Reviewer’s report

**Title:** Cumulative Exposure to Environmental Pollutants during Early Pregnancy and Reduced Fetal Growth: The Project Viva Cohort

**Version:** 1  **Date:** 24 Jan 2018

**Reviewer:** Virissa Lenters

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The authors have thoroughly responded to all comments. I remain somewhat unconvinced about a couple of aspects, including that this study sample has sufficient statistical power to study these specific interactions (and as such is arguably not the most informative study to "present a framework to examine additive interactions between…" (edited lines 100-101)). In addition, the merits of using z-scores (conditioning on a likely causal mediator) instead of birth weight as the outcome are not clear to me, but this admittedly remains an area of contention in the literature.

Overall, the authors have sufficiently addressed the comments. Importantly, the methods are more clearly described. Furthermore, the rationale for selecting this subset of exposures is clearer and the discussion addresses limitations in a more nuanced way.

One final comment: The authors added the following paragraph to the discussion (lines 424-429):

"A limitation of any environmental epidemiologic analysis is potential for model misspecification or confounding by exposures that are not accounted for or unmeasured. The multi-pollutant model approach minimizes co-exposure confounding while simultaneously allowing for evaluation of joint effects. Although collinearity between exposures in a multi-pollutant model could decrease precision of effect estimates, this was not a limitation of the present analysis, as the exposures we studied were not tightly correlated."

I would caution that multi-pollutant models are not a panacea, and there is tradeoff between potential bias amplification (due to e.g., adjustment for irrelevant variables or indirect colliders) and bias reduction (due to e.g., adjustment for confounding co-exposures). Perhaps the line 426 could be edited to "The multi-pollutant model approach is generally expected to minimize co-exposure confounding bias…", with citations, and perhaps followed by caveats related to model misspecification. As in my (Reviewer 1) original comment #6, inducing bias is a risk in multi-pollutant models due to e.g., unmeasured confounders of Ei and Y or due to adjustment for irrelevant variables.
See e.g.:


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