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Response to Invited Commentary

Chang et al. Respond to ''Environmental Exposures and Preterm Birth''

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We thank Dr. Zeger for his commentary (1) on our analysis of ambient fine particulate matter and preterm birth (2). We also welcome his thoughtful discussion on several general inferential issues associated with population-based studies in environmental epidemiology. We wish to highlight several unique design and analytic challenges in the study of preterm birth to motivate future methodological development.

Studies of air pollution and health often distinguish between acute and chronic effects that require different study designs. Unlike the case in studies of chronic air pollution effects, birth records do not provide the detailed lifestyle or demographic data that are available from prospective studies. They do, however, provide a basis for population-level analyses, which complement existing cohort studies. This motivated our 2-stage approach, which aggressively controlled for potential spatial confounding through the use of county-specific regression coefficients and baseline hazards. Because long-term exposures incurred during pregnancy last for several months, the risk may be confounded by seasonal and long-term trends in rates of preterm birth. Dr. Zeger described an interesting effect decomposition analysis for assessing the presence of confounding when examining the effects of yearly average pollution levels. This has potential application to preterm birth studies if we can construct appropriate time and covariate stratifications where the hazard of preterm birth is assumed to be constant.

For short-term effects in late pregnancy, preterm birth studies are also different from studies of the acute relation of air pollution with mortality or morbidity in several ways. First, often the short-term exposure windows of interest for preterm birth last longer than a single day (3), resulting in a decrease in the exposure's temporal variation. Second, on each day, the at-risk population (ongoing pregnancies) is smaller than in studies of mortality or hospital admissions. Moreover, empirical studies have shown that the seasonality in conceptions and births can vary across racial and socio-demographic subgroups (4). These differences increase the possibility of short-term temporal confounding, such as confounding by temperature, and should be explored further. For example, in a time-to-event analysis, lagged average temperature can be included as a time-varying covariate during the at-risk window. A related challenge is the appropriate use of calendar date to control for unmeasured temporal confounders. In our analysis, we used indicators for season and year of conception based on Akaike's Information Criterion and sensitivity analysis, but the choice of smoothness (degrees of freedom) and time reference (e.g., conception vs. birth date) is likely to depend on both the scientific questions and the study locations.

We fully agree with Dr. Zeger that making the health data and analytic software code available will facilitate alternative analyses and methodological development. For instance, the National Mortality, Morbidity, and Air Pollution Study is an exemplary model for examining the acute health effects of ambient pollution (http://ihapss.jhsph.edu). While data from birth records are routinely collected by government agencies, it is uncertain what data infrastructures are needed for allowing public access to identifiable health information, especially when the analysis is conducted on the individual level. An alternative approach may be to establish a set of standards in data collection and analytic approaches to help synthesize findings from different research groups. One recent success is a coordinated international effort to reanalyze existing databases (5).

Finally, we agree that a causal diagram based on biologic processes will be useful in sharpening hypotheses. Examples include identifying exposure windows that correspond to specific stages of fetal development and identifying at-risk windows in which pregnancies are most likely to be preterm due to air pollution. Understanding and quantifying the risks of adverse birth outcomes attributed to ambient air pollution may have significant public health impacts. This warrants a continual effort to develop novel approaches for exposure

assessment and risk estimation that incorporate the unique challenges associated with birth outcome data.

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Conflict of interest: none declared.

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