Author’s response to reviews

Title: Poverty, urban-rural classification and term infant mortality: A population-based multilevel analysis

Authors:
Yousra Mohamoud (ymohamoud@wisc.edu)
Russell Kirby (rkirby@health.usf.edu)
Deborah Ehrenthal (ehrenthal@wisc.edu)

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To the Editor:

Kindly find enclosed our revised manuscript entitled ‘Poverty, urban-rural classification and term infant mortality: A population-based multilevel analysis’ (PRCH-D-18-00636), along with a point-by-point reply to each of the editor and reviewers’ comments.

We would like to thank you and the reviewers for the valuable feedback and suggestions, and the critical appraisal of our work. All of this input has substantially enriched our article and its contribution to the literature. We have revised our manuscript to address each of the editors’ and reviewers’ suggestions and comments and would be pleased to accommodate any other, should the editors or reviewers have any further suggestions. Please note that all line numbers that appear in this response refer to the clean version of the revised manuscript.

RESPONSE TO REVIEWERS

Bernardo Hernández Prado (Reviewer 1)

This is an interesting paper exploring the association of poverty and urban/rural classification with term infant mortality at the US, and controlling for individual factors. The authors make a good description of the problem in the introduction, and clearly describe the methods and results.
We greatly appreciate the reviewers’ thoughtful comments and the chance to revise this paper.

1. In the abstract, mention the number of births included in the analysis, it is impressive and I think should be highlighted.

We thank the reviewer for their suggestion. We have revised the manuscript accordingly (Page 2, line 55).

2. Background. I would suggest to revise the wording of the last paragraph (lines 87-90), where the authors state the purpose. It can be stated in a way simpler and more direct way. The last sentences (lines 91-93) may be better suited in the methods section.

Thank you for this suggestion. We have revised (lines 88-90) of the Background to state our objective more clearly. The lines now state: “The purpose of this study is to build on previous literature by investigating the association between socio-environmental factors and term infant mortality. Specifically, we aim to estimate the independent effect of county poverty and urban-rural classification on term infant mortality.” We also moved lines 91-93 to the Statistical Analysis portion of the Methods section (lines 145-147).


a) Page 5, line 105, why only singleton births?

The author raises a good question. The risk of mortality and morbidity among plural births is known to be different than for singletons [1, 2]. Therefore, it is common practice in the field to restrict analysis to singleton births unless the research question was specific to plural birth. Additionally, plural births make up a very small proportion of all births. In the case of our specific sample, plural births made-up less than 2% of all term births. We were faced with either adjusting for plurality in the model or limiting our analysis to singletons alone. We chose the latter in keeping with convention. However, we have run models on the whole data (plurals + singletons) adjusting for plurality and there were very small differences in our effect estimates from Model 4 and no change in the interpretation of our results. We highlight this in the Results section on of the revised manuscript (lines 220-222). The lines state: “Finally, we re-ran our final
model using the whole data (plurals and singleton births) this time adjusting for plurality and found very small differences in our effect estimates from Model 4 and no change in the interpretation of our results.

b) It is important to give more details about the cases that are excluded from the analysis (page 5, lines 108-114). The excluded States are either poor (Alabama, Arkansas, Mississippi), or rich (Connecticut). More important, cases were excluded because of missing data (we will know 10% in the discussion). Why these cases were lost? Which variables are missing? Is missingness at random? Can a bias be introduced because of this missingness? It is important to give more details here, and expand the corresponding discussion in the discussion section.

The reviewer raises several important points. First, as the reviewer noted the exclusion of data from 10 states due to their lack of implementation of the new birth certificate represents a lesser concern as it likely affects the generalizability rather than validity of our findings. This is because exclusion is determined by the state’s implementation of the new birth certificate, which in this case affects “poorer” states including: Alabama, Arkansas, Mississippi and West Virginia as well as “not so poor” states including New Jersey, Connecticut and Hawaii as well as states in the middle such as Maine, Rhode Island and Arizona. We are assuming that the state’s decision was independent of the characteristics of the individuals giving birth residing in these states. We consider the threat to the generalizability of our results a smaller threat since our data still covers 90% of births in the United States. This potential limitation is highlighted in the discussion section (lines 280-283).

We agree with the reviewer that the second missingness issue (cases excluded due to missing data) represents a greater concern. We conducted a missing data sensitivity analysis to examine patterns of missingness by each county level exposure. Most of the exclusions were driven by missingness in three variables: timing of prenatal care (4% missing), tobacco use during pregnancy (4.8% missing), and Medicaid (6.3%). Most of the missingness in these variables was to births in counties with high poverty and large urban counties. This suggests that if anything the relationship between these county level exposures and term infant mortality are likely underestimated in our models. We also found that missingness patterns are associated with state of residence as most of the missing observations came from three states: Georgia, Virginia and Michigan. This raises additional concerns regarding the generalizability of our results. We have taken the reviewer’s advice to expand the limitations sections in the revised manuscript. In the Methods section (lines 111-114) we now provide more details explaining that: “.. we excluded women with missing data on any covariate of interest to conduct complete case analysis. Ten percent of observations had missing information on a covariate of interest mainly on prenatal
care initiation (4%), tobacco use (5%) and payer source (6%).” We also provide more details in the Discussion section (lines 283-288). The revised manuscript now states: “Additionally, we had to exclude approximately 10% of our sample due to missing data on covariates of interest. Analysis of the missing information patterns across county level exposures shows that most missing observations were among births in high poverty and large urban metro counties. This suggests that we might be underestimating the association between county poverty and term infant mortality. Furthermore, most missing observations came from three states Michigan, Virginia and Georgia, which creates additional concerns about generalizability.”

c) Is it possible to mention the cut-off for the urban-rural categories (lines 120-122)?

We thank the reviewer for their valuable feedback. To improve paper’s clarity, we took the reviewer’s suggestion and expanded the methods section to describe the cut-offs for the urban-rural categories. The urban-rural classification categories used in our paper were defined by the National Center for Health Statistics (NCHS) to study the associations between urbanization level and health. The revised manuscript now includes the following description (lines 123-130):

“According to NCHS, metropolitan counties include: Large central metro counties defined as MSA of 1 million population that: 1) contain the entire population of the largest principal city of the MSA, or 2) are completely contained within the largest principal city of the MSA, or 3) contain at least 250,000 residents of any principal city in the MSA. Large fringe metro counties defined as MSA of 1 million or more population that do not qualify as large central Medium metro counties in MSA of 250,000-999,999 population. While small metro counties are counties in MSAs of population size less than 250,000. Nonmetropolitan counties include: Micropolitan counties in a micropolitan statistical area; and Noncore counties that are not in micropolitan statistical areas [3].”

4. Results:

a) I would start with the description of covariates (table 1) and then start describing infant mortality rate (reverse last 2 paragraphs of page 7).

We appreciate the reviewer’s suggestion. However, given that infant mortality rate is our main outcome of interest and county poverty and urban, rural classification our main exposures of interest we feel that it adds to both the clarity and strength of the manuscript to describe the distribution of our outcome across the main exposure of interest before describing the
distribution of potentially mediating and confounding variables. Therefore, we have opted to maintain the current order of paragraphs on page 7.

b) In this study, the individual variables can be located in the causal chain between poverty and term infant death (e.g. poor counties may have more tobacco consumption, less antenatal care, less maternal education, and therefore higher infant mortality rate). The authors do right in using a multi-level logistic regression approach to account for this. Using just a standard multiple regression approach may not be appropriate, because this fact may not be taken into account. But exactly because of that it is important for the authors to highlight the use of this type of model. When presenting the results and in table 2, models 2 and 3 are an interesting exercise, but I think more emphasis must be given in the results and discussion to model 4. This is the one in which we can see the association between poverty and urban/rural with term infant mortality properly adjusted by individual characteristics. This contribution has to be also highlighted in the discussion.

We appreciate the reviewer’s suggestion. We agree that Model 4 displays the results for our main objective of interest and have highlighted it more in the manuscript. We also believe that Models 1 and 2 have their own importance. They display the overall effect of poverty and urban-rural classification on term infant mortality, something that has not been estimated before. They also highlight the extent by which the association between these county variables and term infant mortality is explained by the characteristics of the individuals giving birth in these counties. Taking the reviewer’s suggestion into account, we have emphasized the relevance of Model 4 in the Results section of the revised manuscript by stating: “Model 4 adjusts for individual sociodemographic, maternal health and obstetric characteristics to isolate the effect of poverty and urban-rural classification on term infant mortality, our main objective of interest” (lines 202-203). We also highlighted the model’s geographic variation results (lines 210-214): “The multilevel approach used in our final model (Model 4) allowed us to estimate the random effect of geographic variation on term infant mortality. Compared to within county heterogeneity, the additional contribution of between-county heterogeneity to the overall variance was very small…”

Similarly in the Discussion section we say (lines 235-237): “Results from our final model (Model 4), show that though attenuated the observed gradient of poverty on term infant mortality persisted after adjusting for sociodemographic, maternal health and obstetric characteristics”. And (lines 248-250): “In the final multilevel model (Model 4), only very rural areas remained significantly associated with survival after adjusting for individual level maternal characteristics (OR: 1.2, 95% CI: 1.0, 1.3).”
c) Given the huge sample size, it is relatively easy to find significant results. I think the discussion of results should concentrate more on the change in magnitude of the estimates, and not only in their significance.

We absolutely agree with the author. Taking this advice into account we reworded the discussion section emphasizing the odds ratios and 95% confidence intervals rather than the p-values. See (lines 237-238) and (line 250) in the revised manuscript.

5. Taking advantage of the huge sample size, would it be possible to assess some interactions between poverty and urban/rural categories? It could be a "model 5", including the covariates in model 4 plus some interactions, and would let us know if the effect of poverty is similar or different across different categories of urban/rural counties.

Thank you for your suggestion. We agree that our huge sample size gives us an opportunity to test for interactions between poverty and urban/rural categories. We have done so (Methods, lines 153-154) and found no statistical evidence of an interaction between the two county variables p=0.49 (Results, lines 219-220). We conclude that there does not seem to be any evidence that the effect of poverty was different across different categories of urban/rural counties.

6. I think the authors can discuss more about limitations of the study: is it possible to have a bias due to missing information? Is the measurement of individual characteristics homogeneous across different levels of poverty and urban/rural counties?

We thank the reviewer for emphasizing this important point. We have expanded our limitations sections to include our results on a sensitivity analysis to check for potential bias due to missing information as previously suggested (See point 3b above). As to potential bias in measurement of individual characteristics across different county level characteristics, data for individual characteristics came from the birth certificate, while data for county level characteristics came from the census data; therefore it is unlikely that there would be information bias across the county level measures. However, as we highlighted in the paper (lines 293-298) “Census data might not accurately characterize the demographic context of study subjects because of the requirement of residential address and because of the undercount, which chiefly affects poor
people and people of color [4]. However, undercount and missing residential address would most likely dilute the association between term infant mortality and poverty, since it produces conservative estimates of the number and hence proportion of poor persons and people of color”.

7. Figure 1: is it possible to include the confidence interval around the estimates provided in each bar?

Thank you for this suggestion. We have modified the figure to include confidence intervals and improved its clarity and quality.

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

No - there are minor issues

OVERALL MANUSCRIPT POTENTIAL - Could an appropriately REVISED version of this work represent a technically sound contribution? Probably - with minor revisions
PEER REVIEWER COMMENTS:

GENERAL COMMENTS: This is in my assessment: a very relevant and very well conducted analysis. A strong paper.

We thank the reviewer for the kind words.

REQUESTED REVISIONS:

I have read this paper with great interest, and highly value the efforts made and the approach taken by the authors. In essence, the authors confirm the overall high neonatal and infant mortality in term cases in the US, with a significant, but also strong association to poverty (OR up to 1.8), even in term cases. This really is a call to action observation, since it is very reasonable to assume that the overall infant mortality in term cases should be 'the best' outcome and this signal is likely only to be worse if we also consider preterm delivery and subsequent outcome (both mortality and morbidity). I have read this paper with a background of a non US colleague (at least at present not active in the US), and therefore I do have some suggestions/considerations to further improve the messages, also for non US readership.

We greatly appreciate the reviewer’s thoughtful comments that improve the quality and clarity of our paper. We respond to the each reviewer’s comment below.

We adjusted for medical payer source (Medicaid yes/no) as a proxy for individual income to further isolate the effect of county poverty from individual socioeconomic status = please elaborate this a little bit more, since the Medicaid is a specific US topic (why is this a proxy).

Thank you this is an important point we do need to clarify. Medicaid is a program that provides health coverage to eligible low-income adults, children, pregnant women, elderly adults and people with disabilities. It is administered by states, according to federal requirements. There are different financial and non-financial criteria that determine Medicaid eligibility. For our population of interest, to be eligible for Medicaid women giving birth have to have a household income below a certain definition of Federal Poverty level that may vary by state. Therefore, women on Medicaid have “low income” and women not on Medicaid (private insurance, self-
pay) are “not low income”. In this way medical payer source can be a proxy for individual income status. To clarify this we have revised the Methods section (lines 136-139) to state: “We adjusted for medical payer source (Medicaid yes/no) as a proxy for individual income to further isolate the effect of county poverty from individual socioeconomic status. Medicaid provides health coverage to eligible low income individuals, therefore having Medicaid as payer source can be a proxy for low individual socioeconomic status, compared private or self-pay.”

It is worth to add a 'map' of the US to highlight all the states/counties with the different 'poverty' levels, to get an idea on the granularity of the data, and to highlight the national relevance of this paper?

We agree with the reviewer. We have received permission to include a map from the US Census highlighting the distribution of poverty for children less than 18 across counties in the US. We refer to this figure in the Discussion section (lines 231-234): “Still, more than 1 in 4 women giving birth in the US live in counties where more than 20% of children live below the poverty level [5]. Figure 2 was produced by the US Census bureau highlighting the distribution of poverty for children less than 18 years across counties in the United States [6].”

The increase in OR is very 'steep', so not only the overall mortality rate is rather high for a high income country, but also the relationship between poverty and mortality is strong. How does this second aspect compare to the Swedish data discussed in the discussion section?

This is a good question though one that is difficult to answer given that we do not have access to Swedish data. However, in the paper cited in the discussion- which the reviewer refers to- the authors do indicate that in Sweden “social differences in infant mortality (as measured by maternal education) exist but are small in comparison to other countries [7].” The authors give examples of Swedish research that found that there is only 40% excess mortality risk among Swedish infants born to women with less education compared to those with higher educational levels. In comparison, for the same time period, US babies born to white mothers with low education had 2.3 times higher mortality risk, and to black mothers with low education had 3.9 times higher mortality risk compared to those born to college educated white mothers. The authors also suggest that in Sweden this modest association between education and infant mortality held true across other definitions of social class [7].
Minor:

Figures as provided are hard to read, please check on quality of these documents.

Thank you for this suggestion. We have modified the figure to include confidence intervals and improved its clarity and quality.

ADDITIONAL REQUESTS/SUGGESTIONS:

Minor suggestions are provided above to further improve the paper.

References:


