Author's response to reviews

Title: Racial disparities in infant mortality: What has birth weight got to do with it and how large is it?

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Version: 3 Date: 25 June 2010

Author's response to reviews: see over
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Version: 2 Date: 24 June 2010

Author's response to reviews: see over
Dear Prof KS Joseph

This is a revision of MS: 1968254060358352 entitled “Racial disparities in infant mortality: What has birth weight got to do with it and how large is it?”. We have attempted to respond to all but a few of the reviewers comments. In so doing we have significantly changed most sections of the manuscript with the exception of the results.

Major changes:

We have replaced Howard Stratton (howard.stratton@gmail.com) with A. Gregory DiRienzo at Howard’s request as Greg has more experience with the counterfactual methods that the reviewers requested that we include.

We have largely rewritten the Background and Modeling sections to include recent extensions of the Wilcox-Russell hypothesis, by Hernandez-Dias et al and others, as well as a discussion of Basso and Wilcox’s work. We have shown where our model fits into the Wilcox-Russell, Hernandez-Dias theories. We view Basso and Wilcox’s work to be addressing a slightly different question, the reverse-J-shape of the birth weight specific mortality curve, one which CDDmlr could also address but which is beyond the scope of the present paper.

Our definitions of direct and indirect stem largely from the work of Geneletti. This differs from the counterfactual approach, e.g. Hernandez-Dias and the approach of many of the reviewers. This has been presented more completely in the modeling section of the paper.

We have explicitly discussed the assumptions necessary to estimate direct and indirect effects under Geneletti’s framework in the Discussion.

The three changes above address the necessary (and central) revisions of all three reviewers.

We have changed Table 5 in the results to bring them fully into Geneletti’s framework.

We list other modifications below as requested by the Reviewers below on attached pages. Our responses are in bold.

Sincerely

Timothy Gage
Reviewer's report

Title: Racial disparities in infant mortality: What has birth weight got to do with it and how large is it?

Version: 1 Date: 29 March 2010

Reviewer: Robert Platt

Reviewer's report:

Major Compulsory Revisions

1. The major issue with this paper is the use of the terms “direct” and “indirect”. These terms have been dealt with in considerable detail in the literature in recent years (eg Vanderweele 2009 epidemiology; Kaufman et al Epi Perspectives Innovations 2004, Cole/Hernan IJE 2002). I am not clear from the paper how the authors define direct and indirect effects, and a review of some of this literature is essential to do so. In addition, the limitations of methods to estimate direct and indirect effects (discussed most clearly in Cole/Hernan) need to be addressed. 2. The authors should also consider the work of Hernandez-Diaz et al, that suggests that birthweight is not on the causal pathway.

We have included Hernandez-Diaz in the background of the paper as an extension of Wilcox Russell. We include discussions of direct and indirect effects references to some of the papers above (as well as others) and the assumptions involved in the modeling section and in the discussion.

2. The section on page 15, starting Racial differences..” is unclear. I am not sure what is meant by rates being “explained by the ‘compromised’ population, for example.

We have replaced “explained by” with “accounted for”. The “normal” and “compromised” subpopulations are essentially a latent dichotomous variable. However, CDDmlr identifies them probabilistically.
3. Conclusions could be clearer, and perhaps are a bit overstated. Also – much is known through other evidence about the role of birth weight and direct/indirect.

**We have tried to clarify the conclusions.**

**Minor Essential Revisions**

1. The “long term goal” at the end of the background should be in the discussion.

**We have removed this statement entirely.**

2. Describe how gestational age was derived from the NCHS cohort. Was it LMP-based, or clinical estimates?

**Done. We use the LMP estimates.**

3. The phrase “defined the African American “race” effect as an indicator variable (z) on each of the 11 parameters” needs clarification I think you mean that you defined an indicator variable, and then defined the race effect by incorporating functions of that variable into multiple steps of the modeling process.

**We have rewritten parts of the methods section, which hopefully clarifies these issues.**

4. Sometimes “compromised” is in quotes; other times not. This should be corrected.

**Done**

**Discretionary Revisions**

1. I, and I suspect other readers as well, am unfamiliar with Kitagawa decomposition; some detail here might help.

\[
t_i - T = \sum_i \frac{T_i + T_i}{2} \left(\frac{n_i}{N_i} - \frac{N_i}{n_i}\right) + \sum_i \frac{n_i + N_i}{2} (t_i - T_i)
\]

Kitagawa decomposition, Eq (2) in Gupta 1979
\[ t = \frac{\sum f(x, y \mid z = 1; \theta, \beta)}{\sum f_i(x \mid z = 1; \theta)} \text{ Total death rate (African Americans)} \]

\[ T = \frac{\sum f(x, y \mid z = 0; \theta, \beta)}{\sum f_i(x \mid z = 0; \theta)} \text{ Total death rate (European Americans)} \]

\[ \frac{n_i}{n} = \pi_i(z = 1) \]

\[ \frac{N_i}{N} = \pi_i(z = 0) \]

\[ t_i = P_i(y = 1 \mid z = 1; \beta^*_i) \]

\[ T_i = P_i(y = 1 \mid z = 0; \beta^*_i) \]

\[ t - T = K_\pi + K_s + K_p \text{ Kitagawa Decomposition} \]

\[ K_\pi = \sum_{i=1}^{n} \frac{P(y = 1 \mid z = 1; \beta^*_i) + P_i(y = 1 \mid z = 0; \beta^*_i)}{2} (\pi_i(z = 1) - \pi_i(z = 0)) \pi \text{ effect} \]

\[ K_s = \pi_s(z = 1) + \pi_s(z = 0) \left( \frac{1}{2} P_i(y = 1 \mid z = 1; \beta^*_i) - P_i(y = 1 \mid z = 0; \beta^*_i) \right) \text{ Secondary rate effect} \]

\[ K_p = \pi_p(z = 1) + \pi_p(z = 0) \left( \frac{1}{2} P_i(y = 1 \mid z = 1; \beta^*_p) - P_i(y = 1 \mid z = 0; \beta^*_p) \right) \text{ Primary rate effect} \]

We have not added this to the paper. But we will if you like.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests

Reviewer's report
The authors consider the pediatric paradox and maternal race, and describe application of covariate density defined mixture of logistic regressions, a method they have developed and previously applied to assessment of the pediatric paradox and gestational age, maternal age, and maternal race (African American versus European American) in other published works. The authors fit these mixture models to data from a national birth dataset from the NCHS to assess direct and indirect effects of birth weight for ‘normal’ and ‘compromised’ births and observe indirect effects of birth weight, though only among ‘compromised’ births. The authors conclude that: while correct for ‘normal’ births, the hypothesis that birth weight is not a cause of infant mortality may not be true for compromised births; differential fetal loss may be responsible for the pediatric paradox, and; elimination of racial disparities requires consideration of race as well as birth weight.

The development of the method and use of the mixture models to fit the data provides another statistical approach to describe the birth weight paradox. Because the method has had limited use otherwise, additional explanation aimed at clarifying the method for general readership would be helpful. Given the authors’ previous published work applying the CDDmlr method to a large births dataset assessing racial disparities, additional discussion to clarify new developments and insights in the current manuscript would be of benefit.

The previous manuscript estimated European and African American models but did not compare the two. In this analysis we essentially determine to what extent the racial disparities are due to differences in birth weight (indirect effects) and independent of the differences in birth weight. In this case we are using a strategy very similar to Geneletti’s method of estimating direct and
indirect effects, except that our model is nonlinear. We have attempted in the new draft to clarify this issue.

Similarly, it would be helpful to better place the paper in context with other work aimed at resolving the paradox, including that cited by the authors. Other models have been proposed based on confounding and/or collider-stratification that fit existing data well and are consistent with birth weight having no direct effect on mortality. Additional discussion of the underlying biology and causal relations, as well as a comparison with the recently proposed alternative explanations for the paradox, would help clarify the implications of these findings for the readership.

We have added more detailed discussions of these in the background and discussion.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests

Reviewer's report

Title: Racial disparities in infant mortality: What has birth weight got to do with it and how large is it?

Version: 1 Date: 19 April 2010

Reviewer: Enrique F Schisterman

Reviewer's report:

The authors present here an interesting example that utilizes analytical techniques developed by the co-authors, in order to answer an important question regarding the role of differences in the birth weight distribution in describing racial disparities in infant mortality. The research question is well stated, and an important one in terms of potential policy implications.
Considerable attention is given to developing the methodology, and in applying it to the question of interest. However, many questions remain unanswered regarding the implementation, and appropriateness of the applied methods. The authors also fail to acknowledge other important developments in the literature relating to the issue of the pediatric (or birth weight) paradox and effect decomposition. Specific comments are given below.

Discretionary Revisions

1. The authors refer in several places to the “pediatric paradox”. Perhaps the authors could acknowledge that they are referring to what is also commonly known as the “birth weight paradox”.

   Done.

Minor Essential Revisions

1. The assumptions of the model itself are not made explicitly clear. A discussion of the assumptions, as well as the appropriateness of the assumptions in this scenario would be helpful for the reader to know when the model can/should be applied. Also, a discussion of other possible applications of the method would be useful.

   We have discussed the assumptions at length in the discussion.

2. The discussion of the pediatric paradox revolves in this case around racial disparities. However, as mentioned in the text, this phenomenon has been observed with various types of stressors. The authors conclude that the direct effect among compromised births is responsible for the pediatric paradox. However, there have been several developments in the literature that demonstrate that the crossing of the curves can be entirely explained by unmeasured confounding factors (Basso & Wilcox 2009), or if not due to unmeasured confounding, then due to an interaction between underlying conditions and birth weight (Hernandez-Diaz et al. 2008). The authors should acknowledge other work done in this area, and describe how their work fits into this body of research. The manuscript also states that a “long term goal is to categorize the various stressors known to influence infant mortality by their corresponding “direct” and “indirect” effects…” Thus, it seems that if this analysis is truly to be applied for each of the various stressors, there should be more of an in depth discussion of the biological rationale for direct and indirect effects for each of the factors. The biological rationale for the observed results should also be given in this case—how would race directly affect mortality (even if it is a proxy for another factor)?
We have included a discussion of the recent developments in the literature more fully. In general followed the same assumption that Hernandez-Diaz (also implicit in Wilcox Russell) in formulating our model. We view Basso and Wilcox 2009 is an explanation, for the reverse-J-shape of the birth weight specific mortality. CDDmrl can resemble this model as well (three Gaussian components with constant mortality on each component). However it is not clear that this model is identified at least in the logistic case. Our rationale in the previous draft and the current draft is that the race effects are likely due to differential fetal loss between the racial groups. This is a biological phenomenon and known to be higher in African Americans then European Americans. We have hypothesized that this is the unmeasured heterogeneity (confounding), which drives the latent characteristics of our model.

3. Can the authors provide a bit more explanation regarding the statement: “the ‘compromised’ subpopulation differs slightly from Wilcox’s ‘residual’ subpopulation given that it also accounts for births in the normal range”? In addition, how does this difference impact the results?

Our compromised subpopulation accounts for births in the normal birth weight range, as well as the majority of low birth weight and macrosomic births. Wilcox in his original model fit a pure normal to the central part of the birth weight distribution and only allowed contamination in the lower tail (and or upper tail). The difference is that our model fits birth weight distributions much better inspite of the fact that Wilcox’s original model has many more parameters. Wilcox’s original model fit the lower tails (and/or upper tail) perfectly. The better fit of our model is due to the fit at normal birth weights.

4. Conclusion #4 reads a bit awkwardly. Perhaps change “larger 3 or 4 fold” to “3 or 4 fold larger”.

We have rewritten the conclusions.

5. It is stated that the model attempts to correct for unexplained heterogeneity in the birth cohort, but no discussion is given to describe how this is achieved. Can the authors speak to this, and for what factors this may account for? In a similar vein, how do the given models adjust for confounding? And which covariates were adjusted for? What impact does this have on the results and interpretation?

We have addressed these issues more fully. The model corrects for this heterogeneity by dividing the birth cohort into two latent groups (which we call “normal” and “compromised”). They correct for heterogeneity in the same way that any dichotomous variable might (e.g. sex in a mortality analysis). We
have shown that this division into “normal” and “compromised” is statistically significant and informative about infant mortality. We have discussed this at some length in previous papers. We have also shown here that the direct effect of race in the compromised subpopulation is responsible for the “pediatric paradox” see graphs 2 and 3. The analysis does not at this point adjust for confounding of observed covariates.

6. Model Fitting section: First sentence is missing a closing parentheses.

Corrected

7. Model Fitting section: The authors state that the bootstrap results are “generally consistent” with conventional bootstrapping. Can the authors expand on what they mean by “generally consistent”?

That is they provide the same statistical result. We have deleted generally.

8. The authors hypothesize that the heterogeneity identified by the CDDmlr model is due to differential fetal loss. Can the authors give more rationale as to why they believe this to be the case? It seems that there could be several other factors that could also contribute to this heterogeneity, and it is unclear how the model corrects for the heterogeneity.

We would be open to other explanations. However, we cannot think of alternatives, which are compelling. The model corrects for this heterogeneity by dividing the birth cohort into two latent groups (which we call “normal” and “compromised”). They correct for heterogeneity in the same way that any dichotomous variable might (e.g. sex in a mortality analysis). We have shown that this latent division into “normal” and “compromised” is statistically significant and informative about infant mortality (in our earlier papers on CDDmlr).

Major Compulsory Revisions

1. The discussion section is lacking a thorough explanation of the strengths and limitations of the application of this method for effect decomposition. The advantages of this approach should be clearly described, and there are also several limitations worth noting. For example, issues of data quality should be addressed, as well as the impact of truncating the data at 500 g or >20 weeks gestation, and the specific advantages/disadvantages to the given analysis method.

Done.
2. Can the authors speak to how these methods compare to other common methods for effect decomposition? Placing these results and the CDDmlr method within the context of other methodological work done in this area would be extremely helpful. How do the assumptions of the current model compare to other models, and are they upheld in this case?

Done. Our method is essentially similar to that of Geneletti.

3. The conclusion made by the authors that the “true racial disparity is obscured by unobserved heterogeneity, probably due to differential fetal loss” is not substantiated by the data presented. The unobserved heterogeneity could be due to other factors, and the results here do not support this statement.

This is (and was) presented as a hypothesis. If it is true (we know there is greater observable fetal loss among African Americans) then uncontrolled confounding occurs between race and infant mortality, which biases the observed racial disparity.

4. The point is made that “Whatever causes the ‘pediatric paradox’ results in a reduction in the observed relative risk for the ‘compromised’ subpopulation. If it is fetal loss as we have hypothesized then it is possible for secular improvements in health...to cause a secular increase in the observed racial disparity.” The paradox can be explained by a number of factors—even unmeasured confounding—thus the authors should be careful to make such statements regarding the benefits of improvements in health based on the results of this study. It remains to be proven whether the direct and indirect effects can be estimated using the analytical methods used here, and how they compare with other techniques. The authors need to address these methodological issues and restate conclusions as necessary.

We have removed this section. We have added additional information concerning how our method fits into the various methods of estimating direct and indirect