Author's response to reviews

Title: Alcohol consumption during pregnancy and birth outcomes: the Kyushu Okinawa Maternal and Child Health

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Ms. No.: 3216211761111394
Title : Alcohol consumption during pregnancy and birth outcomes: the Kyushu Okinawa Maternal and Child Health Study
First author: Miyake Y.

Dear Sir:

Thank you for your email of January 22, 2014. We are pleased that you are interested in our manuscript for possible publication as an original article in BMC Pregnancy and Childbirth. We appreciate the thoroughness with which the reviewers considered our manuscript. We have addressed the comments made by the reviewers and have carefully revised the manuscript accordingly. We hope that it is now suitable for publication in your esteemed journal. We understand that final acceptance depends on satisfactory resolution of the points raised by the reviewers.

I am sending the revised manuscript with all the changes indicated in red text.

Responses to the reviewers and detailed explanations of our revisions are provided below.

I have checked the entire manuscript thoroughly, and it has been carefully reviewed by an experienced medical editor whose first language is English and who is specialized in the editing of papers written by physicians and scientists whose native language is not English.

We thank you in advance for your consideration. We look forward to hearing from you.

Yours sincerely,

Yoshihiro Miyake, MD, PhD
Associate Professor of Preventive Medicine and Public Health
Reviewer: Manuela Pfrender
Reviewer's report:
Comment
Title: Alcohol consumption during pregnancy and birth outcomes: the Kyushu Okinawa Maternal and Child Health Study
Summary:
This paper reports on the relation between maternal alcohol consumption during pregnancy and the risk of low birth weight (LBW), preterm birth (PTB) and small for gestational age (SGA). No associations were found between maternal alcohol intake during pregnancy and LBW and SGA. The risk of PTB was increased in women who consumed 1 gram of alcohol and more per day.
Abstract:
1. Results: The authors should only focus on the key findings of the paper (Minor Essential Revisions).

Response:
Thank you very much for your careful review and insightful comments. We have carefully revised the manuscript in response to your remarks.

We would agree with this comment if the Abstract were restricted to 200 or 250 words. In BMC Pregnancy and Childbirth, however, the Abstract may be as long as 350 words. Given this higher upper limit, in order to make our study easier for readers to understand, we decided to provide as many details of our results as possible in the Abstract. We decided not to change the Abstract.

Background:
2. Why should one investigate the association between alcohol consumption during pregnancy and the pregnancy outcomes despite the fact that there is a multiplicity of studies that investigated this association previously? What can this study add to the research state? The single “novelty” that the authors emphasize is that this is the first study in Japan on the association between alcohol intake during pregnancy and perinatal outcomes. The literature research was obviously not very carefully as there are a couple of studies from Japan reporting on these associations, such as Ogawa et al., 1991, Sasaki et al., 2006, etc. (Major compulsory revision)

Response:
Thank you very much for this insightful comment. We are very sorry for our careless literature search.

In the abovementioned paper by Ogawa et al., entitled “Passive smoking by pregnant women and fetal growth” (J Epidemiol Community Health 1991; 45(2): 164-8), alcohol drinking during pregnancy was divided into four categories (never, stopped, occasionally, and every day) and was used as a confounding factor. In multiple analyses concerned with passive smoking and birth weight or LBW, results regarding the lack of associations between alcohol drinking during pregnancy and birth weight or LBW in 5336 women who had never smoked were shown. Although the null results were not main results in that paper, we decided to cite that paper.

In the paper by Sasaki et al. entitled “Maternal smoking during pregnancy and genetic
polymorphisms in the Ah receptor, CYP1A1 and GSTM1 affect infant birth size in Japanese subjects.” (Mol Hum Reprod 2006; 12(2): 77-83), alcohol consumption during pregnancy was used as a confounding factor, but the association between alcohol consumption during pregnancy and birth weight was not reported.

We also found a paper that showed no association between alcohol intake during pregnancy and birth weight (Cancer Sci 2007; 98(6): 869-73) and a paper showing no relationship between alcohol consumption during pregnancy and LBW (Acta Paediatr 1998; 87(3): 304-9).

The passage in relation to the first study in Japan in the Introduction was changed to “To our knowledge, there have been only three previous studies on alcohol consumption during pregnancy and birth weight or LBW in Japan, none of which have revealed any associations [9-11]; however, no epidemiological studies in Japan have examined the association of maternal alcohol consumption during pregnancy with the risk of PTB and SGA.” (Page 3 Lines 18-23 in the revised manuscript).

The following references, mentioned in the above passage, were also added:

The passage in relation to the first study in Japan in the Conclusions section was changed to “To our knowledge, the present study is the first study in Japan to show that maternal alcohol consumption of 1.0 g or more per day during pregnancy was significantly positively associated with the risk of PTB but not LBW or SGA.” (Page 11 Lines 13-16 in the revised manuscript).

Methods:
3. Measurements: The authors should report here on the measurement of the independent variables, the dependent variable and the confounders. Everything else belongs to the description of the study. (Major compulsory revision)

Response:
We think that the measurement of the exposure under study is described in the second paragraph in the Measurements subsection and that the measurements of the outcomes under study are described in the last paragraph in the Measurements subsection. Also, the measurements of the confounders under study are described in the second and fourth paragraphs in the Measurements subsection. We thus have not made any revisions in response to this comment.

4. There is no precise information on the alcohol intake variable. How was alcohol intake during pregnancy assessed? Can the authors provide the question from the questionnaire and the answer categories? (Major compulsory revision)
Response:
We added the following passage to the Methods section: “The DHQ included questions on consumption of six types of alcoholic beverages: beer, Japanese sake (rice wine), shochu (a distilled alcoholic beverage made in Japan), chuhai (made with shochu and carbonated water), whisky, and wine. Consumption of each type was calculated based on the reported consumption frequency per week or per month and 12 portion sizes. Estimated average amounts of alcohol consumed per day for all beverage types were summed, yielding an average daily total alcohol intake in g/day.” (Page 5 Lines 7-13 in the revised manuscript).

5. Birth weight and LBW are measures of SGA, thus birth weight and LBW are superfluous measures in this context. (Major compulsory revision)

Response:
A meta-analysis by Parta et al. in 2011 (Ref. #2 in this study) assessed the relationship between alcohol consumption and the risk of LBW, PTB, and SGA. In our population, active maternal smoking throughout pregnancy was significantly associated with SGA and birth weight, while no significant relationship was found between active smoking during pregnancy and LBW (BMC Pregnancy Childbirth 2013; 13: 157). The definitions of birth weight, LBW, and SGA differ from one another. In epidemiological studies, the definitions of exposures as well as outcomes and confounders are quite important. In this context, we do not think that birth weight and LBW are superfluous.

In accordance with the third reviewer’s comment that ‘the LBW analysis should not be adjusted for GA or results will be of similar interpretation to the SGA analysis!’, gestational age at birth was removed when the association with the risk of LBW was examined.

Statistical analyses:
6. The measurement of alcohol consumption during pregnancy is not part of the statistical analyses and should be described in the measurements section. (Major compulsory revision).

Response:
We think that the measurement of the exposure under study is described in the second paragraph in the Measurements subsection. We thus have not made any revisions in response to this comment.

7. The category of alcohol intake seems to be very arbitrary. Can the authors provide references or reasonable justifications for this classification with <1 gram per day (please consider that a standard glass of beer, for example, contains already 10.0 grams of pure alcohol). How did the authors measure 1 gram/day?? This is a main variable and it has to be described in very much detail! (Major compulsory revision!!)

Response:
As mentioned above, we added additional details on the estimation of alcohol consumption. As described in the Results section, the range of maternal alcohol consumption during pregnancy was 0.0 to 11.7 g per day: 1356 (86.7%) mothers were abstainers and the 95th percentile value was 0.84 g per day. In this situation, we wanted to assess the relationships under study after alcohol...
consumption was divided into three categories. We selected 1 g/day as the cutoff point among non-abstainers in terms of the distribution of alcohol consumption. We did not add any comment to the text regarding this circumstance.

8. The classification of the variables is not part of the statistical analyses! (Major compulsory revision)

Response:
We do not agree with this comment. In our papers, including BMC Pregnancy Childbirth 2013; 13: 157, the classification of the variables is described in the Statistical analysis subsection. We would like to use this style of description.

Results:
9. Can the authors provide references for the classification of heavy drinkers on >14 grams per day?

Response:
As mentioned in the text, there were no heavy drinkers (defined as more than 14 g per day). We did not add any comment to the text concerning this issue.

10. The authors tested interactions between alcohol and smoking but did not mention any hypothesis with respect to the interactions. (Major compulsory revision)

Discussion:

Response:
We added the following passage to the Discussion section: “In our population, a significant positive association was found between maternal smoking during pregnancy and PTB [20].” (Page 11 Lines 3-4 in the revised manuscript).

The following reference, mentioned in the above passage, was also added:

11. The authors did not discuss potential explanations for their results on the associations between alcohol intake during pregnancy and SGA and LBW. Also, the discussion of the literature is not very well developed. (Major compulsory revision)

Response:
Because there were no significant relationships between maternal alcohol consumption during pregnancy and LBW or SGA, we do not think that it is necessary to discuss potential explanations for these findings.

We added the phrase “but are consistent with the current results regarding LBW and SGA” to the
Reviewer: Michele Drehmer
Reviewer's report:
Major Compulsory Revisions:
1) The authors have interesting data, but they didn't explored, in discussion, the clinical significance and what represent 1 gram of alcohol consumption/day in pregnancy in terms of public health recommendations. It is difficult to bring and discuss this data. Since no safe level of alcohol consumption has been established, in the literature, at any stage of pregnancy, the current guidelines recommends that pregnant women and women who are planning a pregnancy should abstain from alcohol.

Response:
Thank you very much for your careful review and insightful comments. We have carefully revised the manuscript in response to your remarks.

We added the following passage to the Conclusions section: “Given the present results, women should abstain from alcohol as soon as possible after conception, and ideally even in the preconception period.” (Page 11 Lines 19-21 in the revised manuscript).

2) The sample was recruited by a convenience method. Why the authors didn't tried to do a probabilistic sample of women that followed prenatal in obstetric hospitals in Japan. Probably the total of 1757 pregnant women was not representative of 423 obstetric hospitals in the eight prefectures.

Response:
In general, Japanese people are not familiar with epidemiological studies and are reluctant to disclose personal information; thus, in Japan, it is difficult to conduct epidemiological studies. Moreover, our research fund was quite limited. We recruited pregnant women based on their voluntary participation. One advantage of voluntary participation is the expectation of a high follow-up rate. As described in the third paragraph in the Discussion section, our subjects were probably not representative of Japanese women in the general population.

We added the following passage to the Discussion section: “Nevertheless, the participation rate must have been fairly low, given that the present study used data from only 970 pregnant women who lived in Fukuoka Prefecture, while, according to the government of Fukuoka Prefecture, the number of childbirths was 46,393 in 2007 and 46,695 in 2008.” (Page 10 Lines 10-14 in the revised manuscript).

3) The pregnancy women came from primary care attention? The authors excluded the patients who had pregnancy complications like gestational diabetes, preeclampsia, etc?

Response:
Study subjects came from primary, secondary, and tertiary medical care without exclusion criteria.
We did not add any comment to the text regarding this circumstance.

4) Where the alcohol questions were in the DHQ? These items were in the beginning, in the middle or in the final list in the DHQ? How the alcohol grams were calculated? In food questionnaire, how many alcoholic beverages were listed?

Response:
Alcohol-related questions appeared late in the DHQ. We did not add any comment to the text regarding this issue.

We added the following passage to the Methods section: “The DHQ included questions on consumption of six types of alcoholic beverages: beer, Japanese sake (rice wine), shochu (a distilled alcoholic beverage made in Japan), chuhai (made with shochu and carbonated water), whisky, and wine. Consumption of each type was calculated based on the reported consumption frequency per week or per month and 12 portion sizes. Estimated average amounts of alcohol consumed per day for all beverage types were summed, yielding an average daily total alcohol intake in g/day.” (Page 5 Lines 7-13 in the revised manuscript).

5) Why authors didn’t use Poisson multivariate regression analysis? The confidences intervals with poisson regression with robust variation could be more precise. It is not clear about the criteria that included variables in multivariate models.

Response:
We think that multiple logistic regression analysis is reasonable in this study.

As described in the Statistical analysis subsection, a priori potential confounders were selected. We did not add any comment to the text regarding this issue.

6) A standard alcoholic drink contains approximately 14 grams of alcohol, which is equivalent to 12 fluid ounces of beer, 5 fluid ounces of wine, 3.5 fluid ounces of fortified wine (e.g., sherry or port), or 1.5 fluid ounces of liquor (distilled spirits) (Linus Pauling Institute).

Moderate Alcohol Consumption (as defined by the U.S. Department of Agriculture)

- Women: No more than one standard alcoholic drink/day
- Women: 8 or more standard alcoholic drinks/week or 4 or more alcoholic drinks on any given occasion

More moderate alcohol consumption during pregnancy (7-14 drinks/week) has been associated with more subtle effects on cognitive and behavioral development.

The present study used 1 gram as a reference of alcohol consumption.

What is the clinical significance of 1 gram of alcohol? How this study can do a recommend with these data?

People often did not consume 1 gram/day. They consume drinks. Maybe, the authors can change 1gram/day by how many drinks per week or per month during pregnancy in discussion.
Response:
As mentioned above, alcohol consumption was estimated using a DHQ. In nutritional epidemiology, the quality of evidence based on dietary intake as estimated using a semiquantitative food frequency questionnaire is generally higher than that based on information on food frequency alone. For this reason, we would not like to change our assessment of exposure. We thus have not made any revision in response to this comment.

7) For give more information, a graphic of a J-shaped could better indicate this association between alcohol consumption and obstetric outcomes.

Response:
Table 3 presents the main results in this study. We do not think that more information is necessary.

Minor Essential Revisions
1) Do not use this term “monotonically”. Substitute by another word.

Response:
The word “monotonically” in the Introduction was changed to “linearly” (Page 3 Line 13 in the revised manuscript).

Discretionary Revisions
1) In the background, second statement, please inform the magnitude of the association between heavy and light to moderate maternal alcohol consumption and obstetrics outcomes in that described meta-analysis.

Response:
The dose-response relationships in that meta-analysis were shown in figures only. Thus, we cannot report the point estimates in a simplistic form.

2) An inherent limitation was the report of alcohol consumption in pregnancy. Most of the women could not relate alcohol consumption because this habit is frequently not recommended in this period of life. The information about that 86.7% mothers were abstainers during pregnancy could be biased.

Response:
We added the following passage to the Discussion section: “Nevertheless, alcohol consumption during pregnancy in our study population was likely to be similar to that in the general population. In a study of 689 Japanese mothers whose children had undergone four-month checkups publicly provided by a municipality in 2007, the prevalence of alcohol consumption during pregnancy was 9.1% [18].” (Page 10 Lines 21-25 in the revised manuscript).

The following reference, mentioned in the above passage, was also added:
18. Matsumura T, Taniguchi C, Hamagashira N: Current state of smoking and alcohol drinking

Reviewer: Luisa Zuccolo
Reviewer's report:
This is a clearly written and presented paper examining the association between maternal alcohol use in pregnancy and pregnancy outcomes, for the first time in a Japanese population. Evidence on this subject matter predominantly comes from European origin populations, so this is a welcome and original contribution to the literature. However, this particular study’s results are potentially affected by two major limitations which the authors should investigate and discuss more: residual confounding and power. Limited information is available on the mothers relative to important characteristics that could confound the alcohol-outcomes associations, chiefly the amount of cigarette smoke in pregnancy. Statistical power is very limited due to the combination of low sample size, low prevalence of the exposure, and limited exposure range, and the authors are invited to highlight this limitation more.

**Major Compulsory Revisions**

**Introduction**

1. First paragraph - the synthesis of literature to date could be substantially shortened, especially in view of the fact that many of the studies cited individually already were included in the systematic reviews and meta-analyses cited at the beginning.

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

In accordance with this comment and the next comment, associated with differences between populations, the passage regarding previous papers on low to moderate maternal alcohol consumption during pregnancy and birth outcomes in the Introduction was changed to “Four studies in the USA have shown significant positive relationships between low to moderate maternal alcohol consumption during pregnancy and the risk of LBW, PTB, and/or SGA [3-6], while equally significant inverse associations have been observed in two studies in Canada and Spain [7, 8].” (Page 3 Lines 15-18 in the revised manuscript).

2. More emphasis instead should be given to outlining potential limitations of existing studies and differences between populations that would justify this new study as an important contribution to the literature. Do any of the US based studies include Asian-American women? This would provide an interesting angle for the background. Also, the authors could briefly report rates of these pregnancy complications in different ethnic groups, worldwide and within the US for example (to give an idea of ‘migrant’ effects of the new environment).

**Response:**
The phrase “It should be noted, however, that no studies conducted in Asian countries were included in this meta-analysis” was added to the Introduction (Page 3 Lines 14-15 in the revised manuscript).
These four previous US studies (Ref. #3-6) analyzed white and black subjects.

It is difficult for us to briefly discuss rates of birth outcomes in different ethnic groups in the context of the association between maternal alcohol consumption during pregnancy and birth outcomes. With regard to the latter comment associated with ethnicity, we did not add any comment to the text.

**Methods**

3. The LBW analysis should not be adjusted for GA or results will be of similar interpretation to the SGA analysis!

**Response:**

Gestational age at birth was removed when associations with the risk of LBW were examined.

The results in relation to LBW and footnotes in Table 3 were changed.

The word “preterm birth” was changed to “LBW and PTB” in the Statistical analysis subsection (Page 6 Line 18 in the revised manuscript).

4. The authors should show Table 1 by levels of alcohol intake to show distribution of potential confounders. Is there no detailed smoking information? Is the smoking question only asked retrospectively? Both these factors could introduce substantial residual confounding... The authors should present additional analyses excluding mothers reporting smoking in pregnancy – would there be any women left consuming 1+ g alcohol/day?

**Response:**

We newly added Table 2, which shows the distributions of confounding factors according to maternal alcohol consumption during pregnancy.

We added the following paragraph to the Results section: “Table 2 shows the distributions of confounding factors according to maternal alcohol consumption during pregnancy. Maternal alcohol consumption during pregnancy was positively associated with living in Fukuoka Prefecture, number of children, body mass index, and maternal smoking throughout pregnancy and inversely with maternal education and gestational age.” (Page 7 Lines 24-28 in the revised manuscript).

In the second survey, which was performed after delivery, information on active maternal smoking status in the first (≤15 weeks’ gestation), second (16–27 weeks’ gestation), and third (≥28 weeks’ gestation) trimesters was obtained, and this information was used in this study.

We added the following paragraph to the Results section: “In a subgroup restricted to 1427 women who had never smoked during pregnancy, the adjusted ORs for PTB for maternal alcohol consumption of less than 1.0 g and 1.0 g or more per day during pregnancy were 1.47 (95% CI: 0.55–3.31) and 1.73 (95% CI: 0.41–5.08), respectively (P for trend = 0.27).” (Page 8 Lines 14-17 in the revised manuscript).

There were 53 women who consumed alcohol of 1 g or more per day among the 1427 women. This figure was not added to the text.
Discussion

5. First paragraph. In line with my previous comment on the Introduction’s opening paragraph, I think this could be shortened and individual studies should only be mentioned where they are not included in a referenced review, or are of particular significance (because of a similar population/base, large numbers, etc). It would also make it easier for the reader to follow this comparison with the literature if the authors proceeded with looking at one outcome at a time.

Response:
The passage associated with Ref. #5 and #6 in the first paragraph in the Discussion section was deleted in the revised manuscript.

6. It is not clear why the authors mention CRP in the second paragraph. Please expand on this if you think CRP is a (the?) possible causal mediator between alcohol consumption and risk of preterm birth.

Response:
In the second paragraph in the original manuscript, we mentioned CRP as a possible mechanism; however, we do not think that higher CRP is a possible causal mediator with regard to the observed positive association between low to moderate alcohol consumption during pregnancy and PTB because the CRP concentrations were lowest in women who consumed 15 g or less per day (lower than those in non-drinkers and drinkers of 15 g or more) in a study of Portuguese subjects. We decided to delete this paragraph in the revised manuscript.

7. Third paragraph – I agree with the authors that the exposure assessment is a limitation of this study as it introduces some potential bias in the form of exposure misclassification, particularly since alcohol intake was assessed in last month prior to completing q.aire, that is to say the timing varies within the cohort. Since timing of exposure has been linked with fetal outcomes, the authors should report the distribution of alcohol intake by gestational age at recruitment (q.aire completion), and if appropriate comment on the type and direction of possible biases introduced by this design feature. It is true that non-differential misclassification on average tends to bias results towards the null. But why should this be non-differential? The authors could clarify their thinking a little, here. Many women stop drinking in very early pregnancy but they might start again later on if the pregnancy is uncomplicated, hence alcohol intake at a later gestational age (in a healthy pregnancy) could be associated with better pregnancy outcomes - how do the authors plan to assess the potential for such (differential) misclassification bias and its consequences?

Response:
We added the following passage to the Discussion section: “When subjects were divided into two groups according to gestation at baseline, the proportion of drinkers was 11.4% in women who had completed the baseline survey between the 5th and 17th weeks of pregnancy (n = 789) and 15.3% in women who had completed the baseline survey between the 18th and 39th weeks of pregnancy (n = 776). The adjusted OR for PTB for maternal alcohol consumption of 1.0 g or more per day during
pregnancy was 2.47 (95% CI: 0.67–7.23, P for trend = 0.21) in women who had completed the baseline survey between the 5th and 17th weeks of pregnancy and 3.23 (95% CI: 0.67–11.59, P for trend = 0.03) in women who had completed the baseline survey between the 18th and 39th weeks of pregnancy. In women who had completed the baseline survey prior to the 18th week of pregnancy, the proportion of drinkers might be underestimated; in that case, the association between maternal alcohol consumption and PTB might be attenuated.” (Page 9 Line 20–Page 10 Line 4 in the revised manuscript).

8. Fourth paragraph – this point (response rate, representativeness of the underlying population) should relate to the study findings and discuss how/whether bias might be introduced in the present study (for example if a large proportion of the alcohol drinking mothers with more at risk pregnancies did not take part).

Response:
We added the following passage to the Discussion section: “Nevertheless, alcohol consumption during pregnancy in our study population was likely to be similar to that in the general population. In a study of 689 Japanese mothers whose children had undergone four-month checkups publicly provided by a municipality in 2007, the prevalence of alcohol consumption during pregnancy was 9.1% [18].” (Page 10 Lines 21–25 in the revised manuscript).

The following reference, mentioned in the above passage, was also added:

9. Fifth paragraph – this should be considerably expanded. Please provide a power calculation based on your sample size and exposure prevalence. The sample size and consequent limited power (further affected by the low exposure prevalence and limited exposure range) is a critical limitation of this study and should be emphasised more. Please also expand the discussion on the potential for residual confounding (mainly from cigarette smoking but also other factors such as drug taking, family circumstances, stress....).

Response:
We added the following passage to the Discussion section: “According to the statistical power calculation using QUANTO version 1.2 [19], our sample size gives us 48% of the power needed to detect an association between maternal alcohol consumption of 1.0 g or more per day during pregnancy and PTB.” (Page 10 Line 27–Page 11 Line 2 in the revised manuscript).

The following reference, mentioned in the above passage, was also added:

There were no illegal drug users in this population. The passage “Data on stress and family circumstances were not available in this study.” was added to the Discussion section (Page 11 Line 9 in the revised manuscript).
Minor Essential Revisions

Results

10. Last paragraph of results mentions for the first time some interaction analyses – these should be introduced in the methods section and results of point estimates for alcohol consumption in the various strata of the potential effect modifiers should be presented (perhaps as additional files available online). The reason for examining these as potential effect modifiers should be explicitly stated. However, there clearly is very limited statistical power in this sample to expect statistical evidence for interaction, so the discussion of these results should be balanced accordingly.

Response:
The passage “The interaction was tested using a term of the product of two variables in a multiple logistic regression model.” was added to the Methods section (Page 7 Lines 10-12 in the revised manuscript).

The passage regarding interactions in the Results section was changed to “In a subgroup restricted to 1427 women who had never smoked during pregnancy, the adjusted ORs for PTB for maternal alcohol consumption of less than 1.0 g and 1.0 g or more per day during pregnancy were 1.47 (95% CI: 0.55–3.31) and 1.73 (95% CI: 0.41–5.08), respectively (P for trend = 0.27). In a subgroup of 138 women who had smoked during pregnancy, on the other hand, the corresponding figures were 4.76 (95% CI: 0.47–40.13) and 15.11 (2.22–142.12), respectively (P for trend = 0.004). There was no significant interaction between maternal alcohol consumption of 1.0 g or more per day and maternal smoking during pregnancy with respect to the risk of PTB (P for interaction = 0.27).” (Page 8 Lines 14-22 in the revised manuscript).

We added the following passage to the Discussion section: “In our population, a significant positive association was found between maternal smoking during pregnancy and PTB [20]. The positive association between maternal alcohol consumption during pregnancy and PTB was stronger in women who had smoked during pregnancy than in women who had never smoked during pregnancy; however, the interaction was not statistically significant.” (Page 11 Lines 3-7 in the revised manuscript).

The following reference, mentioned in the above passage, was also added:

General

11. The PTB result is interesting and could be explored a bit more. What is the distribution of these preterm births in terms of gestational age? Are there many extremely preterm babies? How do these results compare to the studies based on European origin populations only?

Response:
Here, we show the distribution according to gestational age among the 62 infants with PTB.

<table>
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<th>Gestation</th>
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<td>38</td>
</tr>
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</table>
There were only two infants who were born between the 25th and 27th weeks of pregnancy (0.13%).

According to a study of women with live singleton births in Sweden from 1992 through 2010 (JAMA 2013; 309: 2362-70), among 1,599,551 deliveries, 3082 were extremely preterm (0.19%); this rate is not much different from that in our population. I do not think that it is necessary to include this issue in the text.