CKD and CKDu in Northern Peru: a cross-sectional analysis under the DEGREE protocol

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Abstract

Aims:

This study estimated the prevalence of low eGFR in those without known hypertension, T2DM or heavy proteinuria as a surrogate marker for chronic kidney disease of unknown cause (CKDu) among adults in the North of Peru.

Methods:

A cross-sectional study was conducted following the Disadvantaged Populations eGFR Epidemiology (DEGREE) Study protocol. Low eGFR was defined based on a single eGFR $\leq$ 60 mL/min/1.7 m^2 estimated using the CKD-EPI equation. Environmental conditions related to CKDu (i.e. work in agriculture or sugarcane, water source, heat, and pesticide exposure) were evaluated, in addition to traditional risk factors for CKD (i.e. smoking, heavy drinking, physical activity, hypertension, type 2 diabetes mellitus, urolithiasis, among others).

Results:

A total of 1514 subjects were included in the study, mean age 45.1 (SD: 16.4), and 55.2% were females. Overall, only 26 cases (1.7%; 95%CI: 1.1% – 2.5%) had an eGFR < 60 mL/min/1.7 m^2 compatible with CKD definition; when those with hypertension and type-2 diabetes or heavy proteinuria were excluded, according to the DEGREE protocol, the estimate fell to 0.9% (95%CI: 0.4% – 1.5%). Low physical activity levels (OR = 1.99; 95%CI: 1.18–3.34), hypertension (OR = 2.07; 1.26–3.41), and urolithiasis (OR = 1.97; 95%CI: 1.18–3.27) were factors associated with low eGFR.

Conclusions:

A low population-based prevalence of low eGFR (as a surrogate for CKDu), both in rural and urban settings areas, in the Northern Peru, was found. Low physical activity levels, hypertension and urolithiasis were factors associated with low eGFR. Interventions to prevent CKD cases may be focused on well-known CV risk factors and urolithiasis.

Introduction

In less than a decade, chronic kidney disease (CKD) has increased from the 18th to the 6th leading cause of death worldwide, affecting nearly 850 million people and causing 2.4 million deaths annually [1]. Age-related non-communicable diseases (NCDs) and conditions such as hypertension (HT) and type 2 diabetes mellitus (T2DM) are the main risk factors associated with CKD; in addition, other causes include autoimmune disease, congenital abnormalities of the urinary tract, and obstructive uropathy. Recently, cases of chronic kidney disease of unknown cause (CKDu), a condition not related to NCDs, age, or any of the above aetiologies, have emerged as a significant problem in South Asia and Central America [2, 3].

CKDu is also referred to by various regional names including Meso-American Nephropathy (Pacific Coast of Central America) [4], Sri Lankan Nephropathy [5], and Uddanam Nephropathy [6], affecting mostly young farmers between 30–50 years old. The causes of CKDu are unknown [7], but the hypothesized causes include pesticide exposure and heavy metal poisoning associated with agriculture work, as well as heat stress in low-altitude areas. The latter hypothesis proposes that environmental heat, in combination with recurrent dehydration and high-levels of physical exertion lead to recurrent acute kidney injury episodes and eventually CKD [8]. However, CKDu has not been reported in other countries where this combination of risk factors could be found [9, 10].

Latin America, mainly Mexico, has amongst the highest rates globally of renal replacement therapy (RRT), including haemodialysis, peritoneal dialysis, and kidney transplant [11]. However, epidemiologic data on CKD are mostly from Brazil, and a few other countries in South America. Although, in the Brazilian northeast region the temperature could regularly rise over 38 °C (100°F), neither a higher prevalence of CKD, nor CKDu cases, have been reported among Brazilian agricultural workers [12]. Peru, a country closer to the equator, has reported a CKD prevalence of 13–21% [13, 14], which is comparable to that in El Salvador and Nicaragua [15, 16]. Approximately 50% of the end stage population of CKD in Peru does not receive dialysis or renal replacement therapy (RRT), since the health system does not have the necessary resources (technological and human) [17, 18]. Moreover, in Peru, 2.0% of the deaths at the national level were attributable to CKD, being in the top ten causes of death [19].

Therefore, the purpose of this study was to estimate the prevalence of low eGFR (< 60 ml/min /1.7 m^2) in those without known hypertension, T2DM or heavy proteinuria as a surrogate marker for CKDu among participants from the Tumbes region, in the North of Peru. In addition, we assessed the factors associated with the prevalence of impaired kidney function (i.e. low eGFR) in general and surrogate CKDu in particular.

Methods

Study design and setting

A cross-sectional study was conducted following the protocol of the Disadvantaged Populations eGFR Epidemiology Study (DEGREE) [20]. This study was conducted in Tumbes, a region located in the North of Peru, on the border with Ecuador, and where approximately 90% of the population is urban. In addition, nearly 20% and 1% of the population respectively are considered poor and extremely poor, and 15% do not have basic sanitation services [21].

Tumbes was chosen for the following reasons: agriculture workers (up to 10% of the active economic population), contamination of the Rio Puyango, the main source of water (i.e. cadmium, arsenic), and warm climate with low precipitation rates. The temperature of the city has an annual average temperature of 27ºC, reaching almost 35 ºC during the summer [22].

Study participants

Adults aged ≥ 18 years, resident in Tumbes, were invited to participate using the most updated census in the area (2014). Pregnant women, those who declined to give blood and urine samples, and those with mobility disabilities preventing bioimpedance assessment, were excluded from the study. The sample was stratified so that participants were from urban and rural areas in similar proportions (50%). In addition, we decided not to recruit more women after their number reached 60% for each of these two subgroups.

Outcome

We calculated the estimated Glomerular Filtration Rate (eGFR) using the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation. We defined three categories of kidney function based on eGFR results: moderate or established kidney dysfunction (< 60 mL/min/1.7 m^2), mild kidney dysfunction (60–90 mL/min/1.7 m^2), and normal (≥ 90 mL/min/1.7 m^2). CKD was defined as the proportion of individuals with moderate or established kidney function (eGFR < 60 mL/min/1.7 m^2) in the overall sample; whereas the prevalence of CKDu was estimated using the same indicator but excluding individuals with previous diagnosis of HT and/or T2DM, and those having a heavy proteinuria, defined as 3 + in urine dipstick (equivalent to ≥ 300 mg/dl of protein) according to the DEGREE protocol [20].

Other variables of interest

We also gathered information on key reported risk factors for CKD and CKDu. Age was considered as both a continuous and categorical variable. Level of education was classified in three categories (< 7, 7–11, ≥ 12 years of education). We also considered socioeconomic status as monthly household income dichotomised with a cut off point of 850 PEN (250 USD, minimum salary wage at the moment of the study).

We also collected information on ever working in agriculture, sugarcane, and pesticide use; these variables were built as categorical (yes/no). Due to potential sources of contamination of water, we chose *access to piped water* as a potential confounder. Heat exposure was considered to have occurred if the participant reported to have fainted when exposed to hot weather. We built a variable *medicine intake risk* due to the variety of potential nephrotoxic medications (including herbal medicine use) usually sold without prescriptions. For this, we focused on the ever use of analgesics and intramuscular antibiotics. In addition, history of some diseases because their impact on CKD was also included: tuberculosis, hepatitis B, and leptospirosis.

Heavy drinking (consuming at least 6 alcoholic standard beverages, monthly), and current smoking within the last 12 months. Physical activity was dichotomised in low vs. moderate/high according to the International Physical Activity Questionnaire (IPAQ). Body mass index (BMI) was calculated according to the WHO recommendations, and then split into three categories (< 25 kg/m^2, between 25 and < 30 kg/m^2, and ≥ 30 kg/m^2). HT was defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and/or previous diagnosis by a physician and current medication. To estimate the values for systolic and diastolic blood pressure, we used the mean of the last two (out of three) measurements conducted. T2DM was defined as a fasting (8–12 hours) glucose ≥ 126 mg/dl or self-report of previous diagnosis and treatment. The cut-off point for glycosuria was ≥ 250 mg/dl, urinary density ≥ 1020 (as a proxy for dehydration) and proteinuria if the urine level marker of protein was ≥ 30 mg/dl (equivalent to 1 + in urine dipstick).

Questionnaires

During the first visit, questionnaires were used to gather information on socio-demographic factors (age, sex) and socioeconomic status (education, employment status, house-hold income and health insurance). Environmental conditions associated with CKDu (previous or current work in agriculture or sugarcane, water source, heat, and pesticide exposure) were addressed. Information on past medical history was focused on cardiovascular diseases (HT, T2DM, myocardial infarction, stroke, and hypercholesterolemia), and behavioural risk factors (alcohol, smoking, and physical activity). We also included questions on CKD and its associated causes, including congenital kidney malformation, diabetic nephropathy, polycystic kidney disease, urolithiasis, use of nephrotoxic medications (non-steroidal anti-inflammatory, parenteral use of antibiotics, and herbal medicine), tuberculosis, hepatitis B, and leptospirosis.

Clinical assessment

Participants were invited for another visit to obtain blood samples for fasting glucose and creatinine, urine samples (dipstick urinalysis) and clinical examination. We asked the participants to refrain from eating meat, caffeine, tobacco and paracetamol 8 hours prior to taking the sample. The clinical evaluation included three blood pressure measurements taken after 5 minutes of resting (seated) position and 5 minutes apart from each other (evaluated with an automatic digital calibrated sphygmomanometer OMRON HEM-780, Tokyo, Japan), stand height (cm), weight (kg) by standardized procedures, and body composition (i.e. body fat percentage), for which we used a supine bioimpedance analyzer balance (BodyStat 1500, BodyStat Limited, British Islands) calibrated at a single frequency (50 Hz).

Analysis of biological samples

Urine dipstick analyses yielded semi-quantitative values of blood, proteins, leukocytes, glucose, pH and urine density. We measured serum creatinine in 5 ml of blood sample using a mass spectrometry method calibrated according to isotope dilution (IDMS, English acronym). As in the DEGREE Study protocol, serum samples were stored at -20 °C for future Cystatin C determination.

Sample size

We planned for a sample size of 750 participants in each study group (urban and rural). According to the DEGREE protocol this sample size provides: (i) power of at least 90% to detect a difference of 5 ml/min (SD = 30) between the average of a population compared with another (between countries); and (ii) power of at least 80% to detect a difference of at least 7 ml/min between the means of any population subgroups (if at least in each subgroup there are 250 participants) [23, 24].

Data analysis

We conducted descriptive analyses of socio-demographic, socioeconomic, cardiovascular risk profile and CKD risk profiles according to the study population group and kidney function. These comparisons were conducted for the overall sample (compatible with CKD) and among those without known HT, T2DM or heavy proteinuria (as a proxy of CKDu). Chi-square tests for comparison of categorical variables, and Student's t test or Mann-Whitney U was used for comparison of numerical variables. In addition, the prevalence of CKD and CKDu were also estimated with their respective 95% confidence intervals (95%CI).

As very few cases with eGFR levels compatible with CKD and CKDu (i.e. eGFR < 60 mL/min/1.7 m^2) were found, we analysed factors associated with impaired kidney function (eGFR < 90 mL/min/1.7 m^2) rather than factors associated with eGFR < 60. We used logistic regression models to determine associated factors for impaired kidney function. As a result, crude model and adjusted models are shown. The first adjusted regression model was controlled by age (as continuous variable) and sex; whereas the second regression model included also population group and education level as potential confounders.

Ethics

The protocol was submitted and approved by the Ethics Review Committees of the Universidad Peruana Cayetano Heredia, Lima, Peru, and London School of Hygiene and Tropical Medicine, London, UK. The tests results were shared with the participants. A physician provided clinical advisory and referral to their health care facility was provided when needed.

Results

Characteristics of the study participants

A total of 1514 of 1818 (83.3%) contacted subjects consented to be included in the study. Socio-demographic, occupational and lifestyle characteristics of the overall sample are summarized in Supplementary Table 1. More than half of participants were < 50 years old (overall mean age 45.1 [SD: 16.4] years) and 55.2% were females. The employment rate was 55.9% and higher in men (89.4%) than women (28.6%). Only 33.9% of the study population reported to have worked in agriculture and were mostly male rural dwellers (56.2%). The prevalence of measured HT was 15.6% (mean SBP: 115.7 [SD: 18.9]) and increased to 20.8% when self-reported HT diagnosis was added (Supplementary Table 2). The mean fasting glucose was 95.9 (SD: 39.5) mg/dl, with a prevalence of 8.3% for T2DM. The mean BMI was 27.5 (SD: 4.5) kg/m^2 with a prevalence of 43.5% for overweight and 26.8% for obesity. A total of 274 (18.1%) participants self-reported a previous diagnosis of CKD, although mean creatinine was 0.7 (SD: 0.2) mg/dl, and urolithiasis was reported in 15.7% of the total sample (Supplementary Table 3).

After excluding those with known HT, T2DM or heavy proteinuria, a total of 1272 subjects were analysed. Socio-demographic and lifestyle characteristics of this population are summarized in Table 1. Over 70% of the subjects were younger than 50 years and over half of them were employed, 20.8% reported having worked with pesticides, and 33.7% had worked in agriculture. Almost all the urban dwellers had access to piped water. Undiagnosed HT and T2DM were found in 11.2% and 2.1% of the population (Table 2). Of note, only 2 (0.2%) had proteinuria (1 + in urine dipstick).

Table 1
Sociodemographic, occupational and lifestyle characteristics by study group and sex

	Urban		**Rural**	
	Male	**Female**	**Male**	**Female**
	(n = 261)	**(n = 364)**	**(n = 298)**	**(n = 349)**
Age, mean (SD)	45.2 (16.6)	41.9 (14.4)	45.0 (15.9)	39.3 (14.4)
Age (categorized)				
< 50 years	165 (63.2)	266 (73.1)	191 (64.1)	274 (78.5)
50 + years	96 (36.8)	98 (26.9)	107 (35.9)	75 (21.5)
Education (in years)				
0–7 years	69 (26.4)	96 (26.4)	115 (38.6)	129 (36.9)
7–11 years	128 (49.1)	161 (44.2)	125 (42.0)	136 (39.0)
> 12 years	64 (24.5)	107 (29.4)	58 (19.5)	84 (24.1)
Work				
Employed	229 (87.8)	112 (30.7)	286 (96.0)	99 (28.4)
Student	10 (3.8)	18 (5.0)	6 (2.0)	15 (4.3)
Homemaker & unpaid	0 (0.0)	223 (61.3)	1 (0.3)	223 (63.8)
retired	10 (3.8)	0 (0.0)	0 (0.0)	2 (0.6)
Unemployed	11 (4.6)	11 (3.0)	5 (1.7)	10 (2.9)
Pesticide exposure (ever)				
Yes	28 (10.7)	5 (1.4)	199 (66.8)	32 (9.2)
Sugarcane work				
Yes	3 (1.2)	1 (0.3)	18 (6.0)	6 (1.7)
Agriculture work				
Yes	53 (20.3)	9 (2.5)	259 (86.9)	107 (30.7)
Heat exposure at work				
Yes	97 (37.2)	16 (4.4)	187 (62.8)	71 (20.3)
Monthly household income				
< 850 PEN (≈ 258 USD)	110 (48.9)	194 (64.9)	159 (61.2)	231 (78.6)
Water source				
Piped water	232 (99.1)	305 (100.0)	10 (3.4)	15 (4.4)
Well	2 (0.9)	0 (0.0)	193 (66.4)	229 (67.2)

	Urban		Rural	
River	0 (0.0)	0 (0.0)	62 (21.3)	54 (15.8)
Trunk	0 (0.0)	0 (0.0)	26 (8.9)	43 (12.6)
Health insurance				
Yes	224 (85.8)	330 (90.7)	239 (80.6)	315 (90.3)
Current smoking				
Yes	63 (24.1)	5 (1.4)	81 (27.2)	6 (1.7)
Heavy drinking				
Yes	53 (20.3)	7 (1.9)	67 (22.5)	3 (0.9)
Physical activity				
Low	189 (72.4)	334 (91.8)	164 (55.0)	288 (82.5)
Medicine intake risk				
Yes	100 (38.3)	222 (61.0)	129 (43.3)	194 (55.6)
Herbal medicine use				
Yes	108 (41.4)	154 (42.3)	158 (53.0)	181 (51.9)

Table 2
Clinical characteristics by study group and sex

	Urban		Rural	
	Male	**Female**	**Male**	**Female**
	(n = 261)	**(n = 364)**	**(n = 298)**	**(n = 349)**
SBP, mean (SD)	118.3 (13.8)	107.7 (13.5)	120.0 (16.6)	106.9 (14.9)
DBP, mean (SD)	79.5 (9.9)	75.4 (9.4)	78.8 (10.6)	73.8 (9.9)
Hypertension				
Yes	37 (14.2)	23 (6.3)	54 (18.1)	29 (8.3)
Previous stroke				
Yes	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)
High cholesterol				
Yes	29 (11.1)	59 (16.3)	31 (10.7)	89 (26.3)
Tuberculosis				
Yes	5 (1.9)	2 (0.6)	9 (3.0)	5 (1.4)
Hepatitis B				
Yes	0 (0.0)	3 (0.8)	6 (1.4)	1 (0.3)
Leptospirosis				
Yes	0 (0.0)	2 (0.6)	2 (0.7)	1 (0.3)
CKD (self-report)				
Yes	50 (19.2)	67 (18.4)	42 (14.1)	55 (16.1)
Urolithiasis				
Yes	46 (17.6)	58 (15.9)	38 (12.8)	50 (14.3)
Glucose, mean (SD)	88.6 (16.9)	90.3 (20.2)	88.7 (16.0)	88.8 (21.7)
Type 2 diabetes				
Yes	4 (1.5)	9 (2.5)	5 (1.7)	9 (2.6)
Body fat %, mean (SD)	23.6 (6.0)	38.4 (6.3)	23.5 (5.7)	38.3 (6.3)
Body mass index, mean (SD)	27.3 (4.4)	28.5 (4.6)	25.7 (3.8)	27.5 (4.5)
BMI categorized				
Normal	77 (29.5)	83 (22.8)	129 (43.3)	102 (29.2)
Overweight	122 (46.7)	152 (41.8)	128 (43.0)	151 (43.3)
Obese	62 (23.8)	129 (35.4)	41 (13.7)	96 (27.5)

	Urban		Rural	
Creatinine, mean (SD)	0.9 (0.2)	0.6 (0.1)	0.9 (0.1)	0.6 (0.1)
eGFR, mean (SD)	100.6 (17.4)	111.5 (16.0)	104.1 (16.0)	114.0 (17.3)
Urine density				
≥ 1020	166 (63.6)	203 (55.8)	216 (72.5)	230 (65.9)
Urine protein				
Negative	260 (99.6)	363 (99.7)	297 (99.7)	348 (99.7)
Trace	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
Positive	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
Glucosuria				
≥ 250 mg/dl	6 (2.3)	7 (1.9)	1 (0.3)	5 (1.4)

Prevalence of low eGFR and proxy CKDu

In the overall sample and according to the CKD-EPI formula, only 26 cases (1.7%; 95%CI: 1.1% − 2.5%) had an eGFR < 60 mL/min/1.7 m^2 compatible with the definition of CKD. When these estimates were calculated in the subsample according to the DEGREE protocol, only 11 individuals (0.9%; 95%CI: 0.4% − 1.5%) had an eGFR < 60 mL/min/1.7 m^2, compatible with CKDu.

In bivariate analysis, those with impaired kidney function were older, male, with low education level, reported having worked in agriculture, had more access to piped water, reported using herbal medicine, had higher systolic and diastolic blood pressure, and consequently higher hypertension prevalence, and low urine density (Table 3).

Table 3
Baseline characteristics of study population by eGFR results

	eGFR categories			
	< 60	**60–90**	**≥ 90**	**p-value**
	(n = 11)	**(n = 165)**	**(n = 1096)**	
Age, mean (SD)	66.5 (13.8)	62.4 (14.4)	39.3 (12.9)	< 0.001
Age categorized				
< 50 years	1 (9.1)	34 (20.6)	861 (78.6)	< 0.001
50 + years	10 (90.9)	129 (79.4)	235 (21.4)	
Sex				
Male	8 (72.7)	107 (64.9)	444 (40.5)	< 0.001
Female	3 (27.3)	58 (35.1)	652 (59.5)	
Site				
Urban	7 (63.6)	95 (57.6)	523 (47.7)	0.04
Rural	4 (36.7)	70 (42.4)	573 (52.3)	
Education (in years)				
0–7 years	8 (72.7)	110 (66.7)	291 (26.6)	< 0.001
7–11 years	3 (27.3)	38 (23.0)	509 (46.4)	
> 12 years	0 (0.0)	17 (10.3)	296 (27.0)	
Pesticide exposure (ever)				
Yes	2 (18.1)	35 (21.2)	227 (20.7)	0.97
Sugarcane work				
Yes	1 (9.1)	3 (1.8)	24 (2.2)	0.28
Agriculture work				
Yes	4 (36.4)	69 (41.8)	355 (32.4)	0.06
Heat exposure at work				
Yes	3 (27.3)	52 (31.5)	316 (28.8)	0.77
Monthly household income				
< 850 PEN (≈ 258 USD)	3 (50.0)	97 (69.3)	594 (63.7)	0.34
Water source				
Piped water	6 (60.0)	90 (58.4)	465 (46.2)	0.007
Well	2 (20.0)	39 (25.3)	383 (38.1)	

	eGFR categories			
River	0 (0.0)	19 (12.4)	97 (9.6)	
Trunk	2 (20.0)	6 (3.9)	61 (6.1)	
Health insurance				
Yes	11 (100.0)	150 (90.9)	947 (86.4)	0.12
Current smoking				
Yes	1 (9.1)	20 (12.1)	134 (12.2)	0.95
Heavy drinking				
Yes	0 (0.0)	12 (7.3)	118 (10.8)	0.21
Physical activity				
Low	8 (72.7)	137 (83.0)	830 (75.7)	0.11
Medicine intake risk				
Yes	4 (36.4)	82 (49.7)	559 (51.0)	0.60
Herbal medicine use				
Yes	7 (63.6)	98 (59.4)	496 (45.3)	0.002
SBP, mean (SD)	130.8 (26.1)	125.4 (19.7)	110.4 (14.0)	< 0.001
DBP, mean (SD)	83.5 (14.8)	81.1 (11.5)	75.8 (9.8)	< 0.001
Hypertension				
Yes	4 (36.4)	44 (26.7)	95 (8.7)	< 0.001
High cholesterol				
Yes	2 (18.2)	36 (22.0)	170 (15.8)	0.14
Tuberculosis				
Yes	0 (0.0)	3 (1.8)	18 (1.7)	0.90
Hepatitis B				
Yes	0 (0.0)	1 (0.6)	7 (0.6)	0.97
Leptospirosis				
Yes	0 (0.0)	0 (0.0)	5 (0.5)	0.67
Urolithiasis				
Yes	2 (18.2)	33 (20.0)	157 (14.3)	0.16
Glucose, mean (SD)	104.4 (54.6)	91.7 (19.1)	88.7 (18.4)	0.005
Type 2 diabetes				

eGFR categories				
Yes	1 (9.1)	4 (2.4)	22 (2.0)	0.26
Body fat %, mean (SD)	32.8 (10.2)	33.6 (9.5)	31.7 (9.5)	0.05
Body mass index, mean (SD)	25.9 (4.5)	27.2 (4.3)	27.4 (4.5)	0.54
BMI categorized				
Normal	5 (45.5)	52 (31.5)	334 (30.5)	0.64
Overweight	5 (45.5)	74 (44.9)	474 (43.3)	
Obese	1 (9.0)	39 (23.6)	288 (26.2)	
Urine density				
≥ 1020	4 (36.4)	78 (47.3)	733 (66.9)	< 0.001
Urine protein				
Negative	10 (90.9)	165 (100.0)	1093 (99.7)	< 0.001
Trace	1 (9.1)	0	1 (0.1)	
Positive	0 (0.0)	0	2 (0.2)	
Urine glucose				
≥ 250 mg/dl	1 (9.1)	0 (0.0)	18 (1.6)	0.03

Factors associated with impaired kidney function (eGFR < 90 mL/min/1.7 m^2)

Table 4 shows the findings adjusted for age and sex (model 1) and further adjusted for population group and education. In the fully adjusted model, low physical activity levels (OR = 1.99; 95% CI: 1.18–3.34), hypertension (OR = 2.07; 95% CI: 1.26–3.41), and urolithiasis (OR = 1.97; 95% CI: 1.18–3.27) were factors associated with impaired kidney function. On the other hand, sugarcane work was associated with lower odds of impaired kidney function (OR = 0.28; 95% CI: 0.08–0.96) in adjusted model. The same factors, but not sugarcane work, were associated with impaired kidney function when the analysis was conducted with the entire study sample (Supplementary Table 4).

Table 4
Factors associated with impaired kidney function*: adjusted models

	Adjusted model 1	Adjusted model 2
	OR (95%CI)	OR (95%CI)
Pesticide exposure (yes)	**0.55 (0.33–0.92)**	0.70 (0.39–1.25)
Sugarcane work (yes)	**0.25 (0.07–0.82)**	**0.28 (0.08–0.96)**
Agriculture work (yes)	**0.55 (0.35–0.86)**	0.72 (0.40–1.29)
Heat exposure at work (yes)	0.72 (0.45–1.14)	0.84 (0.51–1.37)
Water source (access to piped water)	**1.66 (1.11–2.49)**	0.96 (0.42–2.20)
Current smoking (yes)	0.66 (0.36–1.23)	0.66 (0.36–1.23)
Heavy drinking (yes)	0.91 (0.44–1.87)	0.97 (0.47–2.01)
Physical activity (low levels)	**2.23 (1.24–3.71)**	**1.99 (1.18–3.34)**
Medicine intake risk (yes)	1.03 (0.69–1.54)	1.04 (0.69–1.56)
Herbal medicine use (yes)	0.99 (0.66–1.48)	1.05 (0.69–1.58)
Hypertension (yes)	**1.94 (1.19–3.17)**	**2.07 (1.26–3.41)**
Type 2 diabetes (yes)	0.99 (0.31–3.13)	1.11 (0.34–3.61)
Body mass index		
Overweight	1.22 (0.76–1.98)	1.17 (0.72–1.91)
Obesity	1.28 (0.74–2.22)	1.11 (0.63–1.96)
Urolithiasis (yes)	**2.06 (1.24–3.40)**	**1.97 (1.18–3.27)**
Tuberculosis (yes)	1.13 (0.28–4.58)	1.20 (0.30–4.81)
Hepatitis B (yes)	1.66 (0.16–16.9)	1.74 (0.16–19.1)
Leptospirosis (yes)	–	–

Impaired kidney function was defined as eGFR < < 90 mL/min/1.7 m^2

Adjusted model 1: controlled by age and sex

Adjusted mode 2: controlled by age, sex, population group, and education.

Discussion

Main findings

The findings of this study are interesting because this has been conducted in a setting with high frequency of environmental exposures that have been hypothesized to be associated with CKDu in other populations. Thus, one might have expected to find a substantial prevalence of low eGFR (surrogate of CKDu), but in fact we found a prevalence of less than 1%, consistent with what has been observed in other ‘non-epidemic’ settings. Factors associated with increased probability of impaired kidney function were hypertension, urolithiasis, and low physical activity levels; nevertheless, sugarcane work was associated with low probability of impaired kidney function but only in the DEGREE protocol subsample and not in the entire sample.

Comparison with previous studies

There is strong evidence that CKDu exists in Central America [25] and Sri Lanka [26]. There have been unconfirmed case reports in other locations such as India [27], Saudi Arabia [28], and Egypt and Senegal [29]. A cross-sectional study found CKDu prevalence in most affected areas of Sri Lanka was as high as 22.9% [26]. Globally, the increasing prevalence of end-stage CKD in African American, Hispanic and Native American populations is at least 50% attributable to T2DM [20]. In contrast, the contribution of CKDu to overall CKD burden in Peru seems to be negligible.

Tumbes is a region located on the border with Ecuador, and the inhabitants have a constant exposure to a hot and sub-tropical weather. Most of the regions where CKDu has been reported have a tropical environment, with humidity levels above 85%; however, Tumbes climate is arid, and thus, subtropical, and humidity tends to be lower, compared to Uddanam, El Salvador and Nicaragua. Nevertheless, considering the variability of tropical climate, the annual average ranges of humidity, precipitation, and annual temperature in the hotspots for CKDu are not considerably different (Table 5).

Table 5
Environmental and demographic characteristics of Tumbes and regions with CKDu

	Tumbes	Andhra Pradesh/Uddanam	El Salvador (coastal region)	Egypt El-Sharkia	Sri Lanka	Nicaragua
Population	240,590	14,807	238,244	8,017,894	21,358,975	206,264
Urbanicity	94.1% (urban)	24% (urban)	67% (urban)	77% (urban)	77% (urban)	81.6% (urban)
Climate	Arid and subtropical	Hot tropical	Tropical	Arid	Tropical	Tropical
Humidity	76%	70% – 90%	62% – 100%	Over 90%	70% – 95%	65% – 80%
Precipitation	131.4 mm	1067 mm	13 to 155 mm	4 mm (no rain season)	200 mm	181 mm
Temperature	21–40 °C	34.3 °C	23–35 °C	32.6 °C	36 °C	35 °C
Average annual temperature	25.3 °C	31.5 °C	26 °C	26.2 °C	27 °C	32.5 °C
Altitude	Sea level	60–70 m	90 m	4–8 m	81 m	109 m
Agriculture	Rice, lime, banana	Rice coconuts and cashew	Sugarcane	Cotton	Chena, rice cultivations	Banana, sugarcane
Pesticide	Paraquat, methomyl 90SP	Organochlorides	Paraquat	Cadmium, nickel and mercury	Glyphosate	Pyrethroids and chlorpyrifos
Metal contamination	Arsenic	Silica	Arsenic, cadmium	Cadmium	Cadmium	Aluminum, arsenic, lead
Leptospira	0.02% – 5%	61.8%	–	49.7%	53%	36%
Hypertension rates	26.9%	38.5% – 615%	30%	–	26%	22%
Type 2 diabetes mellitus	10.3%	7.2% – 30%	8.8%	–	8.6%	10%
CKDu	< 1%	1.6% – 4.8%, up to 60%	25%	17.7%	15% – 21%	19%

Despite the fact that exposures to agrochemicals and heavy metal are frequent in Tumbes region [30], we could not find a high number of cases of CKDu. Mining activities in Ecuador led to heavy metal contamination of Rio Puyango [31], the main source of water for dwellers in Tumbes; and nearly 60% and 90% of the rural male dwellers from our study reported previous pesticide exposure and having worked in agriculture, respectively. The evidence supporting pesticide use and its relationship with CKDu relies on chronic exposure more than acute major nephrotoxic damage [32]. Thus, male farmers from Chichigalpa (Nicaragua) had one of the highest prevalence of impaired kidney function in the region (41.9%) and this was reported to be associated with sugarcane cutting and pesticide inhalation [33]. A relatively recent systematic review found no association between CKDu and pesticide exposure [34], which was the case in our study. Surprisingly, sugarcane work was associated with lower odds of impaired kidney function, perhaps due to residual confounding or over-adjustment as few individuals reported work in sugarcane.

The factors that we found to be associated with impaired kidney function in our study are consistent with those widely reported in literature, and are not related to CKDu. For example, a recent systematic review has reported that combined aerobic and resistance exercise improves renal function, especially among patients with CKD [35]. Hypertension and obstructive nephropathy have been described as main causes of impaired kidney function.

Public health relevance

CKD has emerged as a public health concern in Peru due to its increasing mortality and lack of early detection. A study using healthcare and death records from the Peruvian Ministry of Health evidenced an increase of 300% of CKD prevalence between 2010 and 2016, especially in the Tumbes region [36]. In addition, another study reported that the proportionate mortality due to CKD has also increased in this region during the last 15 years [19].

Despite of this, cases of CKD are mainly attributed to hypertension and type 2 diabetes mellitus, but also obstructive nephropathy and low physical activity levels have been described. This study shows that very few cases are probably due to CKDu, even though the region selected for this study may have several environmental and weather conditions that have been hypothesized to cause CKDu; these include humidity, temperature, pesticide use, and metal contamination (Table 5). From the public health perspective, interventions to prevent CKD cases may be focused on well-known CV risk factors (i.e. HT and T2DM) as well as promoting physical activity and prevent or appropriately treat urolithiasis. According to our results, it does not appear that CKDu is a major problem, at least in the Tumbes region. This finding is potentially important internationally, since the cause(s) of CKDu are still unknown, but the main hypotheses involve heat and pesticide exposure – we have found CKDu to not be present in a region which has these hypothesized causal exposures.

Strengths and limitations

This exploratory study has several strengths including appropriate sample size, high response rates, representativeness, and internationally referenced laboratory validation. The sample size was considered to analyse associated factors of CKD and CKDu among rural and urban dwellers, as performed in previous studies [37, 38]. As expected, recruited subjects showed a similar risk profile for CKD and CKDu considering environmental and socio-demographic factors.

Limitations, however, are also present. First, this is a cross-sectional study, and we are not able to confirm that the relevant exposures (e.g. pesticides) occurred before the relevant outcomes (low eGFR). Nevertheless, the focus of the study was to determine the prevalence of CKD and CKDu and factors evaluated were those which are considered as potential causes of these conditions. Second, only a single eGFR measurement was carried out, so we were not able to confirm cases of CKD as we were unable to demonstrate chronicity – however, this would not affect our main finding that CKDu prevalence was very low. In addition, the CKD–EPI equation has not been validated in Peru and may potentially underestimate the number of cases with eGFR < 60, especially among women [39]. Nonetheless, due to the low prevalence of eGFR < 60 and even < 90 in young adults, it is unlikely that this would explain our findings. Third, recall bias may be a concern as we collected information by using self-report of current and past behaviours and other exposures. Finally, selection bias may arise as only one Peruvian region with the environmental characteristics for CKDu was chosen for the study.

Conclusions

Despite having appropriate environmental conditions and work-related stressors that have been hypothesized to cause CKDu, this study found a low population-based prevalence of CKDu, both in rural and urban settings areas in the Northern Peru. Low physical activity levels, hypertension and urolithiasis were the factors associated with CKD in this sample. From the public health perspective, interventions to prevent or delay CKD cases may be focused on well-known CV risk factors and urolithiasis, and CKDu does not appear to be a problem in the Tumbes region of Peru.

Declarations

CONTRIBUTORS

BC, JJM, NP and AB-O conceived the idea of the manuscript. AOR-A drafted the first version of the manuscript and led the statistical analysis with help of AB-O. BC, JJM, NP and AB-O conceived, designed and supervised the overall study. AOR-A, JJM and ABO coordinated and supervised fieldwork activities in Tumbes. All authors participated in writing of manuscript, provided important intellectual content and gave their final approval of the version submitted for publication.

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COMPETING INTERESTS

None declared.

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