Reviewer’s report

Title: Maternal pre-pregnancy body mass index, smoking in pregnancy, and alcohol intake in pregnancy in relation to pubertal timing in the children

Version: 0 Date: 11 Jan 2019

Reviewer: Kristine Marceau

Reviewer's report:

The present study is an analysis of how prenatal exposure to maternal obesity, smoking, and alcohol was associated with timing of puberty using a new marker (HD:SDS). I admit that I came into this manuscript very skeptical of the measure of puberty, but the authors have convinced me that it may be a useful measure. Overall, I thought this paper was strong and well written. My major concerns were in the introduction, missing data/participants, and limitations sections, detailed below.

Introduction:
1. It was unclear why these three specific factors were selected above the myriad other prenatal exposures that may have an effect on pubertal timing. A statement on why these three (beyond showing that these three matter, which is done well) would be useful.
2. The introduction clearly conceptualizes prenatal risk as a cause. However, prenatal exposures could just as well be a marker of genetic risk (see the large literature on smoking during pregnancy and birth weight and ADHD/externalizing outcomes using IVF or sibling comparison designs for an example of this). The causal language should be toned down, and the possibility that these prenatal exposures may not be causally linked to puberty should be discussed somewhere in the intro or discussion.
3. I take issue with the statement that hormonal analyses are invasive. Puberty is now assessed via hair hormones and salivary hormones which are generally considered non-invasive. Blood assessments certainly are invasive. Please either remove 'invasive' or clarify that it is hormones assessed via blood/serum that is invasive. I would not like to spread misinformation that might lead researchers away from hormone assessment of puberty.

Methods:
4. The definition of height SDS in the methods section could be clearer. I assume you judged the difference of a person's actual height from expected based on the growth charts that were mentioned elsewhere? Perhaps you could add an example that makes it clearer where the standard deviation comes from- is the standard deviation ISD from the population of those differences? A graphic might be useful as well. It is a hard concept for someone who doesn't use it, and clarity would help researchers to adopt the method.
5. The inclusion of how children were excluded was helpful. However, there is no information on how excluded children compared to the included children, which is important for generalizability. This is even more important for the puberty subsample - they must at least be compared for the HD:SDS measure so that we can understand whether the HD:SDS measure is validated for the whole sample, or
perhaps in particularly average, early, or late youth.

6. The fact that the puberty cohort was sampled according to prenatal exposures of interest came as a shock in the statistical analysis. This should be disclosed when the sample is introduced. Using weights is appropriate, but more thought should be given to what this will mean for the analysis and validation in particular.

7. At the bottom of page 8, I assume that (in categories) means the binned categories listed a few sentences above, and that this was done to improve the distribution? Please be more explicit.

Results:

8. I very much appreciate the inclusion of the validation findings. This was critical. It may be useful to include the correlations of the other milestones, either in Table 2 or as supplementary data. This will help to show that HD:SDS is as correlated with other phenotypes as any two other puberty phenotypes (which I assume is the case based on prior literature).

9. It would be important to quantify the error of assessment of adult height. I would be surprised if there are no height data on adults and their parents in the registry that could be used… how wrong could this procedure of using the average of parents' heights be, and is it systematic or random? If systematic, would it affect results?

Limitations:

10. The authors were clearly aware of the limitations that I saw. However, I would like to see them stated more strongly - particularly those related to the HD:SDS measure and the selection of the puberty subsample.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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