Author's response to reviews

Title: Birth and Developmental Correlates of Birth Weight

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Author's response to reviews: see over
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Dear Dr. Crow:

Thank you for providing us with an opportunity to undertake a major revision of our manuscript (MS: 2054094156684772) “Medical, Developmental, and Academic Correlates of Birth Weight” now entitled “Birth and Developmental Correlates of Birth Weight” for publication in the BMC Pediatrics as a Research Article. We truly appreciate the referees’ detailed comments and suggestions. We have followed the suggestions of the referees. Consequently, the manuscript is much clearer.

Based on the reviews, we made several major changes to the manuscript. As suggested by Referee 1, we re-analyzed the data by separating participants by birth weight categories (extremely low birth weight, very low birth weight, low birth weight, normal birth weight, and high birth weight) and gestational age classification (small for gestational age, appropriate for gestational age, and large for gestational age) based on currently accepted definitions. Based on recommendations by Referee 2 and Referee 3, we have removed the obesity argument from the manuscript and instead revised the introduction and discussion to focus on the relationship between birth weight (the dependent variable) and birth history, developmental milestone achievement, birth weight category, and gestational age classification (the independent variables). Also, as suggested by Referee 2 and Referee 3, we have revised the tables to provide better alignment between the text and data reported in the tables.

Below, we describe how we have addressed each of the concerns raised by the reviewers.

REFEREE 1: Rosemarie Bigsby

We greatly appreciate the referee’s comments and feel that the comments will help to make the paper stronger. We hope we have addressed the referee’s concerns.

1- I would expect the authors to revise the manuscript with, at a minimum, the birth weight categories specified according to currently accepted definitions for ELBW, VLBW, LBW, SGA, AGA, and LGA. 15.8% of the infants are listed as premature, but there is no indication how many of these were ELBW vs. VLBW, vs. LPT (late preterm). There also is a growing literature relating problems with executive function
and externalizing behavior among infants born as late pre-terms, and yet these infants are not identified in the sample.

We thank the referee for this important comment. To address Dr. Bigsby’s concerns, we reconfigured the groups for the participants in our sample based on two things: 1) birth weight category: We have now divided the sample into ELBW (extremely low birth weight), VLBW (very low birth weight), LBW (low birth weight), NBW (normal birth weight), and HBW (high birth weight) infants and 2) gestational age classification: We also separated participants based on whether they were SGA (small for gestational age), AGA (appropriate for gestational age), or LGA (large for gestational age). Due to small n’s in the ELBW and VLBW categories, those infants were not included in analyses (see page 6, second paragraph). However, we felt that their data would be of interest to readers, so we did include data from these groups in Table 4. Table 4 also gives information about how many pre-term versus late pre-term infants were represented in each birth weight category and gestational age classification.

2- Specify more clearly the medical involvement of the sample who spent time in an ICU - term vs. preterm. 5.8% had “birth injuries” but these also are not specified: HIE (hypoxic ischemic injury)? BPI (brachial plexus injury)? Of the 15.8% who were premature, how many were in each of the above categories? Which of these infants were premature vs. term?

As stated above, Table 4 lists information on how many pre-term and late pre-term infants were in each birth weight category and gestational age classification. The specific medical involvement of the sample included: for LBW children a swollen head, for NBW children head bruises, face or head abrasions, broken clavicles, shoulder dystocia, a swollen head, umbilical cord around the neck, minocin, low muscle tone, dislocated hip, effusion of the forehead or nose, cranial bleeding, eye irritation, a benign mass on the neck, or a hernia, and for HBW children head bruises, face or head abrasions, broken clavicles, shoulder dystocia, low muscle tone, or cyanosis. According to gestational age classification, reported related birth complications included for SGA head bruising, a swollen head, and the umbilical cord around the neck, for AGA head bruises, face or head abrasions, broken clavicles, shoulder dystocia, a swollen head, umbilical cord around the neck, minocin, low muscle tone, dislocated hip, effusion of the forehead or nose, cranial bleeding, eye irritation, a benign mass on the neck, or a hernia, and for LGA head bruises, face or head abrasions, broken clavicles, shoulder dystocia, low muscle tone, or cyanosis. Parents of premature infants reported head bruising, a swollen head, or the umbilical cord wound around the neck.

3- Feeding issues also are only grossly defined.

The larger study does include a question in which parents indicated whether their infants had feeding issues. In our sample, a total of 199 participants were reported as
having feeding problems. However, most of the infants were either NBW \( (n = 150) \) or AGA \( (n = 136) \). Therefore, we did not account for feeding issues in our analyses.

4- It would be relevant to have specific information about the types of diabetes where diabetes is present, and whether the child was formula or breastfed, given breastmilk by bottle, and for how long.

We agree that the above information is important to know in light of later predictors of children’s weight status. However, we do not have information specifically about whether infants and parents were diabetic nor about whether infants’ were formula fed or breastfed. Since we have removed the focus of obesity from the manuscript as well as the body mass index measure, information about the presence of diabetes and the type of milk offered to infants is now less relevant to our manuscript.

5- The means for developmental milestones show a wide standard deviation, which may imply the need for additional statistical measures to deal with this issue.

The age at which parents reported children saying words and speaking sentences was very variable. We believe that this variation is due to the fact that 1) these milestones are very variable in children and 2) the retrospective chart review did not allow for us to clarify with parents what their definition of the milestones were (i.e. Were they reporting their infants’ first words that others could understand or that only they could understand). The same could be true of any of the milestone onest ages parents’ reported. We state in the revised discussion (see page 12-13) that the use of the retrospective chart review is a limitation of our study.

6- The discussion section is concerning because there are some statements that reflect a poor understanding of the newborn population. Stating that higher birth weight infants are less likely to experience assisted delivery is naive. In fact, infants who are LGA are more likely to have shoulder dystocia, brachial plexus injuries, and hypoxic injury.

We agree with the referee about our original presentation of the discussion. Revising the paper to separate participants by birth weight category and gestational age classification helped us to better state our points. We acknowledged in the introduction (see the end of page 3) that LGA infants are more likely to have the injuries highlighted by the referee. The statement that higher birth weight infants are less likely to experience assisted delivery has been removed from the discussion.

7- Infants born at ELBW, VLBW and LBW are likely to require assisted ventilation at delivery due to immature lung development, and the distinction should be made between infants who are LBW but AGA, vs. SGA.

We appreciate the referee’s comment. All of the 39 LBW infants in our sample were SGA.
8- The suggestion that mothers of infants born at low birth weights may have had poor nutritional status ignores the myriad reasons for premature birth.

We agree with the referee that there are many factors that are related to the causes for premature births. Since we no longer focus the paper on obesity, we have removed the comment about mothers’ nutritional status from the discussion.

9- Finally, the finding that infants with higher birth weights had earlier acquisition of certain skills may not hold up when the infants are grouped more specifically into appropriate weight groups. We know that infants born LGA are more likely to be born to women with diabetes (need to specify type) and that subgroup has additional risks for outcome.

We thank the referee for this helpful observation. We re-ran the analyses and rewrote the results to reflect results by birth weight category and gestational age classification (see pages 8 to 10 for results on developmental milestones). When examined the data by birth weight category, our findings showed that for HBW, NBW, an LBW infants that higher birth weights were still correlated with earlier acquisition of some milestones (i.e. earlier sitting for HBW infants, eating solids sooner for NBW, and earlier walking for NBW and LBW infants). Analyses looking at gestational age classification demonstrated that for LGA, AGA, and SGA infants also had higher birth weights that were associated with earlier milestone acquisition (i.e. earlier rolling for LGA infants, earlier walking and saying words for AGA infants, and earlier independent sitting for SGA infants). In the discussion, we posit why larger birth weights for these infants may have been associated with earlier milestone achievement (see pages 11 and 12).

10- The sample should be described as convenience data, taken retrospectively and categorized from what appears to be their intake form at the clinic.

To address the referee’s concern about how the sample was described, we have added in that the participants were a convenience sample with retrospective data that consisted of parents’ responses to a developmental/sensory history questionnaire completed as part of an evaluation at an occupational therapy clinic (see page 4 under method at the beginning of the first paragraph).

REFEREE 2: Nicoletta Salerni

We appreciate the referee’s thoughts on how to clarify the paper. We hope we have addressed the referee’s concerns.

1- The introduction focuses on obesity and its possible developmental outcomes (physical and psychological). However, this variable does not correspond to the one considered in the study which, instead, focuses on birth weight. Consequently, the literature on the basis of which the study is built, must be revised, extending the role of birth weight on child development.
We are grateful for the referee’s suggestions and have taken her advice. As suggested by the referee, we have removed the focus on obesity and made birth weight (the dependent variable) the focus of the paper instead. This is reflected in the revised literature review in the introduction, in the revised results, and in the revised discussion.

2- In fact, although the authors reported a statistically significant correlation between birth weight and current body mass, this analysis was conducted only on 82 children, whose individual characteristics are unknown. So, this finding does not allow birth weight to be used as a valid index of the current body mass index of all participants (and even less so as a measure of obesity).

We agree with the referee’s sentiment, and we have omitted the correlation between birth weight and current body mass index.

3- The authors claimed that participants were 602 children. It would be useful to give information about how many developmental/sensory histories were fully compiled and how much information (parents’ responses to each question) was missing.

We thank the referee for this comment. We have clarified the total number of participants and information about missing data (see page 4 in the first paragraph under the Method section). We originally matched participants according to age to ensure that equal numbers of children from each age group was represented. However, to avoid bias, we have eliminated matching. This allowed for more participants to be included in the analyses according to our inclusion and exclusion criteria. Therefore, we now have 663 participants.

4- Medical diagnosis. Some of the medical conditions refer to genetic syndromes. Therefore, the reason that leads the authors to consider them as possible correlates of birth weight is not at all clear and further, these could be eliminated since, in any case, they did not occur in the sample.

We appreciate the referee’s comment. As suggested, we have eliminated genetic syndromes. To better focus the paper, we have removed medical diagnoses, whether children received referrals, and school skills from the manuscript.

5- Moreover, as the data collected are retrospective, the authors should critically discuss their accuracy, especially with regard to developmental milestones. For example, they conducted a partial correlation in order to control the possible influence of age on the relationship between children's milestones and birth weight. However, this analysis is not adequate to control for possible errors of parents’ judgment in the compilation of reports. This analysis would be meaningful only if the children’s age at evaluation, correlates with birth weight and with the other variables included in the analysis.
We thank the referee for this very valid comment. To address the referee’s concern, we have acknowledged in the discussion that a limitation of collecting the data retrospectively is that we could not verify the accuracy of parents’ responses (see pages 12-13 in the last paragraph of the discussion). We have also removed the partial correlation with age to clarify our results. Instead, as suggested by the referee, we conducted correlations with each developmental milestone. The only significant correlation for age at evaluation was with rolling for LGA infants ($r(30)=0.45, p=0.013$); older ages at evaluation were associated with rolling later.

6- The measures calculated from the coding of parents’ responses must be specified.

Based on the referee’s suggestion, we have clarified the coding that was done on parents’ responses (see page 5 at the end of the first paragraph). Parents’ answers were coded to be able to run analyses on their responses. For example, under Birth History in Table 1, yes and no responses were coded as “0” for no and “1” for yes.

7- All values reported in the Tables should be checked, since in some cases the number of children and the percentages reported do not correspond. It is not clear how to integrate data reported in Tables 2 (%), 3 and 4 (number of children) with the results mentioned in the text. For example, Tab. 2 reports that the percent of children diagnosed with ADD/ADHD is 17.2% (an equivalent of about 103 children); however, the degrees of freedom of the t test are 155 and so the subjects should be 157 (as reported in Table 3 for Medical diagnoses - 79 yes; 78 no; note, also, that while the text refers to the diagnosis of ADD/ADHD, Tables 3 and 4 refer to ‘medical diagnoses’. Consequently it is unclear to which participants the t test refer. Is that an effect of the matching procedure described on pag. 4? It is necessary to specify the exact Ns of the participants for each comparison and for each independent variable. The same considerations apply to all other aspects taken into account (Other evaluations; Birth/ Delivery related Factors; School Skills).

Thank you for this comment. Although the data were correct, in the original manuscript, we did not delineate how many participants contributed to each finding. The number contributing varied because of the matching procedure used in the original manuscript. We have clarified the number of participants for each analysis by eliminating the matching procedure and, in the revised version of Table 4, we have included how many participants contributed to each finding based on birth weight category and gestational age classification.

8- It is not clear for what reason the correlation between birth weight and age at evaluation are reported for the variables considered (Medical diagnoses, Other evaluations; Birth/ Delivery related Factors; School Skills) and this should be specified.
We conducted the correlation between age at evaluation and birth weight for birth history to examine whether children’s age at evaluation was related to the responses. This is a general way of examining variations in parents’ responses based on the age of their children.

9- All results on the differences between children with low vs. high birth weights may be determined by preterm birth that is associated to low birth weight (preterm children are, in fact, about 95). Since preterm birth affects several aspects of development (e.g., language, motor development, ADHD) examined in this study, it is necessary to control the effect of this variable in the analyses.

We have delineated in the revised version of Table 4, how many pre-term infants were included in each analysis. We felt that the unequal n’s for pre-term vs. full-term infants in our sample did not allow for us to adequately control for this variable in our analyses. Our hope was to provide descriptive information for readers for the basis of future study on this topic.

10- The Discussion has to be revised on the basis of the above-mentioned considerations.

As suggested, the discussion has been revised (see pages 10 to 13).

11- Page 8, line 5: “79%....(Table 5)”: this paragraph needs to be reformulated because it is not clear; for example, what does “birth weights for children who spoke sentences…” mean? To which children does this refer?

Table 5 in the original manuscript has been eliminated. In the revision, Table 4 includes data for developmental milestones according to birth weight category and gestational age classification.

12- Descriptive information. The information about the distribution of participants in the three categories of birth weight is redundant, since it is reported both in terms of numbers and percentages of children.

We have included birth weight information based on gestational age classification and birth weight category in Tables 2 through 4.

REFEREE 3: Andrea F. de Winter

We are glad that the referee thought that this paper reflected “an important topic.” We are very appreciative of the referee’s comments and hope that we have addressed the referee’s concerns.
1- The introduction describes the problem of obesity and its consequences. The link between birth weight and obesity should be more supported by evidence in the literature. I think that the construct “birth weight” should be the central focus of this article and not obesity/overweight. In my opinion birth weight should be the independent variable.

We agree with the referee. We have eliminated the argument about obesity and have instead highlighted the relationship between birth weight and birth history as well as developmental milestones in light of birth weight category and gestational age classification.

2- Information on study participation and information on the recruitment procedures are missing. How were the eligible individuals invited? Were all consecutive eligible individuals with sensory processing problems starting treatment invited to participate? The response rate of the larger study is not described. Inclusion and exclusion criteria for this and the larger study are not described.

We have revised the Method section to clarify the paper. We have added more information about study participation, the recruitment procedures, the response rate, and inclusion and exclusion criteria (see pages 4 to 5).

3- Sampling in a clinical setting might introduce bias or this might have impact on the generalizability if the research findings. For example, a large number of boys (73%) are participating in this study.

We thank the referee for this comment. Since we eliminated the matching procedure and were able to add more participants, the percentage of boys increased to 74%. We have acknowledged in the discussion section that a limitation of retrospective data collections are the lack of control over equalizing sample sizes according to sex. In addition, this study had a disproportionate number of boys because boys are significantly more likely to have sensory processing problems and thus seek clinical services (see pages 12-13 in the last paragraph of the discussion section).

4- Assessment of the main dependent variable: body mass index using birth weight. Is the dependent variable adequately valid and reliable to limit misclassification bias? My answer would be “unsure” or “no”. Participants were children between 4-12 years. Significant variability in height and weight gain especially in specific groups such as preterm born children may be present. Excessive growth in early childhood may predict overweight and obesity better than birth weight. Furthermore, birth weight is related to gestational age. Full terms are more likely to be classified as “high birth weight”, whereas late preterms are more likely to be classified as normal or low birth weight although late preterms might have a high weight in relation to their gestational age. In my opinion the correlation between both variables is not very high (.38). Furthermore, this gives no insight in the reliability of the classification which is used in this article (low, normal and high
birth weight). A measure of reliability (e.g., kappa) is more adequate. Relevant for this study might be the meta-analysis of Zhao et al. (Eur J Pediatr, 2012) showing that high birth weight (>4,000 g), but not low birth weight (<2,500 g) was associated with an increased risk of overweight in adults.

We thank the referee for these comments. Body mass index has been removed from the analyses. Obesity is no longer a central argument in the manuscript.

5- It is unclear if missing data might have an important effect on the assessment of the relationship between birth weight and body mass index. Parents with obese children are more reluctant to report their weight and length?

This is an important point brought up by the referee. We have clarified the reason and amount of missing data in the manuscript (see page 6 at the beginning of the second paragraph). Since the study is retrospective, we are unable to confirm the exact reasons for missing data or categorize the parents who did not provide data.

6- Research shows (Jaspers et al, 2010; assessing the validity of parental recall that parental recall of birth weight and gestational age is valid (no systematic error) but not very precise. However, Jaspers et al. showed that the recall of early child behavior was poor (kappa values of 0.03 to 0.10). The retrospective data collection in this study might have introduced information bias and this should be discussed as an important limitation of this study.

We agree with the referee. We have discussed the limitations of this retrospective study in the discussion (see pages 12-13 in the last paragraph of the discussion).

7- It is not clear what the assumptions of the authors were when they decided to examine ‘age at time of evaluation’ as a co-variable in all analyses.

We conducted the correlation between age at evaluation and birth weight for birth history to examine whether children’s age at evaluation was related to the responses. This is a general way of examining variations in parents’ responses based on the age of their children.

8- The relationship between the results and the tables could be strengthened. For example, in the results frequencies are mentioned but those cannot be found in the tables. Furthermore, more concise writing would improve the result section.

We have revised the tables to strengthen the relationship between the text in the Results and the tables (see Tables 2 through 4). We have also revised the writing in the results section (see pages 6 to 10).

9- The p-values of all tests should be included in the tables to provide a clear overview of all results.
We have included the exact p-values for the analyses in the results (see pages 6 to 10).

10- In Table 2 data are presented on medical diagnoses, treatment, skills etc for the total group. It would be more informative if data are presented for the total group and low, normal and high weight group. Furthermore, to improve the connection with the other tables it might be relevant to present the frequency of medical diagnoses (yes/no), other evaluations etc.

To clarify the focus of the paper, we have eliminated Medical diagnoses, other evaluations and treatment, and school skills.

11- In Table 3-5 the number of children varies. In the method section the authors stated that 602 children participated in the study. However, the number of children with medical diagnoses (yes/no) is only 157.

In the original manuscript, we matched the data to create an even number of participants in each category. However, to clarify our findings, we have eliminated the matching procedure. Therefore, we were able to include more participants in the study (now 663). In Table 4, we have specified how many participants contributed to each finding. We have clarified the reason and amount of missing data in the manuscript (see page 6 at the beginning of the second paragraph).

12- In the discussion the concept “birth weight/ overweight obesity” is related to other research findings but it might be confusing because the concept is used as independent and dependent variable in the discussion. Furthermore, the limitations of the study are not presented in the discussion.

We revised the discussion to match the new focus of the paper on birth weight as the dependent variable. At the end of the revised discussion section, we provide limitations to the study (see pages 12 to 13).

Again, we thank the reviewers for their great help and thoughtful comments. We believe that the manuscript presents a unique perspective on how birth history, developmental milestone achievement, birth weight category, and gestational age classification relate to birth weight for the population of children with sensory processing disorder. We hope that the revised manuscript is now suitable for publication in *BMC Pediatrics* as a *Research Article*.

Thank you.

Regards,

Simone V. Gill