Author’s response to reviews

Title: Caffeine is a Risk Factor for Osteopenia of Prematurity in Preterm Infants: A Cohort Study

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BPED-D-15-00154

Caffeine is a Risk Factor for Osteopenia of Prematurity in Preterm Infants: A Cohort Study

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BMC Pediatrics

Dear Dr Ali,

Please accept our apologies for the delays you have experienced with your manuscript.

Your manuscript "Caffeine is a Risk Factor for Osteopenia of Prematurity in Preterm Infants: A Cohort Study" (BPED-D-15-00154) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Pediatrics.
Their reports, together with any other comments, are below. Please also take a moment to check our website at

for any additional comments that were saved as attachments. Please note that as BMC Pediatrics has a policy of open peer review, you will be able to see the names of the reviewers.

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In addition to the reviewers comments, please amend your manuscript according to the following editorial requests:

1. Please note that all manuscripts must contain all the following sections under the heading 'Declarations':

   Abbreviations

   Ethics approval and consent to participate

   Consent for publication

   Availability of data and material

   Competing interests

   Funding

   Authors' contributions

   Acknowledgements

   Authors' information (optional)

Please see here for details on the information to be included in these sections:

https://bmcpediatr.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

The changes: the Declarations include all required sections. Just after the title page.

2. Please make sure the abstract follows the format outlined in our submission guidelines.
The changes: The abstract has been changes according to the format found in the guidelines. Please make sure the submission data is also updated with any abstract changes. No changes were done in the data

3. Figure files should contain only the image/graphic, as well as any associated keys/annotations. If titles/legends are present within the figure files, please remove them.

The change: All titles in the Figure files have been removed

4. Please rename 'Graph' to 'Figure'

The change: All Graphs have been changed to Figures

5. Please provide a completed STROBE guidelines checklist (see http://www.strobe-statement.org/index.php?id=strobe-home)

All points in the STORBE guidelines are fulfilled.

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If you are able to fully address these points, we would encourage you to submit a revised manuscript to BMC Pediatrics. Once you have made the necessary corrections, please submit online at:

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A point-by-point response letter must accompany your revised manuscript. This letter must provide a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text and where these can be viewed (e.g. Methods section, line 12, page 5). Please also ensure that all changes to the manuscript are
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A decision will be made once we have received your revised manuscript, which we expect by 26 Oct 2016.

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Please be aware that we may investigate, or ask your institute to investigate, any unauthorised attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

I look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Benny Yau

on behalf of

Nawsheen Boodhun
Reply to the Reviewers:

Thank you so much for your valuable comments and instructions, all are highly appreciated and well taken.

The following are the changes done to the manuscript by points:

Reviewer reports:

Reviewer #1: Thank you for submitting your manuscript describing your observations of caffeine use for apnoea in premature infants and evidence to support this being a possible contributor to the development of osteopaenia of prematurity (OP). You have studied 109 premature infants weighing less than 1500gm and less than 31 weeks gestation, from a single site retrospectively. You cite your exclusion criteria, but were not clear about how you actually identified the infants for your study (presumably from an institutional database) and how consent was obtained for these infants.

Answer: The infants who met the inclusion criteria were included from that period of time of the study, 2007-2012. The inclusion criteria are infants less than 1500gm and less than 31 weeks, with at least 12 weeks of hospital stay, from one institution. The data were collected from the charts in the medical record. The consent were taken from the institution ethics board for retrospective chart review study. There were no consent taken from the patients themselves as it is database review.

The changes are written in red color in the manuscript in (section methods)

From your lengthy and detailed introduction you clearly appreciate the multi-factorial nature of osteopaenia of prematurity, however the retrospective design of your study remains a weakness.

It is difficult to implement case control study using infants with no caffeine intake, all infants admitted less than 33 weeks are on caffeine by hospital guidelines. This pilot retrospective study is to highlight the effect of caffeine on osteopenia of prematurity.

Clearly phosphate metabolism is a very important factor in the development of OP. What was your reasoning for analysing the serum phosphate as categorical data rather than as a continuous variable?
From statistical point: It would be more reasonable to analyse the phosphate as a continuous variable but the phosphate data was not linear when tested against the log of the outcome on preparing the data for analysis. Moreover, from the clinical point of view: it was agreed between the authors to use serum phosphate as a categorical variable to differentiate between normal, low or very low phosphate in relation to osteopenia od prematurity, as it is more plausible for clinical practice and interpretation.

Overall, given that this is a preliminary retrospective study, the introduction and discussion needs to be substantially shortened and more focussed with the number of references reduced, focussing on key recent references.

The introduction and the discussion have been shortened to be more focussing on the main subject

Reviewer #2: Ali and colleagues present a retrospective analysis of the effects of neonatal caffeine administration on the severity of osteopenia of prematurity. This is an interesting topic worthy of study. The manuscript would benefit from significant editing for brevity and clarity. See my specific comments

Background

This section would benefit from extensive editing - as written it is too long and seems disorganized.

• Consider removing text regarding the effects of steroids and diuretics.

The text regarding steroids and diuretics are removed.

The manuscript as written, is focused on the effects of caffeine, therefore I would remove the statements about "secondary outcomes" and address these as "covariates of interest" or "potential confounders" in your methods and results section.

The secondary outcome statement was removed and replaced by covariates of interest.

Page 4 - paragraph starting on line 23 is a fragment, combine with subsequent paragraph
The two paragraphs were combined

Page 4 - line 56 - why would a compensatory increase in vitamin D negatively impact bone? Please clarify this statement.

This was corrected in the manuscript; these are animal studies including preterm rats with high prolonged caffeine dose and there was a decrease in serum calcium and increased PTH not Vitamin D.

Methods

- Please explain the grading scale for OP in more detail. A table or figure might be helpful

A table was added to the manuscript. Table 1 explaining the grades of osteopenia.

- Were all radiographs interpreted by the same radiologist? If not, provide data regarding inter-rater reliability and/or discuss this as a limitation.

The X-rays were interpreted by both of the corresponding author and the pediatric radiologist. At the time of the interpretation, both the corresponding author and the pediatric radiologist were blind about the infants’ other characteristics. Any disagreement was resolved via consensus. Corrected in the manuscript Method section.

Results

- I would like to see more explicit presentation of how the OP outcome changed over the study period - something along the lines of Table 2, or possibly even a figure. I would show both average OP grade, and percent with severe OP

I hope Figure 1 is providing the same idea as the probability of osteopenia increased over the time of hospital stay and over the same time the caffeine dose increased as well. In our data we dichotomized the outcome for the statistical analysis. Unfortunately, I did not have the plot of osteopenia over time without any confounding factors.

- Did you test for a caffeine dose*gestational age interaction?
The interaction between caffeine and the gestational age was not significant when included in the mixed model with other variables, weight, steroid and vitamin D. that is why the interaction was not included.

Discussion

- See comments regarding background. This should be shortened and more organized.

The discussion was shortened and organized.

I would remove detailed discussion regarding steroids, diuretics, vitamin D, as these are not the focus of the manuscript and the findings do not seem surprising.

The discussion regarding Vitamin D, steroids were removed, discussion regarding diuretics was shortened as it might be related to caffeine diuretic effect.

- The findings of a dose*gestational age difference on OP outlined in Figures 1 and 3 seems of interest and I think warrants inclusion in the discussion. Any idea why this may be?

I included some discussion about the Figures in the discussion section with explanation of the results.

Figures

- Please provide n values. For example, how many 25 vs 30 wga infants in figures 1,3

The numbers were provided in the Figures

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For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must state that data will not be shared, and provide reasons for this in the manuscript text. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page - http://www.biomedcentral.com/submissions/editorial-policies#availability+of+data+and+materials.

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