Author's response to reviews

Title: The independent effects of maternal obesity and gestational diabetes on the pregnancy outcomes

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Author's response to reviews:

Dear Editor,

We thank the reviewers for their constructive comments and below are point-to-point reply to their reviews. The authors have reanalyzed the data in this re-submission and adopted a different approach for data analysis and changed the methodology, the results and the discussion sections accordingly:

Reviewer Lynn Yee

Major compulsory revisions

1. INTRODUCTION – The authors review the prevalence of obesity and discuss the pregnancy-related consequences of obesity in the introduction. However, the introduction would benefit from further discussion of gestational diabetes. What proportion of GDM patients in the region are obese? Can you discuss other literature that examines the combined effect of obesity and GDM? What is lacking in the existing literature on this topic? Additionally, what is the study hypothesis?

A paragraph was added to the introduction to address the reviewer’s comments on the introduction (highlighted in yellow)

2. METHODS – Although it is appropriate to use the initial visit weight to calculate BMI, it is problematic that the booking visits were on average at nearly 22 weeks. Gestational weight gain is certainly a confounding factor. This limitation is addressed at length in the Discussion. Can the authors state what proportion of women had first trimester weight measurements?

We are aware of the effect of weight gain during pregnancy on the classification of mothers into BMI categories and we have addressed that in the limitation of this study. In the re-submitted version of the article we regroup the cohort into two groups; non-obese BMI <30kg/m2 and obese >/= 30kg/m2 and compared the different outcomes between them, this is mainly to limit the effect of weight
gain. 44% of our population were obese a proportion similar to that reported by El-Gilany et al (reference 4 in the manuscript) in a Saudi pregnant population measured during the first trimester of pregnancy. The proportion of women who had first trimester BMI calculated was 36%.

3. METHODS – The World Health Organization uses BMI classifications of underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), and obese (>30). The authors chose different BMI classifications for underweight and normal weight – can they clarify the reasons for this?

The methodology has changed and the cohort has been grouped into two groups obese and non-obese in the re-submission.

4. METHODS – Did women without documented prior diabetes but with risk factors undergo an early pregnancy/1st visit screen for pregestational diabetes?

Yes, however all women were screened as they are from at risk ethnic group (Middle Eastern). Please see methodology text highlighted in yellow page 5of the manuscript.

5. METHODS – The OGTT used to diagnose diabetes is described as a 75g glucose load, but the diagnostic thresholds given and the number of positive values used to establish the diagnosis are consistent with the 100g load. Typically, the 75g load is a 2-hour test (not 3), with thresholds of 92/180/153 (the authors describe Carpenter-Coustan criteria for a 100g load), and with one positive value required for a diagnosis of GDM (not two). Please clarify the diagnostic methods. Additionally, if a 100g 3h OGTT was used, was this done on all women, or was it part of a two-step process after a positive 50g OGTT screen?

The full protocol for screening of GDM is detailed on page 5 and previous mistakes in reporting the obstetric department at King Khalid University Hospital protocol for diagnosing GDM were corrected.

6. METHODS – The authors stated that the perinatal outcomes data were gathered from participants in the postpartum ward. Does this mean the women were asked the information directly, or that it was gathered from the medical chart?

Data on the demographic characteristics and the pregnancy outcomes were collected from the records and data on tobacco smoking were collected from the mothers in the postnatal ward. (page 6-7 highlighted in yellow)

7. RESULTS – There is a major contradiction in the descriptions of the models.
In the Methods section (last paragraph), the models are described as: Model 1 adjusts for confounding factors but not GDM and Model 2 adjusts for confounding factors and GDM. However, the footnotes of Table 4 state the reverse; they state that Model 1 includes GDM and Model 2 does not. Please correct this contradiction.

In the re-submitted version of the article we adopted an approach different from the previous models, which is stratification of the study group, for quantification of the independent effect of GDM and obesity on the outcome of pregnancy (Please see page 6 highlighted in yellow)

8. RESULTS - The text describing the results of the multivariable regression is somewhat confusing. The explanation of the models in the Methods states that one model (presumably Model 2, although see comment above) controls for diabetes, whereas the text in the Results implies that the models compare women with and without diabetes. For example, the 2nd paragraph of the “multivariable logistic regression analysis” section describes all women (in the first sentence), and then women with GDM (in the 2nd sentence). It seems that the more appropriate second sentence in that paragraph would be “This risk increased to more than threefold when controlling for GDM.” The same comment applies to the next paragraph in the results.

After re-analysis according to the stratification of the study group the results were reported and all previous text was replaced with a new text according to the results (Please see page 8-9, highlighted in yellow)

9. DISCUSSION – In the discussion, the authors describe the relative effects of obesity compared to combined GDM/obesity or GDM alone. Although the data suggest that obesity has an independent effect on the outcomes (since the OR remains significant after controlling for diabetes), there are no analyses describing the impact of GDM alone (ie, models comparing GDM to no GDM and adjusting for obesity). Thus, it is not possible to conclude anything about the effect of GDM alone. In addition, the authors state “maternal obesity was the only determinant of the risk of CS at delivery.” It seems the more appropriate statement would be “maternal obesity remained an independent risk factor for CS even after controlling for diabetes.” The conclusions (and title) would benefit from re-wording to more accurately reflect the analyses done.

The independent effect of obesity and GDM became more obvious after we
stratified the cohort into 4 groups and the discussion has been streamlined with results.

10. TITLE – The title perhaps should be reworded to state “Maternal obesity has an impact on pregnancy outcomes independent of gestational diabetes.”

The title has been changed to reflect the results.

Minor essential revisions
1. RESULTS – The statement “sedentary lifestyle cannot be ruled out as 76% of the women in this study were housewives” is unnecessary in the results, as the concept is explained at length in the Discussion.

Done

2. TABLE 1 – Please add units to the neonatal characteristics (gestational age, birth weight, head circumference, and length).

Done

3. RESULTS (2nd paragraph in Maternal characteristics) – The statement on newborn length and NICU admission is unnecessary.

The statement in question has been changed according to the results of the re-analysis (please see page 8-9 highlighted in yellow)

4. DISCUSSION – Spelling error of the Pedersen hypothesis in paragraph 3.

Done

5. DISCUSSION – In the last sentence of paragraph 3, the use of references 22 and 23 is somewhat confusing. It is my understanding that both studies cited are studies of only diabetic women, not comparisons of diabetics versus non-diabetics. Please clarify.

We agree with the reviewer and the text of the manuscript has been changed accordingly. The reference (Murphy et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial, BMJ. 2008 Sep 25;337:a1680. doi: 10.1136/bmj.a1680) has been removed from the text.

6. METHODS – “chi square” is spelled incorrectly in the statistical analysis section.

Corrected

Discretionary revisions
1. METHODS – Neonatal head circumference and length were chosen as outcomes of interest. Can the authors explain why these were thought to be
related to obesity and diabetes?

All newborn anthropometric measurements are affected by its weight [1-3].

Reference List


Reviewer: Yvonne cheng

Reviewer's report:

1. Abstract, Methods section—does the authors mean “multiple” logistic regression analysis or “multivariable” logistic regression analysis?

We used the multivariable logistic regression models. Every model was developed based on the outcome as present or absent e.g. macrosomia (yes/no) and CS (yes/no). The independent variables as the covariates for each outcome were included and defined as required (Statistician response).

2. Maternal obesity is considered a risk factor for diabetes mellitus and gestational diabetes mellitus, and pregnant women who are obese or have other risk factors of DM or GDM (family history, personal history, or history of macrosomia, etc) are often screened for GDM in the first trimester or at initiation of prenatal care. Were women who were obese screened for GDM early in pregnancy in this study?

Yes, however all women were screened as they are from at risk ethnic group. Please see methodology text highlighted in yellow page 5-6 of the manuscript.

3. Why did the authors use 75-gm OGTT to screen, but define GDM using Capreenter-Coustan criteria that is based on 100-gm OGTT? While there are many different diagnostic criteria of GDM (e.g. HAPO (Hyperglycemi and
Adverse Pregnancy Outcome that used 75gm OGTT with 92, 180 and 153 mg/dL as cutoffs (for fasting, 1-hour, and 2-hour values), the WHO that used 75gm OGTT that used 126 and 140mg/dL for fasting and 2-hour values) and the National Diabetes Data Group and the Carpenter-Coustan criteria that utilize 2-step screen and diagnosis method), I am not aware the diagnostic criteria described and used by this study in terms of its sensitivity, specificity and validation.

The full protocol for screening of GDM is detailed on page 5 and previous mistakes in reporting the obstetric department at King Khalid University Hospital protocol for diagnosing GDM were corrected.

4. How did the authors define gestational hypertension and preeclampsia, and pregnancy-induced hypertension (PIH) as well as chronic hypertension?

The only outcome we investigated in the re-analysis of this study was pre-eclampsia and the definition is highlighted in yellow on page 7

5. Was the amount of tobacco smoking exposure quantified?

No that was not possible in this study as only very small proportion of the cohort re-called the exposure duration.

6. Do authors have information on other neonatal outcomes often associated with insulin resistance in pregnancy, such as neonatal jaundice/hyperbilirubinemia, hypoglycemia, birth injury, shoulder dystocia?

Due to the retrospective nature of this study and the poor documentation of the these complication in the mother medical records, the authors were not able to get such information, however the authors are members in an investigating team for a prospective multicenter cohort study already started which will gather all the important outcomes.

7. I am concerned about the fact that the mean gestational age at initiation of prenatal care was 21.8, or 22 weeks gestation. This certainly can bias the authors’ classification of women in various BMI category.

We agree on that the late booking for antenatal care imposes risk of bias and we have mentioned that on the limitation of this study in addition in the re-submitted version of the article we regroup the cohort into two groups; non-obese BMI <30kg/m2 and obese >/= 30kg/m2 and compared the different outcomes between them, this is mainly to limit the effect of weight gain. 44% of our population were obese a proportion similar to that reported by El-Gilany et al (reference 4 in the manuscript) in a Saudi pregnant population measured during the first trimester of pregnancy.
8. Ideally, the assessment of body mass composition and pregnancy outcome should consider women’s normal weight outside of pregnancy, or shortly after pregnancy so that the assessment would not be biased by gestational weight gain as well. Do the authors have information on gestational weight gain?

We don’t have the gestational weight gain for the whole cohort due to the late booking and the poor recall of the pre-pregnancy weight of most of the women in the cohort.

9. For the multivariable logistic regression models, how did the authors decide to use the so mentioned covariates? How were the models tested for goodness of fit?

Covariates were included based on detailed discussion with the researchers. Some simple Directed acyclic graphs (DAGs) were developed and simplified to decide which confounders to be included in each model. The final decision for inclusion or exclusions of covariates was taken by the research team and mainly according to the clinical point of view (Statistician response).

10. Why was only term delivery limited for the regression analysis but not for the univariate analysis?

In the resubmitted article we stated the inclusion criteria to be term pregnancy for the entire cohort (please see page 5)

11. Did the authors examine the effect of gestational weight gain on outcomes?

No, we did not as this was not in the objectives of this study and the data were not available.

12. Tables: please provide units to corresponding outcomes examined

Done