Author's response to reviews

Title: Active and passive maternal smoking during pregnancy and birth outcomes: the Kyushu Okinawa Maternal and Child Health Study

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Version: 2 Date: 30 April 2013

Author's response to reviews:

Reviewer: Anastasia Iliadou
Reviewer's report:
This study elucidates the effects of active and passive smoking during pregnancy on prenatal outcomes such as birth weight, preterm birth and small for gestational age (SGA). The nice aspects of the study is that they have information about smoking habits at all three trimester of the pregnancy as well as reports of passive smoking.

Here are my comments:

Major Compulsory Revisions

1. Throughout the text the authors use the term “westernized countries”, “in the West”. I find it a bit awkward since many countries in the “east” are developed and have been developed enough for the past 20-30 years. So I suggest that they change the wording to developed countries.

Response:
We are very grateful for your careful review and insightful comments. We have carefully revised the manuscript according to your remarks.

We used the terms “Western countries” and “in the West” in the Abstract and Background. All of the investigations in relation to References from #4 to #24 in the revised manuscript were conducted in Western countries. On the other hand, we could not find any previous epidemiological studies on the relationship between maternal smoking during pregnancy and birth outcomes that were performed in Asian (Eastern) countries except for Reference #25 (in the revised manuscript) that was conducted in Japan. In this manuscript, we would like to point out the difference in the accumulation of epidemiological evidence between Western countries and Asian countries, especially Japan. In this context, we think that such terms are appropriately used and we decided not to change the text.

2. In page 4, 2nd paragraph, line 7 they mention that “quitting maternal smoking
in early pregnancy was not found to affect the risk for LBW, preterm or SGA”. I suggest that they scan the literature better since I found one study for example where pregnant smokers who quit in the first trimester lowered their risk of delivering preterm and SGA newborns to a level similar to that of pregnant nonsmokers (Polakowski LL et al Obstet Gynecol. 2009).

Response:
We added the following reference (#24) to the Methods section in the revised manuscript. We could not find other epidemiological studies that were not included in our manuscript and that investigated the relationship between quitting maternal smoking in early pregnancy and birth outcomes.


We added the following passage to the Discussion section:

“In a retrospective cohort analysis of US birth certificates, which compared women who smoked throughout pregnancy with those who quit during their pregnancy, those who quit smoking in the first trimester had lower risk of delivering preterm non-SGA, term SGA, and preterm SGA newborns, and this risk was similar in magnitude to those who never smoked [24].” (Page 11, Lines 11-15, in the revised manuscript).

3. Maybe this is just my misunderstanding but in the methods section you report that the seven prefectures on Kyushu and Okinawa have a total population of 1.37 million. But the largest of the seven prefectures had a total population of 5.04 million and then further down the six prefectures except Fukuoka have a total population of 8.22 million. Maybe as I mentioned I might have misunderstood but a clearer description would help the reader a lot.

Response:
Okinawa Prefecture has a total population of 1.37 million. We moved the phrase “an island chain in southwest Japan with a total population of nearly 1.37 million” to a sentence after the next (Page 5, Lines 11-12, in the revised manuscript).

4. In page 6, last paragraph you mention that gestational age is either estimated through ultrasound or first day of last menstrual period. Do you know how many were estimated from each method? I would suspect that all of them would have been estimated by ultrasound.

Response:
No, we did not know how many were estimated from each method. Maybe, all of them had been estimated by ultrasound. According to a clinical professor in our university, the following sentence is reasonable: “In Japan, generally, an obstetrician’s estimate of gestational age at the time of delivery is based on early ultrasound examination and/or the first day of the last menstrual period and birth
weight is measured right after birth.” The professor stated that another sentence “The gestational age was determined by the last menstrual period and confirmed by the ultrasonography at 9-11 weeks' gestation.” is available. As a result, we decided not to change the original sentence.

5. Page 7 statistical analysis. You mention that the categories of smoking were, smoking during 1st trimester, smoking during 2nd or 3rd and smoking through the whole pregnancy. What about the category smoking during 1st and 2nd trimester? Did you not have any women who fell into that category? And are these categorizations based only on the questionnaire that was administered after delivery or did you create some kind of algorithm to combine answers from both questionnaires?

Response:
Active smoking status was determined based on only the second questionnaire that was administered after delivery. In the questionnaire, with respect to each trimester, subjects chose from among three options: 1) had never smoked, 2) quit smoking, and 3) had smoked through the trimester. Based on these three answers, active maternal smoking during pregnancy was classified into four categories: 1) never smoked during pregnancy, 2) smoked only in the first trimester, 3) smoked in the second and/or third trimesters but not throughout the pregnancy, and 4) smoked throughout pregnancy.

The first category consisted of subjects who answered “had never smoked” in all trimesters. The second category included those who answered “quit smoking” or “had smoked throughout the trimester” in the first trimester, but answered “had never smoked” in both second and third trimesters. The fourth category included those who answered “throughout the trimester” in all trimesters. The other women who were not included in the first, second, or fourth category were included in the third category. Thus, women who had smoked in the first and second trimesters were included in the third category.

To make this situation clear, we added the phrase “regardless of smoking status in the first trimester” to the sentence in relation to categorization of active smoking status in the Methods section (Page 7, Line 27, in the revised manuscript).

6. Page 9, results. This is a bit related to my previous comment. I believe that it is a bit difficult to understand the trend analyses. Is it considered worse to smoke only on the first trimester compared to 2nd and 3rd or vice versa? I think it would make more sense to categorise smoking as 1) smoked during 1st trimester, 2) smoked during 1st and 2nd, 3) smoked during 2nd and 3rd, 4) smoked during whole pregnancy. Then we can have test of trend as things either worsen or get better.

Response:
As mentioned above, women who had smoked during first and second trimesters and those who had smoked second and third trimesters were included in the third
category. The third category consisted of only 28 women. We think that the trend analyses in the original manuscript are reasonable.

7. Page 11, discussion, first paragraph, 2nd row."...,while smoking until conception but quitting after conception. I think the phrase “but quitting after conception” is unnecessary to mention since smoking until conceptions implies they didn’t smoke after.

Response:
The phrase “but quitting after conception” in the Discussion section was deleted in the revised manuscript.

8. General comment about discussion. Although the authors refer to many studies, they seem to merely report on the results from different studies and end the paragraphs by stating "our results are in partial agreement with previous studies". Although these are the facts, it would be nice to have a more thorough discussion of how their results relate to other studies and why they find different results or opposing results compared to other studies.

Response:
We added the following passages to the Discussion section: “In particular, the current results confirm prior research that has demonstrated that those who quit smoking in early pregnancy can achieve the same lower risk of adverse birth outcomes as those who never smoked during pregnancy” (Page 11, Lines 17-19, in the revised manuscript). We also added: “The discrepancies among studies may be explained, at least in part, by differences in characteristics, smoking habits, and lifestyle of the populations examined” (Page 12, Lines 7-9, in the revised manuscript).

9. You only have self-reports on smoking as you state in discussion, and you dismiss this with a reference from Pickett stating that a previous validation with urine samples have shown good overall agreement. However, Picket also stated in his paper that there is considerable variation within women reports and the correlations with urine samples were low. What are the implications in your study looking at different trimesters? What about recall bias?

Response:
We added the following passage to the Discussion section: “Although data on maternal smoking status at different trimesters were available, such data were collected using the second questionnaire after birth. Consequently, the possibility of recall bias should be considered; however, any resulting exposure misclassification would be non-differential and would have yielded an underestimation of values in our results” (Page 12, Lines 21-25, in the revised manuscript).

10. Page 12, last paragraph. You mention in your limitations that you didn’t have a representative sample of the population and perhaps you captured the more
educated ones. What are the implications on your results?

Response:

We added the following passage to the Discussion section: “Nevertheless, cigarette-smoking status in our study population was likely to be similar to that of the general population. In the National Health and Nutrition Survey in Japan of 2007, the percentages of currently-smoking, formerly-smoking, and non-smoking women aged 30 to 39 years were 17.2%, 11.4%, and 71.4%, respectively, although data specific to pregnant women were not available [32]. At baseline, 31.7% of the present study subjects had ever smoked” (Page 13, Lines 11-16, in the revised manuscript).


We don not know the implications on our results. Because at least the distribution of exposures was not likely to be biased, the effects of the above-mentioned selection bias on the present results are likely to be minor. Nevertheless, we cannot comment authoritatively on this issue, and we do not mention it in the text.

11. Page 13 conclusion. I think it is expected that the most obvious and morally correct conclusions is to state that pregnant women should stop smoking. I believe though that a more valid conclusion in your study is that replication is definitely needed and in a more representative sample of the Japanese population.

Response:

We added the following passage to the Conclusions subsection of the Abstract: “Thus, women who smoke should quit smoking as soon as possible after conception” (Page 3, Lines 3-4, in the revised manuscript).

The phrase “it is clear that” in the Conclusions section was deleted.

Minor Essential Revisions

12. Lastly in your tables you have a column that you refer to as risk (%). Please report these rates in a homogeneous manner. I would rather call them rates or frequencies and make sure they are presented the same way in all tables. Right now in Table 3 you have given the actual rates and frequencies in parenthesis, but you do not do that in the rest of the Tables.

Response:

The words “Risk (%)” was changed to “Rate (%)” in Tables 2-4 in the revised manuscript.

In Table 3, it is difficult to show the number of subjects in each category by sex. To present information in the same way, for example, the figure “50/703 (7.1)”
was changed to “7.1 (n = 703)”.

Reviewer: Robin Gandley
Reviewer’s report:
1. Page 5 line 20 should read “In total,”
Response:
Thank you very much for your careful review and insightful comments. We have carefully revised the manuscript in response to your remarks.
We corrected this typo (Page 5, Line 20, in the revised manuscript).

2. Please discuss the potential confounding of the data by self-reported smoking status. While the accuracy of smoking throughout pregnancy is likely very good, the other groups may have reporting biases.
Response:
We added the following passage to the Discussion section: “Although data on maternal smoking status at different trimesters were available, such data were collected using the second questionnaire after birth. Consequently, the possibility of recall bias should be considered; however, resulting exposure misclassification would be non-differential and would have yielded an underestimation of values in our results” (Page 12, Lines 21-25, in the revised manuscript).

3. Please discuss the potential overlap between the smokers and the ETS exposure groups. Is it possible to rank women by the amount they smoke and reported ETS exposure to get the highest and lower exposures?
Response:
Based on data obtained from a self-administered questionnaire, it is less common to rank subjects by the amount they smoke and reported ETS exposure. If salivary, serum, or hair cotinine levels were available, we could categorize subjects according to the cotinine levels regardless of smoking status and ETS status. Distinguishing between smokers and non-smokers on the basis of cotinine measurement is not entirely straightforward. To avoid your suggested potential overlap, the present analysis of the effects of ETS on birth outcomes was performed on the 1427 pairs who had never smoked during pregnancy. In the analysis of the effects of active smoking on birth outcomes, such effects were likely to be much greater than the effects of ETS. In this circumstance, we do not think that it is necessary to add a comment regarding the relation to potential overlap between the smokers and the ETS exposure groups.

4. With the subdivisions of smokers examined, does the study have adequate power to detect differences in the groups with small numbers?
Response:
Insufficient statistical power is one of the methodological limitations of this study. We think that the passage “The current study did not have substantial statistical power although significant associations were detected” in the last paragraph of the Discussion section of the original manuscript adequately addressed this limitation (Page 13, Lines 17-18, in the revised manuscript).