Reviewer’s report

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

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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.

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).

Methods

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

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?

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.

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.

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?

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).

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....).

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.

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?

**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.