of residence were statistically the same. Subjects in the highest-$PM_{2.5}$ counties had no greater risk of death than those in the lowest-$PM_{2.5}$ counties. The overall relationship was RR = 1.00 (0.98-1.02) per 10 $\mu g/m^3$ increase in $PM_{2.5}$, before or after adjusting for confounding variables. The RRs varied somewhat among subgroups defined by sex, age, education, smoking status, and health status, but none was statistically different from 1.0.

Conclusions These epidemiologic results do not support a causal relationship between fine particulate pollution and total mortality in elderly Californians, but they do not rule out a small effect.

Keywords: epidemiology, air pollution, fine particles, mortality, California

Word count: ~2,800

101104

FINE PARTICULATE AIR POLLUTION AND TOTAL MORTALITY AMONG ELDERLY CALIFORNIANS, 1980-98

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ABSTRACT

Background Selected epidemiologic evidence shows significant mortality effects associated with long-term fine particulate air pollution. These findings have lead to stricter air quality regulations but are still controversial because of methodological issues, lack of support from toxicology studies and some epidemiology studies, and lack of a pausible causal mechanism.

Methods This is an epidemiologic evaluation of the long-term relation between fine particulate air pollution and total mortality among a cohort of 30,977 elderly Californians defined in 1959 and 1972. Sample measurements of outdoor ambient concentrations of fine particles ($PM_{2.5}$, median diameter < 2.5 μm) were made in 11 counties during 1979-84. Proportional hazards regression was used to determine the relative risk of death (RR) and 95% confidence interval (CI) during 1980-98 among cohort members as a function of $PM_{2.5}$ level. Also, RRs by county of residence were calculated for 43,209 cohort members in 25 California counties, with Los Angeles serving as the baseline county.

Results After controlling for age, sex, and eight confounding variables, all RRs by county of residence were statistically the same. Subjects in the highest-$PM_{2.5}$ counties had no greater risk of death than those in the lowest-$PM_{2.5}$ counties. The overall relationship, RR = 1.00 (0.98-1.02) per 10 $\mu g/m^3$ increase in $PM_{2.5}$, was similar before or after adjusting for eight confounding variables. The RRs varied somewhat among subgroups defined by sex, age, education, smoking status, and health status at entry, but none was statistically different from 1.0.

Conclusions These results do not support a causal relationship between fine particulate pollution and total mortality in elderly Californians, but they do not rule out a small effect of up to 2% increase in risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$. These results support the concept that no single cohort can adequately represent the entire United States and that local data should be used to estimate local effects.

Keywords: epidemiology, air pollution, fine particles, mortality, California

Word count: ~2,800

INTRODUCTION

Many observational epidemiological studies have reported associations between air pollution from combustion sources and human health (1). During past severe air pollution events, such as the 1952 London fog incident (2), extremely high concentrations of particulate air pollution were accompanied by major increases in coincident (acute) mortality. In more recent years, health effects have also been associated with much lower concentrations of particulate air pollution (3). While most recent research has focused on short-term exposures (4), several studies suggest that long-term exposures may be more important. In particular, prospective studies of two cohorts (5-7) have shown significantly stronger mortality associations with outdoor concentrations of fine particles ($PM_{2.5}$, median aerodynamic diameters less than 2.5 microns). Other cohort studies have found significant mortality associations with air pollutants other than $PM_{2.5}$ (8-11).

These and other studies have led to new national ambient air quality standards for fine particles (12), as well as to stricter California standards (13). These standards are specific with respect to particle size, but not with respect to chemical composition. All particles measured by the approved methods are considered equally toxic. Fine particles are generated mainly by combustion processes and their atmospheric sequellae. However, the chemical composition of airborne particulate matter varies appreciably across the nation and within metropolitan areas. $PM_{2.5}$ is thus a variable mixture, rather than a defined chemical compound as in the case of gaseous air pollutants.

The associations of low-level air pollution with mortality remain controversial, in part because the epidemiologic studies that have examined these health effects are subject to the methodological limitations of ecological studies (1,14-18). Actual exposures to air pollution are difficult to determine accurately in large cohorts. Indeed, the exposure of each individual has not been directly measured in cohort studies but has usually been defined by ambient outdoor concentrations in the county or metropolitan area of residence. Also, one major national study has not found fine particles associated with mortality (9,11) and experimental evidence does not support an association (15). Most importantly, it is etiologically unclear how fine particles cause respiratory or cardiovascular diseases because there is no plausible mechanism (14,15).

California is a large, diverse state that has long been concerned about the health effects of air pollution and that has recently issued new stricter ambient standards (13). However, no previous cohort study has focused on mortality with respect to measured $PM_{2.5}$ in California, although one small study used atmospheric visibility as a surrogate measure of fine particles in selected California areas (19). Here, we have used a large cohort of elderly Californians to examine long-term relationships between mortality from all causes during 1980-98 and $PM_{2.5}$ measured during 1979-84.

METHODS

The California Cancer Prevention Study (CA CPS I) is the extended follow-up of the 118,094 California subjects from the original Cancer Prevention Study (CPS I) of 1,078,894 adults from 25 states. CPS I was initiated by the American Cancer Society (ACS) beginning in

1959 and CA CPS I has been independently conducted at the University of California, Los Angeles (UCLA) since 1991, as described in detail elsewhere (20,21). The subjects in this prospective cohort study were enrolled from October 1959 through February 1960 using a detailed four-page questionnaire. Surviving cohort members completed short questionnaires in 1961, 1963, 1965, and 1972, and a two-page questionnaire in 1999. Deaths through 1972 were identified primarily by surviving study subjects and were confirmed with death certificates. The later deaths were identified at UCLA primarily from computerized and manual matches with the California death file and the nationwide Social Security Death Index, using name and other identifying variables (20,21). The CPS I cohort has only once before been used to assess the relationship between air pollution and mortality and this assessment was limited to lung cancer during the 1960s (22).

This paper focuses on the subjects in the 25 counties with the largest number of CA CPS I subjects who reported their cigarette smoking status in both the 1959 and 1972 questionnaires and were alive as of January 1, 1980. There were a total of 43,209 traceable subjects alive as of January 1, 1980 in these counties, of whom 28,551 died as of December 31, 1998. An additional 4,006 subjects lost as of December 31, 1998 have been omitted from further analysis. Of these subjects, there were 30,977 traceable subjects alive as of January 1, 1980 in the 11 counties with $PM_{2.5}$ data, of whom 20,396 died as of December 31, 1998. Most of the surviving subjects had their 1999 address determined from a match with California driver's license (DL) identifying information and 33% of them responded to a two-page smoking and lifestyle questionnaire that was mailed in mid 1999 to their DL address (20,21). Based on the questionnaire information in late 1959 and late 1972, and 1999 DL address information, and the death information, the county of residence and county of death was determined for most subjects as of late 1959, late 1972, and early 1999. About 86% of the deaths were identified on the California death file and the remainder were identified on the Social Security Death Index.

The independent air quality variable in this analysis was $PM_{2.5}$, as measured during 1979-84 in 11 California counties (23,24). These data were averaged over time and across the available monitoring stations in each county and have the same source as those used the recent national cohort study (7). No routinely measured $PM_{2.5}$ data exist before 1979 and routine statewide measurements were not resumed until 1999. The average county-level $PM_{2.5}$ value was assigned to the traceable subjects alive as of January 1, 1980 based on their county of residence as of late 1972. This analysis was based on the deaths from January 1, 1980 until December 31, 1998. This period essentially encompasses that of the $PM_{2.5}$ data and is roughly the same as that used in the recent national cohort study (7).

The age-adjusted relative risk of death (RR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression, specifically the SAS PHREG procedure (21), including age at baseline in 1 year intervals and sex, as a function of fine particulate level in units of 10 $\mu g/m^3$. The "fully-adjusted" relative risks were calculated using a model that includes age, sex, and eight potential confounding variables at baseline: race (white, nonwhite), education level (<12, 12, >12 years), cigarette smoking status (never, former, 1-9, 10-19, 20, 21-39, 40+ cigarettes per day), exercise (none/slight, moderate, heavy), body mass index (<20, 20-23, 23-26, 26-30, >30 kg/m2), male occupational exposure (no, yes), marital status (married, widowed, single, separated, divorced), and fruit/fruit juice intake (0,1,2,3,4,5,6,7 days/week). One

additional variable, health status at entry (good, fair, poor, ill, sick/CA/CHD/stroke), was evaluated as a sensitivity analysis. The confounding variables are defined at entry into study in late 1959, except for cigarette smoking status, which was updated in late 1972.

Subgroup analysis was done by sex, year of birth, education level, cigarette smoking status, health status, and education level, as well as by residential mobility and follow-up subperiod (1980-89, 1990-98). Finally, the relative mortality rates by county of residence were calculated as an alternative method to assess the influence of the varying pollution levels, similar to the method used in the Harvard Six Cities Study (5). The Los Angeles county subjects are used as the referent in estimating the fully adjusted 1980-98 RRs for each of the other 24 counties. Subject-weighted correlations between the 1979-84 $PM_{2.5}$ values and the fully adjusted RRs were computed for the 11 counties with $PM_{2.5}$ data. The residential mobility of subjects was assessed by calculating the percentage of subjects who lived or died in the same county from late 1972 to 1999.

RESULTS

Table 1 shows the late 1959 demographic and lifestyle characteristics (confounding variables) of the CA CPS I subjects (12,794 males and 18,183 females) in the 11 counties with 1979-84 $PM_{2.5}$ data (mean = 23.4 $\mu g/m^3$). Table 1 also shows the same characteristics for the subjects in the two counties (Kern and Riverside) with the highest $PM_{2.5}$ levels (mean = 36.1 $\mu g/m^3$) and in the two counties (Contra Costa and Santa Barbara) with the lowest $PM_{2.5}$ levels (mean = 13.1 $\mu g/m^3$). The average characteristics are quite similar, irrespective of the mean pollution levels. The mean age of the subjects alive as of 1/1/1980 was 70.5 years for males and 69.8 years for females.

Table 2 shows the 1980-98 mortality risks relative to Los Angeles County, adjusted for eight confounding variables, for the 25 counties with the most CA CPS I subjects, including the 11 counties with 1979-84 $PM_{2.5}$ data. While some variation is seen, all of the risks are statistically consistent with RR=0.990, the weighted average for all 25 counties combined. A homogeneity test yields Woolf's statistic $\chi 2$=22.5 for 24 degrees of freedom (p=0.489) and confirms that the RRs are statistically equal. The two counties with highest $PM_{2.5}$ levels (Kern and Riverside) had an RR of 0.943 (0.890-0.999), whereas the two counties with the lowest $PM_{2.5}$ levels (Contra Costa and Santa Barbara) had an RR of 1.013 (0.954-1.077). The weighted correlation between 1979-84 $PM_{2.5}$ and the 1980-98 RRs was an insignificant r=-0.148 (p=0.5). This means that during 1980-98 the CA CPS I subjects had similar death rates throughout the state that were independent of the $PM_{2.5}$ levels, which varied by a factor of 4 (10.6 to 42.0 $\mu g/m^3$). These results indicate no relationship between $PM_{2.5}$ and total mortality. Based on their counties of residence and counties of death, about 66% of the subjects remained in the same county from late 1972 to 1999, indicating relative stability of residence.

Table 3 shows the relationship of 1980-98 mortality to 1979-84 $PM_{2.5}$ concentrations, calculated by Cox proportional hazards regression, based on an increase in long-term mean ambient concentration of 10 $\mu g/m^3$. The RR (95% CI) is shown to three decimal places in order to facilitate accurate comparisons with other estimates based on $PM_{2.5}$ (7,9). The age-adjusted RRs and the fully adjusted RRs were both consistent with 1.0 for males, females, and both sexes

Although the effects in this study are quite small and none are statistically significant, they suggest slightly higher risks from $PM_{2.5}$ for younger subjects, for females, for better-educated subjects, for never- smokers, and for those who were healthy at enrollment. All of these trends run counter to the findings from daily mortality studies that emphasize the frailty of affected individuals (1,3,4), but they are consistent with the finding of non-significant and negative associations between $PM_{2.5}$ and long-term male mortality in the Veterans' Study (9,11). Further, the finding of slightly weaker effects during 1990-98 compared with 1980-89 is consistent with the temporal trend in the Veterans Study. The net impression is one of competing risks, such that long-term air pollution effects may be apparent only when more important risk factors are absent. The RRs reported in this study and their relatively small confidence intervals suggest that any long-term risks of all-cause mortality associated with $PM_{2.5}$ in California are similar to those seen in studies of associations with daily mortality, but smaller than those reported in long-term studies of other cohorts (5-7).

Failure to find a suspected effect in an epidemiological study may be because the effect does not actually exist or because the study was incapable of detecting it. In general, the requirements for statistical significance include a sufficient number of observations, accurate measurements, and an adequate range of values of the independent variable of interest (here, ambient $PM_{2.5}$). The range of $PM_{2.5}$ values (31 $\mu g/m^3$) in this study is greater than the range (20 $\mu g/m^3$) in the largest cohort study (7), although the data are from the same database. Part of the range difference is due to the use of counties in the present analysis, as opposed to entire metropolitan areas in ACS CPS II (7).

In addition, there may be questions as to the basis for estimating actual exposures to $PM_{2.5}$, even though $PM_{2.5}$ often has a large regional component and is known to penetrate structures relatively efficiently. The assumption that individual exposures, especially those of decedents, are the same as group averages, given here by a few centrally-located monitors, is known as the "ecological fallacy" and can lead to incorrect conclusions in extreme cases (18). However, it is impractical to adequately monitor individual exposures, especially over the long-term. Here, we use the smallest practical geographic unit (counties), given typical mobility of subjects, in hopes of minimizing any such exposure errors. There are also questions about the timing of exposures in a long-term study (9); we consider deaths up to 20 years after exposure. However, these results do not suggest stronger effects of cumulative exposures, nor do any of those summarized in Table 5.

Within the paradigm of present ambient air quality standards, which do not recognize chemical differences in $PM_{2.5}$ sampled at various locations, the substantial differences in findings shown in Table 5 must relate to differences in the cohorts *per se,* rather than to the relative statistical powers of the studies. It thus follows that no single cohort can adequately represent the entire United States and that local data should be used to estimate local effects. As the largest and most detailed examination of the long-term relationship between $PM_{2.5}$ and total mortality in elderly Californians, this study presents valuable new local data.

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Table 1. Demographic and lifestyle characteristics in 1959 for California CPS I subjects who resided as of 1972 in the 11 counties having 1979-84 $PM_{2.5}$ measurements, provided 1972 cigarette smoking status, and were alive as of 1/1/1980.

Characteristic	Males			Females		
	1959 value (11 $PM_{2.5}$ counties)	1959 value (2 highest $PM_{2.5}$ counties)	1959 value (2 lowest $PM_{2.5}$ counties)	1959 value (11 $PM_{2.5}$ counties)	1959 value (2 highest $PM_{2.5}$ counties)	1959 value (2 lowest $PM_{2.5}$ counties)
Mean level of 1979-84 $PM_{2.5}$ ($\mu g/m^3$)	23.4	36.1	13.1	23.4	36.1	13.1
Number of subjects alive or lost as of 1/1/1980	13,542	831	889	20,315	1,333	1,216
Lost to follow-up during 1980-98 (%)	5.5	3.9	6.1	10.5	10.8	11.7
Number of subjects alive 1/1/1980 and not lost during 1980-98	12,794	799	835	18,183	1,189	1,074
Age as of 1/1/80 (mean in years)	70.5	71.5	69.5	69.8	71.1	68.8
Race (% white)	98.3	98.7	97.6	98.2	99.2	97.7
Marital status (% married)	97.5	97.9	98.2	85.2	83.7	88.6
Education (% $\geq$ 12 years)	73.9	75.1	79.8	77.7	78.5	83.4
Height (mean in inches)	69.5	69.6	69.9	63.8	63.8	64.0
Weight (mean in pounds)	173.3	173.1	174.7	136.9	138.0	135.3
History of serious diseases (% yes)	8.1	10.1	6.8	8.7	9.8	8.6
Cancer	4.2	5.4	3.6	5.3	6.7	5.5
Heart Disease	3.4	3.7	2.9	3.0	2.7	2.6
Stroke	0.5	1.0	0.3	0.4	0.4	0.5
Sick at the present time (% yes)	6.7	6.0	4.7	8.0	7.7	5.8
Occupation (% professional)	11.0	13.2	9.7	15.5	21.6	15.5
Residence location (% urban)	98.1	99.4	98.8	97.8	99.0	98.1
Exercise (% moderate or heavy)	72.5	78.0	78.0	80.1	83.8	83.6
Cigarette smoking (% current in 1959)	40.6	38.8	44.0	32.6	29.0	39.7
Cigarette smoking (% current in 1972)	22.6	24.3	24.9	23.0	19.7	28.5
Fruit/fruit juices (7+ times/week)	63.4	59.5	64.3	73.8	75.8	74.1

Table 2. Fully-adjusted relative risk of death from all causes (RR and 95% CI) by county of residence relative to Los Angeles county, during 1980-98 for both sexes, for the 25 counties with the most subjects, based on 10/1/1972 county of residence. Levels of 1979-84 $PM_{2.5}$ for 11 counties and correlations with RRs are shown.

County of residence as of 10/1/1972	1980-98 deaths/subjects	% alive or dead same co in 1999	8 variable-adjusted 1980-98 RR(95% CI)	1979-84 $PM_{2.5}$ µg/m3
Alameda	2,442/3,760	60.7	0.982 (0.939-1.027)	14.4
Butte	339/460	73.1	0.988 (0.883-1.104)	15.5
L Contra Costa**	902/1,451	60.1	1.013 (0.945-1.085)	13.9
H Fresno	606/948	80.0	0.950 (0.874-1.032)	18.4
Humboldt	304/432	79.3	1.005 (0.895-1.129)	
H Kern*	449/687	79.5	0.949 (0.862-1.045)	30.9
Marin	447/696	57.2	0.928 (0.843-1.022)	
Napa	361/544	73.4	1.020 (0.918-1.135)	
Orange	1,743/2,595	65.1	1.002 (0.952-1.055)	
H Riverside*	906/1,301	59.6	0.940 (0.877-1.007)	42.0
L Sacramento	989/1,494	77.2	0.997 (0.933-1.065)	
San Bernardino	965/1,400	63.5	0.994 (0.930-1.063)	
San Diego	2,161/3,124	84.4	1.021 (0.974-1.070)	18.9
San Francisco	1,173/1,805	48.3	0.993 (0.934-1.056)	16.4
San Joaquin	180/288	71.9	0.912 (0.783-1.061)	
L San Mateo	1,031/1,589	58.0	0.965 (0.904-1.030)	
L Santa Barbara**	302/458	67.4	1.015 (0.903-1.140)	10.6
Santa Clara	1,301/2,004	63.5	0.950 (0.896-1.007)	17.8
Santa Cruz	204/319	64.7	0.863 (0.748-0.995)	
Solano	284/438	59.8	0.902 (0.799-1.017)	
L Sonoma	319/471	75.7	0.917 (0.819-1.026)	
Stanislaus	401/600	83.7	1.010 (0.912-1.119)	
H Tulare	632/937	78.7	1.031 (0.950-1.119)	
Ventura	295/429	69.1	1.083 (0.962-1.218)	
H Los Angeles	9,815/14,979	64.4	1.000	28.2
Two highest exposure counties*		66.5	0.943 (0.890-0.999)	36.1
Two lowest exposure counties**		61.9	1.013 (0.954-1.077)	13.1
Weighted mean (1979-84 $PM_{2.5}$ counties)			0.992	23.5
Weighted mean (all 25 counties)			0.990	
Weighted correlation (1979-84 $PM_{2.5}$ versus RR without LA county)				-0.530
Weighted correlation (1979-84 $PM_{2.5}$ versus RR with LA county)				-0.148

1999 L ≤ 14.0
H ≥ 19.4

Table 3. Relative risk of death from all causes (RR and 95% CI) associated with change of 10 µg/m3 in 1979-84 $PM_{2.5}$, based on 10/1/1972 county of residence. Subgroups defined by sex, year of birth, education level, health status as of 10/1/1959; by cigarette smoking status as of 10/1/1972; by follow-up period; and by subjects living in the same county as of 10/1/1972 and 10/1/1959.

Subgroups	Deaths/subjects	Model: Age-adjusted RR (95% CI)	Model: 8 variable-adjusted RR (95% CI)
County of residence in 1972		Follow-up period 1980-98	
All subjects	20,396/30,977	0.995 (0.976-1.014)	0.998 (0.979-1.017)
All males	9,507/12,794	0.986 (0.959-1.014)	0.984 (0.957-1.013)
All females	10,889/18,183	1.004 (0.978-1.030)	1.012 (0.986-1.039)
Born 1910-1929	7,397/15,791	1.020 (0.988-1.054)	1.025 (0.992-1.059)
Born 1885-1909	12,999/15,186	0.982 (0.959-1.005)	0.983 (0.960-1.007)
<12 years educ	5,707/7,348	0.991 (0.957-1.028)	0.988 (0.952-1.025)
12 years educ	4,571/7,651	0.994 (0.955-1.034)	0.994 (0.955-1.035)
>12 years educ	10,027/15,857	0.995 (0.969-1.023)	1.005 (0.978-1.033)
Never smoker	8,288/13,374	1.012 (0.983-1.042)	1.009 (0.979-1.040)
Former smoker	7,061/10,525	0.991 (0.960-1.024)	0.992 (0.960-1.026)
Current smoker	5,047/7,078	0.992 (0.955-1.030)	0.989 (0.951-1.027)
Healthy	15,945/24,795	0.994 (0.973-1.015)	0.997 (0.976-1.019)
Unhealthy	3,882/5,397	0.971 (0.930-1.015)	0.980 (0.938-1.025)
		Follow-up period: 1980-89	
All subjects	11,121/30,977	0.996 (0.971-1.022)	1.002 (0.976-1.028)
		Follow-up period: 1990-98	
All subjects	9,275/19,856	0.993 (0.966-1.021)	0.992 (0.964-1.021)
Same county of residence in 1972 and 1959		Follow-up period: 1980-98	
All subjects	19,234/29,228	0.999 (0.979-1.019)	1.004 (0.984-1.025)

Table 4. Relative risk of death from all causes (RR and 95% CI) associated with change of 10 µg/m3 in 1979-84 $PM_{2.5}$, for 30,977 subjects based on 10/1/1972 county of residence. Age, sex, and eight confounding variables are added to the proportional hazards regression model one variable at a time. * = age-sex adjusted RR; ** = 8-variable adjusted RR.

Cumulative PHREG model based on adding one variable at a time	1980-98 Chi-square	1980-98 deaths/subjects	RR (95% CI)
1979-84 PM2.5	0.77	20,396/30,977	1.018 (0.998-1.037)
+ age	10,010.34	20,396/30,977	0.993 (0.975-1.012)
+ sex	309.50	20,396/30,977	0.995 (0.976-1.014)*
+ race	0.16	20,396/30,977	0.995 (0.976-1.014)
+ cigarette smoking	1,319.59	20,396/30,977	1.000 (0.981-1.019)
+ education	41.77	20,305/30,856	0.998 (0.980-1.017)
+ martial status	15.68	20,199/30,709	0.998 (0.979-1.017)
+ body mass index	184.46	20,199/30,709	0.997 (0.979-1.016)
+ occupational exposure	3.97	20,179/30,684	0.997 (0.979-1.016)
+ exercise	2.26	19,951/30,344	0.997 (0.978-1.016)
+ fruit/fruit juice intake	26.28	19,541/29,808	0.998 (0.979-1.017)**
+ health status	81.25	19,024/29,089	0.993 (0.974-1.013)

Table 5. Relative risk (RR) and 95% confidence interval (CI) for long-term all cause mortality per 10 µg/m3 increase in $PM_{2.5}$, for major US cohort studies involving data circa 1980. * indicates that values were recalculated from published data.

Cohort (year, reference)	PM2.5 data period	PM2.5 mean (range) (µg/m3)	Subjects Number	Subjects Mean age	Subjects Follow-up period	RR (95% CI)
Males						
Six Cities 1993 (5)	1979-88	19 (11-30)	3,671	~50	1975-89	1.15 (1.02-1.30)*
US CPS II 1995 (6)	1979-81	18 (9-34)	~128,743	57	1982-88	1.07 (1.03-1.11)*
CA AHSMOG 2000 (19)	1973-77	32 (17-45)	1,347	58	1976-92	1.09 (0.98-1.21)*
US Veterans 2000 (9)	1979-81	24 (6-42)	26,067	51	1982-88	0.90 (0.85-1.05)
US CPS II 2002 (7)	1979-83	21 (10-30)	~157,000	57	1982-98	1.05 (1.01-1.10)
CA CPS I 2004	1979-84	24 (11-42)	12,794	70	1980-98	0.98 (0.96-1.01)
Females						
Six Cities 1993 (5)	1979-88	19 (11-30)	4,440	~50	1975-89	1.12 (0.96-1.30)*
US CPS II 1995 (6)	1979-81	18 (9-34)	~166,480	57	1982-88	1.06 (1.01-1.12)*
CA AHSMOG 2000 (19)	1973-77	32 (17-45)	2,422	58	1976-92	~1.00*
US CPS II 2002 (7)	1979-83	21 (10-30)	~202,000	57	1982-98	1.02 (0.98-1.06)
CA CPS I 2004	1979-84	24 (11-42)	18,183	70	1980-98	1.01 (0.99-1.04)
Both Sexes						
Six Cities 1993 (5)	1979-88	19 (11-30)	8,111	~50	1975-89	1.13 (1.04-1.23)*
US CPS II 1995 (6)	1979-81	18 (9-34)	295,223	57	1982-88	1.07 (1.04-1.10)*
US CPS II 2002 (7)	1979-83	21 (10-30)	~359,000	57	1982-98	1.04 (1.01-1.08)
CA CPS I 2004	1979-84	24 (11-42)	30,977	70	1980-98	1.00 (0.98-1.02)