VOLUME 21 NO 1 PP 41–51 JANUARY 2016

Altitude and regional gradients in chronic kidney disease prevalence in Costa Rica: Data from the Costa Rican Longevity and Healthy Aging Study

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Abstract

OBJECTIVES Recent studies in Central America indicate that mortality attributable to chronic kidney disease (CKD) is rising rapidly. We sought to determine the prevalence and regional variation of CKD and the relationship of biologic and socio-economic factors to CKD risk in the older-adult population of Costa Rica.

METHODS We used data from the Costa Rican Longevity and Health Aging Study (CRELES). The cohort was comprised of 2657 adults born before 1946 in Costa Rica, chosen through a sampling algorithm to represent the national population of Costa Ricans >60 years of age. Participants answered questionnaire data and completed laboratory testing. The primary outcome of this study was CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2.

RESULTS The estimated prevalence of CKD for older Costa Ricans was 20% (95% CI 18.5–21.9%). In multivariable logistic regression, older age (adjusted odds ratio [aOR] 1.08 per year, 95% CI 1.07–1.10, $P < 0.001$) was independently associated with CKD. For every 200 m above sea level of residence, subjects' odds of CKD increased 26% (aOR 1.26 95% CI 1.15–1.38, $P < 0.001$). There was large regional variation in adjusted CKD prevalence, highest in Limon (40%, 95% CI 30–50%) and Guanacaste (36%, 95% CI 26–46%) provinces. Regional and altitude effects remained robust after adjustment for socio-economic status.

CONCLUSIONS We observed large regional and altitude-related variations in CKD prevalence in Costa Rica, not explained by the distribution of traditional CKD risk factors. More studies are needed to explore the potential association of geographic and environmental exposures with the risk of CKD.

keywords Chronic kidney disease, Costa Rica, Epidemiology, Mesoamerican nephropathy, Tropical chronic disease, Altitude

Introduction

Many developing countries have experienced a surge in chronic disease states, including chronic kidney disease (CKD) [1–3]. CKD is a major risk factor for cardiovascular morbidity and mortality, and among the world's growing elderly population, CKD is also an independent risk factor for physical and cognitive dysfunction and poor quality of life [4, 5]. As adverse outcomes can often be prevented by early identification of CKD, improving knowledge of population-specific distributions and determinants of CKD is a public health priority [6, 7]. At present, the burden and determinants of CKD have been thoroughly characterised only in high-income countries [8]. For example, in the United States (USA), there is an estimated national prevalence of CKD of 11.6% [9], although higher prevalence is observed in socio-economically disadvantaged subgroups [10, 11]. Older age is the strongest predictor of CKD in the USA [12, 13]; where, the prevalence of CKD in individuals over the age of 60 years is 20%, and 35% among those over 70 years [9]. However, little is known about the epidemiology of CKD in low- and middle-income countries, where populations are also ageing but there are fewer resources to handle the sequelae of CKD including high healthcare costs, disability, morbidity and mortality. Additionally, there are likely determinants of CKD that are distinct to developing countries. For example, in sub-Saharan Africa, high rates of communicable disease (e.g. human immunodeficiency virus) [14] and unique population genetics have been postulated to confer vulnerability to developing CKD [15].

In Central America, the rates of renal replacement therapy and transplantation for CKD have steadily increased in recent years, and some countries have reported alarming increases in mortality rates attributed to CKD [16, 17]. Costa Rica is a middle-income country in Central America that is known for its population's longevity, social development, universally available healthcare and decline in mortality from communicable disease [18]. However, a study of Costa Rican vital statistics revealed that age-standardised mortality rates from CKD doubled among men and quadrupled among women from 1970 to 2012 [19].

The Costa Rican population is comprised of 4.3 million inhabitants, 7% aged 65 years and older, with 24% residing in the three lowland and primarily agricultural provinces of Guanacaste and Puntarenas on the Pacific coast and Limón on the Caribbean coast (Figure 1). The remaining population resides in four more urbanised central provinces, namely San Jose, Alajuela, Cartago and Heredia, with the majority of the population living in the highlands of the Central Valley, including the metropolitan area of San Jose [20].

Previous work has highlighted the increasing prevalence of traditional CKD risk factors in Costa Rica, including an ageing population [21], and increased prevalence of hypertension [22] and diabetes [23]. In addition, a recently characterized nephropathy called CKDnT

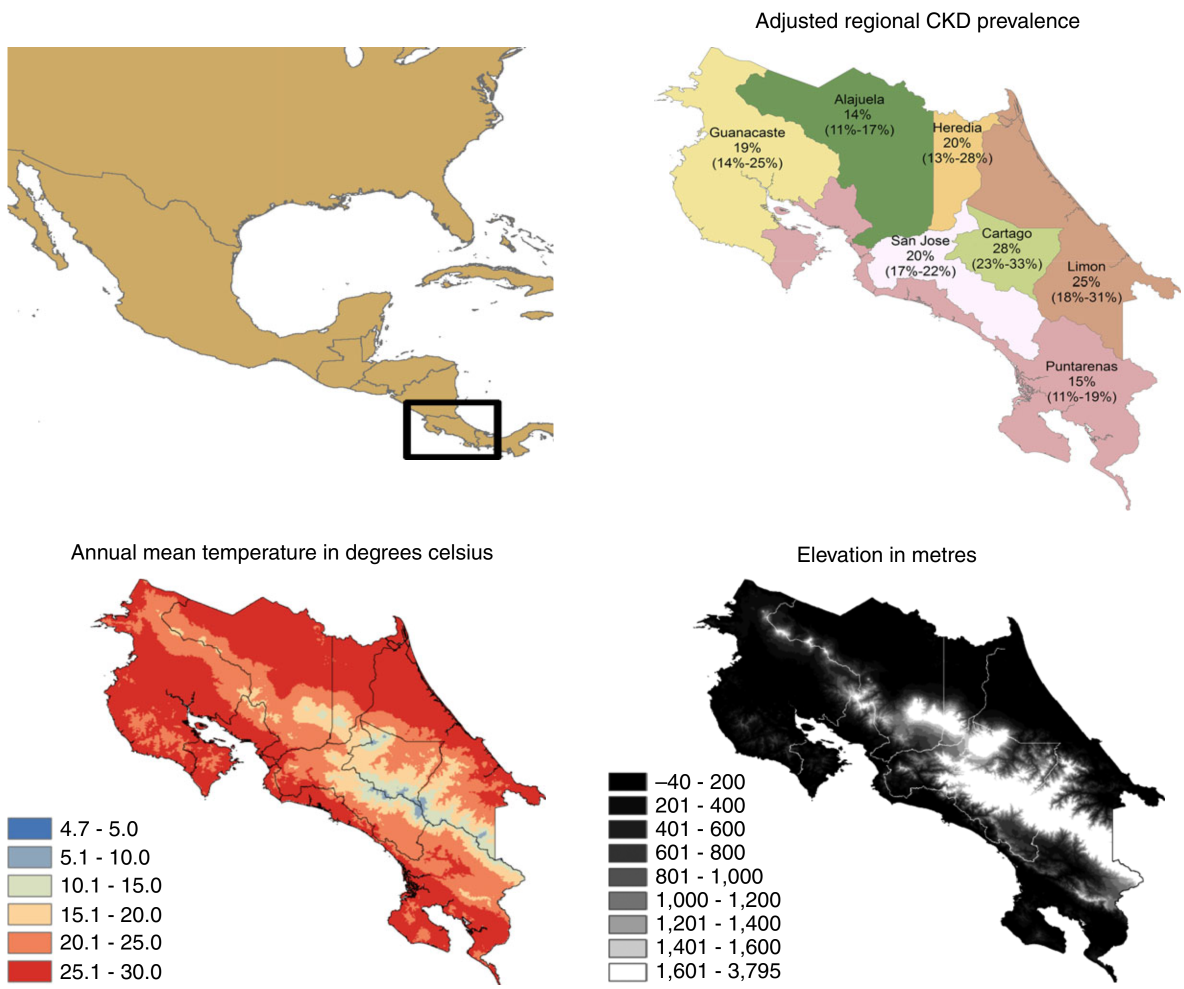

Figure 1 Map of Costa Rica with regional CKD prevalence, annual heat exposure and altitude

(CKD of non-traditional causes) [24, 25] has been discovered at epidemic levels among young Costa Ricans and other Central Americans without traditional CKD risk factors, and may partially explain the rising mortality from CKD in the region. Hypotheses for the causative factor of CKDnT include toxic exposures (e.g. traditional medicines, pesticides) [26], geographic factors (e.g. heat and altitude effects) and harsh working conditions of agricultural workers [14, 27–30].

As the population worldwide is ageing, there is a need to identify potential risk factors for CKD in older populations in developing countries such as Costa Rica, including geographic, socio-economic and educational differences among citizens that drive health behaviours [31] and disparate access to medical care [32]. Therefore, using nationally representative data from the Costa Rican Study of Longevity and Healthy Aging (CRELES), our objectives were to determine: (i) the prevalence levels of CKD in the older-adult population of Costa Rica, (ii) the relationship of biologic and socio-economic factors to CKD risk and (iii) the regional variation in CKD prevalence in Costa Rica.

Methods

Data source and study participants

Our data source was the publicly available CRELES database [33]. CRELES is a longitudinal study of a nationally representative sample of 2827 Costa Rican adults born in or prior to 1946. We used data from the first two waves of surveys, which took place mostly in 2005 and 2007. The first survey wave of CRELES collected data on 2827 individuals. The sampling strategy for the study, which included oversampling of older ages, has been described elsewhere [34]. Approximately 5% of participants declined to provide the blood sample in each wave. The final sample in the first survey wave comprised 2657 individuals (94%) who had laboratory data collected on renal function.

Participants completed in-depth interviews on self-reported health status, functional status, healthcare utilisation and life-course socio-economic conditions. All data and specimens in the study were collected at the participants' homes, usually during two visits, using hand-held computers. During the first visit, participants answered a 90-minute questionnaire (including some mobility tests and two blood pressure measures) and a 10-minute food frequency questionnaire. The interviewer also checked and recorded all medication prescribed by a healthcare professional. During a second visit early the next day, fasting blood samples were collected by venipuncture: 1 EDTA purple top tube (for 3–4 ml of whole blood) and 2 serum-separating tubes with a clot activator (for 10–12 ml of blood, to obtain 4–6 ml of serum). Specimens were analysed in several laboratories (three laboratories for serum creatinine) according to the methods described elsewhere, which include linear adjustments to have comparable measurements across laboratories [35]. Serum creatinine measurements were calibrated using the Roche method for isotope dilution-mass spectrometry [36]. The institutional review board of the University of Costa Rica granted human subjects approval to CRELES, and all participants granted their informed consent by means of their signature.

Definition of CKD

We calculated estimated glomerular filtration rate (eGFR) based on the 2009 CKD-EPI equation [37, 38]. The CKD-EPI equation utilises data on participant age, sex and race, although race was not relevant in the current analysis. We then categorised eGFR categories per the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, as follows: G1) eGFR≥90 ml/min/1.73 m^2, G2) eGFR ≥60 and <90 ml/min/1.73 m^2, G3a) eGFR ≥45 and <60 ml/min/1.73 m^2, G3b) eGFR ≥30 and <45 ml/min/1.73 m^2, G4) eGFR< 30 and ≥15 ml/min/1.73 m^2, G5) <15 ml/min/1.73 m^2. As urine albumin data were not available to identify CKD at higher eGFR levels, only participants with eGFRs in categories G3a, G3b, G4 and G5 were categorised as having CKD [39].

Hypothesised risk factors

We explored the following putative risk factors for CKD that are unique to Central America and Costa Rican older adults: province of residence [19] and altitude of residence above sea level [30]. We also explored the association of socio-economic status (SES, based on a country-specific wealth scale) and educational attainment on the risk of CKD. The residential altitude of the CRELES respondents was an ecological variable representing the mean altitude of their district of residence, which is the smallest geographic unit in Costa Rica (i.e. there are 473 districts among the seven Costa Rican provinces).

Known CKD risk factors

We examined the strength of the association between known CKD risk factors to CKD prevalence in Costa Rica by considering the subjects' medical history of hypertension and diabetes. We also adjusted for metrics of poor metabolic control that may lead to CKD including elevated glycosylated haemoglobin (HbA1C, ≥6.5%) [40], poorly controlled blood pressure (SBP ≥150 mmHg or DBP ≥90 mmHg) [41] and obesity (defined as having a body mass index (BMI) higher than 30 kg/m^2). We adjusted for reported medication use for diabetes, hypertension or hyperlipidaemia. The following variables were also considered potential confounders in this analysis: sex, age, income, years of education, recent physician visits and smoking history.

Statistical analysis

To identify the association of our hypothesised risk factors with CKD among elderly Costa Ricans, we first explored their univariate associations with CKD. Then, we estimated the prevalence of CKD by sex, age, altitude and province. Finally, we fit multivariable logistic regression models for CKD using covariates that were significant (*P*-value threshold <0.2) at the univariate level. To identify regions with risk of CKD above that expected by traditional risk factors, we estimated CKD prevalence per region after adjustment for covariates identified in our multivariable model. Statistical analyses were conducted using STATA MP version 13.0 (Stata Corporation, 2013). Descriptive statistics included proportions for categorical variables, and means for continuous variables, with 95% confidence intervals (CI). All statistical analyses took into account differential sampling weights.

Sensitivity analysis

As the CKD definition based on KDIGO guidelines includes evidence of consistently low eGFR in repeat testing after 90 days [39], we performed a sensitivity analysis utilising repeat measures of eGFR from the second wave of CRELES, conducted close to two years later.

Results

Bivariate analysis

The first survey wave of CRELES collected data on 2827 individuals, of whom 2657 (94%) had laboratory data collected on renal function. Of these individuals, 744 survey participants had evidence of CKD by eGFR criteria (eGFR<60 ml/min/1.73 m^2) [39]. The average age of the study sample was 76 years (standard error 1.3 years); 45% were male and 20% were diabetic. Subjects with CKD were more likely to be older, female, diabetic and hypertensive (Table 1). Subjects with CKD also had lower educational attainment, higher systolic blood pressure, and were more likely to be taking medications for diabetes, hypertension and hyperlipidaemia. A greater proportion of subjects with CKD had recently seen a physician and lived at higher altitude. There were also differences in the proportion of subjects with CKD between provinces. There were no significant (at the $P < 0.05$ level) bivariate associations between CKD and income or wealth status.

National CKD prevalence

The estimated prevalence of CKD for older Costa Ricans was 20% (95% CI: 19–22%); 23% (95% CI: 21–26%) among females; and 17% (95% CI: 14–19%) among males. CKD prevalence increased in a nearly linear fashion with age, from about 15% at age 60 years to greater than 50% at age 90 years (Figure 2). When further categorised by stage of CKD [39], prevalence of stage 3a was 14% (95% CI: 12–16%) among males and 20% (95% CI: 17–22%) among females, whereas stages 3b-5 CKD were present in 6% (95% CI: 4–7%) of males and 6% (95% CI: 5–7%) of females. Women exhibited a higher CKD prevalence than men at all ages, although among individuals over the age of 80 years, the difference between sexes was no longer statistically significant.

Aetiologic model of CKD

The results of our multivariable modelling approach for CKD among elderly Costa Ricans are reported in Table 2. In the first model, we examined the association of province and altitude of residence, adjusted for age and gender, on the risk of CKD. In this model, subjects of older age (aOR 1.08 per year, 95% CI: 1.07–1.10, $P < 0.001$) and female subjects (aOR 1.44, 95% CI: 1.13–1.83, $P = 0.003$) were more likely to have CKD. Adjusted for age and gender, living at higher altitudes was independently associated with higher risk of CKD (aOR 1.28 for every 200-m increase above sea level, 95% CI: 1.13–1.83, $P < 0.001$). Also, compared to the capital province of San Jose, residence in Guanacaste (aOR 3.43, 95% CI: 1.84–6.38, $P < 0.001$), Puntarenas (aOR 1.99, 95% CI: 1.14–3.48, $P = 0.02$) or Limon (aOR 4.84, 95% CI: 2.56–9.15, $P < 0.001$) was independently associated with higher risk of CKD. Adding SES and comorbidity risk factors to the multivariable model did not substantively change our findings of altitude and regional effects, but did attenuate the effect of female gender on CKD risk. In the fully adjusted model, other risk fac-

Table 1 Characteristics of elderly Costa Ricans by CKD status in Wave 1

	No CKD n = 1913	CKD (stage 3a-5) n = 744	P-value
Mean age, years	69.2 [68.8–69.6]	74.6 [73.7–75.4]	<0.001
Per cent male (n = 1211)	49.6 [46.9,52.3]	39.4 [34.9,44.1]	<0.001
Per cent with reported diabetes (n = 517)	20.1 [18.1,22.4]	25.4 [21.5,29.9]	0.02
Per cent with reported hypertension (n = 1307)	45.1 [42.4,47.8]	63.1 [58.5,67.5]	<0.0001
Mean years of education	5.3 [5.0–5.5]	4.9 [4.5–5.3]	0.17
Education category, %			
Less than primary school (n = 1862)	50.1 [47.4,52.8]	56.9 [52.0,61.7]	0.02
Primary school and beyond (n = 795)	49.9 [47.2,52.6]	43.1 [38.3,48.0]	
Mean income (monthly thousands of Colones)	307 [247–367]	261 [203–320]	0.34
Per cent visited physician in last 12 months (n = 2380)	86.8 [84.7,88.6]	95.2 [92.7,96.9]	<0.0001
Mean wealth proxy/scale of goods	8.2 [8.1–8.3]	8.2 [8.1–8.4]	0.66
Mean altitude of home above sea level, m	795 [767–824]	931 [882–979]	<0.001
Per cent rural residence (n = 981)	35.3 [32.8,37.9]	32 [27.9,36.3]	0.20
Province of residence, %			
San Jose (n = 928)	35.7 [33.1,38.3]	36.3 [31.9,40.9]	<0.001
Alajuela (n = 425)	16.6 [14.7,18.7]	10.3 [8.1,13.1]	
Cartago (n = 413)	13.9 [12.2,15.9]	23 [19.2,27.4]	
Heredia (n = 188)	8.3 [6.8,10.0]	7.7 [5.3,11.1]	
Guanacaste (n = 275)	9.5 [8.0,11.2]	8.8 [6.6,11.7]	
Puntarenas (n = 254)	9.8 [8.3,11.5]	6.3 [4.7,8.5]	
Limon (n = 174)	6.3 [5.1,7.8]	7.5 [5.6,10.1]	
Per cent current smoker (n = 211)	11.2 [9.5,13.2]	5.1 [3.3,7.7]	<0.001
Mean HbA1C, %	5.7 [5.7–5.8]	5.9 [5.8–6.0]	0.008
Per cent with HbA1C ≥ 6.5% (n = 350)	13.3 [11.6,15.3]	17 [13.6,21.0]	0.07
Mean systolic blood pressure, mmHg	143.4 [142.2–144.6]	147.0 [144.7–149.3]	0.006
Mean diastolic blood pressure, mmHg	83.9 [83.3–84.5]	83.5 [82.2–84.8]	0.49
Per cent with measured hypertension (>150/90) (n = 1212)	42.2 [39.5,44.9]	50.5 [45.8,55.1]	0.002
Per cent BMI > 30 kg/m^2 (n = 593)	27.4 [24.9,29.9]	26.4 [22.3,30.9]	0.70
Per cent taking medication for			
Diabetes (n = 424)	16.3 [14.4,18.4]	23.3 [19.4,27.7]	0.002
Hypertension (n = 1210)	39.5 [36.9,42.2]	61.2 [56.5,65.6]	<0.0001
Hyperlipidaemia (n = 498)	18.8 [16.8,21.0]	30.7 [26.3,35.4]	<0.001

CKD defined as eGFR<60 ml/min/1.73 m^2.
Continuous variables are reported as means, and categorical variables as percentages, with 95% confidence intervals in brackets.
The reported sample sizes (n) for categorical variables are the number of survey participants within each category. CKD, chronic kidney disease.

tors for CKD included having poorly controlled blood pressure (aOR 1.60, 95% CI: 1.10–2.32, P = 0.01), taking diabetes medication (aOR 1.73, 95% CI: 1.04–2.87, P = 0.04), hypertension medication (aOR 1.52, 95% CI: 1.06–2.18, P = 0.02), and lipid-lowering medication (aOR 1.48, 95% CI: 1.10–1.99, P = 0.01). The adjusted CKD prevalence increased monotonically from 10.4% (95% CI: 6.8–13.9%) for regions below 200 m to 26.5% (95% CI: 18.2–34.1%) for regions at 1400–1799 m above sea level (Figure 3). There were not enough observations of subjects living at altitudes higher than 1800 metres (n = 23) to produce stable estimates in this model.

Regional variation in CKD prevalence

Estimates of CKD prevalence by province differed substantially depending on whether altitude effects were included (Table 3, Figure 1). Adjusting for age and gender, the lowest CKD prevalence rates were observed in Alajuela and Puntarenas (14% and 15%, respectively), while the highest prevalence rates were observed in Cartago and Limon (28% and 25%, respectively). However, after further adjusting for the effect of altitude, San Jose, Alajuela and Heredia had the lowest CKD prevalence (16% for all), and Guanacaste and Limon had the highest (37% and 42%, respectively).

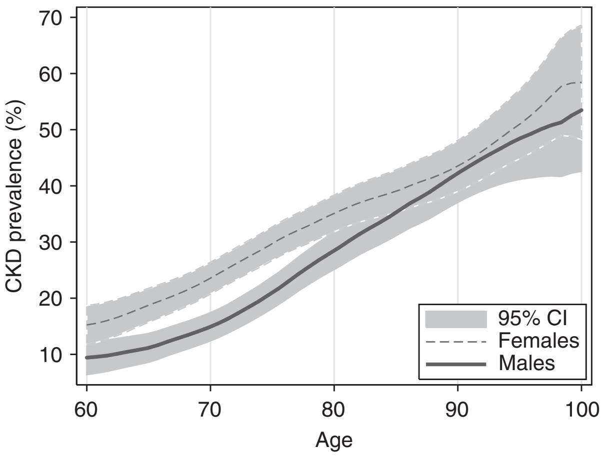

Figure 2 Prevalence of CKD by age and sex (smoothed with locally weighted polynomials)

Sensitivity analysis

Appendix 1 reports the results of a sensitivity analysis incorporating available longitudinal data on subjects, collected from the second survey wave of CRELES (conducted two years after the first wave). Seventy-seven per cent of subjects had repeat eGFR measures in the second survey wave; the resulting analytical sample for the sensitivity analysis contained 4740 observations. We found that the strength of the associations observed between age, region, altitude and CKD risk remained consistent and statistically significant, although the observed elevated risk of CKD in Limon and Guanacaste provinces was lower (aOR of 2.72 *vs*. 4.53 and 2.66 *vs*. 3.65, respectively). The use of the two waves of survey data resulted in slightly higher estimates of national CKD prevalence: 26% (95% CI: 24–28%) among all older adults, 23% (95% CI: 20–25%) among older males and 29% (95% CI: 27–34%) among older females.

Table 2 Aetiologic model of CKD in Costa Rica: regional and traditional risk factors

	Model 1			Model 1 + SES & comorbidities		
	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Age (per 1-year increase)	1.08	[1.07,1.10]	<0.001	1.08	[1.07,1.10]	<0.001
Female	1.44	[1.13,1.83]	0.003	1.20	[0.93,1.56]	0.16
Altitude (per 200-m increase from sea level)	1.28	[1.17,1.40]	<0.001	1.26	[1.15,1.38]	<0.001
Province of Residence*						
Alajuela	1.01	[0.69,1.49]	0.95	1.02	[0.69,1.51]	0.93
Cartago	1.37	[0.97,1.94]	0.07	1.37	[0.96,1.95]	0.09
Heredia	0.93	[0.55,1.58]	0.79	0.84	[0.51,1.41]	0.51
Guanacaste	3.43	[1.84,6.38]	<0.001	3.65	[1.91,6.97]	<0.001
Puntarenas	1.99	[1.14,3.48]	0.02	2.14	[1.19,3.83]	0.01
Limon	4.84	[2.56,9.15]	<0.001	4.53	[2.35,8.76]	<0.001
Education (per 1-year increase)				1.00	[0.97,1.03]	0.84
Recent MD Visit				1.64	[0.94,2.87]	0.08
Current smoker				0.65	[0.36,1.16]	0.15
Diagnosed with DM				0.63	[0.39,1.03]	0.07
Diagnosed with HTN				1.25	[0.87,1.80]	0.22
HbA1C % (per 1-% increase)				1.11	[0.95,1.29]	0.18
HbA1C% > 6.5				0.89	[0.47,1.71]	0.74
Systolic blood pressure (per 1-mmHg increase)				0.99	[0.99,1.00]	0.08
BP >150/90				1.60	[1.10,2.32]	0.01
BMI> 30 kg/m^2				0.93	[0.69,1.25]	0.64
Prescribed medication for:						
DM				1.73	[1.04,2.87]	0.04
HTN				1.52	[1.06,2.18]	0.02
Hyperlipidaemia				1.48	[1.10,1.99]	0.01

*Reference: San Jose.

aOR, adjusted odds ratio; CI, confidence interval; CKD, chronic kidney disease; SES, socio-economic status; m, metre; MD, medical doctor; DM, diabetes mellitus; HTN, hypertension; HbA1C, glycosylated haemoglobin; mmHg, millimetre mercury; BP, blood pressure; BMI, body mass index.

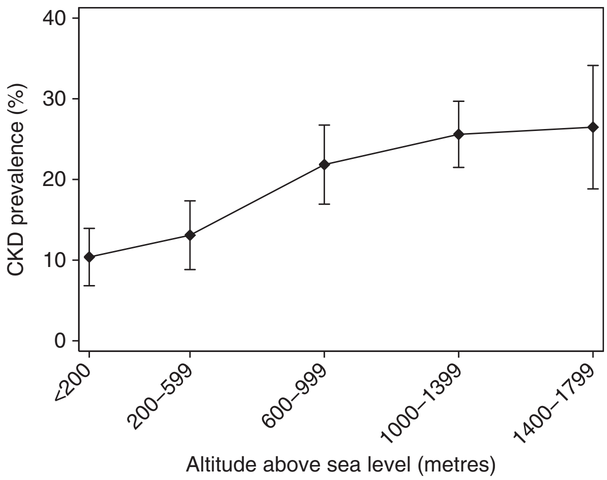

Figure 3 Prevalence of CKD by altitude of residence, adjusted for age, gender, comorbidities and province of residence

Table 3 Adjusted CKD prevalence by province

	Age and gender adjusted		Age, gender and altitude adjusted	
Province	Prevalence (%)	95% CI	Prevalence (%)	95% CI
San Jose	20	(17–22)	16	(14–19)
Alajuela	14	(11–17)	16	(12–19)
Cartago	28	(23–33)	23	(18–28)
Heredia	20	(13–28)	16	(10–22)
Guanacaste	19	(14–25)	37	(25–48)
Puntarenas	15	(11–19)	25	(17–33)
Limon	25	(18–31)	42	(31–54)

CI, confidence interval; CKD, chronic kidney disease.

Discussion

The prevalence of CKD is increasing worldwide, likely driven by an ageing population [8]. Worldwide death rates attributable to CKD have also risen dramatically, with a median increase of 36.9% from 1990 to 2013 [42]. In addition to heightened mortality risk, older adults with CKD are also more likely to suffer disability from physical and cognitive dysfunction [5]. However, determinants of CKD are poorly understood in the ageing population of developing countries, including those in Central America. In this study, we explored traditional and novel risk factors for CKD in a nationally representative sample of elderly Costa Ricans. We have identified that the prevalence of CKD among older Costa Ricans is 20%, similar to the CKD prevalence previously described among older adults in the USA [9]. Our study also found that the prevalence of CKD among older Costa Rican women is higher than among older Costa Rican men. Previous studies have highlighted that women in Costa Rica have higher burdens of hypertension, diabetes and obesity [43]. Consistent with these reports, our study showed that after adjustment for comorbidities and SES, the association of female gender and CKD was no longer statistically significant. Also, while wealth and education disparities are also known to drive differential risk for chronic disease states including CKD [10, 16, 31, 32, 44], our study did not find wealth or education gradients with CKD among elderly Costa Ricans. This may be explained by the fact that while most of the subjects had low educational attainment, the vast majority also had recent access to medical care. Indeed, nephrologic clinical services have been freely accessible in Costa Rica since 1968, as part of the national social security system that ensures that citizens have free access to medical attention as needed [45]. Therefore, the lack of socio-economic gradients in CKD may represent a success in Costa Rica's adoption of widespread health care coverage [18].

Our study also highlighted a potential relationship between altitude of residence and risk of CKD. The association between altitude and CKD risk remained robust after adjustment for age, comorbidities, region, wealth, education and access to recent medical care. Living at high altitudes is a known risk factor for high-altitude renal syndrome (HARS), a syndrome resulting from chronic hypoxia that is characterised by polycythaemia, hyperuricaemia, hypertension and proteinuria [30, 46, 47]. However, this syndrome has generally been described at altitudes higher than 2400 m above sea level, and most Costa Ricans live either at sea level or in the Central Valley, about 1200 m above sea level. It is possible that the direct renal injury or reduction in renal plasma flow observed in HARS is present to a lesser degree at the highest altitudes in Costa Rica and that older adults are particularly susceptible to these exposures. However, further studies are needed to understand possible factors related to higher altitude that may explain the patterns observed in this study.

This study also identified Guanacaste and Limon provinces as the regions in Costa Rica with the highest prevalence rates of CKD. A recent study of Costa Rican death records over the last 40 years noted that Guanacaste province had the most marked rise in age-adjusted CKD mortality [19]. These findings in aggregate warrant future studies to further investigate risk factors specific to these regions, including factors that may distinguish Guanacaste and Limon from Puntarenas, the other low-altitude coastal province in Costa Rica. In terms of putative differences in environmental exposures, residents of the low-altitude provinces typically encounter warmer weather than the central provinces (Figure 1) and rely more on agriculture for commerce than residents of the Central Valley. The agricultural products of these regions are distinct: according to the 2014 agricultural census, the main crops in Guanacaste are beef, sugar cane and rice, whereas in Limon, bananas and other fruits are the predominant export items [48]. Guanacaste and Limon have also attracted the highest proportions of immigrants from other Central American countries, including Nicaragua, where the epidemic of CKDnT has been extensively documented [29, 49, 50]. While the causes of CKDnT are unknown [50], hypotheses include heat stress caused by year-round extreme high temperatures and humidity, heavy agricultural work and toxic pesticides. These factors are thought to predispose certain individuals to recurrent volume depletion, resulting in activation of both intrarenal and extrarenal pathways that drive renal injury [51]. However, while CKDnT have been characterised as a tubulointerstitial nephropathy with low-grade proteinuria [24, 52], previous reports of kidney biopsies performed among Costa Ricans with CKD have identified focal and segmental glomerulosclerosis, membranous nephropathy, mesangial proliferative glomerulonephritis and crescent glomerulonephritis as the most common findings [45]. Future studies, ideally including data on environmental exposures and kidney biopsies, will be important to elucidate the nature of CKD found among populations living in different regions of Costa Rica.

Study limitations

Our study has several limitations that must be acknowledged. As some of our data are cross-sectional, we cannot make inferences on causality. Also, while we attempted to remain as consistent as possible to the 2012 Clinical Practice Guidelines from the KDIGO working group recommendations on the diagnosis of CKD [39], we did not have data on proteinuria that is necessary to characterise early CKD (e.g. stage 2, eGFR between 60 and 90 ml/min). Therefore, we chose to categorise subjects as having CKD only at later stages (i.e. 3a and beyond), as proteinuria is not a necessary component for diagnosis at later stages of renal dysfunction, and the CKD-EPI formula is more precise [39]. In addition, there is an active debate on whether stage 3a CKD represents a pathologic condition or a consequence of natural ageing among the elderly [53]. However, in one global study of over two million participants, Hallan and colleagues found that while older age attenuated the risk of mortality with declining eGFR, the relative risk of mortality was significantly higher, even among the oldest participants (age>75 years), when eGFR was 56 ml/min/1.73 m^2 or lower [54]. The health consequences of CKD for older adults include higher risk of morbidity and mortality, even at higher levels of eGFR [5, 12]. Therefore, we chose to include mild reductions in eGFR (corresponding to CKD stage 3a) in our estimates. CRELES investigators did not perform serial measurements of eGFR during the first wave of surveys. Therefore, as the classification of CKD requires two eGFR measurements at least 90 days apart [39], we completed a sensitivity analysis including data from the second survey wave, completed two years after the initial wave. The resulting longitudinal random-effects models confirmed the significant associations we observed between province, altitude and CKD in Costa Rica.

Conclusion

In Central America, where data are scarce on the epidemiology of CKD, studies are urgently needed to explain the rising prevalence of CKD and precipitous rise in CKD-related deaths. While we did not identify socio-economic disparities in CKD risk among elderly Costa Ricans, our findings of potential geographic and regional determinants of CKD in Costa Rica provide a platform for further investigation.

Acknowledgements

The CRELES study was funded by grants from the Wellcome Trust; the National Heart, Lung And Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases of the United States National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Wellcome Trust. MNH is supported by a grant from the National Institute of Diabetic and Digestive and Kidney Diseases (K23-DK105207-01).

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Appendix1
Longitudinal aetiologic model of CKD in Costa Rica.

	Model 1			Model 1 + SES & comorbidities		
	aOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Age	1.13	[1.11,1.15]	<0.001	1.13	[1.11,1.15]	<0.001
Female	1.55	[1.23,1.97]	<0.001	1.23	[0.97,1.57]	0.09
Altitude (per 200 m) above sea level	1.25	[1.14,1.36]	<0.001	1.23	[1.13,1.34]	<0.001
Province of Residence*						
Alajuela	0.92	[0.61,1.37]	0.67	0.95	[0.64,1.43]	0.82
Cartago	1.22	[0.86,1.72]	0.27	1.29	[0.91,1.83]	0.15
Heredia	1.49	[0.97,2.30]	0.07	1.31	[0.85,2.01]	0.22
Guanacaste	2.33	[1.27,4.28]	0.01	2.66	[1.45,4.89]	0.00
Puntarenas	1.22	[0.68,2.19]	0.50	1.38	[0.77,2.48]	0.28
Limon	2.95	[1.53,5.68]	<0.001	2.72	[1.41,5.25]	<0.001
Years of education				1.02	[0.99,1.05]	0.24
No insurance				0.91	[0.67,1.24]	0.57
Recent MD visit				1.07	[0.72,1.61]	0.73
Current smoker				0.6	[0.38,0.95]	0.03
Diagnosed with DM				0.71	[0.44,1.16]	0.18
Diagnosed with HTN				1.8	[1.31,2.48]	<0.001
HbA1C %				1.1	[0.96,1.26]	0.17
HbA1C % > 6.5				1.88	[1.24,2.86]	0.00
Systolic BP (per mmHg rise)				0.99	[0.98,1.00]	0.01
BP > 150/90				1.3	[0.96,1.76]	0.09
BMI > 30 kg/m^2				0.97	[0.75,1.25]	0.81
Prescribed medication for:						
DM				1.29	[0.78,2.14]	0.32
HTN				1.6	[1.18,2.16]	<0.001
Hyperlipidaemia				1.53	[1.20,1.96]	<0.001

N = 2681 individuals and 4740 observations.

*Reference: San Jose.

aOR, adjusted odds ratio; CI, confidence interval; m, metre; SES, socio-economic status; MD, medical doctor; DM, diabetes mellitus; HTN, hypertension; HbA1C, glycosylated haemoglobin; mmHg, millimetre mercury; BP, blood pressure; BMI, body mass index.