Author's response to reviews

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

Authors:

Tareq M Islam (tislam@tulane.edu)
Caroline S Fox (foxca@nhlbi.nih.gov)
Devin Mann (devin.mann@mssm.edu)
Paul Muntner (paul.muntner@mssm.edu)

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Author's response to reviews: see over
Referee 4

I have read the authors' response and appreciate their response to the points raised by me and the other reviewers. The only outstanding issue to my mind is the interpretation of what their findings mean, namely the fact that factors other than HTN and DM assume increasing importance of causal risk factors in CKD among older patients. The authors have chosen not to address the issue of cardiovascular/atherosclerotic disease at all, which I think leaves the reader with a mistaken impression.

There are a lot of older people who have atherosclerotic disease without HTN & DM, or any of the other covariates in the model. Just age >70 alone in men predicts a 12-15% risk of a coronary event over 10 years in the Framingham model, so the prevalence of atherosclerosis is higher than that. If the population burden of atherosclerosis is high, then even small associations between "idiopathic" atherosclerosis and CKD would lead to a significant population impact. For example, there is evidence that renal artery stenosis is found in 20-30% of patients with ESRD (van Ampting, Nephrol Dial Transplant 2003) and we know that a substantial minority of patients with RAS are not hypertensive (Rimmer, Annals Internal Medicine 1993). RAS is progressively more prevalent and relevant in older patients. The role of MI leading to CHF may not be as clear, but we certainly know that CHF and CKD are linked. All of this is to say that I think the authors need to consider this entire issue from a clinical perspective, and provide a thoughtful discussion, which shouldn't take more than a few sentences. I am not sure that we fully understand the risk factors for age-related atherosclerosis (i.e., why there are so many points for age in the Framingham score, independent of other specific risk factors), but at least this issue needs to be addressed in the context of identifying the cause of CKD in older adults.

Response: We appreciate these points and agree that atherosclerosis, including sub-clinical disease, is very common among older adults and may be an important risk factor for CKD. In addition to the study by van Ampting cited above, a study by Shlipak (Atherosclerosis 2008) also demonstrates sub-clinical atherosclerosis as a risk factor for the accelerated progression of kidney disease. We have added text to the discussion to address this putative cause of CKD. Specifically, we state the following on page 14 of the revised manuscript:

Atherosclerosis is another possible factor contributing to the high burden of stage 3 or 4 CKD and albuminuria among older adults. Atherosclerosis is very common among older adults and can affect the renal vasculature resulting directly in renal damage. Also, the presence of more severe atherosclerosis may be a marker for developing heart failure resulting in decreased renal perfusion. A study by Shlipak and colleagues found, after multivariable adjustment, among adults ≥ 65 years of age without a history of clinical cardiovascular disease, an ankle-brachial index <0.9 was associated with a 1.61 times higher risk of a rapid
decline in eGFR defined as $\leq -3\text{ ml/min/1.73m}^2\text{/year}$. Additionally, participants in their study with a common carotid intima-medial thickness $\geq 1.19$ and internal carotid intima-medial thickness $\geq 1.82$ were 1.34 and 1.41 times more likely to have a rapid decline in eGFR, respectively. The current study did not have data on sub-clinical atherosclerosis, precluding investigation of increased levels of this risk factor on the development of stage 3 or 4 CKD and albuminuria.

**Referee 5:**
The authors have greatly improved their manuscript since their last submission. They have addressed all the reviewers' previous recommendations and made all the suggested changes except one last one regarding the issue of the prevalence of CKD among the non-exposed (those without hypertension or diabetes).

In their answer to the reviewers, the authors state that these results are presented at the bottom of table 1 and table 3. However, tables 1 and 3 describe the prevalence of risk factors among those with and without CKD or albuminuria and not the prevalence of CKD among those with or without these risk factors.

In addition, the 2 paragraphs in answer to comment number 2 (pages 8 -9 of the "Answer to the reviewers" document) do not refer to the same prevalence. The first one refers to the prevalence of CKD, the second one to the prevalence of hypertension/diabetes.

Response: We apologize for this omission from the manuscript and the confusion in the response letter. We have added the prevalence of stage 3 or 4 CKD and albuminuria among individuals without diagnosed or undiagnosed diabetes mellitus or hypertension by age group on pages 9 and 10 of the manuscript, respectively. Specifically, we state:

On page 9:
The age-specific prevalence of stage 3 or 4 CKD at 20 to 49, 50 to 69 and $\geq 70$ years of age was 1.5%, 11.7%, and 39.0%, respectively, among individuals with diagnosed or undiagnosed diabetes mellitus or hypertension and 1.0%, 6.6% and 27.8%, respectively, among individuals without diabetes mellitus or hypertension.

On page 10:
Among individuals 20 to 49, 50 to 69 and $\geq 70$ years of age, the prevalence of albuminuria was 14.0%, 14.9%, and 26.3%, respectively, among individuals with hypertension or diagnosed or undiagnosed diabetes mellitus and 3.7%, 6.9% and 14.0%, respectively, for those without diagnosed or undiagnosed diabetes mellitus or hypertension.
As noted on page 12-14 of the discussion, these data suggest a substantial burden of stage 3 or 4 CKD and albuminuria among older adults without hypertension or diabetes mellitus. The reasons for their kidney disease warrant future study.

Reference List

