

MJ - Decision on  
Manuscript ID  
BMJ.2018.044966

**Body:**

12-Jul-2018

Dear Dr. Khandwala

Manuscript ID BMJ.2018.044966 entitled "The Association of Paternal Age and Perinatal Outcomes between 2007 and 2016 in the United States"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Tiago Villanueva  
Associate Editor  
tvillanueva@bmj.com

\*\*\* PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. \*\*\*

[https://mc.manuscriptcentral.com/bmj?URL\\_MASK=f5d482fa9d714c2fae116df3d5f266bf](https://mc.manuscriptcentral.com/bmj?URL_MASK=f5d482fa9d714c2fae116df3d5f266bf)

**\*\*Report from The BMJ's manuscript committee meeting\*\***

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Jose Merino (chair), Rafael Perera (statistician), Elizabeth Loder, Sophie Cook, John Fletcher, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

-Our statistician made the following comments;

Very interesting study. Not sure why the temporal aspect is relevant and believe it is not explored (or at least presented) as best as it could have been.

I think there is a need for more information on the methods used. Why they used IPW? How was the model fitted to account for different years? What model was fitted? Did it use paternal age bands for each birth? This is slightly unclear but it is mainly a matter of better reporting as I do not think this would substantially change the findings.

Having said that, the observation of the secondary sex ratio is not consistent with the results reported. This might need to be changed or defended.

With regards to maternal age as confounder, I was reassured by their stratified analyses presented in Figure 1 by maternal age. These show relative consistent dose/effect trends particularly in the last two paternal age groups.

His comments are detailed in a statistical report (see comments from reviewer 4 ).

- One editor felt the paper addressed an interesting topic. Like reviewer Brown, he had a number of reservations about the plausibility of causality and the mechanisms. Is NICU care free or do parents pay? If parents pay then an obvious alternative explanation is older fathers may be better able to pay for care. This might apply to some other diagnoses too (such as maternal diabetes) depending on how they were ascertained in the database. How complete are the data items? You describe a method for accounting for missing data but he couldn't see which were missing or how much.

- Another editor said the study addressed a refreshing research question in view of the more common emphasis on maternal factors. She wondered why paternal age was categorized in such large age bands, and worried about control for maternal age. She added that the abstract should give the reader some idea of the absolute magnitude of the increased risk of these outcomes.

- Another editor likes the research question and would like you to make clearer the rationale between paternal age and maternal outcomes, as this doesn't seem clear as it could be at present. Moreover, it's hard to know what this will mean from a clinical/public health point of view.

- Another editor said he shared a concern raised by the reviewers about the effect of paternal age on maternal outcomes. What is the rationale for including this outcome?

- Another editor would like you to add a patient involvement statement.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

This is an interesting study looking at the association between paternal age and various adverse perinatal outcome. Paternal factors are rarely examined in this context, so this is a potentially important and novel contribution to the literature.

The article is clear and the methods seem straightforward. However, I think that the authors need to do more to justify the observed associations and to ensure that they are valid. I have several major comments:

1. The most important question in this study is why paternal age could affect perinatal outcomes. The authors discuss epigenetic effects in their discussion. However, because of the range of outcomes examined, the explanation is not sufficient. For example, how could paternal age result in outcomes ranging from maternal (gestational diabetes) to fetal (preterm birth)? The authors need to (1) provide a stronger rationale in their introduction / methods about the choice of outcomes included in the study and why they are relevant and (2) provide a more precise explanation for the effect for each outcome or type of outcome.

2. My biggest question was whether maternal age could explain the association, since maternal and paternal age tend to be correlated,. The authors use multivariable models to control for confounders including maternal age, and I wonder if this is sufficient. Research has shown that multivariable regression is inferior to propensity score matching and inverse probability of treatment weights in controlling for confounding. The authors state that they used weighting, but it appears they did so to deal with missing data and improve generalizability rather than deal with confounding. This should be clarified. The authors should discuss in greater detail the potential for residual confounding.

3. I have several other questions and suggestions related to confounding and the presentation of the data. (1) The authors should present the baseline covariate data according to paternal age groups (rather than for the cohort overall) so that the extent of probable confounding can be assessed. (2) The authors should consider using additional methods to tease apart the role of maternal age, including matching (see comment #2, above).

4. Most of the odds ratios are actually fairly small, as noted by the authors. What are the implications of these results? Is the effect big enough to be of public health importance? If so, what actions are required? The literature on preconception health and reproductive life planning could be drawn on here. This should be further detailed in the Discussion.

Smaller points:

1. The authors should provide both unadjusted and adjusted values in the regression models so that the extent of confounding in the association can be assessed.

2. Did the authors include more than one delivery to the same father in the sample? If so, how did they account for clustering in the data (which can affect p values).

3. Did the authors account for multiple testing given the large number of outcomes assessed?

Additional Questions:

Please enter your name: Hilary Brown

Job Title: Assistant Professor

Institution: University of Toronto

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A  
HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-check  
lists/declaration-competing-interests'target='\_new'> (please see BMJ policy)  
</a>please declare them here: n/a

Reviewer: 2

Recommendation:

Comments:

This is an interesting paper.

General comments:

Why was paternal age categorized and not analysed on a continuous scale? The categories seem rather arbitrary.

Was the increased risk of NICU admission independent of gestational age? In the abstract this is not indicated, but the methods show that this was done. I suggest to add a clarification in the abstract.

Specific points:

Abstract: the abbreviation APA should be explained (even though it is obvious)

Introduction: line 3 ... continues to rise.

Line 14: shouldn't it be 'unequivocal'?

Methods:

P3, Line 37: 'systemic' should be 'systematic'?

P3, Lines 54-55: 'The perinatal outcomes utilized within this study were selected based on availability within the NVSS data files. All relevant variables were included and evaluated.' This is unclear. Only available data were used but all relevant variables were included? Was there a prespecified list of relevant variables?

P4, lines 16-20: 'To account for inconsistent reporting of paternal data across various demographics, a logistic regression model incorporating maternal age, race, birth year, and education was utilized to estimate the probability of paternal reporting for each birth. Inverse probability weighting was subsequently applied to all statistical analyses to maximize generalizability.' Why was it necessary to apply IPW? The data collection procedures seem quite rigorous. What method was used?

P4, lines 26-27: 'To test for a systematic change in sex-ratio between paternal age groups, a non-parametric test of trend was conducted using the Wilcoxon rank-sum test followed by regression analyses.' It is not clear how this was done, please clarify.

Results:

In general, refrain from reporting p-values.

P4, line 41: Table 1 should include all neonatal outcomes that were analysed (see Table 2a).

What is 'Adverse Event' in table 2a?

The very small difference in birth weight less than 100 gram versus the association with low birth weight <2500g suggest an uneven contribution of old age fathers to the occurrence of low birthweight. Please comment on this. Would non-linear regression analysis add more information? (how is this impacted by the probability weighting).

P4, lines 43-47: 'The weight-adjusted estimate of the number of fathers 55 years or older increased from 11,348 (0.26%) in 2007 to 16,212 (0.40%) in 2016, while the number of fathers between the ages of 45 and 54 years increased from 121,590 (2.70%) to 137,802 (3.38%) per year over the same time period ( $p < 0.001$  and  $p < 0.001$ , respectively)' Does the 'weight-adjusted estimate' refer to the probability weighting? If there are more older fathers it is logical that there less younger fathers. Why is this reported in this way and not as one trend analysis?

Discussion:

Generally, results should be discussed in terms of magnitude and not in terms of significance give the extremely large study size (this also applies to comparisons to other studies).

P6, lines 19-20: ' The addition of IPW further reduces the overrepresentation of certain demographics of fathers: mostly older, college-educated fathers who are more likely to be present at birth.' Does the availability of paternal data depend on their presence at birth? Please explain.

P6, line 50-51: inverse propensity weighting?

P6, line 27-37: The paragraph on implications on healthcare costs seems far-fetched and does not add much to the paper.

References:

The author names for reference 21 do not match with those on PubMed

Tables:

The layout of table 2a is unusual, I would prefer putting paternal age categories in columns and the dependent variables in rows, which would make the table much more compact. p-values can be deleted.

Henk Groen

Additional Questions:

Please enter your name: Henk Groen

Job Title: Epidemiologist

Institution: University of Groningen, University Medical Center Groningen

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A  
HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-check  
lists/declaration-competing-interests'target='\_new'> (please see BMJ policy)  
</a>please declare them here: None

Reviewer: 3

Recommendation:

Comments:

Many thanks for asking me to review this large scale population based study looking at the effects of paternal age on perinatal complications. The hypothesis is interesting and relevant to public health statistical analyses are appropriate and the reporting is adequate. The population attributable risk associated with increased paternal age over 45 years adds further value. I have some minor concerns that would need to be addressed:

1. My main concern is regarding the size of the dataset and the small differences with very tight confidence intervals found in the study. The authors talk at length about previous studies being under powered but have they considered that their study may be over- powered? I would at least use 99% confidence intervals to account for this.
2. The data spans a considerable length of time during which many changes to clinical practice and guidelines will have occurred. For example while paternal age has been rising over time, the thresholds for NICU admissions have been falling. How did the authors take this into account?
3. Although the authors have adjusted their analyses for various paternal and maternal factors, many of the outcomes such as low birth weight, low Apgar and NICU admission are associated with preterm birth. The authors need to demonstrate in their analyses whether these effects are independent of preterm birth.
4. With regard to Apgar score, the authors should specify the cut off for low score was.
5. I cannot find any variable describing the parity or birth order - was this not available? Related to this point, I would imagine that parents, especially older ones

will have occurred several times in the dataset having had more than one child in the long time period under study - how was this clustering taken into account?  
6. It is a shame that stillbirths were not available for analysis but it would be good to discuss what effect this might have had on the analyses.  
7. Finally, I observe dose response relationships in many of the outcomes studied. This should be highlighted in the text.

Additional Questions:

Please enter your name: Sohinee Bhattacharya

Job Title: Senior Lecturer

Institution: University of Aberdeen

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A

href="http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-check-lists/declaration-competing-interests"target="\_new"> (please see BMJ policy)

</a>please declare them here: I have no competing interests to declare

Reviewer: 4

Recommendation:

Comments:

BMJ44966 The Association of Paternal Age and Perinatal Outcomes between 2007 and 2016 in the United States

This is a very interesting study showing association between paternal age and a range of outcomes. Although the data have been collected over ten years, the analyses do not focus on the temporal aspect of this dataset and instead treats it as a large cross-sectional study while including year as a covariate in adjusted analyses. It might be useful to mention this early on in the methods for clarity to the readers as well as in the discussion (why this is valid).

There are some issues in the reporting of the methods used. It is unclear to me what paternal data are missing or why use a two stage approach to fit the model: first determining probabilities based on a logistic regression and then fitting the model based on IPW. Regarding this, please report in a Table (possibly similar to



Table 1) what are the missing variables and for what proportion of the births (and if possible their association with some or all of the outcomes studied). It is unclear to me how the IPW approach allows for adjustment for missing information, please clarify in your manuscript or at least in your response to this review.

A critical issue in all analyses is the correlation with maternal age and the way this covariate is included in the adjusted models needs to be made clearer. The stratified analyses presented for adverse outcomes verify the results presented in the adjusted models. Therefore it would be extremely useful to provide similar stratified results for ALL outcomes and not only for adverse events. These could be included as supplementary material. If there is not enough power for other outcomes this will need to be discussed/clarified.

For most of the outcomes evaluated, a j-shaped association appears present. Alternative modeling strategies (based on splines) would highlight this potential shape of the association (instead of using logistic regression). At least this association should be commented on. The consistency in the direction and the shape of the association also make these findings more robust.

For the sex-ratio analysis, however, there is no clear dose-effect association between paternal age and a decreasing trend in the sex ratio. This will need some adjustment in their discussion. Not clear why the p-value is significant for the non-parametric test. The actual rate of the 55+ is the same as the reference group.

Additional Questions:

Please enter your name: Rafael Perera

Job Title: Professor of Medical Statistics

Institution: University of Oxford

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A

HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-check-lists/declaration-competing-interests'target='\_new'> (please see BMJ policy)

</a>please declare them here: none

