Author’s response to reviews

Title: Prenatal Maternal and Childhood Bisphenol A Exposure and Brain Structure and Behavior of Young Children

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Author’s response to reviews:

Editor's comments: Thank you for the revision. As you can see, the reviewers are not yet completely satisfied that you have appropriately covered effect modifications and reported all relevant findings. The interpretation needs to be cautious.

We would like to thank the reviewers for their supportive comments and suggestions. We have updated the manuscript accordingly.

Reviewer #1: The authors have adequately addressed most of my comments with some exceptions. Moreover, I have a few additional comments.

1. The authors state that they only examined modification by child sex if sex was a significant predictor of the outcome. However, I am not aware of the requirement that a modifier be a significant predictor of the outcome in order to modify the association between an exposure and the same outcome. Again, I strongly encourage the authors to report sex-stratified analyses (regardless of statistical significance), and associated sex x exposure effect measure modification p-values. Thus, the statement on Page 15, lines 19-36 is incorrect and cannot be evaluated without reviewing the sex-stratified analysis. Also, with regard to the age modification, the analyses should be presented stratified by age.

Potential sex X exposure and age X exposure effects for all associations of tract and maternal BPA are now examined and reported within the methods and results sections. Additionally, we also now include models stratified by child sex and age at scan, with all results reported in Tables 3 and 4.

2. Page 17, line 55: The maternal and prenatal seem redundant in this sentence and are potentially confusing since it could imply that this is the mother's BPA exposure while she was a fetus.

As suggested by the reviewer, we have removed “maternal” from this sentence for clarity.

3. Results section: It would be helpful and avoid problems with selective reporting if the authors
presented all the betas/CIs in a table or supplement so that they can be fully evaluated or considered in future reviews/meta-analyses. This is particularly important given the study's low statistical power. All regression coefficients are now reported in Tables 3-6.

4. Figure 2: Please specify what was adjusted for in this model.

We have included all covariates adjusted for within the Figure 2 caption, as well as in the text of the Results. The mediation model was adjusted for child sex and age at scan, as well as maternal urinary creatinine.

5. It is still not completely clear what covariates were adjust for in the final model. Clarifying this with the table suggested above would help. Page 12, line 43 implies that sex and age were included in the final model. It seems particularly important to evaluate the impact of adjusting for age on the beta coefficient (not the p-value) given that MD decreases with age (Page 14, line 41).

Rather than doing stepwise addition of covariates, we now adjust for child sex and age at scan, as well as creatinine levels (maternal or child as relevant), in all models. This has been clarified in the Statistical analysis section and Results section of the manuscript accordingly.

In Tables 5 and 6, we report both the unadjusted and adjusted results. In Table 4, the effect of adjusting for age on regression coefficients can be found.

6. Page 12, line 19: Urine creatinine is typically reported in mg/dL.

Urine creatinine values are now reported as mg/dL.

Reviewer #2: This revised manuscript addresses almost all of this reviewer's concerns about the initial MS.

The one exception is in regard to the underlying hypothesis related to white matter disruption and scores on the CBCL. The authors state that prior research has shown that BPA exposure is related to poorer externalizing and internalizing scores and that white matter disruption is very likely with prenatal and early childhood exposure. But they don't state why they think that white matter abnormalities would be related to CBCL scores. It would seem to this reviewer that there are other brain structures and systems that are more obviously related to CBCL outcomes.

We have now included additional information within the introduction to support our reasoning for investigating the relationships between white matter and CBCL scores.

1 Introduction (page 5):

“Previous studies have shown that widespread alterations in white matter microstructure are associated with higher scores on internalizing (i.e., anxiety and depression) [56, 57] and externalizing (i.e., attention) [58, 59] behaviors measured using the Child Behavior Checklist (CBCL) [60]. Therefore, we also investigated if altered behavior associated with early life exposure to BPA was related to underlying alterations in white matter microstructure. To accomplish this, post-hoc analyses were conducted to
investigate whether white matter alterations mediated the associations between BPA exposure and behavior that have been commonly reported in pediatric studies.”