PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Maternal glucose level and body mass index measured at gestational diabetes mellitus screening and the risk of macrosomia – results from a perinatal cohort study
AUTHORS	Liu, Jian; Leng, Junhong; Tang, Chen; Liu, Gongshu; Hay, John; Wang, Jing; Wu Wen, Shi; Li, Zhenling; She, Ye

VERSION 1 - REVIEW

REVIEWER	Miroslava Gojnic Dugalic clinical centre serbia clinic for gyn and obs university belgrade medical faculty
REVIEW RETURNED	11-Feb-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Pawel Gutaj, MD Department of Obstetrics and Women's Diseases. Poznan University of Medical Sciences. Poland
REVIEW RETURNED	20-Feb-2014

GENERAL COMMENTS	Liu et al. examined the role of maternal BMI and glucose level measured at GCT on the risk of macrosomia in the perinatal cohort of Chinese women. They found that both of these parameters might be used in the assessment of the risk of LGA/macrosomia. Moreover, they showed that maternal BMI is stronger predictor of LGA/macrosomia than maternal glucose at GCT. Overall the study might be reconsidered, however I have a number of major and minor comments. Abstract does not meet Journal's requirements- (321 words, instead of 300)- please try to make it shorter. Authors wrote that participants were <40 years? Does it mean that the study group included underage patients? Please clarify this issue. Authors define LGA in their study as BW>90 percentile for gestational age at birth. The percentage of LGA newborns in this perinatal cohort was calculated as 24,7%. It is very high number (in a healthy population it should be around 10% based on the definition of LGA). In the discussion, authors state that the study population was almost pregestational diabetes free (one patient with type 1 diabetes was included in the analysis). What about the incidence of GDM in this cohort? It should be clearly stated, because GDM is an important determinant of LGA. It might at least partly explain the high rate of LGA in this study.

	Which criteria has been used by the authors in the diagnosis of GDM with 75 OGTT? Is it IADPSG? I'm asking, because authors define abnormal glucose values from OGTT as fasting>=5.0 or 1h>=10.0 or >=8.5 mmol/L. Acording to standards based on IADPSG criteria (HAPO study) fasting glucose should be >=5.1 mmol/L in order to diagnose GDM. Please comment. In the Methods authors state that all the details of the study design and data collection are found in different publication. In my opinion, this information should be described in this manuscript for it's clear understanding. Gestational age calculation was based on LMP in this study. As this parameter might be inappropriate in a significant number of patients (due to menstrual irregularities) it should be confirmed by CRL measurement in the first trimester. Do the authors have such data? In the results authors summarize group characteristics. What do the authors mean "positive disease history". What kind of diseases they took into consideration? I also do not fully understand the term "reproductive insurance". Page 9, line 27- authors wrote that male infants had a "slightly" shorter gestational age. I would avoid such words while describing statistics, as this difference is indicated by p<0,001 suggesting rather strong statistical significance. Receiver operating characteristic (ROC) analyses need more detailed description. Area under the curve (AUC), specificity, sensitivity and p value should be given for every analysis. References should be checked and corrected to meet the BMJ open standards. Article also needs some language corrections before being published. To summarize, the authors performed an interesting study, which may give new insight to LGA risk assessment in the second part of pregnancy. However, an article needs major revision before being reconsidered for publication in BMJ open.

REVIEWER	Dr Yannan Jiang The University of Auckland New Zealand
REVIEW RETURNED	17-Mar-2014

GENERAL COMMENTS	ABSTRACT: The primary outcome of this study is macrosomia, as stated in the manuscript title. However, LGA is reported as one of the primary outcomes with much more details. The conclusions are not well supported by the results, with only two risk factors assessed at one single gestational time-point. Note that maternal height/weight can be measured separately from GDM screening during the pregnancy. Design and Analysis: One major concern here is the lack of information on the level of correlation between two main risk factors. As stated in the INTRODUCTION, maternal hyperglycemia is also associated with maternal obesity status. If they are highly correlated, adding both in the same regression model violates the assumption of independent variables. In addition, with the known difference in BMI measured at 24-28 weeks gestation and potential influence of maternal BMI before pregnancy, the results are less convincing without proper adjustment on the baseline values. BMI as a combined index using body height and weight, is better understood as normal weight, overweight and obese in

	categorization. The authors didn't explain why BMI quintiles were used for analysis. Further justification on the selection of covariate variables, and their contribution to the final regression model should be added. Why is Table 1 presented by gender rather than overall, and tested between two groups? The comparisons contribute nothing to the final results and conclusions, with gender fitted as one of the covariates same as other variables. A better analysis strategy is to collect repeated data on maternal weight and BMI from pre-pregnancy (or early-pregnancy). This can be assessed separately from GDM screening at 24-28 weeks gestation, which mainly focuses on blood glucose control. The weight gain during pregnancy is easier to understand and monitor, and the change over time can be evaluated to see which gestational time-point is most critical to the clinical outcomes. The perinatal cohort is from one large district in Tianjin city, China, with the majority of Han-ethnicity (>90%). So the participants cannot represent well of the study population in China, with known geographic, socioeconomic and ethnic differences. Some minor points on the reporting of statistical analysis and results. The terms used for two outcome measures need to be consistent in the manuscript. More emphasis should be made on macrosomia than LGA if they are defined differently. It's unclear what the "univariate analyses" are, for Table 1? For pre-defined covariates, they must be reported consistently in tables and figures. Please check carefully whether any variable was missing, e.g. marital status. Table 1 needs to report both n and % for categorical variables. Information on maternal weight and BMI quintiles used should be presented. In Table 2, does GCT actually mean BG? Figure 3 is quite hard to read and understand, suggest revising the format or using appropriate table.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Pawel Gutaj, MD
Institution and Country Department of Obstetrics and Women's Diseases. Poznan University of Medical Sciences. Poland
Please state any competing interests or state ‘None declared’: None declared

Liu et al. examined the role of maternal BMI and glucose level measured at GCT on the risk of macrosomia in the perinatal cohort of Chinese women. They found that both of these parameters might be used in the assessment of the risk of LGA/macrosomia. Moreover, they showed that maternal BMI is stronger predictor of LGA/macrosomia than maternal glucose at GCT. Overall the study might be reconsidered, however I have a number of major and minor comments.

Abstract does not meet Journal’s requirements- (321 words, instead of 300)- please try to make it shorter.
Response: Thank you for bringing this to our attention the abstract has been shortened.

Authors wrote that participants were <40 years? Does it mean that the study group included underage patients? Please clarify this issue.
Response: Participants younger than 19 have been excluded and the corrected age range is 19 – 42.

Authors define LGA in their study as BW>90 percentile for gestational age at birth. The percentage of LGA newborns in this perinatal cohort was calculated as 24,7%. It is very high number (in a healthy population it should be around 10% based on the definition of LGA).
Response: the reason for having such high prevalence is that the cut-offs of LGA for China are much lower than that for western countries. To avoid confusion, and in response to another reviewer's comment, in the revised manuscript we only refer to macrosomia.

In the discussion, authors state that the study population was almost pregestational diabetes free (one patient with type 1 diabetes was included in the analysis). What about the incidence of GDM in this cohort? It should be clearly stated, because GDM is an important determinant of LGA. It might at least partly explain the high rate of LGA in this study.
Response: The reviewer is correct and we have we added information regarding incidence of GDM in the discussion.

Which criteria has been used by the authors in the diagnosis of GDM with 75 OGTT? Is it IADPSG? I'm asking, because authors define abnormal glucose values from OGTT as fasting>=5.0 or 1h>=10.0 or >=8.5 mmol/L. Acording to standards based on IADPSG criteria (HAPO study) fasting glucose should be >=5.1 mmol/L in order to diagnose GDM. Please comment.
Response: Thank you for catching this typo - it has been corrected.

In the Methods authors state that all the details of the study design and data collection are found in different publication. In my opinion, this information should be described in this manuscript for it's clear understanding.
Response: We have added a paragraph briefly describing the study design and data collection used in the earlier study.

Gestational age calculation was based on LMP in this study. As this parameter might be inappropriate in a significant number of patients (due to menstrual irregularities) it should be confirmed by CRL measurement in the first trimester. Do the authors have such data?
Response: We do not have this information but have recognized this as a potential limitation in the discussion.

In the results authors summarize group characteristics. What do the authors mean "positive disease history". What kind of diseases they took into consideration?
Response: We have now detailed our definition of positive disease history in the paper.

I also do not fully understand the term "reproductive insurance".
Response: We have replaced this term with more understandable descriptor "maternity insurance" and provided information as to its definition.

Page 9, line 27- authors wrote that male infants had a "slightly" shorter gestational age. I would avoid such words while describing statistics, as this difference is indicated by p<0,001 suggesting rather strong statistical significance.
Response: point well taken and we have removed the word "slightly".

Receiver operating characteristic (ROC) analyses need more detailed description. Area under the curve (AUC), specificity, sensitivity and p value should be given for every analysis.
Response: We have added information regarding specificity and sensitivity as suggested.

References should be checked and corrected to meet the BMJ open standards.
Response: Thank-you this has been done.

Article also needs some language corrections before being published.
Response: We have carefully examined and edited.

To summarize, the authors performed an interesting study, which may give new insight to LGA risk assessment in the second part of pregnancy. However, an article needs major revision before being reconsidered for publication in BMJ open.
Response: Thanks for your careful review and valuable comments.

Reviewer Name Dr Yannan Jiang
Institution and Country The University of Auckland
New Zealand
Please state any competing interests or state 'None declared': None declared

ABSTRACT: The primary outcome of this study is macrosomia, as stated in the manuscript title. However, LGA is reported as one of the primary outcomes with much more details.
Response: although many studies used the term of macrosomia to indicate larger size infants either defined as LGA (90th percentile of BW) or as macrosomic infants (often defined as BW>4000g), we agreed to just focus on macrosomia (BW > 4000g) since the cutoffs of LGA for Chinese population are much less than that for western populations and, thus, less comparable.

The conclusions are not well supported by the results, with only two risk factors assessed at one single gestational time-point. Note that maternal height/weight can be measured separately from GDM screening during the pregnancy.
Response: Our conclusion is "High BMI measured at GCT was the most important determinant for risk of macrosomia." We think our results are very supportive of this conclusion and believe that one single time point measurement of risk factors can be used to examine "disease" risk association. For example, most lipids-heart disease risk associations were reached through an examination of the impact of the (single-point) baseline lipid profile on the risk of heart disease. Lacking a measurement of pre-pregnancy weight may limit our capability to examine the impact of weight change between GDM screening and before pregnancy on the risk of macrosomia (and we have recognized this as a potential limitation in the discussion), but it should not affect the risk association identified at GDM screening between obesity status and macrosomia.

Design and Analysis: One major concern here is the lack of information on the level of correlation between two main risk factors. As stated in the INTRODUCTION, maternal hyperglycemia is also associated with maternal obesity status. If they are highly correlated, adding both in the same regression model violates the assumption of independent variables.
Response: Thank-you, we have added the correlation information into the results.

In addition, with the known difference in BMI measured at 24-28 weeks gestation and potential influence of maternal BMI before pregnancy, the results are less convincing without proper adjustment on the baseline values.
Response: we agree that if weight change is of interest, e.g., weight gain between GDM screening and pre-pregnancy, one then definitely needs to adjust for pre-pregnancy weight. However, the focus of this study was not weight change, but weight status at GDM screening and its risk association with macrosomia; therefore, there is no need for "baseline" values. This does raise the need for subsequent research to examine the role of weight change.

BMI as a combined index using body height and weight, is better understood as normal weight, overweight and obese in categorization. The authors didn't explain why BMI quintiles were used for analysis.
Response: We agree, however while there are criteria to use BMI to categorize as underweight, normal weight, overweight or obese for women prior to pregnancy, no such criteria exist for women who are pregnant. We have provided this explanation in the text.

Further justification on the selection of covariate variables, and their contribution to the final regression model should be added.
Response: the foci of this study are to examine whether BMI measured at GDM screening affects the risk of macrosomia; and whether maternal BG levels interact with BMI, and how macrosomia risk is associated with this interaction. Many of the covariates in models are known risk factors for macrosomia, but they are not focus in this study. We don't think it is necessary to discuss these factors beyond recognizing the need to include them in the model and so that their potential impacts have been taken into account.

Why is Table 1 presented by gender rather than overall, and tested between two groups? The comparisons contribute nothing to the final results and conclusions, with gender fitted as one of the covariates same as other variables.
Response: It is important to compare characteristics between genders even though in the multiple regression models gender is just one covariate. The main reason is to determine if they are comparable and therefore reasonable to pool genders in multiple regression analyses.

A better analysis strategy is to collect repeated data on maternal weight and BMI from pre-pregnancy (or early-pregnancy). This can be assessed separately from GDM screening at 24-28 weeks gestation, which mainly focuses on blood glucose control. The weight gain during pregnancy is easier to understand and monitor, and the change over time can be evaluated to see which gestational time-point is most critical to the clinical outcomes.
Response: We agree this is an ideal research design, but it seems no study to date has been able to attain that level. However, we believe that the relationship identified between weight status at GDM screening and risk of macrosomia is important. Since everyone needs to access their BG levels, it would be a good opportunity to advise pregnant women that they not only need to monitor their BG for risk for GDM, but also their weight status for risk of macrosomia.

The perinatal cohort is from one large district in Tianjin city, China, with the majority of Han-ethnicity (>90%). So the participants cannot represent well of the study population in China, with known geographic, socioeconomic and ethnic differences.
Response: We now note that the cohort is very representative to Tianjin population and do not attempt to generalize beyond that fact.

Some minor points on the reporting of statistical analysis and results.

The terms used for two outcome measures need to be consistent in the manuscript. More emphasis should be made on macrosomia than LGA if they are defined differently.
Response: Thanks, it has been changed accordingly.

It's unclear what the "univariate analyses" are, for Table 1? For pre-defined covariates, they must be reported consistently in tables and figures. Please check carefully whether any variable was missing, e.g. marital status.
Response: t-tests for continuous variables and chi-square tests for categorical variables are considered as univariate analyses. We have checked for consistency of covariates used between tables and figures.

Table 1 needs to report both n and % for categorical variables. Information on maternal weight and BMI quintiles used should be presented.
Response: Thank you this has been changed as requested.

In Table 2, does GCT actually mean BG?
Response: Yes, it is. We have followed suggestions to change this to blood glucose measured at GDM.

Figure 3 is quite hard to read and understand, suggest revising the format or using appropriate table.
Response: figure 3 presents the key findings of this study. We recognize this is a challenging figure but believe that putting these results into a table will produce a result at least as difficult and less able to convey the information.

Reviewer(s)' Comments to Author:

Editorial comments

1. What do you mean when you asked about 'disease history'?
Response: We have added information for this term.

2. Did you adjust for other risk factors for macrosomia (eg previous baby with macrosomia, excessive wt gain during pregnancy, overdue pregnancy)?
Response: The large majority of them were first time mothers which is not surprising given China's one child policy. We don't have pre-pregnancy weight information, so we cannot calculate if there was excessive weight gain. Adjusting for gestational age may have largely accounted for any impact from overdue pregnancies.

VERSION 2 – REVIEW

REVIEWER	Pawel Gutaj Department of Obstetrics and Women's Diseases, Poznan University of Medical Sciences, Poland
REVIEW RETURNED	11-Apr-2014

GENERAL COMMENTS	My first question relates to the age of participants. In the previous version, the authors wrote that study participants were < 40, so I've asked for clarification. Now, the age range is 19-42. Does it mean, that the authors have included new patients in the analysis? In my previous review I wrote: "Authors define LGA in their study as BW>90 percentile for gestational age at birth. The percentage of LGA newborns in this perinatal cohort was calculated as 24,7%. It is very high number (in a healthy population it should be around 10% based on the definition of LGA). " Response of the authors was: the reason for having such high prevalence is that the cut-offs of LGA for China are much lower than that for western countries. To avoid confusion, and in response to another reviewer's comment, in the revised manuscript we only refer to macrosomia. LGA (large for gestational age) is a population-based term. The certain cut-off values for LGA differs according to the gestational age

	at birth, sex, and importantly- the population based on which percentile charts were designed. The fact, that cut-offs for LGA in China are different (lower) than those based on European populations is understandable. However, the term LGA still represents the same- newborns with birthweight >90pc for the representative population, which means that these newborns weigh more than 90% of all newborns of the same gestational age. So, at least theoretically, it gives 10% of LGA newborns in general population. In my review, I've asked the authors how they can explain relatively high number of LGA newborns in their cohort. One of the possible explanations might be exclusion of newborns with birthweight< 2500g (as I have occasion I would like to ask the authors, why they've done so). In my opinion, LGA is always more appropriate to define abnormal fetal growth as it refers to the reference population (the same age, sex, and optimally- nationality). Using term macrosomia only, lead to bias, because certain number of LGA newborns is not included in the analysis. In such big cohort as this one, this number might be significant. That's why I don't fully understand why authors changed the methods of analysis and resigned from using term LGA in classification o newborns. I would suggest to use previous approach and define in mat&met what kind of percentile charts (national, regional, etc.?)the authors used in the analysis.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name Pawel Gutaj
Institution and Country Department of Obstetrics and Women's Diseases, Poznan University of Medical Sciences, Poland
Please state any competing interests or state 'None declared': None declared

I would like to thank the authors for their thorough reply. However, I still have some concerns.

My first question relates to the age of participants. In the previous version, the authors wrote that study participants were < 40, so I've asked for clarification. Now, the age range is 19-42. Does it mean, that the authors have included new patients in the analysis?

Response: we didn't include any new patients in analysis. Simple correcting the mistake made in the previous writing. The reason for having <40 in the previous manuscript might due to that we were also drafting a research proposal then and we restricted our participants less than 40 years in that proposal; somehow we thought we used the same criteria in this study and didn't check it. When you raised this question, we did re-examine the age range and found that the actual age range was from 15 – 42. There were two aged 15 and two aged 18. To avoid the impact of teens' pregnancy as you suggested, we reanalyzed and presented the new results with exclusion of these teens.

In my previous review I wrote:
"Authors define LGA in their study as BW>90 percentile for gestational age at birth. The percentage of LGA newborns in this perinatal cohort was calculated as 24,7%. It is very high number (in a healthy population it should be around 10% based on the definition of LGA). "

Response of the authors was: the reason for having such high prevalence is that the cut-offs of LGA for China are much lower than that for western countries. To avoid confusion, and in response to another reviewer's comment, in the revised manuscript we only refer to macrosomia.

LGA (large for gestational age) is a population-based term. The certain cut-off values for LGA differs according to the gestational age at birth, sex, and importantly- the population based on which percentile charts were designed. The fact, that cut-offs for LGA in China are different (lower) than those based on European populations is understandable. However, the term LGA still represents the same- newborns with birthweight >90pc for the representative population, which means that these newborns weigh more than 90% of all newborns of the same gestational age. So, at least theoretically, it gives 10% of LGA newborns in general population. In my review, I've asked the authors how they can explain relatively high number of LGA newborns in their cohort. One of the possible explanations might be exclusion of newborns with birthweight< 2500g (as I have occasion I would like to ask the authors, why they've done so). In my opinion, LGA is always more appropriate to define abnormal fetal growth as it refers to the reference population (the same age, sex, and optimally- nationality). Using term macrosomia only, lead to bias, because certain number of LGA newborns is not included in the analysis. In such big cohort as this one, this number might be significant. That's why I don't fully understand why authors changed the methods of analysis and resigned from using term LGA in classification o newborns. I would suggest to use previous approach and define in mat&met what kind of percentile charts (national, regional, etc.?)the authors used in the analysis.

Response: we appreciated very much of your suggestions. When newborns with BW <2500 were included (n=44), the prevalence of LGA was 24.2%. Since mothers whose babies' BW <2500g had an average BMI of approximately 24 at GDM screening and majority of them were in the Q2 the reference group. Including them into the analysis might introduce a biased OR for LGA or macrosomia.
The possible reason for having such high prevalence LGA might due to that the criteria used in this study was from a national study conducted between 1986- 1987 among 15 large Chinese municipalities including Tianjin, the city where we had this cohort study. In addition, the criteria used the same cut-offs for both genders, which may artificially categorize many boys into LGA group since boys in general are heavier than girls at birth (e.g., the cut-offs for gestation week 30 is 2255g, for gestation week 35 is 3169g, for gestation week 40 is 3749g, and for gestation week 44 is 3965g) . We cannot find any newly updated Chinese newborns' birth weight percentiles distribution by gender; therefore, we believe that it might be more appropriate in this study to only report macrosomia's results though the LGA's results are similar.

VERSION 3 - REVIEW

REVIEWER	Pawel Gutaj, MD Department of Obstetrics and Women's Diseases, Poznan University of Medical Sciences, Poland
REVIEW RETURNED	29-Apr-2014

GENERAL COMMENTS	Article might be considered for publication in BMJ Open in its present form.