Author's response to reviews

Title: Age-related associations of hypertension and diabetes mellitus with chronic kidney disease

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Author's response to reviews: see over
March 17, 2009

Editor,
BMC Nephrology

Dear Sir/Madam:

Thank you for reviewing of our manuscript entitled, “Age-related associations of hypertension and diabetes mellitus with chronic kidney disease”. Attached please find the revised manuscript for resubmission. Our responses to the review are outlined below, with pertinent changes to the manuscript highlighted to ease in your review. We appreciate the comments and suggestions of the reviewers, and have made changes as appropriate. Thank you very much.

Sincerely yours,

Paul Muntner, PhD
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Reviewer 1
Comment 1. 1) The authors have presented cholesterol data in the abstract that is significant at a p=0.07, but yet haven't established why this is being presented as an outcome? I would only suggest to remove this from the abstract and concentrate on presenting the prevalence ratios for proteinuria as this may be more relative to the hypothesis and support the conclusions made.

Response: We have removed the cholesterol results from the abstract. However, to reflect the results presented in the full manuscript, we think it's important to present both CKD and albuminuria in the abstract.

Comment 2. I presume the investigators are looking at risk factors for CKD and did include diabetes, hypertension, dyslipidemia, proteinuria and didn't report obesity as it relates to age?

Response: The obesity results have been included in the revised manuscript on pages 9 and 10. Specifically, we state:

No patterns were present across age groups in the prevalence ratio of stage 3 or 4 CKD associated with … obesity (Table 2).

…..progressively weaker associations of albuminuria with female gender, obesity, and high cholesterol at older age groups were present (Table 4).

Comment 3. In the limitations section would also make a comment that with the cross-sectional design and the small sample size in those <50 conclusion can not be made on population attributable "risk" as well as causality.

Response: We agree that the small sample size for the CKD results is a limitation. Due to the small number of NHANES participants < 50 years with CKD, some of the point estimates may be unstable. This has been added to the limitations section (page 14). Of note, the NHANES analytic guidelines specifically state that results based on small sample sizes should not be suppressed. We note results in Tables 1 and 2 that are based on small sample sizes with an asterisk and footnote in the revised manuscript. Given the higher prevalence of albuminuria, this is only an issue for prevalent CVD among individuals <50 years of age. This has been noted in Tables 3 and 4.

Reviewer 2.
Comment 1. The study of US veterans cited on p.11 should have a reference at the end of the sentence.

Response: We apologize for this omission and have added this citation (O’ Hare 2006).
Comment 2. I think the last sentence before the “Implications” section (p.15) should end with “albuminuria at older ages is noteworthy” (the word “ages” is missing)

Response: We apologize for this typo. This sentence has been corrected by adding the word “ages” such the sentence now reads:

The consistency of the trends of lower prevalence ratios for both stage 3 or 4 CKD and albuminuria at older age is noteworthy.

Comment 3. In addition to the Rule paper cited, I recommend also considering that there paradoxically may be less bias in the MDRD-based CKD designation among younger people than older ones, since MDRD makes age such a large component of GFR.

Response: This is an interesting point. While this hypothesis could explain the association reported, we are unaware of data showing the bias in the MDRD equation is larger among younger versus older individuals. We have added a sentence on page 15 of the revised manuscript:

The differential impact of the MDRD study equation on classifying CKD by age group warrants further study.

Reviewer 3.
Comment 1. If someone uses anti-hypetensive medications, the prevalence data of hypertension is not completely defined. The prevalence ratio of high-cholesterol should be also modified by the use of lipid-lowering drugs. From these aspects, the author should re-analyze these data.

Response: We apologize for the lack of clarity in describing the definition of hypertension and high cholesterol. Individuals were defined as having hypertension and high cholesterol if they were taking antihypertensive medications or lipid lowering medications, respectively. This is clarified on page 6 of the revised manuscript:

“Three blood pressure measurements were obtained using a standard protocol and hypertension was defined as an average systolic or diastolic blood pressure ≥140 mmHg or 90 mmHg, respectively, or current use of blood pressure lowering medication” and “high cholesterol was defined as total cholesterol ≥240 mg/dL or pharmacologic lipid lowering treatment.”

Comment 2. The number is not 12778 from the data of Table 3 (should be 12798).
Response: We apologize for the typo. The correct sample size is 12778. This error has been corrected in table 3 of the revised manuscript where the number of individuals \( \geq 70 \) years without albuminuria is 1925 and not 1945 as was reported in the original manuscript submission. We have carefully reviewed the manuscript and have not identified other typos.

Comment 3. The prevalence data is different from the Data of Table 1. They should be 1.2\%, 9.5\%, 37.6\% among 20-49, 50-69, >70 years, respectively. From calculating the data of Table 3, prevalence ratio of albuminuria was 6.8\%, 14.8\%, 26.8\% among 20-49, 50-69, >70 years respectively.

Response: The sample sizes in Tables 1 and 3 do not reflect the weighting that were incorporated in the prevalence estimates per the analytic guidelines in NHANES. Specifically, the prevalence estimates are weighted to reflect the overall prevalence among US adults. We have added the weighted prevalence to Tables 1 and 3 along with a footnote indicating that the prevalence of CKD and albuminuria reported are weighted. Specifically, the footnote states:

†Weighted albuminuria prevalence calculated by applying NHANES 1999-2004 sampling weights

Reviewer 4.

Comment 1. Please run additional analyses using the gender-specific albuminuria cutoffs, which are frequently used in research papers, in order to show that the results are robust to changing definitions.

Response: We have repeated the analyses using gender-specific cut-points (\( \geq 20 \) mg/g among men and \( \geq 30 \) mg/g among women; de Jong and Curhan 2006). The results are markedly consistent (see Table below). On page 7 of the revised manuscript we have added a sentence to the methods on page stating that the albuminuria analyses were repeated using gender-specific cut-points for defining albuminuria with markedly consistent results.

Prevalence ratios of albuminuria (using gender specific cut-points - \( \geq 30 \) mg/g among men and \( \geq 20 \) mg/g among women) associated with selected risk factors by age group.

<table>
<thead>
<tr>
<th></th>
<th>Age 20 to 49 years</th>
<th>Age 50 – 69 years</th>
<th>Age ≥ 70 years</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black race</td>
<td>1.17 (0.96 – 1.42)</td>
<td>1.36 (1.08 – 1.71)</td>
<td>0.95 (0.77 – 1.18)</td>
<td>0.087</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.88 (0.74 – 1.06)</td>
<td>0.68 (0.55 – 0.83)</td>
<td>0.62 (0.53 – 0.73)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td>1.28 (1.01 – 1.62)</td>
<td>1.21 (0.94 – 1.57)</td>
<td>1.44 (1.11 – 1.87)</td>
<td>0.862</td>
</tr>
<tr>
<td>Obese</td>
<td>1.25 (0.95 – 1.64)</td>
<td>1.25 (0.98 – 1.60)</td>
<td>1.10 (0.91 – 1.34)</td>
<td>0.065</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.12 (1.50 – 2.99)</td>
<td>1.36 (1.08 – 1.71)</td>
<td>1.45 (1.12 – 1.87)</td>
<td>0.016</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>1.05 (0.78 – 1.41)</td>
<td>1.02 (0.83 – 1.25)</td>
<td>0.90 (0.74 – 1.09)</td>
<td>0.093</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed diabetes</td>
<td>3.63 (2.51 – 5.25)</td>
<td>2.55 (1.99 – 3.27)</td>
<td>1.43 (1.16 – 1.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Undiagnosed diabetes</td>
<td>4.96 (2.91 – 8.47)</td>
<td>2.88 (1.84 – 4.51)</td>
<td>1.56 (1.06 – 2.30)</td>
<td>0.003</td>
</tr>
<tr>
<td>Prevalent CVD</td>
<td>0.95 (0.38 – 2.41)</td>
<td>1.22 (0.92 – 1.63)</td>
<td>1.08 (0.88 – 1.34)</td>
<td>0.886</td>
</tr>
</tbody>
</table>
Numbers in table represent prevalence ratio (95% confidence interval)  
Adjusted for age, race, sex, hypertension and self-reported diabetes (except hypertension which is adjusted for age, race, sex, and diabetes and diabetes which is adjusted for age, race, sex and hypertension)

Comment 2. Since results from NHANES are often cited as representative estimates, the NCHS is concerned about unreliable results generated from small sample sizes. While all results should be reported, those that are not reliable should be noted with an asterisk, so that future authors do not cite them as "fact" (e.g. 12.5% of blacks aged 20-49 have Stage 3-4 CKD) based on a handful of individuals.

Response: As noted in our response to comment 3 from reviewer 1, we have added asterisks where appropriate in Tables 1 and 3.

Comment 3. What was done to account for missing data? Clearly multiple imputation is ideal, but if those cases were simply excluded the authors should at least report whether differences of large magnitude were seen between included and excluded participants.

Response: We agree that multiple imputation is a useful approach for the adjustment of covariables. However, we chose not to impute key variables (serum creatinine, urinary albumin or creatinine, blood pressure, etc.) in the current analysis. As such, we have excluded individuals missing these data. We have conducted an analysis to ascertain differences in individuals missing versus not missing serum creatinine and urinary albumin or creatinine data. Specifically, we state the following on Page 5 of the revised manuscript:

Women and non-Hispanic blacks were more likely than men and non-Hispanic whites to be missing serum creatinine while older participants and non-Hispanic blacks were more likely than younger individuals and non-Hispanic whites to be missing urinary albumin or urinary creatinine data.

Comment 4. The discussion paragraph identifying reasons for the "weaker" association between HTN/DM and Stage 3/4 CKD in older age needs more careful consideration and discussion. Currently, readers are left with the impression that lead and cadmium exposure play a large part in CKD among older adults. For one thing, there are some local obstructive processes more common in older adults that may play a role, such as BPH with obstruction, other intraabdominal tumors, etc. Secondly, there are a subset of older people with cardiovascular disease who do not have DM/HTN, and these people are going to be at high risk for CKD (consider myocardial infarction, CHF, renal artery stenosis and how they may affect renal function).

Response: We agree that the reasons for the associations observed in the current study are unknown and may include obstructive disease. We have added this to the discussion on page 13 such that we mention environmental exposures, nephrotoxic...
medications and obstructive diseases as potential factors may contribute to the high prevalence of kidney disease in older adults.

Comment 5. The authors need to explore what I consider to be the primary contribution of this manuscript, namely the association between DM/HTN and CKD at younger ages in the context of higher mortality of CKD at younger ages. As few CKD cases progress to ESRD, a major public health benefit of identifying Stage 3 and 4 CKD is the aggressive prevention of CHD mortality. The results of this paper suggest that CKD may be a different condition at the physiologic and tissue level among younger adults, due to different etiologies. Are some of subclinical differences tied to age-related differences in CKD mortality? At the least, the authors should call for additional studies of these issues.

Response: This is an interesting point. We agree that the aggressive prevention of CHD is important in individuals with CKD. Furthermore, the study highlights that CKD in young adults may be a physiologically different condition in young adults. Unfortunately, we do not have data available to explore this hypothesis. We have added two sentences on the bottom of page 13 and top of page 14 of the revised manuscript calling for studies of physiological differences in CKD at different ages. Specifically, we state:

Furthermore, the age-dependent association between hypertension and diabetes with CKD suggests that it may be a different physiologic condition when present in younger versus older adults. Future studies are needed to evaluate these differences by age.

Comment 6. Were menstruating women really excluded from the analyses of Stage 3-4 CKD? I can't think of why this would be necessary. This should be clarified and explained if this was done.

Response: We apologize for this typo. While pregnant women were excluded from the current analyses, menstruating women were not excluded. This has been corrected in the revised manuscript.

Comment 7. Are a "history of diabetes mellitus" and "self-report of a prior diagnosis of diabetes mellitus" the same thing?

Response: We had used these terms inter-changeably in the original submission. However, we understand the confusion that could arise. Therefore, we have changed the term “history of diabetes mellitus” to “self-report of a prior diagnosis”.

Comment 8. Please drop the sentence on the prevalence rates for high cholesterol from the abstract; this is distracting and does not fit with the main thrust of the manuscript.
Response: To make the abstract easier to interpret we have removed the cholesterol results from the abstract.

Comment 9. I would like to see a sensitivity analysis defining diabetes as only a self-report of a prior diagnosis of DM. While I understand that this may incorrectly capture some patients without DM (e.g. people who misunderstood a prior diagnosis of GDM) I am concerned that some older patients with DM (75-80 years old) may not be on antiglycemic medications. These patients have little to gain in the way of long-term glycemic control, and a high risk of complications from hypoglycemia as medications are excreted more slowly in renal failure. Such a sensitivity analysis would reassure me that the association between DM and CKD is not being underestimated at older ages.

Response: We have repeated the analyses defining diagnosed diabetes mellitus based on self-report. As noted in tables below, the results are markedly similar.

<table>
<thead>
<tr>
<th>DIABETES BASED ON SELF-REPORT (IGNORING MEDICATION USE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 20 to 49 years</td>
</tr>
<tr>
<td>Stage 3 – 4 CKD</td>
</tr>
<tr>
<td>No (N=6164)</td>
</tr>
<tr>
<td>1.4%†</td>
</tr>
<tr>
<td>No (N=3346)</td>
</tr>
<tr>
<td>11.6</td>
</tr>
<tr>
<td>No (N=1612)</td>
</tr>
<tr>
<td>12.5</td>
</tr>
</tbody>
</table>

Table 2 - Prevalence ratios of stage 3-4 chronic kidney disease associated with selected risk factors by age group.

<table>
<thead>
<tr>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed diabetes, %</td>
</tr>
<tr>
<td>Age 20 to 49 years</td>
</tr>
<tr>
<td>2.8</td>
</tr>
<tr>
<td>11.6</td>
</tr>
<tr>
<td>12.5</td>
</tr>
</tbody>
</table>

Table 3- Demographic characteristics and cardiovascular disease risk factors among NHANES 1999-2004 with and without albuminuria by age grouping

<table>
<thead>
<tr>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed diabetes, %</td>
</tr>
<tr>
<td>Age 20 to 49 years</td>
</tr>
<tr>
<td>2.2</td>
</tr>
<tr>
<td>9.8</td>
</tr>
<tr>
<td>12.1</td>
</tr>
</tbody>
</table>

Table 4 - Prevalence ratios of albuminuria associated with selected risk factors by age group.

<table>
<thead>
<tr>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed diabetes, %</td>
</tr>
<tr>
<td>Age 20 to 49 years</td>
</tr>
<tr>
<td>4.03 (2.80 – 5.80)</td>
</tr>
</tbody>
</table>
Comment 10. Is it necessary to mention the medical centers that analyzed the labs in NHANES?

Response: This information has been deleted from the revised manuscript.

Comment 11. I do not understand the relevance of glycated hemoglobin among non-DM patients and would drop that from the tables, or limit it to patients with DM.

Response: We have removed glycated hemoglobin from the table.

Comment 12. The last sentence of the manuscript comes out of left field, and I would drop this since the issue of prevention is really not mentioned in the paper.

Response: We have deleted this sentence from the manuscript.

Reviewer 5.
Comment 1. Approximately 18\% of the NHANES participants are excluded from the study for the analysis of stage 3-4 CKD and 17\% from the analysis of albuminuria. Are the study samples still representative of the overall population? A comparison of the demographic characteristics between the study samples and NHANES would be helpful.

Response: We have conducted an analysis to ascertain differences in individuals missing versus not missing serum creatinine and urinary albumin or creatinine data. Specifically, we state the following on Page 5 of the revised manuscript:

Women and non-Hispanic blacks were more likely than men and non-Hispanic whites to be missing serum creatinine while older participants and non-Hispanic blacks were more likely than younger individuals and non-Hispanic whites to be missing urinary albumin or urinary creatinine data.

Comment 2. The attenuation of the association between exposure (hypertension or diabetes) and CKD at older age is very likely due to the higher prevalence of CKD among the non-exposed in older adults. Consequently, the difference between the prevalence in the exposed and the prevalence in the non-exposed is expected to be smaller among the elderly than among the young adults. The authors address this issue in the discussion page 13 but do not base their discussion on concrete results and do not provide a clear conclusion. The prevalence of CKD in the non-exposed groups by age-group should be presented in the results section and this issue discussed earlier in the discussion section.

Response: A side-by-side comparison of the prevalence of CKD and albuminuria is presented in the bottom of tables 1 and 3 of the revised manuscript. This highlights a
larger absolute difference in the prevalence of CKD and albuminuria comparing individuals with versus without risk factors (e.g., hypertension or diabetes) at younger ages. This is noted on page 13 of the revised manuscript where we state:

However, the absolute difference in the prevalence of hypertension and diabetes mellitus for those with and without stage 3 or 4 CKD and albuminuria was also larger among younger versus older adults.

**Comment 3. What is the rationale for not including undiagnosed diabetes (in addition to diagnosed diabetes) among the confounders in the regression models?**

Response: By design, only a sub-sample of NHANES participants was asked to fast overnight prior to their study visit. Therefore, fasting glucose, and undiagnosed diabetes, is not available on a majority of the NHANES sample (see Page 6 of the revised manuscript). Adjusting for undiagnosed diabetes would result in relying on a sub-sample of participants. We have added a sentence to the revised manuscript (page 8) indicating why undiagnosed diabetes mellitus is not included in all analyses. Specifically, we state:

Undiagnosed diabetes mellitus was not included in all regression models as fasting plasma glucose was measured only on a sub-sample of NHANES participants.

**Comment 4. What is the reference category for the prevalence ratio associated with non-Hispanic black?**

Response: The comparison group includes all other individuals besides non-Hispanic blacks (i.e., non-Hispanic whites, Mexican-Americans, and individuals of other races and ethnicities). This has been clarified in footnotes to tables 2 and 4.

**Comment 5. Some of the results presented in the text do not match the numbers calculated from the tables. For example, according to the text page 5, the total sample size for the analysis of albuminuria is 12,778 whereas according to table 3 it is 12,798. According to the text page 8, the prevalences of stage 3-4 CKD are 1.4%, 9.9% and 38.3%, whereas when calculated from table 1 they are 1.2%, 9.5% and 37.6%. Likewise the prevalence of albuminuria according to age groups are different when calculated from table 3 (6.8%, 14.8% and 26.8%) from the ones cited in the text page 10 (5.8%, 11.4% and 22.7%).**

Response: These items have been clarified in the revised manuscript as noted in responses to Reviewer 3, comments 2 and 3.

**Comment 6. The sentence “Trends of lower prevalence ratios of stage 3 or 4 CKD at older age were present for diagnosed (p=0.067) and undiagnosed diabetes mellitus (p=0.369)” is misleading since the p values are not significant (page 9). Likewise page 10, it should be added that the p value for trend was not significant for obesity and high cholesterol.”**
Response: We have tempered this statement to make clear that the results are not statistically significant. Specifically, on page 10 of the revised manuscript we state:

Although not statistically significant, a trend towards lower prevalence ratios of stage 3 or 4 CKD at older age were present at older age for diagnosed (p-trend=0.067) and undiagnosed diabetes mellitus (p-trend=0.369).

Comment 7. The first sentence of the discussion (page 11) is not accurate. Associations between hypertension and stage 3-4 CKD or between diabetes and stage 3-4 CKD were not present for all age groups. Several 95% confidence intervals include 1 (all of the CIs associated with undiagnosed diabetes, and the one associated with hypertension in the youngest age group)

Response: We apologize for this inaccuracy. We have edited this paragraph to more accurately reflect the data. Specifically, the first paragraph of the discussion now reads:

In the current study, associations were present between diagnosed diabetes mellitus and stage 3 or 4 CKD for all age groups. Additionally, although not statistically significant among the youngest age group, associations were present between hypertension and stage 3 or 4 CKD. However, for both hypertension and diagnosed diabetes, these associations were stronger among younger adults. Also associations between hypertension and diagnosed or undiagnosed diabetes mellitus with albuminuria were present across the adult lifespan but were stronger for younger adults.