Author’s response to reviews

Title: Association between ambient particulate matter concentration and fetal growth restriction stratified by maternal employment

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Author’s response to reviews:

Dear Dr. Zhu,

We are resubmitting our revised manuscript entitled “Effect modification by maternal employment in the association between outdoor particulate matter and fetal growth restriction” (PRCH-D-19-00020). We revised our manuscript taking into account the suggestions of the editors and reviewers. The major changes were made based on our extended additional analyses for effect modification, unadjusted spatial variability, and fixed exposure period for the third trimester, as suggested by reviewers. In particular, our the assessment of effect modification by maternal employment includes examination of additive interaction and careful interpretations of findings. We responded to each point of the comments in details and highlighted corresponding changes of the text in our enclosed responses.

Thank you for consideration of our revised manuscript.

Sincerely,

Sun-Young Kim, PhD
Department of Cancer Control and Population Health
Reviewer 1:

This study examined the effect modification of mothers’ employment status on the association between outdoor particulate matter and fetal growth restriction. The findings of this study are of great importance for the public health. I provided a few comments for the authors to consider:

Response: We appreciate this positive comment.

Comment 1: The statistical methods should be a mix-effect model, as they assessed the exposure at the district level, rather than real individual level. Also people living in the same district may share some similar characteristics. Please refer to a few similar studies: Ritz B, (2007). American Journal of Epidemiology 166(9): 1045-1052. Lin H, (2017). Hypertension 69(5): 806-812.

Response 1: We applied mixed models using eight district groups (downtown and areas 1 to 7) based on geographical proximity and regional SES to consider correlation within each of the district groups to examine the robustness of primary results (Lines 214-218 and 271-274 in the revised manuscript). The patterns of mixed model results were similar to our original results without including random effects. We added the analysis method and results of mixed models to the main text and supplemental materials (Supplemental Table 1 and 2).

Comment 2: How did the authors assess the employment, for example, some pregnant women may be employed during the early stage of pregnancy, and then unemployed at late stage.

Response 2: We agree that identification of actual duration of employment would be important to assess possible exposure misclassification. As a retrospective study of birth registry data,
however, the duration of employment during pregnancy for each mother was not available. We mentioned this limitation in the Discussion (Lines 356-360 in the revised manuscript).

Comment 3: How did the authors examine the statistical significance of the difference between the two groups, employed VS unemployed?

Response 3: We used chi-square test and student t-test for categorical and continuous variables of mothers’ individual characteristics and prevalence of SGA and LBW to examine the difference between employed and non-employed mothers. Due to the large sample size, most results indicated statistically significant difference between the two groups. We described our methods and the result for SGA and LBW in the Methods and Results (Lines 194-196 and 245-247).

Comment 4: Are there any different between the included and excluded mothers?

Response 4: LBW were similar between included and excluded mothers, whereas some difference in SGA and PM exposure. We provided detailed information in this similarity and difference in the Methods (Line 131-136).

Comment 5: Any missing data for air pollution?

Response 5: When we applied our inclusion criteria for days and sites and computed daily average concentrations of PM10, there was 6.9% of missing days of air pollution measurements for 11 years and at 25 monitoring sites. We do not believe that this small percentage of missing affected our results. We added the information of missing days to the Methods (Lines 169-170).

Comment 6: For the third trimester, I would suggest to use a fixed time period, for example, 1 week or 2 weeks, as the current definition would lead to different exposure length.
Response 6: As the reviewer suggested, we recalculated the PM10 concentrations for the fixed 3rd trimester from ‘28+0 to 36+6 weeks’ and replaced our original results for a non-fixed period (Line 174).

Reviewer 2: This is an interesting study. The authors examined the association between outdoor particulate matter and fetal growth restriction and how the association differed by maternal employment status. The data available to the authors represents unique strengths and makes this a valuable piece of work. It can be improved by more rigorous presentations of the results, as well as some explanations and clarification.

Response: We appreciate the positive comment and constructive suggestions.

Comment 1: In the abstract, the authors mentioned "Proportions were different for LBW (1.5% in employed and 1.6% in non-employed, P < 0.001) and similar for SGA (12.7% and 12.8%, P= 0.124).". In the main text results section, the authors stated "Proportions of both SGA and LBW were consistent between employed and non-employed mothers (12.7 and 12.8% for SGA, 1.5 and 1.6 % for LBW).". It is confusing whether the authors wanted to interpret the percentages among the employed and non-employed as consistent or not. Also it is not clear whether 1.5% and 1.6% was considered as different but 12.7% and 12.8% was consider as similar because of the P-value.

Response 1: We agree that our description would confuse readers. Although p-values indicated statistically significant difference because of the large sample size, the differences in LBW and SGA between employed and non-employed mothers were only 1% which is tiny. We revised our text to provide statistical results without conclusions and clarified that significant difference is largely driven by large sample size (Lines 245-247 in the revised manuscript).

Comment 2: In the results the authors stated "At the time of birth, 35.5% (293,440) were employed and 66.4% (549,270) were non-employed (Table 1).". However, 35.5% + 66.4% is greater than 100% and the numbers do not seem to match, i.e. 816,661*35.5% = 289,915 and 816,661*66.4% = 542,263. Also numbers listed in this sentence do not seem to match with Table 1. In Table 1, the number of employed and non-employed are 277,482 and 539,179, respectively.
Response 2: Thanks to the reviewer, we corrected the numbers. At the time of birth, 34.0% (279,856) were employed and 66.0% (544,155) were non-employed. In addition, we should note that the total number of mothers is 824,011 in the revised manuscript instead of 816,661 in our original manuscript, because we found some mothers had been mistakenly excluded (Lines 243-244).

Comment 3: Similarly, in the results the authors mentioned "In our study population of 816,661 singleton term births, SGA and LBW comprised 12.8% (104,142) and 1.6% (12,749), respectively". However, 816,661*12.8% = 104,533 and 816,661*1.6% = 13,067, which do not match with the sentence.

Response 3: The differences occurred because of rounding: 12.75217 and 1.561113 % to 12.8 and 1.6 %. As the total population was changed to 824,011 as described in our response to the Comment 2, we recalculated these percentages (Lines 225-226).

Comment 4: Table 2 and 3 represent results for 2002-2012 (PM10) and 2008-2012 (PM2.5), respectively. However, based on the title the sample size was the same for these two tables. It is important to mention the sample size in 2008-2012 in the main text methods section since all analyses for PM2.5 were performed with this instead of the total of 816,661.

Response 4: We agree with this suggestion. We clarified that the study population for PM2.5 includes 386,483 mothers for 2008-2012 (Table 3).

Comment 5: The authors interpreted OR=1.02 as "2% higher probability"; however, this is incorrect. The 2% increase should be on the Odds scale, i.e. for every IQR increase of PM10, the Odds of having the outcome was increased by 2%. If the authors want to interpret the OR on the probability scale they should transform Odds back to probability using the formula: Odds = P/(1-P).

Response 5: We agree with the reviewer’s point and revised the text (Lines 259-260).
Comment 6: The authors concluded effect modification by employment status based on stratified analysis. In fact, stratified analysis along is not sufficient for effect modification because heterogeneity cross strata may indicate different things, such as confounding, effect modification, both, or neither. To examine effect modification, the authors need to at least add interaction term between air pollution and employment status in the model and present the joint effect, the estimates of the interaction term, the effect of PM only, as well as the effect of employment only. Other approaches, such as relative excess risk due to interaction (RERI) are also often used in many studies.

Response 6: We appreciate this suggestion. We added the concept of RERI and analysis results to the Methods and Results of the revised manuscript. Based on our findings of RERI’s close to null for all pairs of PM and pregnancy periods, we provided our conclusion of no evidence of effect modification (Method and Discussion section).

Comment 7: In this study, PM estimates were measured based on maternal residential addresses. There could be other sources of PM air pollution at workplace. I wonder whether the authors could refine the title and main text to make it clear that this study focused on outdoor PM near residential locations instead of occupational locations.

Response 7: We considered to change our title. We however were concerned about that the change may confuse readers because we used district-level residential addresses instead of full addresses. In addition, because most literature of air pollution and birth outcomes relies on residential exposure of mothers, adding ‘residential’ to the title may gain little value. Thus, we decided to keep the current title. However, we clarified our limitation without incorporating exposure at work in the Discussion.

Comment 8: In many epidemiological studies that use maternal residential address to estimate air pollution, residential mobility is an issue to be discussed as women could have moved during pregnancy, and if the air pollution level varied at different locations it may introduce measurement error by using incomplete residential address histories to estimate air pollution during pregnancy. I wonder whether the authors could elaborate in more details on this, i.e. whether they took into account multiple addresses per woman into account.
Response 8: We agree that there can be misclassification bias in estimating maternal exposure based on residential addresses at the time of birth. We added this limitation to the Discussion. We also mentioned a weak possibility of this misclassification affecting our results because of relatively small proportion of moving for mothers compared to that for general Korean population. According to previous report of a population-based sample cohort in Korea, proportion of relocation across district (“gu”) or province was 8-25% for the employed and the non-employed during the same period (2003-2012) (Kim et al., 2017). (Lines 374-377).


Comment 9: In the discussion the authors mentioned that there is possible selection bias because mothers in this study are mostly residents in Seoul which less represent deprived socio-economic conditions which also contribute to poor fetal growth. However, this is more like an external validity problem, i.e. results in this study may not be extrapolated to other populations, such as populations that include all residents in both urban and rural areas.

Response 9: We agree with this point. We removed the term “selection bias” and revised the text to suggest mothers’ characteristics in Seoul as one of the possible explanations for our results (Lines 382-383).

Comment 10: The authors mentioned healthy worker effect, i.e. in general employed mothers are likely to have a more favorable health status than general population. I wonder whether the authors examined the possibility that the effect of PM on growth restriction could be confounded by employment status. For example, mothers with higher SES status are more likely to be living in urban areas with higher levels air pollution, meanwhile these mothers are also more likely to work, have higher education level and better health status, therefore are less likely to develop growth restriction during pregnancy. If employment status was on the confounding pathway, controlling for it may change the effect estimates of PM on growth restriction.

Response 10: To examine the role of maternal employment in the association between air pollution and fatal growth restriction, we conducted DAG analysis based on the previous study findings (Supplemental Fig 1). Maternal employment was associated with exposure (P = 0.040
for entire pregnancy PM10 and -0.049, P < 0.001 for entire pregnancy PM2.5) and outcome (P < 0.001 for SGA and -0.091, P < 0.001 for LBW) with adjustment for all covariates. We added the DAG analysis and results to the Methods and Results, and a possible role of maternal employment as a confounder in the Discussion (Lines 181-184 and 291-292).

Comment 11: Employment status could be a proxy of many things, such as higher SES, more work demands and job stress. On the other hand, it is also possible that women who commute between home and work have higher chance to be exposed to traffic-related air pollution. If this is the case, when stratifying by (or adjusting for) employment status it could "over-adjust" outdoor PM exposure and the effect of PM on growth restriction observed in this study could be diluted. I wonder if the authors could discuss some of the possible mechanisms of the impact of employment status on growth restriction in more details.

Response 11: We added the relationship between mothers’ employment status with SES and exposure to the Discussion (Lines 312-316).

Reviewer 3:
This study examined effect modification by maternal employment in the association between exposure to PM10 and PM2.5 during pre-pregnancy and pregnancy and fetal growth restriction (LBW and SGA). This study included a large representative sample and conducted proper statistical analysis. However, the exposure assessment could be improved, and the results need better interpretation.

Abstract
Comment 1: Background: please state the main objective (i.e., to examine effect modification) clearly in the background section.

Response 1: We clarified the study objective as the assessment of effect modification in the Background section (Line 37-38 in the revised manuscript).

Comment 2. Methods: "Individual-level" seems to be conflicting with "district-level". It may be more clear just to say "district-level".
Response 2: We changed to “maternal” (Line 42).

Comment 3. Results: the sentence "Proportions were different for LBW (1.5% in employed and 1.6% in non-employed, P < 0.001) and similar for SGA (12.7% and 12.8%, P= 0.124)." is not very convincing when the differences between 1.5% and 1.6% was simply due to a "statistically significant" p-value. Please rephrase.

Response 3: We agree with the reviewer’s comment. We revised the phrase in the abstract (Lines 53-55). The differences were statistically significant between the two groups due to the large size of population, although the difference is only 1 %. We clarified this point in the Results (Lines 245-247).

Comment 4. Results: again, it is not convincing to claim an association of SGA for PM10 with an OR=1.02 or OR=1.01 with a 95% lower confidence limit of 1.00.

Response 4: To apply a more conservative criterion, we relied on p-value instead of 95% confidence interval and revised our manuscript (Lines 54-57 in the revised manuscript). We bolded the values with P < 0.05 in Tables (Tables).

Comment 5. Results: according to my comments above, I believe there is insufficient evidence to support the conclusion that maternal employment modifies the association.

Response 5: We agree with the reviewer’s comment. We additionally used relative excess risk due to interaction (RERI) to assess additive interaction by maternal employment in the revised manuscript (Line 59). In our results, we did not find evidence of effect modification by maternal employment. We described our findings close to null from interaction analysis in the text and Tables.

Background
Comment 6. Third paragraph: I suggest the authors to focus more on the biological mechanism of particulate matter potentially causing fetal growth restriction and the reason why there is effect modification. Are there any other justifications for the proposed effect modification other than misclassification of exposure?

Response 6: We added the description of possible underlying mechanisms proposed by previous studies to the Introduction (Lines 88-91). For effect modification, physical work demands and job stress in employed mothers were related with higher risk of LBW (Niedhammer et al., 2009). Longer time spent in transit among working mothers resulting higher traffic-related air pollutants and noise which is also related with less optimal fetal growth (Nieuwenhuijsen et al., 2017). On the other hand, the actively employed are likely to have a more favorable health status than general population at large (Pearce et al., 2007) (Lines 101-105).


Comment 7: Line 95: "In addition, misclassification of exposure is possibly larger than for the non-employed, …" Is there an extra "than" in the sentence?

Response 7: We corrected the sentence (Lines 105).

Methods
Comment 8. Line 131: please explain why "we excluded measurements at urban roadside sites located next to large and busy roads". This might result in the lack of exposure contrast leading to almost null associations.

Response 8: We agree that exclusion of roadside sites reduced exposure variability. However, because urban roadside sites are located right next to busy and large roads for monitoring air pollution from traffic sources, these sites would not represent residential exposure. In contrast, urban background monitoring sites are mostly located at the community-service centers in largely populated residential areas. We believe that these urban background monitoring sites only would better represent the level of air pollution exposure for people. We added this information to the Methods (Lines 153-158).

Comment 9. Line 133: the district-level exposures with a coarse spatial resolution may also explain the lack of association, especially when the authors focused on term births with LBW and SGA. Is there any way to improve the exposure assessment first to increase the main effect of PM on fetal growth restriction before even looking at effect modification?

Response 9: We estimated maternal PM exposure based on district because maternal residential address was available only at the district level (average size of districts= 25 km2) in the national birth registry data. Since temporal variability is much larger than spatial variability in daily averages of air pollution exposures in Korea (Yi et al., 2016), the impact of exposure measurement error resulting from spatial misclassification may not be substantial. We agree that the association using more refined individual exposure measure would improve the precision of effect estimates. We clarified this limitation and our related discussion in the Discussion (Lines 166-167 and 380-383).

Comment 10. Last paragraph discussing effect modification should have its own subheading (e.g., effect modification) and moved above "statistical analysis".

Response 10: We created the new subsection “Assessment of confounding and effect modification” and moved the sentences for effect modification to the section (Lines 180-191).

Results
Comment 11: Line 188: "Proportions of both SGA and LBW were consistent between 189 employed and non-employed mothers (12.7 and 12.8% for SGA, 1.5 and 1.6 % for LBW)." This is different from what the authors concluded in the abstract. Please be consistent and make the appropriate statement.

Response 11: We changed the sentences consistent with those in abstract (Lines 53-55 and 244-245).

Comment 12: Table 2: It's difficult to find a difference in ORs for SGA between employed mothers and unemployed mother. They all seem to be very close to the null associations with borderline 'statistical significance'.

Response 12: To assess the significance of difference in ORs, we presented RERI’s. As the reviewer commented, the differences were not significant. We clarified this finding (Table 2 and 3).

Discussion/Conclusions

Comment 13: Please update the first paragraph of discussion and conclusions according to the abovementioned comments.

Response 13: We revised our conclusion to clarify the lack of evidence for effect modification by maternal employment status in the association between air pollution and fetal growth restriction (Lines 285 and 291-292).

Reviewer 4:

This study assessed the modification effects of maternal employment on the association between outdoor PM exposure and fetal growth restriction. They observed that maternal employment can modify the association between PM and fetal growth restriction. However, I have several major concerns:

Generally, I prefer to handle the employment status as a potential confounding factor rather than a modification factor, since the employment is related to maternal seriocomic status and exposure misclassification, as the authors stated, which may lead to confounding bias to their
results. Although the authors have observed significantly different associations of PM10 with fetal growth restriction between pregnant women with and without employment, the tiny differences (OR: 1.01 vs 1.02; SGA: 11.2% vs 11.2; LBW: 1.5% vs 1.6%) have very weak public health significance, and the statistical significance may be due to by chance because they included a very large sample size. In addition, they did not observe the significant effects of PM2.5 on fetal health, which is inconsistent with many previous studies which have found more toxic effects of PM2.5 than PM10.

Response: We agree with the reviewer’s point. As we presented additional analysis results based on the DAG (Supplemental Fig. 1), employment status can be a confounder in the potential causal association between PM exposure and fetal growth restriction. Given that a confounder can be also an effect modifier, we assessed additive interaction by maternal employment using relative excess risk due to interaction (RERI). RERI’s for PM10 and PM2.5 indicated there is no significant additive interaction. Based on our findings in the revised paper, we concluded that there is lack of evidence indicating significant effect modification by maternal employment status in the association between air pollution and fetal growth restriction. We updated the manuscript accordingly.

Minor comments

Comment 1: In the abstract, the authors stated that the PM2.5 data was selected during 2008-2012. However, the duration was changed to 2007-2012, which is contradictory.

Response 1: That is because we included PM concentration for one year before birth in the analysis. As the PM2.5 was available only from the year of 2007, we restricted the analysis to birth data in 2008-2012 for PM2.5. We revised the manuscript to clarify the study period for PM2.5 is for births between 2008 and 2012 (Lines 162-163).

Comment 2: The explanation on the modification effects of employment in the discussion is not convince.

Response 2: We agree with the reviewer’s comment. As mentioned above, we added effect modification analysis and revised the conclusion to clarify that there is lack of evidence for the effect modification (Lines 294 and 312-316).
Reviewer 5:

Choe et al examined maternal residential air pollution exposure and fetal growth in Seoul and explored effect modification by maternal employment status. Most of the results were similar between employed and non-employed mothers, with a few exceptions. I have some concerns that need to be addressed concerning exposure assessment and interpretations of results.

Exposure Assessment:

Comment 1: Why did the authors exclude monitor sites near large and busy roadways? Excluding these monitors decreases the average PM measurements and may explain why ORs are not significant and so close to the null.

Response 1: We agree that our exclusion of roadside sites decreased average measurements. However, because urban roadside sites are located right next to busy and large roads for monitoring air pollution from traffic sources, these sites would not represent residential exposure. In contrast, urban background monitoring sites are mostly located at the community-service centers in largely populated residential areas. We believe that these urban background monitoring sites only would better represent the level of air pollution exposure for people. We added this information to the Methods (Lines 153-158).

Comment 2: How large is a district or gu? Are districts smaller than the city of Seoul?

Response 2: In the city of Seoul with the area of 605 km2, there are 25 districts or gu’s ranged from 10 to 47 km2 (Lines 158-160).

Results

Comment 3: The same IQR was used for all analyses - what are the other IQRs? Is the full year IQR the most appropriate?
Response 3: We applied the same IQR value obtained from the one year consistently for PM10 or PM2.5. Although there are some differences in IQRs across different antenatal periods, we used the identical increment to allow the comparison of effect estimates across different periods.

Comment 4: Are the ORs between employed and non-employed mothers significantly different (for the same exposure and outcome association)? They all are close to 1.00 and do not appear to be different.

Response 4: We agree with the reviewer’s comment. We additionally used relative excess risk due to interaction (RERI) to assess additive interaction by maternal employment in the revised manuscript. In our results, we did not find evidence of effect modification by maternal employment. We described our findings close to null from interaction analysis in the text and Tables (Lines 207-208 and 262-263).

Discussion

Comment 5:The authors indicate that prior studies of air pollution and fetal growth are not consistent, possibly because of maternal employment. Did these studies adjust for employment in their models?

Response 5: Most of previous studies on air pollution and low birth weight at term did not consider maternal employment or job. Covariates used in most of studies were mother’s age, education, parity, prenatal care, race/ethnicity and the infant’s sex (Fleischer et al., 2014; Laurent et al., 2016). A study on effect modifier in the association between air pollution and adverse birth outcomes assessed maternal smoking, low and high BMI and low SES (Westegaard et al., 2017) (Lines 108-114 and Supplemental Fig. 1).


Comment 6: How do the present study's findings compare to the prior studies that examined PM and fetal growth cited in the introduction?

Response 6: The magnitude of the relationship between PM10 or PM2.5 and LBW at term was lower in our study than in previous studies which employed population-based birth record data (Candido da Silva et al., 2014; Ha et al., 2017; Michikawa et al., 2017). In addition to lower LBW, this might be due to potential misclassification driven by the restricted address information in our data. (Shah and Balkhair, 2011) (Line 332-335).


Comment 7: Another limitation is unmeasured confounding by income and neighborhood socioeconomic status. Since exposure is measured at the district level the authors should consider measuring an index for district-level SES to include in all of their models to address this limitation.

Response 7: To account for unmeasured area-level confounders such as district-level SES, we applied mixed models including random effect at the district groups. The eight district groups (downtown and areas 1 to 7) were defined based on geographical proximity and regional SES in a previous study (Lines 215-219 and 272-273). The findings of this mixed model were consistent with our original findings without random effect. We added our mixed effect model and analysis results to the Methods and Results (Supplemental Table 1 and 2).

Minor Comments

Comment 8: Why didn't the authors explore the association between PM and preterm births?

Response 8: To address the association with preterm, we would need to consider perinatal complication such as hypertensive disorders in pregnancy which inevitably leads to preterm birth to determine spontaneous or medically indicated preterm birth. Since our national birth data does not provide this information, we restricted our study population to term birth.

Comment 9: Line 166-167 needs a citation

Response 9: We added a citation (Line 212).

Comment 10: The sample sizes in line 187 and percentages in line 189 do not match those in Table 1

Response 10: We corrected total sample size and corresponding numbers (Lines 243-244).
Comment 11: The decrease in birthweight over time (shown in Figure 1) is not mentioned at all. Was it a statistically significant decrease?

Response 11: We added the description for the temporal trend of mean birth weight in term births to the Results (Line 236).

Comment 12: Supplemental Figure 1 is hard to read (blurry)

Response 12: We uploaded the revised figure with improved resolution (Supplemental Fig. 2).

Comment 13: Line 227 doesn't make sense "This was not evident in those employed who have been growing portion of mothers."

Response 13: We revised this sentence to “Although we reached different conclusions between employed and non-employed mothers, there was lack of evidence indicating additive interaction by maternal employment status in the association between air pollution and fetal growth restriction.” (Lines 284-287).