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Letter to the Editor Re: Enstrom JE. Fine particulate and total mortality in Cancer Prevention Study cohort reanalysis. *Dose-Response*. 2017;15(1):1-12.

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Enstrom's article[1] based on data from the American Cancer Society's Second Cancer Prevention Study (CPS-II) is an important contribution to the literature on long-term relationships between mortality and air pollution exposure. It focuses on exposure uncertainties and regional differences. Neither topic has been explored in the many previous articles or critiques of CPS-II, and Enstrom's article is the first truly independent analysis of these data. Here I discuss some additional implications of Enstrom's results, their application to other studies based on CPS-II, and aspects of long-term air pollution studies in general.

The CPS-II data are the basis for the US National Ambient Air Quality Standard for ambient particles with median aerodynamic diameters <2.5 μg/m^3 ("fine" particles, $PM_{2.5}$) and for similar standards worldwide.[2,3] The CPS-II database includes survival and personal data for about 1 million volunteers, beginning in 1982. Prior to 1999, ambient data for $PM_{2.5}$ were only available from an experimental and privately operated national network (the Inhalable Particulate Network [IPN])[4] supported by the US Environmental Protection Agency (US EPA) that measured particulate mass segregated by median aerodynamic diameter from 1979 to 1984.

I assembled a national data set from IPN raw data reports such as Suggs et al[5] for use in my 1988 analysis of ecological relationships with mortality[6] that include a listing of the $PM_{2.5}$ data that I used, as assigned to central cities. These data were adopted by Pope et al in their 1995 analysis of relationships with survival in CPS-II[7] but were assigned to multicounty Standard Metropolitan Statistical Areas (SMSAs). The US EPA then published more formal reports based on the IPN data.[8,9] Unlike other data used to support ambient air quality regulations, IPN data have never been made available in digital form, thus requiring manual efforts to create the necessary digital databases.

Comments Specific to Enstrom's Article

Enstrom[1] performed a valuable task in combing through these data reports and made use of his findings in new analyses. He showed that $PM_{2.5}$ discrepancies are critical in estimating the effects on mortality in CPS-II survivors from 1982 to 1990. Some of these discrepancies may have resulted from using SMSAs rather than counties or cities. Another important contribution is the contrast between $PM_{2.5}$ mortality in the Ohio Valley and the rest of the nation; the former risk is about 5 times the latter.

I analyzed Enstrom's results in more detail by computing air pollution–related death counts (APRD) defined as:

$$\text{APRD} = \text{total deaths} \times (\text{RR} - 1)/\text{RR where RR is the relative risk.}$$

By considering the relative size (number of deaths) in each subgroup, APRDs give a better idea of their relative importance than does RR per se.

Using data from Enstrom's Table 2, I computed APRDs for the entire United States, for the Ohio Valley, and for the remainder of the United States. Based on 50 counties, Enstrom's APRDs are 274 for the entire United States and 126 and −220 for the two separate regions, a difference of 367 extra deaths based on the entire United States. The corresponding APRDs based on Health Effects Institute (HEI) exposure data are 850 for the entire United States and 265 and 209 for the 2 regions, yielding a difference of 376 excess deaths for the nation, reducing the RR to 1.042.

There are 2 important aspects to these APRD calculations. Enstrom's results based on IPN data and 85 counties show that 82% of the national risk comes from the Ohio Valley. All 3 examples show that estimated risks based on the entire United States greatly exceed the sums of the risks from the 2 regions. This implies that adverse health effects *between* regions may be just as important as those *within* regions. Since there are many aspects of between-region health effects besides air pollution,

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spatial confounding is implied. Total and summed APRDs match much better in other studies.

Comments on Other Published Studies Based on CPS-II

Following their 1995 article,[7] Pope et al obtained digitized $PM_{2.5}$ data from EPA for 1999 to 2001 and reported estimated risks consistently higher than those based on the earlier IPN $PM_{2.5}$ data.[10] Averages of the 2 data sets were used in 2004,[11] and comparisons between the data sets were made in 2009.[12] The HEI sponsored major critiques of CPS-II studies[13] in 2000 and again in 2009.[14] To my knowledge, all of these analyses were based on SMSA exposures and included the earlier IPN data (which were often cited incorrectly). For this reason, the exposure discrepancies reported by Enstrom should be taken seriously.

More recently, exposures were based on land-use regression modeling for the 1999 to 2008 period.[15] Since it would have been very difficult to estimate exposures back to cohort recruitment using this protocol, appropriate long-term trend analysis was not feasible.

The 2000 HEI Reanalysis[13] included regional analyses for particulate sulfate ion (SO_4) and sulfur dioxide (SO_2), but there were too few monitoring stations to include $PM_{2.5}$. The APRDs checked well for SO_4 but the national estimate for SO_2 was considerably higher than the sum over regions. The required death counts were not reported in any of these CPS-II publications; my calculations are thus based on estimates. Another important finding in the reanalysis[13] is that SO_2 risks dominate in 2-pollutant models with either SO_4 or $PM_{2.5}$. Sulfur dioxide was also important in the 2009 reanalysis[14] and in my own work.[6] Given that the substantial spatial uncertainties in SO_2 exposure across an SMSA are expected to have biased the risk estimated toward the null, these findings suggest uncontrolled spatial confounding, perhaps due to using SMSAs.

General Comments on Estimating Long-Term Health Effects

Long-term exposures of individual members of the public at large are essentially unknowable. For example, assuming an annual over-65 mortality rate of 5% and a relative risk of 1.1, only 0.5% of the population may be at risk each year; citywide averages are thus problematic. As surrogates for personal exposures, indoor air samples are drawn from the general public and show substantial spatial variability[16] as seen in Figure 1, which shows no correlation between citywide averages of indoor and outdoor $PM_{2.5}$. It is thus not possible to estimate either individual or small-group personal exposures for the long-term, a serious limitation for long-term studies.[16] However, short-term exposures are experienced indoors and out, with about 50% attenuation as shown in the figure.[16] The contributions of indoor sources may explain the absence of dose–response thresholds based on long-term outdoor exposures.

Temporal exposure trends are important when estimating long-term health effects. An adverse effect is defined as *change* resulting from intervention; spatial distributions do not qualify by this definition even though regulatory assessments have deemed such spatial distributions to be "causal."[19] A person's health might suffer soon after moving to a polluted neighborhood or city, but only long-term exposures can relate to future disease incidence.

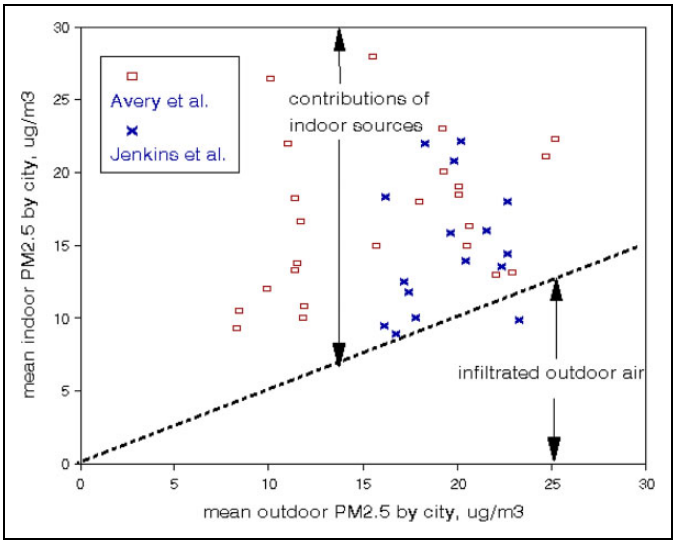

Figure 1. Relationships between indoor and outdoor $PM_{2.5}$ for selected US cities. Data points represent individual city means.[17,18]

How then do we explain the many reports of statistically significant spatial relationships in many different circumstances? The explanation may lie with considerations of timing. Dockery et al[20] suggested that pollution-related effects among the Harvard six cities could include acute (daily) responses, for which evidence from the1952 London fog episode[21] is ineluctable. Lepeule et al[22] analyzed sequential mortality during a 35-year follow-up of the Harvard six cities and found 1 year to be the optimum exposure window, indicating acute rather than chronic effects and exacerbation of preexisting conditions rather than incidence of new disease.

By contrast with the London episode,[21] individual victims of cross-sectional long-term exposure cannot be identified and their cause of death confirmed by autopsy. Mortality associations with long-term exposures are based solely on statistical models involving many potential confounding variables. Data for many of them are available only as group averages as are pollution exposure data, both indoors and out.

The roles of exposure time histories are uncertain. Most long-term studies consider exposures during the period of follow-up with no information on disease latency or induction period. For extended periods of follow-up, historic ambient air quality trends and parallel trends in the efficacy of medical care are important.[23] However, studies that have considered long-term lags[22,23] concluded that responses tend to occur with a few years of exposure, thus blurring the distinctions between traditional long- and short-term studies.

Given these limitations, how should statistically significant long-term associations be interpreted? All long-term effects *ipso facto* include short-term (daily, weekly) effects; thus, any true long-term effect is the *difference* between the 2 types of risk estimates. In addition, such cross-sectional studies indicate mortality variations by *place* but not necessarily by air

pollution *exposure*, which is only one of many relevant geographic factors including climate, population density, ethnicity, traffic density, relative density of green space, and characteristics of housing stock. These factors apply to the entire population and are not limited to the small fractions of the population actually at risk. Thus, statistical significance per se is insufficient to provide a coherent understanding of relationships.

Conclusions

I have tried to establish the merit of independent analysis of data sets, especially those used to establish regulations. The HEI critiques[14,15] were quite thorough in evaluating what the original investigators had *published*. However, they did not evaluate whether these were the only things that *should* have been done or the merits of alternative approaches. Limited access to the CPS-II data is a serious hindrance in this regard.

In this time of ubiquitous politicization, I feel obliged to urge that these comments are not to be considered as anti-environment or politically incorrect but rather as a call for more inclusive analyses, adherence to scientific principles, and thinking outside the regulatory box.

Declaration of Conflicting Interests

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