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: 08 Jan 2019

Reviewer: Lauren Houghton

Reviewer's report:

This study investigates maternal lifestyle factors in relation to pubertal timing as assessed by the HD:SDS. As has been shown in previous studies, this study finds an association between maternal prep-pregnancy obesity and earlier pubertal timing. The study also finds delayed pubertal timing in boys whose mothers drank alcohol during pregnancy. A major strength of the study is the ability to investigate maternal factors in relation to boys' pubertal timing as this is often an understudied topic in this sex. The study has the potential to further explore mediating and effect modification by childhood growth. Such additional analyses and the following recommendations will improve this manuscript:

Introduction
The authors propose that obesity may explain the secular trend in earlier puberty, but the rationale for smoking and alcohol is missing from the introduction. Has maternal use of these products increased or decreased over time?

Please clarify what aspects of puberty timing are declining, is it onset, tempo, a particular Tanner Stage?

Methods
The authors exclude 7858 participants who were missing growth data around the age of PHV. This may introduce selection bias. An alternative to excluding these participants is to use the growth data at other ages to interpolate the height at the age of PHV. See a series of papers by Mary Beth Terry using the EDMD cohort as an example. This would allow for the standardization of age at measurement for all subjects.

Does it make sense to calculate the SDS based on recent Danish growth curves rather than the curves from 2008-2014 (12 years after the years of recruitment)?

The Puberty Cohort assessed puberty at 11.5 which is rather late to capture early Tanner stages for girls. This could skew the results to late developers and may effect the validation of the HD:SDS measure. Can the authors explore this limitaion further?

The statistical methods are not fully clear to me. I am not sure how the authors dealt with censored data in a regression model. Lines 25 -33 on page 8 are specifically unclear.
Results and Discussion

Awkward wording on page 9, lines 50-52.

Please clarify what aspect of pubertal timing the HD:SDS measure is capturing. Based on the strength of the correlation it seems to be capturing middle puberty for boys and pubertal onset (or just after) for girls. Interestingly, it seems to capture breast stage 2 and menarche at the same magnitude for girls, which is slightly puzzling since breast development is usually the first sign of puberty and menarche comes 2-4 years later. F Biro et al has argued that the two events have become less correlated over time and so it is interesting that the HD:SDS is similarly correlated with these two events. Can the authors explain this apparent inconsistency?

The authors suggest that the null association with maternal smoking maybe due to impaired pre-pubertal growth. Houghton et al Ann Epidemiol. 2018 Mar;28(3):197-203 shows how there is effect modification by childhood growth in the association between maternal smoking and age at menarche. The authors have the data to also test for effect modification by child growth in this large dataset.

Th authors suggest that childhood obesity may play a mediating role. The authors have childhood growth data and should be able to test empirically for this mediation instead of speculating.

Can you explain the sex differences in the alcohol results?

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

No

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?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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