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A Critique of "Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1973–2002" by James E. Enstrom, PhD

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In view of the societal importance of the health effects of fine particulates, new studies on the subject are very important. In a previous issue of *Inhalation Toxicology*, Dr. Enstrom presents findings from a long-term follow-up of the ACS I cohort in California, suggesting that there was a slight effect of fine particulate matter (PM) on total mortality over the first 10 yr of follow-up (1973–1982), but none thereafter (1983–2002) (Enstrom, 2005).

A few issues are worth raising as they may help in fuller understanding of the findings.

One is the very long follow-up period. Baseline data on this cohort were obtained in 1959, and only data on smoking were reassessed in 1972. This means that for the later follow-up period (1983–2002), adjustment was based on data obtained 24–43 yr before death for all other variables except smoking, and 11–30 yr for smoking. It is likely that significant changes in smoking as well as diet and other risk factors have occurred over this period, which may have obscured any relationship with air pollution. The data show that smoking especially declined dramatically, and without detailed insight as to when this happened over time in the cohort, inaccuracies in assessment of smoking can easily obscure relationships with less important exposures such as air pollution. Adjustment for exposure to environmental tobacco smoke was absent in this study.

Another issue is exposure assessment. PM2.5 was assigned on the basis of data from just a few monitoring sites and on the basis of sometimes very few measurements: Of 15 monitoring sites in 11 counties, 8 provided less than 100 daily measurements. No discussion was provided as to representativeness of sites; it is surprising that Kern County, for instance, with measurements from Chester Avenue in Bakersfield, ranked higher than Los Angeles (LA). The possible misclassification arising from the paucity of monitoring data is only partially recognized in the discussion; the limitation also applies to analyses of the ASCS II cohort in so far as based on data from the late 1970s and early 1980s only (Pope et al., 1995), but the ACS II follow-up has also utilized new monitoring data from the late 1990s so that a more reliable average could be calculated (Pope et al., 2002). These data must have been accessible to Dr. Enstrom; but they were not used, for reasons that remain unclear.

Residential stability between 1972 and 1999 was 66% but varied from only 48% in San Francisco to 84% in Stanislaus County. There was no mention of an analysis restricted to those who had the same county of residence in 1972 and at death, and the added misclassification due to residential mobility is likely again to have attenuated the association between air pollution and mortality.

In this study, about half of the subjects came from LA County, most other counties only providing a few thousand subjects. Interestingly, a recently published analysis of differences in PM2.5 exposure within the LA Basin (largely LA, Riverside, Orange, and San Bernardino counties) for the ACS II population found a much stronger relationship between PM2.5 and survival than the nationwide ACS II study, and much stronger than the ACS II California results from the HEI reanalysis quoted by Dr. Enstrom (Jerrett et al., 2005). This was attributed by the authors to the much smaller extent of exposure misclassification they were able to achieve with their detailed spatial interpolation techniques. It is quite likely that similarly large spatial differences in PM2.5 exposure occurred in the ACS I cohort as well, as the period of observation between the two was largely the same (1980s and 1990s). This must mean that the current analysis is likely, and heavily, attenuated by PM2.5 exposure misclassification.

It is interesting that over the first 10 yr of follow-up, despite these problems, a significant association between PM2.5 and mortality was found, with the fully adjusted effect estimate of 1.039 per 10 $\mu g/m^3$ PM2.5 not being different from the ACS II estimate of 1.04. The effect estimate was even higher (1.064) for

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the younger part of the cohort, which was closer in birth dates to the ACS II cohort although still somewhat older. An interesting feature of this study is the much smaller effect among the elderly part of the cohort, born between 1873 and 1909. It is of interest to note that some studies found very important cohort effects in effect estimates for active smoking among subjects born in roughly similar time periods, such as the British Doctors cohort: The relative risk of death among lifelong smokers compared to lifelong nonsmokers increased from only 1.16 in subjects born in the 1860s and 1870s to 2.83 among those born in the 1920s and 1930s (Doll et al., 2004). The British Doctors study demonstrated that survival among active smokers was independent of birth cohort, whereas survival among life time nonsmokers clearly improved with each successive birth cohort—so the difference between the two became bigger and bigger. Similarly, the 1989 Surgeon General report on smoking and health reported a notably greater decline in coronary heart disease among non-smokers than among smokers, and the 2004 Surgeon General report shows an increase of the mortality risk of smoking among men from 1.7 to 2.3 and for women from 1.2 to 1.9 over the mid 1960s to mid 1980s interval. As the relevant periods of birth of the British Doctors study largely overlap with the birth dates of the ACS I cohort, we believe the observations from the British doctors, followed in much greater detail than the ACS I subjects, and from the Surgeon General reports carry an important message for the air pollution cohorts—namely, that we should look for what happened in the younger cohorts much more than what happened in the older cohorts such as ACS I, which is the oldest of all. In the HEI-sponsored reanalysis of the Six Cities and the ACS II cohorts, there was also a clear gradient of larger pollution effects in the younger part of the cohort in the Six Cities Study (from 1.17 to 2.11), but not in the ACS II study (Krewski et al., 2000, 2005).

In the reanalysis of the Harvard Six Cities and the ACS II cohort studies, a strong effect modification by educational status was found. In the present report, an equally strong effect modification is found in the early part of the follow-up (Table 6). As both ACS cohorts, being volunteer cohorts, were more highly educated than a representative population sample would have been, this effect modification also leads to underestimating pollution effects on mortality as they would apply to a random population sample.

To sum up: We believe that several reasons may have contributed to the lack of pollution effects in this study over the last part of the observation period. One is exposure misclassification, which has likely attenuated effect estimates; another is cohort effects; which may have contributed to attenuation of the pollution effects in much the same way as effects of active smoking were attenuated in the early cohorts of the British Doctors study; and yet another is the long time passed since enrollment (1959) and follow-up (1973–2002), which must have been associated with many changes in diet, smoking, occupation etc. that the author could not control for adequately. Although it is very important to increase our insight into long-term effects of air pollution exposure on survival, it is even more important to do so using truly informative studies. We think the current study in the end contributes preciously little to what we really need to know—which is the effect of more contemporary pollutant exposures on more contemporary populations.

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