Author’s response to reviews

Title: Age at Menarche and Risk of Gestational Diabetes Mellitus: A Population-Based Study in Xiamen, China

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Response to Reviewers' Comments

We are grateful to the Editor and Reviewers for the critical comments and expert advices. Following your suggestions, we have polished our manuscript. The changes are highlighted in red.

Reviewer reports:

Youjie Wang (Reviewer 1): The authors have answered my questions, but the authorship did not answer this question specifically. "is there any difference in characteristics between the subjects
included (70041) for the analysis and those not included (279992). They should compare the main characteristic between the included and excluded group.

Author’s response: Thank you very much for your expert comments. The 279,992 records were whole that were not the excluded records. We have compared the main characteristic between the included and excluded group that founded there was no difference existed in characteristic between the subjects included and those not included. 209,951 participants were excluded, 70,041 participants were included. The specific characteristics as following: age, 28.4 ± 4.8 vs. 28.4 ± 4.1, P = 0.291; BMI, 21.1 ± 3.0 vs. 21.0 ± 2.9, P = 0.236; plasma glucose, 4.5 ± 0.5 vs. 4.5 ± 0.4, P = 0.342; Systolic blood pressure, 107.6 ± 10.4 vs. 107.5 ± 10.7, P = 0.443; Diastolic blood pressure, 65.7 ± 7.8 vs. 65.6 ± 7.9, P = 0.551; Education (≤ 9 years), 24.1% vs. 23.5%, P = 0.360; Family history of diabetes, 2.7% vs. 2.6%, P = 0.523; Family history of hypertension, 6.4% vs. 6.4%, P = 0.481.

Socioeconomic status is usually measured by income, education level or type of job, the authors could not assume that the study subjects are relatively homogenous cohort without data to support it.

Author’s response: Thank you very much for your expert comments. We did not take something into enough consideration. Because we did not have the data of income or type of job, therefore we have deleted the associated contents in the paper.

Clive Petry, PhD (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Author’s response: Thank you very much for your expert comments. We have revised the format of response to all comments for the authors based on this require. Please refer to new format Word text.

I believe that this manuscript has been improved by the revisions made. I still have a couple of minor concerns that I believe need addressing:

1. The literature cited concerning studies where associations between age at menarche and future GDM risk were tested is still incomplete.

Author’s response: Thank you very much for your expert comments. We have red some new relatively literatures ([13, 14]) (Page 3) that studied the associations between age at menarche
and future GDM risk that have cited in the paper. Additionally, we have added some new literatures that studied the association between early age at menarche and adverse outcomes ([8], [9, 10], [11]) (Page 3).

2. The manuscript is a little difficult to read in parts and I would suggest that minor changes to the English language used are made by either a native English speaker or a professional who provides such services.

Author’s response: Thank you very much for your expert comments. We have changed the English language by a native English speaker.

Danielle Schoenaker (Reviewer 3): The authors have improved their manuscript by appropriately addressing many of the comments, however, I have some remaining concerns about the statistical analysis and the interpretation of the results. More specifically:

- The authors state that three categories of early age at menarche were analysed, because early age at menarche (13 years) is consistent with categories used in other research. The meta-analysis conducted by Sun et al includes five studies, that have all defined early age at menarche as age 11 or younger. Moreover, it remains unclear why not more categories were examined given the large sample size as mentioned in my previous comment, or why age at menarche was not examined as a continuous variable in for example a spline analysis to provide a more detailed examination of the (potentially non-linear) relationship between age at menarche and GDM and add to the existing literature.

Author’s response: Thank you very much for your expert comments. According to your suggestion, we have analyzed the data in detail.

At first, age at menarche was categorized as 8-11, 12, 13, 14, and 15-19 years old. The outcomes showed that there -were only 672 individuals in 8-11years old group. Therefore we merged 8-11 years ld into 12 years old revealed in Table 1. In addition, age at menarche was known to be affected by BMI, socioeconomic status, maternal age at menarche, and ethnicity (references 1-3). The participants of our study were from south part of China, age at menarche in genetic and nutritional parameters, age at menarche of our participants was later than that in some studies.

In addition, we have also examined the age at menarche as a continuous variable to provide more detailed examination of the relationship between age at menarche and GDM. Age at menarche menopause was treated as a continuous variable, the results showed that the crude OR for GDM per 1 year older at menarche was 0.98 (95% CI 0.96, 0.99), however, these associations attenuated towards the null following adjustment for blood pressure and BMI (Table 3) (Page 7).
Furthermore, multivariable-adjusted spline regression models showed a linear dose-response association between age at menarche and GDM (P for nonlinearity, 0.203; P for linearity, 0.006) (Annex Figure) (Page 7).

- The order in which covariates were added to the models remains unclear, and is inconsistent across Tables 2 and 3. As previously suggested, BMI and blood pressure are likely intermediates of the association between age at menarche and GDM, and should therefore either not be included in the models, or added in separate models at the end.

Author’s response: Thank you very much for your expert comments. We have adjusted the inclusion order for blood pressure and BMI adding in separate models at the end. The specific results indicated in Table 2, Table 3, and Table 4.

Model 1, adjustment for family history of diabetes; Model 2, adjustment for Model 1 plus education levels, age at delivery, and chronic hepatitis B virus status; Model 3 adjusted for variables in model 2 plus systolic blood pressure and diastolic blood pressure; Model 4 adjusted for variables in model 3 plus pre-pregnancy BMI.

- The authors have expanded the discussion on the interpretation of the findings on 1-hour and 2-hour glucose outcomes, however, a discussion on the magnitude of these findings was not added. Coefficients for these outcomes were very small (Table 3) (despite the statistically significant p-values due to the large sample size), which should be discussed and integrated as part of conclusions.

Author’s response: Thank you very much for your expert comments. We have added the magnitude of these findings in part of discussion (Page 10) as follows: Interestingly, our study indicated that the OGTT 60 minute and 120 minute glucose concentrations were higher at earlier age at menarche than mean or later age at menarche. It is noteworthy that multivariable linear regression showed that the coefficient was very small for association between glucose concentrations and age at menarche, despite the statistically significant p-values due to the large sample size. In addition, we have also integrated as part of conclusions (Page 12) as following: One significant additional finding from this study was that earlier menarche was inversely associated with pregnancy glucose concentrations following a glucose load. However, the coefficients for the outcomes were small.
References

