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# Response to "A Critique of 'Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1973–2002'" By Bert Brunekreef, PhD, and Gerard Hoek, PhD

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I agree with Drs. Brunekreef and Hoek that new studies of the health effects of fine particulates are very important (Brunekreef & Hoek, 2006). They have raised a number of important issues regarding the findings in my article on the relationship between $PM_{2.5}$ and mortality in elderly Californians (Enstrom, 2005). I have addressed their issues by clarifying my published findings and by providing additional results.

## RISK FACTOR CHANGES

The California Cancer Prevention Study (CA CPS I) does involve very long-term follow-up (Enstrom, 2005). The risk factor changes in the cohort during follow-up are addressed in detail in Tables 1 and 2 with data from the original 1959 enrollment survey and the 1999 follow-up survey of survivors. Of the eight confounding variables analyzed, three (race, education, and prior occupation exposure) cannot change, three (body mass index, exercise, and fruit/fruit juice intake) changed only slightly, and one (marital status) changed substantially as expected from married to widowed. The eighth variable (cigarette smoking) changed dramatically due to cessation. However, much of the cessation occurred between 1959 and 1972, and only 23% of the subjects were still smoking when mortality follow-up began in 1973. Cessation continued among all subjects, and only 3% of the surviving respondents were smoking in 1999. Furthermore, the risk factor patterns and changes were similar in all the counties. This is documented in Tables 1 and 2, which compare risk factors in the 2 highest $PM_{2.5}$ counties, the 2 lowest $PM_{2.5}$ counties, and in all 11 counties.

Thus, there is no reason to expect confounding factors or changes in them to have a substantial influence in this cohort. Indeed, the analyses in Tables 5–7 show that adjustment for the confounding variables had little impact on the relative risk of death (RR) and 95% confidence interval (CI). For the subjects as a whole, full adjustment for confounders changed the age-sex-adjusted RRs by at most 1.5%. For never smokers and former smokers as separate subgroups, smoking status did not change after 1972 and full adjustment changed the age-sex-adjusted RRs by at most 0.1%. No control for environmental tobacco smoke (ETS) was necessary because a separate study showed that ETS was not related to mortality among the never smokers in this cohort (Enstrom & Kabat, 2003). Given these considerations, confounding variables have not biased or obscured the relationship between $PM_{2.5}$ and mortality in this cohort to any substantial extent.

## $PM_{2.5}$ EXPOSURE ASSESSMENT

The $PM_{2.5}$ exposure assessment is a major limitation of this study, as it is with other cohort studies (Pope et al., 1995, 2002) that have relied upon the same U.S. EPA Inhalable Particulate Network (IPN) data. This limitation was clearly identified and discussed in the article and the specific details about the $PM_{2.5}$ measurements can be found in the comprehensive U.S. EPA reports (Hinton et al., 1984, 1986). The 15 monitoring sites described in Appendix Table 1 were selected based on a number of criteria and may not have yielded results that were representative of the entire county in which they were located. The selection criteria included U.S. EPA Office of Air Quality Planning and Standards (OAQPS) recommendation, Regional EPA Office concurrence, local agency approval, and land owner permission (Hinton et al., 1984).

Substantial differences were found in the county values for 1979–1983 $PM_{2.5,}$ which ranged from 10.6 to 42.0 $\mu g/m^3$. The lowest levels were found in Santa Barbara, Contra Costa, and Alameda counties, and the highest levels were found in Riverside, Kern, and Los Angeles counties. There are no $PM_{2.5}$ data before 1979 or during 1984–1998 equivalent to the

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TABLE A
Fine particulate ($PM_{2.5}$) levels ($\mu$g/m$^3$) from the 1979–1983 Inhalable Particulate Network (IPN) and 1999–2001 Aerometric Information Retrieval System (AIRS) of the U.S. EPA for the 11 California counties with 1979–1983 data

| | $PM_{2.5}$ ($\mu$g/m$^3$) | | |
|---|---|---|---|
| California county | 1979–1983 | 1999–2001 | Average 1979–1983/ 1999–2001 |
| Santa Barbara | 10.6 | 10.7 | 10.65 |
| Contra Costa | 13.9 | 14.0 | 13.95 |
| Alameda | 14.4 | 14.4 | 14.4 |
| Butte | 15.5 | 15.4 | 15.45 |
| San Francisco | 16.4 | 15.4 | 15.9 |
| Santa Clara | 17.8 | 17.0 | 17.4 |
| Fresno | 18.4 | 20.2 | 19.3 |
| San Diego | 18.9 | 15.2 | 17.05 |
| Los Angeles | 28.2 | 20.4 | 24.3 |
| Kern | 30.9 | 19.4 | 25.15 |
| Riverside | 42.0 | 21.1 | 31.55 |

1979–1983 data. Regular monitoring was resumed in 1999, and extensive $PM_{2.5}$ data are available from the U.S. EPA Aerometric Information Retrieval System (AIRS) and the California Air Resources Board database.

Table A presents the 1979–1983 and 1999–2001 $PM_{2.5}$ values for the 11 counties with 1979–1983 data, along with the average of the 2 sets of data. Note that there is a high correlation between these sets of measurements. Also, the 1999–2001 $PM_{2.5}$ values, which only ranged from 10.7 to 21.1 $\mu$g/m$^3$, do not materially alter the relative $PM_{2.5}$ ranking of the counties established in 1979–1983. Ideally there should be much more monitoring data in order to establish truly representative $PM_{2.5}$ levels by county over the entire 1973–2002 period. However, in spite of their limitations, the existing data have yielded a relative $PM_{2.5}$ ranking of 11 counties that agrees with what is known from several sources about the air pollution conditions in these counties.

Table B shows that RRs based on the average of the 1979–1983 and 1999–2001 $PM_{2.5}$ values for all subjects and for never smokers do not differ substantially from the RRs based on 1979–1983 $PM_{2.5}$. The most etiologically plausible findings for all subjects in Table B are the fully adjusted 1973–1982 RR of 1.039 (1.010–1.069) based on 1979–1983 $PM_{2.5}$ data and the fully adjusted 1983–2002 RR of 0.995 (0.968–1.024) based on 1979–1983/1999–2001 $PM_{2.5}$ data. Note that the 1983–2002 RRs are all essentially the same and consistent with the null RR (1.00), whether based on 1979–1983 or 1979–1983/1999–2001 $PM_{2.5}$ data. Furthermore, Table 5 shows that the RRs were very similar during both 1983–1992 and 1993–2002. Thus, use of “a more reliable average” of $PM_{2.5}$ does not change the results during 1983–2002 in any significant way and does not substantiate the concern about “possible misclassification arising from the paucity of monitoring data.”

## RESIDENTIAL STABILITY

Data on residential stability are an added feature of this cohort and indicate that the majority of the subjects remained in the same county from 1972 to 1999. Of particular note is the fact that

TABLE B
Age-adjusted and fully adjusted relative risk of death from all causes (RR and 95% CI) during 1973–2002, 1973–1982, and 1983–2002 associated with change of 10 $\mu$g/m$^3$ in 1979–1983 $PM_{2.5}$ and 1979–1983/1999–2001 $PM_{2.5}$ for all 35,783 California CPS I subjects, for the 33,745 subjects who lived in the same county in 1959 and 1972, and for all 15,181 never smokers

| | 1979–1983 $PM_{2.5}$ | | 1979–1983/1999–2001 $PM_{2.5}$ | |
|---|---|---|---|---|
| Subgroups | Age-sex-adjusted RR(95% CI) | Fully adjusted RR(95% CI) | Age-sex-adjusted RR(95% CI) | Fully adjusted RR(95% CI) |
| All 35,783 subjects | | | | |
| 1/1/1973–12/31/2002 | 1.005 (0.989–1.021) | 1.010 (0.994–1.026) | 1.007 (0.983–1.031) | 1.015 (0.992–1.040) |
| 1/1/1973–12/31/1982 | 1.032 (1.003–1.062) | 1.039 (1.010–1.069) | 1.049 (1.005–1.094) | 1.061 (1.017–1.106) |
| 1/1/1983–12/31/2002 | 0.992 (0.973–1.011) | 0.997 (0.978–1.016) | 0.988 (0.960–1.016) | 0.995 (0.968–1.024) |
| 33,745 subjects who lived in the same county in 1959 and 1972 | | | | |
| 1/1/1973–12/31/2002 | 1.008 (0.991–1.025) | 1.015 (0.998–1.032) | 1.010 (0.985–1.035) | 1.021 (0.996–1.047) |
| 1/1/1973–12/31/1982 | 1.030 (0.999–1.061) | 1.040 (1.009–1.072) | 1.045 (0.999–1.092) | 1.060 (1.014–1.109) |
| 1/1/1983–12/31/2002 | 0.998 (0.978–1.019) | 1.004 (0.984–1.025) | 0.994 (0.965–1.025) | 1.005 (0.975–1.036) |
| All 15,181 never smokers | | | | |
| 1/1/1973–12/31/2002 | 1.020 (0.995–1.045) | 1.019 (0.994–1.044) | 1.031 (0.994–1.070) | 1.029 (0.991–1.068) |
| 1/1/1973–12/31/1982 | 1.038 (0.993–1.086) | 1.038 (0.992–1.085) | 1.059 (0.990–1.133) | 1.056 (0.987–1.130) |
| 1/1/1983–12/31/2002 | 1.011 (0.982–1.042) | 1.011 (0.981–1.041) | 1.019 (0.975–1.065) | 1.017 (0.973–1.063) |

stability was similar in the two highest $PM_{2.5}$ counties (66%), the two lowest $PM_{2.5}$ counties (62%), and in Los Angeles County (64%). Based on estimated mobility patterns between 1972 and 1999, almost 90% of subjects lived in the same county as of 1/1/1983 as they did in late 1972. The degree of stability is high enough to establish that the subjects as a whole in the high $PM_{2.5}$ counties had more exposure to $PM_{2.5}$ than the subjects as a whole in the low $PM_{2.5}$ counties. Given the long-term $PM_{2.5}$ exposure patterns shown in Table A and the relative residential stability shown in Table 3, exposure misclassification did not obscure the relationship between $PM_{2.5}$ and mortality in this cohort to a large extent. Another indication that exposure misclassification did not have a major impact on the results is the relatively small 95% confidence intervals associated with the RRs in Table B and in Tables 5–7. These are the smallest confidence intervals seen in among the major cohort studies summarized in Table 10. This made it possible to detect a small positive relationship during the first decade of follow-up that was no longer present as of the second decade of follow-up.

It is not possible to do a proper follow-up analysis of subjects who remained in the same county, because it is not known specifically when or why individual subjects moved from their 1972 county of residence. The county of residence was only determined at enrollment in 1959, at the time of 1972 follow-up, at the time of 1999 follow-up, and/or at the time of death. The 33,745 subjects who lived in the same county in both 1959 and 1972 remained in the same county from 1972 and 1999 to a somewhat greater extent than all 35,783 subjects. Table B shows that the RRs for the more stable subgroup of 1959–1972 nonmovers is similar to the RRs for all subjects.

## LIFE TABLE ANALYSIS

To get another perspective on the various RRs presented in this study, which are dependent upon the validity of proportional hazards regression, key results are presented in Table C based on life table survival analysis (Anderson, 1999; California DHS, 1998). This is a completely independent method of analysis and is quite appropriate for determining mortality patterns in long-term follow-up studies. Remaining life expectancy from age 55 was calculated by the abridged life table method based on the deaths and person-years of observation by attained age that occurred from 1/1/1973 to 12/31/2002. In addition, the annual age-adjusted death rate (55+ yr) standardized to the 2000 U.S. population was calculated based on the 5-yr age-specific death rates that were used in the calculation of remaining life expectancy.

Note that over the 30-yr follow-up period there is no significant difference in remaining life expectancy or in age-adjusted death rate as a function of county of residence, including the highest and lowest $PM_{2.5}$ counties. These results are adjusted only for age and sex, but, based on the small influence of confounders on the proportional hazards regression results, adjustment for confounders would change them only slightly. The results in Table C are based on the same five groups of $PM_{2.5}$ counties that were used in Table 4. Each of these groups contains a sufficient number of subjects and deaths to make possible stable abridged life table calculations and age-specific death rates. The Table C results are the same for each county group, within the limits of statistical fluctuation.

While Table C shows small differences by county of residence, Table D shows large differences by 1972 cigarette smoking status based on life table analysis. There is a 7.5-yr difference in life expectancy and a twofold difference in age-adjusted death rate between never smokers and heavy smokers. The life table results in Tables C and D are consistent with the proportional hazard regression results in Tables 4 and 9. They conclusively show that cigarette smoking is a very strong risk factor in this cohort, while air pollution is a very weak risk factor. This

TABLE C
Remaining life expectancy in years from age 55 and annual age-adjusted total death rate standardized to 2000 U.S. population for ages 55+ yr, by county of residence during 1973–2002, by sex, for the 35,789 California CPS I subjects in rank order of $PM_{2.5}$ level for groups of the 11 counties with 1979–1983 $PM_{2.5}$ data

| | Remaining life expectancy from age 55 | | | Age-adjusted total death rate (55+ yr) | | |
|---|---|---|---|---|---|---|
| County of residence as of 10/1/1972 | Males | Females | Both sexes (average) | Males | Females | Both sexes (average) |
| Two lowest exposure counties (Contra Costa and Santa Barbara) | 23.44 | 29.16 | 26.30 | 0.04201 | 0.02459 | 0.03330 |
| Next lowest exposure counties (Alameda, Butte, San Francisco) | 23.79 | 28.63 | 26.21 | 0.04047 | 0.02553 | 0.03300 |
| Medium exposure counties (Fresno, San Diego, Santa Clara) | 23.90 | 28.38 | 26.14 | 0.04001 | 0.02575 | 0.03288 |
| Reference county (Los Angeles) | 23.87 | 28.11 | 25.99 | 0.04010 | 0.02659 | 0.03335 |
| Two highest exposure counties (Kern and Riverside) | 23.67 | 28.65 | 26.16 | 0.04037 | 0.02523 | 0.03280 |
| Total 11 counties | 23.82 | 28.36 | 26.09 | 0.04027 | 0.02600 | 0.03313 |

TABLE D
Remaining life expectancy in years from age 55 and annual age-adjusted total death rate standardized to 2000 U.S. population for ages 55+ yr, based on follow-up during 1973–2002 by sex for the 35,789 California CPS I subjects by 1972 cigarette smoking status

| Cigarette smoking status as of 10/1/1972 | Remaining life expectancy from age 55 | | | Age-adjusted total death rate (55+ yr) | | |
|---|---|---|---|---|---|---|
| | Males | Females | Both sexes (average) | Males | Females | Both sexes (average) |
| Never as of 1959 and 1972 | 26.60 | 29.98 | 28.29 | 0.03161 | 0.02229 | 0.02695 |
| Former (as of 1959 and 1972) | 25.85 | 29.87 | 27.86 | 0.03390 | 0.02239 | 0.02814 |
| Former (as of 1972 only) | 23.72 | 28.14 | 25.93 | 0.04125 | 0.02634 | 0.03380 |
| Current (1–19 cigs/day as of 1972) | 22.79 | 27.12 | 24.96 | 0.04561 | 0.03072 | 0.03817 |
| Current (20 cigs/day as of 1972) | 20.29 | 24.33 | 22.31 | 0.05622 | 0.03934 | 0.04778 |
| Current (21+ cigs/day as of 1972) | 19.19 | 22.02 | 20.61 | 0.06430 | 0.04797 | 0.05614 |
| Total CA CPS I subjects | 23.82 | 28.36 | 26.09 | 0.04027 | 0.02600 | 0.03313 |
| 1990 California population | 23.32 | 27.51 | 25.42 | | | |

*Note*. Cigs, cigarettes.

contrast is also consistent with the results of sensitivity analysis for the proportional hazards regression model in Table 8, where the 1973–2002 chi-square was much greater for cigarette smoking (1610.59) than for 1979–1983 $PM_{2.5}$ (0.68). In addition, Table 9 shows that the relationship between cigarette smoking and mortality was just as strong during 1983–2002 as it was during 1973–1982.

Regarding the representativeness of the CA CPS I cohort, note that the remaining life expectancy from age 55 for the cohort as a whole (23.82 yr for males and 28.36 yr for females) is close to that of the 1990 California population (23.32 years for males and 27.51 years for females) (California DHS, 1998). Thus, the CA CPS I cohort has overall mortality patterns that are fairly similar to those of the entire California population aged 55 yr and older.

When evaluating the relationship between $PM_{2.5}$ and mortality in my study, one must look at the totality of the evidence presented. The RRs based on county of residence, the RRs based on $PM_{2.5}$ level, the remaining life expectancy by county of residence, and the age-adjusted death rate by county of residence are all consistent with no significant relationship between $PM_{2.5}$ level and mortality in the CA CPS I cohort over the full 30-yr follow-up period. To the extent that there is a relationship, it is concentrated in the first decade of follow-up. There is no suggestion of a relationship during the second and third decades of follow-up. However, because of the uncertainties and statistical fluctuations in the data analysis, these results do not rule out a small effect of $PM_{2.5}$on total mortality.

## COMPARISON WITH OTHER STUDIES

There is extensive epidemiologic evidence regarding $PM_{2.5}$ and total mortality in California, including some recently published findings in the Los Angeles basin (Jerrett et al., 2005), but a review of all this evidence is beyond the scope of this response. Also, most of this evidence cannot be directly compared to my findings because it is based on different methodology, different segments of the California population, different definition of the population unit, and/or different $PM_{2.5}$ data. Given these substantial differences, it is not surprising that some of the results differ from mine. However, as noted in my article, the findings of the CA CPS I study appear to be consistent with the comparable California findings of the American Cancer Society CPS II study during 1982–1989, as shown in the Health Effects Institute Special Report (Krewski et al., 2000). The CPS II results, shown in Figure A, indicate that there was no clear relationship between $PM_{2.5}$ levels and mortality risk in California during 1982–1989 (p. 197 of Krewski et al., 2000).

Southern California is designated as an area of "Medium Fine Particulate Levels and Medium Mortality." The part of Central California near Fresno is designated as an area of "Low Fine Particulate Levels and Low Mortality." The rest of California is designated as "Low Fine Particulate Levels and Medium Mortality." Obviously, it is necessary to know the details of the California portion of the CPS II analysis before a precise comparision can be made. The authors of the original CPS II cohort analyses (Pope et al., 1995, 2002) could produce results equivalent to those in my article by using the same 1979–1983 $PM_{2.5}$ data for the same 11 counties. Based on the results that are published in my study and in Figure A, the relationship between $PM_{2.5}$ and mortality in California since 1982 appears to be very weak. Also, Figure A, indicates that there is substantial geographic variation in the relationship between $PM_{2.5}$ and mortality throughout the United States.

## SUMMARY

The long-term effects of fine particulates on mortality are difficult to determine because these small effects are near the limit of detectability by epidemiologic methods. The most reliable findings are obtained by applying appropriate epidemiologic methods to the analysis of available cohorts, keeping in mind the limitations of both the methods and the underlying data. I appreciate the opportunity that Drs. Brunekreef and

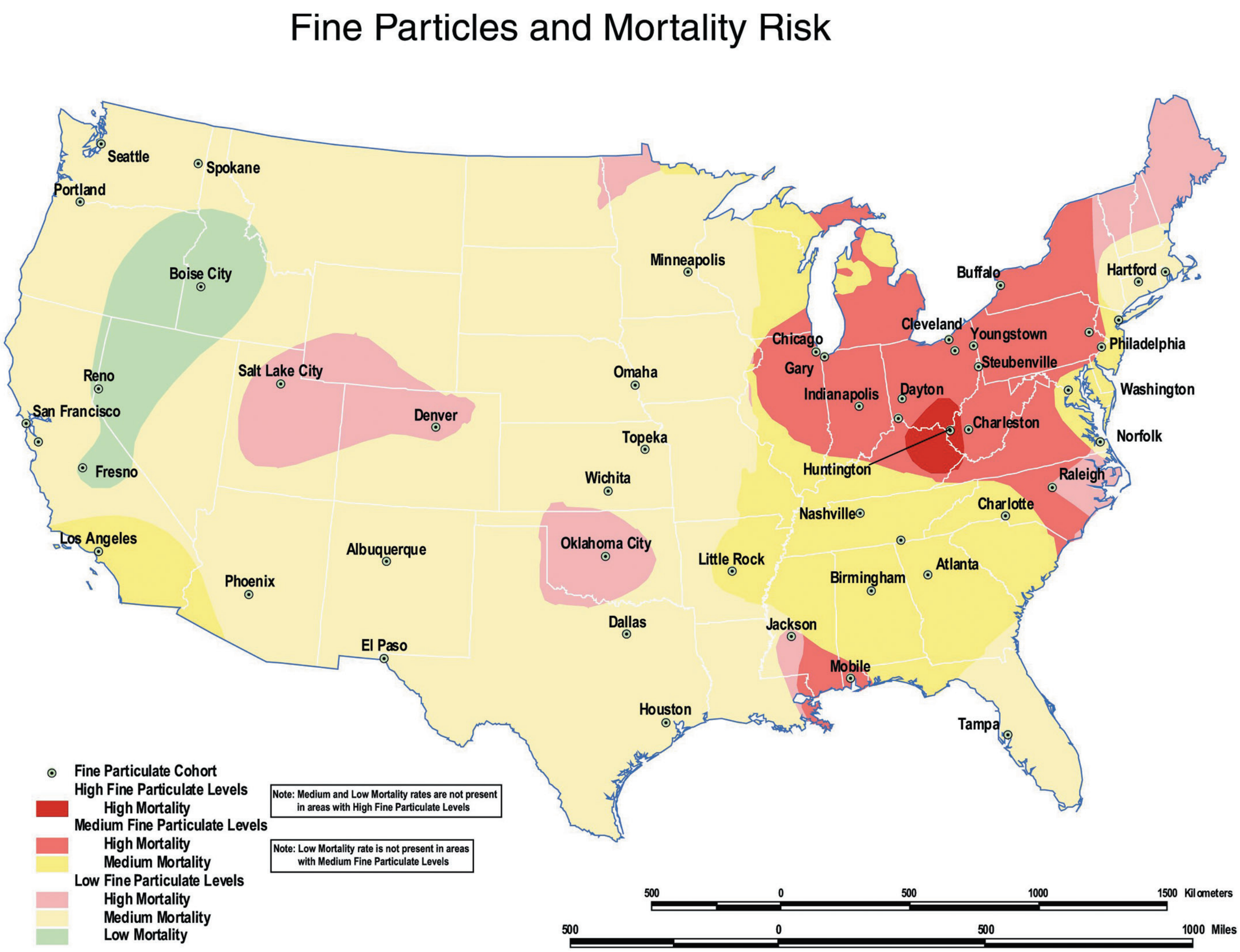


FIG. A. Spatial overlay of fine particle levels and relative risk of mortality. Interval classifications for fine particles (in $\mu g/m^3$): low 8.99–17.03; medium 17.03–25.07; high 25.07–33. Interval classifications for relative risks of mortality: low 0.502–0.711; medium 0.711–0.919; high 0.919–1.128. Reprinted from Figure 21 of Krewski et al., 2000, with permission.

Hoek have given me to elucidate and expand upon my published findings.

I have shown that my published findings are robust with respect to the several issues they have raised. (1) The confounding factors and temporal changes in them did not impact the findings in any major way. (2) My analyses utilized the available 1979–1983 $PM_{2.5}$ data in ways similar to those in other major cohort studies. When these analyses were augmented with 1999–2001 $PM_{2.5}$ data, there was no substantive difference in the results. The temporal trends in $PM_{2.5}$ levels in California from 1979 to 2001 preserved the relative exposure differences at the county level. (3) New results for those subjects who resided in the same county in 1959 and 1972 were the same as the published results for all subjects defined by their 1972 county of residence. (4) The results of a particular analysis depend upon the cohort studied, the methods of analysis used, and the monitoring data available. When these factors differ, differences can legitimately exist among study results.

This study is important because it uses reliable, county-level $PM_{2.5}$ data to analyze the large, well-defined, and relatively stable CA CPS I cohort, which has been successfully followed from 1959 through 2002. This study has sufficient statistical power to detect a weak relationship between $PM_{2.5}$ and total mortality, and the resulting RRs have the smallest 95% confidence intervals of any published cohort study. Several different methods of analysis have yielded similar results for this cohort during 1973–2002. These extensive analyses do not support a current relationship between fine particulate pollution and total mortality in elderly Californians, but they do not rule out a small effect, particularly before 1983. Given the relative strengths of this study within the realm of published epidemiologic evidence, these results are highly relevant to the relationship between $PM_{2.5}$ and mortality.

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