Author's response to reviews

Title: Association of Gestational Diabetes Mellitus (GDM) with Subclinical Atherosclerosis: a systemic review and meta-analysis

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Author's response to reviews: see over
Dear Editor and Reviewers,

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Association of Gestational Diabetes Mellitus (GDM) with Subclinical Atherosclerosis: a systemic review and meta-analysis”. Those comments are all valuable and very helpful for revising and improving our paper as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked highlighting in the paper.

The main corrections in the paper and the responds to the reviewer’s comments are as follows:

For editors:

1. It should be better explained if in the original studies the association between subclinical atherosclerosis and gestational diabetes mellitus was evaluated at multivariate analysis or not. We added comment: “Only the study of Gunderson[19] was evaluated at multivariate analysis (adjusted for age, race, parity, pre-pregnancy BMI, HOMA-IR, weight gain, year 20- HOMA-IR+DBP, incident diabetes and metabolic syndrome in 20 years), other studies used unadjusted data.” Changes have been made on Page 3, Line 30.

2. It is not clear if the relationship was established exploiting adjusted observational results, in order to reduce confounders (for example patients with high body mass index) or not. This should be added:
   - Much more data about baseline features of included studies should be added
   As there are many data about baseline features of included studies, such as BMI, parity, weight, serum cholesterol, HDL, LDL, smoking, waist, weight gain, family history of DM and so on. We added BMI and waist in Table 1, other data (serum cholesterol, HDL, LDL, parity) has been put into the supplemental material due to limited space in Table 1. Other factors such as weight gain, family history of DM, smoking, gestational age are not reported in more than half of all included studies thus we did not put them into our article.

3. Meta regression analysis should be performed for age at pregnancy, length of pregnancy etc.
   We did Meta regression analysis on publish year, age at pregnancy, no. patients, BMI of GDM, measuring time, duration and criteria. As meta-regression result of “age at pregnancy” was different from that of stratified analyses, we discussed this factor with caution this time, and deleted the statement like “the association between GDM and larger cIMT was stronger in younger GDM patients”.

4. Even subclinical atherosclerosis may be reduced by drugs, this should be commented
   We added comment: “We find cIMT does not increase years after GDM has been diagnosed. A possible explanation is that these patients take certain drugs to delay the process of atherosclerotic formation, it’s been reported that even subclinical atherosclerosis may be reduced by drugs [33]. As the medications of these patients were not fully reported in included studies, future researches are needed to study this issue.” Changes have been made on Page 4, Line 42.

For reviewer 1:
1. **Major Compulsory Revisions:** Page 5, line 4: "Second, most of included studies used previous recommendations for the diagnosis of GDM (Carpenter and Coustan criteria) because they designed before the new recommendations were applied.". In my opinion this aspect cannot be discussed only to the “study limitations” but should be assessed more broadly. Your work evaluates potential correlations between GDM and cIMT, cannot leave aside a careful assessment of the criteria with which the various studies define GDM. In the literature studies such as "Int J Endocrinol. 2013 :2013:248121. doi: 10.1155 /2013/248121 . Epub 2013 Jan 10” clearly describe how the diagnosis of gestational diabetes significantly changed on the basis of the diagnostic criteria used. Some of your results, as the correlation between a more thicker cIMT and younger age, could be explained by the use of different diagnostic criteria. In my opinion before publishing the article you need to reevaluate the results of your meta-analysis in the light of the diagnostic criteria for GDM used in the various studies analyzed.

We reevaluated our results, added GDM criteria as a factor both in meta-regression and subgroup analyses. We added all these in results parts and added discussion "We find that the diagnostic criteria of GDM may influence the impact of GDM on cIMT. Diagnosis of gestational diabetes significantly changed on the basis of the diagnostic criteria used, and influenced clinical outcomes [33, 34]. However, too few studies included in NDDG, WHO, ADA 75g subgroups. In fact the NDDG criteria indicate more severe GDM than Carpenter-Coustan one. But we got no statistically different result in NDDG subgroup analysis, while a statistically different one in Carpenter-Coustan subgroup. The heterogeneity among different studies is relatively large, which may also cause this phenomenon”. We also added diagnostic criteria in the supplemental material.

2. Page 2 line 40-41: "cIMT was not measured in both gestational diabetes and cIMT groups" For "cimt group" you mean "control group"? It is unclear what you mean, specify it better please.

We have corrected this error. Changes have been made on Line 40-41, Page 2.

3. Page 3 line 42 and 43: "(WMD: 0.07, 95% CI: 0.03–0.10 for those published after 2013 and WMD: 0.05, 95% CI: 0.02–0.08 for those after 2013)" Perhaps you have written two times "after 2013"

We have corrected this error. Changes have been made on Line 42-43, Page 3.

4. Page 4 line 1-2: "duration (WMD: 0.05, 95% CI: 0.01–0.09 for duration>4 and 1 WMD: 0.05, 95% CI: 2 0.01–0.09 for duration between 0 and 4)" Duration of what? It is unclear what you mean, specify it better please.

We added statement: “duration between the time of GDM diagnosed and cIMT measured”. Changes have been made on Line 1-2, Page 4.

For Reviewer 2:

1. I think that in the "conclusion" it would be useful to notice the clinical relevance of the evidences reported in the study.

We added statement: “Weight control may be useful to prevent cardiovascular diseases for GDM patients.” in the Conclusion part.

2. about clinical perspective? Correlation between GDM-cIMT and Risk of developing CV
accidents should help clinicians to evaluate strategies to reduce CV Risk.

We added statement: “It is reported that cIMT adds predictive value to the Framingham risk score for cardiovascular events[5], is a level IIa recommendation for cardiovascular risk evaluation[36], cIMT has been confirmed to be able to predict incident coronary heart diseases[37].” Changes have been made on Line 12, Page 5.

Despite all the shortages as above mentioned, we will try our best to improve this study. Please give us a chance to improve this study.

Thanks a lot.

Sincerely,
Ying-Bin Xiao