Author's response to reviews

Title: Biomonitoring of bisphenol a level in maternal and umbilical cord blood relevant to birth outcomes and adipokine expression: a birth cohort study in Taiwan

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Response to Reviewers’ Comments for MS-1312412857516153

Thanks for these valuable comments greatly improving the quality of this manuscript. The manuscript has been revised with the comments carefully considered. The following are the detailed responses to each comment. We use the yellow markings to highlight the changes and new entries in the text.

Major compulsory Revisions:

1. Recruitment and sampling methods: This is clearer but is it true that 100% of subjects who were approached for the study consented to participate in the study? Is this true and if not what was the response rate?
   Response: Thanks for your comment. This study recruited 157 pregnant women, and 134 completed a self-reported questionnaire. The response rate is 85.3%. We added the description at the page 6 (Study subjects).

2. Laboratory methods: The additional information is helpful in terms of reproducibility of the analyses. No information is given about recovery from blanks, an important issue in light of the situation with regards to background levels of BPA in laboratories generally.
   Response: The QA/QC materials were prepared from a plasma pool obtained from multiple anonymous pregnant women donors in analysis with standard, reagent blank, and unknown samples. We performed external calibration using the chromatographic responses of seven standard concentrations in their corresponding solvent. The recovery rates of blanks were 96-109%. The relative standard deviation (RSD) among triplicate analyses were 1.99-7.53%, and the recovery percentage was 96.1% with an RSD of 7.53%. We added the description at the page 7-8 (Chromatographic system and conditions).

3. Data analysis: The authors used LOD/2 to impute for non-detects. First they should report the percentage of samples that were reported as ND and second use of LOD/sqrt(2) is less biased for imputing ND when data are lognormally distributed.
   Response: The analysis of this study has been revised based on your comments and modified the description about “ND” in page 8.
4. Regression analysis: Lines 180-185 are not completely clear. The dependent variables are LBW, SGA, adiponectin and leptin. It appears that independent variables for LBW and SGA outcomes were selected based on two prior studies of leptin levels and neonatal growth, as well as empirically based on the data analysis. The last sentence in this section needs to be rewritten. The text implies that the authors found no significant differences in LBW or SGA vis-a-vis smoking or socioeconomic status; this would be rather unexpected. Looking at Table 2, I wonder if what was intended was to state that smoking and socioeconomic status were not associated with whether mothers were in “high” or “low” BPA groups and that is why these variables were not considered as potential confounders?

Response: Thanks for your comments. We rewrote the sentences in page 9 (Statistical analysis) for clearly describing the selection of confounders. We included the smoking and socioeconomic status as potential confounders in the analysis of this study.

5. Results: In the authors’ response to the editors they draw a nice u-shaped dose response curve. However they do not address the points that I made about the extent to which their findings actually follow a u-shaped dose response. To be clear, here is an alternative interpretation, how the dose response curves would appear to me, based on the modeling by quartiles in Table 2: a. Male Neonates i. LBW: Q1: Control, Q2 significant increase in LBW, Q3 significant decrease in LBW, Q4: significant increase in LBW. Shape of curve: Z-shaped. ii. SGA: Q1: Control, Q2 significant decrease in SGA, Q3 significant decrease in SGA, Q 4: significant increase in SGA. Shape of curve: U-shaped but “adverse” effect only at highest exposure quartile. iii. Adiponectin: Same as SGA. iv. Leptin: Same as LBW only the decreased level at Q3 is not significant. b. Female Neonates i. LBW: No effect ii. SGA: Q1: Control, Q2 significant increase in SGA, Q3 no effect, Q 4: significant increase in SGA. Shape of curve: Z-shaped and “adverse” effect occurs at 2nd and 4th exposure quartiles. iii. Adiponectin: Q1: Control, Q2 significant decrease in adiponectin, Q3 non-significant decrease in adiponectin, Q4: significant decrease in adiponectin. Shape of curve: “threshold” iv. Leptin: Q1: Control, Q2 significant decrease in leptin, Q3 significant decrease in leptin, Q 4: significant increase in leptin. Shape of curve: U-shaped but “adverse” effect only at highest exposure quartile.

Response: Thanks for your comments. We have added description in page 12 (Multivariable adjusted ORs for neonate outcomes by quartiles of maternal BPA level) based on your mention to interpret the dose response curves modeling by quartiles in Fig. 2.
Minor Essential Revisions:
1. There is still need for a thorough edit of the manuscript.
Response: The manuscript has been revised by Wallace English Editing.

2. Background: Lines 89-91 contain more description about BPA levels in adipose tissue however the authors refer to levels found in adipose as “accumulation”. It would be more accurate to refer to these as follows: “BPA has been detected in adipose tissue.”
Response: We have revised the sentence based on your comments in page 5 “BPA has been detected in adipose tissue to alter the release of adiponectin and leptin”.

3. Results: As noted above some of the odds ratios in Figure 2 are “elevated”: and statistically significant and these (except one, the OR for leptin at Q2 for males) are labeled. Others are significantly lower than one but are not labeled: (e.g., male, LBW, Q3; male, SGA, Q2 and Q3; male, adiponectin, Q2 and Q3; female, adiponectin, Q2 and Q3; and female, leptin, Q2 and Q3). For consistency perhaps all significant findings (high and low) should be labeled.
Response: Thanks. We have clearly described the results of Fig. 2 in the text of this manuscript as well as labeled the significant findings in Fig. 2.

4. Discussion: On line 375 and following that, please look more carefully at the paper that is cited that provides evidence that glucuronidated BPA has been “demonstrated’ to cross the placenta and be deconjugated in the fetus. This has been reported in only one study and needs to be cited more cautiously. Also in general be careful about appearing to infer causality on the basis of single studies (or your own study) including in lines: 75-80, 281-284, and 289-291.
Response: We revised the sentences in page 17 “Nishikawa et al. reported that maternal BPA-glucuronide (BPA-GA) may cross through placenta and deconjugate to BPA in the fetus” to describe more carefully the results.