Author’s response to reviews

Title: A Retrospective cohort study of factors relating to the longitudinal change in birth weight

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Dear Editors,

Thank you for continuing to consider my manuscript, “A Retrospective cohort study of factors relating to the longitudinal change in birth weight.” We have received the reports of the reviewers and have made changes to our manuscript based on their comments. We are submitting our revised manuscript and have included below our detailed responses to their comments.

The manuscript has not been and will not be submitted to any other journal while it is under consideration by _BMC Pregnancy and Childbirth_. It was accepted and presented as a poster presentation at the Society for Gynecologic Investigation 58th Annual Scientific Meeting, March 16-19, 2011 Miami Beach FL. There are no other prior publications or submissions with any overlapping information, including studies and patients.

We continue to feel this manuscript would be of interest to readers of _BMC Pregnancy and Childbirth_ as it deals with the timely issues of birth weight and fetal adiposity. Given the changing demographics in the obstetric population as well as the evolving understanding of how the _in utero_ environment impacts childhood and adult health, we believe our results will further the understanding in the field and be hypothesis generating for other researchers and clinicians. We feel this article is suited to the wide, international readership of _BMC Pregnancy and Childbirth_.

This research is the product of all four authors. I, Kelly S Gibson, MD, collected the data, performed the initial analysis, and wrote the first draft of the manuscript. Dr. Waters assisted in study design, the initial analysis, and portions of the manuscript. Dr. Gunzler performed the secondary and advanced statistical analysis and critically reviewed the manuscript. Dr. Catalano provided guidance on the study design, assisted in data interpretation, and has critically reviewed the manuscript.

No honorarium, grant, or other form of payment was given to anyone to produce the manuscript. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. None of the authors report any conflicts of interest, specifically no conflicts of interest regarding the study design;
the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

This project was approved by the MetroHealth System Institutional Review Board as protocol IRB10-00426 on 06/08/2010, and it is still currently approved.

Thank you again for your consideration,

Kelly S. Gibson, MD
Response to Reviewers’ reports
Reviewer#1: Russell Kirby Reviewer's report:
In this manuscript, the authors use a single center perinatal database to examine trends in birth weight among term singleton deliveries from 1995-2009. The study also examines trends in birth length and ponderal index. While the latter adds new information, most of the covariates for the analysis of birth weight could be obtained from population-based sources.

Major compulsory revisions

1. The authors do not explain why the study ends in 2009, given that the manuscript was submitted in 2015. There could be arguments supporting the choice to end in 2009, including perhaps that the hospital implemented a no unindicated intervention policy, but the authors need to substantiate this if it is true.

The collection of data ended in 2011 and analysis took another year. One of the authors (TW) relocated to another institution after the data was collected and the manuscript had been rejected after lengthy submission to another journal.

2. There is no attempt to explain how generalizable these data may be. How has the case-mix of the hospital obstetrical cases changed over time? How representative of the Cleveland metropolitan area are these data, and how if at all has this changed over the study period?

The population of the hospital represents that of an inner city population that is economically stressed. There has been a shift in the population of pregnant women with a decrease in the white population and an increase in the Black population from 37.2% to 45.4%. Further there has been an influx of Latina patients who now represent 11.3% of parturients at the hospital. The later 2 groups representing the largest prevalence of overweight and obese women of reproductive age in the US.

(Page 7, Lines 170-171, Page 8, Lines 179-181)

3. Where are the results of the separate regressions by race/ethnicity (p 5 line 105-6)?
We have included this in the Results section and also created a supplemental table with the results (Page 7, Lines 156-159; supplemental table 3)

4. In table 1, what statistical test was used to determine significance as shown in the last column? Did the authors conduct a test for trend, either by 3-year interval or single year?
There are sufficient data to conduct JoinPoint regression for single year - this test determines if there is a significant trend, and also if there are one or more inflection points to the trend. There are other potential tests as well.
We now conduct a test for trend by 3-year interval for table 1. For binary variables we use the Cochran-Armitage test for trend. For continuous variables, we perform linear regression using contrasts to test for a linear trend (using the 3-year intervals as different categories in defining an ordinal predictor). We also explained this in the text and in the table legend (Page 5, Lines 99-104; Table 1)

5. It is hard to make sense of the regression results provided in Tables 2-4. What data are provided in the first column - headed ‘standard estimate (correlation coefficient)’? Is this in fact ‘r’? If so, it would be better to label the column thusly. It would also be helpful to show the t-statistic for each variable, as this gives the reader a sense of the relative contribution of each variable. It would seem, and unsurprisingly, that gestational age is the biggest contributor in each model. Also, give a measure of goodness of fit for each model as a footnote below.
Yes, this is equivalent to ‘r’ and we now label the column accordingly. We have also added a
column for the t-statistic for each variable. The models in these tables are multiple regression models, which we make clearer now in the table legends. Thus, we have provided an adjusted r-squared value as a measure of goodness of fit for each model. (Tables 2-4)

6. In Figure 1, be consistent in terms of capitalization - shouldn't 'time' be capitalized in the title for each panel? And what is 'mean' - its really not that, it is the overall without respect to the subgroups shown in each panel. What is 'wga'? This is an unfortunate abbreviation - better to say 37 weeks, 38 weeks, etc, and indicate its gestational age in the panel title.

We agree and have made the changes to the Tables

Continuing, how were the trend lines fitted in each panel of Figure 1? The bolded line in each of the figures is the mean value for the total data. This is stated in the figure legends.

7. In discussing limitations, no mention is made of the fact that this is a single-center study and its rather difficult to assess its broader generalizability.

We agree, and we have included a sentence in the limitations. (Page 7, Lines 170-171, Page 8, Lines 179-181)

8. Given the comments about Zhang's work, why did the authors not examine also the patterns among spontaneously induced deliveries?

At the time of this study, our database did not include data for elective inductions of labor. Approximately 13% of the deliveries were induced, and the majority were medically indicated. The Zhang paper had a 27% rate of induction in the final year included in the study, the majority of which were elective inductions and thus not directly comparable to our data.

9. Given the almost non-findings regarding the Ponderal Index (over R-sq of 0.05, corr coeff as indicated in Table 4 of 0.11), the statements about its utility (p 9, 203-210 as well as comments in conclusion) seem unwarranted.

1 cm represents a 2 % decrease in length. Whereas the change in weight represents a 2 % (72/3325) change in weight both together, i.e. the Ponder index change over time (2.61/2.71) represents a 9.6% change in PI. (Page 10, Lines 221-223. We think that this is an important result of our analysis.

10. There is a much broader literature on this subject, including now studies examining maternal weight growth velocity during pregnancy, and also work examining effects of weight retention between pregnancies on perinatal outcome in subsequent pregnancy. It would be interesting for the authors to comment on this in terms of implications for future work, and also to see if the there are sufficient subjects in the sample with two consecutive pregnancies to conduct a substudy on this topic.

We agree with the reviewer that the ability to look at the effect from 1 pregnancy to the next would be very interesting. However, since we do not record the weight at the first visit it would be impossible to determine if the weight at the end of the second pregnancy was due to retention of excess weight after the first pregnancy or excessive gestational weight gain in the second pregnancy. In a small substudy using another data set we determined that 84% of women begin their second pregnancy with increased weight as compared to the first pregnancy. In the 16% of women with weight loss between pregnancies there is a decrease in birth weight of the second baby, primarily due to a decrease in fat mass rather than lean mass. These data are being incorporated into a separate manuscript and will not be included in the revised manuscript. We agree with the reviewer that this is an important issue but have elected
not to include the data in this manuscript.

Minor essential revisions

1. p 5, line 99 and elsewhere: this would read better as 'as well as in three-year intervals' - epoch is usually reserved for much larger periods of time
   We agree and have made this change throughout the paper.

2. place each table on a separate page. Add information about what statistical tests were performed.
   We have moved the tables to separate pages and added details about the statistical tests used.
Reviewer: Naho Morisaki

Reviewer's report:
The authors state decline in birth weight could mostly be explained by change in demographics. However, this statement is most likely due to a large misinterpretation of statistical results.

The methods, results and discussion should be largely revised.

However their finding that PI increased while BW decreased is interesting.

In addition there are quite a few typographical/literal errors, and the tables do not stand alone which also needs to be fixed.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
The reference we use is from Dr. Oken's publication with Donahue et al as the first author from 2010. This reference is more recent than the mentioned references by the reviewer. We are happy to update other references, but please specify which reference you feel is now outdated.

2. Line 180: I think my previous article has put an end to the discussion whether birth weight is decreasing or not in the US (the conflicting results between Zhang and Donahue.) and would think it would be a useful study to refer to in the discussion. (Obstet Gynecol. 2013 Jan;121(1):51-8.)
That study is very interesting but the population is quite different from our population. The population was from the Utah/Idaho region with less than 1 % Black patients. In our population the percentage of Black patients increased to 45.4%. Also the gestational age at delivery did not change over that period of time i.e. 39.1 weeks whereas in our population gestational age decreased. Last in the referenced paper only 14-17% of the population was obese and only 20-22% were overweight. Again in our population the percentage of obese and overweight increased. We have elected to include this reference and a comment to this paper in the revised manuscript. (Pages 8-9, Lines 195-198)

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
3. Alexander method. The authors seem to misinterpret the Alexander method, as this method does not trim birthweights at 2 SD (line 85). They use a table modified from 2.5SD. Please consult original paper (Table 1 has the numbers that should be used) and trim the sample accordingly.
Thank you for catching this error. This table was used, but misquoted as 2SD rather than 2.5SD. We have amended the text to say 2.5SD. (Page 4, Line 84)

4. The methods is difficult to read as they do not follow the order that they were done (line
100-110). Usually the multivariate analysis is done after simple tests. It is also unclear when the parametric tests were used and when the non-parametric tests were used and why, as well as when (for which data) which test was used.

*We agree and have re-written the methods section and included the univariate followed by the multivariate analysis. This makes the methods much clearer.* (Pages 3-5, Lines 71-120)

5. Many parts of the paper and table lack units of measurement. This is important information and should be included in all places.

*We have reviewed the paper and included the units of measure throughout.*

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

6. The results section line 141-152 leaves me in doubt whether the authors understand what they are doing. In addition to the lack or mistakes in units, there is large misinterpretation of the computer outputs. The authors need a statistician to help them. First line 143 “Nine expert derived factors were significantly associated with change in BW over time and line 147 “…..were all associated with a decrease in BW over the fifteen year period” is most likely wrong. The statistical outputs shown in Table 2-4 show how each factor is associated with BW (or length or PI), for each unit of measurement. In table 1, they show how each characteristic has changed over the 15 years. The effect of “change” of each characteristic on the “change” in BW (or length or PI) would be the product of these two. My calculation shows change in race attributed to -12g, change in GA attributed -55g, and unexplained (change over 15 years) was -26 grams (they do not add to 72 grams because of rounding). Please revise the results section accordingly for the other outcomes.

*Dr. Gunzler, one of our co-authors, is a statistician. We now made the changes as you suggest to the results section.* (Pages 6-7, Lines 142-155)

7. The authors define SGA and LGA however these are not used anywhere in the results tables. It would be most appropriate if analysis on SGA and LGA is done using multinomial regression, similar to analysis on BW. If this is difficult, atleast show the change in Table 1, or delete mentioning SGA/LGA in the manuscript altogether

*We have deleted this from the manuscript as we did not discuss either SGA or LGA.*

8. Line 121, it is obscure what was independent to gestational age, and how they statistically tested this. Please make it clearer.

*We attempted to make our modeling much more clear in the revision: “We initially evaluated if the changes in BW, BL and PI (dependent variables) over time were correlated with the changes in all available independent variables (maternal age, parity, BMI at delivery, race, smoking, diabetes mellitus, and hypertension and neonatal gestational age) in univariate correlation analyses (supplemental table 1). We then included all the significant independent variables into multiple regression models for each outcome (BW, BL and PI). These multivariate models were used to determine the contribution of each independent variable, adjusted for the potential confounding of other included variables, with BW BL and PI, respectively.”* (Page 5, Lines 107-112)

9. This interpretation should be amended in the Abstract as well. Of course year of birth would only contribute to a small amount in variability of birth weight and the information of variance is not needed. However their study does not show year of birth contributes little to decrease in birth weight, on the contrary, they show that even after adjustment, birthweight decreased by 1.7*15=26 grams. (This number is similar to previous reports by Morisaki and by Donahue.) Please replace the numbers to “over 15 years” for BL and PI as well.
We agree this is a reasonable way to estimate the data over the total time period. We have amended the abstract results section (Page 2, Lines 37-41)

10. In abstract do not state multiple regression, but document what factors you adjusted for. We have made this change (Page 2, Lines 37-38)

11. Line 39 “changes in race or gestational age” is grammatically incorrect, as race and gestational age do not change. Proportions or averages change. We agree and made this change (Page 2, Lines 40-41)