Author’s response to reviews

Title: Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy

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Author’s response to reviews:

Dear Editor,

Thank you for your letter and comments on our manuscript titled “Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy” (ENHE-D-18-00201R2). These comments helped us improve our manuscript, and provided important guidance for future research.

We have addressed the reviewers’ comments to the best of our abilities, and revised the manuscript accordingly. Revisions were highlighted in red. We hope this meets the requirements for a publication. Thank you and the reviewers for the useful comments. Our responses are as follows:

Editor's comments: We still need further clarifications, and we suggest that you consider additional statistical analysis of the joint and separate effects of the PFASs.

Reply: Thank you for your suggestions. We have presented the separate effects of the PFAS in the current version. We have now conducted new statistical analyses. We used structural equation model (SEM) to examine the association between joint effect of all the PFAS and each outcome (Figure S2). The odds ratio and corresponding 95% confidence interval (95% CI) of
PFAS were 0.99 (0.97, 1.02), 0.98 (0.95, 1.01) and 0.98 (0.94, 1.01) for preeclampsia, gestational hypertension, and hypertensive disorders of pregnancy, respectively. As each PFAS was associated with the outcome of interest differently, the joint effect was towards the null. Therefore, we did not present the joint effects in the current manuscript. But at the end of the Results section, we mentioned that “We also explored the joint effect of the PFAS on hypertensive disorders in pregnancy using the structural equation model (Appendix Figure S2). The odds ratio and corresponding 95% confidence interval (95% CI) of PFAS were 0.99 (0.97, 1.02), 0.98 (0.95, 1.01) and 0.98 (0.94, 1.01) for preeclampsia, gestational hypertension, and hypertensive disorders of pregnancy, respectively.” (Page 13).

Reviewer 1

Major Comments:

C1. The specific hypotheses regarding PFBS in particular are still not clear in the introduction.

R1: Thank you for the suggestion. We have now added a concise summary in the Introduction: “Experimental studies have reported adverse effects of PFBS on the immune and endocrine functions of human cells. It is possible that these adverse effects may also interfere with the remodeling of uterine spiral arteries, the pivotal feature of normal placentation, and contribute to the development of preeclampsia and gestational hypertension. But whether PFBS is associated with preeclampsia and gestational hypertension is still unknown.” (Page 6).

C2. As noted previously, this is a cross-sectional analysis of data obtained from women presenting at the time of birth. Even if these women are currently enrolled in a prospective study, it is inappropriate to characterize the present analysis as a ‘prospective birth cohort’ (in the abstract). It should be made clear in the abstract and the methods that the analysis presented in this paper is cross-sectional. Characterizing this analysis as prospective is misleading.

R2: The point is very well taken. We have now omitted the short phrases containing “prospective study”, and revised the Abstract and Methods, making it clear that the present analysis is a cross-sectional study.

C3. The authors indicate that covariates were selected in a DAG and refer to a Figure 1, but no DAG was included in the revision, and Figure 1 refers to presentation of correlation coefficients among the PFAS compounds. Please clarify and include the DAG used to guide your covariate selection for the benefit of others, even if it is included as a supplement.

R3: We referred DAG to Figure 1 in the response letter. Sorry for the confusion. We have now added the DAG as additional file (Figure S1) in this revision.
C4. Are the authors suggesting that maternal age, education, parity and BMI made up the minimal sufficient adjustment set based on the specified DAG?

R4: Yes, in our study population, as the prevalence of smoking is low (0.4%) in our study, maternal age, education, parity and pre-pregnancy BMI made up the minimal sufficient adjustment set based on the DAG.

C5. The authors now include a secondary analysis in a supplementary table. But, no mention of these results is made in the results section of the paper. Some general statement of these results should be mentioned.

R5: We have now added some general statements in the Results section: Table S1 shows the results of the association between PFAS and hypertensive disorders of pregnancy with further adjustment of gestational age and birth weight in addition to those adjusted in the model presented in Table 5. Similar results were found.

Reviewer #2: The response to reviewer 2, comment 26, is not adequate. The question was about the correlation of PFAS concentrations in maternal serum during the relevant etiologic window (early-mid pregnancy) with cord levels. The correlation coefficient will be informative about how much measurement error might have attenuated the measures of association between the outcomes and the exposures. It was easy to find at least two papers that presented data on the correlations (see citations below). The relevant correlations need to be added to the manuscript. The ratio of levels between mothers and cord is less important and does not deserve much emphasis. Otherwise the response and revised manuscript are acceptable.

Placental Transfer of Perfluorooalkyl Substances and Associations with Thyroid Hormones: Beijing Prenatal Exposure Study.


PMID: 26898235

Changes in serum concentrations of maternal poly- and perfluoroalkyl substances over the course of pregnancy and predictors of exposure in a multiethnic cohort of Cincinnati, Ohio pregnant women during 2003-2006.

Kato K, Wong LY, Chen A, Dunbar C, Webster GM, Lanphear BP, Calafat AM.


PMID: 25026485
R1: Thank you for your suggestions. We have now cited these two references, and mentioned in the manuscript: “It has been reported that PFAS in maternal and cord blood samples could be highly correlated, with correlation coefficients ranging from 0.52 to 0.95. Low correlation might have attenuated the association between PFAS and HDP.” (Page 15).