**Author's response to reviews**

**Title:** Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of National Health and Nutritional Examination Survey data, 2001-2010

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**Author's response to reviews:** see over
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Dear Dr Parekh,


(MS #: 1413879380863799)

My co-authors and I have the pleasure of submitting a re-revised version of this Research Article for further consideration for publication in *BMC Nephrology*.

We thank Reviewer 1 for their additional comments on this manuscript. Where appropriate, we have updated the manuscript accordingly. The reviewer’s comments, our responses to them, and any changes that have been made to the revised manuscript (shown in red text) are outlined on the following pages.

Also, whilst addressing the reviewer’s additional comments, we realized that an assessment of the proportion of participants with CKD at very high risk of a future CV event — those with CKD and concomitant CVD or diabetes — who achieved the optional LDL-C goal of <70 mg/dL would be helpful to include, especially in light of more recent guidelines. This more-stringent LDL-C goal is suggested as a therapeutic option in current national treatment recommendations for patients at very high CV risk. We found that only ~20% of these very high-risk individuals were achieving the more-stringent LDL-C goal of <70 mg/dL. Although current trends in BP management may see BP targets being relaxed somewhat, future recommendations around LDL-C targets will likely advocate more-stringent lipid goals to reduce absolute CV risk in high-risk patients, based on evidence from clinical trials. Therefore, we feel it is important to highlight current underachievement of the LDL-C <70 mg/dL goal in US adults with CKD so that healthcare professionals can consider this option in appropriate high-risk patients with CKD as...
they work towards optimizing CV risk factor management strategies to reduce the overall burden of CVD associated with CKD. We hope that the editorial team feels comfortable with the addition of these data at this late stage, as it will help support clinicians’ decision-making in accordance with today’s current LDL-C targets in very high-risk patients with CKD.

We hope that these responses sufficiently address the additional comments from Reviewer 1, and thank you again for your consideration of this revised manuscript for publication in *BMC Nephrology*.

Yours sincerely,

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RESPONSE TO ADDITIONAL COMMENTS FROM REVIEWER 1 ON:


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We thank Reviewer 1 for their additional helpful comments on this revised version of the manuscript, which have been taken into consideration during the preparation of this resubmission. These comments, our responses to them, and any changes that have been made to the revised manuscript (shown in red text) are outlined below.

REVIEWER 1 COMMENTS FOR THE AUTHOR

Minor Compulsory Revisions

1. Methods: Current recommendations for BP and LDL-C goals were published in 2003 and 2004, respectively. Can the authors describe why they included NHANES participants from 2001-2002?

NHANES participants from the 2001-2002 study cycle were included in the analysis so as to provide sufficient sample sizes that would allow meaningful interpretation of the results, particularly where the data are stratified by CKD stage (Table 2, 3) as the sample size in these subpopulations is much smaller, most notably for CKD Stage 4 (n=60). Moreover, as we also evaluated changes in LDL-C and BP treatment and control over time (Figure 1), it is generally preferable to use a longer period of follow-up when conducting a time-series analysis such as this; hence, we think it is important to include this earlier NHANES study cycle. In addition, the fact that this first study cycle in the NHANES dataset predates current recommendations for BP and LDL-C goal attainment allows the reader to evaluate the potential impact of the treatment recommendations over time. For example, we observed an increase in the use of lipid-lowering
medications and LDL-C goal attainment between 2001-2002 and 2005-2006, which may have been influenced by the revised guidelines. On the other hand, this trend does not appear to exist for BP-lowering agents and BP goal attainment.

We have added the following statement to the Study Design subsection of the Methods so that the benefit of including the 2001-2002 study cycle is highlighted to the reader:

“Data from the 2001–2002 study cycle were included in this analysis to enable the assessment of linear trends in CV risk factor treatment and control before and after the release of current lipid and BP treatment guidelines for patients with CKD in 2003 and 2004, respectively [11, 12].”

We have also added the following statement to the final paragraph of the Introduction, where the study objectives are listed:

“A time-trend analysis of lipid and BP treatment and control in US adults with CKD was also conducted to assess linear trends in CV risk factor management over the five 2-year NHANES study cycles between 2001 and 2010.”

2. Discussion: As a limitation, it’s important to note that NHANES participants don’t all have routine medical care. Thus, the population cannot be considered a “medicalized” cohort.
We thank the reviewer for pointing this out. The following statement has been added to the Limitations section:

“It is important to note that not all NHANES participants receive routine medical care; while this allows for the generalizability of the data to the overall US population, it could be considered a limitation when interpreting lipid and BP treatment and control rates.”

3. Discussion: In the beginning of paragraph 3, please delete “As for hyperlipidemia”.

We have deleted “As for hyperlipidemia” as suggested by the reviewer.

Discretionary Revisions:

1. Methods: The authors should consider mentioning in the methods section (bottom of page 7) that ACEi/ARB were included as antihypertensive medications. It is mentioned in a footnote of the table, but since these agents are often used for proteinuria reduction rather than for treatment for hypertension, it’s important to mention up front that they were included as anti-hypertensive medications.

We have included more specific information on antihypertensive medications in the Methods section, as suggested by the reviewer. For consistency, we have also provided more specific information on lipid-lowering medications in the Methods section. Respectively, these sentences now read:
“Hypertension was defined as an average BP >130 mmHg systolic or >80 mmHg diastolic, or self-reported use of antihypertensive agents (including \(\beta\)-blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and other BP-lowering agents).”

“Hyperlipidemia was defined as fasting levels of LDL-C above the specific goal for each CHD risk category designated in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [27] (LDL-C level \(\geq\)160 mg/dL for individuals with \(\leq\)1 CHD risk factor, \(\geq\)130 mg/dL for individuals with \(\geq\)2 CHD risk factors, and \(\geq\)100 mg/dL for individuals with a history of CHD or CHD risk equivalents), or self-reported use of lipid-lowering agents (including statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors and other antihyperlipidemic agents).”

2. Results: The results in Table 4 are mentioned verbatim in the text. Consider shortening the text considerably on page 13 and just referring readers to the appropriate table. This would help shorten a lengthy manuscript.

We agree with the reviewer that the results in Table 4 could be described more succinctly, and have modified the corresponding text in the Results section accordingly. Additionally, in reviewing the results presented in Table 4, we realized that an assessment of the proportion of participants with CKD and concomitant CVD or diabetes who achieved the optional LDL-C goal of \(<\)70 mg/dL would be appropriate and of interest to the readership. This more-stringent LDL-
C goal is suggested as a therapeutic option in current national treatment recommendations (NCEP ATP III guidelines; AHA/ACC secondary prevention guidelines; NKF KDOQI guidelines) for those individuals classified as being at very high risk of future CV events (e.g., those with CKD plus diabetes or CKD plus established CHD). We found that only ~20% of these very high-risk individuals were achieving this more-stringent LDL-C goal. Although current trends in BP management may see BP targets relaxed from 130/80 to 140/90 mmHg, future recommendations around LDL-C targets will likely advocate more-stringent lipid goals to reduce absolute CV risk in high-risk patients. Therefore, we feel it is important to highlight current underachievement of the LDL-C <70 mg/dL goal in US adults with CKD so that healthcare professionals can optimize CV risk factor management strategies to reduce the burden of CV complications associated with CKD. Hence, we have added these data to Table 4 (the values highlighted in yellow below) and revised the text in the Results section that relates to Table 4 as follows:

“Table 4 shows lipid and BP treatment and control rates in persons with CKD and concomitant CVD or diabetes. For those with concomitant CKD and CVD, 50.7% reported using lipid-lowering agents and 52.8% had an LDL-C <100 mg/dL; 21.9% achieved the optional LDL-C goal of <70 mg/dL. BP treatment and control rates in this population were 72.7% and 46.3%, respectively (Table 4). For those with concomitant CKD and diabetes, 44.6% reported using lipid-lowering agents and 51.2% had an LDL-C <100 mg/dL; 17.5% achieved the optional LDL-C goal of <70 mg/dL. BP treatment and control rates in this population were 69.9% and 40.8%, respectively (Table 4).”
We have also added a brief explanatory sentence to the Definition of Treatment Goals subsection of the Methods section as follows:

“In participants with CKD and concomitant CVD, or CKD and concomitant diabetes, attainment of the optional LDL-C goal of <70 mg/dL [28-30] was also examined.”

Finally, we have made slight modifications to the Discussion where appropriate:

“Furthermore, this analysis revealed that despite the very high-risk combination of CKD and CVD, or CKD and diabetes, dyslipidemia was undertreated in these individuals, with only around half of the CKD population with concomitant CVD or diabetes receiving any form of lipid-lowering therapy and a similar proportion achieving an LDL-C <100 mg/dL; fewer still (~1 in 5) attained the optional goal of <70 mg/dL recommended for those individuals classified as being at very high risk of future CV events.”

“Given the high prevalence of CV-related comorbidities and CV risk factors observed in this analysis of NHANES participants with CKD, aggressive LDL-C–lowering therapy to an optional goal of <70 mg/dL may be warranted in those with multiple high-risk factors (eg, CKD plus diabetes or CKD plus established CHD), as suggested in current national treatment recommendations for patients at very high risk of future CV events [28-30]. However, we found that only ~20% of those individuals with CKD and concomitant CVD or diabetes were achieving this more-stringent LDL-C goal.”
3. Discussion: The discussion is also relatively lengthy and could benefit from some additional focus. Consider the following suggestions:

- Paragraph 1 could be shortened by deleting the sentence with the percentages. This detail has already been presented in the results section and does not need to be recounted.

The sentence has been deleted as suggested by the reviewer.

- The paragraph pertaining to the new KDIGO CKD staging guidelines (page 17) is interesting, but is not relevant to the authors’ main point – that CV risk modification is suboptimal among patients with CKD. Consider deleting this paragraph.

Given the recent debate within the nephrology community around the proposed revisions to the CKD classification system, and the recent publication of the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (Kidney Int Suppl. 2013;3:1-150), we would prefer to retain this timely discussion of the evolution of the CKD classification system and how our observation that CVD burden increases markedly between Stage 3a and 3b CKD supports these revisions. We have updated the language and referencing of this paragraph to reflect the release of the new KDIGO guideline, which was published following the submission of our manuscript to BMC Nephrology.
• The cost-effectiveness paragraph could start with a topic sentence that states that there is a business case to be made for better CV risk modification among patients with CKD. The last sentence of this paragraph is not pertinent to this discussion, as the authors do not have any data about generic medication use in their population.

We have modified the first sentence of the cost-effectiveness paragraph to include mention of the cost benefit associated with CV risk reduction in patients with CKD, as follows:

“The additional economic burden associated with CVD in the context of CKD is substantial, and effective CV risk factor modification in patients with CKD has the potential to significantly reduce healthcare costs and improve patient outcomes.”

The last sentence relating to generic medication has been deleted as suggested by the reviewer, and some minor edits have been made to the remainder of the paragraph to improve flow.

• Use of CKD-EPI is not a limitation of this manuscript and I would consider removing it from the limitations paragraph.

This is a very good point; we would agree with the reviewer that the use of the CKD-EPI equations is not a limitation of this analysis and should be discussed elsewhere. The discussion as to why CKD prevalence differed between our study and earlier analyses of NHANES data was extended at the request of the other reviewer following the first round of comments to include CKD-EPI versus MDRD equation use as a potential reason for this apparent discrepancy. We
have removed this discussion from the Limitations section and included it further up in the general Discussion section where, in fact, it adds to and improves the flow of the Discussion overall.