## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Impact of adolescent age on maternal and neonatal outcomes in the Born in Bradford Cohort |
| **AUTHORS** | Marvin-Dowle, Katie; Kilner, Karen; Burley, Victoria; Soltani, Hora |

## VERSION 1 – REVIEW

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| **REVIEWER** | Ali Khashan<br>University College Cork, Ireland |
| **REVIEW RETURNED** | 12-Mar-2017 |

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| **GENERAL COMMENTS** | The present hospital-based cohort study was performed to examine the association between maternal age and the risk of maternal and neonatal adverse outcome measures with a specific focus on adolescent and advanced maternal age women. The study used a unique dataset from a community with large non-white population and adds to the existing body of evidence on maternal age and adverse pregnancy outcomes. The authors may wish to address the following comments:<br><br>1) It seems that the study hospital applies universal screening for GDM, however, are the results based on women who were screened or all women regardless of whether they were tested or not?<br>2) Do the authors have data on emergency vs elective Caesarean section? Combining all Caesarean sections is less interesting than reporting results for elective and emergency Caesarean section separately.<br>3) Describe the social deprivation score, what indicators are included in this measure and provide a reference.<br>4) Instead of excluding women with missing data, the authors could have included those women in a separate category. This would have allowed the authors to keep the whole cohort using established methods of dealing with missing data (especially when missing data is less than 10%). It would also give an idea about whether women with missing data had different risk of adverse pregnancy outcome.<br>5) In addition to analysing birthweight in categories, the authors should have performed linear regression to examine the association between maternal age and birthweight.<br>6) For the categorical birthweight, please describe whether the analysis was performed for several binary birthweight outcomes and if this were the case, what was the reference group for each of these outcomes. For example, for the very low birthweight, was the reference group all the other children or only children with birthweight between 2.5-4kg or something else? Or was this performed by multinomial logistic regression? This applies to the |

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| | premature birth (which should be called preterm birth as premature may indicate fetal growth restriction or preterm birth).<br>7) Table 1: For each categorical variable, report n(%) with missing data. The whole cohort included 641 women aged <19 years, however, continuous BMI is reported for 660 women? Does the 641 represent women included in the analysis? For other variables, the number of women in this group is 709?<br>8) Tables 3 and 4: Please report the number of exposed cases included in each analysis.<br>9) Discuss the limitations of study design including unmeasured confounding as well as unknown confounding. Some of the results have very wide confidence intervals due to limited number of cases which should also be discussed.<br>10) Do the authors have data on whether Pakistani women were born in the UK or first generation immigrants? It would be interesting to see whether the effect of maternal age on adverse pregnancy outcome depends on country of birth (as a proxy measure of first vs second generation immigrants).<br>11) In addition to the study we published in PLOS ONE on advanced maternal and adverse pregnancy outcome (Kenny et al., 2013; reference 6), we published a paper from the North Western Region cohort on teenage pregnancy and adverse pregnancy outcome (Khashan, Baker, Kenny, 2010; PMCID: PMC2909926), which is relevant for the present manuscript. In this study we examined the association between teenage pregnancy based on three age groups but also whether parity had a modification effect on any observed associations. |

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| **REVIEWER** | Fernando Althabe<br>Instituto de Efectividad Clínica y Sanitaria<br>Buenos Aires, Argentina |
| **REVIEW RETURNED** | 09-Jun-2017 |

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| **GENERAL COMMENTS** | General comment<br><br>Important topic, large database. However there are some important methodological limitations, and a questionable general approach that would need to be addressed by the authors before considering the manuscript for publication.<br><br>Specific comments<br><br>Introduction<br><br>It seems too ambitious to address the association of several maternal AND perinatal outcomes, with adolescence (including two subgroups), AND age above 35 (two subgroups) in only one paper. As the authors mention, the mechanisms by which different extremes of age may affect those so different outcomes may vary. Thus the conceptual and methodological approach may different by the different exposures, outcomes or both. For example, the potential mechanisms by which age >35y might be associated with stillbirths or DBT are different than the mechanisms of associations between early adolescence and preterm birth or pre-eclampsia. I suggest the authors to choose a more narrow scope for the analysis. That may facilitate a more detailed methodological approach<br><br>Most of the justification and references are for the association |

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| | between adolescence and adverse outcomes, with very few to older age and adverse outcomes. This should be balanced if the authors keep with the same objectives. It seems to me that the main interest of the authors is adolescence, but I may be wrong.<br><br>The references for studies in adolescence need to be improved. There are several other important papers assessing the issue in other settings to be mentioned here, but most importantly, in the discussion section. (Conde-Agudelo A,2005; Ganchimed 2013; Weng 2014; Chen 2010; de Vienne 2009; Fraser N Engl J Med 1995).<br><br>Methods<br><br>More details of the Bradford cohort are needed: it seems more a hospital based cohort than a population based cohort. Please explain. What was the original objective? How many of women enrolled have been followed up at delivery? What criteria you used to select women for this analysis? And how many women were then excluded from the analysis. A flowchart would benefit the manuscript.<br><br>It is not clear whether the outcome variables were measured for the original cohort study following a predefined , or were collected from the clinical records. For variables like pre-eclampsia, gestational age, this issue is of importance. Proteinuria was measured in all women? How was gestational age calculated?<br><br>Statistical analysis<br><br>The decision of which variables to use for adjusting for confounding needs more justification. For example, in adolescence BMI can be more a mediator than a confounder, as the authors mention at the introduction. Thus should probably not be used. Same with smoking, which is different at different ages. Please discuss.<br><br>Please add a paragraph about what power you had to detect differences at the planning stage. All the outcomes were of equal importance?<br><br>Results<br><br>Unclear the approach to deal with missing data. You described the missing for several variables, but for outcome variables, it seems that no missing data were on gestational age, status at birth, birthweight? Please give more details.<br><br>Discussion<br><br>There should be a much more detailed interpretation of the findings, including a comparison with other important studies. For example, your findings on pre-eclampsia and adolescence contradict other studies. Methodological limitations, including misclassification of outcomes can be alternative explanations? I understand that it is very complicated to do that for every outcome and every comparison. However, clearly the limitations and interpretations can be different for each one. |

## VERSION 1 – AUTHOR RESPONSE

The authors would like to thank the reviewers for their insightful and detailed comments.

Extensive revisions have been made to the manuscript as a result including, as suggested by reviewer 2, the authors have reconsidered the scope of the article and have now excluded older women from the analysis, therefore this paper now addresses outcomes in adolescent pregnancies compared to a reference group only. Analysis of data relating to older women will be written up separately and submitted for review at a later date.

The study population has been altered to include only women aged 15-34 and has also now been limited to primiparous women delivering a singleton in order to make the two study groups more comparable and reduce the number of confounding variables in the regression analysis. Only deprivation and ethnicity have now been included as confounding variables in the regression analysis to avoid problems with different mechanisms effecting outcomes at different ages as suggested by reviewer 2. This has also had the effect of removing the problem of missing data as only women who have a valid age at delivery have been included in the analysis.

Clarification regarding the initial purpose of the Born in Bradford study and how the data have been used in this study has been added. This includes the addition of a flow chart detailing the participants in the parent study and the sub-set selected for this analysis. Additional details regarding the measurement of variables and clarification of reference groups has also been added.

Further comparison to previous studies has been added in both the introduction and discussion sections including suggested studies. The discussion section has been expanded to include further limitations including the discussion of unmeasured or unknown confounding variables and results with wide confidence intervals.

As this is a secondary analysis of epidemiological data is was not considered appropriate to include a post-hoc power calculation.

Unfortunately any distinction between elective and emergency Cesarean section is not available in the data set, this has been explained.

Details of women's country of birth have been added to table 1.

Description of the index of multiple deprivation score and reference has been added.

Linear regression to examine the association between maternal age and both birthweight and gestation at delivery has been added.

The term 'Premature' has been replaced with 'preterm' throughout.

Tables have been updated to include % with missing data and numbers of exposed cases in each analysis.

## VERSION 2 – REVIEW

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| **REVIEWER** | Fernando Althabe<br>Institute for Clinical Effectiveness and Health Policy<br>Buenos Aires, Argentina |

| REVIEW RETURNED | 13-Dec-2017 |
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| GENERAL COMMENTS | Introduction<br>The paragraph describing other studies on outcomes associated to adolescence is a bit confusing and may be improved. Actually there are two paragraphs starting with "A number of studies have suggested that babies born to adolescent mothers are at higher risk of premature birth and low birthweight ...". and "A number of studies have suggested that neonatal outcomes are less favourable among babies born to adolescent mothers". I suggest to improve the redaction.<br><br>The paragraph starting with "Some work has already..." is unrelated to the porblem. I suggest to eliminate and make the introduction very specific.<br><br>Methods<br><br>Please describe what proportion of the births occurring annually in Bradford were captured by the cohort<br><br>Why the limit of 15 years old? Please discuss and explain<br><br>SGA definition: which is the reference standard used?<br><br>Outcome variables: it seems that birthweight and GA as continuous outcomes were also included as outcomes. Please clarify.<br><br>Statistical analysis: The description of the binary logistic regression is a bit confusing to me. I imagine that you compared the rates of each outcome (LBW, PTB, etc) between adolescents and non-adolescentes and estimated the association using ORs. The way is expressed right now is confusing. Please clarify.<br><br>Power: please mention how you estimated the power the cohort has to detect associations, given that the number of women exposed were only 640. It seems that the analysis for women of 15 years old has no sense as the number is very low<br><br>Results<br><br>Please explain the denominators used for the outcome comparisons. It is unclear whether you excluded the stillbirths for the neonatal outcomes (eg, the numbers are the same for stillborn than for Apgar scores). Please clarify<br><br>Discussion<br><br>The limitations of the study and their implications on the findings should be more and better described:<br>- The cohort: how representative of the population of Bradford they are<br>- The data: use of routine data.<br>- Chance: sample size<br>- Residual confounding is also a likely explanation of the associations. Please discuss.<br><br>Interpretation<br>Please discuss the potential mechanisms of the findings on extreme PTB and LBW. The age, the different habits or behavior during |
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| | pregnancy? |

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| **REVIEWER** | Ali Khashan<br>University College Cork, Ireland |
| **REVIEW RETURNED** | 17-Dec-2017 |

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| **GENERAL COMMENTS** | I would like to thank the authors for addressing my comments. Ideally, the authors should have provided response to each comment rather than a summary of the revision.<br><br>The authors describe logistic regression for the analysis of categorical outcomes. Logistic regression is used for the analysis of binary and not categorical outcomes. For the preterm birth and low birthweight outcomes, have the authors used logistic or multinomial logistic regression analysis? If logistic regression was used, this means there were three different models to analyse preterm, very preterm and extremely preterm birth based on a binary variable for each of these outcomes. If this were the case, it should be clarified. If multinomial logistic regression was used for such outcome, this should be clarified and in that case the estimates should be reported as relative risk ratios and not odds ratios. The same applies to birthweight and any other categorical outcomes. |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 2

Reviewer Name

Fernando Althabe

Introduction

The paragraph describing other studies on outcomes associated to adolescence is a bit confusing and may be improved. Actually there are two paragraphs starting with "A number of studies have suggested that babies born to adolescent mothers are at higher risk of premature birth and low birthweight ...". and "A number of studies have suggested that neonatal outcomes are less favourable among babies born to adolescent mothers". I suggest to improve the redaction.

Changes have been made to both paragraphs to improve clarity on pages 3 and 4.

The paragraph starting with "Some work has already..." is unrelated to the porblem. I suggest to eliminate and make the introduction very specific.

Findings of the previous studies have been removed to make the introduction more specific. The references have been retained in order to signpost readers to other similar work from the same cohort on page 5

Methods

Please describe what proportion of the births occurring annually in Bradford were captured by the cohort

Detail added on page 6

Why the limit of 15 years old? Please discuss and explain

No women aged younger than 15 were recruited to the cohort, this has been clarified on page 6

SGA definition: which is the reference standard used?

Reference added for SGA and LGA on page 7

Outcome variables: it seems that birthweight and GA as continuous outcomes were also included as outcomes. Please clarify.

Clarification added on page 7

Statistical analysis: The description of the binary logistic regression is a bit confusing to me. I imagine that you compared the rates of each outcome (LBW, PTB, etc) between adolescents and non-adolescentes and estimated the association using ORs. The way is expressed right now is confusing. Please clarify.

This description has been altered to improve clarity (page 8) and description of the comparator groups for binary variables has been moved to the section describing outcome variables (page 7)

Power: please mention how you estimated the power the cohort has to detect associations, given that the number of women exposed were only 640. It seems that the analysis for women of 15 years old has no sense as the number is very low

A post-hoc power analysis has not been carried out as it is not appropriate. Observed power is directly derived from the p-value of the statistical test, therefore providing a post-hoc power calculation is superfluous; where the tests produce a statistically non-significant result it can be assumed that the study is insufficiently powered to detect an effect of the size obtained in the study (Hoenig and Heisey, 2001). There is of course the possibility of type 2 errors having occurred which is addressed in the discussion on page 24.

Hoenig, J. M., & Heisey, D. M. (2001). The abuse of power: the pervasive fallacy of power calculations for data analysis. The American Statistician, 55(1), 19-24.

Results

Please explain the denominators used for the outcome comparisons.

Denominators are explained, this description has been moved from the statistical analysis section to the outcome variables section.

It is unclear whether you excluded the stillbirths for the neonatal outcomes (eg, the numbers are the same for stillborn than for Apgar scores). Please clarify

It is not clear to what this comment refers; there were 31 total still births in the cohort, 531 APGAR scores <7 at 1 minute and 160 APGAR scores <7 at 5 minutes which is documented in table 2.

Stillbirths were excluded from the sub-group analysis due to small numbers of events; columns have been added to table 4 displaying the number of events for each outcome in the sub-group analysis as these are not reported elsewhere.

Discussion

The limitations of the study and their implications on the findings should be more and better described:

- The cohort: how representative of the population of Bradford they are

- The data: use of routine data.

- Chance: sample size

- Residual confounding is also a likely explanation of the associations. Please discuss.

Discussion of limitations has been expanded and these specific areas addressed on pages 23 and 24

Interpretation

Please discuss the potential mechanisms of the findings on extreme PTB and LBW. The age, the different habits or behavior during pregnancy?

Discussion of this topic has been added on page 20

Reviewer: 1

Reviewer Name

Ali Khashan

Ideally, the authors should have provided response to each comment rather than a summary of the revision.

Format of responses to comments has be amended.

The authors describe logistic regression for the analysis of categorical outcomes. Logistic regression is used for the analysis of binary and not categorical outcomes. For the preterm birth and low birthweight outcomes, have the authors used logistic or multinomial logistic regression analysis? If logistic regression was used, this means there were three different models to analyse preterm, very preterm and extremely preterm birth based on a binary variable for each of these outcomes. If this were the case, it should be clarified. If multinomial logistic regression was used for such outcome, this should be clarified and in that case the estimates should be reported as relative risk ratios and not odds ratios. The same applies to birthweight and any other categorical outcomes.

The binary nature of the outcome variables has been clarified on page 7 and the logistic regression analysis clarified on page 8

**VERSION 3 – REVIEW**

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| **REVIEWER** | Ali Khashan<br>University College Cork, Ireland. |
| **REVIEW RETURNED** | 10-Feb-2018 |

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| **GENERAL COMMENTS** | The authors have addressed my comment and clarified it as necessary in the manuscript. I have no further comments. |