Author's response to reviews

Title: Association between 24-hour blood pressure variability and chronic kidney disease: A cross-sectional analysis of African Americans participating in the Jackson Heart Study

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Author's response to reviews: see over
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Re: MS 2129233902161143

Dear Dr. Sozio:

Thank you for reviewing our manuscript entitled, “Association between 24-hour blood pressure variability and chronic kidney disease: A cross-sectional analysis of African-Americans participating in the Jackson Heart Study.” Attached please find the revised manuscript for resubmission. Our responses to the review are outlined below, with pertinent changes to the manuscript in highlight to ease your review.

We appreciate the comments and suggestions of the reviewers, and have made changes as appropriate. The reviewers’ insightful suggestions have resulted in a manuscript that is markedly improved. Finally, we have accounted for the formatting, word count and style recommendations of the journal. Thank you very much.

Sincerely yours,

Paul Muntner, PhD
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REVIEWER 1 COMMENTS

1. BPV is rather a wide concept that depends on the time range considered. Authors must be more precise when they state that 'CKD is associated with higher BP variability'. 24h BPV is commonly considered the short term BPV as it differs for example from the long term BPV calculated on a visit-to-visit basis. This needs to be clarified both in the methods and discussion sections.

Response: We appreciate the reviewer’s comment and the importance of this distinction. In the revised manuscript, we have added “24-hour” or “visit-to-visit” to each mention of BP variability, except in the fourth paragraph of the discussion, when we are referring to BP variability in general.

2. How did the authors chose the determinants for the multivariate analysis? Did they adopt the determinants which were significantly associated with the outcome parameters in the univariate analysis? Also I assume the variables are normally distributed?

Response: We used a priori selected variables for our multivariable analysis. This has been clarified on page 7 of the revised manuscript. This approach has been recommended in prior studies (Hernán, Am J Epidemiol 2002).

3. The authors did consider only SD and ARV as BPV parameters. However it would be important to try to better describe BPV adding other parameters for example dipping status.

Response: Thank you for your comment. Other Jackson Heart Study investigators are studying diurnal BP patterns such as dipping in a separate manuscript. Therefore, we were not permitted to use these phenotypes in the current study.

4. Supplemental Table 2 is rather difficult to interpret. I don’t see the p value for the t statistic tests.

Response: We have added p-values to supplemental tables 2 and 3. Also, we have revised the titles of these tables for clarity.

5. Do the authors have any data on the type of BP lowering medications? It would be interesting to know if a specific class of antihypertensives is associated with lower BPV in patients with CKD

Response: We have added antihypertensive medication classes to the revised table 1 and supplemental tables 2 and 3. Individuals with CKD were more likely to be taking an ACE inhibitor or calcium channel blocker compared to those without CKD. Alpha blocker use was associated with higher SD$_{24h}$ of SBP among participants with CKD. We added a description of these findings to the revised manuscript on pages 8 and 9.

REVIEWER 2 COMMENTS

6. I would urge caution at using strong language suggesting an association between BP variability and CKD (lines 223 - 224, lines 281 - 282).
Response: We appreciate your comment. In response, we have revised these lines as follows:

Lines 223-224: “This population-based study of African American adults suggests an association between CKD and higher SD_{dn} of BP and ARV of DBP.”

Lines 281-282: “In conclusion, data from the current study suggest that CKD may be associated with higher SD_{dn} of SBP and DBP and ARV of DBP over 24-hours.”

7. In table 2 and 3, should there be a unit of measurement associated with the BP variability measure (eg mmHg)? It is not entirely clear from reading the table.

Response: We have revised the two tables to include the units of BP variability (mm Hg).

8. The strengths and limitations may be better placed in the discussion section rather than the conclusions section.

Response: Thank you for the suggestion. In the revised manuscript, we have made the strengths and limitations the final paragraph of the discussion section.

9. It would be helpful to know the number of antihypertensives used by the two populations, and the distribution of RAAS blocker, alpha blockers etc. One of the postulates put forward is autonomic dysfunction, and the authors mention adjusting for antihypertensive use, but it would be interesting to see if there were differences in the use of those medications and what kind. This could be displayed in Table 1.

Response: We appreciate your comment. We present these data in Table 1 of the revised manuscript.

10. Furthermore, some studies have looked at levels of markers of adrenergic activation such as plasma metanephrines to delineate the cause of BP variability. Was there any attempt to do so by the authors in this study?

Response: Unfortunately, the Jackson Heart Study does not have data on plasma metanephrines. We recognize this as a limitation of our study on page 12 of the revised manuscript. Specifically, we state, “We were not able to assess the effect of plasma metanephrines, a marker of adrenergic activation, on 24-hour BP variability.”

11. Was there any analysis regarding visit to visit variability? This is an important metric that has been shown to have associations with cardiovascular events as shown by a recent meta analysis by Diaz et al in hypertension in 2014. They did not specifically look at CKD. It would be interesting to know if there was a relationship present.

Response: We appreciate your comment. While we agree that this would be interesting, we do not think that it would be appropriate to study visit-to-visit BP variability in the Jackson Heart Study. Specifically, studies have shown that 5-7 visits over a period of months is optimal for the assessment of visit-to-visit variability (Levitan, J Clin Hypertens 2012). The Jackson Heart Study has only 3 visits and they are 4 years apart, which we feel would not yield a good measure of visit-to-visit BP variability.

12. Was heart rate variability assessed in the study?
Response: Heart rate variability was assessed in the Jackson Heart Study. However, heart rate variability is a different phenotype with separate underlying physiologic mechanisms. Given the amount of data in the current manuscript, we think it would be best to present the association between chronic kidney disease and heart rate variability in a separate manuscript. This presents an opportunity for future research.