Author's response to reviews

Title: Assessing fetal growth impairments based on family data as a tool for identifying high-risk babies. An example with neonatal mortality

Authors:

Carsten B Pedersen (cbp@ncrr.dk)
Yuelian Sun (YS@SOCL.AU.DK)
Mogens Vestergaard (MOGENS.VESTERGAARD@ALM.AU.DK)
Jorn Olsen (jo@ucla.edu)
Olga Basso (bassoo2@niehs.nih.gov)

Version: 2 Date: 4 September 2007

Author's response to reviews: see over
Dear Editor

Thank you very much for the reviewers’ helpful comments, and for the opportunity to submit a revised version of the manuscript. We have modified the manuscript according to the reviewers’ suggestions, and we hope that the manuscript is now suitable for publication in BMC Pregnancy and Childbirth. Below please find a detailed description of the changes made, as well as our responses to the points raised.

Please find attached the revised version of the manuscript and the electronic version of the figures in the manuscript.

I look forward to receiving your response.

Below, the reviewers’ comments are shown with *italics* typeface, while our response is shown with **bold** typeface.
Referee 1: Waldemar (Wally) Carlo

Comment 1:
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached) The study includes data collected over a 23 year span over which there were many improvements in perinatal care (e.g. surfactant) that may have affected survival differently among various birth weight groups and thus, result in a dissociation of the associations reported here. It is not shown if the associations persist if data are analyzed for various periods or from a period after newer therapies were in place. If the additional data analysis is not possible, this must be addressed as a major limitation.

Response:
The risk of neonatal death decreased roughly 2-fold during the study period. Due to the relatively small absolute number of neonatal deaths, we could not perform more detailed analysis. However, further adjustment of the estimates in Figure 3 by year of birth had no impact on our results. Estimates in figure 3 are now adjusted for year of birth (and indicate as much in the text), and we state this as a limitation in the discussion, as follows: ”Our study spans a long time period, during which important improvements in the care of premature newborns have occurred. The relatively small absolute number of deaths in our study did not permit analyses of separate time periods. However, adjusting for year of birth did not change our estimates.”

Comment 2:
Infants with congenital anomalies or congenital infections that lead to lower birth weight and/or growth restriction were not excluded from the data on the second born. Many of these infants have an increased risk for mortality. It would be ideal to exclude infants with these pathological conditions to determine the real association between restriction of constitutional growth and mortality. Alternatively, if the analysis is not possible, acknowledgement of this limitation is important.

Response: We did not have information on congenital anomalies or infections in either first or second births, and we agree that these infants are likely to be smaller and have a higher risk of neonatal death. We now acknowledge this limitation in the discussion, as follows: “Our study is further limited by the lack of information on congenital anomalies or infections, as these conditions increase the risk of both growth restriction and neonatal death. This will limit the predictive value of our estimates, especially at the lower weights. As these conditions may be
present in both pregnancies, this mechanism may, in part, explain the strong predictive risk of a small achieved birth weight among babies who appeared to have fulfilled their growth potential.”

Comment 3:

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Although the association of birth weight of the second child to birth weight of the first appears to be evident, the association is not present in the second born term infant when the first sibling’s weight was below 2.5 kg (Figure 1). The lack of association is important as this subgroup of second born encompasses the majority of the infants. This limitation needs to be addressed explicitly.

Response:

The first paragraph of the result section actually addresses the reviewers concern (Figure 1), and in the second paragraph of the result section we describe that “However, when we stratified the results shown in Figure 1 by the first-born’s gestational age (Figure 2), we observed a linear association between the second-born’s birth weight and the first-born’s birth weight for all birth weights of the first-born, including birth weights below 2500 grams” We have now rewritten the second paragraph of this section to clarify the results.
Referee 2: Robert Platt

Comment 1:
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
Page 9, describing the model for second-born birth weight: It is not clear how the model works, and in particular where the variance component comes in. The box on page 10 describes an ordinary regression model. I assume that the variance component is included to deal with gestational age, but it needs to be explained more clearly.

Response:
We have clarified the reason for using the variance component model. In addition, the description of variance component model has been moved to the method section in the paragraph entitled “Prediction of birth weight in second-born babies”, and the equation used to predict the second borns’ birth weight now indicate the first and second borns gestational age and sex.

Comment 2:
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Page 7, line 6: Newton-Raphson

Response:
We corrected the mistake.

Comment 3:
Page 8: “Expected birth weight” is used here, but not explicitly defined until the results section. I think a sentence in the methods describing the modeling strategy to compute expected birth weight is essential.

Response:
We now describe the model used to predict the second borns’ birth weight in the method section. Please see paragraph entitled “Prediction of birth weight in second-born babies”.
Comment 4:
Page 8: log-linear Poisson regression implies that you are estimating a rate ratio rather than a relative risk. Clarification would help.

Response:
It is true that we in principle estimate incidence (density) rate ratios. However, since the incidence rate ratio is an estimate of the relative risk, and readers generally are more familiar with relative risks as opposed to incidence rate ratios, we prefer to use the term “relative risks”. Of course, we are willing to change this if preferred by the Editor.

Comment 5:
Page 13 line 4-5: “increased risk of neonatal death relative to those between 90 and 110% of predicted.”

Response:
We changed the sentence as suggested.

Comment 6:
Discretionary Revisions (which the author can choose to ignore) Throughout the paper – I think it would be clarifying to decide on either “expected” or “predicted” weight for the second born and to use this consistently. The simultaneous use of both terms can be confusing.

Response:
We agree. Throughout the paper we now use “predicted” birth weight.

Comment 7:
Page 6-7: Some additional references on inconsistencies in gestational age might be useful.

Response:
We have added two references on inconsistencies in gestational age.
Comment 8:
Page 7, bottom: what percentage of the total population is the cohort – is there some way to describe how representative the first borns, for example, are of the total population of first borns?

Response:
We do not expect the population of first borns with younger siblings to be representative of the total population of first borns, as many factors may affect why mothers have more children (health of mother, health of father, social factors, health of the first-born child, etc). Since the paper relies on older siblings to predict the birth weight in their younger siblings, only children are not relevant to the paper. However, we now state how many sibships are used in this study with respect to the total, and we now write the following sentence in the methods section: “The included sibships constitute 86% (=411,957/481,526) of the total number of sibships where the first and second baby were both born in Denmark during the study period.”

Comment 9:
Page 9: to what extent is there regression to the mean important in the prediction of second born birth weight? That is, a very large first born would give a large expected weight for the second born, and it is likely that these babies would be smaller than expected due to RTM.

Response:
In the methodological considerations in the discussion we have now included the following text: “When the birth weight of the first baby is extremely small or extremely high, due to either measurement error or natural variability, this will lead to attenuation of the relation between the birth weights of the two siblings. While this may reduce the ability of the model to predict birth weight, gestational age and birth weight of the older child still explained a large fraction (48%) of the total variation of the birth weight of the younger child.”

Comment 10:
Page 10: why is the gestational age categorization different for first vs. second borns?

Response:
In the method section we have now included the following explanation: “Since we expected gestational age of the second-born babies to be more important for predicting their own birth weight than gestational age of their older sibling, we decided *a priori* to use a more detailed categorization of gestational age for the second-born.”.
Referee 3: Russell Kirby

Comment 1:
General Comments on ‘Assessing fetal growth impairments based on family data – a tool to identify babies at risk’
The authors should clearly specify what is meant by ‘risk’ in the title and ‘mortality’ in the abstract and introduction. The paper appears to focus on neonatal mortality risk, so why not say this explicitly?

Response: We have now changed the title, hopefully in a way that conveys our intention. Our study is on neonatal death, but we would like to see the method used to investigate other outcomes.

Comment 2:
On the title page, Dr. Olsen’s affiliation is incorrectly indicated as being in Louisiana, the correct state abbreviation is ‘CA’. Dr. Basso’s state abbreviation could be more correctly indicated as ‘NC’

Response: We have corrected this.

Comment 3:
Abstract:
In the first sentence, clarify what is meant by ‘mortality’ and ‘other health conditions’? Do the authors mean to imply across the lifespan, or explicitly associate low birth weight with infant health? Do the authors have an explicit research hypothesis? If so perhaps this might be stated in the abstract . . . ‘We hypothesized that . . . etc’.

Response: We have clarified the first sentence. We have also stated our aim more explicitly, which was to quantify the risk associated with the failure to fulfil the estimated growth potential across the whole distribution of birth weight, with particularly to babies in the normal range. Given the existing evidence on the topic, we felt it was more honest not to state a hypothesis that we knew beforehand was very likely to be fulfilled, and our aim was rather to provide quantitative estimates. We could, however, state a hypothesis, if the Editor so prefers.
Comment 4:
The methods section is fairly sparse considering that the methodology for estimating expected birth weight is relatively novel.

Response:
We have moved the description of the prediction model from the result section to the method section, and have extended its description. Please see the paragraph entitled “Prediction of birth weight in second-born babies” in the method section.

Comment 5:
The results could include some more specific quantitative findings. At present this information is presented in cursory fashion.

Response:
We have included additional quantitative results regarding the adjusted relative risks shown in Figure 3: “Among babies who achieved their predicted birth weight within ±10% and using 3500-3999 grams as the reference category, the estimated relative risks were 20.6 (95% CI: 11.0-38.6) for babies weighing <1500 grams, 13.9 (95% CI: 7.7-24.9) for those weighing 1500-1999 grams, 7.0 (95% CI: 4.1-12.0) for those with a birth weight between 2000 and 2499 grams, 2.8 (95% CI: 1.8-4.3) for those weighing 2500-2999 grams, and 1.5 (95% CI: 1.1-2.0) for those who weighted 3000-3499 grams. Among babies who weighed 3500-3999 grams, however, those who achieved 80-90% of the predicted birth weight had a relative risk of 2.0 (95% CI: 0.9-4.3) compared with those who achieved the predicted birth weight within ±10%. Those who exceeded their predicted birth weight also had slightly elevated, although not statistically significant, relative risks [1.4 (95% CI: 0.8-2.4) among babies who achieved 110-120% of the predicted birth weight and 2.3 (95% CI: 0.9-5.8), among those who achieved more than 120% of their predicted birth weight].”

Comment 6:
Background:
Reference 1 deals with perinatal and infant mortality, but the first sentence implies more. If the authors wish to imply broader associations of low birth weight with child or adult mortality, these assertions can and should be documented with other references.
Response:
We already had two references that were specific to adult morbidity. However, we have added two more references at this point, and we have generally expanded our list of references across the manuscript.

Comment 7:
Consider referencing other material on approaches to estimating optimal birth weight and deviation from optimal birth weight. This reviewer is traveling presently and doesn’t have full access, but recalls an interesting paper from Australia two or three years ago on this topic, also in a BMC journal (either Pregnancy and Childbirth or Pediatrics).

Response:
We have now added the suggested paper, as well as another reference on the topic.

Comment 8:
Do the authors have any explicit hypotheses – if so, the last paragraph of the background section is the best place to state these.

Response:
We have restated our aim, although not in the form of a hypothesis (please see response to the 3rd point raised by this reviewer).

Comment 9:
The last phrase of the last sentence of the background, “which was calculated . . .’ is not necessary, as this is discussed in considerably more detail in the methods.

Response:
We have deleted the text as suggested

Comment 10:
Methods:
The dataset is well described. The authors might justify the choice of 100g as opposed to 50g rounding for birth weight. Presumably the data from 1997 on were converted to completed weeks of gestational age to be consistent with the earlier data.

Response:
Digit preference occurred mostly to the nearest 100 grams interval. In the method section we now write: “Due to digit preference primarily to the nearest 100 grams intervals, we rounded birth weight to the nearest 100 grams interval”.

When we describe the categorisation used for gestational age in the method section we always state that we consider completed weeks.

Comment 11:
For references to SAS procedures, unless there is something specific in the documentation it is not necessary to cite the specific procedure. A general reference to the version of SAS used, in the body of the text, should be sufficient.

Response:
Since others may want to apply this procedure, we feel that a full reference to the methods used may be helpful. However, we deleted the name of the specific procedures used from the body of the text. The relevant procedure used is still described in the literature references.

Comment 12:
Somewhere in the methods some details on how expected birth weight was calculated should be discussed. Instead some of this material is included in the first paragraph of the results section.

Response:
We have moved the description of the prediction model to the method section. Please see the paragraph entitled “Prediction of birth weight in second-born babies” in the method section.

Comment 13:
Results:
The equation at top of p 10 should be expressed in conventional mathematical form, using beta-naught for intercept, beta-one for slope, etc.

Response:
We have made the suggested change. Please see the paragraph entitled “Prediction of birth weight in second-born babies” in the method section.

Comment 14:
In the discussion of neonatal mortality results, do the models take year of birth into account? Given that mortality risks improved considerably over the lengthy study period but improvement varied across the gestational age distribution this might be important.

Response:
In the method section and in Figure 3, we now describe that all estimates of relative risks were adjusted for year of birth.

Comment 15:
Also, the analysis includes only sibships of first and second born infants, neither of which was a stillbirth? This appears to be the case from reading the manuscript, but could be stated more clearly in the methods.

Response: We stated this more clearly (please see 2nd line of the paragraph “Identification of sibships”).

Comment 16:
Do not interpret your results in the results section – merely present them here (ie second para on p 10 comparing fit of Danish and Norwegian models).

Response:
We have changed the text as to not interpret our results at this point.

Comment 17:
Figures 1 and 2 – spell out 1.st and 2.nd – it’s only a few more keystrokes and there is plenty of room!
Response: There is not enough room to spell out the full text, i.e., first-born baby, second-born baby.

Comment 18:
Figure 3 – include a note indicating what the bars at each data point represent – presumably these are 95% CIs? But this should be stated clearly.

Response: This information was stated in the legend to Figure 3, but we had erroneously described the bars as “horizontal” instead of “vertical”. We apologize for this mistake, which is now corrected.

Comment 19:
Discussion:
The discussion would be strengthened by reference to a specific hypothesis or (es) in the first paragraph, followed by interpretation of this study results in relation to the hypothesis.

Response: We have done as suggested, although we do not refer to a specific hypothesis – but we have clarified our aim (please see response to the 3rd point raised by this reviewer), and structured the discussion accordingly.

Comment 20:
The decision re not adjusting birth weight for year might make sense, but mortality is an entirely different issue. In the limitations, some discussion of generalizability re stillbirths, multiple births, etc should be included. What about the role of maternal morbidity associated with a specific pregnancy (either first or second)?

Response: We now describe that the estimates of relative risks presented in Figure 3 were adjusted for birth year. In the method section we now write “Using data on family members recorded in the CRS [17], we identified all sibships in Denmark consisting of first- and second-born singletons born alive between 1979 and 2002 (481,526 sibships).”

We also added the following text to the discussion: “Our results only refer to neonatal mortality in singleton live births. Results for post-neonatal mortality may be different.”
Comment 21:
How much additional information is provided based on the methods presented in this paper? Is it clinically significant and useful for obstetrical practice? Are the authors aware of a recent paper by Boulet et al (Am J Obstet Gyneco 2006) which also examines mortality risk in relation to birth weight and gestational age (but not among sibships)?

Response: We have expanded our discussion about what this paper adds. We doubt that, in the presence of detailed clinical information, it could help clinicians, and we now state as much. However, we also add that a discrepancy in birth weight with a previous sibling may constitute a warning sign, even in the absence of obvious pathology. We are aware of the paper by Boulet et al. However, this paper provides a quantification of risk among the smallest babies as a function of their gestational age at birth. We have not added this reference, since it seemed outside the scope of our paper.

Comment 22:
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The authors should make an explicit statement of hypothesis(es), then test these and discuss. The authors should also make a frank and candid assessment of the contribution of their work to the field.

Response: For the previously mentioned reasons (please see response to the 3rd point raised by this reviewer), we did not formulate our aim in the form of a hypothesis. However, we have restated our aim and we have followed this reviewer’s suggestions for the reorganization of the text. We have also stated what we believe to be the usefulness and limitations of our contribution.

Comment 23:
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
The authors should also address and revise the manuscript as suggested in the general comments above.

Response:
Above we have addresses all issues raised by this reviewer.