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 resubmitting a revised version of this Research Article for further consideration for publication in *BMC Nephrology*.

We thank the reviewers for their thoughtful and constructive comments on this manuscript. We have updated the manuscript accordingly. The reviewers’ 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.

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

Yours sincerely,

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RESPONSE TO REVIEWER COMMENTS ON:


MS #: 1413879380863799

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We thank the reviewers for their careful evaluation of this manuscript and for providing helpful comments, which have been taken into consideration during the preparation of this revised 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**

**Major Compulsory Revisions**

1. Abstract: Analytic methods are not specified. The last sentence of the introduction addresses this partially and might be better placed in the Methods section of the abstract, with description of the analytic method used. Please reconcile the 9915 participants that were identified for the analysis (in the method section) with the 1428 (10.2%) participants with CKD. 1428 represents 10.2% of which cohort?

*We have incorporated the reviewer’s suggestion by moving the last sentence of the Background section of the Abstract to the beginning of the Methods section of the Abstract, and modified the wording of the Abstract so that the analytical method used is now briefly specified (this is limited by the word count for the Abstract; further details on the analytical method and sample weighting have been added to the main Methods section of the manuscript in response to comments from both reviewers). We have added a new final sentence to the Background section of the Abstract to summarize the study’s objective. These sections of the Abstract now read:*
“**Background:** For chronic kidney disease (CKD) patients, national treatment guidelines recommend a low-density lipoprotein cholesterol (LDL-C) goal <100 mg/dL and blood pressure (BP) target <130/80 mmHg. This analysis assessed the current status of cardiovascular (CV) risk factor treatment and control in US adults with CKD.

**Methods:** Weighted prevalence estimates of CV-related comorbidities, utilization of lipid- and BP-lowering agents, and LDL-C and BP goal attainment in US adults with CKD were assessed among 9,915 men and nonpregnant women aged ≥20 years identified from the fasting subsample of the 2001–2010 National Health and Nutritional Examination Survey (NHANES). Analyses were performed using SAS survey procedures that consider the complex, multistage, probability sampling design of NHANES. All estimates were standardized to the 2008 US adult population (≥20 years).”

With respect to reconciling the 9915 participants identified for the analysis with the 1428 (10.2%) participants with CKD, we thank the reviewer for bringing this ambiguity to our attention. The 10.2% represents a weighted estimate of the prevalence of CKD extrapolated to the general US adult population. So from the 9915 NHANES participants identified for the analysis, 1428 participants (14.4%) were classified as having CKD. Population-level prevalence estimates were then obtained by adjusting participant sampling weights to the July 2008 US census population ≥20 years of age. Depending on their demographic profile, some participants may be weighted more heavily than others. Thus, although the crude prevalence of CKD in the NHANES responders was 14.4%, when the population weights were applied, the weighted estimate of CKD prevalence in the general US adult population was 10.2%. We have modified the wording of the first sentence of the Results section of the Abstract to read:
“Results: Of the 9,915 NHANES participants identified for analysis, 1,428 had CKD (Stage 1–4), corresponding to a prevalence estimate for US adults aged ≥20 years of 10.2%.”

2. Abstract: In the methods section, when describing CKD stages, please use more simple descriptions that match those used in the manuscript (stage 3a: 45-59ml/min/1.73m$^2$ and stage 3b: 30-44 ml/min/1.73m$^2$).

We have incorporated the reviewer’s comment as suggested.

3. Methods: The authors need to explain upfront why the analysis was restricted to NHANES participants with fasting labs. The current explanation is in the discussion section, which is much too late. Also, why was the fasting subsample of participants used to examine BP control and use of anti-hypertensive medications? I would think that the authors could use the entire subsample with CKD and medication/survey data for that analysis.

We have added the following statement to the Sample Population subsection of the Methods so that the reason for using the fasting NHANES subsample is explained to the reader upfront:

“This analysis was restricted to the fasting subsample of NHANES to enable the identification of participants with diabetes and hyperlipidemia, the definitions of which require valid fasting plasma glucose and LDL-C levels, respectively (described in further detail below).”
We chose to use the fasting subsample for both the lipid and BP analyses to avoid confusion and ensure consistency across all analyses. As the fasting subsample has its own designated weight to account for the additional probability of selection and non-response, it is likely there would be little difference in the results between the fasting vs non-fasting NHANES samples. Restricting the analysis to the fasting subsample of NHANES identified 1,428 participants with CKD and 8,487 participants without CKD. We have examined the non-fasting NHANES sample for the same period and identified 1,321 participants with CKD and 12,307 participants without CKD. As the non-fasting NHANES sample contains fewer participants with CKD, we feel there would be little to gain by analyzing the lipid and BP parameters in separate populations.

4. Methods: In the “Data collection” subsection, please clarify how drug utilization was self-reported. Was this based on the NHANES questionnaire or based on prescription bottles provided by the participant to the study staff? Also, the NCEP ATP guidelines for cholesterol level are based on CHD risk factors. Please describe what those risk factors are. Is CKD of any stage considered a CHD equivalent?

*Self-reported drug utilization was based on the NHANES questionnaire; we have now clarified this in the Data Collection and Laboratory Measurements subsection of the Methods:*

“All disease history and drug utilization was self-reported based on the NHANES questionnaire.”
A description of NCEP ATP III CHD risk factors and CHD risk equivalents has now been added to the Data Collection and Laboratory Measurements subsection of the Methods:

“CHD risk factors included cigarette smoking, hypertension (BP ≥140/90 mmHg or on antihypertensive medication), low levels of high-density lipoprotein cholesterol (HDL-C; <40 mg/dL), family history of premature CHD (male first-degree relative <55 years; female first-degree relative <65 years), and older age (men ≥45 years; women ≥55 years). CHD risk equivalents included diabetes and 2 or more risk factors conferring a 10-year risk for CHD >20%; information on non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease; also considered CHD risk equivalents) was not available in NHANES.”

CKD is not currently recognized as a CHD risk equivalent according to NCEP ATP III guidelines, although this may change with the release of ATP IV. However, CKD is classified as a CHD risk equivalent according to the latest NKF KDOQI guidelines and by the AHA Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. CHD risk equivalence is not limited to a particular stage or stages of CKD. The JNC 7 guidelines also list CKD as a high-risk condition and a “compelling indication” for the use of a specific antihypertensive regimen to achieve a BP goal <130/80 mmHg.

5. Methods: Given the current controversy re: blood pressure target among individuals with CKD, consider performing a sensitivity analysis using a BP goal of <140/90. Results:
There must be a mistake in the first paragraph. 10.2% of 9915 is not 1428. Please reconcile.

How many participants from the fasting subsample were excluded from the analysis because of missing data? What data are missing – renal status, medications, BP or laboratory results?

We acknowledge the current debate regarding intensive BP control in patients with CKD and the inconclusive evidence from recent clinical trials that compare strict versus standard BP control in this and other patient groups. Using a less-stringent BP goal of <140/90 mmHg in our analysis will certainly increase proportion of patients achieving this goal. We performed a sensitivity analysis to investigate the effect of increasing the threshold for BP goal attainment to \( \leq 140/90 \text{ mmHg} \) and found this increased the proportion of those with CKD classified as achieving BP goal by one-third, to 66.5%. We have included these results in the Blood Pressure Treatment and Control in Persons with CKD subsection of the Results, as well as including mention of this sensitivity analysis in the Methods and Discussion, as follows:

*In the Definition of Treatment Goals subsection of the Methods:* “A sensitivity analysis to investigate the effect of increasing the threshold for BP goal attainment to \( \leq 140/90 \text{ mmHg} \) was also performed.”

*In the Blood Pressure Treatment and Control in Persons with CKD subsection of the Results:* “A sensitivity analysis increasing the threshold for BP goal attainment to \( \leq 140/90 \text{ mmHg} \) found this increased the proportion of persons with CKD classified as achieving BP goal by one-third, to 66.5%.”
In the Discussion: “As for hyperlipidemia, hypertension (defined as an average BP >130 mmHg systolic or >80 mmHg diastolic, or self-reported use of antihypertensive agents) was also prevalent in the 2001–2010 US adult CKD population (76.1%). Current treatment recommendations indicate that, for most patients with CKD, the use of multiple antihypertensive agents will be required to achieve a BP goal of <130/80 mmHg and reduce CV risk [12]. Despite this, only around half of individuals with CKD reported using any antihypertensive medication (54.4%), and less than half achieved a BP goal of ≤130/80 mmHg (44.6%). A sensitivity analysis increasing the threshold for BP goal attainment to ≤140/90 mmHg increased the proportion of persons with CKD classified as achieving their BP goal to 66.5%. The lack of conclusive evidence from randomized controlled trials as to the CV benefit of strict versus standard BP control [37] has sparked intensive debate on the subject of an appropriate BP goal for patients with CKD. However, the observation from our analysis that over half of all US adults with CKD are not meeting the current BP treatment goal of ≤130/80 mmHg, and one-third are not meeting the less-stringent target is of ≤140/90 mmHg, indicates that suboptimal management of hypertension persists in this high-risk population.”

With respect to reconciling the 9915 participants identified for the analysis with the 1428 (10.2%) participants with CKD, again we thank the reviewer for bringing this ambiguity to our attention. As discussed in the response to Comment 1 above, the 10.2% represents a weighted estimate of the prevalence of CKD extrapolated to the general US adult population. We have modified the wording of the first sentence of the Prevalence of CKD subsection of the Results section to read:
“Of the 9,915 NHANES participants identified from the 2001–2010 survey period, 1,428 had CKD (Stage 1–4), corresponding to a prevalence estimate for US adults aged ≥20 years of 10.2%.”

With respect to the number of participants excluded due to missing data, and the nature of the missing data, we thank the reviewer for pointing out this omission. We now include a description of the participant flow during the identification of the study population in the Sample Population subsection of the Methods section:

“From the total 2001–2010 NHANES population of 52,195 participants, after excluding participants <20 years of age (n=24,611), participants that did not attend the mobile examination center (n=1,276), participants without fasting laboratory measurements (15,162), pregnant women (n=407), participants with missing lipid or BP data (n=788) and participants with Stage 5 CKD (n=36), a sample population of 9,915 participants was identified for this analysis.”

6. Results: In the first sentence of the third paragraph, please clarify which entities are CV co-morbidities and which entities are CV risk factors. Breaking this sentence up into 2 different sentences would be helpful. Also, change sentence structure such that the reader is reminded that CVD is defined by presence of CHD, CVA or CHF.

We have modified the sentence as suggested by the reviewer to read:
The prevalence of CV-related comorbidities in persons with CKD was high: 19.6% had CHD; 10.3% stroke; and 9.7% congestive heart failure (CHF). CVD—a composite of CHD, stroke or CHF—was prevalent in 28.4% of those with CKD. The prevalence of CV risk factors in persons with CKD was also high: 31.5% had diabetes; 53.9% hyperlipidemia; and 76.1% hypertension.

7. Results: Do the data in Tables 1-3 and Figure 1-2 pertain to the NHANES participants included in this study or are the data extrapolated to represent the US population? The title of each table should clarify whether or not these are population-level estimates.

All data presented are extrapolated to represent the US population by standardization to the July 2008 US census population ≥20 years of age. Although the footnote to Table 1 suggests this, we would agree that it is not clear. The titles of all tables and figures have now been modified to make this clear for the reader, as suggested by the reviewer. We have also edited the text throughout the manuscript to clarify that these are population-level estimates.

8. Results: Are the data presented in Figure 1 the same as those in Table 2? If so, the figure is redundant.

Yes, the data presented in Figure 1 the same as those in Table 2. We have deleted this figure as suggested by the reviewer.

9. Discussion: The authors spend too much time discussing statin use among patients with ESRD on dialysis. Given that the current study is restricted to individuals with non-dialysis
requiring CKD, the discussion should focus on CKD. Results from the AURORA and ALERT trials are not pertinent to the analyses presented in this manuscript.

This point was also raised by the other reviewer. We included these studies to provide a balanced discussion on the differential CV benefit of statin therapy in CKD vs ESRD patients. However, we would agree that too much detail is provided for 4D and AURORA. This detail has been removed and these studies are now just cited to support a more general statement on the differential effects of statins in CV event reduction in CKD vs ESRD patients.

Minor Essential Revisions:

1. Methods: Please define stage 5 CKD in the “Sample Population” subsection.

Stage 5 CKD (<15 mL/min/1.73 m²) has been defined as suggested by the reviewer.

2. Discussion: The authors state that 10.2% of NHANES survey participants have CKD, representing 22.6 million Americans. Why is this different from the “26 million affected by CKD” that is cited in the introduction? I believe that Coresh et al used NHANES in that analysis as well.

The apparent discrepancy with the Coresh et al. study (Coresh J, et al. JAMA 2007, 298:2038-2047), which is also based on NHANES data, is currently discussed in the Limitations section (modifications shown in red):
“Furthermore, the restriction of this analysis to the fasting subsample of NHANES due to the requirement of valid LDL-C measurements may explain the somewhat counterintuitive fall in prevalence of CKD Stage 1–4 observed between this analysis of NHANES 2001–2010 data (10.2%; 22.6 million US adults; standardized to the 2008 US adult population) and an earlier analysis of NHANES 1999–2004 data (13.1%; 26.3 million US adults; standardized to the 2000 US adult population) [3], as the prevalence estimates presented here were based on around three-quarters of the number of NHANES participants as the previous study (n=9,915 versus n=13,233, respectively).”

Also, the use of the CKD-EPI equation (this study) vs the MDRD equation (2007 Coresh study) may have contributed to the apparent decrease in estimated CKD prevalence. In the 2009 paper describing the new CKD-EPI equation (Levey AS, et al. Ann Intern Med 2009, 150:604-612), a comparison of the MDRD vs CKD-EPI equations using NHANES 1999–2006 data (n=16,032) led to a downward revision of the Coresh CKD prevalence from 13.1% to 11.5%, respectively. The tendency of the CKD-EPI equation to more accurately classify lower-risk patients into higher eGFR categories and result in lower prevalence estimates of CKD has also been documented in a number of other studies (e.g., Matsushita K, et al. Am J Kidney Dis 2010 55:648-659; Stevens LA, et al. Am J Kidney Dis 2011 57:S9-16; McFarlane SI, et al. Am J Kidney Dis 2011 57:S24-31). With this in mind, we have added the following statement to the existing paragraph mentioned above, which also includes mention of the latest USRDS prevalence estimates for CKD, as requested by the other reviewer:
“Also, the use of the CKD-EPI equation in this analysis versus the Modification of Diet in Renal Disease (MDRD) Study equation in the earlier analysis [3] may have also contributed to the reduced estimated CKD prevalence we observed. A comparison of the MDRD and CKD-EPI equations using the earlier NHANES 1999–2006 data (n=16,032) led to a downward revision of CKD prevalence from 13.1% to 11.5% [26]. The tendency of the CKD-EPI equation to more accurately classify lower-risk patients into higher eGFR categories and result in lower prevalence estimates of CKD has also been documented in a number of other studies [45, 46]. However, the most recent report from the US Renal Data System, using the CKD-EPI equation to calculate eGFR, puts the overall prevalence of CKD (including Stage 5 CKD) in the NHANES 2005–2010 population as high as 14.0% [47].”

Discretionary Revisions:

1. Introduction: Suggest removing the sentence about non-traditional CV risk factors, as these are not addressed in the current analysis.

We have modified the text as suggested by the reviewer.

2. Results: Tables 2 and 3 -- consider including a column entitled “No CKD”. Then, the last several rows of Table 1 could be eliminated. Also, please clarify in the footnote how the p-values listed in the right-most column were determined. Consider calculating a non-parametric trend across all CKD categories.

We have modified the text as suggested by the reviewer.
We have modified Table 1, 2 and 3 as suggested by the reviewer by including “No CKD” and “All CKD” columns in Table 2 and 3 and populating this information from Table 1. The last several rows of Table 1 have therefore been deleted, as suggested by the reviewer. We have also edited the relevant results sections of the manuscript to account for these changes in the presentation of the results.

We have now included footnotes to Tables 1, 2 and 3 stating how the P values in these tables were calculated and included further information in the Methods section of the manuscript:

Footnote to Table 1: “Rao-Scott chi-square P values for categorical variables were obtained using the SAS procedure SURVEYFREQ; between-cohort P values for continuous variables were obtained using the SAS procedure SURVEYREG (see Methods).”

Footnote to Tables 2 and 3: “P values are for Stage 1 versus Stage 4 CKD, obtained using the SAS procedure SURVEYLOGISTIC; P values for No CKD versus All CKD are all <0.001, obtained using the SAS procedure SURVEYFREQ (see Methods).”

Methods section: “Rao-Scott chi-square P values for categorical variables were obtained using SURVEYFREQ. Between-cohort P values for continuous variables were obtained using SURVEYREG. Each continuous outcome was regressed on the indicator variable CKD=1 or No CKD=0, and a contrast statement was used to generate the between-cohort P value.” and “P values for Stage 1 versus Stage 4 CKD were obtained using SURVEYLOGISTIC. Each outcome
was regressed on the 5-level class variable CKD stage (Stage 1, 2, 3a, 3b or 4), and a contrast statement was used to generate the Stage 1 versus Stage 4 P value.”

With regards to calculating a non-parametric trend across all CKD categories, as we do not treat CKD stage as a continuous variable, it is difficult to find a suitable approach to conduct a non-parametric trend test of proportions that takes into account the complex sample design of NHANES. Hence, we have chosen to present the Stage 1 versus Stage 4 P values only. However, in response to a comment from the other reviewer, we have added a statement in the Limitations section noting that, as Stage 4 has only 60 participants, caution should be exercised in drawing inferences on US populations trends based on these data:

“Finally, caution should be exercised in drawing strong inferences on US population trends based on comparisons between Stage 1 and Stage 4 CKD due to the low number of participants with CKD Stage 4 (n=60) identified from the NHANES 2001–2010 fasting subsample.”

**REVIEWER 2 COMMENTS FOR THE AUTHOR**

**Major Comments:**

1. The key finding in this paper is that while the prevalence of CVD risk factors is high in the US population with CKD, two of the modifiable risk factors, hyperlipidemia and hypertension, are both undertreated. I think this is where the paper should focus on in
terms of presentation of results. The paper will be greatly improved by highlighting these findings and exploring these differences within different subgroups.

We would agree with the reviewer that the undertreatment of hyperlipidemia and hypertension in the US CKD population is the key finding of this analysis. With respect to the presentation of results, we feel that there is a logical progression in the way the manuscript is currently structured in that, first, CVD burden is assessed in this CKD stage 1–4 population and found to be high, and, second, lipid and BP treatment and goal attainment rates are then ascertained in this same population. However, we agree that subgroup analyses (e.g., CKD plus CVD or DM; see Comment 10 below), as well as an investigation of dual LDL-C and BP goal attainment in these subgroups and the overall CKD population, would further emphasize current treatment gaps in the management of CV risk factors in the US CKD population. To this end, we have made the following modifications to the manuscript:

Two new Results sections have been added for (1) subgroup analyses (CKD plus CVD or DM) and (2) dual LDL-C and BP goal attainment, and the Discussion section has been modified to include mention of these new results. Note that these new analyses have not been stratified by CKD stage due to the small numbers of participants within these subgroups. The new material is presented as follows:

New Results section 1: “Lipid and BP Treatment and Control in Persons with CKD and Concomitant CVD or Diabetes
The self-reported use of lipid-lowering agents by persons with concomitant CKD and CVD was 50.7% and the overall proportion of this population achieving the LDL-C goal of <100 mg/dL was 52.8% (Table 4). For those with concomitant CKD and diabetes, lipid treatment and control rates were 44.6% and 51.2%, respectively (Table 4). The self-reported use of antihypertensive agents by persons with concomitant CKD and CVD was 72.7% and the overall proportion of this population achieving the BP goal of ≤130/80 mmHg was 46.3% (Table 4). For those with concomitant CKD and diabetes, BP treatment and control rates were 69.9% and 40.8%, respectively (Table 4).”

New Results section 2: “**Dual Lipid and BP Goal Attainment in Persons with CKD, with or without Concomitant CVD or Diabetes**

The overall proportion of persons with CKD who simultaneously achieved both an LDL-C <100 mg/dL and a BP ≤130/80 mmHg was 19.5%. Dual lipid and BP goal attainment was achieved in 28.1% of the population with concomitant CKD and CVD, and 24.9% of those with concomitant CKD and diabetes.”

New text in the Discussion: “**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. Although a higher proportion of these very high-risk individuals received antihypertensive medications (~70%), still less than half were at BP goal ≤130/80 mmHg. Moreover, only ~1 in 5 people with CKD are achieving both the LDL-C and BP treatment**
targets simultaneously, with a slightly higher proportion (~1 in 4) of those considered to be at very high risk of future CV events (those with concomitant CVD or diabetes) at both LDL-C and BP goal.”

2. The presentation of percentages in the paper is confusing in its current format. I suspect that the percentages represent the US population percents and not the actual proportion of the participants but this is not clear. This needs to be clearly stated and repeated as necessary throughout the paper.

This point was raised by the other reviewer also, and we thank both reviewers for bringing this ambiguity to our attention. All data presented are extrapolated to represent the US population by standardization to the July 2008 US census population ≥20 years of age. We have edited the text throughout the manuscript to clarify that these are population-level estimates.

3. Since NHANES are cross-sectional data, it is not possible to comment on progression of CKD and “improvement” in levels. This comes up in a number of places and needs to be modified.

We have modified the text accordingly to address the reviewer’s comment: eg, “increased with CKD progression” has been changed to “increased between CKD Stage 1 and 4”; “significant improvements were seen in lipid and BP treatment and control rates” has been changed to “significant increases were seen in lipid and BP treatment and control rates”.

4. Under the sample population, the total population of NHANES needs to be described. Also describe what number of participants were excluded and for what reason to reach the final N of 9,915. Also describe how the included differ from the excluded.

We thank both reviewers for pointing out this omission. We now include a description of the participant flow during the identification of the study population in the Sample Population subsection of the Methods section:

“From the total 2001–2010 NHANES population of 52,195 participants, after excluding participants <20 years of age (n=24,611), participants that did not attend the mobile examination center (n=1,276), participants without fasting laboratory measurements (15,162), pregnant women (n=407), participants with missing lipid or BP data (n=788) and participants with Stage 5 CKD (n=36), a sample population of 9,915 participants was identified for this analysis. This analysis was restricted to the fasting subsample of NHANES to enable the identification of participants with diabetes and hyperlipidemia, the definitions of which require valid fasting plasma glucose and LDL-C levels, respectively (described in further detail below).”

5. CHD definition includes “heart disease” which is vague and should be limited to coronary artery disease, angina and myocardial infarction.

We thank the reviewer for bringing this to our attention and have modified the definition of CHD in the manuscript to be consistent with the NHANES questionnaire. The NHANES Medical Conditions Questionnaire asks the respondent: Has a doctor or other health professional ever
told [you/SP] that [you/s/he] . . . had coronary heart disease? Has a doctor or other health professional ever told [you/SP] that [you/s/he] . . . had angina, also called angina pectoris? Has a doctor or other health professional ever told [you/SP] that [you/s/he] . . . had a heart attack (also called myocardial infarction)?

6. Please describe which sampling weights were used and if new weights were constructed for the analysis.

We have added further details with respect to sampling weights in the Statistical Methods subsection of the Methods section of the manuscript:

“Statistical analyses were performed using survey analysis procedures available in SAS software version 9.22 (SAS Institute Inc., Cary, North Carolina) that take into account the complex sampling scheme of NHANES, and used sampling weights to account for differential probabilities of sample selection and non-response. The fasting sampling weights of the 9,915 participants included in the analysis were adjusted to the July 2008 US census population ≥20 years of age (n=221,419,638). Each 2-year fasting sample weight within an NHANES 2-year study cycle was multiplied by the 2008 US census count and divided by the 2-year weighted total sample count from the analysis data set of persons in the 2-year study cycle. The population sizes for each study cycle were 180,717,445 for 2001–2002; 184,340,382 for 2003–2004; 190,068,016 for 2005–2006; 201,486,048 for 2007–2008; and 203,258,815 for 2009–2010. For example, the fasting sampling weight for each study participant from 2001–2002 was multiplied by
221,419,638/180,717,445; the fasting sampling weight for each study participant from 2003–
2004 was multiplied by 221,419,638/184,340,382; and so on for all 5 study periods.”

7. Table 1: Consider creating Table 1 by categories of interest in this paper. Suggest a table
with columns for characteristics, overall, Goal BP and Lipids (yes, no and p), goal BP (yes,
no and p) and goal lipids (yes, no and p). Could break into supplemental tables.

As suggested by the reviewer, we have included a comparison of demographic and clinical
characteristics of the US adult CKD population by LDL-C and BP goal attainment status as a
supplementary table (Additional File 1: Table S1). This is referred to in the Characteristics of
Persons with and without CKD subsection of the Results section as follows:

“A comparison of the demographic and clinical characteristics of the US adult population with
CKD stratified by LDL-C and BP goal attainment status is provided in Additional File 1: Table
S1. Those at LDL-C goal had a lower eGFR; had lower BP and lipid levels; had higher levels of
medication use; and were more likely to have a history of CVD and diabetes but less likely to
have hyperlipidemia compared with those not at LDL-C goal. Similar results were obtained for
the BP goal and dual goal (LDL-C and BP) cohorts, with the exception that those at BP goal
were younger and had a higher eGFR but lower body mass index compared with those not at BP
goal.”

8. In Tables, please be very specific about the %s (sample vs. population %) and repeat
footnotes at the bottom of each table that are relevant to that table.
All data presented are extrapolated to represent the US population by standardization to the July 2008 US census population ≥20 years of age. Although the footnote to Table 1 suggests this, we would agree that it is not clear. The titles of all tables have now been modified to make this clear for the reader. We have also edited the general text of the manuscript to clarify that these are population-level estimates. Footnotes have now been included for all tables.

9. Figures: is the % sample vs. US population?

All data presented are extrapolated to represent the US population by standardization to the July 2008 US census population ≥20 years of age. The title of the figure has now been modified to make this clear for the reader. We have also edited the general text of the manuscript to clarify that these are population-level estimates.

10. Consider further stratified analyses by CVD and diabetes status. I would like to see if the treatment varies based on these two conditions in patients with CKD.

As noted in the response to Comment 1 above, a new Results sections has been added for subgroup analyses (CKD plus CVD or DM) and the Discussion section has been modified to include mention of these new results. Note that these new analyses have not been stratified by CKD stage due to the small numbers of participants within these subgroups. The new material is presented as follows:
New Results section 1: “Lipid and BP Treatment and Control in Persons with CKD and Concomitant CVD or Diabetes

The self-reported use of lipid-lowering agents by persons with concomitant CKD and CVD was 50.7% and the overall proportion of this population achieving the LDL-C goal of <100 mg/dL was 52.8% (Table 4). For those with concomitant CKD and diabetes, lipid treatment and control rates were 44.6% and 51.2%, respectively (Table 4). The self-reported use of antihypertensive agents by persons with concomitant CKD and CVD was 72.7% and the overall proportion of this population achieving the BP goal of ≤130/80 mmHg was 46.3% (Table 4). For those with concomitant CKD and diabetes, BP treatment and control rates were 69.9% and 40.8%, respectively (Table 4).”

New text in the Discussion: “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. Although a higher proportion of these very high-risk individuals received antihypertensive medications (~70%), still less than half were at BP goal ≤130/80 mmHg.

11. Comparisons among CKD stages: Stage 4 has only 60 participants so I would be careful with strong inferences about the US population trends based on comparing stage 4 CKD to other stages.
We have added a statement in the Limitations section noting that, as Stage 4 has only 60 participants, caution should be exercised in drawing inferences on US populations trends based on these data:

“Finally, caution should be exercised in drawing strong inferences on US population trends based on comparisons between Stage 1 and Stage 4 CKD due to the low number of participants with CKD Stage 4 (n=60) identified from the NHANES 2001–2010 fasting subsample.”

12. Discussion: I am not sure why there is such a long discussion about 4D and AURORA? The main study that needs to be discussed is SHARP. There are no dialysis patients in this study.

This point was also raised by the other reviewer. We included these studies to provide a balanced discussion on the differential CV benefit of statin therapy in CKD vs ESRD patients. However, we would agree that too much detail is provided for 4D and AURORA. This detail has been removed and these studies are now just cited to support a more general statement on the differential effects of statins in CV event reduction in CKD vs ESRD patients.

13. The difference in prevalence of CKD noted in this study and previous papers is likely to be due to a different subsample and the use of CKDEPI equation. The authors should compare their prevalence estimates to those reported using CKDEPI equation by the USRDS atlas of CKD (www.usrds.org) and by Levey et al (PubMed ID: 19414839).
Indeed, we would agree with the reviewer that the difference in CKD prevalence noted in our study and that of the Coresh et al. study (Coresh J, et al. JAMA 2007, 298:2038-2047), which is also based on NHANES data, is likely due to differences in study subsample (most likely subsample size) as well as the use of the CKD-EPI equation (this study) vs the MDRD equation (Coresh study). With respect to differences in the size of the study subsample between the 2 analyses, this is currently discussed in the Limitations section (modifications shown in red):

“Furthermore, the restriction of this analysis to the fasting subsample of NHANES due to the requirement of valid LDL-C measurements may explain the somewhat counterintuitive fall in prevalence of CKD Stage 1–4 observed between this analysis of NHANES 2001–2010 data (10.2%; 22.6 million US adults; standardized to the 2008 US adult population) and an earlier analysis of NHANES 1999–2004 data (13.1%; 26.3 million US adults; standardized to the 2000 US adult population) [3], as the prevalence estimates presented here were based on around three-quarters of the number of NHANES participants as the previous study (n=9,915 versus n=13,233, respectively).”

As noted above, the use of the CKD-EPI equation (this study) vs the MDRD equation (Coresh study) may have contributed to the apparent decrease in estimated CKD prevalence between the 2 studies. In the 2009 paper describing the new CKD-EPI equation (Levey AS, et al. Ann Intern Med 2009, 150:604-612), a comparison of the MDRD vs CKD-EPI equations using NHANES 1999–2006 data (n=16,032) led to a downward revision of the Coresh CKD prevalence from 13.1% to 11.5%, respectively. The tendency of the CKD-EPI equation to more accurately classify lower-risk patients into higher eGFR categories and result in lower prevalence estimates
of CKD has also been documented in a number of other studies (e.g., Matsushita K, et al. Am J Kidney Dis 2010 55:648-659; Stevens LA, et al. Am J Kidney Dis 2011 57:S9-16; McFarlane SI, et al. Am J Kidney Dis 2011 57:S24-31). With this in mind, and to address the reviewer’s comment, we have added the following statement to the existing paragraph mentioned above:

“Also, the use of the CKD-EPI equation in this analysis versus the Modification of Diet in Renal Disease (MDRD) Study equation in the earlier analysis [3] may have also contributed to the reduced estimated CKD prevalence we observed. A comparison of the MDRD and CKD-EPI equations using the earlier NHANES 1999–2006 data (n=16,032) led to a downward revision of CKD prevalence from 13.1% to 11.5% [26]. The tendency of the CKD-EPI equation to more accurately classify lower-risk patients into higher eGFR categories and result in lower prevalence estimates of CKD has also been documented in a number of other studies [45, 46]. However, the most recent report from the US Renal Data System, using the CKD-EPI equation to calculate eGFR, puts the overall prevalence of CKD (including Stage 5 CKD) in the NHANES 2005–2010 population as high as 14.0% [47].”