BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057509
Article Type:	Original research
Date Submitted by the Author:	17-Sep-2021
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Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Glomerulonephritis < NEPHROLOGY, Renal transplantation < NEPHROLOGY

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Prevalence and Risk Factors Associated with Chronic Kidney Disease in Nepal: Evidence from a Nationally Representative Population Based Study

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Abstract

Objective: This study aimed to determine population based prevalence of Chronic Kidney Disease (CKD) and its associated factors in Nepal.

Study Design: The study was a nationwide population-based cross sectional study

Setting & Participants: nationally representative sample of 12109 adults aged 20 years and above between 2016 and 2018 in Nepal.

Primary and secondary outcome measures: Primary outcome in this study was population based prevalence of CKD in Nepal. Presence of CKD defined by using Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline criteria. 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. The secondary outcome measure was factors associated with CKD in Nepal. The co-variate adjusted association of risk factors and CKD was calculated using weighted multivariable binary logistic regression.

Results: The overall weighted prevalence of CKD was 6.0%. (95% CI: 5.5-6.6), and was similar across provinces. The prevalence of CKD was higher among male, participants with no formal education, urban residents and religious minority group. Other factors independently associated with CKD included older age, hypertension, diabetes, raised total cholesterol and increased waist-to-hip ratio.

Conclusion: This nationally representative study shows that the prevalence of CKD in the adult population of Nepal is substantial, and it is independently associated with several

cardiometabolic traits. These findings warrant longitudinal studies to identify the causes of CKD in Nepal and effective strategies to prevent it.

Keywords: Chronic Kidney Disease, Nepal, adults, prevalence, eGFR, serum creatinine

Strengths and limitations of this study

- This is the first large scale nationwide population-based prevalence of CKD in Nepal.
- Strict training processes and vigorous quality assurance programs were used to ensure the quality of data collection
- The use of standardized definitions of CKD as per Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline facilitates international comparisons of CKD prevalence and risk factors.
- High overall response rate
- Causal inference is unknown

Background

Chronic Kidney Disease (CKD) is one of the most rapidly growing non-communicable diseases (NCDs) worldwide [1]. According to the Global Burden of Disease (GBD) study, CKD was the 11th leading cause of death in 2019, up from 19th in 1990 accounting for 2.53% of total deaths[2]. CKD is also associated with substantial morbidity, mortality, and healthcare costs. Although it is largely preventable, over 9% of the population worldwide is estimated to be affected by the condition, particularly developing countries [3,4], and it is associated with diabetes type II, hypertension and obesity, which are also growing at an alarming rate. The rapid increase of CKD is likely to impose a great socioeconomic and public health burden in in resource-poor setting[5].

The evidence on the prevalence of CKD in South East Asia is relatively limited, but it consistently shows a high prevalence of CKD[6–8], however data remain poorly characterized due to inconsistent assessment of kidney function and nonstandard approaches which might distort the true estimates of CKD prevalence. There are few studies in Nepal already warned the higher prevalence of CKD[9–11] and reported data largely depends on the population studied (rural/ urban/or general/at high risk group) methods and the lack of representativeness from the general population. Nepal has overcome many of the critical health challenges to survive the first five years of life, and that NCDs and burden of potential underlying risk factors such as obesity, hypertension, and diabetes and unhealthy lifestyle habits including poor diets are highly prevalent[12].

Understanding the burden and risk factors associated with CKD is important for making health care planning, designing screening strategies, and prevention of these diseases in this resource

constrains setting, where access to renal replacement therapy is costly. Therefore, this study aimed to determine the population based prevalence of CKD and its associated factors in Nepal.

Methods

Study design and subjects

The Nepal Health Research Council designed and implemented the "National Population based Prevalence Survey of Selected NCDs in Nepal". This was a population-based survey to investigate the prevalence of NCDs including CKD, chronic obstructive pulmonary disease carried out between 2016 and 2018 in adult's ≥20 years old from seven provinces of the country. Full details of the design and protocols of the survey are available elsewhere[13].

The sample size for the survey was calculated taking as reference the prevalence of raised blood glucose (p=4%) from NCD risk factors: STEPwise approach to Surveillance(STEPS) survey 2013[14], Z value of 1.96 at 95% confidence level and margin of error (d) of 20%, design effect of 2, adjusting the sample across three domains of the Terai, hills and mountains and adding a non-response rate of 20% yielded a sample size of 12,965. With a plan to enroll 33 participants in each cluster (400), the final sample size was 13,200. A ward (lowest administrative unit of the -then Village Development Committees (VDCs) and Municipalities) was considered as a cluster-Primary Sampling Unit (PSU) of the study design. With the support from Central Bureau of Statistics, a total of 400 clusters were sampled. The survey team members in the field used official or socially mapped household list to select 33 households (Secondary Sampling Units – SSUs) from each cluster using systematic random sampling. One participant out of the eligible candidates (⩾20 years and above, resident in the study area at least 6 months and able to provide informed consent) was selected to take part in the survey using the KISH method. Of 13,200 participants who were approached for interview, 12,557 responded to the invitation in Day 1,

Among 12,557 who accepted the invitation, only 12,148 participants responded in day 2 of clinical setting. For the present study, data from 12,109 subjects were available for analyses, as 39 (0.32%) were excluded, because they refused providing blood and urine samples to evaluate renal function in day 2.

Data collection and measurements

Data collection was performed in 400 clusters within 72 districts of Nepal. Data collection teams at each site consisted of five member having academic background of nursing, general medicine, Bachelor in medical laboratory technology or public health.

Participants' appointment for face to face personal interview at convenient and accessible site or at home on two occasions (Day 1 and Day 2): Following written informed consent, from the participants in Day 1, a structured questionnaire was administered to collect information about participants' general health and socio-demographic characteristics. Participants self-reported their health and socio-demographic status, personal and family medical histories and history of medicine used. Information concerning their lifestyle factors (cigarette smoking, alcohol intake) was collected, and then physical and clinical measurements were performed. The clinical examination included measurements of height, weight, waist hip ratio and blood pressure (BP) following standard protocols. Height was measured in centimeters with a portable Bioplus® stature meter and weight with a portable digital seca® 874 weighing scale (Seca, Germany) and recorded in kilograms ensuring that the participant was wearing light clothes and was without footwear. Waist circumference was measured using Seca tape in cm at the level midway between the twelfth rib and the uppermost lateral border of the iliac crest during normal expiration. Blood pressure was measured at least three times with a minimum 3 min, and then averaged to be recorded by using an Omron digital automatic blood pressure monitor model HEM-8712 (Omron

Health Care Co., Ltd, Japan) with appropriate sized cuffs [15]. Participants were classified as hypertensive when the Raised BP is defined as having systolic BP ≥140 mm of Hg and/or diastolic BP ≥90 mm of Hg during the study, or being previously diagnosed as having hypertension.

We used fasting, at least an 8-hour fast, and two hour post prandial (PP) blood sample to test various biochemical parameters. Following aseptic technique, blood samples were drawn by a trained enumerators using vacutainers to test laboratory parameters such as fasting blood glucose level, PP blood glucose level, serum creatinine, total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) cholesterol, and serum creatinine. The well trained enumerators collected around 10 ml of blood sample at the fasting state and provided 82 grams of glucose monohydrate (equivalent to 75 grams of anhydrous glucose) in 250 ml water to drink. Second blood sample was collected at 2 hours of glucose intake. Fasting blood glucose, TC, TG, HDL cholesterol and serum creatinine were measured with the fasting sample and two hours PP sample was used for measuring PP blood glucose only. We carried out biochemical analysis with Biolyzer® 100 Clinical Chemistry Analyzer (Semi-automatic biochemistry analyzer, Analyticon, Germany) and used glucose oxidase-peroxidase (GOD-POD) method for blood glucose, cholesterol oxidase/phenol aminophenazone (CHOD-PAP) for TC, glycerol-3-phosphate oxidase/phenol aminophenazone (GPO-PAP) for TG, HDL cholesterol by poly ethylene glycol/ cholesterol oxidase/ phenol aminophenazone (PEG/CHOD-PAP) and serum creatinine measured by Jaffe Reaction method. The laboratory supervisors calculated the low-density lipoprotein (LDL) cholesterol by Freidewald's Formula using TC, TG, and HDL cholesterol.

Outcome measurements

A spot urine sample was collected from single voided specimen to measure urine albumin and creatinine using the same semi-automatic biochemistry analyzer (AnalyticonBiolyzer® 100 Clinical Chemistry Analyzer, Germany). Laboratory supervisors measured urine albumin concentration by Turbidimetric tests and urine creatinine concentration by Jaffe Reaction method and finally albumin-creatinine ration (ACR) was calculated and expressed in mg/g. Renal function was evaluated by using estimated GFR (eGFR), based on the widely used 4-variable Modification of Diet in Renal Disease Study (MDRD) equation. 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. Initially the enumerators took written informed consent from the participants. Then they collected 5 ml blood and random urine samples from the participants using similar procedures as mentioned above.

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 m^2 at baseline and in follow up[16]. The secondary outcome measure was factors associated with CKD in Nepal

Data management and analysis

We used android mobile phones inbuilt with data collection software (REMO) to collect data digitally. Data cleaning including correction of inconsistencies was performed in SPSS version 20.0. We then exported the dataset to STATA version 13 for analysis. To adjust for unequal distribution of selection and to to produce estimates that are representative of the general (national) population, all the estimation was based on sampling weight. Results are expressed as a percentage and odds ratio with 95% CI. Bivariate analysis was conducted to analyze the

unconditional association between each explanatory variable and CKD status. To be included in multivariable modeling, the level of significance α=0.25 was used during bivariate analysis (i.e., P-value 0.25 was not statistically significant). Independent variables included demographics (age, gender, ethnicity, education, province and place of residence), existing comorbidities (hypertension, diabetes, raised total cholesterol, increased waist hip ratio), any hypertension, any diabetes (self-reported or physician diagnosed [fasting blood glucose ≥126 mg/dl)], lifestyles (smoking and alcohol consumption), overweight or obesity (Body Mass Index [BMI] ≥25 kg/m^2).

Multicollinearity, the variance inflation factor (VIF) was assessed for all the independent variables found to be statistically significant from the bivariate analysis. Multivariable logistic regression modeling was conducted with CKD as a dependent variable using the independent variables identified as being statistically significant from the bivariate analysis.

Results

A total of 12,109 subjects aged 20-60 years were included in the analyses. Among them 61.1% were female, two fifth were adults in the age group 20-59 years (41.6%), one third was from upper caste ethnic group (34.2%), and just above half of them were either illiterate or had no formal schooling (54.6%). Detailed demographic characteristics of the study population weighted to be representative of the Nepalese adult population are presented in Table 1.

Table 1: Socio-demographic characteristics of the study participants (N=12,109)

Characteristics	n	%

Age		
20-39 years	4336	35.8
40-59 years	5034	41.6
60 years and above	2739	22.6
Sex		
Male	4708	38.9
Female	7401	61.1
Ethnicity		
Upper caste group	4144	34.2
Disadvantaged janajati	2546	21.0
Relatively advantaged janajati	2018	16.7
Disadvantaged non-dalit terai caste	1836	15.2
Dalit	1225	10.1
Religious minorities	340	2.8
Education		
Illiterate/No formal schooling	6607	54.6

Below secondary (<10 years)	2742	22.6
Secondary and above (≥10 years)	2760	22.8
Province		
Province 1	2049	16.9
Province 2	2003	16.5
Bagmati Province	3096	25.6
Gandaki Province	1315	10.9
Lumbini Province	2030	16.8
Karnali Province	588	4.9
Sudurpashchim Province	1028	8.5
Place of residence		
Rural	6107	50.4
Urban	6002	49.6

Table 2: Bivariate and multivariable analysis of sociodemographic risk factors for CKD among the study participants (N=12,109)

Characteristics			Chronic Kidney Disease		
	N	n (%)	COR (95% CI)	AOR (95% CI)	p-value
Age					
20-39 years	4336	118 (2.6)	1(ref)	1	
40-59 years	5034	294 (5.8)	2.3(1.8-3.0)***	1.4(1.0-1.8)**	0.021
60 years and above	2739	316 (11.5)	4.9 (3.8-6.3)***	2.6(1.9-3.6)***	0.001
Sex					
Female	7401	415 (5.7)	1(ref)		
Male	4708	313 (6.5)	1.2(1.0-1.4)	1.2 (0.8-1.6)	0.425
Ethnicity					
Upper caste	4144	212 (5.1)	1(ref)		
Disadvantaged Janajati	2546	138 (5.4)	1.1(0.8-1.4)	1.1(0.9-1.5)	0.339
Dalit	1225	84 (7.1)	1.4 (1.0-1.9)*	1.6 (1.1-2.3)	0.011
Disadvantaged non-Dalit	1836	116 (6.4)	1.3(0.9-1.7)	1.4 (0.9-2.1)	0.114

terai caste					
Religious minorities	340	25 (8.0)	1.6 (1.0-2.7)	1.7(1.0-2.9)	0.060
Relatively advantaged Janajati	2018	153 (7.4)	1.5(1.1-2.0)**	1.4(1.0-1.9)	0.028
Education					
Illiterate/No formal schooling	6607	459 (7.0)	1 (ref)		
Below secondary (<10 years)	2742	146 (5.4)	0.8(0.6-0.9)**	1.1 (0.9-1.5)	0.367
Secondary and above (≥10 years)	2760	123 (4.5)	0.6(0.5-0.8)***	1.1 (0.7-1.4)	0.894
Province					
Karnali Province	588	30 (4.7)	1 (ref)		
Province 1	2049	100 (5.2)	1.1 (0.7-1.8)	1.1(0.6-2.0)	0.728
Province 2	2003	133 (6.6)	1.4(0.9-2.3)	1.2 (0.6-2.2)	0.578
Bagmati Province	3096	196 (6.5)	1.4(0.9-2.2)	1.1 (0.6-1.9)	0.706
Gandaki Province	1315	93 (6.8)	1.5 (0.9-2.3)	1.2 (0.7-2.0)	0.575
Lumbini Province	2030	118 (5.7)	1.2(0.7-2.2)	0.9 (0.5-1.6)	0.705

Sudurpashchim Province	1028	58(5.9)	1.3(0.7-2.2)	1.4 (0.7-2.6)	0.309
Place of residence					
Rural	6107	341 (5.8)	1 (ref)	-	
Urban	6002	387 (6.5)	1.2(1.0-1.4)	1.0(0.8-1.3)	0.894

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Table 3 Bivariate and multivariate analysis of Behavioral and biological characteristics for CKD among the study participants (N=12,109)

Characteristics		Chronic Kidney Disease			p- value
	N	n (%)	COR (95%CI)	AOR (95%CI)	
Smoking habit					
Non smoker	8305	443 (5.3)	1(ref)	1(ref)	
Smokers	3804	285 (7.6)	1.5(1.2-1.7)***	1.2(1.0-1.5)	0.104
Alcohol consumption					
No	9131	537 (6.0)	1(ref)		
Yes	2978	191 (6.2)	1.0(0.9-1.2)		
Blood pressure					
Normal	7754	256 (3.3)	1(ref)	1(ref)	
Raised	4355	472 (10.8)	3.6 (3.0-4.3) ***	2.4 (2.0-3.0)***	0.001
Body mass index (N=12108)					
Normal	6896	377 (5.5)	1 (ref)	1(ref)	
Underweight	1494	88 (6.2)	1.1(0.9-1.5) *	1.1(0.8-1.6)	0.531

Overweight and obese	3718	263 (6.9)	1.3(1.1-1.5) **	0.9 (0.7-1.1)	0.153
Total cholesterol (N=10861)					
Normal	7741	398 (5.2)	1(ref)	1(ref)	
Raised	3120	254 (8.2)	1.6(1.3-2.0) ***	1.3(1.0-1.6)**	0.032
Waist hip ratio					
Normal	5095	282 (5.4)	ref		
Increased	6884	440 (6.6)	1.2(1.0-1.5)	1.6(1.2-2.3)	0.005
Diabetes Mellitus					
No	10393	506 (4.8)	1(ref)		
Yes	878	172 (19.8)	4.9(3.8-6.2) ***	3.2(2.5-4.1)	0.001

Factors associated with CKD

The multivariable analyses to investigate the association of independent factors and CKD are shown in Table 3.

In the bivariate analysis, age, smoking, BMI, ethnicity, education, having diabetes mellitus (DM), being hypertensive and having raised cholesterol were found to be statistically significantly associated with CKD. Therefore, those 8 factors including place of residence and sex of participants (P-value ≤.0.25) were considered in the multiple logistic models. After

adjustment, only six variables: age, ethnicity, diabetes, hypertension, raised TC, and increased waist hip ratio, were found to be significant predictors of CKD. There was a strong positive association between age and CKD, i.e. the odds of having CKD were about 1.4 (95% CI = 1.0-1.8) and 2.6(95% CI= 1.9-3.6) times higher for people aged 40–59 years and ≥60 years respectively, compared with people aged 20-39 years. Participants with DM had about 3.2 (95% CI = 2.5-4.1) times higher odds of occurrence of CKD than non-diabetic participants. Similarly, participants with raised BP had 2.4 (95% CI = 2.0-3.0) higher odds of having CKD than non-hypertensive/normal participants.

Participants with raised total cholesterol had 1.3 (95% CI = 1.0-1.6) times higher odds of having CKD relative to participants who had normal cholesterol level, whereas those with raised waist hip ratio had 1.6(95% CI: 1.2-2.3) times higher odds than normal participants to have CKD. Individuals who were classified as Dalit by ethnicity were 1.6 (95% CI: 1.1-2.3) times or relatively advantaged janajati had 1.4 (OR = 95% CI: 1.0-1.9) times higher odds of having CKD when compared to individuals with an upper caste.

Discussion

This is the first large scale nationwide population based representative study to report prevalence of and factors associated with CKD in Nepal among population aged 20 years and above. CKD was prevalent among 6% of the population. Moreover, increased age, diabetes, hypertension, raised TC, increased waist hip ratio, and education were independently associated to it.

The findings show that approximately one every sixteen adults in Nepal is affected by CKD. This value is higher than the 4.7% found in Ghana [17] , similar to 6.8% in South Korea [18], but much lower than the prevalence of many south Asian countries with 29.9% in Pakistan [8], 26.2 %

in Bangladesh [19] and 17.2 % in India [20]. However, a comparison between studies depends on the CKD diagnostic criteria, study design, and methodology. It is also lower than the prevalence reported by a community-based study in eastern part of Nepal [11]. We hypothesized some reasons for the lower prevalence of CKD noted in our study compared to studies from India, Pakistan and eastern Nepal. Most of these previous studies were restricted to more of urban centric, specific setting (e.g. hospital) , occupations and age where prevalence of risk factors are higher [6,19,21–23].

CKD was not found to be associated with gender in our targeted participants. Earlier literature in this regard has shown different findings. The association between CKD and gender has been reported in some other studies[24–26].

We also could not find significant association between CKD and alcohol consumption, place of residence, and provinces. Compared to rural settings, CKD seems to be more prevalent in urban areas despite the lack of statistical difference as rapid and unplanned urbanization, has contributed to the rise of kidney disease and other NCDs in Nepal which has led to lifestyles characterized by unhealthy nutrition, reduced physical activity and tobacco and alcohol consumption. However, the prevalence of CKD was not much different among provinces of Nepal.

In our study, CKD was more common in participants having lower education level and those from Relatively Advantaged Janajati and Dalit; however, the association was not found to be statistically significant. The association between smoking and CKD was supported by evidence of a dose-response relationship[27,28]. The association between smoking and CKD was reported in bivariate analysis only in our study and remained marginally significant in multivariable

analysis.Our multivariable analysis found that CKD was independently associated with older age, hypertension, diabetes, raised TC and increased waist hip ratio ($p < 0.05$ for each) which are all major NCDs risk factors and consistent with previous findings [29–33].

Age is a well-established risk factor for development of CKD[34]. As expected, age was found to be the most strongly associated risk factor in our study, we observed nearly three times higher odds of occurrence of CKD among people aged 60 years or older compared to people aged 20 to 39 years. Generally, as a part of the normal physiologic process, renal function (GFR) starts to decline even in a healthy individual by 1 mL /min/1.73 m^2 per year after the age of 30 years[35]. A similar steep increase in CKD prevalence by age has also been reported by others[36–38].

The number of patients with kidney failure treated by dialysis and transplantation has increased dramatically in Nepal. Because of the costs, limited ability to afford dialysis and the complexity of its treatment, very few patients are able to obtain adequate treatment, and CKD places a heavy financial burden on any individual and society[39,40]. Furthermore, there are many challenges concerning prevention and management kidney diseases in Nepal, firstly we currently lack population –based epidemiological data and national registry of kidney diseases. In order to reduce the frequency of disease occurrence, project the management needs of those who would acquire the disease, there is need of a data of its prevalence and associated factors to the extent possible and such knowledge only be obtained from population-based epidemiological studies.

The increase in prevalence of CKD and its progression to end-stage renal failure worldwide are mainly a result of the rising global diabetes and hypertension pandemic. In line with other surveys in South East Asia, our findings show that the odds of CKD occurrence was significantly and independently higher by around 2-fold with the presence of hypertension; this supports

previous reports[35,41–43] indicating the importance of early detection and treatment of hypertension in Nepal. In our study people with diabetes mellitus had more than three times higher odds of occurrence of CKD than people without diabetes. Almost one fifth of people with diabetes had CKD as well. Supporting findings from our research, studies around the world indicate diabetes is independently associated with development of CKD[44,45].A survey across 10 Asian countries showed that the most common cause of End Stage Renal Disease (ESRD) in 9 out of 10 countries was diabetic nephropathy[46]. In addition; elevated total cholesterol was substantially associated with higher odds for CKD.

Despite finding an association between CKD and several known established risk factors including waist hip ratio, no association was found between CKD and BMI. The correlation between CKD and waist hip ratio and not BMI is plausible since this ratio is a more sensitive marker for central obesity ,metabolic syndrome and potentially less influenced by muscle mass than BMI, this is in agreement with earlier studies[47–49].

Evidence suggested that the adverse outcomes of CKD can be prevented or altered through therapeutic interventions during early stages, including regular BP control, blood glucose control in diabetic patient, treatment with angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors and, dietary protein restriction. Given the double burden of disease and the early onset of NCDs in the country – at age 40 people are already having CKD and other co-morbidities, as shown in this manuscript, these findings have important medical and public-health implications, in targeting these “high-risk” population subgroup of the population, to reduce progression and delay the onset of cardiovascular complications and ESRD[50].

Our study poses several strengths. To the best of our knowledge, no national survey of CKD has been done in the context of Nepal as per Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline; using (eGFR <60mL/min/1.73m^2, presence of albuminuria≥30mg/g and chronicity confirmed by repeated testing after three months) to confirm presence of CKD. This is the first study to report prevalence of CKD using a validated standardized estimation of the glomerular filtration rate by the MDRD study equation which is carried out in a large representative population-based sample of the adult population in Nepal following the strict guideline and protocols, strict training processes and vigorous quality assurance programs were used to ensure the quality of data collection. Additional strengths of the study include a high overall response rate and analyses based on survey weights which ensure geographic representativeness of the study. Thus, our findings would be generalizable to the general population. However, the limitations of our analysis definitely deserve comment; potential limitations include dependency on estimation of GFR, rather than direct measurement using injection of an exogenous marker factors as well as cross-sectional design of the study which does not permit inferences regarding causal relationships.

Conclusions

This is the first population-based epidemiological survey of CKD using the protocols recommended by KDOQI in Nepal. The prevalence of CKD was found to be 6.0%. CKD was independently associated with older age, hypertension, diabetes mellitus, increased waist hip ratio and raised total cholesterol. Our findings highlight the need for early preventive measures to manage predisposing conditions such as diabetes and hypertension which could ultimately lead to CKD and to reduce the prevalence and mortality arising from the associated comorbidities in Nepal.

Declarations

Acknowledgements: The authors would like to thank all the individuals and organizations that provided technical support for the design and implementation of the main survey. The authors are grateful Dr. Shiva raj Mishra, Research Fellow in Epidemiology and Intervention Melbourne School of Population and Global Health, for reviewing the manuscript for language and grammar.

Funding: The authors have not received specific grant from any agency for this research.

Competing interests: The authors declare no conflict of interest.

Data sharing statement: The datasets used and/or analyzed will be made from the corresponding author on reasonable request

Author's contributions: KBK, KKA and MD conceived the study. LG and DKC helped in data entry and management. AP, BB and NS was involved in conducting data analysis. AP wrote the manuscript. AKJ supported in monitoring overall data quality. PG, VGL, UK, DAG and SKS revised and edited the manuscript. Each author provided intellectual content during manuscript drafting and revision, accepts accountability for their contributions.

Ethics statement: The study protocol was approved by the Ethical Review Board (ERB) of Nepal Health Research Council, Government of Nepal (Reg.no.110/2016). Written informed consent was taken from all participants before proceeding for data collection.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not required.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8-9*
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5-7
		(c) Consider use of a flow diagram	na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-17
		(b) Indicate number of participants with missing data for each variable of interest	10-17
Outcome data	15*	Report numbers of outcome events or summary measures	10-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	10-17

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	10-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence and Risk Factors Associated with Chronic Kidney Disease in Nepal: Evidence from a Nationally Representative Population Based Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057509.R1
Article Type:	Original research
Date Submitted by the Author:	10-Dec-2021
Complete List of Authors:	Poudyal, Anil; Nepal Health Research Council Karki, Khem; Goethe University Frankfurt Institute of Occupational Social and Environmental Medicine; Department of Community Medicine, Maharajgunj Medical Campus, Kathmandu, Nepal Shrestha, Namuna; Public Health Promotion and Development Organization; Aryal , KK; MOMENTUM Country and Global Leadership, Save the Children Nepal, Kathmandu, Nepal, Research Section Mahato, Namra ; Nepal Health Research Council Bista, Bihungum; Nepal Health Research Council, Research Ghimire, Laxmi; Sanjeevani College of Medical Sciences K.C., Dirghayu; Public Health Promotion and Development Organization. Kathmandu, Nepal, Research Gyanwali, Pradip ; Nepal Health Research Council Jha, Anjani; Nepal Health Research Council Garcia Larsen, Vanessa; Johns Hopkins University Bloomberg School of Public Health, International Health Kuch, Ulrich; Goethe University Frankfurt Institute of Occupational Social and Environmental Medicine, Social and Environmental Medicine Groneberg, David; Goethe University Frankfurt Institute of Occupational Social and Environmental Medicine Sharma, Sanjib Kumar; BP Koirala Institute of Health Sciences, Department of Internal Medicine Dhimal, Meghnath; Nepal Health Research Council; Goethe University Frankfurt Institute of Occupational Social and Environmental Medicine
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Urology
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Glomerulonephritis < NEPHROLOGY, Renal transplantation < NEPHROLOGY

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Prevalence and Risk Factors Associated with Chronic Kidney Disease in Nepal: Evidence from a Nationally Representative Population Based Cross sectional Study

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Abstract

Objective: This study aimed to determine population based prevalence of Chronic Kidney Disease (CKD) and its associated factors in Nepal.

Study Design: The study was a nationwide population-based cross sectional study

Setting & Participants: Cross-sectional survey conducted in a nationally representative sample of 12109 Nepalese adult from 2016 to 2018 on selected chronic non-communicable diseases were examined. Multistage cluster sampling with a mix of probability proportionate to size (PPS) and systematic random sampling was used for the selection of individuals aged 20 years and above.

Primary and secondary outcome measures: Primary outcome in this study was population based prevalence of CKD in Nepal. 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 m^2 at baseline and in follow up using modification of diet in renal disease study (MDRD) equations. The secondary outcome measure was factors associated with CKD in Nepal. The co-variate adjusted association of risk factors and CKD was calculated using multivariable binary logistic regression.

Results: The overall prevalence of CKD in Nepal was 6.0% (95% CI: 5.5-6.6). Factors independently associated with CKD included older age, (adjusted OR (AOR) 2.6, 95% CI: 1.9 to 3.6), Dalit caste (AOR 1.6, 95% CI: 1.1 to 2.3), hypertension, (AOR 2.4, 95% CI: 2.0 to 3.0) diabetes mellitus (AOR 3.2, 95% CI: 2.5 to 4.1), raised total cholesterol (AOR 1.3, 95% CI: 1.0 to 1.6) and increased waist-to-hip ratio (AOR 1.6, 95% CI: 1.2 to 2.3).

Conclusion: This nationally representative study shows that the prevalence of CKD in the adult population of Nepal is substantial, and it is independently associated with several cardiometabolic

traits. These findings warrant longitudinal studies to identify the causes of CKD in Nepal and effective strategies to prevent it.

Keywords: Chronic Kidney Disease, Nepal, adults, prevalence, eGFR, serum creatinine

Strengths and limitations of this study

- This is the first large scale nationwide population-based prevalence of CKD in Nepal.
- Strict training processes and vigorous quality assurance programs were used to ensure the quality of data collection
- The use of standardized definitions of CKD facilitates international comparisons of CKD prevalence and risk factors.
- High overall response rate of 91.7. % in first visit and 86.9% in follow up visit.
- Causal inference is unknown

Background

Chronic Kidney Disease (CKD) is one of the most rapidly growing non-communicable diseases (NCDs) worldwide [1]. According to the Global Burden of Disease (GBD) study, CKD was the 11th leading cause of death in 2019, up from 19th in 1990 accounting for 2.53% of total deaths[2]. CKD is also associated with substantial morbidity, mortality, and healthcare costs. Although it is largely preventable, over 9% of the population worldwide is estimated to be affected by the condition, particularly developing countries [3,4], and it is associated with diabetes type II, hypertension and obesity, which are also growing at an alarming rate. The rapid increase of CKD is likely to impose a great socioeconomic and public health burden in in resource-poor setting[5].

The evidence on the prevalence of CKD in South East Asia is relatively limited, but it consistently shows a high prevalence of CKD[6–8], however data remain poorly characterized due to inconsistent assessment of kidney function and nonstandard approaches which might distort the true estimates of CKD prevalence. There are few studies in Nepal already warned the higher prevalence of CKD[9–11] and reported data largely depends on the population studied (rural/ urban/or general/at high risk group) methods and the lack of representativeness from the general population. Nepal has overcome many of the critical health challenges to survive the first five years of life, and that NCDs and burden of potential underlying risk factors such as obesity, hypertension, and diabetes and unhealthy lifestyle habits including poor diets are highly prevalent[12].

Understanding the burden and risk factors associated with CKD is important for making health care planning, designing screening strategies, and prevention of these diseases in this resource constrains setting, where access to renal replacement therapy is costly. Therefore, this study aimed to determine the population based prevalence of CKD and its associated factors in Nepal.

Methods

Study design and subjects

The Nepal Health Research Council designed and implemented the "National Population based Prevalence Survey of Selected NCDs in Nepal". This was a population-based survey to investigate the prevalence of NCDs including CKD, chronic obstructive pulmonary disease carried out between 2016 and 2018 in adult's ≥20 years old from seven provinces of the country. Full details of the design and protocols of the survey are available elsewhere[13].

Participants, sample size, and study setting

The sample size for the survey was calculated taking as reference the prevalence of raised blood glucose (p=4%) from NCD risk factors: STEPwise approach to Surveillance(STEPS) survey 2013[14], Z value of 1.96 at 95% confidence level and margin of error (d) of 20%, design effect of 2, adjusting the sample across three domains of the Terai, hills and mountains and adding a non-response rate of 20% yielded a sample size of 12,965. With a plan to enroll 33 participants in each cluster (400), the final sample size was 13,200. A ward (lowest administrative unit of the -then Village Development Committees (VDCs) and Municipalities) was considered as a cluster-Primary Sampling Unit (PSU) of the study design. With the support from Central Bureau of Statistics, a total of 400 clusters were sampled. To select a representative sample of cluster; the rural and urban areas within each region were identified as the main sampling strata and the sample was selected in two stages in which ecological belts (Terai, Hill and Mountains) and five development region (Central, Eastern, Mid-Western, Western and Far western , stratification was taken into account.

The survey team members in the field used official or socially mapped household list to select 33 households (Secondary Sampling Units – SSUs) from each cluster using systematic random sampling. One participant out of the eligible candidates (⩾20 years and above, resident in the study area at least 6 months and able to provide informed consent) was selected to take part in the survey using the KISH method. Of 13,200 participants who were approached for interview, 12,557 responded to the invitation in Day 1, Among 12,557 who accepted the invitation, only 12,148 participants responded in day 2 of clinical setting. For the present study, data from 12,109 subjects were available for analyses with a response rate of 91.7%, 39 (0.32%) were excluded, because they refused providing blood and urine samples to evaluate renal function in day 2.

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 using 2011 population for Nepal with the support from Central Bureau of Statistics.

Data collection and measurements

Data collection was performed in 400 clusters (figure 1) within 72 districts of Nepal. Data collection teams at each site consisted of five member having academic background of nursing, general medicine, Bachelor in medical laboratory technology or public health.

Participants' appointment for face to face personal interview at convenient and accessible site or at home on two occasions (Day 1 and Day 2): Following written informed consent, from the participants in Day 1, a structured questionnaire was administered to collect information about participants' general health and socio-demographic characteristics. Participants self-reported their

health and socio-demographic status, personal and family medical histories and history of medicine used. Information concerning their lifestyle factors (cigarette smoking, alcohol intake) was collected, and then physical and clinical measurements were performed. The clinical examination included measurements of height, weight, waist hip ratio and blood pressure (BP) following standard protocols. Height was measured in centimeters with a portable Bioplus® stature meter and weight with a portable digital seca® 874 weighing scale (Seca, Germany) and recorded in kilograms ensuring that the participant was wearing light clothes and was without footwear. Waist circumference was measured using Seca tape in cm at the level midway between the twelfth rib and the uppermost lateral border of the iliac crest during normal expiration. Blood pressure was measured at least three times with a minimum 3 min, and then averaged to be recorded by using an Omron digital automatic blood pressure monitor model HEM-8712 (Omron Health Care Co., Ltd, Japan) with appropriate sized cuffs [15]. Participants were classified as hypertensive when the Raised BP is defined as having systolic BP ≥140 mm of Hg and/or diastolic BP ≥90 mm of Hg during the study, or being previously diagnosed as having hypertension.

We used fasting, at least an 8-hour fast, and two hour post prandial (PP) blood sample to test various biochemical parameters. Following aseptic technique, blood samples were drawn by a trained enumerators using vacutainers to test laboratory parameters such as fasting blood glucose level, PP blood glucose level, serum creatinine, total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) cholesterol, and serum creatinine. The well trained enumerators collected around 10 ml of blood sample at the fasting state and provided 82 grams of glucose monohydrate (equivalent to 75 grams of anhydrous glucose) in 250 ml water to drink. Second blood sample was collected at 2 hours of glucose intake. Fasting blood glucose, TC, TG, HDL cholesterol and serum creatinine were measured with the fasting sample and two hours PP sample

was used for measuring PP blood glucose only. We carried out biochemical analysis with Biolyzer® 100 Clinical Chemistry Analyzer (Semi-automatic biochemistry analyzer, Analyticon, Germany) and used glucose oxidase-peroxidase (GOD-POD) method for blood glucose, cholesterol oxidase/phenol aminophenazone (CHOD-PAP) for TC, glycerol-3-phosphate oxidase/phenol aminophenazone (GPO-PAP) for TG, HDL cholesterol by poly ethylene glycol/ cholesterol oxidase/ phenol aminophenazone (PEG/CHOD-PAP) and serum creatinine measured by Jaffe Reaction method. The laboratory supervisors calculated the low-density lipoprotein (LDL) cholesterol by Freidewald's Formula using TC, TG, and HDL cholesterol.

Outcome measurements

A spot urine sample was collected from single voided specimen to measure urine albumin and creatinine using the same semi-automatic biochemistry analyzer (AnalyticonBiolyzer® 100 Clinical Chemistry Analyzer, Germany). Laboratory supervisors measured urine albumin concentration by Turbidimetric tests and urine creatinine concentration by Jaffe Reaction method and finally albumin-creatinine ration (ACR) was calculated and expressed in mg/g. Renal function was evaluated by using estimated GFR (eGFR), based on the widely used 4-variable Modification of Diet in Renal Disease Study (MDRD) equation. 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) was less than 60 mL/min/1.73 m^2 at baseline and in follow up[16]. The secondary outcome measure was factors associated with CKD in Nepal

Follow up of study participants to determine CKD

Participants having albumin-creatinine ratio (ACR) greater than or equal to 30 mg/g in the baseline were revisited again after 3 months in their place of residence to ensure the chronicity of the renal

disease. Written consent was taken prior to blood and urine sample collection using similar procedures as mentioned above. Out of 1382 participants having a high ACR ratio in the baseline, 1202 gave consent. However, data of ACR was missing for 8 participants making the availability of complete data for 1194 participants for analysis, with a response rate of 86.9%.

Data management and analysis

We used android mobile phones inbuilt with data collection software (REMO) to collect data digitally. Data cleaning including correction of inconsistencies was performed in SPSS version 20.0. We then exported the dataset to STATA version 13 for analysis. To adjust for unequal probability of selection, appropriate sampling weights with complex sampling analysis were used to provide valid estimates for the relevant Nepalese population which is based on 2011 national population and housing census data. Results are expressed as a percentage and odds ratio with 95% CI. Bivariate analysis was conducted to analyze the unconditional association between each explanatory variable and CKD status. To be included in multivariable modeling, the level of significance α=0.25 was used during bivariate analysis (i.e., P-value 0.25 was not statistically significant). Independent variables included demographics (age, gender, ethnicity, education, province and place of residence), existing comorbidities (hypertension, diabetes, raised total cholesterol, increased waist hip ratio), any hypertension, any diabetes (self-reported or physician diagnosed [fasting blood glucose ≥126 mg/dl)], lifestyles (smoking and alcohol consumption), overweight or obesity (Body Mass Index [BMI] ≥25 kg/m^2).

Ethnicity/ caste data were self-reported and categorized into six major groups based on the caste coding by government of Nepal and STEPS survey Nepal, 2013 categorization[17]. (1) Upper Caste Groups (population with relatively higher socio economic and education status, mostly Brahmins, Chhetris, Thakuri and Sanyasi);(2) Disadvantaged Janajatis (disadvantaged group of people and

also indigenous, with relatively lower socio-economic and education status);(3) Dalit (untouchables, most disadvantaged marginalized group of people, with relatively lower socio-economic and education status); (4) Disadvantaged non Dalit Terai Caste Groups (disadvantaged group of people from the Terai, the lowlands, with relatively lower socio-economic and education status but not the dalit groups); (5)Religious Minorities (Muslim, Christian, etc.); (6) Relatively advantaged Janajatis (indigenous group of people with relatively higher socio-economic status, such as Gurung , Newar and Thakali)

Multicollinearity, the variance inflation factor (VIF) was assessed for all the independent variables found to be statistically significant from the bivariate analysis. Multivariable logistic regression modeling was conducted with CKD as a dependent variable using the independent variables identified as being statistically significant from the bivariate analysis.

Results

A total of 12,109 subjects aged 20 years and above were included in the analyses. Among them 61.1% were female, two fifth were adults in the age group 20-59 years (41.6%), one third was from upper caste ethnic group (34.2%), and just above half of them were either illiterate or had no formal schooling (54.6%). Table 1 presents the unweighted numbers and proportions of different demographic characteristics of the study population as measured in the study.

198 **Table 1: Socio-demographic characteristics of the study participants (N=12,109)**

Characteristics	n	%
Age		
20-39 years	4336	35.8
40-59 years	5034	41.6
60 years and above	2739	22.6
Sex		
Male	4708	38.9
Female	7401	61.1
Ethnicity		
Upper caste group	4144	34.2
Disadvantaged janajati	2546	21.0
Relatively advantaged janajati	2018	16.7
Disadvantaged non-dalit terai caste	1836	15.2
Dalit	1225	10.1
Religious minorities	340	2.8
Education		

Illiterate/No formal schooling	6607	54.6
Below secondary (<10 years)	2742	22.6
Secondary and above (≥10 years)	2760	22.8
Province		
Province 1	2049	16.9
Province 2	2003	16.5
Bagmati Province	3096	25.6
Gandaki Province	1315	10.9
Lumbini Province	2030	16.8
Karnali Province	588	4.9
Sudurpaschim Province	1028	8.5
Place of residence		
Rural	6107	50.4
Urban	6002	49.6

Table 2 Factors associated with chronic kidney disease by univariate and multivariate analysis (N = 12109)

Characteristics	Count	Chronic Kidney Diseases(CKD)		
	N	CKD prevalence (n %)	COR (95% CI)	AOR(95% CI)
Age				
20-39 years	4336	118 (2.6)	1	1
40-59 years	5034	294 (5.8)	2.3(1.8-3.0)***	1.4(1.0-1.8)*
60 years and above	2739	316 (11.5)	4.9 (3.8-6.3)***	2.6(1.9-3.6)***
Sex				
Female	7401	415 (5.7)	1	1
Male	4708	313 (6.5)	1.2(1.0-1.4)	1.2 (0.8-1.6)
Ethnicity				
Upper caste	4144	212 (5.1)	1	1
Disadvantaged Janajati	2546	138 (5.4)	1.1(0.8-1.4)	1.1(0.9-1.5)
Dalit	1225	84 (7.1)	1.4 (1.0-1.9)*	1.6 (1.1-2.3) **
Disadvantaged non-Dalitterai caste	1836	116 (6.4)	1.3(0.9-1.7)	1.4 (0.9-2.1)
Religious minorities	340	25 (8.0)	1.6 (1.0-2.7)	1.7(1.0-2.9)

Relatively advantaged Janajati	2018	153 (7.4)	1.5(1.1-2.0)*	1.4(1.0-1.9)*
Education				
Illiterate/No formal schooling	6607	459 (7.0)	1	1
Below secondary (<10 years)	2742	146 (5.4)	0.8(0.6-0.9)**	1.1 (0.9-1.5)
Secondary and above (≥10 years)	2760	123 (4.5)	0.6(0.5-0.8)***	1.1 (0.7-1.4)
Province				
Karnali Province	588	30 (4.7)	1	1
Province 1	2049	100 (5.2)	1.1 (0.7-1.8)	1.1(0.6-2.0)
Province 2	2003	133 (6.6)	1.4(0.9-2.3)	1.2 (0.6-2.2)
Bagmati Province	3096	196 (6.5)	1.4(0.9-2.2)	1.1 (0.6-1.9)
Gandaki Province	1315	93 (6.8)	1.5 (0.9-2.3)	1.2 (0.7-2.0)
Lumbini Province	2030	118 (5.7)	1.2(0.7-2.2)	0.9 (0.5-1.6)
Sudurpashchim Province	1028	58(5.9)	1.3(0.7-2.2)	1.4 (0.7-2.6)
Place of residence				
Rural	6107	341 (5.8)	1	1

Urban	6002	387 (6.5)	1.2(1.0-1.4)	1.0(0.8-1.3)
Smoking habit				
Non smoker	8305	443 (5.3)	1	1
Smokers	3804	285 (7.6)	1.5(1.2-1.7)***	1.2(1.0-1.5)
Alcohol consumption				
No	9131	537 (6.0)	1	1
Yes	2978	191 (6.2)	1.0(0.9-1.2)	
Blood pressure				
Normal	7754	256 (3.3)	1	1
Raised	4355	472 (10.8)	3.6 (3.0-4.3) ***	2.4 (2.0-3.0)***
Body mass index (N=12108)#				
Normal	6896	377 (5.5)	1	1
Underweight	1494	88 (6.2)	1.1(0.9-1.5)	1.1(0.8-1.6)
Overweight and obese	3718	263 (6.9)	1.3(1.1-1.5) **	0.9 (0.7-1.1)
Total cholesterol (N=10861)#				
Normal	7741	398 (5.2)	1	1

Raised	3120	254 (8.2)	1.6(1.3-2.0) ***	1.3(1.0-1.6)*
Waist hip ratio (N=11979)#				
Normal	5095	282 (5.4)	1	1
Increased	6884	440 (6.6)	1.2(1.0-1.5) *	1.6(1.2-2.3) *
Diabetes Mellitus (N=11271)#				
No	10393	506 (4.8)	1	1
Yes	878	172 (19.8)	4.9(3.8-6.2) ***	3.2(2.5-4.1)***
Total	12109	6.0 (95% CI: 5.5 -6.6)		

Definition of chronic kidney disease status: Urinary albumin to creatinine ratio of ≥30 mg/g and/or glomerular filtration rate <60 ml/min/1.73 m^2 both at baseline and follow up)

OR: odds ratio; CI: Confidence interval; COR: Crude odds ratio; AOR: Adjusted odds ratio. Adjusted OR estimated from the stepwise multivariate logistic regression model with all the above variables added except alcohol consumption.

[1] Reference group.

* Indicated the corresponding variable had significant impact on the occurrence of CKD.

*p value≤0.05 **p value≤0.01***p value≤0.0001

[#] Missing value; refusal for blood sample collection led to variation in the sample size

Prevalence of CKD

The overall prevalence of CKD based on the eGFR MDRD equation, (urinary albumin to creatinine ratio of ≥30 mg/g and/or glomerular filtration rate <60 both at baseline and follow up) was 6.0% (95% CI: 5.5-6.6). The prevalence was higher in males compared to female (6.5 vs 5.7) though not statistically significant. Prevalence increased with increasing age (11.5% among 60 years and above and 2.6 % among 20-39 years age group). (Table 2). The mean (±SD) eGFR in baseline was 92.6 (± 22.1) mL/min/1.73 m^2 for male and 88.2 (± 20.5) mL/min/1.73 m^2 for female (figure 2) .The mean (± SD) eGFR was 88.0 (± 25.7) mL/min/1.73 m^2 for male and 81.1 (± 23.4) mL/min/1.73 m^2 for female in follow up(figure 3).

Factors associated with CKD

The multivariable analyses to investigate the association of independent factors and CKD are shown in Table 2. In the bivariate analysis, age, smoking, BMI, ethnicity, education, having diabetes mellitus (DM), being hypertensive, increased waist hip ratio, and having raised total cholesterol were found to be statistically significantly associated with CKD. Therefore, those 9 factors including place of residence, province, and sex of participants (P-value ≤0.25) were considered in the multiple logistic models. After adjustment, only six variables: age, ethnicity, diabetes, hypertension, raised TC, and increased waist hip ratio, were found to be significant predictors of CKD. There was a strong positive association between age and CKD, i.e. the odds of having CKD were about 1.4 (95% CI : 1.0-1.8) and 2.6(95% CI: 1.9-3.6) times higher for people aged 40–59 years and ≥60 years respectively, compared with people aged 20-39 years. Participants with DM had about 3.2 (95% CI: 2.5-4.1) times higher odds of occurrence of CKD than non-diabetic participants. Similarly, participants with raised BP had 2.4 (95% CI: 2.0-3.0) higher odds of having CKD than non-hypertensive/normal participants.

Participants with raised total cholesterol had 1.3 (95% CI: 1.0-1.6) times higher odds of having CKD relative to participants who had normal cholesterol level, whereas those with raised waist hip ratio had 1.6(95% CI: 1.2-2.3) times higher odds than normal participants to have CKD. Individuals who were classified as Dalit by ethnicity were 1.6 (95% CI: 1.1-2.3) times or relatively advantaged janajati had 1.4 (95% CI: 1.0-1.9) times higher odds of having CKD when compared to individuals with an upper caste.

Discussion

This is the first large scale nationwide population based representative study to report prevalence of and factors associated with CKD in Nepal among population aged 20 years and above. In the absence of population validated e-GFR equation for our population, MDRD equation as done in previous studies was chosen over the CKD-EPI equation to facilitate comparison of results, CKD was prevalent among 6% of the population. The findings show that approximately one every sixteen adults in Nepal is affected by CKD. This value is higher than the population based study conducted in Morocco 5.1%[18] and Vietnam 3.1%[19], almost similar to 6.8% in South Korea [20], east African countries including Uganda and Kenya[21] but much lower than the prevalence of many Asian countries with 10.2% in china[22],17.5% in Thailand[23], 18.9% in Iran[24] and 17.2 % in India [25]. Prevalence of CKD in Nepal is lower than the global burden of disease study estimated prevalence of 8%–10%[3] globally. However, these differences in the prevalence of CKD may be in part due to the differences in CKD diagnostic criteria, study design, laboratory methods and lack of validated measures for eGFR for Nepalese population.

Our multivariable analysis found that CKD was independently associated with age, hypertension, diabetes, raised TC , ethnicity and increased waist hip ratio ($p < 0.05$ for each) which are all major NCDs risk factors and consistent with previous findings[26–30].Age is a well-established risk factor for development of CKD[31]. As expected, age was found to be the most strongly associated risk factor in our study, we observed nearly three times higher odds of occurrence of CKD among people aged 60 years or older compared to people aged 20 to 39 years. Generally, as a part of the normal physiologic process, renal function (GFR) starts to decline even in a healthy individual by 1 mL /min/1.73 m^2 per year after the age of 30 years[32]. A similar steep increase in CKD prevalence by age has also been reported by others[33–35].

In line with other surveys in South East Asia, our findings show that the odds of CKD occurrence was significantly and independently higher by around 2-fold with the presence of hypertension; this supports previous reports[32,36–38] indicating the importance of early detection and treatment of hypertension in Nepal. In our study people with diabetes mellitus had more than three times higher odds of occurrence of CKD than people without diabetes. Almost one fifth of people with diabetes had CKD as well. Supporting findings from our research, studies around the world indicate diabetes is independently associated with development of CKD[39,40].A survey across 10 Asian countries showed that the most common cause of End Stage Renal Disease (ESRD) in 9 out of 10 countries was diabetic nephropathy[41]. In addition; elevated total cholesterol was substantially associated with higher odds for CKD.Given the double burden of disease and the early onset of NCDs in the country – at age 40 people are already having CKD and other co-morbidities, as shown in this manuscript, these findings have important medical and public-health implications, in targeting these "high-risk" population subgroup of the population, to reduce progression and delay the onset of cardiovascular complications and ESRD[42].

Nepal is an ethnically diverse country with more than 125 castes/ethnic groups. Interestingly ethnicity/ caste was another factor contributing to CKD in our study. Compared with upper caste participants, Dalit participants had a significantly higher prevalence of CKD. The mechanism underlying these differences might be multifactorial, including cultural differences such as smoking and drinking habit, lifestyle and genetic factors. By ethnicity, Dalit group of people are considered as one of the most marginalized in terms of socioeconomic, education, political and health indicators, resulting in decreased access to resources and higher vulnerability to poor health outcomes. This calls for future studies regarding CKD on ethnic differences.

Despite finding an association between CKD and several known established risk factors including waist hip ratio, no association was found between CKD and BMI. The correlation between CKD and waist hip ratio and not BMI is plausible since this ratio is a more sensitive marker for central obesity ,metabolic syndrome and potentially less influenced by muscle mass than BMI, this is in agreement with earlier studies[28,43,44]. The association between smoking and CKD was reported in bivariate analysis only in our study.

In general, the prevalence of CKD was higher among women compared to men, and this difference has been demonstrated in the past by several population based cross sectional studies.[45] However in the present study, though not statistically significant, we found slightly higher prevalence of CKD among male participants. These discrepancies in the prevalence may be due to the traditional risk factors such as hypertension and hyperglycemia being prevalent among male participant in our study. We also could not find significant association between CKD and alcohol consumption, place of residence, and provinces.

Traditional risk factors such as diabetes and hypertension are the major cause of CKD in most developed and developing countries[46,47], and several other nontraditional and environmental risk factors such as infectious diseases, analgesic abuse, exposure to heavy metal (Lead, Arsenic, Mercury and Uranium), pesticides, herbal medications, and environmental pollution, impose an additionally threat worsening CKD especially in developing countries[48] including Nepal . However, we lack information about environmental and some of the nontraditional risk factor, which could be used to quantify the effects of these factors on CKD

Our study poses several strengths. To the best of our knowledge, no national survey of CKD has been done in the context of Nepal as per Kidney Disease Outcomes Quality Initiative (KDOQI)

clinical practice guideline; using (eGFR <60mL/min/1.73m^2, presence of albuminuria≥30mg/g and chronicity confirmed by repeated testing after three months) to confirm presence of CKD. This is the first study to report prevalence of CKD using a validated standardized estimation of the glomerular filtration rate by the MDRD study equation which is carried out in a large representative population-based sample of the adult population in Nepal following the strict guideline and protocols, strict training processes and vigorous quality assurance programs were used to ensure the quality of data collection. Additional strengths of the study include a high overall response rate and analyses based on survey weights which ensure geographic representativeness of the study. Thus, our findings would be generalizable to the general population. However, the limitations of our analysis definitely deserve comment; potential limitations include dependency on estimation of GFR, rather than direct measurement using injection of an exogenous marker factors as well as cross-sectional design of the study which does not permit inferences regarding causal relationships.

Conclusions

This is the first population-based epidemiological survey of CKD using the protocols recommended by KDOQI in Nepal. The prevalence of CKD was found to be 6.0%. The prevalence of CKD was higher among male, participants with no formal education, urban residents, smokers and participants with overweight and obese. CKD was independently associated with older age, hypertension, diabetes mellitus, increased waist hip ratio, raised total cholesterol and individual belonging to the Dalit caste by ethnicity. Our findings highlight the need for early preventive measures to manage predisposing conditions such as diabetes and hypertension which could ultimately lead to CKD and to reduce the prevalence and mortality arising from the associated comorbidities in Nepal.

Declarations

Acknowledgements: The authors would like to thank all the individuals and organizations that provided technical support for the design and implementation of the main survey. The authors are grateful Dr. Shiva raj Mishra, Research Fellow in Epidemiology and Intervention Melbourne School of Population and Global Health, for reviewing the manuscript.

Funding: The authors have not received specific grant from any agency for this research.

Competing interests: The authors declare no conflict of interest.

Data sharing statement: The datasets used and/or analyzed will be made from the corresponding author on reasonable request

Author's contributions: KBK, KKA and MD conceived the study. LG and DKC helped in data entry and management. AP, BB and NS was involved in conducting data analysis. AP wrote the manuscript. AKJ supported in monitoring overall data quality. PG, VGL, UK, DAG and SKS revised and edited the manuscript. Each author provided intellectual content during manuscript drafting and revision, accepts accountability for their contributions.

Ethics statement: The study protocol was approved by the Ethical Review Board (ERB) of Nepal Health Research Council, Government of Nepal (Reg.no.110/2016). Written informed consent was taken from all participants before proceeding for data collection.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not required.

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Figure legend

Figure 1: Map of Nepal showing the study clusters (400 clusters)

Figure 2: Histogram of estimated glomerular filtration rate (eGFR) distribution among 12097 participants in baseline by sex

Figure 3: Histogram of estimated glomerular filtration rate (eGFR) distribution among 1194 participants in follow up by sex

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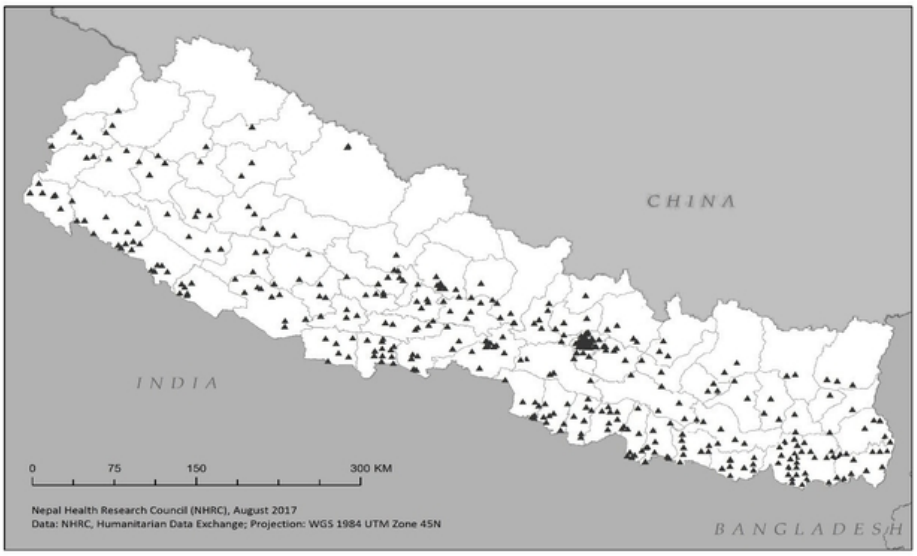

Figure 1: Map of Nepal showing the study clusters (400 clusters)

56x38mm (300 x 300 DPI)

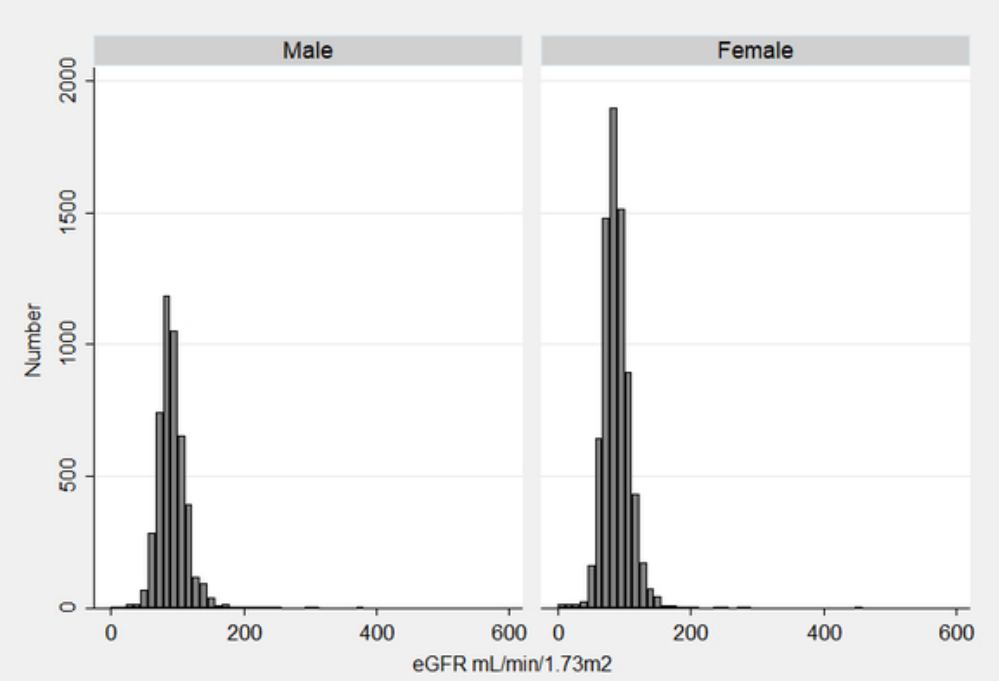

Figure 2: Histogram of estimated glomerular filtration rate (eGFR) distribution among 12097 participants in the baseline by sex

24x16mm (600 x 600 DPI)

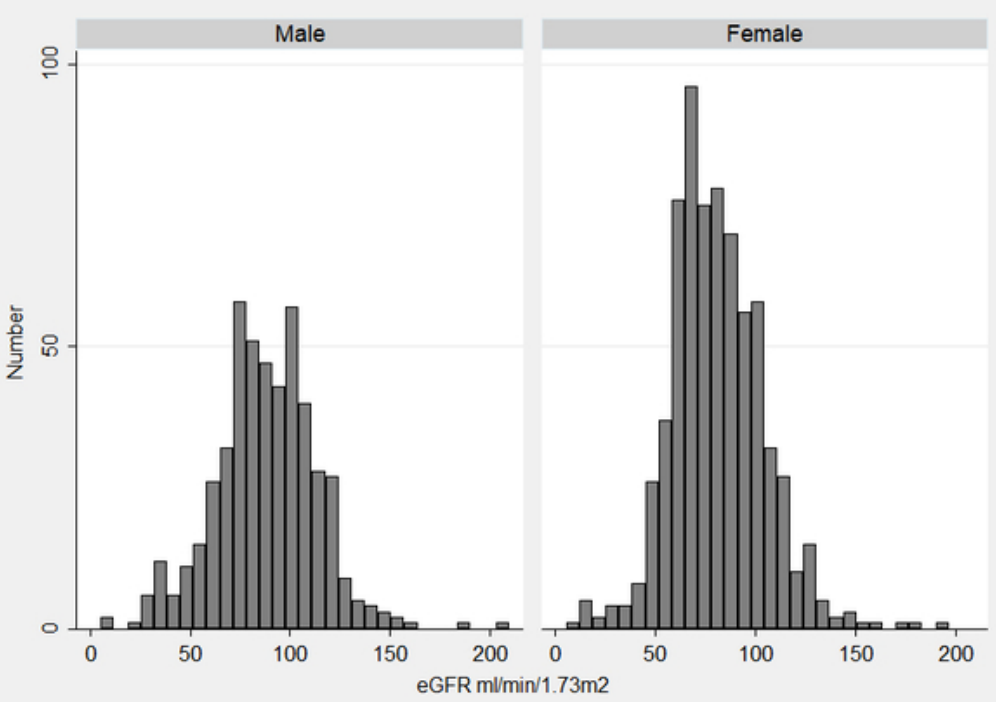

Figure 3: Histogram of estimated glomerular filtration rate (eGFR) distribution among 1194 participants in follow up by sex

24x17mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8-9*
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5-7
		(c) Consider use of a flow diagram	na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-17
		(b) Indicate number of participants with missing data for each variable of interest	10-17
Outcome data	15*	Report numbers of outcome events or summary measures	10-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	10-17

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	10-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence and Risk Factors Associated with Chronic Kidney Disease in Nepal: Evidence from a Nationally Representative Population-Based cross-sectional Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057509.R2
Article Type:	Original research
Date Submitted by the Author:	24-Jan-2022
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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Urology
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Glomerulonephritis < NEPHROLOGY, Renal transplantation < NEPHROLOGY

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Prevalence and Risk Factors Associated with Chronic Kidney Disease in Nepal: Evidence from a Nationally Representative Population Based Cross sectional Study

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Abstract

Objective: This study aimed to determine population based prevalence of Chronic Kidney Disease (CKD) and its associated factors in Nepal.

Study Design: The study was a nationwide population-based cross sectional study

Setting & Participants: Cross-sectional survey conducted in a nationally representative sample of 12109 Nepalese adult from 2016 to 2018 on selected chronic non-communicable diseases were examined. Multistage cluster sampling with a mix of probability proportionate to size (PPS) and systematic random sampling was used for the selection of individuals aged 20 years and above. **Primary and secondary outcome measures:** Primary outcome in this study was population based prevalence of CKD in Nepal. 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 m^2 at baseline and in follow up using modification of diet in renal disease study (MDRD) equations. The secondary outcome measure was factors associated with CKD in Nepal. The co-variate adjusted association of risk factors and CKD was calculated using multivariable binary logistic regression.

Results: The overall prevalence of CKD in Nepal was 6.0% (95% CI: 5.5-6.6). Factors independently associated with CKD included older age, (adjusted OR (AOR) 2.6, 95% CI: 1.9 to 3.6), Dalit caste (AOR 1.6, 95% CI: 1.1 to 2.3), hypertension, (AOR 2.4, 95% CI: 2.0 to 3.0) diabetes mellitus (AOR 3.2, 95% CI: 2.5 to 4.1), raised total cholesterol (AOR 1.3, 95% CI: 1.0 to 1.6) and increased waist-to-hip ratio (AOR 1.6, 95% CI: 1.2 to 2.3).

Conclusion: This nationally representative study shows that the prevalence of CKD in the adult population of Nepal is substantial, and it is independently associated with several

cardiometabolic traits. These findings warrant longitudinal studies to identify the causes of CKD in Nepal and effective strategies to prevent it.

Keywords: Chronic Kidney Disease, Nepal, adults, prevalence, eGFR, serum creatinine

Strengths and limitations of this study

- This is the first large scale nationwide population-based prevalence of CKD in Nepal.
- Strict training processes and vigorous quality assurance programs were used to ensure the quality of data collection
- The use of standardized definitions of CKD facilitates international comparisons of CKD prevalence and risk factors.
- High overall response rate of 91.7. % in first visit and 86.9% in follow up visit.
- Causal inference is unknown

Background

Chronic Kidney Disease (CKD) is one of the most rapidly growing non-communicable diseases (NCDs) worldwide [1]. According to the Global Burden of Disease (GBD) study, CKD was the 11th leading cause of death in 2019, up from 19th in 1990 accounting for 2.53% of total deaths[2]. CKD is also associated with substantial morbidity, mortality, and healthcare costs. Although it is largely preventable, over 9% of the population worldwide is estimated to be affected by the condition, particularly developing countries [3,4], and it is associated with diabetes type II, hypertension and obesity, which are also growing at an alarming rate. The rapid increase of CKD is likely to impose a great socioeconomic and public health burden in in resource-poor setting[5].

The evidence on the prevalence of CKD in South East Asia is relatively limited, but it consistently shows a high prevalence of CKD[6–8], however data remain poorly characterized due to inconsistent assessment of kidney function and nonstandard approaches which might distort the true estimates of CKD prevalence. There are few studies in Nepal already warned the higher prevalence of CKD[9–11] and reported data largely depends on the population studied (rural/ urban/or general/at high risk group) methods and the lack of representativeness from the general population. Nepal has overcome many of the critical health challenges to survive the first five years of life, and that NCDs and burden of potential underlying risk factors such as obesity, hypertension, and diabetes and unhealthy lifestyle habits including poor diets are highly prevalent[12].

Understanding the burden and risk factors associated with CKD is important for making health care planning, designing screening strategies, and prevention of these diseases in this resource

constrains setting, where access to renal replacement therapy is costly. Therefore, this study aimed to determine the population based prevalence of CKD and its associated factors in Nepal.

Methods

Study design and subjects

The Nepal Health Research Council designed and implemented the "National Population based Prevalence Survey of Selected NCDs in Nepal". This was a population-based survey to investigate the prevalence of NCDs including CKD, chronic obstructive pulmonary disease carried out between 2016 and 2018 in adult's ≥20 years old from seven provinces of the country. Full details of the design and protocols of the survey are available elsewhere[13].

Participants, sample size, and study setting

The sample size for the survey was calculated taking as reference the prevalence of raised blood glucose (p=4%) from NCD risk factors: STEPwise approach to Surveillance(STEPS) survey 2013[14], Z value of 1.96 at 95% confidence level and margin of error (d) of 20%, design effect of 2, adjusting the sample across three domains of the Terai, hills and mountains and adding a non-response rate of 20% yielded a sample size of 12,965. With a plan to enroll 33 participants in each cluster (400), the final sample size was 13,200. A ward (lowest administrative unit of the -then Village Development Committees (VDCs) and Municipalities) was considered as a cluster-Primary Sampling Unit (PSU) of the study design. With the support from Central Bureau of Statistics, a total of 400 clusters were sampled. To select a representative sample of cluster; the rural and urban areas within each region were identified as the main sampling strata and the sample was selected in two stages in which ecological belts (Terai, Hill and Mountains) and five

development region (Central, Eastern, Mid-Western, Western and Far western , stratification was taken into account.

The survey team members in the field used official or socially mapped household list to select 33 households (Secondary Sampling Units – SSUs) from each cluster using systematic random sampling. One participant out of the eligible candidates (⩾20 years and above, resident in the study area at least 6 months and able to provide informed consent) was selected to take part in the survey using the KISH method. Of 13,200 participants who were approached for interview, 12,557 responded to the invitation in Day 1, Among 12,557 who accepted the invitation, only 12,148 participants responded in day 2 of clinical setting. For the present study, data from 12,109 subjects were available for analyses with a response rate of 91.7%, 39 (0.32%) were excluded, because they refused providing blood and urine samples to evaluate renal function in day 2.

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 using 2011 population for Nepal with the support from Central Bureau of Statistics.

Data collection and measurements

Data collection was performed in 400 clusters (figure 1) within 72 districts of Nepal. Data collection teams at each site consisted of five member having academic background of nursing, general medicine, Bachelor in medical laboratory technology or public health.

Participants' appointment for face to face personal interview at convenient and accessible site or at home on two occasions (Day 1 and Day 2): Following written informed consent, from the

participants in Day 1, a structured questionnaire was administered to collect information about participants' general health and socio-demographic characteristics. Participants self-reported their health and socio-demographic status, personal and family medical histories and history of medicine used. Information concerning their lifestyle factors (cigarette smoking, alcohol intake) was collected, and then physical and clinical measurements were performed. The clinical examination included measurements of height, weight, waist hip ratio and blood pressure (BP) following standard protocols. Height was measured in centimeters with a portable Bioplus® stature meter and weight with a portable digital seca® 874 weighing scale (Seca, Germany) and recorded in kilograms ensuring that the participant was wearing light clothes and was without footwear. Waist circumference was measured using Seca tape in cm at the level midway between the twelfth rib and the uppermost lateral border of the iliac crest during normal expiration. Blood pressure was measured at least three times with a minimum 3 min, and then averaged to be recorded by using an Omron digital automatic blood pressure monitor model HEM-8712 (Omron Health Care Co., Ltd, Japan) with appropriate sized cuffs [15]. Participants were classified as hypertensive when the Raised BP is defined as having systolic BP ≥140 mm of Hg and/or diastolic BP ≥90 mm of Hg during the study, or being previously diagnosed as having hypertension.

We used fasting, at least an 8-hour fast, and two hour post prandial (PP) blood sample to test various biochemical parameters. Following aseptic technique, blood samples were drawn by a trained enumerators using vacutainers to test laboratory parameters such as fasting blood glucose level, PP blood glucose level, serum creatinine, total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) cholesterol, and serum creatinine. The well trained enumerators collected around 10 ml of blood sample at the fasting state and provided 82 grams of glucose

monohydrate (equivalent to 75 grams of anhydrous glucose) in 250 ml water to drink. Second blood sample was collected at 2 hours of glucose intake. Fasting blood glucose, TC, TG, HDL cholesterol and serum creatinine were measured with the fasting sample and two hours PP sample was used for measuring PP blood glucose only. We carried out biochemical analysis with Biolyzer® 100 Clinical Chemistry Analyzer (Semi-automatic biochemistry analyzer, Analyticon, Germany) and used glucose oxidase-peroxidase (GOD-POD) method for blood glucose, cholesterol oxidase/phenol aminophenazone (CHOD-PAP) for TC, glycerol-3-phosphate oxidase/phenol aminophenazone (GPO-PAP) for TG, HDL cholesterol by poly ethylene glycol/ cholesterol oxidase/ phenol aminophenazone (PEG/CHOD-PAP) and serum creatinine measured by Jaffe Reaction method. The laboratory supervisors calculated the low-density lipoprotein (LDL) cholesterol by Freidewald's Formula using TC, TG, and HDL cholesterol.

Outcome measurements

A spot urine sample was collected from single voided specimen to measure urine albumin and creatinine using the same semi-automatic biochemistry analyzer (AnalyticonBiolyzer® 100 Clinical Chemistry Analyzer, Germany). Laboratory supervisors measured urine albumin concentration by Turbidimetric tests and urine creatinine concentration by Jaffe Reaction method and finally albumin-creatinine ration (ACR) was calculated and expressed in mg/g. Renal function was evaluated by using estimated GFR (eGFR), based on the widely used 4-variable Modification of Diet in Renal Disease Study (MDRD) equation. 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) was less than 60 mL/min/1.73 m^2 at baseline and in follow up[16]. The secondary outcome measure was factors associated with CKD in Nepal

Follow up of study participants to determine CKD

Participants having either albumin-creatinine ratio (ACR) greater than or equal to 30 mg/g in the baseline and/or decreased eGFR (<60 mL/min/1.73 m2) were revisited again after 3 months in their place of residence to ensure the chronicity of the renal disease. Written consent was taken prior to blood and urine sample collection using similar procedures as mentioned above. Out of 1382 participants having a high ACR ratio and/or decreased eGFR, 1202 gave consent. However, data of ACR was missing for 8 participants making the availability of complete data for 1194 participants for analysis, with a response rate of 86.9%.

Data management and analysis

We used android mobile phones inbuilt with data collection software (REMO) to collect data digitally. Data cleaning including correction of inconsistencies was performed in SPSS version 20.0. We then exported the dataset to STATA version 13 for analysis. To adjust for unequal probability of selection, appropriate sampling weights with complex sampling analysis were used to provide valid estimates for the relevant Nepalese population which is based on 2011 national population and housing census data. Results are expressed as a percentage and odds ratio with 95% CI. Bivariate analysis was conducted to analyze the unconditional association between each explanatory variable and CKD status. To be included in multivariable modeling, the level of significance α=0.25 was used during bivariate analysis (i.e., P-value 0.25 was not statistically significant). Independent variables included demographics (age, gender, ethnicity, education, province and place of residence), existing comorbidities (hypertension, diabetes, raised total cholesterol, increased waist hip ratio), any hypertension, any diabetes (self-reported or physician diagnosed [fasting blood glucose ≥126 mg/dl)], lifestyles (smoking and alcohol consumption), overweight or obesity (Body Mass Index [BMI] ≥25 kg/m^2).

Ethnicity/ caste data were self-reported and categorized into six major groups based on the caste coding by government of Nepal and STEPS survey Nepal, 2013 categorization[17]. (1) Upper Caste Groups (population with relatively higher socio economic and education status, mostly Brahmins, Chhetris, Thakuri and Sanyasi);(2) Disadvantaged Janajatis (disadvantaged group of people and also indigenous, with relatively lower socio-economic and education status);(3) Dalit (untouchables, most disadvantaged marginalized group of people, with relatively lower socio-economic and education status); (4) Disadvantaged non Dalit Terai Caste Groups (disadvantaged group of people from the Terai, the lowlands, with relatively lower socio-economic and education status but not the dalit groups); (5)Religious Minorities (Muslim, Christian, etc.); (6) Relatively advantaged Janajatis (indigenous group of people with relatively higher socio-economic status, such as Gurung , Newar and Thakali)

Multicollinearity, the variance inflation factor (VIF) was assessed for all the independent variables found to be statistically significant from the bivariate analysis. Multivariable logistic regression modeling was conducted with CKD as a dependent variable using the independent variables identified as being statistically significant from the bivariate analysis.

Results

A total of 12,109 subjects aged 20 years and above were included in the analyses. Among them 61.1% were female, two fifth were adults in the age group 20-59 years (41.6%), one third was from upper caste ethnic group (34.2%), and just above half of them were either illiterate or had no formal schooling (54.6%). Table 1 presents the unweighted numbers and proportions of different demographic characteristics of the study population as measured in the study.

202 **Table 1: Socio-demographic characteristics of the study participants (N=12,109)**

Characteristics	n	%
Age		
20-39 years	4336	35.8
40-59 years	5034	41.6
60 years and above	2739	22.6
Sex		
Male	4708	38.9
Female	7401	61.1
Ethnicity		
Upper caste group	4144	34.2
Disadvantaged janajati	2546	21.0
Relatively advantaged janajati	2018	16.7
Disadvantaged non-dalit terai caste	1836	15.2
Dalit	1225	10.1
Religious minorities	340	2.8
Education		

Illiterate/No formal schooling	6607	54.6
Below secondary (<10 years)	2742	22.6
Secondary and above (≥10 years)	2760	22.8
Province		
Province 1	2049	16.9
Province 2	2003	16.5
Bagmati Province	3096	25.6
Gandaki Province	1315	10.9
Lumbini Province	2030	16.8
Karnali Province	588	4.9
Sudurpaschim Province	1028	8.5
Place of residence		
Rural	6107	50.4
Urban	6002	49.6

Table 2 Factors associated with chronic kidney disease by univariate and multivariate analysis (N = 12109)

Characteristics	Count	Chronic Kidney Diseases(CKD)		
	N	CKD prevalence (n %)	COR (95% CI)	AOR(95% CI)
Age				
20-39 years	4336	118 (2.6)	1	1
40-59 years	5034	294 (5.8)	2.3(1.8-3.0)***	1.4(1.0-1.8)*
60 years and above	2739	316 (11.5)	4.9 (3.8-6.3)***	2.6(1.9-3.6)***
Sex				
Female	7401	415 (5.7)	1	1
Male	4708	313 (6.5)	1.2(1.0-1.4)	1.2 (0.8-1.6)
Ethnicity				
Upper caste	4144	212 (5.1)	1	1
Disadvantaged Janajati	2546	138 (5.4)	1.1(0.8-1.4)	1.1(0.9-1.5)
Dalit	1225	84 (7.1)	1.4 (1.0-1.9)*	1.6 (1.1-2.3) **
Disadvantaged non-Dalitterai caste	1836	116 (6.4)	1.3(0.9-1.7)	1.4 (0.9-2.1)
Religious minorities	340	25 (8.0)	1.6 (1.0-2.7)	1.7(1.0-2.9)
Relatively	2018	153 (7.4)	1.5(1.1-2.0)*	1.4(1.0-1.9)*

advantaged Janajati				
Education				
Illiterate/No formal schooling	6607	459 (7.0)	1	1
Below secondary (<10 years)	2742	146 (5.4)	0.8(0.6-0.9)**	1.1 (0.9-1.5)
Secondary and above (≥10 years)	2760	123 (4.5)	0.6(0.5-0.8)***	1.1 (0.7-1.4)
Province				
Karnali Province	588	30 (4.7)	1	1
Province 1	2049	100 (5.2)	1.1 (0.7-1.8)	1.1(0.6-2.0)
Province 2	2003	133 (6.6)	1.4(0.9-2.3)	1.2 (0.6-2.2)
Bagmati Province	3096	196 (6.5)	1.4(0.9-2.2)	1.1 (0.6-1.9)
Gandaki Province	1315	93 (6.8)	1.5 (0.9-2.3)	1.2 (0.7-2.0)
Lumbini Province	2030	118 (5.7)	1.2(0.7-2.2)	0.9 (0.5-1.6)
Sudurpashchim Province	1028	58(5.9)	1.3(0.7-2.2)	1.4 (0.7-2.6)
Place of residence				
Rural	6107	341 (5.8)	1	1
Urban	6002	387 (6.5)	1.2(1.0-1.4)	1.0(0.8-1.3)

Smoking habit				
Non smoker	8305	443 (5.3)	1	1
Smokers	3804	285 (7.6)	1.5(1.2-1.7)***	1.2(1.0-1.5)
Alcohol consumption				
No	9131	537 (6.0)	1	1
Yes	2978	191 (6.2)	1.0(0.9-1.2)	
Blood pressure				
Normal	7754	256 (3.3)	1	1
Raised	4355	472 (10.8)	3.6 (3.0-4.3) ***	2.4 (2.0-3.0)***
Body mass index (N=12108)#				
Normal	6896	377 (5.5)	1	1
Underweight	1494	88 (6.2)	1.1(0.9-1.5)	1.1(0.8-1.6)
Overweight and obese	3718	263 (6.9)	1.3(1.1-1.5) **	0.9 (0.7-1.1)
Total cholesterol (N=10861)#				
Normal	7741	398 (5.2)	1	1
Raised	3120	254 (8.2)	1.6(1.3-2.0) ***	1.3(1.0-1.6)*

Waist hip ratio (N=11979)#				
Normal	5095	282 (5.4)	1	1
Increased	6884	440 (6.6)	1.2(1.0-1.5) *	1.6(1.2-2.3) *
Diabetes Mellitus (N=11271)#				
No	10393	506 (4.8)	1	1
Yes	878	172 (19.8)	4.9(3.8-6.2) ***	3.2(2.5-4.1)***
Total	12109	6.0 (95% CI: 5.5 -6.6)		

Definition of chronic kidney disease status: Urinary albumin to creatinine ratio of ≥30 mg/g and/or glomerular filtration rate <60 ml/min/1.73 m^2 both at baseline and follow up)

OR: odds ratio; CI: Confidence interval; COR: Crude odds ratio; AOR: Adjusted odds ratio. Adjusted OR estimated from the stepwise multivariate logistic regression model with all the above variables added except alcohol consumption.

[1] Reference group.

* Indicated the corresponding variable had significant impact on the occurrence of CKD.

*p value≤0.05 **p value≤0.01***p value≤0.0001

Missing value; refusal for blood sample collection led to variation in the sample size

Prevalence of CKD

The overall prevalence of CKD based on the eGFR MDRD equation, (urinary albumin to creatinine ratio of ≥30 mg/g and/or glomerular filtration rate <60 both at baseline and follow up) was 6.0% (95% CI: 5.5-6.6). The prevalence was higher in males compared to female (6.5 vs 5.7) though not statistically significant. Prevalence increased with increasing age (11.5% among 60 years and above and 2.6 % among 20-39 years age group). (Table 2). The mean (±SD) eGFR in baseline was 92.6 (± 22.1) mL/min/1.73 m^2 for male and 88.2 (± 20.5) mL/min/1.73 m^2 for female (figure 2) .The mean (± SD) eGFR was 88.0 (± 25.7) mL/min/1.73 m^2 for male and 81.1 (± 23.4) mL/min/1.73 m^2 for female in follow up(figure 3).

Factors associated with CKD

The multivariable analyses to investigate the association of independent factors and CKD are shown in Table 2. In the bivariate analysis, age, smoking, BMI, ethnicity, education, having diabetes mellitus (DM), being hypertensive, increased waist hip ratio, and having raised total cholesterol were found to be statistically significantly associated with CKD. Therefore, those 9 factors including place of residence, province, and sex of participants (P-value ≤0.25) were considered in the multiple logistic models. After adjustment, only six variables: age, ethnicity, diabetes, hypertension, raised TC, and increased waist hip ratio, were found to be significant predictors of CKD. There was a strong positive association between age and CKD, i.e. the odds of having CKD were about 1.4 (95% CI : 1.0-1.8) and 2.6(95% CI: 1.9-3.6) times higher for people aged 40–59 years and ≥60 years respectively, compared with people aged 20-39 years. Participants with DM had about 3.2 (95% CI: 2.5-4.1) times higher odds of occurrence of CKD than non-diabetic participants. Similarly, participants with raised BP had 2.4 (95% CI: 2.0-3.0) higher odds of having CKD than non-hypertensive/normal participants.

Participants with raised total cholesterol had 1.3 (95% CI: 1.0-1.6) times higher odds of having CKD relative to participants who had normal cholesterol level, whereas those with raised waist hip ratio had 1.6(95% CI: 1.2-2.3) times higher odds than normal participants to have CKD. Individuals who were classified as Dalit by ethnicity were 1.6 (95% CI: 1.1-2.3) times or relatively advantaged janajati had 1.4 (95% CI: 1.0-1.9) times higher odds of having CKD when compared to individuals with an upper caste.

Discussion

This is the first large scale nationwide population based representative study to report prevalence of and factors associated with CKD in Nepal among population aged 20 years and above. In the absence of population validated e-GFR equation for our population, MDRD equation as done in previous studies was chosen over the CKD-EPI equation to facilitate comparison of results. The findings show that approximately one in every sixteen adults (6%) is affected by CKD in Nepal. This value is higher than the population based study conducted in Morocco 5.1%[18] and Vietnam 3.1%[19], almost similar to 6.8% in South Korea [20], east African countries including Uganda and Kenya[21] but much lower than the prevalence of many Asian countries with 10.2% in china[22],17.5% in Thailand[23], 18.9% in Iran[24] and 17.2 % in India [25]. Prevalence of CKD in Nepal is lower than the global burden of disease study estimated prevalence of 8%–10%[3] globally. However, these differences in the prevalence of CKD may be in part due to the differences in CKD diagnostic criteria, study design, laboratory methods and lack of validated measures for eGFR for Nepalese population.

Our multivariable analysis found that CKD was independently associated with older age, hypertension, diabetes, raised TC, dalit and relatively advantaged janajati ethnicity and increased waist hip ratio ($p < 0.05$ for each) which are all major NCDs risk factors and consistent with previous findings[26–30].Age is a well-established risk factor for development of CKD[31]. As expected, age was found to be the most strongly associated risk factor in our study, we observed nearly three times higher odds of occurrence of CKD among people aged 60 years or older compared to people aged 20 to 39 years.

In line with other surveys in South East Asia, our findings show that the odds of CKD occurrence was significantly and independently higher by around 2-fold with the presence of

hypertension; this supports previous reports[32–35] indicating the importance of early detection and treatment of hypertension in Nepal. Similarly, people with diabetes mellitus had more than three times higher odds of occurrence of CKD. Studies around the world show diabetes to be independently associated with development of CKD[36,37]. A survey across 10 Asian countries showed that the most common cause of End Stage Renal Disease (ESRD) in 9 out of 10 countries was diabetic nephropathy[38]. In addition; elevated total cholesterol though marginal was associated with higher odds of CKD.

Nepal is an ethnically diverse country with more than 125 castes/ethnic groups. Interestingly ethnicity/caste was another factor associated with CKD in our study. Compared with upper caste participants, Dalit participants had a significantly higher prevalence of CKD. The mechanism underlying these differences might be multifactorial, including cultural differences such as smoking and drinking habit, lifestyle and genetic factors. By ethnicity, Dalit group of people are considered as one of the most marginalized in terms of socioeconomic, education, political and health indicators, resulting in decreased access to resources and higher vulnerability to poor health outcomes. This calls for future studies regarding CKD on ethnic differences.

Despite finding an association between CKD and several known established risk factors including waist hip ratio, no association was found between CKD and BMI. The correlation between CKD and waist hip ratio and not BMI is plausible since this ratio is a more sensitive marker for central obesity, metabolic syndrome and potentially less influenced by muscle mass than BMI, this is in agreement with earlier studies[28,39,40]. The association between smoking and CKD was reported in bivariate analysis only in our study.

In general, the prevalence of CKD was higher among women compared to men, and this difference has been demonstrated in the past by several population based cross sectional studies.[41] However in the present study, though not statistically significant, we found slightly higher prevalence of CKD among male participants. These discrepancies in the prevalence may be due to the traditional risk factors such as hypertension and hyperglycemia being prevalent among male participant in our study. We also could not find significant association between CKD and alcohol consumption, place of residence, and provinces.

Traditional risk factors such as diabetes and hypertension are the major cause of CKD in most developed and developing countries[42,43], and several other nontraditional and environmental risk factors such as infectious diseases, analgesic abuse, exposure to heavy metal (Lead, Arsenic, Mercury and Uranium), pesticides, herbal medications, and environmental pollution, impose an additionally threat worsening CKD especially in developing countries[44] including Nepal . However, we lack information about environmental and some of the nontraditional risk factor, which could be used to quantify the effects of these factors on CKD

Our study poses several strengths. To the best of our knowledge, this is the first national survey with a large representative population-based sample of the adult population to report prevalence of CKD in Nepal as per Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline; using (eGFR <60mL/min/1.73m^2, presence of albuminuria≥30mg/g and chronicity confirmed by repeated testing after three months) to confirm presence of CKD. The study has used a validated standardized estimation of the glomerular filtration rate by the MDRD equation and all necessary protocols, standard operating procedures and quality assurance mechanism were followed to ensure the quality of data collection. Additional strengths of the study include a high overall response rate and analyses based on survey weights which ensure geographic

representativeness of the study making the study findings generalizable to the general population. At the same time, potential limitations include dependency on estimation of GFR, rather than direct measurement using injection of an exogenous marker factors as well as cross-sectional design of the study which does not permit inferences regarding causal relationships.

Conclusions

This is the first population-based epidemiological survey of CKD using the protocols recommended by KDOQI in Nepal. The prevalence of CKD was found to be 6.0% with higher prevalence among male, participants with no formal education, urban residents, smokers and participants with overweight and obese. CKD was independently associated with older age, hypertension, diabetes mellitus, increased waist hip ratio, raised total cholesterol and individual belonging to the Dalit caste by ethnicity. Our findings highlight the need for early preventive measures to manage predisposing conditions such as diabetes and hypertension which could ultimately lead to CKD and to reduce the prevalence and mortality arising from the associated comorbidities in Nepal.

Declarations

Acknowledgements: The authors would like to thank all the individuals and organizations that provided technical support for the design and implementation of the main survey. The authors are grateful Dr. Shiva raj Mishra, Research Fellow in Epidemiology and Intervention Melbourne School of Population and Global Health, for reviewing the manuscript.

Funding: The authors have not received specific grant from any agency for this research.

Competing interests: The authors declare no conflict of interest.

Data sharing statement: The datasets used and/or analyzed will be made from the corresponding author on reasonable request

Author's contributions: KBK, MD, KKA and AKJ were involved with conception ,design and implemented the study. AP, NS and NKM, implemented the study on the field, completed data collection, overall supervision of the study. AP drafted the manuscript and conducted data analysis with input from NS, BB, LG, NKM and DK. SKS, PG, VGL, UK, DAG all contributed to critical revision of the manuscript, provided feedback on the initial draft and approved the final version. SKS, KKA, NS, PG, and MD were also involved responding to the comments raised by BMJ Open Journal reviewers; each authors reviewed the reversed manuscript critically and provided improvements, accepts accountability for their contributions. The corresponding author attests that all listed authors meet the authorship criteria.

Ethics statement: The study protocol was approved by the Ethical Review Board (ERB) of Nepal Health Research Council, Government of Nepal (Reg.no.110/2016). Written informed consent was taken from all participants before proceeding for data collection.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not required.

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Figure legend

Figure 1: Map of Nepal showing the study clusters (400 clusters)

Figure 2: Histogram of estimated glomerular filtration rate (eGFR) distribution among 12097 participants in baseline by sex

Figure 3: Histogram of estimated glomerular filtration rate (eGFR) distribution among 1194 participants in follow up by sex

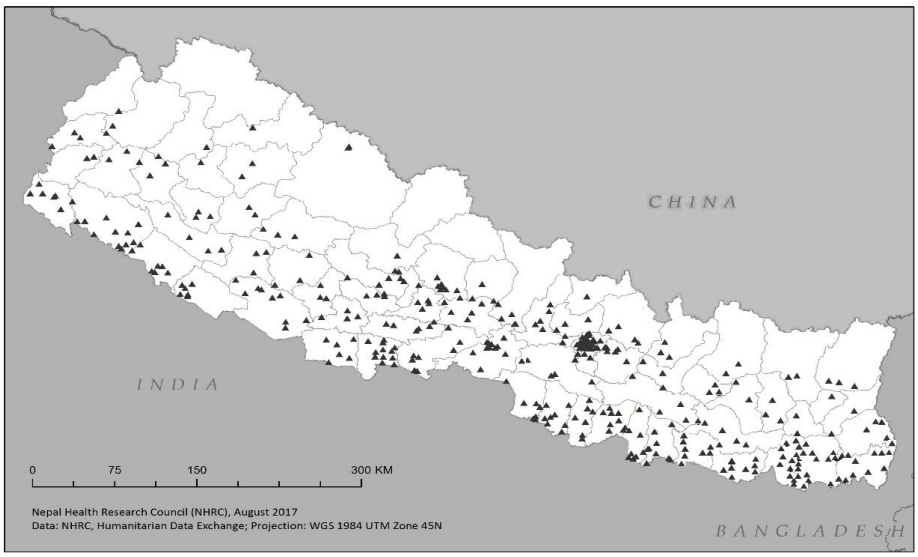

Figure 1: Map of Nepal showing the study clusters (400 clusters)

56x38mm (600 x 600 DPI)

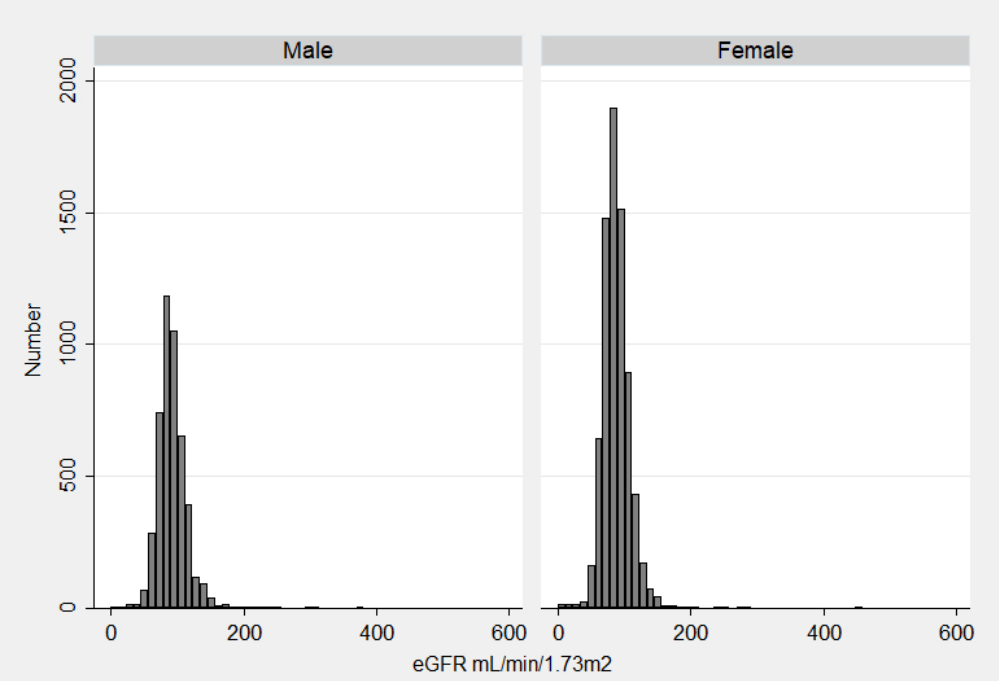

Figure 2: Histogram of estimated glomerular filtration rate (eGFR) distribution among 12097 participants in the baseline by sex

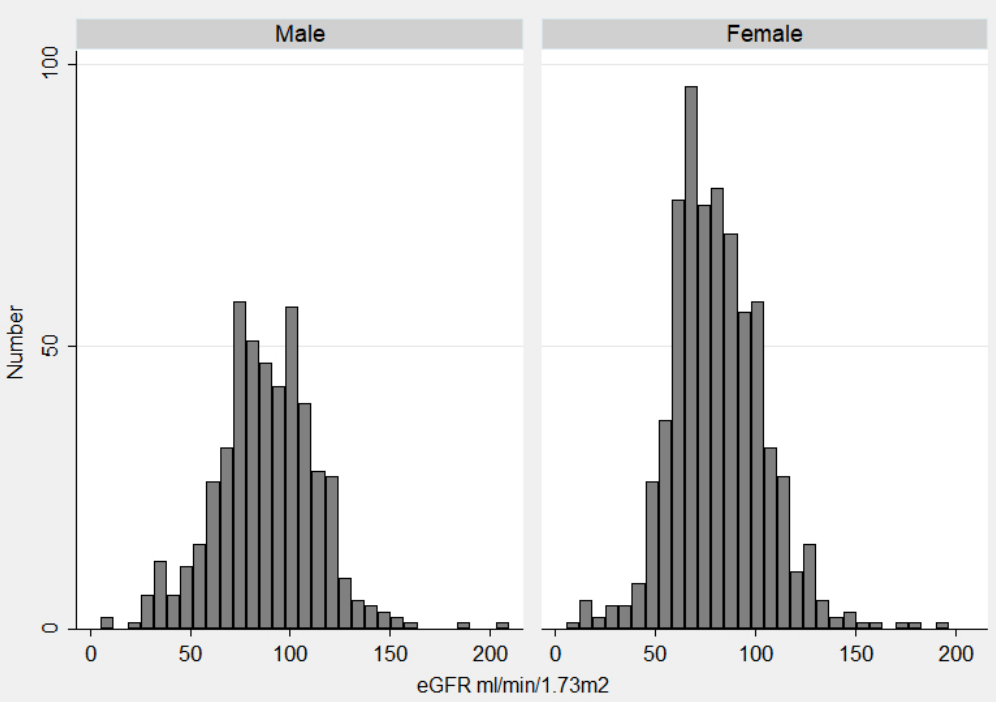

Figure 3: Histogram of estimated glomerular filtration rate (eGFR) distribution among 1194 participants in follow up by sex

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8-9*
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5-7
		(c) Consider use of a flow diagram	na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-17
		(b) Indicate number of participants with missing data for each variable of interest	10-17
Outcome data	15*	Report numbers of outcome events or summary measures	10-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	10-17

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	10-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.