RE: "IS THE RELATION BETWEEN OZONE AND MORTALITY CONFOUNDED BY CHEMICAL COMPONENTS OF PARTICULATE MATTER? ANALYSIS OF 7 COMPONENTS IN 57 US COMMUNITIES"

We read with interest the article by Anderson et al. (1) in which the authors investigated whether the ozone-mortality relationship is confounded by 7 components (sulfate, nitrate, silicon, elemental carbon, organic carbon matter, sodium, and ammonium) of particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) across 56–57 communities in the United States. They concluded that the ozone-mortality relationship was robust to control for these common $PM_{2.5}$ components, which make up most of the $PM_{2.5}$ mass. However, there are several study limitations that should be addressed to determine how robust the study findings are.

First, Anderson et al. (1) pooled estimates across all communities and seasons with available data (34 out of 56 or 57) even though, as they noted, there is both spatial and temporal heterogeneity in ozone concentrations and $PM_{2.5}$ composition. This heterogeneity was demonstrated by Bell et al. (2), who reported stronger correlations between $PM_{2.5}$ and ozone in certain regions of the United States (e.g., the Midwest and Northeast) and during certain seasons (e.g., spring and summer), as well as differences in mortality effect estimates across regions and seasons. Similarly, Katsouyanni et al. (3) found evidence of confounding by particulate matter (PM) in summer-only analyses of US cities that was much less evident in the year-round analyses. Franklin and Schwartz (4) limited their analysis to the summer months, when $PM_{2.5}$ and ozone levels are higher, and demonstrated that the confounding effects of sulfates on ozone mortality effect estimates occurred differentially across communities. This might be due to sulfate-enriched $PM_{2.5}$ in some areas in the Midwest and Northeast, where the correlations between PM and ozone are also strongest (2). Because pooling estimates across all communities can mask heterogeneity, the relative contributions of PM components in each community and how correlations differ depending on PM composition are unknown. Stronger correlations in some communities and during certain seasons may be why confounding is not observed for pooled estimates.

Second, Anderson et al. (1) did not show whether the $PM_{2.5}$ components were independently associated with mortality. If the $PM_{2.5}$ components are not associated with mortality, it is not likely that they confounded the ozone-mortality association.

Third, Katsouyanni et al. (3) found that ozone-mortality associations in the United States were sensitive to time and weather model specifications, but Anderson et al. (1) did not conduct sensitivity analyses using alternative model specifications with respect to these factors. Thus, the impact on results of varying these different model specifications is unknown.

Lastly, with regard to uncertainty, Anderson et al. (1) acknowledged that their results were subject to exposure measurement error, but they did not indicate the impact of this on their results. Studies have shown that ambient ozone concentrations are poorly correlated with personal exposures (5, 6). Each PM component also has specific ambient-personal correlations, adding a level of complexity that was not addressed in the analysis by Anderson et al.

Overall, although the article contributes much-needed research, the analysis should be expanded to evaluate confounding by region and season, include correlations between PM components and mortality, conduct sensitivity analyses for different model specifications, and address measurement error.

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THE AUTHORS REPLY

We appreciate Sax and Goodman's interest (1) in our study (2). Although controlled experimental studies have shown that ozone pollution can harm human health (3, 4), observational studies are critical to quantify the impact of real-world ambient ozone on human health and to provide

guidance to decision-makers who are establishing health-based ozone regulations. Observational ozone-health studies are, like all observational studies, subject to potential confounding. Our study adds to research (5–7) that investigated whether measured ozone-mortality associations are sensitive to particulate matter pollution. As in previous studies in which investigators found no sensitivity of the ozone-mortality relationship to particulate matter with an aerodynamic diameter less than or equal to 10 μm or less than or equal to 2.5 μm ($PM_{2.5}$) measured by mass (5, 6), we found no evidence that 7 $PM_{2.5}$ components confounded the ozone-mortality associations observed across numerous US communities (2).

Sax and Goodman raise concerns about estimating the ozone-mortality association (1) that we welcome the opportunity to address. First, although there is regional and temporal heterogeneity across the United States in concentrations of ozone and $PM_{2.5}$ and in the composition of $PM_{2.5}$ (8), this heterogeneity does not prevent combining of community-level estimates of ozone-mortality associations or affect the interpretation of such results. Additionally, our study presented community-level results, including histograms of community-level correlations between ozone and $PM_{2.5}$ components (Figure 1 in our original article (2)) and community-level measurements of confounding (Figure 2 in our original article). These results show, at most, low to moderate correlations between each $PM_{2.5}$ component and ozone and indicate little or no evidence that our overall estimates mask substantial community-level confounding within certain communities.

As Sax and Goodman note, a smaller previous study in which analysis was limited to summer months showed some evidence of confounding by sulfate (7), but this result was less relevant to our analysis, in which we used year-round data. We chose to conduct our analysis using year-round data to correspond with the modeling process used to estimate the ozone-mortality association in several national-scale US studies (5, 9, 10). Using models, communities, and times of year similar to those considered in other studies, we found no evidence that results from previous studies were sensitive to model control for 7 components of $PM_{2.5}$.

Second, it is true that if certain $PM_{2.5}$ components are not associated with mortality, they would not confound the ozone-mortality relationship. However, this question does not affect the validity of the analysis performed here. Regardless of why these $PM_{2.5}$ components do not confound the ozone-mortality relationship, we found no evidence of confounding. Although quantifying the associations between $PM_{2.5}$ components and mortality risk is very important, it was beyond the scope of our study and was not our focus.

Third, in an extensive study of 95 US communities, models almost identical to those used in our study were found to be robust to a variety of changes in model control for long-term and seasonal mortality trends and weather (5). Finally, measurements of ambient pollution may not be perfectly correlated with personal exposure (11, 12). Although exposure measurement error can bias estimated associations between pollutants and health, the only cases in which the true effect of one pollutant is likely to be attributed to a second pollutant because of exposure measurement error are 1) when concentrations of the 2 pollutants are strongly positively correlated; 2) when exposure measurement errors of the 2 pollutants are strongly negatively correlated; and 3) when the pollutant with a true effect is measured with much less certainty than the pollutant with no effect (12). It is unlikely that these conditions were met in our study, and so our findings were likely not qualitatively affected by exposure measurement error. A more likely repercussion is that the ozone-mortality associations estimated in our and other studies that use ambient ozone data underestimate the true association between ozone and mortality risk (12). Future research could explore these questions more thoroughly.

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