Author's response to reviews

Title: Periodontal disease, chronic kidney disease and mortality: Results from the Third National Health and Nutrition Examination Survey

Authors:

Ana C Ricardo (aricar2@uic.edu)
Ambarish Athavale (dr.ambarish@yahoo.com)
Jinsong Chen (jinsongc@uic.edu)
Hemanth Hampole (hhampole@uic.edu)
Daniel Garside (garside@uic.edu)
Phillip Marucha (marucha@ohsu.edu)
James P Lash (jplash@uic.edu)

Version: 3 Date: 30 May 2015

Author's response to reviews: see over
May 30, 2015

Deidra Crews, MD
Associate Editor
*BMC Nephrology*

Dear Dr. Crews,

We appreciate the Editor and Reviewers’ thoughtful and thorough review of the manuscript “Periodontal disease, chronic kidney disease and mortality: Results from the Third National Health and Nutrition Examination Survey” which was submitted for consideration to be published in *BMC Nephrology*.

Please find enclosed a point-by-point description of the changes made in response to the Editor and Reviewers’ recommendations.

Sincerely,

Ana C. Ricardo, MD, MPH, MS
Author's response to reviews

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Version: 2 Date: 30 May 2015

Author's response to reviews: see over
EDITORIAL COMMENTS

1. Please add some additional details to the Introduction to define periodontal disease and briefly mention the mechanisms by which it may be causally associated with CKD and mortality.

   - We appreciated the Editor’s recommendation. We have expanded the introduction of the revised manuscript to include the definition of periodontal disease as well as an outline of the potential mechanisms by which periodontal disease might be associated with CKD and mortality (Page 3, lines 9-21).

2. In the Methods section, please detail the definitions/measurement of all covariates mentioned later in the manuscript in the text or tables (i.e. fibrinogen, family history of CVD, income, etc.). Please also describe how cardiovascular mortality was defined (i.e. what NDI codes were included). The Fibrinogen sensitivity analysis performed should be mentioned in the Methods.

   - As suggested by the Editor, the revised methods section includes a description of each variable mentioned in the manuscript (Page 5, line 26 and Page 6, lines 1-20) as well as the codes used to define cardiovascular mortality (Page 5, lines 19-22). The sensitivity analysis previously conducted by adding fibrinogen to fully-adjusted regression models, and reported in the original submission is not presented in this revision in response to the recommendation from Reviewer 1 of removing inflammatory markers from the regression model to avoid adjusting for factors in the causal pathway between periodontal disease and mortality.

3. In the Results section, please detail which covariates were missing. The total of 1,596 excluded due to missing covariates is substantial, and concerning for potential selection bias. Please add the p interaction for CKD x periodontal disease in the fully adjusted model

   - The revised results section includes detailed information regarding the number of individuals missing specific covariates, and also a comparison of demographic characteristics of individuals included vs. excluded from the analysis due to missing data (Page 7, lines 22-26; Page 8, lines 1-2).

   - The p value for interaction is included in the revised manuscript (Page 9, line 7-8).

REVIEWER 1

Title: Periodontal disease, chronic kidney disease and mortality: Results from the Third National Health and Nutrition Examination Survey

Version: 2 Date: 22 March 2015

Reviewer: Vanessa Grubbs
Reviewer's report:
The authors used NHANES III data linked with mortality data to examine the association of periodontal disease and/or CKD with cardiovascular death and all-cause mortality. This manuscript is well-written, important, and interesting.

Major Compulsory Revisions:
None

Minor Essential Revisions
1. How was cardiovascular mortality defined--what diagnoses were included?
   - The codes used to define cardiovascular disease were included in the revised methods section of the manuscript (Page 5, lines 19-22).

2. In Discussion, authors assert that only small Japanese study examined association between periodontal disease and renal outcomes. This is not true. Shultis and colleagues did (Diabetes Care 2007); this work should be cited.
   - We appreciate the reviewer’s recommendation and reference provided which has been incorporated in the revised manuscript discussion section (Page 10, lines 17-19)

3. Suggest adding a line to page 10 in Discussion. Yes, not having interval dental treatment data is a limitation, but would expect this to bias findings towards the null.
   - The reviewer brings up a very important point which has been included in the discussion section (Page 12, lines 5-6)

Discretionary Revisions
1. It unclear why "dental care use" is included as a covariate. It seems lack of dental care may have a lot to do with getting periodontal disease, but would be highly correlated with periodontal disease.
   - As pointed out by the reviewer, the correlation between periodontal disease and dental care was high. Therefore, we have removed dental care from the regression models.

2. Similarly, it seems inflammatory markers would be on the causal pathway between periodontal disease and mortality, so should not be adjusted for.
   - As stated in the revised introduction (Page 3) and indicated by the reviewer, inflammation has been postulated to play an important role in the causal pathway connecting periodontal disease with adverse outcomes. Therefore, we have removed C-reactive protein, white blood cell count and fibrinogen from the regression models (Page 5, lines 5-8).
Major Compulsory Revisions
1. Since you are evaluating the joint effect of two exposures, it is essential to add tests for additivity and multiplicativity. This would require examination of association of each exposure (CKD and periodontal disease) for marginal estimates as well.

   - As recommended by the reviewer, we conducted additional analyses testing for additivity and multiplicativity between periodontal disease and chronic kidney disease on the outcomes of all-cause and cardiovascular mortality. As noted in the results section of the revised manuscript, we found no evidence of additivity or multiplicativity (Page 9, lines 6-8).

Minor Essential Revisions
1. Please check use of abbreviations, varies back and forth between abbreviation and full word(s) such as BMI, CVD, etc. Make sure all abbreviations are spelled out at first use and then consistently used throughout the manuscript.

   - We have carefully reviewed the manuscript to ensure that every abbreviation is spelled out at first use and used consistently throughout the manuscript.

2. Please describe in the methods section the statistical tests used for p-values in table 1.

   - The statistical test used in table 1 are described in the revised methods section (Page 6, line 26 and Page 7, line 1).

3. Please do not refer to table 1 as bivariate analyses.

   - This mistake has been corrected.

4. Please explain if differences in lab measurements are also clinically different as well as statistically different.

   - Given the magnitude of the differences, it is unclear whether they are also clinically significant. This statement has been included in the revised manuscript (Page 8, lines 18-20).
5. Page 7, line 17 use these "differences" were not statistically significant in place of "associations"

- This changed is reflected in the revised manuscript (Page 8, line 19)

6. Please revise Background Paragraph: indicated CKD stages 1-5 affects approximately 26 million. Add "is" for It is well established on line 3, on line 4 mortality "compared to" the general population in place on "than", and line 6 replace "this" population with "the CKD" population.

- The recommended changes were made (Page 3, lines 1-6)

7. A figure and potentially a cross table to evaluate additivity and multiplicativity would be helpful in visualizing and understanding results.

- We agree with the reviewer that a figure or a table will be helpful in understanding the results. However, given that we found no evidence of additivity or multiplicativity we decided not to include it.

8. Authors indicated a possible causal pathway regarding inflammation. I believe that this can be developed a bit more regarding what is known about the two exposures individually and the CVD and non-CVD mortality outcomes. Also please comment on the differing results for the two outcomes studied.

- As mentioned above (Editorial Comment #1), we expanded our introduction to include a brief description of the potential pathways linking periodontal disease with chronic kidney disease and mortality (Page 3). A comment regarding the differing results between all-cause and cardiovascular mortality was added to the discussion (Page 11, lines 5-7)

9. What do the authors conclude regarding a non-significant test for interaction, but still write in conclusions "This study provides the first evidence that periodontal disease increases the risk of mortality in individuals with CKD"?

- In the revised manuscript we clarified that the statement above which has been modified (Page 11, line 14), refers to analyses stratified by CKD status (Page 9, lines 10-12).

Reference List