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.

COMMENTS TO AUTHOR:

Reviewer # 1: the research data used in the study were extracted from the medical birth registry system, incomplete data or missing data are common in such registry system, how did the author deal with the missing or incompletely data?
Authors’ response: Thank you very much for your expert comments. In this study, there were 70,041 pregnant women registered specific OGTT data in 0 h, 1h, and 2 h. Other 279,992 pregnant women missed the information of OGTT, so we excluded the all data of those women. Moreover, the incomplete data was a limitation in this study that we discussed in part of discussion as following: “It is inevitable that the linked and registered data are a potential source of bias in results of researches, yet researchers often discover it difficult to evaluate the extent of bias, because of the separation of linkage and analysis processes” (Page 12). Furthermore, multiple imputation was conducted for missing data in the multivariable analyses.

Reviewer # 1: is there any difference in characteristics between the subjects included (70041) for the analysis and those not included (279992)

Author’s response: Thank you very much for your expert comments. The numbers of data about the specific OGTT value were 279,992. Of those FPG was recorded in 925 cases, 1 hour OGTT value recorded in 93,725 cases, 2 hour OGTT value recorded in 93,613 cases, and other records totally counted of 140. After cleaning and integrating the relevant test results, 82,031 records of pregnant women were obtained with 3 values of OGTT. Data of 78,572 pregnant women with OGTT results were correlated with the maternal information database of Xiamen municipal health and family planning commission. Of these data, 70,041 cases were completed with all the factors we needed. Data were dropped due to data errors, data contractions, poor correlation and other reasons that cannot be analyzed. Due to the incompleteness of the required influencing factors, the data are omitted account for a relatively small proportion and will not produce a large deviation to the overall result.

Reviewer # 1: hepatitis B surface antigen (HBsAg) positive seems higher in these study subjects, do the author have any reason to explain it. Why hepatitis B surface antigen (HBsAg) was adjusted in the regression model, is there any evidence to show the relationship between hepatitis B surface antigen (HBsAg) and GDM?

Author’s response: Thank you very much for your expert comments. Many studies indicated the significant association between hepatitis B surface antigen (HBsAg) positive and GDM. We have updated and cited the relevant references [19-21] (Page 8) in discussion.

Reviewer # 1: In the method part, the author showed that they also have extracted the data on pregnancy, labor, gestational weight gain, hypertension in pregnancy. These factors are related with GMD. Why the authors did not adjust this characteristic in the regression model
Author’s response: Thank you very much for your expert comments. Pregnancy, labor, and delivery characteristics were general terms that included gestational diabetes mellitus, gestational weight gain, gestational age at delivery, hypertension in pregnancy, and so on. The reasons of excluded factors as following: firstly, poor data quality and unreliable sources, for example there are only a few thousand records of gestational weight gain available. Secondly, after multivariate logistic regression, it was found that the factor had a strong linear relationship with other factors that had been included, and the P value of the model was too large after this factor was included, such as hypertension in pregnancy.

Reviewer # 1: In the discussion part, the author declared that their study is the first study to demonstrate the association between an earlier age at menarche and elevated glucose levels after a glucose load. It was not true, several studies focus on this topic were published.

Author’s response: Thank you very much for your expert comments. We have revised the sentence “our study is the first study to demonstrate the association between an earlier age at menarche and elevated glucose levels after a glucose load” in discussion as” To our knowledge, there are a few studies to demonstrate a significant association between an earlier age at menarche and elevated glucose levels after a glucose load in China” (Page 8).

Reviewer # 1: in the discussion part, "Moreover, our study population was a relatively homogeneous cohort of women; thus, the findings are less likely to be confounded by factors associated with socioeconomic status". Does this means the study population are homogeneous in socioeconomic status? The author should give some data to support this statement.

Author’s response: Thank you very much for your expert comments. The data of socioeconomic status was missed in this study. Further, this was only our speculation. We have revised the sentence “Moreover, our study population was a relatively homogeneous cohort of women; thus, the findings are less likely to be confounded by factors associated with socioeconomic status” as “Moreover, our study population was a relatively homogeneous cohort of women who could pay healthcare fee. Most of populations live in downtown, few live in countryside. These women are permanent residents of Xiamen, sharing a similar living environment and lifestyle and medical insurance. Therefore, we supposed that the findings were less likely to be confounded by factors associated with low economic income status and living environment” (Page 10).

Reviewer # 2: The cited literature in this area is incomplete at present.
Author’s response: Thank you very much for your expert comments. We have reviewed more literatures and we have updated and cited the relevant references [14] in introduction and [18], [22], [19-21], and [27] in discussion.

Reviewer # 2: Please comment on the fact that the average AAM is higher in this population than in many of the published studies in this area.

Author’s response: Thank you very much for your expert comments. We have discussed this result in discussion as following: In addition, our study indicated that the average age at menarche (14.1±1.6) is higher in this population than in many of the published studies. A study showed the overall mean age at menarche was 12.7 years in Korean girls [18]. Besides, another Chinese study expressed that mean age at menarche was 13.1±1.2 years in Wuhan, a city located in Hubei province, China [15]. A large population in China with significant differences in ethnicities, diets, and lifestyles may lead to differences in mean age at menarche reported in various regions (Page 8).

Reviewer # 2: Please comment on how AAM was originally collected for the database.

Author’s response: Thank you very much for your expert comments. We have updated the specific method of originally collecting AAM in part of methods as following: This was defined as the age at the first menstrual period. The information on age at menarche was obtained by questionnaire: “At what age did you have your first menstrual period?”. The MBRX summarized the data that came from the Women and Children Medical and Healthcare Centre of Xiamen (Page 5).

Reviewer # 2: Given that the cohort that was studied was so large, why was the age at menarche (AAM) studied as an ordinal rather than a continuous variable? I think that it would have been much more interesting to use it as a continuous variable and to be able to judge the presence or absence of any non-linearity etc.

Author’s response: Thank you very much for your expert comments. We had tried to include AAM as a continuous variable in the logistic regression model, and the results were not much different. Therefore, we chose the AAM as a categorical variable. Firstly, data sources were not precise, such as the age of menarche was dictated by the patient’s physician that many were estimates or a range of ages. Secondly, this classification method can make the number of people in each section relatively consistent. In the linear regression method, AAM was used as a continuous variable.
Reviewer # 2: There have been 3 recent systematic reviews and meta-analyses published in this area. One of them used a dose response approach and, as well as a linear negative association between AAM and GDM risk, also found a significant non-linear term (due to a slight u-shaped curve in the association between AAM and GDM risk). To be able to analyse these in the present data the AAM would have to be analysed as a continuous variable by polynomial logistic regression. Does this population show a (slight) increased risk of GDM in women with a late AAM? It would be worth commenting on.

Author’s response: Thank you very much for your expert comments. We have performed the univariable logistic regression when AAM was more than 15 years old. Of this analysis, the AAM was as continuous variable. The results (OR, 1.206; 95%CI, 0.98-1.067; P=0.211) indicated that when AAM of pregnant women was more than 15 years old, there was not existed significant association between AAM and GDM. Furthermore, we have discussed those research results in discussion as following: “Meanwhile, later age at menarche may be not related with gestational diabetes mellitus” (Page 8).

Reviewer # 2: One recently published study already showed a negative linear association between AAM and OGTT 60 minute glucose concentrations in pregnancy. This needs acknowledging.

Author’s response: Thank you very much for your expert comments. We have discussed this negative linear association between AAM and OGTT 60 minute glucose concentrations in pregnancy in discussion as following: Whereas, the KORA F4 study founded that young age at menarche was significantly related to higher fasting plasma glucose, and 120 minute glucose concentrations [25]. Meanwhile, one published study showed a negative linear association between age at menarche and OGTT 60 minute glucose concentrations in pregnancy [15]. Besides, a research elucidated that there was no significant association existed between menarche age and diabetes [27]. The sample sizes of populations and methods of statistical analysis may be lead to aforementioned differences (Page 10).

Reviewer # 2: In the confounder analyses, the statistical models of the associations between AAM and both GDM risk and OGTT fasting glucose concentrations lost significance when adjusted for maternal age, BMI and blood pressure (as well as educational level, family history of diabetes, and hepatitis B surface antigen in some circumstances). However it is not appropriate to adjust for BMI as many publications have already published strong associations between AAM and BMI in adult life. Negative associations have also been published between AAM and risk of pre-eclampsia in pregnancy, so adjusting for pregnancy blood pressures may
also not be appropriate. Both increased BMI and blood pressures are likely to be associated with insulin resistance in pregnancy which has also been shown to be negatively associated with AAM. This needs careful discussion.

Author’s response: Thank you very much for your expert comments. We have conducted analysis as following: firstly, the result of unadjusted variable of BMI was elucidated in Table 1. Secondly, the outcome of unadjusted variables of BMI and blood pressure was showed in Table 2. According to the correlation between AAM and BMI, we did not consider to include the BMI in final model.

Table 1

<table>
<thead>
<tr>
<th>menarche age</th>
<th>&lt;=13</th>
<th>14</th>
<th>&gt;=15</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR(95%CI)</td>
<td>1.058(0.990-1.131)</td>
<td>1</td>
<td>0.934(0.872-0.999)</td>
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Table 2

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<td>OR(95%CI)</td>
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<td>1</td>
<td>0.928(0.867-0.993)</td>
<td>&lt;0.001</td>
</tr>
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In addition, we have discussed those research results in discussion as following:” Both increased BMI and blood pressures are likely to be associated with insulin resistance in pregnancy which has also been shown to be negatively associated with AAM. However, our further research showed that the results of unadjusted variable of BMI or BMI and blood pressure all indicated the earlier age at menarche was significantly associated with GDM” (Page 9).

Reviewer # 2: The BMIs of the study cohort are very low (at least by Western standards) and so the results may be less relevant to non-Asian populations (and vice versa). The "low" BMIs may explain why the effect sizes in this study are so much smaller than has been observed in other studies. It would be worth discussing this point.

Author’s response: Thank you very much for your expert comments. We have discussed this point in discussion as following: As well, the BMI of three categories in this research was lower than a U.S. study [23]. L.W. Chen et al., indicated that mean age at menarche at 13 years, the BMI of pre-pregnancy (23.3±4.1 kg/m2) was higher than our study (21.3±3.0 kg/m2). This significant difference was original from the difference of ethnics and smaller sample size compared with other study (Page 9).

Reviewer # 3: The abstract and introduction state that findings on age at menarche and GDM are inconsistent based on previous studies. The meta-analysis by Sun et al (2018) was referenced, but their results should be discussed in more detail as findings show that women with menarche
at an early age (≤11 years) had a higher GDM risk with no significant heterogeneity between studies (P = 0.17; I2 = 38).

Author’s response: Thank you very much for your expert comments. We have revised the introduction state that” Some studies report no association, whereas others show an inverse association” as “Some studies founded a potential association [14-16], whereas others show no association [17]” (Page 3). Furthermore, we discussed the more detail in discussion as following: In addition, a meta-analysis showed that women with menarche at an early age (≤ 11 years) had a higher GDM risk with no significant heterogeneity between studies (P = 0.17; I2 = 38) [20] (Page 8).

Reviewer # 3: A major strength of the study is the large sample size, which would allow detailed subgroup analysis. The authors categorised age at menarche in three categories, and not in line with previous studies for comparison (i.e. most studies define early menarche as ≤11 years). I would suggest a more detailed breakdown of categories of age at menarche, to explore the extremes and shape of the association across categories.

Author’s response: Thank you very much for your expert comments. We have showed the reason of age at menarche categorized three groups in part of methods as following: For our analysis, the age at menarche of participants was divided into three categories: early (≤ 13 years), average (14 years), and late (≥ 15 years) age at menarche. The early age at menarche (≤ 13 years) that consistent with the categories used in other research [18] (Page5).

Reviewer # 3: The order in which covariates were added to the models is not clear. If the hypothesis is that pre-pregnancy BMI is the main factor that would attenuate/mediate the association, than this should be added separately to the last model. Moreover, family history is present prior to childhood and should be included as a confounder in the first model. Although the authors may have a specific rationale for their current models, my suggestion would be to adjust for education level, family history and maternal age at delivery in model 2, add blood pressure in model 3, and add BMI in model 4, to be able to determine the change in odds ratios and influence of these covariates and potential mediators.

Author’s response: Thank you very much for your expert comments. We have adjusted for education, family history of diabetes, maternal age in model 2. The results showed in Table 1. Furthermore, we have adjusted for blood pressure in model 3. The outcomes indicated in Table 1. In addition, we have adjusted for BMI in model 4. The result elucidated in Table 3.
Table 1

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<th>&gt;=15</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>1.010 (0.944-1.080)</td>
<td>1</td>
<td>0.970 (0.905-1.039)</td>
<td>0.461</td>
</tr>
</tbody>
</table>

Reviewer # 3: The prevalence of GDM (17.6%) in this population is very high compared with other populations. Please comment on this in the discussion section, and how findings may be applicable to other specific populations.

Author’s response: Thank you very much for your expert comments. We have discussed about the prevalence of GDM in this population is very high compared with other populations in part of discussion as following: In this study, we found that the prevalence of GDM (17.6%) is higher than other populations in this study. One research reported that the total incidence of GDM in mainland of China was 14.8% [22]. A vast territory and a large population in China with significant differences in ethnicities, diets, lifestyles, and regions, and these factors may result in differences in prevalence of GDM reported in various regions (Page 8).

Reviewer # 3: While the findings on 1-hour and 2-hour glucose show significant findings in the final models, please discuss the magnitude and potential implications of these associations.

Author’s response: Thank you very much for your expert comments. We have discussed the magnitude and potential implications of these associations in part of discussion as following: 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. Studies reported that earlier age at menarche might be associated with adulthood higher estrogen levels and lower serum sex hormone-binging globulin levels among women [12], which could result in higher OGTT 60 minute and 120 minute glucose levels (Page 10).
Reviewer #3: The conclusion that "early menarche is associated with an increased risk of gestational diabetes may allow clinicians who follow pregnant women to institute early monitoring for signs of GDM, better enabling them to intervene in a timely fashion should this condition arise" is unclear given the study findings. Findings show a weak association with minimal adjustments, and no association after further adjustments. This needs to be reflecting in a concluding statement on the implications of the findings.

Author’s response: Thank you very much for your expert comments. We have revised the conclusion that “early menarche is associated with an increased risk of gestational diabetes may allow clinicians who follow pregnant women to institute early monitoring for signs of GDM, better enabling them to intervene in a timely fashion should this condition arise” as “Taken together, this association between age at menarche and GDM should be further investigated in other study populations to identify our observations and expand on our results. Furthermore, the mechanistic researches are needed that elucidate underlying pathophysiologic mechanisms of observed correlation may help confirm therapeutic targets of a disorder related to significant offspring mortality. In addition, association between early age at menarche and GDM may help confirm women at high risk of GDM and adopt early prevention strategies.” (Page11).