**Reviewer’s report**

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

**Version:** 0 **Date:** 15 Nov 2017

**Reviewer:** Jillian Ashley-Martin

**Reviewer's report:**

ENHE-D-17-00265 review

This manuscript explores the potential cumulative impact of prenatal exposure to multiple environmental contaminants on birth weight. The authors have previously published associations between the measured contaminants and birth weight in the Project Viva cohort. As such, this study focuses on the potential for synergistic fetal growth related effects among PFOS, black carbon, and smoking.

- As this study focuses on evaluating interaction among chemicals, I recommend a greater discussion of the rationale for and limitations of the interaction methods used in the present study. For example, consider clarifying the type of interaction assessed, the rationale for the current approach, whether the study was sufficiently powered to assess interaction, and the advantages and limitations of evaluating joint exposures based on cutoffs identifying 10% of the population. There is a considerable amount of fairly recent epidemiological literature devoted to this topic (see Knol (https://www.ncbi.nlm.nih.gov/pubmed/22253321, https://www.ncbi.nlm.nih.gov/pubmed/19034025), VanderWeele TJ, Knol MJ. A tutorial on interaction. Epidemiologic Methods. 2014: 3;33-72 as a few examples) and it would be appropriate to highlight some of this literature in the present study.

- The authors conclude that 'early pregnancy exposure to maternal smoking, residential black carbon and PFOS are associated with additive reductions in fetal growth.’ In both the single and multi-pollutant models, the parameter estimates for each exposure are very close to the null value and only statistically significant for black carbon. Thus, any exposure related fetal growth reduction is marginal. Clarify in abstract and discussion whether the observed results are being interpreted as a lack of individual effects, lack of greater than additive effects, or both.

**Minor issues:**

- Writing is clear but, at times, sentence structure and pronoun use is overly repetitive (e.g. methods).
Methods

- It would be helpful to report correlation coefficients for the three exposures and discuss potential collinearity in the multi-pollutant model.

- Provide more detail on study eligibility. Were there any restrictions regarding gestational age or multiple births? Use of GA BW z-score removes some of the issues regarding inclusion of preterm births. However, this approach may not completely negate the question of whether observed fetal growth reduction could be related to an exposure related effect on timing of delivery.

- Clarify why ultrasound was used for the estimation of GA in all women (rather than as back up for LMP)

- Is cigarette smoke a potential source of black carbon exposure? If so, comment on implications of measuring the same chemical with different approaches.

- Report actual birth weight in g in table 1 as it is easier to interpret than z scores.

Results

- The authors note a 126 g BW difference between those in the --- and +++ exposure groups (Figure 1). Considering the nearly overlapping confidence intervals, and likely small number of women in the high exposure group, comment on the implications of these findings. Is this degree of difference clinically meaningful?

- Provide descriptive statistics for PFNA.

- It is not clear why the authors state that 'PFNA may attenuate associations of smoking and black carbon with lower fetal growth.' This statement appears supported by the supplemental figure but not by the supplemental table as the parameter estimates for smoking and BC are not attenuated in the full model compared to the single or multiple additive exposure models. The results in the figure are based on dichotomous exposure groups and the group with all exposures are likely composed of a very small number of individuals. Please clarify.
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