Author’s response to reviews

Title: Association between Pre-and Postnatal Growth and Longitudinal Trends in Serum Uric Acid Levels and Blood Pressure in Children aged 3 to 7 years

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Version: 3 Date: 26 Sep 2019

Author’s response to reviews:

September 27, 2019

Dear Dr. Darren Byrne,

Thank you very much for reviewing our manuscript titled “Association between Pre-and Postnatal Growth and Longitudinal Trends in Serum Uric Acid Levels and Blood Pressure in Children aged 3 to 7 years” (reference number BPED-D-18-00674R2). We greatly appreciate the constructive comments and suggestions provided by the reviewers, which we have carefully reviewed, and have revised our manuscript accordingly. Our point-by-point responses are given below.

We hope that the revised manuscript is suitable for publication in the BMC Pediatrics.

I look forward to hearing from you.

We hope the revised manuscript is suitable for publication in the BMC Pediatrics. I look forward to hearing from you.
Sincerely,

Hyesook Park, MD, PhD

Response to Reviewer 1:
1. This manuscript aims to show the difference between uric acid levels and blood pressure in 55 LBW children with catch up growth versus those in 308 NBW children. However there is a case mix of preterm and term children LBW with catch up and preterm children outnumber the term children by a factor 2. Authors seem to claim that all preterm children in their cohort had catch up growth. That is hard to believe. Nevertheless the strongest effect comes from the term LBW. That would in itself merit publication but the number of observations is very low, 20 at inclusion. At age 7, only 11 children in the 55 LBW cohort are left. But we do not learn whether they are preterm or term.

Response:
There were two children who were born with LBW and didn’t experience catch-up growth, one of whom was premature and the other was born at term. As we described in the manuscript, two LBW children who did not exhibit catch-up growth were excluded from the analysis, as most LBW children (95%) experienced catch-up growth.

In terms of the number of preterm at 7, 3 out of 11 LBW children at age 7 were preterm, and this information has been added to the manuscript (p.11, lines 232):

“To assess the effect of LBW due only to intrauterine growth restriction without the effect of preterm birth, children born as LBW due to preterm birth (7 children at 5-year-old follow-up and 3 children at 7-year-old follow-up) were excluded in the second analysis and only LBW-at term children were included.”

2. Important information is missing. For example BMI in the LBW group at age 3, 5 and 7 is lower, while weight gain is higher in the LBW group. So we are missing details about height.

Response: There was no significant difference in BMI between the NBW and LBW groups (p = 0.06, 0.88, and 0.78, respectively). In addition, there was no significant difference in weight and height at 3 years of age between the NBW and LBW groups (p=0.06 and 0.37, respectively). As suggested by the reviewer, height at 3 years of age was added to Table 1.

Response to Reviewer 3:
1. The study adds to the existing knowledge on the Association between Pre-and Postnatal Growth and Longitudinal Trends in Serum Uric Acid Levels and Blood Pressure in Children aged 3 to 7 years. The authors have responded to all the queries in my earlier revision. However, the proof that some of the claimed revision was not evident in the manuscript. For instance, the authors should present a Q-Q plot that justifies the claim of normality tests. The plots of the residuals versus each of the variables should be shown clearly to justify the non-violation of the linearity assumption. These charts can appear as an appendix in the manuscript. Convincing information on how the normality test was conducted and how the authors justified the assumption of linearity must be provided.

Response: Information on how the normality and linearity tests were conducted has been added to the manuscript (p. 8, lines 180–183):
“The assumptions for the mixed model were checked and confirmed to be verified in all models: Normality was tested by a quantile-quantile plot and linearity was confirmed using plots of the residuals versus each of the variables. Figures have been added to show this in more detail [Additional file 1-2].”

A Q-Q plot that justifies the claims of normality tests and the plots of the residuals versus each of the variables to justify the non-violation of the linearity assumption were added as additional files.

2. Page 8: lines 150-159. The authors should specify which of the variables apply to mean or median.
Response: Birth weight and gestational age were presented as means ± SD, and the other continuous variables as medians (IQR). Information on the variables presented as means and medians is provided in Table 1.

Response to Reviewer 4:

1. Although you have tried to separate preterm from term infants, LBW remains limited as a proxy measure for IUGR as smallness-for-gestational age (statistical concept) with true growth restriction (dynamic concept), defined as failure of the fetus to reach its genetically predetermined growth potential. This should be acknowledged as a limitation in the Discussion.

Response: As suggested by the reviewer, the following text has been added to the Discussion section (p. 17, lines 339–344):

“LBW could be because of prematurity, intrauterine growth restriction (IUGR), or both. IUGR is a dynamic concept defined by insufficient growth of the fetus in relation to its constitutional or genetically determined growth potential. Although we attempted to separate prematurity from LBW-at term, the utility of LBW was limited as a proxy measure for IUGR by the difficulty of diagnosing pathologic growth retardation of the fetus.”

2. The design of the present study is unable to test for a direct causal link between uric acid levels and hypertension, per your hypothesis. This should be more clearly acknowledged and presented as association rather than causation.

Response: The relationship between the uric acid level and hypertension is presented as an association, not causation, throughout the manuscript, which is acknowledged as a limitation (p. 17, lines 337–339): “First, because of the study design, we were unable to test the causality of the relationship between the uric acid level and hypertension but evaluated, instead, their association.”

3. Page 10 Line 205: The statement "17 children had SUA concentrations greater than normal (2.0-5.5mg/dl) at any follow-up point" is ambiguous. Does this mean the combined total "n" over all three time points i.e. does it take into account those with elevations at more than one time point? What was the consistency of elevated uric acid levels over time for patients with more than one measurement?

Response: Seventeen children had SUA concentrations greater than normal (2.0–5.5 mg/dL) at one, at least, of the follow-up points. In terms of consistency, nine of 13 children with more than one measurement had a consistently elevated uric acid level of greater than quartile three at each follow-up point.

The above has been added to the manuscript as follows (p.10, lines 206–209):
“Seventeen children had SUA concentrations greater than normal (2.0–5.5 mg/dL) at one, at least, of the follow-up points, and nine of 13 children with more than one measurement showed a consistently elevated uric acid level of greater than quartile three at each follow-up point.”

4. Page 10 Line 211: In table 1, please indicate which rows represent mean/SD and which represent median/IQR. It might be more transparent to show the former as mean +/- SD and latter as median [IQD] per general convention.

Response: As suggested by the reviewer, information on the rows showing mean/SD and median/IQR has been added to Table 1. Also, the results are presented as means ± SD or medians (IQR).

5. Page 13 Line 253: It would be more accurate to say "tendency towards a significant difference" than "borderline significance" [same comment applies to other uses of this expression throughout].

Response: In response to the reviewer’s suggestion, all relevant sections have been revised.

6. Page 15 Line 292: Please add citations to support your statements that "an increase in uric acid during pregnancy is a risk factor for LBW" and that "the increased uric acid in the pregnant mother passes freely into the fetal circulation". Moreover, to what degree is this due to the association with LBW and pre-eclampsia specifically?

Response: The citations have been added to the manuscript (reference numbers 1, 30–32), as has the following text (p.15, lines 298–302):
“An increase in the uric acid level during pregnancy was associated with adverse maternal and fetal outcomes, such as preeclampsia progression and low birth weight. Bellomo et al. reported that the uric acid level was associated with preeclampsia with an OR of 8–9, and with giving birth to a small-for-gestational-age infant with an OR of 1.6–1.7.”

7. Page 16 Line 315: Your assertion that there "the results of this study suggest... a critical intervention period to maintain an appropriate level of uric acid, thereby reducing the risk of elevated blood pressure in children" is pure conjecture and not supported by the data. Please temper your language.

Response: The section has been revised as follows (p.16, lines 323-326):
“The findings of this study suggest that further studies be performed to gain a deeper understanding of the association and the pathological pathways between low birth weight, uric acid, and hypertension in children, and to determine whether uric acid plays a role as a mediating factor for an early intervention of hypertension.”