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A Systematic Study of the Prevalence and Risk Factors of CKD in Uddanam, India

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Introduction: Despite reports of a high prevalence of chronic kidney disease (CKD) from the coastal Uddanam region of Andhra Pradesh, India, there are no accurate data on the distribution of kidney function abnormalities and CKD risk factors in this region.

Methods: A total of 2419 participants were recruited through multistage cluster random sampling from 67 villages. Serum creatinine and urine protein creatinine ratio were measured using validated methodologies. All abnormal estimated glomerular filtration rate (eGFR) and urine protein creatinine ratio values were reconfirmed after 3 months. A range of sociodemographic factors were evaluated for their association with CKD using Poisson regression.

Results: Of 2402 eligible subjects (mean ± SD age, 45.67 ± 13.29 years; 51% female), 506 (21.07%) had CKD (mean ± SD age, 51.79 ± 13.12 years; 41.3% female). A total of 246 (10.24%) had eGFR <60 ml/min/1.73 m^2, whereas 371 (15.45%) had an elevated urine protein creatinine ratio (>0.15 g/g). The poststratified estimates, adjusted for age and sex distribution of the region for CKD prevalence, are 18.7% (range, 16.4%–21.0%) overall and 21.3% (range, 18.2%–24.4%) and 16.2% (range, 13.7%–18.8%) in men and women, respectively. Older age, male sex, tobacco use, hypertension, and family history of CKD were independently associated with CKD. Compared with those with higher eGFR, those with eGFR <60 ml/min/1.73m^2 were older, were more likely to be uneducated, manual laborers/farmers, or tobacco users, and were more likely to have hypertension, a family history of CKD, a diagnosis of heart disease, and a lower body mass index. Among those with low eGFR, there was no difference between those with urine protein creatinine ratio <0.15 or >0.15, except a lower frequency of males in the former.

Conclusion: We confirmed the high prevalence of CKD in the adult population of Uddanam. The cause was not apparent in a majority. Subjects with a low eGFR with or without elevated proteinuria were phenotypically distinct from those with proteinuria and preserved eGFR. Our data suggest the need to apply a population-based approach to screening and prevention and studies to understand the causes of CKD in this region.

Kidney Int Rep (2020) **5,** 2246–2255; https://doi.org/10.1016/j.ekir.2020.10.004
KEYWORDS: chronic kidney disease; CKD of unknown etiology; hypertension; proteinuria; risk factors; Uddanam

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Received 19 August 2020; revised 18 September 2020; accepted 4 October 2020; published online 16 October 2020

The increasing prevalence of CKD and its health consequences are recognized the world over. While the global population prevalence of CKD is in the range of 7% to 12%,[1] geographic clusters with a high CKD burden have been reported, mostly from low- and lower middle-income countries.[2] This population consists of young males from agricultural communities

presenting with kidney failure without hypertension or proteinuria. Where available, histology shows bland interstitial nephritis. Since the exact cause of kidney disease is not clear in these clusters, they are classified under the general category of CKD of uncertain etiology (CKDu).[2]

In India, a high burden of CKDu has been reported from the Uddanam region of Srikakulam District, Andhra Pradesh, a geographically distinct rural coastal area with rich cashew and coconut plantations.[3,4] Over last 10 years, an estimated 34,000 people have been reported to have CKDu ("Uddanam nephropathy"), with >4500 deaths. The nature of Uddanam nephropathy has not been well characterized. Unpublished cross-sectional data claimed a CKD prevalence of 30% to 60%. A recent study estimated the prevalence of CKD at 18.3%.[4] Standardized study designs, methodologies, and definitions were not used, making comparisons difficult.[5] Speculations about possible etiologic factors have been made on the basis of extrapolation of findings from other parts of the world with CKDu.[6,7]

The Disadvantaged Populations Estimated Glomerular Filtration Rate Epidemiology (DEGREE) Study Group has provided a roadmap to advance the understanding of etiologic factors in these CKD clusters.[8,9] The main recommendation is creating a population-representative cohort that included patients in early stages of CKD and collecting data on the distribution of kidney function abnormalities and sociodemographic, medical, and occupational risk factors as a prelude to exploring disease etiology.

The Study to Test and Operationalize Preventive approaches for CKDu (STOP CKDu)[10] aims to estimate the true proportion of individuals with reduced eGFR, describe their clinical presentation, and establish a community-based cohort to identify risk factors associated with poor and declining kidney function in Uddanam. Here we report the prevalence and the clinico-demographic correlates of CKD and establish differences between those in different eGFR and proteinuria categories to identify a CKDu phenotype.

METHODS

Study Area and Setting

The study area consists of the geographically contiguous Uddanam region of Srikakulam District (118 villages with a population 451,188 according to the 2011 census). The region is divided into 7 administrative regions (mandals). The details of the study design including sample size estimates and study instruments have been previously published.[10] Briefly, the study uses a cluster random sampling technique using probability proportional to size methodology[11] aiming to recruit 2400 participants from 40 clusters comprising 67 villages.

Households were identified based on hand-drawn structural maps of villages. A total of 60 households were selected within each cluster by a systematic random sampling technique. Within each household, 1 individual participant >18 years of age was selected using preassigned quota based on sex and age groups (eg, 18–29, 30–44, 45–69, and >69 years of age). The study was approved by the Ethics Committee of The George Institute for Global Health India, and all subjects provided written consent.

The study aimed to recruit 2400 subjects with a goal to estimate the prevalence of CKD within 20% of the true prevalence (relative precision) with 95% confidence. We assumed a prevalence of 10%, and are therefore be able to estimate the prevalence within 2 percentage points of true prevalence. We considered a design effect of 2 to account for the clustered sampling design. We inflated the sample size to account for a 25% loss to follow-up.

Study Procedures

Community meetings were conducted from December 2017 to May 2018 to understand expectations and ensure participation. Recruitment started in May 2018. Demographic profile, socioeconomic status, occupational history, medical history, and health-seeking behavior were recorded. Blood pressure was measured with an automated clinically validated sphygmomanometer (Omron HEM 7121, Tokyo, Japan). An average of 3 readings was recorded and was repeated at least 1 month later.

Serum and urine creatinine were tested using the modified Jaffe assay traceable to isotope dilution mass spectrometry reference standard. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Urine protein was measured using a pyrogallol test and corrected for creatinine, and glycosylated hemoglobin was performed on automated analyzer (Hb-Vario, Erba Lachema, Brno, Czech Republic, and Transasia Bio-Medicals, Mumbai, India) in compliance with National Glycohemoglobin Standardization Programme. All tests were conducted on the day of collection. Plasma, serum, buffy coat, and urine samples were stored at −80 °C in barcoded cryovials.

All subjects with eGFR <60 ml/min/1.73 m^2 or urine protein creatinine ratio (uPCR) >0.15 g/g underwent repeat testing after 3 months.

Hypertension was defined as blood pressure ≥140/90 mm Hg or if the participant had ever been told by doctor that they had hypertension, whereas diabetes was defined as a glycosylated hemoglobin ≥6.5 or any

individual who was taking any allopathic medication for diabetes. CKD was defined and classified as per Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[12]

Data Management

Study questionnaires and samples were labeled using unique identifiers and barcoded. Data were entered into a customized electronic data capture system hosted on secure servers with end-to-end data encryption. Validation and quality monitoring were undertaken by exporting the data into Excel (Microsoft Inc, Redmond, WA) and undertaking random checks against the original data. Discrepancies were corrected and an audit trail was maintained. Data management procedures followed the standard operating practices of the George Institute (Data Management SOP/DM–SOP-32, version 3.0) and the guidelines of the Indian Council of Medical Research.

Statistical Analysis

The primary outcome was the binary variable of CKD. A range of risk factors were considered: age, sex, education, occupation, household income, tobacco use, alcohol consumption, pain killer medication use, family history of CKD, presence of hypertension and diabetes, and body mass index. The distribution of these risk factors among study participants was examined; percentages were reported for the categorical variables, means and standard deviations were reported for continuous variables with bell-shaped distributions, and medians and interquartile ranges (IQRs) were reported for those with skewed distributions. All prevalence estimates and 95% confidence intervals (CIs) were calculated accounting for the clustered sampling design. The probability proportional to size sampling of villages and the systematic sampling of households within villages helped ensure representativeness of sample at household level. To address the imbalance in age distribution among men and women resulting from quota-based sampling of individuals from households, we used the age distribution for men and women of Srikakulam district from Census 2011 and calculated poststratified estimates of prevalence.[13] To measure the association between the risk factors and the outcomes, prevlaence ratios were estimated using modified Poisson regression accounting for clustered sampling design. $P < 0.05$ was considered statistically significant. Analyses were carried out using R statistical software (version 3.6.1; available at http://www.R-project.org/).

RESULTS

Figure 1 shows the flow of participants through the study. A total of 2419 participants were recruited between May and December 2018, of whom 598 were found to have abnormal eGFR or PCR values on initial testing. Repeat testing was done between January and March 2019. We excluded 17 participants from the analytic sample: 5 who had migrated, 10 who withdrew consent, and 2 who died from non-CKD causes, for a total of 2402 participants.

The sociodemographic and economic characteristics of study participants by gender are shown in Table 1. The mean age of the participants was 45.7 ± 13.3 years, with women constituting 51%. A plurality (38.3%) had not received any formal education, and 75.6% were manual workers or farmers. Most of the participants reported monthly household incomes of 3000 to 10,000 Indian rupees (163 Int'l$–544 Int'l$, $40–$135 USD) per month.

Tobacco use was more prevalent among men, with smokeless tobacco use being more common (85% of tobacco consumers used tobacco in chewing form, 4% used smoking tobacco products, and 10% used both). About 43.7% of subjects reported regular use of over the counter pain relief medications, the proportion being higher in women.

In terms of the traditional CKD risk factors, 998 (41.6%) had hypertension, 215 (8.9%) having the diagnosis for ≥5 years, 317 (13.1%) had diabetes, and 334 (13.9%) had a family history of CKD. About a quarter (25.8%) of the participants were overweight. Of all the subjects with hypertension and diabetes, 28.8% and 43.5% were newly diagnosed, respectively.

Distribution of Renal Function and Characteristics of Subjects with CKD

The median (IQR) eGFR and uPCR of the study population were 103.6 (26.13) ml/min/1.73 m^2 and 0.09 (0.04) g/g, respectively. After both rounds of testing, the diagnosis of CKD was confirmed in 506 (21.1%) subjects. Of these, 246 (10.23%) had eGFR <60 ml/min/1.73 m^2 and 371 (15.4%) had uPCR >0.15 g/g (Supplementary Table S1). The eGFR and uPCR distributions are shown in Figure 2.

The diagnosis was made on the basis of abnormal eGFR alone in 183 (36.2%), abnormal uPCR alone in 247 (48.8%), and both parameters were abnormal in 138 (27.2%) participants (Supplementary Table S1). Four (0.79%) participants had high-grade proteinuria (uPCR ≥3 g/g). Of these, 2 had underlying diabetes or longstanding hypertension and the other 2 had glomerulonephritis proven with a biopsy specimen. A

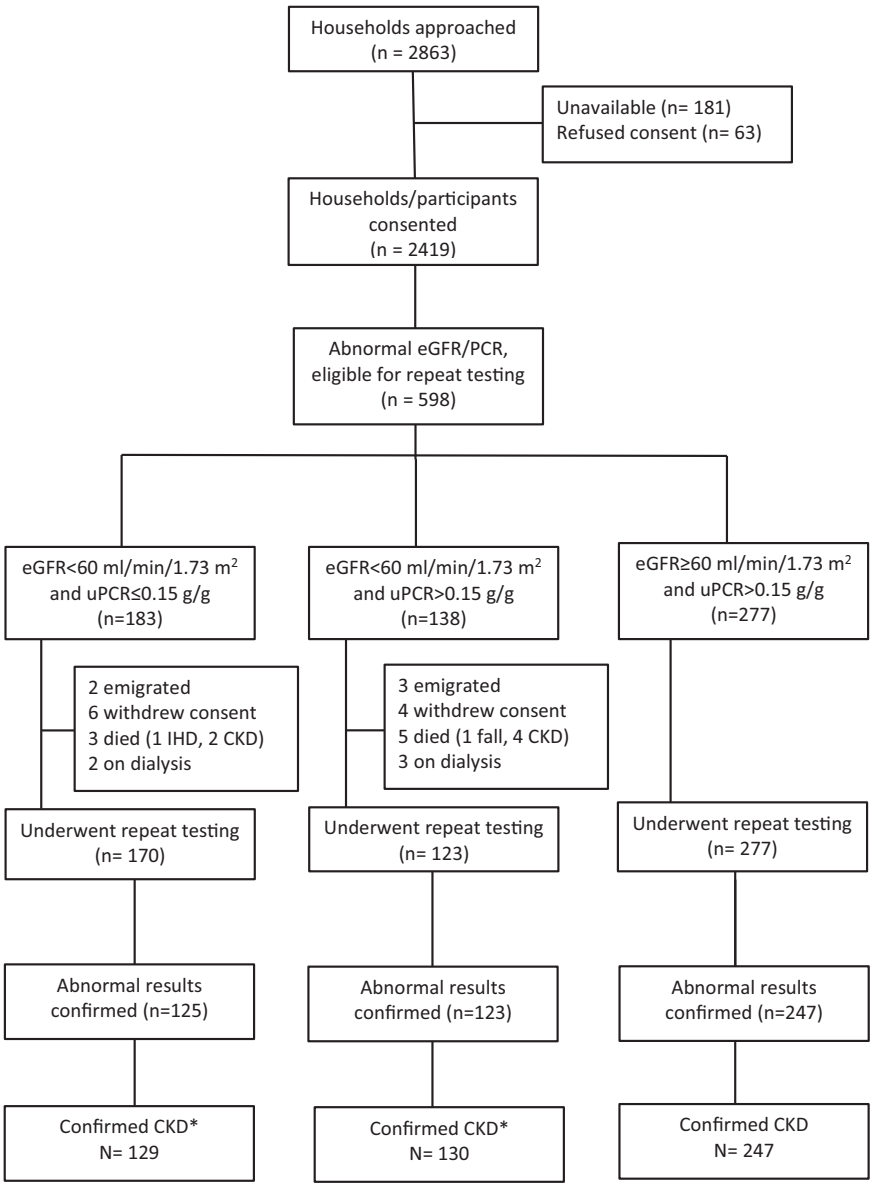

Figure 1. Flow of subjects through the Study to Test and Operationalize Preventive approaches for CKD of uncertain etiology study. *Confirmed CKD includes those with abnormal values plus deaths due to CKD plus patients on dialysis. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; uPCR, urine protein creatinine ratio.

total of 122 (24.11%) participants were aware of the diagnosis of CKD before the survey. Of these, 64 (52.46%) had undergone an ultrasound examination of kidneys; 10 were advised to have a biopsy specimen of the kidney obtained, but only 4 had underdone the procedure, with a diagnosis of minimal change disease and mesangiocapillary glomerulonephritis, vascular changes of hypertension with glomerular obsolescence, and nonspecific tubule-interstitial fibrosis in 1 case each.

The mean age of participants with CKD was 51.79 ± 13.12 years, and 209 (41.3%) were women. An overwhelming majority was ≥45 years of age, engaged in outdoor or manual work, and had a monthly family income of ≤10,000 Indian rupees (≤544 Int'l$, ≤$135 USD). These patients reported a high prevalence of tobacco use and the regular consumption of pain relief medications.

Table 2 presents the sociodemographic characteristics of participants with CKD according to the abnormal eGFR and proteinuria categories. Compared with those with higher eGFR, those with eGFR <60 ml/min/1.73 m^2 were older, more likely to be uneducated, manual laborers/farmers, tobacco users, have hypertension, a family history of CKD, a diagnosis of heart disease, and a lower body mass index. Among those with eGFR <60 ml/min/1.73 m^2, the only difference between those with uPCR <0.15 (A1–2) or >0.15 (A3) was the lower frequency of males in the former group ($P < .01$).

Table 1. Sociodemographic, economic, lifestyle, and clinical characteristics of the study population by gender

Characteristics	Male, n = 1180	Female, n = 1222	Total, n = 2402
Sociodemographic, economic, and lifestyle			
Age, yrs, n (%)			
<25	81 (6.86)	50 (4.09)	131 (5.45)
25–34	164 (13.9)	225 (18.41)	389 (16.19)
35–44	272 (23.05)	343 (28.07)	615 (25.6)
45–54	311 (26.36)	314 (25.7)	625 (26.02)
≥55	352 (29.83)	290 (23.73)	642 (26.73)
Age, yrs, mean (SD)	46.8 (13.99)	44.57 (12.49)	45.67 (13.29)
Education, n (%)			
No formal education	302 (25.59)	618 (50.57)	920 (38.3)
School education	481 (40.76)	410 (33.55)	891 (37.09)
College education	397 (33.64)	194 (15.88)	591 (24.6)
Occupation, n (%)			
Not working	79 (6.69)	340 (27.82)	419 (17.44)
Sedentary workers	114 (9.66)	53 (4.34)	167 (6.95)
Manual workers/farmers[a]	987 (83.64)	829 (67.84)	1816 (75.6)
Family income, INR/month, n (%)			
<3000	41 (3.47)	50 (4.09)	91 (3.79)
3000–10,000	924 (78.31)	994 (81.34)	1918 (79.85)
10,001–20,000	185 (15.68)	156 (12.77)	341 (14.2)
>20,000	30 (2.54)	22 (1.8)	52 (2.16)
Current or past tobacco use, n (%)	649 (55)	383 (31.34)	1032 (42.96)
Alcohol use, n (%)	670 (56.78)	18 (1.47)	688 (28.64)
Pain relief medication use, n (%)	459 (38.9)	591 (48.36)	1050 (43.71)
Clinical			
Family history of CKD, n (%)	157 (13.31)	177 (14.48)	334 (13.91)
Self-reported medical history, n (%)			
Hypertension	403 (34.15)	308 (25.2)	711 (29.6)
Longstanding hypertension (≥5 yrs)	119 (10.08)	96 (7.86)	215 (8.95)
Diabetes	120 (10.18)	61 (4.99)	181 (7.54)
Heart disease	138 (11.69)	111 (9.08)	249 (10.37)
CKD	93 (7.88)	55 (4.5)	148 (6.16)
Hypertension,[b] n (%)	575 (48.73)	423 (34.62)	998 (41.55)
Diabetes,[b] n (%)	182 (15.44)	131 (10.72)	313 (13.04)
BMI, kg/m^2, n (%)			
<18.5	172 (14.58)	202 (16.53)	374 (15.57)
18.5-25	703 (59.58)	704 (57.61)	1407 (58.58)
≥25	305 (25.85)	316 (25.86)	621 (25.85)
Hemoglobin, g/dl, mean (SD)	14.27 (2.12)	12.13 (1.51)	13.18 (2.13)
uPCR, g/g, n (%)			
≤0.15	949 (80.42)	1082 (88.54)	2031 (84.55)
>0.15–<0.5	110 (9.32)	91 (7.45)	201 (8.37)
0.5–<3	119 (10.08)	47 (3.85)	166 (6.91)
≥3	2 (0.17)	2 (0.16)	4 (0.17)
eGFR, ml/min/1.73 m^2, n (%)			
≥60	1036 (87.8)	1120 (91.65)	2156 (89.76)
30–<60	77 (6.53)	62 (5.07)	139 (5.79)
>15–<30	45 (3.81)	22 (1.8)	67 (2.79)
≤15	22 (1.86)	18 (1.47)	40 (1.67)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, Indian rupee; SD, standard deviation; uPCR, urine protein creatinine ratio.
[a]Skilled, semiskilled, unskilled manual laborers, and farmers.
[b]Self-reported and newly diagnosed.

In addition, we compared those with CKD with diabetes, recent or longstanding hypertension, and those without either condition (Supplementary Table S2). The last group was younger, had a lower frequency of males, tobacco and alcohol users, consumers of pain relief medications, family history of kidney disease, and higher eGFR.

We noticed some geographic heterogeneity in the prevalence of CKD. Sompeta mandal had the lowest prevalence of CKD (13.4% [95% CI 9.7%–17.1%]) whereas Kaviti showed the highest prevalence (25.4% [95% CI 18.9%–32.0%]; Figure 3 and Supplementary Table S3).

Figure 4 shows the distribution of PCR and eGFR as per KDIGO risk categories. According to this

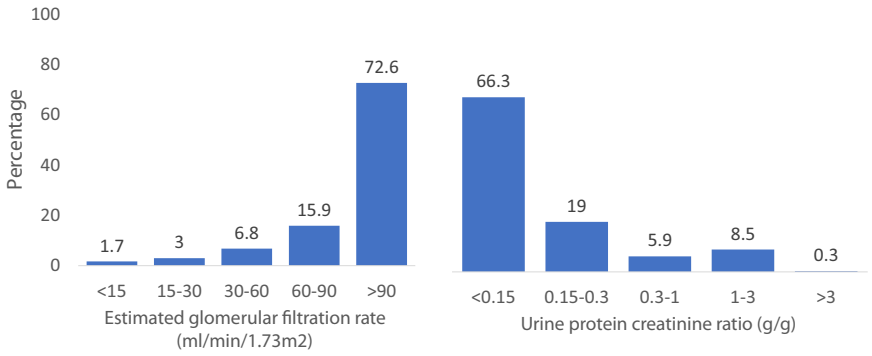

Figure 2. Distribution of estimated glomerular filtration rate and urine protein creatinine ratio in the study population.

framework, 27.9% and 28.9% of those with CKD were categorized as high and very high risk for cardiovascular disease, respectively.

Table 3 presents the crude and adjusted prevalence ratio estimates from the unadjusted and adjusted modified Poisson regression analyses. In the unadjusted analysis, older age, being a male, not having formal education, having history of hypertension, diabetes, family history of CKD, tobacco use, alcohol use, being a laborer by occupation, and being underweight were found to significantly associated with higher risks of CKD. After adjusting for all the risk factors, older participants (adjusted prevalence ratio [aPR] = 1.70 [1.33–2.20]), males (aPR = 1.35 [1.05–1.73]), tobacco users (aPR = 1.25 [1.01–1.54]), participants with hypertension (aPR = 1.74 [1.42–2.14]), and those with family history of CKD (aPR = 1.33 [1.05–1.67]) were found to have a higher risk of CKD.

DISCUSSION

This population-based study establishes the prevalence of CKD in the Uddanam region and provides an understanding of the population-level characterstics of those without and with CKD disaggregated according to the degree of proteinuria and eGFR values. We found the overall age and sex adjusted prevalence of CKD to be 18.7%: 21.3% in men and 16.2% in women, 2.5 to 3.3 times the population prevalence of CKD described from other parts of India.[14] We also identified the sociodemographic and clinical characteristics that are independently associated with CKD in Uddanam. A striking finding was the relatively high (42%) prevalence of hypertension, with about 30% being identified for the first time.

Most of the newly identified cases did not have any of the traditional CKD risk factors, such as hypertension, diabetes, or other identifiable causes. Among those with low eGFR, typically referred to as having CKDu, or Uddanam nephropathy,[2,15] we did not find any difference in the sociodemographic and clinical characteristics between groups with A1 and A2 to A3 proteinuria (except a lower proportion of males in the former), including the proportion of those with diabetes or hypertension, suggesting a continuum rather than distinct presentations depending on the degree of proteinuria. A number of case definitions have been proposed for CKDu. While all of them require the absence of diabetes and longstanding or severe hypertension, the proteinuria threshold is not clearly defined. Some definitions from Sri Lanka and Latin America allow inclusion of moderate proteinuria, but others limit the diagnosis of CKDu only to those with A1.

We identified another population that exhibited low- to moderate-grade proteinuria with preserved eGFR. This population was younger, had a lower prevalence of hypertension, and used tobacco. Interestingly, the frequency of undetected hypertension was higher in this group compared with those with grade 3 to grade 5 disease (35.6% vs. 13.8%, $P < .01$). Our finding is similar to the report by Aguilar-Ramirez *et al.*[16] among adults from an agricultural community in Tierra Blanca, Mexico. They diagnosed CKD on the basis of A3 or higher proteinuria alone in about 24% of subjects with grade 1 to grade 2 disease. Other reports on endemic nephropathies from Central America and Sri Lanka do not focus on proteinuria, apart from mentioning that low- to moderate-grade proteinuria is consistent with a diagnosis of CKDu.[15,17] The natural history of patients with isolated low-grade proteinuria within the overall framework of a population with CKDu is not known because there are no longitudinal studies of these subjects in India.

Since the populations with low eGFR are relatively homogeneous, irrespective of the presence or absence of diabetes or hypertension, we have refrained from ascribing cause to CKD. The fact that a significant proportion of cases with diabetes and hypertension were identified during the survey suggests the

Table 2. Sociodemographic, economic, lifestyle, and clinical characteristics of study participants with CKD

Characteristics	Group 1, *n* = 129	Group 2, *n* = 130	Group 3, *n* = 247	*P* value group (1 + 2) vs. 3
Sociodemographic, economic, and lifestyle				
Age, yrs, *n* (%)				<0.01
<25	0 (0)	0 (0)	12 (4.86)	
25–34	2 (1.55)	4 (3.08)	33 (13.36)	
35–44	8 (6.2)	19 (14.62)	64 (25.91)	
45–54	41 (31.78)	38 (29.23)	66 (26.72)	
≥55	78 (60.47)	69 (53.08)	72 (29.15)	
Age, yrs, mean (SD)	57.68 (10.32)	55.64 (12.16)	46.69 (12.98)	<0.01
Males, *n* (%)	63 (48.84)	90 (69.23)	144 (58.3)	0.93
Education, *n* (%)				<0.01
No formal education	86 (66.67)	63 (48.46)	93 (37.65)	
School education	31 (24.03)	48 (36.92)	96 (38.87)	
College education	12 (9.3)	19 (14.62)	58 (23.48)	
Occupation, *n* (%)				0.02
Not working	18 (13.95)	14 (10.77)	48 (19.43)	
Sedentary workers	4 (3.1)	7 (5.38)	19 (7.69)	
Manual workers/farmers[a]	107 (82.95)	109 (83.85)	180 (72.87)	
Family income, INR/month, *n* (%)				0.04
<3000	10 (7.75)	8 (6.15)	6 (2.43)	
3000–10,000	104 (80.62)	107 (82.31)	203 (82.19)	
10,001–20,000	14 (10.85)	12 (9.23)	36 (14.57)	
≥20,000	1 (0.78)	3 (2.31)	2 (0.81)	
Current or past tobacco use, *n* (%)	89 (68.99)	81 (62.31)	124 (50.2)	<0.01
Regular alcohol use, *n* (%)	49 (37.98)	62 (47.69)	86 (34.82)	0.08
Pain relief medication use, *n* (%)	64 (49.61)	72 (55.38)	109 (44.13)	0.07
Clinical				
Family history of CKD, *n* (%)	38 (29.46)	35 (26.92)	26 (10.53)	<0.01
Self-reported medical history, *n* (%)				
Hypertension	83 (64.34)	86 (66.15)	76 (30.77)	<0.01
Longstanding hypertension (≥5 yrs)	32 (24.81)	35 (26.92)	23 (9.31)	<0.01
Diabetes	20 (15.5)	18 (13.95)	20 (8.1)	0.03
Heart disease	25 (19.38)	30 (23.08)	33 (13.36)	0.03
CKD	53 (41.09)	61 (46.92)	8 (3.24)	<0.01
Hypertension,[b] *n* (%)	94 (72.87)	102 (78.46)	118 (47.77)	<0.01
Diabetes,[b] *n* (%)	21 (16.28)	23 (17.69)	47 (19.03)	0.63
Absence of diabetes and hypertension, *n* (%)	32 (24.81)	27 (20.77)	121 (48.99)	<0.01
Body mass index, kg/m^2, *n* (%)				<0.01
<18.5	29 (22.48)	28 (21.54)	49 (19.84)	
≥18.5–<25.0	80 (62.02)	83 (63.85)	132 (53.44)	
≥25	20 (15.5)	19 (14.62)	66 (26.72)	
Hemoglobin, g/dl, mean (SD)	11.46 (1.63)	11.4 (2.27)	13.57 (2.1)	<0.01

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, Indian rupee; SD, standard deviation; uPCR, urine protein creatinine ratio.
[a]Skilled, semiskilled, unskilled manual laborers, and farmers.
[b]Self-reported and newly diagnosed.
Group 1: eGFR <60 ml/min/1.73 m^2 and uPCR ≤0.15 g/g. Group 2: eGFR <60 ml/min/1.73 m^2 and uPCR >0.15 g/g. Group 3: eGFR ≥60 ml/min/1.73 m^2 and uPCR >0.15 g/g.

possibility of missed diagnosis because of a lack of access to care rather than true absence of the condition. Our data suggest the need to apply a population-based approach to CKD in this region rather than focusing on the presence or absence of a pre-existing condition or particular eGFR or proteinuria cutoffs. All cases of CKD, including those with diabetes and hypertension, should be included because the same common factors might be operating in these people as well. Following-up with individuals with newly discovered kidney disease will help understanding of disease cause(s) and determinants of progression. The latter, however, might be affected by the medical care they will now receive.[9] In addition to occupational or environmental causes, etiologic considerations for CKD should include previously undiagnosed glomerulonephritis or low birth weight giving rise to low-grade proteinuria and progressive CKD later in life.

About 1 of every 5 subjects with CKD had ≥1 first-degree relative with CKD. This figure is higher than those reported from other population-based surveys. This could suggest a genetic basis, and requires detailed evaluation using modern sequencing techniques.[18] An alternate explanation is exposure to

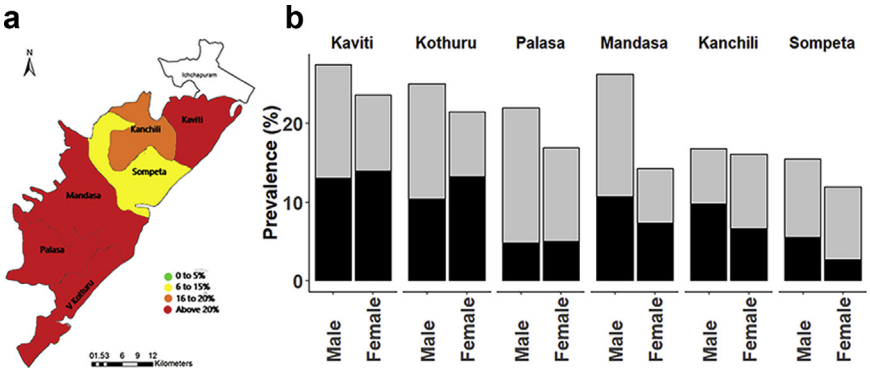

Figure 3. Prevalence of chronic kidney disease across mandals, by sex. The darker shaded areas indicate chronic kidney disease not associated with diabetes and longstanding hypertension.

common environmental risk and unique gene–environment interactions.

An important finding was the high (42%) population prevalence of hypertension. In part, this could be a consequence of CKD. However, the prevalence was 36% in the non-CKD population as well. According to data from the fourth round of the Indian National Family Health Survey (2015–2016), the prevalence of hypertension among 15- to 49-year-old women and men in rural Andhra Pradesh was 11.7% and 16.9%, respectively.[19] A population-based survey using a modified World Health Organization stepwise approach to surveillance survey methodology in Chittoor district estimated the overall hypertension prevalence at 27% in the population ≥15 years of age, with 56.7% of the hypertensive patients being diagnosed for the first time during the survey.[20] Whether this high burden of hypertension is linked to CKD needs investigation. Our findings also support the need for an integrated case finding approach that targets multiple non-communicable diseases.

We noticed the existence of "diagnostic nihilism" as shown by the limited workup of patients who had already received a diagnosis of CKDu. Only about half were advised an ultrasound examination of kidneys, which is typically an early test to establish chronicity. Just about 8% were advised to have a kidney biopsy specimen obtained, 60% of whom did not undergo the biopsy procedure.

Our study has several strengths. It is the first population-based prevalence study for CKD undertaken using rigorous and standardized methodology, including robust sampling that allowed determination of variation in prevalence between clusters and confirmation of all abnormal findings at a second time as recommended by KDIGO.[12] We also reconfirmed the diagnosis of hypertension in all newly diagnosed cases by repeating the readings. Our findings are unlikely to be affected by selection bias, since the study cohort was randomly selected from the entire at-risk population based on a community census, included both sexes, and included the entire range of occupations. Another major strength was a low refusal rate and near-universal availability for repeat testing, secondary to strong community engagement. Questionnaires were administered and data collected by trained and qualified field research personnel who were residents of the study area. Serum creatinine and proteinuria tests were performed on the day of collection using validated methodologies. We have obtained a detailed understanding the population profile, which provides us with the basis to undertake studies to ascertain etiology of this condition. Stored biosamples will allow future exploration of additional hypotheses including using "omics" technologies.

eGFR (ml/min/1.73m^2)	Urine protein creatinine ratio (mg/g)		
	<150	150-500	>500
≥ 90	1516 (63.1)	180 (7.5)	61 (2.5)
60 – 89	335 (13.9)	41 (1.7)	23 (1)
45 – 59	43 (1.8)	13 (0.5)	10 (0.4)
30 – 44	44 (1.8)	13 (0.5)	16 (0.7)
15 – 29	25 (1)	12 (0.5)	36 (1.5)
<15	7 (0.3)	6 (0.2)	21 (0.9)

Figure 4. Chronic kidney disease classification as per Kidney Disease: Improving Global Outcomes risk categories in the population. eGFR, estimated glomerular filtration rate.

Table 3. Association between chronic kidney disease and sociodemographic, economic, lifestyle, and clinical characteristics of participants

Characteristics	Crude PR (95% CI)	Adjusted PR (95% CI)
Age 45–54 vs. <45 yrs	1.76 (1.39–2.22)	1.30 (1.01–1.67)
Age ≥55 vs. <45 yrs	2.67 (2.16–3.31)	1.70 (1.33–2.20)
Male vs. female	1.45 (1.22–1.73)	1.35 (1.05–1.73)
No formal education vs. any formal education	1.53 (1.28–1.82)	1.23 (1.00–1.52)
Income ≤10,000 vs. >10,000 INR per month	1.06 (0.82–1.40)	0.92 (0.70–1.22)
Outdoor workers vs. others	1.31 (1.06–1.62)	1.12 (0.90–1.39)
Tobacco use vs. never	1.84 (1.54–2.21)	1.25 (1.01–1.54)
Alcohol use, yes vs. no	1.56 (1.30–1.87)	0.99 (0.77–1.29)
Pain killer use, yes vs. no	1.17 (0.96–1.43)	1.02 (0.83–1.25)
Hypertension, yes vs. no	2.34 (1.95–2.82)	1.74 (1.42–2.14)
Diabetes, yes vs. no	1.42 (1.12–1.77)	1.07 (0.84–1.35)
Overweight/obese (≥25 kg/m^2) vs. normal/underweight (<25.0 kg/m^2)	0.79 (0.63–0.97)	0.81 (0.64–1.00)
Family history of CKD, yes vs. no	1.35 (1.07–1.69)	1.33 (1.05–1.67)

CI, confidence interval; CKD, chronic kidney disease; INR, Indian rupee; PR, prevalence ratio.

One weakness is the lack of a detailed evaluation for the cause of kidney disease, including imaging and histopathologic examination. Even though the detailed questionnaire allowed us to exclude an obvious cause, the presence of an identifiable cause in a small proportion cannot be totally ruled out. The causal association of well-known risk factors (e.g., diabetes, hypertension) with CKD is usually assumed by the duration of these conditions. However, the timing of diagnosis of these conditions in this rural population could be related to variations in access to care, as suggested by the relatively high proportion of newly diagnosed cases. Another source of uncertainty is the lack of validation of eGFR equation in this study population. Our work (done in a different population) has shown that serum creatinine–based eGFR formulas overestimate the GFR in Indians.[21] If that was to be confirmed in this population, the prevalence of CKD could be even higher. At this stage we do not speculate on the cause because detailed studies to establish the cause of kidney disease will follow.

In conclusion, this population-based study for the first time provides an accurate estimate of the prevalence of CKD in the adult population of Uddanam using an internationally accepted protocol and establishes that the prevalence in this area is indeed higher than studies from other parts of India. Our data suggest the need to apply a population-based approach to understanding of causes of CKD as well as screening and prevention in this region rather than focussing on groups defined according to eGFR or proteinuria cutoffs. The longitudinal study will help to clarify understanding of etiology, risk factors, and natural history of CKDu in Uddanam. Additional studies, including those addressing the identification of biomarkers, are needed to accurately identify the CKDu phenotype in Uddananm. The findings will contribute to the policy development to tackle CKD in the region and permit international comparisons with other regions that report high CKD burden.

DISCLOSURE

VJ has received grant funding from GSK, Baxter Healthcare, and Biocon and honoraria from NephroPlus and Zydus Cadilla, with the policy of all honoraria being paid to the George Institute for Global Health. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

Supported by a grant from the Government of Andhra Pradesh (GoAP) under the Indian Council of Medical Research – GoAP Grand Challenge Scheme (G.O Rt No. 417 HM&FW(D) 20.07.2017). We thank all community members, especially the study participants and the field workers, for their contributions. We thank Aakash Shingada for the visual abstract.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Number of study participants with abnormal findings at first and second evaluation.

Table S2. Sociodemographic, economic, lifestyle, and clinical characteristics of study participants with CKD, by diabetes and hypertension status.

Table S3. Prevalence (95% CI) of CKD across mandals, by sex and overall.

STROBE Checklist.

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