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Original Investigation

Decreased Kidney Function Among Agricultural Workers in El Salvador

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Background: An epidemic of chronic kidney disease of unknown cause has emerged along the Pacific coast of Central America, particularly in relatively young male sugarcane workers. In El Salvador, we examined residence and occupations at different altitudes as surrogate risk factors for heat stress.

Study Design: Cross-sectional population-based survey.

Setting & Participants: Populations aged 20-60 years of 5 communities in El Salvador, 256 men and 408 women (participation, 73%): 2 coastal communities with current sugarcane and past cotton production and 3 communities above 500 m with sugarcane, coffee, and service-oriented economies.

Predictor: Participant sex, age, residence, occupation, agricultural history by crop and altitude, and traditional risk factors for CKD.

Outcomes: Serum creatinine (SCr) level greater than the normal laboratory range for sex, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, and proteinuria categorized as low (protein excretion ≥30-<300 mg/dL) and high grade (≥300 mg/dL).

Results: Of the men in the coastal communities, 30% had elevated SCr levels and 18% had eGFR <60 mL/min/1.73 m^2 compared with 4% and 1%, respectively, in the communities above 500 m. For agricultural workers, prevalences of elevated SCr levels and eGFR <60 mL/min/1.73 m^2 were highest for coastal sugarcane and cotton plantation workers, but were not increased in sugarcane workers at 500 m or subsistence farmers. Women followed a weaker but similar pattern. Proteinuria was infrequent, of low grade, and not different among communities, occupations, or sexes. The adjusted ORs of decreased kidney function for 10-year increments of coastal sugarcane or plantation work were 3.1 (95% CI, 2.0-5.0) in men and 2.3 (95% CI, 1.4-3.7) in women.

Limitations: The cross-sectional nature of the study limits etiologic interpretations.

Conclusion: Agricultural work on lowland sugarcane and cotton plantations was associated with decreased kidney function in men and women, possibly related to strenuous work in hot environments with repeated volume depletion.

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INDEX WORDS: Agriculture; cotton; sugarcane; chronic kidney disease; Central America; descriptive epidemiology; El Salvador; occupational and environmental health; heat stress; volume depletion.

Chronic kidney disease (CKD) is a widespread major health problem that has led to expansion in the need for renal replacement therapy.[1-3] Cardiovascular risk factors such as diabetes, obesity, and hypertension are linked to CKD as both causes[4,5] and consequences.[6] Smoking and phenacetin use are further established risk factors.[7,8] Occupational and environmental determinants for CKD have been reviewed[9]; cadmium stands out as the best documented.[10-15] Dietary exposure to a nephrotoxic plant alkaloid, aristolochic acid, emerged as the cause for the Balkan nephropathy,[16] and in Tunisia, ochratoxin A is suspected.[17]

In regions of Central America, end-stage renal disease (ESRD), particularly in younger men, has increased noticeably.[18,19] In El Salvador, the CKD mortality rate increased 10-fold between 1984 and 2005.[20] A strong public belief exists that sugarcane workers tend to die of kidney failure at a higher rate than other workers.[19,21,22]

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A Central American workshop in 2005 acknowledged increasing CKD as a severe public health problem. Chemical exposures and hard work with muscular exertion in a hot climate resulting in severe chronic volume depletion were suspected major risk factors.[21] Recent studies confirmed a CKD epidemic in northwestern Nicaragua.[23-25] The present survey in El Salvador was designed to parallel one[23] of these studies. There is no recognized cadmium pollution in the region or known consumption of nephrotoxic plants, and the cause of the CKD epidemic in these countries is still unclear. This study aimed to establish the prevalence of decreased kidney function measured by serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) in men and women aged 20-60 years of 5 communities in El Salvador, with different economic activities and at different altitudes, as surrogates for occupational and environmental exposures and heat stress.

METHODS

Study Design and Setting

The study was requested by the Salvadorian health authorities. Approval was obtained from the Bioethical Review Board of the Universidad Nacional in Costa Rica because there was no such entity in El Salvador at the time. All participants signed informed consent.

We selected 5 communities in El Salvador. Sugarcane production was the dominant economic activity in 2 sea-level communities on the Pacific Coast, 1 rural and 1 semirural. Previously, cotton production was important in these communities. ESRD previously had been observed as occurring in men in these communities. Three additional communities, for which there was no previous information about kidney problems, were selected to represent a range of economic activities and altitudes. The economy of one such community, found at an elevation of 500 m above sea level (masl), also was based on sugarcane production, with average temperatures during harvest seasons 1987-2000 that were ~4°C lower than at sea level. A community with heavy coffee production was chosen as an example of another agricultural activity at high altitude (1,650 masl). The final community was an urban neighborhood at 650 masl with a service-oriented economy, assumed to reflect the background distribution of SCr levels in El Salvador.

Study Population

A house-to-house census of all adults was completed in each community, combined with an open informational meeting. One week later, written invitations were delivered to all adults aged 20-60 years. Between November 2006 and June 2007, two 3-day visits to the communities followed, 1 during weekdays and 1 including a weekend. The coffee and urban communities also were visited during 2 evenings. People were reminded at their homes and reasons for nonparticipation were noted. All examinations were conducted in health centers or schools.

Data Generation

Data Collection Methods

Demographic and lifestyle data and occupational and medical histories were obtained through questionnaire. Blood pressure, weight, and height were measured with a calibrated digital sphygmomanometer and scale. Two certified laboratory technicians drew blood samples with 10-cc vacuum tubes containing a coagulation activator. Participants provided a nonfasting morning spot urine sample in a sterile 50-mL collector.

Occupational Exposure

Current occupation was categorized into primary (agricultural workers), secondary (construction and textile factory workers), and tertiary (street vendors and workers in transport, public sector, commercial establishments, etc) sectors and economically inactive population (unemployed, students, and women working in the home). Home-based women who worked daily on their subsistence crops or were seasonal coffee or corn workers were classified as agricultural workers. Sugarcane, (past) cotton, and coffee work frequently overlapped with subsistence (corn and beans) activities. Years of work in sugarcane, cotton, coffee, subsistence crops, and their combinations were computed. Sugarcane work and subsistence farming were subdivided into coastal lowland or highland.

Medical Conditions and Lifestyle

Hypertension was defined as self-reported medically treated hypertension or blood pressure ≥140/90 mm Hg at the examination; diabetes, as self-reported medically treated diabetes or glucosuria (glucose excretion ≥100 mg/dL) at examination; and obesity, as body mass index ≥30 kg/m^2. Self-reported intake of nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of chronic arthritis and self-reported history of nephrolithiasis were recorded. Lifetime tobacco smoking and alcohol consumption were summarized into current and ever variables.

Laboratory Analyses

Blood samples were transported on ice to the clinical laboratory of the Rosales Hospital in San Salvador, where they were centrifuged and analyzed for SCr and serum urea nitrogen[26] using the Jaffé compensated method.[27] A duplicate blood sample from each 10th participant was analyzed in the quality control laboratory of the Social Security in San Salvador with the same type of equipment and methods, resulting in 81% within 1 standard deviation and all within 2 standard deviations of the original measurement. Technicians measured glucosuria (positive [+] at glucose excretion ≥100 mg/dL) and proteinuria (at protein excretion ≥30-<300 mg/dL and ≥300 mg/dL) with reactive strips for chemical analyses[28] at the examination. Of the 29 samples (4.4% of total) collected in the evening, none had detectable glucosuria.

Main Outcomes

SCr level >1.2 mg/dL for men and >0.9 mg/dL for women was used as an indicator of decreased kidney function. We estimated GFR (eGFR) based on the isotope-dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation ($eGFR_{MDRD}$),[29] categorized into ≥60 and <60 mL/min/1.73 m^2. We also calculated eGFR with the CKD Epidemiology Collaboration (CKD-EPI) creatinine-based equation ($eGFR_{CKD-EPI}$).[30] Proteinuria was categorized as low grade (protein excretion ≥30-<300 mg/dL) and high grade (≥300 mg/dL).

Statistical Analysis

All analyses were performed separately for men and women using SPSS, version 16.0 (IBM, www-01.ibm.com/software/analytics/spss). Differences between communities and occupational groups were assessed using 2-sided χ^2 tests (Fisher exact test at expected frequencies <5) and 1-way analysis of variance for continuous variables. Univariate logistic regressions examined

Table 1. Characteristics of Study Participants

	Rural Coastal Sugarcane (0-50 masl)	Semirural Coastal Sugarcane/ Services (0-50 masl)	High-Altitude Sugarcane (>500 masl)	Coffee (1,650 masl)	Urban (650 masl)	P^a	Total (0-1,650 masl)
M:F	53:76	60:99	56:64	40:84	47:85		256:408
Age (y)							
Men	37.0 ± 11.5	37.9 ± 11.1	37.0 ± 11.9	35.2 ± 12.6	37.2 ± 11.4	0.9	37.0 ± 11.6
Women	36.8 ± 11.9	36.0 ± 10.4	35.3 ± 9.4	37.3 ± 11.3	38.5 ± 12.0	0.4	36.8 ± 11.1
Diabetes							
Men	4 (7.5)	4 (6.7)	2 (3.6)	0 (0)	1 (2.1)	0.3	11 (4.3)
Women	6 (7.9)	2 (2.0)	2 (3.1)	2 (2.4)	4 (4.7)	0.3	16 (3.9)
Obesity							
Men	12 (22.6)	17 (28.3)	8 (14.3)	5 (12.5)	19 (40.4)	0.009	61 (23.8)
Women	25 (32.9)	42 (42.4)	18 (28.1)	28 (33.3)	24 (28.2)	0.3	137 (33.6)
Use of NSAIDs							
Men	6 (11.3)	11 (18.3)	6 (10.7)	12 (30.0)	4 (8.5)	0.04	39 (15.2)
Women	14 (18.4)	16 (16.2)	24 (37.5)	25 (29.8)	15 (17.6)	0.006	94 (23.0)
Tobacco smoking current							
Men	11 (20.8)	6 (10.0)	11 (19.6)	14 (35.0)	14 (29.8)	0.03	56 (21.9)
Women	2 (2.6)	0 (0)	0 (0)	2 (2.4)	6 (7.1)	0.02	10 (2.5)
Tobacco smoking ever							
Men	24 (45.3)	23 (38.3)	26 (46.4)	29 (72.5)	29 (61.7)	0.006	131 (51.2)
Women	13 (17.1)	3 (3.0)	3 (4.7)	8 (9.5)	20 (23.5)	<0.001	47 (11.5)
Alcohol consumption current							
Men	18 (34.0)	20 (33.3)	28 (50.0)	16 (40.0)	31 (66.0)	0.004	113 (44.1)
Women	7 (9.2)	10 (10.1)	5 (7.8)	7 (8.3)	33 (38.8)	<0.001	62 (15.2)
Hypertension							
Men	14 (26.4)	20 (33.3)	21 (37.5)	19 (47.5)	17 (36.2)	0.3	91 (35.5)
Women	12 (15.8)	13 (13.1)	15 (23.4)	21 (25.0)	18 (21.2)	0.3	79 (19.4)
Self-reported nephrolithiasis							
Men	3 (5.7)	5 (8.3)	2 (3.6)	0 (0)	4 (8.5)	0.3	14 (5.5)
Women	15 (19.7)	3 (3.0)	1 (1.6)	15 (17.9)	12 (14.1)	<0.001	46 (11.3)
Sector of current occupation							
Men							
Primary	38 (71.7)	20 (33.3)	52 (92.9)	33 (82.5)	1 (2.1)	<0.001	144 (56.3)
Secondary	3 (5.7)	6 (10.0)	1 (1.8)	1 (2.5)	1 (2.1)		12 (4.7)
Tertiary	11 (20.8)	31 (51.7)	2 (3.6)	6 (15.0)	41 (87.2)		91 (35.5)
Economically inactive	1 (1.9)	3 (5.0)	1 (1.8)	0 (0)	4 (8.5)		9 (3.5)
Women							
Primary	10 (13.2)	11 (11.1)	17 (26.7)	31 (36.9)	5 (5.9)	<0.001	74 (18.1)
Secondary	0 (0)	8 (8.1)	5 (7.8)	0 (0)	3 (3.5)		16 (3.9)
Tertiary	9 (11.8)	22 (22.2)	3 (4.7)	2 (2.4)	47 (55.3)		83 (20.3)
Economically inactive	57 (75.0)	58 (58.6)	39 (60.9)	51 (60.7)	30 (35.3)		235 (57.6)

Note: Unless otherwise indicated, continuous variables given as mean ± standard deviation, and categorical variables, as number (percentage). Includes inhabitants aged 20-60 years of 5 communities in El Salvador with various economic profiles and located at different altitudes.

Abbreviations: F, female; M, male; masl, meters above sea level; NSAID, nonsteroidal anti-inflammatory drug.

[a]Two-sided tests for differences: 1-way analysis of variance (age) and χ^2 or Fisher exact test (all other factors).

associations between elevated SCr level and known risk factors. In multivariate models for elevated SCr level and eGFR <60 mL/min/1.72 m^2 with coastal sugarcane/cotton plantation work as the exposure variable, we added covariates at change in the effect estimate >10%.[31] Because hypertension and nephrolithiasis can be determinants as well as consequences of CKD, we added them to the adjusted models in a second step to examine changes in effect estimates. The effect of work history on sugarcane/cotton lowland plantations was investigated further in inhabitants of the coastal communities. Hypertension and nephrolithiasis were examined as secondary outcomes.

RESULTS

Study Setting and Participant Characteristics

We examined 664 persons with no exclusions (Table 1). The participation rate was 73%: 77% for women and 66% for men. The lowest response was 49% (men in the coffee community) and the highest was 86% (men in the high-altitude sugarcane community). The main reasons for refusal were no interest and anxiety

Table 2. Descriptive Parameters of Kidney Function

	No.	SCr (mg/dL)	Elevated SCr[a]	eGFR <60 mL/min/1.73 m² MDRD	eGFR <60 mL/min/1.73 m² CKD-EPI	Proteinuria ≥30 mg/dL	SUN >20 mg/dL
Rural coastal sugarcane (0-50 masl)							
Men	53	1.0 [0.7-4.6]	15 (28.3)	10 (18.9)	7 (13.2)	3 (5.7)	5 (9.4)
Women	76	0.7 [0.5-1.8]	12 (15.8)	6 (7.9)	2 (2.6)	5 (6.6)	2 (2.6)
Semirural coastal sugarcane/services (0-50 masl)							
Men	60	1.0 [0.6-6.2]	19 (31.7)	11 (18.3)	9 (15.0)	5 (8.5)[b]	6 (10.0)
Women	99	0.6 [0.4-8.0]	13 (13.1)	8 (8.1)	7 (7.1)	9 (9.1)	3 (3.0)
High-altitude sugarcane (500 masl)							
Men	56	0.9 [0.6-4.0]	2 (3.6)	1 (1.8)	1 (1.8)	2 (3.6)	1 (1.8)
Women	64	0.6 [0.4-2.2]	3 (4.7)	2 (3.1)	2 (3.1)	3 (4.7)	2 (3.1)
Coffee (1,650 masl)							
Men	40	0.8 [0.6-1.0]	0 (0)	0 (0)	0 (0)	0 (0)	3 (7.5)
Women	84	0.7 [0.5-1.0]	2 (2.4)	1 (1.2)	0 (0)	5 (6.0)	0 (0)
Urban (650 masl)							
Men	47	0.9 [0.7-1.3]	4 (8.5)	0 (0)	0 (0)	0 (0)	1 (2.1)
Women	85	0.7 [0.4-1.2]	9 (10.6)	2 (2.4)	1 (1.2)	2 (2.4)	1 (1.2)
Total (0-1,650 masl)							
Men	256	0.9 [0.6-6.2]	40 (15.6)	22 (8.6)	17 (6.6)	10 (3.9)	16 (6.3)
Women	408	0.7 [0.4-8.0]	39 (9.6)	19 (4.7)	12 (2.9)	24 (5.9)	8 (2.0)
P[c]							
Men			<0.001	<0.001	0.001	0.1	0.2
Women			0.02	0.09	0.05	0.4	0.5

Note: For male and female inhabitants aged 20-60 years of 5 communities with various economic profiles and located at different altitudes in El Salvador. Continuous variables given as median [range]; categorical variables given as number (percentage). Conversion factors for units: SCr in mg/dL to μmol/L, ×88.4; eGFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667.

Abbreviations: CDK-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; masl, meters above sea level; max, maximum; MDRD, Modification of Diet in Renal Disease; min, minimum; SCr, serum creatinine; SUN, serum urea nitrogen.

[a]Greater than the upper limit of the normal laboratory range: men, >1.2 mg/dL; women, >0.9 mg/dL.

[b]N = 59, 1 missing value for patient with end-stage renal disease.

[c]χ^2 test for differences between communities or Fisher exact test if cells have expected numbers less than 5.

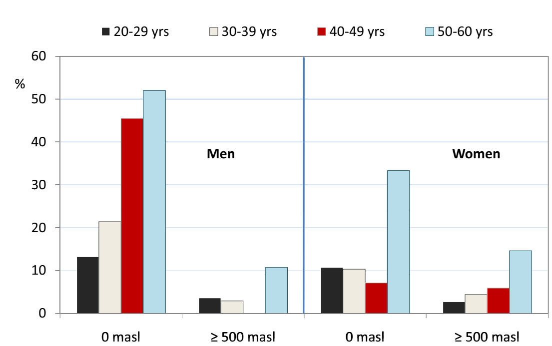

Figure 1. Prevalences of serum creatinine levels greater than the upper limit of the normal laboratory range (men, >1.2 mg/dL; women, >0.9 mg/dL) in communities at sea level and communities at 500 meters above sea level (masl) or higher by sex and age.

about providing a blood sample. Nonresponders were of similar age as participants.

By design, there were marked differences in altitudes and economic activity between the communities and hence in characteristics of the participants (Table 1). At data collection, 56% of men and 18% of women worked in agriculture. Moreover, 78% of men and 45% of women had been agricultural workers at some time. Mean age was younger than 40 years in all communities, with similar age distributions. Hypertension was common in men, particularly in the coffee community, whereas the prevalence of diabetes was low in all communities. Obesity was common, especially in urban men and women in the semirural coastal community. Differences between communities were statistically significant for NSAID use, tobacco smoking, and alcohol consumption in both

Table 3. Prevalence of Elevated SCr Levels

	Men				Women			
		Elevated SCr				Elevated SCr		
	No.	No. (%)	Crude PR	*P*[a]	No.	No. (%)	Crude PR	*P*[a]
All	256	40 (15.6)			408	39 (9.6)		
Agricultural status								
Never worked in agriculture	57	4 (7.0)	Reference		224	20 (8.9)	Reference	
Highland residents	46	4 (8.7)			138	10 (7.2)		
Coastal lowland residents	11	0 (0)			86	10 (11.6)		
Ever worked in agriculture	199	36 (18.1)	2.59	0.04	184	19 (10.3)	1.16	0.7
Highland residents	97	2 (2.1)	0.30	0.2[b]	95	4 (4.2)	0.47	0.1
Coastal lowland residents	102	34 (33.3)	4.76	<0.001	89	15 (16.9)	1.90	0.05
Crop								
Coffee or subsistence/never sugarcane or cotton	52	2 (3.8)	0.54	0.7[b]	85	4 (4.7)	0.53	0.3
Highland farming (≥500 masl)	39	0 (0)		0.12[b]	75	3 (4.0)	0.45	0.2
Coastal lowland farming	13	2 (15.4)	2.20	0.3[b]	10	1 (10.0)	1.12	0.9[b]
Sugarcane (recent and past)	130	29 (22.3)	3.19	0.01	56	7 (12.5)	1.40	0.4
Highland sugarcane (500 masl)	57	2 (3.5)	0.50	0.7[b]	16	0 (0)		0.2[b]
Coastal lowland sugarcane	73	27 (37.0)	5.29	<0.001	40	7 (17.5)	1.97	0.2[b]
Cotton (coastal lowland in the past)	70	26 (37.1)	5.30	<0.001	69	12 (17.4)	1.96	0.05
Coastal lowland sugarcane/never cotton	28	6 (21.4)	3.06	0.07[b]	14	3 (21.4)	2.40	0.1[b]
Cotton/never coastal lowland sugarcane	17	5 (29.4)	4.20	0.03[b]	43	8 (18.6)	2.09	0.1[b]
Coastal lowland sugarcane + cotton	45	21 (46.7)	6.67	<0.001	26	4 (15.4)	1.73	0.3[b]
Coastal lowland sugarcane or cotton								
1-10 y	55	13 (23.6)	3.37	<0.01	58	5 (8.6)	0.97	0.9[b]
≥10 y	43	19 (44.2)	6.31	<0.001	25	10 (40.0)	4.49	<0.001[b]

Note: Elevated SCr level is defined as a measurement greater than the upper limit of the normal laboratory range (men, >1.2 mg/dL; women, >0.9 mg/dL) in the pooled population aged 20-60 years of 5 communities in El Salvador.

Abbreviations: masl, meters above sea level; PR, prevalence ratio; SCr, serum creatinine.

[a]Pearson χ^2 test, 2 sided.

[b]Fisher exact test if cells have expected number less than 5, 2 sided.

sexes; for obesity in men; and for nephrolithiasis in women.

Prevalence of Elevated SCr and Reduced eGFR

The prevalence of elevated SCr level differed significantly among the communities (Table 2) for both men and women, with the highest prevalences in both coastal sugarcane communities (men, 28% and 32%; women, 16% and 13%). The sugarcane and coffee communities at higher altitude had much lower prevalences of elevated SCr levels (men, 4% and 0%; women, 5% and 2%). The prevalence in the urban community was intermediate (men, 11%; women. 8%). The highest prevalence of elevated SCr levels was observed in the oldest age category for both men and women, with a shift to younger age in the coastal sugarcane communities (Fig 1). Notably, in the coastal communities, the prevalence for men aged 40-49 years (46%) came close to the prevalence for men aged 50-60 years (52%), and the prevalence in coastal young men aged 20-29 years was even higher than in men aged 50-60 years at higher altitude (13% vs 10%).

The prevalence of $eGFR_{MDRD}$ <60 mL/min/1.73 m^2 was highest in the 2 coastal sugarcane communities (men, 19% and 18%; women, 8% in both cases), much lower in the high-altitude sugarcane and coffee communities, and absent in the urban neighborhood (Table 2). The CKD-EPI formula yielded lower prevalences of CKD, with 12 participants with $eGFR_{MDRD}$ of 55-59 mL/min/1.73 m^2 reclassified as $eGFR_{CKD\text{-}EPI} \geq$ 60 (range, 61-67) mL/min/1.73 m^2. The pattern across communities and sexes remained.

Only 10 men and 24 women had proteinuria, nonsignificantly distributed between communities (Table 2). Nonetheless, proteinuria was significantly more

Table 4. Factors Associated With Reduced Kidney Function in Univariate and Multivariate Logistic Regression Models

	Men			Women		
	Elevated SCr[a,b]	Crude OR (95% CI)	Adjusted OR (95% CI)[c]	Elevated SCr[a,b]	Crude OR (95% CI)	Adjusted OR (95% CI)[c]
Age						
20-29 y	7 (7.5)	1.0 (reference)		8 (6.2)	1.0 (reference)	
30-39 y	7 (11.1)	1.5 (0.5-4.7)		9 (7.1)	1.2 (0.4-3.2)	
40-49 y	10 (21.3)	3.3 (1.1-9.4)		5 (6.3)	1.0 (0.3-3.3)	
50-60 y	16 (30.2)	5.3 (2.0-14)		17 (23.0)	4.5 (1.8-12)	
Diabetes	2 (18.2)	1.2 (0.2-5.9)		4 (25.0)	3.4 (1.0-12)	
Obesity	32 (16.4)	0.8 (0.3-1.8)		26 (9.6)	1.0 (0.4-2.0)	
Long-term NSAID use	9 (23.1)	1.8 (0.7-4.2)		7 (7.4)	0.7 (0.3-1.7)	
Current smoking	7 (12.5)	0.7 (0.3-1.8)		2 (20.0)	2.4 (0.5-12)	
Ever smoking	26 (19.8)	2.0 (0.9-4.0)		7 (14.9)	1.8 (0.7-4.4)	
Current alcohol use	11 (9.5)	0.4 (0.2-0.9)		7 (11.3)	1.2 (0.5-3.0)	
Ever alcohol use	32 (15.5)	1.0 (0.4-2.2)		12 (12.1)	1.4 (0.7-3.0)	
Hypertension	16 (17.6)	1.2 (0.6-2.5)		15 (19.0)	3.0 (1.4-6.0)	
History of nephrolithiasis	6 (42.9)	4.6 (1.5-14)		5 (10.9)	1.2 (0.4-3.2)	
Residence in coastal vs highland communities	34 (30.1)	9.8 (3.9-25)		25 (14.3)	2.6 (1.3-5.2)	
Time working in coastal sugarcane or cotton (/10-y increase)						
Entire study population	—	3.5 (2.2-5.4)	3.1 (2.0-5.0)	—	2.4 (1.5-3.9)	2.3 (1.4-3.7)
Subpopulation of coastal communities	—	2.5 (1.6-4.1)	1.9 (1.2-3.3)	—	2.0 (1.3-3.2)	1.7 (1.0-2.9)

Note: Reduced kidney function defined as SCr level greater than the upper limit of the normal laboratory range (men, >1.2 mg/dL; women, >0.9 mg/dL) in men and women aged 20-60 years from 5 communities in El Salvador.

Abbreviations: CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SCr, serum creatinine.

[a]Range of estimated glomerular filtration rates in participants with elevated SCr levels: 10.0-75.7 mL/min/1.73 m^2 in men, 5.3-74.6 mL/min/1.73 m^2 in women.

[b]Percentage of participants in the covariable category.

[c]Logistic model: work in coastal sugarcane or cotton plantations (10-year increases), age, and ever smoking.

frequent in participants with eGFR <60 mL/min/1.73 m^2 compared with all other participants (men, 14% vs 3% [$P = 0.04$]; women, 26% vs 5% [$P = 0.003$]). All proteinuria had protein excretion <300 mg/dL, except for 2 women. Only 24 participants (two-thirds of whom were men) had a serum urea nitrogen level >20 mg/dL, 20 of whom had also an elevated SCr level and low $eGFR_{MDRD}$.

Men currently in the agriculture and transport industries had the highest prevalences of elevated SCr levels, 17% based on 24 cases and 19% based on only 4 cases, respectively. Most job categories had too few individuals for analysis. Table 3 lists prevalences and crude prevalence ratios for different agricultural populations compared with participants never in agriculture. Elevated SCr levels concentrated in coastal sugarcane workers and workers on former coastal cotton plantations. Male and female sugarcane workers in the highland sugarcane community and men and women who had worked in coffee or subsistence crops but never on cotton or sugarcane had low prevalences (albeit for male coastal subsistence-only farmers, the data were inconclusive: 2 cases, 15.4%). For the 43 men and 25 women with more than 10 years in coastal cotton or sugarcane plantations, prevalences of elevated SCr level were 44% and 40%, respectively.

Parameters Associated With Decreased Kidney Function

In univariate regressions, elevated SCr level was associated significantly with coastal residency, coastal sugarcane/cotton plantation work, and age in both sexes; with ever smoking and nephrolithiasis in men; and with diabetes and hypertension in women (Table 4). Correlation between coastal residency and coastal

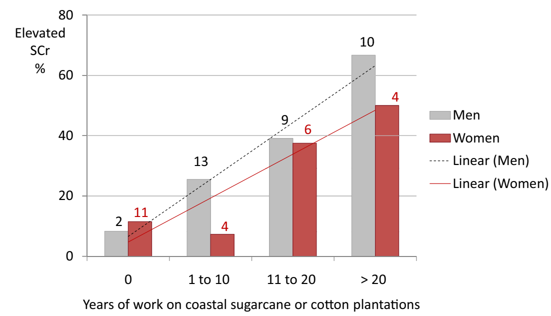

Figure 2. Relative and absolute frequencies of serum creatinine (SCr) levels greater than the upper limit of the normal laboratory range (men, >1.2 mg/dL; women, >0.9 mg/dL) in residents aged 20-60 years of 2 coastal villages by categories of duration of work on coastal sugarcane or cotton plantations.

plantation work (Spearman $r = 0.74$ for men and 0.56 for women) was too high for mutual adjustment. However, with 81% of cases of elevated SCr level in the coastal communities occurring in sugarcane/cotton plantation workers, the high odds ratio (OR) for coastal residency seems to reflect mostly work history on coastal plantations. We therefore dropped the residency from further models.

Only age altered the effect estimates for coastal plantation work for both sexes and ever smoking for men; these variables were kept. Current smoking, alcohol consumption, obesity, diabetes, and NSAID consumption did not alter the risk estimates and were excluded. In the age- and ever-smoking–adjusted models, the ORs for 10-year increments in coastal sugarcane/cotton plantation work were associated significantly with elevated SCr levels in men (OR, 3.1; 95% confidence interval [CI], 2.0-5.0) and women (OR, 2.3; 95% CI, 1.4-3.7). Adding hypertension or nephrolithiasis to the models did not change the ORs. Conversely, coastal sugarcane/cotton plantation work did not emerge as a risk factor for hypertension or nephrolithiasis in models adjusted for age, obesity, diabetes, and smoking (not tabulated). The patterns for eGFR <60 mL/min/1.73 m^2 were similar, although with higher effect estimates and wider CIs due to smaller numbers. A larger number of participants had eGFR <75 mL/min/1.73 m^2; thus, an analysis looking at associations with participant characteristics is given in Table S1 (provided as online supplementary material).

In the subpopulation of coastal villagers, the unadjusted prevalence of elevated SCr level increased linearly over 10-year categories of coastal sugarcane/cotton plantation work, most clearly for men (Fig 2). The age- and ever-smoking–adjusted ORs for 10-year increments in sugarcane/cotton work were 1.9 (95% CI, 1.2-3.3) for men and 1.7 (95% CI, 1.0-2.9) for women (Table 4).

DISCUSSION

This study provides further evidence of a CKD epidemic in Central America and data for several key characteristics. The main findings were: (1) high prevalences of elevated SCr levels and decreased eGFRs in coastal sugarcane communities with infrequent low-grade proteinuria; (2) a lower prevalence for women than men, but with similar trends over pertinent categories; (3) gradient for elevated SCr levels with years of coastal sugarcane or cotton work in men and women; and (4) no increase in reduced kidney function in sugarcane workers at 500 masl or subsistence farmers.

Many clinicians and public health authorities in Central America believe that the CKD epidemic is unrelated to conventional risk factors and limited to younger men, specifically sugarcane workers.[18,19,21-25] The results of our study indicate that women and cotton workers also may be at risk of decreased kidney function.

During the 1960s and 1970s, cotton cultivation prevailed along the Central American Pacific coast, with harsh and hot working conditions. An economic collapse in the 1980s drastically reduced cotton cultivation,[32] with sugarcane emerging as a major source for employment.[33] We observed decreased kidney function associated with job history in either crop (see Table 3). Cotton workers were older than the rest of the population, but the prevalence of elevated SCr levels in cotton-only workers aged 40-60 years was 3 times the prevalence for the population of this same age group in the high-altitude communities (24% vs 8%; $P = 0.003$). This indicates that cotton cultivation is associated with decreased kidney function independently from sugarcane. The high prevalence in the oldest age group of women may reflect agricultural work decades back.

In El Salvador, a considerable number of women were active in agriculture during the civil war in the 1980s and early 1990s and afterward. Women have worked less often in sugarcane and cotton plantations than men and likely have performed less physically strenuous tasks. Although the prevalence of elevated SCr level and eGFR <60 mL/min/1.73 m^2 in women was not as high as in men, trends across communities, altitudes, and different occupational categories closely followed those observed for men. Notably, the adjusted ORs for duration of sugarcane/cotton plantation work were remarkably similar between men and women (see Table 4). The male dominance in CKD occurrence seems to be attributable to a gendered occupational difference rather than a sex difference in disease susceptibility.

Proteinuria was infrequent and mostly low grade, as in Nicaragua.[23,25] This is compatible with kidney disease originating in tubulointerstitial rather than glomerular damage. Glomerulonephritis is unlikely as a dominant cause of CKD in this region also because diabetes and hypertension did not emerge as important risk factors. Repeated volume depletion from heat exposure and muscle exertion is a hypothesis for a causative mechanism. Volume depletion has been related to increased risk of nephrolithiasis,[34,35] which is more likely to occur in hot occupations, but no evidence is available about chronic or repeated episodes of volume depletion as a cause of CKD with or without nephrolithiasis. Volume depletion, often accompanied by rhabdomyolysis, is a well-known cause of acute kidney damage and has been reported, for example, in marathon runners,[36] but as yet, there are no data showing that repeated episodes of volume depletion with or without acute tubular necrosis may precipitate CKD. However, the hypothesis of repeated episodes of volume depletion is consistent with our observation of decreased kidney function in sugarcane cutters and cotton workers with conditions of extreme heat stress, but not sugarcane workers at higher altitude with probably less heat stress or independent subsistence farmers having more control over their working conditions.

Our findings are consistent with the parallel study in Nicaragua, which observed increased elevated SCr levels in sugarcane workers and women in agriculture in a low-altitude community.[23] Our results agree in part with the other 2 Nicaraguan studies from the same region. One of these studies reported an association of CKD with residence at lower altitude (<500 m), whereas associations with agricultural work in general and cotton specifically were not statistically significant in sex- and age-adjusted analyses. Possibly, the results would have been clearer with sex-stratified analyses.[25] The other study, in low-altitude communities, reported associations with any agricultural field work and with banana, rice, and corn, but not cotton, and also with sugar mill jobs, whereas sugarcane field workers were not mentioned.[24] The latter study was based on volunteer screening and women were excluded. This study also identified as risk factors water intake and consumption of illegal alcohol, possibly contaminated with nephrotoxic substances. The intake of large amounts of water may be associated with working hard in a hot climate and repeated episodes of volume depletion, a finding in concert with ours. A moderate nonsignificant association with illegal alcohol intake also was found by O′Donnell et al.[25] In our study, very few participants reported consumption of illegal alcohol and alcohol consumption did not modify the risk estimates. Overall, there is no consistent evidence that alcohol consumption, whatever kind, is an important risk factor for CKD in the region.

That the population of the high-altitude sugarcane community did not show decreased kidney function, contrasting with the sugarcane communities at sea level, is a remarkable finding. Agricultural practices for cane cutting, pesticide use, and current water intake were similar. We did not include a sea-level urban community; in the parallel Nicaraguan study, such a community did not have kidney problems.[23] Without environmental nephrotoxin data, the major difference to date seems to be ambient temperature in combination with strenuous work.

Our participation rates were reasonably high. Participation bias is not likely, except that those with very severe CKD had died or were not present at the examination. Even if differences between coastal and highland communities were overestimated for eGFR <60 mL/min/1.73 m^2 because the coastal communities were selected for having ESRD cases, this is not likely for elevated SCr level, which in most cases is asymptomatic. Most important, the analysis restricted to coastal communities strengthens the overall findings for occupational exposures. For cases with elevated SCr levels, there is no reason to suspect biased reporting of occupational exposures that is differential with respect to outcome because the occupational history was obtained before SCr results were known. The reliability of the SCr determinations seems reasonably high because certified laboratories and sample controls were used. The equations for calculating eGFR are not validated for Central America, but performance is not likely to differ within our study population.

The descriptive and cross-sectional design was a major limitation. With one determination of kidney function, participants cannot be classified into CKD stages according to the guidelines of the National Kidney Foundation.[37] However, the objective of this study was not to establish individual clinical CKD diagnosis, but to compare kidney function biomarkers at the population level. In addition, data for traditional risk factors were based on questionnaires and some variables may have had considerable misclassification. Thus, long-term use of NSAIDs merits further attention, including a possible interaction with heat stress.

Despite limited resources, we documented widespread decreased kidney function in coastal communities related to years of work on coastal sugarcane/cotton plantations. The high prevalence of eGFR <60 mL/min/1.73 m^2 in the coastal communities, 18% of men aged 20-60 years, indicates the severity of the epidemic in a region where there is little to offer to patients and where CKD often progresses to ESRD and death. It is noteworthy that decreased eGFR also is related to cardiovascular morbidity and mortality.

The risk of premature death from cardiovascular disease at CKD stages 3-4 is higher than that for reaching ESRD.[38,39] This study from El Salvador, as well as the recent Nicaraguan studies,[23-25] provides important clues for etiologic studies, particularly heat stress.

It is urgent to assess the causes of this severe public health problem with properly designed etiologic and clinical research. A thorough medical workup including kidney biopsies and histopathologic examinations from a small group of affected individuals in rather early stages of CKD is needed to confirm the interstitial nature of the disease and provide clues with regard to pathogenesis. Etiologic research would use random samples from a proper study base and repeated measurements of all pertinent exposures with emphasis on heat exposure, environmental and water pollutants (particularly pesticide residues and heavy metals), and amount of water intake during work and rest.

Precautionary preventive actions must be implemented already at this stage, providing sufficient water and rest for workers in hot environments. There is a threat that global warming will dramatically increase populations exposed to hard work in hot climates. If heat stress is a causal factor for CKD, this disease will be an added health risk related to climate change.

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SUPPLEMENTARY MATERIAL

Table S1: Factors associated with eGFR <75 mL/min/1.75 m^2 in univariate and multivariate logistic regression models.

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2011.11.039) is available at www.ajkd.org.

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