Author's response to reviews

Title: Albuminuria, serum creatinine, and estimated glomerular filtration rate as predictors of cardio-renal outcomes in patients with type 2 diabetes mellitus and kidney disease: a systematic literature review

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Author’s response to reviews:

Reviewer 1:
In this study, investigators provided systematic review of albuminuria, serum creatinine, and estimated glomerular filtration rate as predictors of renal function decline in patients with type 2 diabetes mellitus and kidney disease. This is a well written though thorough study and will add to the existing medical literature. It is also research in a content area of substantial importance. However, the following issues should be clarified:

1) COMMENT: Authors have achieved their objective of enlightening the audience to much of the literature and provided individual descriptive details of each study however; I think reader will get lost in all the individual details. Importantly, I would prefer authors to perform critical assessment of the literature and highlight the methodological issues, limitations and provide combined summary statistics of the outcomes.

RESPONSE: We thank the reviewer for their insightful comment. As part of the study methodology (page 7, lines 128-132) we performed a critical assessment of all included studies (See Table 1 for summary of Downs & Black quality assessment tool). In addition, we now also provide the complete breakdown of these scores (see Additional Table 4), which displays a more robust critical assessment of the quality and limitations of the included literature. In light of the large variation in the included literature, we determined it was not possible, and indeed not methodologically appropriate, to provide combined summary statistics of the outcomes, which were largely inconsistent and diverse across studies.

2) COMMENT: Have the authors convinced the reader that no relevant literature was missed in their literature review? Why only search MEDLINE, EMBASE and Cochrane.
Also searching Science Citation Index (reviewing all citations that referenced their articles of interest), and a review of Google Scholar would be preferred.

RESPONSE: We followed a validated, robust, and commonly employed literature search approach as outlined in the Cochrane guidelines, as mentioned on pages 5 and 6, lines 89-95, which recommend searching Cochrane central register of controlled trials (central), Medline and Embase (Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated march 2011]. The Cochrane collaboration, 2011. Available from www.handbook.cochrane.org. In addition, as noted in the text (pages 5 and 6, lines 91-92) we searched PubMed from 2013 until May 2016 in an effort to capture more recently published studies that may not yet have been indexed in one of the other databases. Further still, the reference sections of review articles identified in the search (but omitted due to selection criteria) were hand screened in order to identify any other relevant papers (n=2 as shown on page 6, lines 96-98, and in Figure 1) that may have been overlooked during the search process. Although other search methods could have been used, based on the information shared here, we feel that the methods employed in this manuscript reflect the current standard for systematic literature reviews (SLRs), and therefore have not made additional changes.

3) COMMENT: Why the search period restricted to January 2000 through May 2016?

RESPONSE: We selected this timeframe to capture the most up-to-date evidence available in the scientific literature, and to omit any outdated literature, which is a common approach often undertaken when conducting a SLR.

4) COMMENT: I wasn’t clear on their justification for only restricting the review to English language publications only.

RESPONSE: We thank this reviewer for raising this important point. It is possible that this approach may introduce some form of selection bias and overlook certain findings derived from non-English language studies. However, we may add that some evidence (Morrison et al. Int J Technol Assess Health Care. 2012 Apr;28(2):138-44 and Juni et al. Int J Epidemiol. 2002 Feb;31(1):115-23) documented the comparison of studies in both English-only versus languages other than English, and concluded that there were no major differences in findings between both strategies. Although we agree there are benefits to including as many languages as possible, until further evidence becomes available, we believe that an English-language-only approach is suitable; especially given it is the universal language of scientific communications.

5) COMMENT: Repetition of Language in Abstract and Methodology section.

RESPONSE: We designed our abstract to reflect a brief description of the overall manuscript within the word limit set by the journal. For describing the study methods we have now modified the text to be consistent without making major changes that might alter the meaning.

6) COMMENT: Authors may want to report which Statistical software was used for the analysis.
RESPONSE: In the present study, all data presented were extracted and subsequently tabulated by use of Microsoft Excel as highlighted on page 8, lines 154-156. Furthermore, to clarify that this SLR did not include statistical analysis, we have reworded the sentences on page 8, lines 147-154 to read as “Risk estimates were extracted from the included publications. These primarily were hazard ratios, and in some cases relative risks (RR), with 95% confidence limits (where provided) for the association between renal biomarkers and outcomes of interest. Risk estimates reported in the publications were assessed qualitatively by visual inspection for statistical significance as well as directionality (e.g. an increase or reduction in the risk of an outcome of interest according to a particular biomarker). Due to the variation of study biomarker predictors, covariates, outcomes, statistical methods, and risk estimates used in the included publications, quantitative comparison of risk estimates across studies was not possible.”

7) COMMENT: There is subjectivity in screening citations, the ‘industry standard’ is for this to be done in duplicate by persons who are knowledgeable about the content, where a full-text article is retrieved for eligibility assessment if any reviewer identifies the article as potentially relevant. Though the authors mentioned that two reviewers did the literature search but it is unclear if they were nephrologist or persons with knowledge about the subject matter. Authors may want to provide clarification?

RESPONSE: We agree with the reviewer that some level of subjectivity is inevitable in screening citations and that knowledge of the content is important in reducing subjectivity or potential selection bias. We confirm that the screening process was conducted by two authors with knowledge of the content and subject matter. In addition an expert nephrologist author was involved in all steps of the study and manuscript from conception to completion.

8) COMMENT: Consider adding the reference number to the study acronyms/Author et al in Table 1; Similarly, for other tables. Please arrange studies based on Year of publication. It is just a personal suggestion.

RESPONSE: We thank this reviewer for their thoughtful comment. We have now added the reference citations to Table 1, and separately to the Additional Files Tables 1-3.

9) COMMENT: Would like authors to upload pre-specified study protocol with the manuscript?

RESPONSE: As it stands, the manuscript clearly outlines the material contained in the study protocol, and we feel that adding the protocol would unnecessarily duplicate what is already reported in the manuscript. However, if the editor still feels it is essential to include the study protocol, we can provide this as supplementary material at their discretion.

10) COMMENT: Authors have provided combined quality assessment score; readers will benefit from separate supplemental table on quality of studies included in the systematic review.
RESPONSE: Thank you for pointing this out. We now provide a complete breakdown of the quality assessment scores for each individual paper as determined by employing the Downs & Black quality assessment tool (see Additional Supplemental Table 4, now added).

11) COMMENT: Please provide PRISMA check list Table.

RESPONSE: We now include the PRISMA checklist (attached as “other information”). Given the length of the submitted manuscript and additional material already included based on this review, our recommendation, however, would be for the checklist to be omitted from the supplemental materials. We respectfully leave the decision to the Editor as to whether or not to incorporate the PRISMA checklist into the current manuscript.

12) COMMENT: Authors should provide reference for studies in the Result section. For example, in line 169: GFR loss (n = 9; 29.0%) and doubling of serum creatinine (n = 5; 16.1%). Reference for which 9 and 5 studies?

RESPONSE: Thank you for this recommendation. We now provide the specific reference citations throughout the second paragraph of the Results section on page 9, which are highlighted in red.

Reviewer 2:

The authors conducted a systematic review to assess the role of albuminuria, serum creatinine, eGFR, and uric acid in the prediction of kidney disease progression among patients with type 2 diabetes mellitus. The authors found that the methods used to assess the biomarkers and the outcomes in the included studies were highly heterogeneous, which preclude the generalizability of their findings. Consistent to previous reports, this review's findings support the utility of albuminuria as a good predictor of renal function decline. Another conclusion is that biomarker measurements need to be harmonized across studies to better assess the significance of these biomarkers. The authors are to be commended for the choice of a complex topic.

I have a few comments:

1) COMMENT: In my opinion, the title of this study is not an accurate representation of what was done. The title seems to imply that that the outcome of interest in the paper was limited to renal function decline. In reality, the authors assessed several distinct outcomes including kidney disease progression, non-fatal cardiovascular events, and all-cause mortality.

RESPONSE: We wholeheartedly agree with this reviewer and have now modified the title to read more generally, as “Albuminuria, serum creatinine, and estimated glomerular filtration rate as predictors of cardio-renal outcomes in patients with type 2 diabetes mellitus and kidney disease: a systematic literature review” in order to emphasize the additionally studied poor health outcomes. To keep the title from becoming excessively long, we did not add all of the outcomes to the title. However, this could be done at the Editor’s discretion.
2) COMMENT: The study outcomes should be clearly defined in the methods.

RESPONSE: Study outcomes that were reported in the present study are defined on pages 7 and 8, lines 135-138. One challenge in summarizing the information was that similar outcomes were defined differently across studies. In an effort to encompass the substantial number of definitions each study used to determine the outcomes (kidney disease progression, non-fatal cardiovascular events, and all-cause mortality) measured according to the biomarkers assessed, we also provided a breakdown of these approaches within each of the Additional Supplemental Tables 1-3 and hope that this clarifies the different study outcomes.

3) COMMENT: The methods mentioned that included longitudinal studies. Were all the retrospective studies longitudinal by design? If not, I would avoid using the word "longitudinal".

RESPONSE: We can confirm that all of the included publications classified as longitudinal, were indeed longitudinal in design. Table 1, pages 32-34 presents specific follow-up durations according to each of the included publications.

4) COMMENT: I believe the article would benefit from further English language editing.

RESPONSE: A native-English speaking editor employed through a scientific communications and publications company has now reviewed and copyedited the manuscript to ensure appropriate use of grammar and inclusion of vocabulary in a scientific manner. The editor who provided copyediting solutions has also been added to the Acknowledgments.

5) COMMENT: The structure and the flow of the discussion could be improved.

RESPONSE: Thank you for bringing this to our attention. The authors have subsequently revised the Discussion section to improve the structure and flow as per this reviewer’s request.