Author’s response to reviews

Title: Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study

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Author’s response to reviews:

Dear Editor,

Thank you for your and the reviewer’s comments on our manuscript titled “Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study” (ENHE-D-17-00244). These comments helped us improve our manuscript, and provided important guidance for future research.

We have addressed the editor’s and reviewers’ suggestions 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.
Editor's comment:

Editor: When you revise the manuscript, please make sure that the abstract remains within the word limit required. Also, please note that substantial evidence suggests that PFASs are transferred via human milk.

Response: We have revised the abstract as suggested. In addition, breastfeeding has been included in final logistic regression model as a potential confounder.

Reviewer 1

C1: R6. The description on the method used for choosing confounders has been added as follows "Potential confounders were selected based on DAG, and included infant sex, parity (nulliparous and parous), birth weight, gestational weeks at delivery, mode of delivery, maternal pre-pregnancy BMI, maternal age, maternal education, maternal ethnicity, paternal age, paternal education, parental history of allergic disorders, paternal smoking during pregnancy, and family income".

I'm still not sure of what confounders were included in the DAG and which one that came out in the minimal sufficient adjustment set and thus were the ones used in the adjusted analyses. By comparing the confounders listed in the Material & Methods section with the ones listed in the table footnotes, there are some differences. Gestational age, birth weight, mode of delivery are listed as adjustment factors under the table but not in Material & Methods. I believe it would be useful to show the DAG as supplementary figure, then the readers can get a better understanding on how the DAG was built with regard to potential confounding factors included, and thus also for the confounders that were included in the final analyses.

R1: We have added the DAG in supplementary Fig 1 as suggested. Besides, the description on the method used for choosing confounders has been revised as follows "Potential confounders were selected based on a DAG, including infant sex, parity (nulliparous and parous), birth weight, gestational age at delivery, mode of delivery, maternal pre-pregnancy BMI, maternal age, maternal education, maternal ethnicity, paternal age, paternal education, parental history of allergic disorders, paternal smoking during pregnancy, family income and breastfeeding during the first 6 months".
C2: Reviewer 2 mentions in C4 that breastfeeding should be included in the adjusted model. The authors response is that breastfeeding is not a common cause of both the exposure and the outcome and thus probably not a confounder. In DAGs, the confounder might not be directly related to both exposure and outcome, but still be an important confounder in the path between exposure and the health outcome. E.g. there should be an arrow between maternal ethnicity and breastfeeding, parental education and breastfeeding, and between breastfeeding and AD. Thus, I believe that breastfeeding should be included in the DAG.

R2: As suggested, breastfeeding now has been included in final logistic regression model as a confounder. However, little changes were shown after that.

C3: R11. We have corrected statements on the associations between AD and PFNA Q4 and PFDA Q4 as follows "Due to small sample size, the associations of AD with PFNA concentration and PFDA concentration, were both marginally significant".

R18. … In addition, the associations between AD and prenatal exposure to PFNA and PFDA were marginally significant".

R22. … In addition, the association between AD and prenatal exposure to PFNA and PFDA in girls were marginal significant".

I read the expression "marginally significant" as if the results were significant, but since the CI overlap with 1, they are not significant but close to significance. I therefore recommend the authors to revise their sentences to: "...associations between AD with PFNA and PFDA concentrations were close to statistical significance." This also goes for the last sentence in the abstract.

R3: Thank you for the suggestion. We have revised the sentences as suggested.
Should further revision be deemed necessary, please let me know. We really appreciate your time and efforts.

Yours sincerely,

Jun Zhang