Author’s response to reviews

Title: Prenatal exposure to persistent organic pollutants and child overweight/obesity at 5-year follow-up: a prospective cohort study

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Reviewer 1:

This study aims to determine the association between prenatal exposure to selected persistent organic pollutants and overweight/obesity at 5 years of age. The assessment of the role of prenatal exposure to persistent organic pollutants on lipid metabolism in childhood is of scientific interest. I have concerns, however, as to whether the study group used is adequate to answer the study question. The present analysis was conducted on a group of mother-child pairs enrolled in a study of small-for-gestational age births. In the present analysis 25% of children were SGA and the rest were non-SGA. SGA and non-SGA children have different growth trajectories. SGA is known to contribute to faster growth trajectories during infancy, while faster growth trajectories during infancy are associated with overweight status in childhood. The authors should have considered restricting the study group to non-SGA individuals or reporting results separately for SGA and non-SGA. Given reported inverse associations between the persistent organic pollutants studied and fetal growth, and the fact that SGA is not an outcome that has been previously assessed in relation to the pollutants in questions, I find it relevant to first determine and report the association between these pollutants and SGA. Next, it would be important to consider whether the study exposures are antecedent to SGA and whether SGA is an
intermediate factor that should be removed from the pathway such that it is possible to assess the role of the pollutants on excess weight at overweight/obesity at 5 years of age among SGA children.

Editor's comments:
We believe that the concern about SGA as a possible intermediate parameter should be addressed.

Answers:
Thank you for these comments.

We agree that SGA (or prenatal growth) might be a mediator or an intermediate factor in the pathway between exposure to persistent organic pollutants (POPs) and childhood overweight, as highlighted in our directed acyclic diagram (DAG) included as Supplementary Figure S1 in the manuscript. Our DAG was informed by our previous research demonstrating the associations between prenatal exposure to POPs and SGA birth in our study cohort [1]. In this previous study, we found positive associations between increasing levels of some POPs and SGA birth [1]. However, our objective in this study was to estimate the total effect of prenatal exposure to POP on child size, not the effect mediated only through pathways other than intrauterine growth. Adjustment or stratification for SGA birth would therefore not answer our primary research question. Further, one should be cautious when correcting (adjusting or stratifying) by an intermediate factor. In fact, Schisterman et al. (2009) says: “For estimation of total causal effects, it is not only unnecessary but likely harmful to adjust for a variable on a causal path from exposure to disease, or for a descending proxy of a variable on a causal path from exposure to disease. ….. estimation of direct effects of exposures (such as maternal smoking) on outcomes (such as infant mortality) by controlling for an intermediate variable (such as low birth weight) are not valid when there are unmeasured shared causes of low birth weight and infant mortality. Such estimates are vulnerable to collider-stratification bias or exposure interactions with the intermediate variable”[2]. Hence, adjusting or stratifying by SGA status might introduce bias if there are shared unmeasured causes of both SGA status and childhood overweight.

Nevertheless, we acknowledge that a larger proportion of SGA births in our study compared to the general pregnant population might introduce selection bias or problems with generalizability. Hence, as an alternative of doing sensitivity analyses with the non-SGA group or the 10% reference group, we conducted stratum-weighted analyses, which are recommended for studies with analyses of case-control data for additional outcomes [3]. In detail, we weighed SGA and non-SGA births based on the inverse probability of selection to the study (Supplementary
This means that the under-represented group (i.e. non-SGAs) got a weight larger than 1, and those in the over-represented group (i.e. SGAs) got a weight smaller than 1, producing final estimates that are generalizable to a population without oversampling of SGA births. We computed the weights by this formula: percentage in the general pregnant population divided by percentage in the study sample. Hence, SGA births were weighted 0.30 and non-SGA births were weighted 1.35. As the results from the weighted analyses did not differ considerably from the reported results, we have no reason to believe that the oversampling of SGA births introduced bias.

For these reasons, we have chosen not to conduct additional analyses and we have not changed any analyses from the first draft.

References

