Author’s response to reviews

Title: Time-Varying Associations between Prenatal Metal Mixtures and Rapid Visual Processing in Children

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Author’s response to reviews:

We thank all the reviewers for their insightful comments. We have addressed each individual comment below. Please note that substantially updated text in the revised manuscript in marked using red font.

Reviewer #1: ENHE-D-19-00157

Major comments

1. Both jWQS and mWQS are based on addition equation. Do they have prior hypothesis about metal mixture effect?

Yes, we are hypothesizing that mixture effects can be assessed on additive scales by using JWQS and MWQS. We believe that both WQS methods are robust with respect to complex mixture models for the following reasons. The weighted index and corresponding weights approximate an additive relationship where the interpretation of the weights is most accurate; however, in the presence of an interaction, the index is still a first-order approximation of the mixture effect. Because environmental exposures are generally low in most child populations, the overall interaction effect is generally modest due to the low scale of the exposure. So while both models are best under the assumption of additivity, the mixture effect can still be approximated by the weighted index even if the components combine with an interaction.
2. As these methods are not based on a priori hypotheses, you acknowledge that your findings should be replicated in independent populations. How do you believe these methods have substantial value helping researchers in observational studies identify the most relevant exposure timing for chemical mixtures, particularly those assessed longitudinally?

Our primary addition to the literature is that our methods assess mixtures measured across time and both overcome the stated limitations of previous methods. Because our analysis factors in timing of exposure, it can inform critical exposure windows. Because our methods generate weights that reflect the relative contributions of each metal specific to a time point of exposure, the weights should correspond to the role of exposure timing for the metal. Critical exposure windows are virtually never known a priori as they arise from the intersection of life stage specific developmental processes (neuronogenesis, migration, synaptogenesis, synaptic pruning, etc.) and the toxicology of environmental exposures that occur at these specific life stages. Thus, any method to uncover them is generally discovery-based and should, therefore, be replicated. We believe that both of our techniques can be used to identify groups of exposures that most affect the outcome(s) of interest, windows of susceptibility and cumulative effects of mixtures.

ABSTRACT

Line 27, call should be calls

Line 30 focus should be focused

Line 36-37, "Understanding critical windows is key to prevention strategies, as they are the ages at which exposure is most impactful." Should be "Understanding critical windows is key to know the ages at which mixture exposure is most impactful, and then to take prevention strategies"

Line 40 "metal mixtures assessed" should be "assess metal mixture effect"

Line 45, delete "measured,"

Line 58, key words should include novelty method.

We have made these changes to the ABSTRACT section.

BACKGROUND

Line 104, due should be due to

Line 11-113, JWQS or MWQS, jWQS and mWQS should be consistent

Line 117-126, these four sentences should be rephrased in 2 sentences.

We have made these changes to the BACKGROUND section.

METHODS

Line 151, you should describe what equipment for measuring blood metal.
Line 170, classifies should be classified

You should add "data screening and analysis" section

We have made these changes to the METHODS section.

RESULTS

Metal in this part should be abbreviation.

p in this should be italic. β should be italic. Please check Metal in table 2 should use As, Cd, Cr etc. Please check the text.

Table 2 and 3. Table line is missing

We have made these changes to the RESULTS section.

DISCUSSION

In this section, tense is mess. Please check text.

We have gone through the DISCUSSION section and addressed this issue.

Line 411-414, this sentence seems "a method".

Line 441, hypothesize should be hypothesized.

Line 443, may should be might

Line 465-468, These sentences should be addressed in "Introduction"

Line 483-485, declare your aim to support "the delay to the correct response in the RVP"

Line 491 "we find that both jWQS and mWQS determine that Cd and Sb are two of the top three metals in terms of their cumulative effect" should be rephrased

Line 510, pay attention to the tense

We have made these changes to the DISCUSSION section.

CONCLUSIONS

You aim to examine the time-varying critical windows for metal mixtures. However, there is no conclusion about that aim.

We have added a note concluding the examination of this aim to the CONCLUSION section.

Figure 1 and 3 should be improved in resolution.
We have improved the resolutions of Figures 1 and 3. We have also improved the resolution of Figures 2 and 4.

Reviewer #2: In this paper, the authors introduce two extensions of weighted quantile sum (WQS) regression for modeling mixture effects over time. One method, joint WQS, places all the chemical concentration quantiles from different times in one index. The other method, meta WQS, fit an index model for each time point separately and then combines the temporal indices into one final index model where the index weights are estimated. The authors apply these two methods to a study on rapid visual processing (RVP) in children exposed to six metals at two time points (second and third trimesters in pregnancy) in the PROGRESS cohort study. There are several issues with this paper.

1. First, this paper needs a simulation study. New methods are introduced with no evaluation of their accuracy, sensitivity, specificity, etc.

We have added a simulation study to the revised paper.

2. There are reasons to be concerned about the performance of the proposed methods. WQS regression performance is known to suffer when chemical concentrations are highly correlated. This is the so-called breakdown case (Carrico et al. JABES 2015). When the same chemical is measured over time, the measures are likely to be highly correlated. Such strong pairwise correlations can increase bias in the weight estimates and hence be an issue for inference. However, there is no discussion in this paper about the correlation levels between metals measured at the same time and also over time.

Chemical exposures in children are not always highly correlated across time. Unlike adults, children change rapidly with respect to size, behavioral patterns and levels of mobility in very brief time spans. For this reason, exposures levels are at often moderately correlated except in older study populations enrolled before the year 2000. These children were often living in older housing during the time in which leaded gasoline was still used. Their environmental lead exposures were therefore uniformly high and likely led to high correlations across time in blood levels. Lead exposure is no longer uniformly high in contemporaneous populations like ours. To illustrate, we have included a new figure of the correlation matrix between among all the metals/time points we studied (see FIGURE 1). We have also added a short discussion about this point to the RESULTS section.

3. Another related issue with the meta WQS method is that the correlation between chemicals at different times is not considered when estimating the weights for each temporal index given the iterative nature of the method. This can lead to very different weight estimates than when considering all the exposures together when fitting the model. Note that the weights presented in Figure 2 are very different for the meta and joint WQS versions. The joint version tends to give much less weight to one of the two time measurements for the same chemical compared with the meta version. This could be due to the amount of correlation between measurements of the same chemical at different times. This correlation would be accounted for more directly in the joint WQS model.

We have updated the discussion of the strengths and weaknesses of JWQS and MWQS in the DISCUSSION section to include this point.
4. There is no discussion of the training and testing sets used in the analysis. What are set sizes and how were they determined?

We have added new text clarifying these points to the METHODS section.

5. There is no discussion of the distributions of the two outcome variables. Accuracy is a proportion (number of questions answered correctly) that seems as it should be modeled as binomial. Delay to response or a transformation of it could be Gaussian.

Both outcome variables were log transformed and treated as Gaussian distributed in the analyses. This was done based upon visual inspection of the histograms of both variables after applying the log-transformation. We have added a short note on this point to the new Data Screening and Analysis part of the BACKGROUND section.

6. The joint model used for time to response has a quadratic term and linear term associated with the exposure mixture, however, the joint model in equation (4) has only a linear term. The model fitted should be written in notation.

We have added the text to the METHODS section immediately below equation (3) that describes this model.

7. No fit statistics are provided to compare the different models.

We have added fit statistics (Bayesian information criterion, BIC) for all combinations of technique (JWQS and MWQS) and outcome (latency and accuracy) to the RESULTS section.

Reviewer #3: I am happy with the quality of writing and the amount of work performed.

I have two queries:

1. Why authors didn't consider the racial statistics under table 1 and throughout the manuscript? Along with demographic consideration it will be interesting to study.

We did not adjust for racial statistics in this study because participants in the PROGRESS cohort are from a homogeneous racial population in Mexico City.

2. What about the data of metals in blood for first trimester?

While it would be interesting to consider the effects of first trimester exposures in addition to second and third trimester exposures, the subjects were recruited during the second trimester of pregnancy. Few cohorts have 1st trimester levels as women may not know they are pregnant till late in the 1st trimester and are thus harder to identify and enrol.