Reviewer’s report

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

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Reviewer: Kenrik Duru

Reviewer’s report:

1) Major compulsory revisions
a) 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.

b) 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all results should be reported, those that are not reliable should be noted with an asterisk, so that future authors do not cite them as “fact” (e.g. 12.5% of blacks aged 20-49 have Stage 3-4 CKD) based on a handful of individuals.

In these analyses, I am particularly concerned about the reliability of the numbers in Table 1 for Stage 3-4 CKD among those aged 20-49 years. I would refer the authors to the analytic guidelines from NHANES III (available on the website) for guidance of how to use the design effect & assess the sample size of each cell in Tables 1 & 3. Any results derived from sample sizes that are too small should be noted.

c) 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.

d) 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 plan 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).

e) 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.

2) Minor essential revisions
a) The authors should use the past tense to describe results (e.g. "were" associated) in the abstract.
b) 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.
c) Are a "history of diabetes mellitus" and "self-report of a prior diagnosis of diabetes mellitus" the same thing?

3) Discretionary revisions
a) 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.
b) 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.
c) Is it necessary to mention the medical centers that analyzed the labs in NHANES?
d) 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.
e) 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.

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.