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Reply: “Air pollution and cardiovascular events with special reference to labor and delivery”

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To the Editor:

We thank Dr. Kawada for the interest in our article regarding ambient air pollution and cardiovascular events during labor/delivery [1], and for the opportunity to further clarify some important aspects of this study. As Dr. Kawada notes, we used a case-crossover design to evaluate the acute association between air pollution exposures during the week before delivery and the odds of having a labor/delivery affected by cardiovascular events, building on our prior article which examined acute and recent exposures using the full cohort [2]. The results from both studies were consistent, suggesting that time-invariant confounders (either measured or unmeasured) did not explain the effects.

Dr. Kawada raises two issues, one on the lack of mechanistic data or causal attribution and the second on the potential for gestational hypertension or diabetes/metabolic disorders to influence cardiovascular event risk. First, our article aimed to understand the association of ambient air exposures with cardiovascular events at labor/delivery and a detailed investigation of the specific mechanism(s) is beyond the scope of our study. However, the relationship between ambient air exposures and cardiovascular events is well known in the general population including evidence for plausible biologic mechanisms [3]. We believe

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that similar mechanisms may drive the cardiovascular risk for women at delivery (e.g., systemic inflammation, oxidative stress, endothelial cell dysfunction, etc.), but we certainly encourage more research on these relatively rare but very serious complications. The case-crossover study design and our original cohort design estimates the same association (between ambient air exposures and cardiovascular events) by asking slightly different questions. Specifically, the case-crossover design answers the question: among women with labor/delivery affected by a cardiovascular event, were the ambient conditions significantly different during the case period compared with the control periods? This is essentially a “why now” question, compared with the traditional cohort analyses which compare women with and without an event, which is essentially the “why this person/delivery and not another” question. It is reassuring that both methods yielded similar findings, suggesting robust evidence of associations between some common criteria air pollutants, such as fine particles and nitrogen oxides, and cardiovascular events at labor/delivery. Both studies used an obstetric cohort, so as Dr. Kawada correctly points out, causal mechanisms cannot be speculated for women without labor/delivery, although nonpregnant women are represented in general population studies of cardiovascular events [4].

The second point Dr. Kawada raises pertains to potential confounding by other health conditions, particularly metabolic disorders such as gestational hypertension or diabetes. This concern was a primary motivator for us to use the case-crossover design, which is a self-matching study design that allows us to control for timeinvariant characteristics. Since women served as their own controls, everything about them that does not change over the period of a few weeks is controlled for by design and the time-varying air pollution exposures during a case period (e.g. the week before) were compared with the control periods both before and after the event. As a result, any measured and unmeasured person-level characteristics (e.g., genetics, chronic comorbidities including metabolic dysfunction or a susceptibility to hypertension or metabolic disease, etc.) that do not differ between the case and control periods should not affect our results. For most women, hypertension or metabolic disorders likely did not change over this short period.

Finally, Dr. Kawada mentioned that the number of events was limited for some specific outcomes and suggested using an aggregate number to keep the estimates stable. We reported both the aggregate and specific event results. As Dr. Kawada also noted, separating cardiovascular events presents a slightly different pattern of associations. We suspect that this is partially due to small sample size for certain outcomes, but it may indicate that more than one mechanism is involved. We believe our study identifies a vulnerable population that merits further attention. While the risks for incident cardiovascular events and mortality are clear in the general population, more studies are needed to confirm these risks in pregnant women and to elucidate the potential mechanisms that may be amenable to prevention. Given the lack of prior data, we hope that our comprehensive exploration of risks for both specific and overall events encourages others to examine this important question.

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