Correspondence

Comments on “PM2.5 and Mortality in Long-term Prospective Cohort Studies: Cause-Effect or Statistical Associations?”

The lengthy commentary by Gamble (1) is rife with inaccuracies, all of which cannot be commented on in the context of this reply. However, because Gamble’s critique largely is directed toward ecological studies, we wish to focus on a number of widespread misconceptions to which his critique has succumbed. We have discussed these issues at length in a recent publication in EHP (2).

Thus, to his assertion, none of the major studies (cohort, times-series or cross-sectional) cited and criticized by Gamble truly are ecological studies. Having incorrectly categorized the studies, he then proceeded to cite commentaries (3,4) that point out the significant limitations of ecological studies when the target of inference is individual risk.

The hallmark of ecological studies is the lack of individual-level measurements. Thus, the ecological study merely relies on a comparison of aggregate (group)-level prevalence or incidences of outcomes with a some aggregate level of exposure. For example, in a paper cited by Gamble, Brenner et al. (3) used county-specific mortality rates for lung cancer and estimates of the prevalence of smoking for each county to demonstrate the pitfalls of the use of group data to make inferences about individual risk. The cohort and several of the large multicenter cross-sectional studies cited by Gamble differ from Brenner’s example on two crucial points: 1) they contain large sets of individual data (as acknowledged by Gamble), which include most of the relevant risk factors and potential confounders for which adjustment might be necessary; and 2) exposure is not an average proportion of the population that is exposed (as was the case in the Brenner example), but rather a crude average ambient concentration measured in a particular city. It is this second characteristic of what we have called the semi-individual study design (2) that often leads to the misapplication of the term ecological to the study design. Brenner et al. (3) noted that exposure prevalence in a truly ecological study suffers from the fact that the unknown sensitivity and specificity of the exposure assignment has a substantial impact on the potential distortion of the ecological exposure-outcome association relative to the “true” individual-level association. Moreover, prevalence (of smoking, for example), an inherently group-level concept, has no interpretation at the level of the individual. In contrast, in a semi-individual study of the type critiqued by Gamble, the exposure (ambient particle concentration) clearly is of relevance for all individuals who live in a particular region. The ambient levels of particles are not an average between those exposed and unexposed, but rather an estimate of the ambient concentration that applies to all persons. Obviously there will be variability around this estimate, which depends on the exact location of homes and work places, time-activity patterns, use of air conditioners, etc. The distribution of such factors in a population define the level of variability around the central estimate and, indeed, for pollutants with large indoor/outdoor gradients such as ozone, the variability around individual estimates of exposure based on an ambient concentration may be substantial. For fine particles, which have a higher penetration into indoor environments, this variability will be smaller.

In contrast to a true ecological study, the semi-individual studies to which Gamble refers share all of the problems that relate to errors in exposure, i.e., exposure misclassification. Gamble failed to address this issue at all, despite its considerable importance. The critical questions relate to how accurate the ambient concentration is as a surrogate for individual exposure and how the errors in these exposure estimates influence the estimates of the effect of ambient air pollutants on disease morbidity and mortality. In this context, the relationship between the error in exposure and the true exposure and the overall range of exposure across the cities in semi-individual studies are of central concern. Wacholder (5) presented a framework to address the issue of error structures. Other authors have discussed analytical strategies to address these problems in semi-individual studies (6). Gamble seems to be unaware of this work and its relevance to his critique.

Gamble places considerable credibility in the Seventh Day Adventist Study (7), although this study is a prime example of a semi-individual study design. The fact that this study did not show an association between particle exposures and life expectancy, in part, can be attributed to the relatively small sample size and relatively short follow-up times as compared to the Six Cities Study of Dockery et al. (8). The Adventist study did make a concerted attempt to improve the individual exposure estimates by taking into account a number of the factors that can lead to variability of such estimates when they are based solely on a central ambient monitor (7). The approach of these investigators, when combined with a large range of exposures across the study population, may be the most promising strategy to reduce the variability in the exposure estimates (9). We accept that the findings of the Adventist study, with regard to increased air pollution-associated morbidity, is consistent with the coherence criterion (J). However, we have some difficulty in understanding why a population with higher risks for respiratory morbidity should not have reduced life expectancy because chronic respiratory disease and its attendant decrease in lung function are risk factors for increased risk of death (10,11). It is this type of coherence between different health outcomes, both short-term and long-term, which, when taken as a whole, provide the strongest evidence for a causal effect of ambient air pollution and decreased health. Indeed, recent work (12,13) indicates that increased levels of particulate matter are associated with reduced pulmonary function, the latter a strong predictor of mortality (10,11). Seen in this context, lung function may be the link between air pollution and the observed increased mortality. Gamble’s reference to lung function as a potential confounder indicates his lack of appreciation for the fact that lung function may be on the causal pathway—a fact that would disqualify it from being considered as a confounder (14).

It appears that Gamble has applied to the issue of the public health implications of air pollution the same strategies used successfully by the tobacco industry to obscure the public debate on the health consequences of cigarette smoking—offering pseudoscientific critique to cloud the debate. What is required instead is a clearer explanation to the public of the strengths and limitations of various approaches to the study of this problem and an ongoing effort by epidemiologists and environmental scientists to improve the quality of the studies that are to be performed in the future. It appears that Gamble and his company had rather content themselves with clouding rather than clarifying the complex problem of the interface between science and regulation.

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References and Notes
1. Gamble J. PM2.5 and mortality in long-term prospective cohort studies: cause-effect or statistical associations? Environ Health Perspect 106:535-549 (1998).
2. Künzli N, Tager I. The semi-individual study in air
Reply to Künzli and Tager Regarding Causality in PM$_{2.5}$ Cohort Studies

Künzli and Tager suggest that my critique (1) of PM$_{2.5}$ and mortality in long-term prospective cohort studies is full of inaccuracies and misconceptions about ecological studies. As in most arguments, there are issues on which there is agreement, others where there is disagreement, and some areas of misunderstanding. I will briefly discuss those relevant issues on which we disagree.

I believe that the cohort studies are accurately described, that the ambient PM$_{2.5}$ concentrations are inadequate surrogates for individual-level exposure, and that these studies are subject to some biases and inaccuracies common to true ecological studies. In my paper (1), I suggested that risk estimates based on ambient concentration levels should be tested for plausibility using other studies with both individual-level exposure and response data, and I applied such a test. I presented evidence that short-term exposures in time-series studies are not coherent with long-term morbidity findings may not be coherent with mortality. I suggested that the Six Cities results might be confounded, using between-city differences in lung function as one example.

I did not present the air pollution studies as being truly ecological. In my paper (1), I described the cohort studies as “a mixed design incorporating both individual-level data...and group-level data on ambient air pollution concentrations.” More precise terms such as semiecological, or hybrid, or semi-individual may be helpful. In my opinion, a lack of consideration for the limitations inherent in ecological exposure variables has led to significant errors in interpretation.

Künzli and Tager appear to suggest that the pollution exposure variable is not ecological because it is derived from measurement (i.e., it is a “crude, average ambient concentration”). It is true that Brenner et al. (2) state that in “ecologic studies, the exposure status of groups is often defined by the proportion of individuals exposed.” Künzli and Tager apparently missed the word “often” or interpreted it as “always.” Brenner et al. (2) go on to indicate that exposure characterized by a single common measure such as “area air pollution” is an ecologic exposure variable.

We seem to agree that there are errors in using ambient concentrations as surrogate measures for individual exposure, that these errors influence the risk estimates, and that these are critical questions. We appear to disagree on how great is the effect, how to estimate the effect of these errors, and whether I have addressed the issues at all.

I discussed exposure misclassification, and I concluded that since all inhabitants in a given city are assumed to have the same exposure to PM$_{2.5}$, there are large errors for many members of the cohorts (1). Therefore, the group-level exposure variable is not an adequate surrogate for personal exposure, and as a result, the risk estimates may be biased to an unknown extent and direction. The magnitude and direction of this misclassification bias cannot be easily estimated because it has been repeatedly shown that even apparently nondifferential misclassification can cause spurious results in either direction (3–8). In fact, when the true relative risk is near 1.00 (as is the case for PM), an appreciable percentage of studies will overestimate the risk (9). When the true relative risk is exactly 1.00, the misclassified risk estimates are evenly distributed above and below 1.00 (8). While exposure misclassification may be reduced by the use of such individual-level data as time-activity patterns or work exposure [as in the studies of the Seventh Day Adventists (SDAs) (10)], the potential for error still remains.

It is true that semiecological studies gather some covariate estimates for individuals, providing some control of confounding. However, considerable residual confounding can still occur if important confounders are missed or crudely measured (5,11–15). Furthermore, for individual-level confounding to be effectively removed, the nature of the association between the exposure and the confounder should be well specified, which is not possible when exposure information for individuals is lacking.

Some questions regarding the inaccuracies associated with the risk estimates from these studies may be addressed in ways suggested by Künzli and Tager. I go beyond these suggestions to propose that the ultimate validity of the risk estimates in these studies is basically unknown. The risk estimates must be verified or refuted by a different study design utilizing individual-level data for exposure, outcome, and confounding variables (1).

This process of verification or refutation is an essential part of the scientific method in general and epidemiology in particular (16). A primary focus of my critique was to verify and refute the mortality risk estimates from the Six Cities (17) and American Cancer Society (ACS) (18) cohorts. This validity check was done by comparing the cardiopulmonary mortality risk estimates for ambient PM$_{2.5}$ with the risk estimates for tobacco smoke in these same studies. The rationale for this comparison was that the individual-level exposure to tobacco smoke PM was well characterized, that the associations between tobacco smoke and cardiopulmonary mortality are widely accepted as causal, and that tobacco smoke PM is a reasonable surrogate for ambient PM$_{2.5}$. The comparability of the ambient PM$_{2.5}$ and tobacco smoke risk estimates would be a validity check and would provide some estimate of the degree and direction of bias if the results were not comparable. For a given PM$_{2.5}$ concentration, the risk estimates from ambient exposures were orders of magnitude greater than those from tobacco exposures. Therefore, I concluded that the ambient PM$_{2.5}$ risk estimates in the Six Cities (17) and ACS (18) cohort studies are not biologically plausible (1).

I and others (17,19) disagree with Künzli and Tager that short-term mortality in time-series studies is relevant to the coherence argument because the time-series studies look at short-term exposures rather than chronic or lifetime exposures. Also, the health outcomes in time-series studies are usually thought to be in the elderly and other susceptible people (20) rather than in the total population.