PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and Risk Factors Associated with Chronic Kidney Disease in Nepal: Evidence from a Nationally Representative Population-Based cross-sectional Study
AUTHORS	Poudyal, Anil; Karki, Khem; Shrestha, Namuna; Aryal, KK; Mahato, Namra; Bista, Bihungum; Ghimire, Laxmi; K.C., Dirghayu; Gyanwali, Pradip; Jha, Anjani; Garcia Larsen, Vanessa; Kuch, Ulrich; Groneberg, David; Sharma, Sanjib Kumar; Dhimal, Meghnath

VERSION 1 – REVIEW

REVIEWER	Caplin, Ben University College London Medical School, Centre for Nephrology
REVIEW RETURNED	06-Oct-2021

GENERAL COMMENTS	This submission is a description of a population representative survey aimed at identifying the prevalence of CKD in Nepal. CKD is a common problem but under recognised particularly in low-income settings. Routine data from death certificates or registers of those receiving renal replacement therapy (e.g. dialysis) are unhelpful in estimating burden of disease due to substantial misclassification and lack of access to care respectively. Therefore representative cross-sectional data are very valuable. Sampling design, response rates and follow-up tests in those with abnormal results to confirm chronicity are strengths of this study. Methods: Creatinine eQA, specifically IDMS-traceable reference material. 'To confirm CKD, we carried out a follow up test after three months of initial data collection of the participants with albumin creatinine ratio ≥ 30 mg/g' I assume this is an unintentional omission and eGFR was also rechecked in those with initial eGFR <60? Why have the authors used the MDRD equation? A sensitivity analysis using CKD-Epi equation would be useful? Results: A description of the distribution of eGFR across the whole population is needed (e.g. histograms by sex) How do the study sample characteristics compare to estimates for the national population The tables need editing: I assume COR and AOR represent crude and adjusted odds ratios – this needs to be made clear. It is also unclear what multivariable adjustment is being conducted – this needs to be clearly defined in the Table legend. Related to this, I think that coefficients in Table 2 are adjusted for variables in Table 3 which is very confusing. I'd suggest combing tables or alternatively describing the univariate

	and multivariable analyses in different tables. What do the p-values refer to? Most readers will not be familiar with ethnic groups in Nepal and further elaboration is required. Discussion: Overall the discussion is rather long and rather confused and would benefit from being rewritten in a systematic manner. The comparisons with studies undertaken in other countries is useful. Are these estimates age-standardised? It's probably not useful to compare to studies that aren't population representative. A more thorough exploration of the differences with other studies, specifically, demonstration of chronicity and validity of eGFR estimating equations in different ethnic groups. The discussion would also be improved by not describing associations which don't meet standard thresholds of statistical confidence (e.g. rural-urban where 95% CI include 1). The association with dalit ethnicity appears robust to multivariate adjustment but this is not discussed.

REVIEWER	Krishnan , Anand All India Institute of Medical Sciences Centre for Community Medicine
REVIEW RETURNED	16-Nov-2021

GENERAL COMMENTS	This is a large nationally representative study on prevalence of CKD in Nepal, which is worth publishing. The suggested revisions are to improve it further. Abstract: The second line in outcome measures KDOQI can be deleted. AOR with 95% CI of risk factors should be given in the results section. Main Paper: The method of selection of clusters may pls be added. The response rates during the camp may be shifted to Results. Authors have measured CKD twice and CKD was defined only if this was so at both times. Is this a standard procedure? The necessary details of both measurements should be added. How many were positive in first and negative in second and vice versa. During weighting, was population weight and response weight also used or only sampling weights were used. It is not clear what the authors mean by saying " detailed demographic characteristics of the study population " weighted to be representative of Nepalese adult population are presented". Does table 1 – show the sample characteristics (without population weighting) Other wise it does not make any sense. It might be good to add the population proportions in an additional column. Results do not mention the prevalence of CKD and this seems to have been missed out by mistake. Looking at table 3, one is not clear what variables went into the analysis. For example, Age and Sex. From text it appears so but the table has to add a legend of the additional variables in the equation. The lower prevalence and lack of gender difference need a better discussion on the risk factor levels in the population and by gender (DM/HT) etc. Some discussion around the known causes of CKD (infection, DM/HT nephropathy) needs to be added along with the role of chronic metal poisoning.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ben Caplin, University College London Medical School

Comment to the author:
This submission is a description of a population representative survey aimed at identifying the prevalence of CKD in Nepal. CKD is a common problem but under recognised particularly in low-income settings. Routine data from death certificates or registers of those receiving renal replacement therapy (e.g. dialysis) are unhelpful in estimating burden of disease due to substantial misclassification and lack of access to care respectively. Therefore, representative cross-sectional data are very valuable. Sampling design, response rates and follow-up tests in those with abnormal results to confirm chronicity are strengths of this study

	Author Response	**Location in revised clean version** **(Line number)**
Methods: Creatinine eQA, specifically IDMS-traceable reference material. 'To confirm CKD, we carried out a follow up test after three months of initial data collection of the participants with albumin creatinine ratio ≥ 30 mg/g' I assume this is an unintentional omission and eGFR was also rechecked in those with initial eGFR <60? Why have the authors used the MDRD equation? A sensitivity analysis using CKD-Epi equation would be useful?	Thank you so much for pointing out this important issue. We have considered only high albumin creatinine with ≥30mg/g as a criterion for follow up however we have used both (eGFR and albumin creatinine ratio) to define presence of CKD. In absence of population validated e-GFR equation for our population, The abbreviated modification of diet in renal disease (MDRD) equation as done in previous studies was chosen over the CKD-EPI equation to facilitate comparison between our study and other studies in these region We have now highlighted this issue in our discussion sections.	241-243
	Thank you so much.	

Results: A description of the distribution of eGFR across the whole population is needed (e.g. histograms by sex)	The distribution of eGFR graph according to sex has been added in following figure. **Fig2- Histogram of eGFR distribution among 12097 participants in baseline by sex** Fig3-Histogram of eGFR distribution among 1194 participants in follow up by sex	
How do the study sample characteristics compare to estimates for the national population	Data weighting was carried out to make the sampled population comparable to the national population. Data weighting was done using sampling weight. Sample weighting was carried out for probabilities of selection of Primary sampling unit (Ward/cluster), selection of households, and selection of an individual in a household	98-102
The tables need editing:		
I assume COR and AOR represent crude and adjusted odds ratios – this needs to be made clear. It is also unclear what multivariable adjustment is being conducted – this needs to be clearly defined in the Table legend. Related to this, I think that coefficients in Table 2 are adjusted for variables in Table 3 which is very confusing. I'd suggest combing tables or alternatively describing the univariate and multivariable analyses in different tables. What do the p-values refer to?	Thank you very much for the feedback. We have made the changes as suggested. We combined two table into one table (table 2) In this study, p-value of less than 0.25 meant that there is stronger evidence in favor of the alternative hypothesis and we accept that there is some	202

	level of association between independent variable and outcome variable.	
Most readers will not be familiar with ethnic groups in Nepal and further elaboration is required.	We have now added an additional description on ethnicity as suggested.	175-185
Discussion:		
Overall the discussion is rather long and rather confused and would benefit from being rewritten in a systematic manner.	Thank you so much. We have shortened and rewritten the discussion as per the suggestion	239-319
The comparisons with studies undertaken in other countries is useful. Are these estimates age-standardised? It's probably not useful to compare to studies that aren't population representative. A more thorough exploration of the differences with other studies, specifically, demonstration of chronicity and validity of eGFR estimating equations in different ethnic groups.	We thank the reviewer for valuable feedback and now we have deleted some of the reference (previously ref no. 17, 8, 19,etc) which are not population representative and added few population based studies as references (ref no.18, 19,21,22,23,24 etc) added in our manuscript.	245-249
The discussion would also be improved by not describing associations which don't meet standard thresholds of statistical confidence (e.g. rural-urban where 95% CI include 1). The association with dalit ethnicity appears robust to multivariate adjustment but this is not discussed.	Thank you so much. We agree with the reviewer, We have added the discussion regarding ethnicity and remaining factors associated with CKD in the discussion section	276-283
Reviewer: 2 Dr. Anand Krishnan, All India Institute of Medical Sciences Centre for Community Medicine This is a large nationally representative study on prevalence of CKD in Nepal, which is worth publishing. The suggested revisions are to improve it further.		
The second line in outcome measures KDOQI can be deleted. AOR with 95% CI of risk factors should be given in the results section.	Thank you very much for the comment. We have made the changes as suggested.	28-34
Main Paper:		

The method of selection of clusters may pls be added.	Thank you! We have made the suggested changes under the heading of methods – participants sample size and study setting. We also added map of Nepal showing cluster in figure 1	75-102
The response rates during the camp may be shifted to Results.	Thank you for pointing this out. We have added the suggested content to the manuscript on the heading of methods - Participants, sample size, and study setting And Follow up of study participants to determine CKD	96 153
Authors have measured CKD twice and CKD was defined only if this was so at both times. Is this a standard procedure? The necessary details of both measurements should be added. How many were positive in first and negative in second and vice versa.	We thank the reviewer for seeking further clarification on this. As per the standard definition, an individual can only be classified as having CKD only if the measurement in at least 3 months follow up turns out to be positive as per the definition. We have added the suggested content to the manuscript on the heading of Follow up of study participants to determine CKD.	153
During weighting, was population weight and response weight also used or only sampling weights were used. It is not clear what the authors mean by saying " detailed demographic characteristics of the study population " weighted to be representative of Nepalese adult population are presented". Does table 1 – show the sample characteristics (without population weighting) Other wise it does not make any	Weighting was done using sampling weight, population weight and response weight. However, the demographic characteristics presented in the manuscript are unweighted figures. Our apologies for the overlook. We have now	

sense. It might be good to add the population proportions in an additional column.	corrected the statement on the demographic characteristics as a simple statement of describing the unweighted figures. In addition, we have added few lines in the methods about use of weight during analysis.	195-196 163-166
Results do not mention the prevalence of CKD and this seems to have been missed out by mistake.	Thank you so much for pointing this out, apologies for overlooking this. We have now added prevalence of CKD in table as well as in the result section under the heading of prevalence of CKD in the manuscript. Thank you	207
Looking at table 3, one is not clear what variables went into the analysis. For example, Age and Sex. From text it appears so but the table has to add a legend of the additional variables in the equation.	We thank you for this useful suggestion. We have now added the legends in the table	Table-2 202
The lower prevalence and lack of gender difference need a better discussion on the risk factor levels in the population and by gender (DM/HT) etc. Some discussion around the known causes of CKD	We appreciate the reviewer' comments; we have now included known cause of CKD	298-304

(infection, DM/HT nephropathy) needs to be added along with the role of chronic metal poisoning.	and described precisely in discussion section.	
Editor(s)' Comments to Author		
- Please revise your title so that it includes your study design (cross-sectional). This is the preferred format for the journal.	We appreciate the Editor's comments; we have now included *cross sectiona*l in study title	1
- Please revise the strengths and limitations section after the abstract. It should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods of the study reported (see: http://bmjopen.bmj.com/site/about/guidelines.xhtml#articletypes). It should not be a summary of the study and its findings.	Thank you very much for the comment. We have made the changes as suggested.	44-45
- Please add the relevant numbers and statistics (ORs, confidence intervals etc.) to support your statements in the results section of the abstract.	The relevant number, OR and CI has been added in abstract section.	35-39
- Please work on improving the reporting of the methods. For example, how were participants recruited? What were the settings? Sampling strategy? Inclusion criteria? Please avoid referring to other publications for methodological details. All relevant details should be included here.	Further information about the methodological details has been added on the heading of methods- Participants, sample size, and study setting as per your suggestion in the manuscript. Thank you	68-189
- What was the response rate? You have indicated it is high and is a strength of your study, but we couldn't locate where the actual response rate is presented. Please also clarify how it was calculated.	The response rate and calculation has been added under the heading participants , sample size, and study setting in baseline response rate and follow up response rate under the heading Follow up of study participants to determine CKD	Line-96 Line -159

VERSION 2 – REVIEW

REVIEWER	Caplin, Ben University College London Medical School, Centre for Nephrology
REVIEW RETURNED	07-Jan-2022

GENERAL COMMENTS	The revised manuscript is much improved although the discussion is still rather long and would benefit from editing. There remains one important issue that requires clarification. In the abstract it states: 'A participant was considered to have CKD if the Urine Albumin-to- Creatinine Ratio (uACR) was greater than or equal to 30 mg/g and/or estimated Glomerular Filtration Rate (e-GFR) is less than 60 mL/min/1.73 m2 at baseline and in follow up ...' Yet in the methods, and the authors response to the initial review, it is stated that only participants with an ACR>30mg/mmol were revisited to confirm chronicity with no mention of follow-up eGFR assessments. The authors need to positively state whether, they did, or did not, perform a repeat eGFR after >3-months in participants with an eGFR<60mL/min on initial testing. If the authors did not perform these measures the outcome they have assessed is NOT CKD. Their work would nonetheless be valuable but the outcome should be defined as a 'surrogate for CKD' e.g. eGFR<60 on one occasion or an ACR>30 on two occasions - with consequent changes throughout the manuscript. This would also have implications when comparing to other studies as the outcome would differ.

REVIEWER	Krishnan , Anand All India Institute of Medical Sciences Centre for Community Medicine
REVIEW RETURNED	16-Dec-2021

GENERAL COMMENTS	Authors have satisfactorily amended the manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Ben Caplin, University College London Medical School

Comments to the Author:

The revised manuscript is much improved although the discussion is still rather long and would benefit from editing.

There remains one important issue that requires clarification.

In the abstract it states: 'A participant was considered to have CKD if the Urine Albumin-to-Creatinine Ratio (uACR) was greater than or equal to 30 mg/g and/or estimated Glomerular Filtration Rate (e-GFR) is less than 60 mL/min/1.73 m2 at baseline and in follow up ...'

Yet in the methods, and the authors response to the initial review, it is stated that only participants with an ACR>30mg/mmol were revisited to confirm chronicity with no mention of follow-up eGFR assessments.

The authors need to positively state whether, they did, or did not, perform a repeat eGFR after >3-months in participants with an eGFR<60mL/min on initial testing.

If the authors did not perform these measures the outcome they have assessed is NOT CKD. Their work would nonetheless be valuable but the outcome should be defined as a 'surrogate for CKD' e.g. eGFR<60 on one occasion or an ACR>30 on two occasions - with consequent changes throughout the manuscript. This would also have implications when comparing to other studies as the outcome would differ.

	Author Response	Location in revised clean version (Line number)
Discussion		
The revised manuscript is much improved although the discussion is still rather long and would benefit from editing.	We thank the reviewer for valuable feedback and agreeing on the suggestion, we have further revised the discussion and also have shortened it now. All changes are in track changes version.	244-314
Methods		

There remains one important issue that requires clarification. In the abstract it states: 'A participant was considered to have CKD if the Urine Albumin-to- Creatinine Ratio (uACR) was greater than or equal to 30 mg/g and/or estimated Glomerular Filtration Rate (e-GFR) is less than 60 mL/min/1.73 m2 at baseline and in follow up ...' Yet in the methods, and the authors response to the initial review, it is stated that only participants with an ACR>30mg/mmol were revisited to confirm chronicity with no mention of follow-up eGFR assessments. The authors need to positively state whether, they did, or did not, perform a repeat eGFR after >3-months in participants with an eGFR<60mL/min on initial testing. If the authors did not perform these measures the outcome they have assessed is NOT CKD. Their work would nonetheless be valuable but the outcome should be defined as a 'surrogate for CKD' e.g. eGFR<60 on one occasion or an ACR>30 on two occasions - with consequent changes throughout the manuscript. This would also have implications when comparing to other	We thank the reviewer for identifying our error in author responses to the initial review. We apologize that it was overlooked in author response stating that only participants with an ACR>30mg/mmol were revisited to confirm chronicity with no mention of follow-up eGFR assessments. We kindly want to clarified that eGFR was estimated both at baseline and at follow-up. We have revised and added in the methods that eGFR also was used for deciding the follow-up.	158-163

studies as the outcome would differ		

VERSION 3 – REVIEW

REVIEWER	Caplin, Ben University College London Medical School, Centre for Nephrology
REVIEW RETURNED	15-Feb-2022

GENERAL COMMENTS	Thanks for addressing the key methodological issue.