Reviewer’s report

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

Version: 1 Date: 16 Oct 2018

Reviewer: Matthew Longnecker

Reviewer’s report:

ENHE-D-18-00201R1, hypertensive disorders of pregnancy and PFAS, reviewer comments

Please be aware that I work for a consulting company and my work at the company is supported by 3M. I believe that my review was not compromised by this relationship. In addition, please bear in mind that I did see the comments from the editor that resulted in the "R1" version that I reviewed, and that I may not agree with the editor about the best way to present the results.

I find the elastic net regression approach and results interesting, but I believe that this is a relatively new technique in environmental epidemiology and that the data presentation would be enhanced by including what might, by some, be considered a standard analysis, so that the results could be compared. Also, a slightly more didactic approach, where the effect of using the elastic net rather than old-style approaches are examined and explained more, would add great value. I suggest the order of presentation be: first, logistic regression for all 8 PFAS and each outcome separately, and second, the elastic net regression. I have no objection to the author’s focus on the elastic net regression findings as long as the "standard" results are available to the interested reader.

The authors note that preeclampsia might affect kidney function and alter the PFAS concentrations in cord blood. This effect could be especially important for a PFAS that has a short half-life, like PFBS. To improve the assessment of whether such an effect might have occurred, it would be useful to add a sensitivity analysis where the results for PFBS are adjusted for birthweight and gestational age.

Little information is given about the criteria used by doctors in Shanghai to diagnose, e.g., preeclampsia. In other countries, the criteria vary by doctor and do not necessarily agree with criteria published by professional organizations. The reader is left to assume that the outcome ascertainment was imprecise, meaning that the statistical power of the study would be compromised. More consideration of this likely weakness is needed in the last paragraph of the discussion.

The discussion would benefit from consolidation of the three paragraphs about potential mechanisms. If the results are replicated this level of detail and speculation might be warranted, but at this stage, a shorter summary would be more appropriate.
Minor comments (I numbered the pages starting with the title page):

P 2, L 28 (line number in small font in left column): as noted above, would mention the standard logistic regression first.

P 2, L 42: rather than "incidence", "risk" seems more appropriate.

P 4, L 3: would change "is one of" to "are among"

P 4, L 6: would change "pregnancy-related complications" to "complications of pregnancy"

P 4, L 31: would make pollutants plural

P 4, L 56: PFAS is a very broad category of chemicals, and many have short half lives. Perhaps the authors mean that the most frequently studied PFAS have long half lives. Would delete "members" when the wording is revised.

P 5, L 12: would insert "have" before "provided"

P 5, L 23: would delete "Norwegian". (It was an American study of Norwegians, done in collaboration with Norwegians.)

P 6, L 23: would insert "As noted above," before "information"

P 6, section 2.3 somewhere: it would of interest to indicate the volume of plasma that was used for the PFAS analyses. With an LOD so low for PFBS, it suggests that an usually large volume was used, or that PFBS is, for some reason, much easier to measure precisely in low volumes.

P 7, L 1: I think where the authors say "PFBS" they mean "PFAS"?

P 7, L 1 - L 9: this detail was probably already presented in their reference 9 and does not need to be repeated here.

P 7, L 28-31: the LODs are missing for three of the PFAS measured.

P 7, section 2.3, perhaps at the end: the reader needs to be given information about the precision of the assay. For example, what was the between-assay coefficient of variation for each of the 8 compounds?

P 8, L 25: Please insert some citations to important examples of where this technique has been employed in environmental epidemiology studies.

P 8, L 47: where the authors say "a prior", I believe they mean "a priori", and it would be good to italicize that.

P 10, L 2: again, suggest "incidence" be replaced with "risk"
P 10, L 12: please be clearer about what is meant by "college education". Does this mean a degree after 4 years? This level of detail could go in a table footnote.

P 10, L 17: would insert "a" before "higher"

P 11, L 6: would explain that Ben means beta coefficient from the elastic net regression where this is first used in the text.

P 11, L 17: where the authors say "unpenalized", do they mean (standard) logistic regression? This potentially confusing descriptor might be avoided by presenting the logistic regression results first.

P 12, L 60: would delete "human"

P 13, L 1: would change "samples in our previous report" to "in our samples"

P 13, L 6: would delete "bodies"

P 13, L 23-26: rather than "reported epidemiological investigations so far has" would say "previous epidemiologic studies have"

P 15, L 25: where temporality is discussed, it would make sense to move the sentences about reverse causality to the same part of the paragraph, because the issues are so closely related.

P 15, L 31: what is the correlation of PFAS concentrations in cord serum with levels during mid-pregnancy?

P 16, L 9: The possibility of results affected by multiple testing needs to be raised. Twenty-four associations were examined, and one was statistically significant. Did the elastic net procedure somehow reduce the likelihood that a statistically significant result would be obtained by chance?

P 16, L 20: the dose-response pattern was present only for preeclampsia

Table 2: The text label for PFUA needs to be corrected. Currently it says perfluorohexane sulfonate.

Table 3: please add confidence intervals where a non-zero coefficient is presented.

Table 4: please explain how the trend test was constructed.

Figure 1: I did not find the legend for this figure. It might be good to explain what the axis labels are, units, why some of the fitted red lines are not straight, what the asterisks indicate, etc.

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