Reviewer’s report

Title: A birth cohort study to investigate the association between prenatal phthalate and bisphenol A exposures and fetal markers of metabolic dysfunction.

Version: 1
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Reviewer: Joseph Braun

Reviewer’s report:

The manuscript describes a prospective pregnancy and birth cohort study investigating the effect of environmental endocrine disrupting compounds on fetal metabolic indicators. Specifically, the authors assessed the relations between phthalates and BPA measured in early pregnancy urine with cord plasma leptin and adiponectin levels. Overall, this is a very interesting and timely manuscript that draws on the strength of a large, population-based cohort in Canada. Some aspects of the methodology need to be described in greater detail, but this should be easily addressed.

Major Compulsory

1. Several aspects of the polytomous logistic regression are unclear, and necessary description of statistical methods is lacking in the current manuscript.

   • Please provide rationale for the use of polytomous logistic regression in the methods. Were other approaches, such as multivariable linear regression with continuous log-transformed adipokines as outcomes, simple logistic regression using #10th percentile and #90th percentile of adipokines as outcomes, or even quantile regression utilized? I suspect that the investigators had good reason to choose polytomous logistic regression, but this is not reflected in the current manuscript.

   • Please report additional details of the statistical methods that will assist future investigators in replicating your study findings. For example, did the polytomous models account for the ordinal nature of the response categories? Depending upon the parameterization of the polytomous regression models, the interpretation of the resulting odds ratios may not be entirely straightforward. A more detailed interpretation of the odds ratios presented in the results on p. 10 paragraph 3 & 4 would likely be helpful to readers. I’d also suggest adding simple logistic regressions for #10th percentile or #90th percentile of leptin or adiponectin as sensitivity analyses to aid in the interpretation of the results. I
believe the paper would be enhanced by presenting linear regression estimates using quantiles or splines as well.

2. Leptin is a marker of fat mass. Thus, the authors are measuring an association with birth weight in the leptin analysis when they are really interested in identifying exposure related deviations of cord plasma leptin for a given birth weight (really, for a given fat mass, but birth weight is probably a reasonable proxy here). This should be addressed in the analysis or at least discussed. The authors might consider using the residuals of a leptin-birth weight regression to see if phthalates or BPA are associated with deviations in leptin beyond those expected by birth weight.

Minor Essential Revisions

1. Due to the non-collapsible nature of the odds ratio, adjustment variables should be true confounders (associated with the exposure, associated with the outcome, and not on the causal pathway). Gestational weight gain is of particular concern because it occurs after exposure and is probably more accurately treated as a mediator of the exposure-outcome relation. What is the impact on the point estimates if gestational weight gain is removed from the models?

2. In the methods on p. 8 paragraph 2, it is not clear whether molar weights of the component metabolites were used in the creation of the DEHP summary variable. If not, the DEHP analysis is likely driven by MEHHP levels. I’d suggest creating the summary DEHP variable by dividing each measured metabolite concentration by the molar mass of the metabolite and then summing across metabolites (see Watkins et al. 2014 for an example of this approach). Does use of the molar summary measure of DEHP change the observed relations with leptin and adiponectin?


3. The different handling of specific gravity across analyses should be better described and justified. What was the motivation for including specific gravity as a covariate in the multivariate models in the methods on p. 9 paragraph 1? The reference is helpful, but a brief justification for the use of this approach in the present analysis seems warranted.

4. Please provide additional details related to enrollment and selection of the final analytic population. Specifically, when were women enrolled into the cohort? This will give further context to the temporal exposure trends in North America described on p. 12 paragraph 2. Also, were there any differences in terms of exposure levels or other relevant characteristics between the 1237 maternal-infant pairs included in the final analytic population versus the maternal-infant pairs that were excluded?

Discretionary revisions

1. As suggested by the authors, blood measures of BPA are problematic, and
this point could be further emphasized in the discussion related to discrepancies between the present study and those of Chou et al. 2011 on p. 11 paragraph 3.

2. The role of confounding by unmeasured co-exposures or other environmental contaminants should be specifically mentioned in the limitations section of the discussion on p. 13.

Level of Interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician
Declaration of competing interests: I declare that I have no competing interests

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Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
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