Decreased Kidney Function of Unknown Cause in Nicaragua: A Community-Based Survey

Cecilia Torres, MD,[1,2] Aurora Aragón, PhD,[1] Marvin González, MSc,[1] Indiana López, PhD,[1] Kristina Jakobsson, PhD,[3] Carl-Gustaf Elinder, PhD,[4] Ingvar Lundberg, PhD,[2] and Catharina Wesseling, PhD[2,5]

Background: End-stage kidney disease overwhelms health services in Central America. We determined prevalences of decreased kidney function in distinct populations in the most affected region of Nicaragua.

Study Design: Cross-sectional survey.

Setting & Participants: Total populations aged 20-60 years of 5 villages in Northwest Nicaragua: mining/subsistence farming (elevation, 100-300 m above sea level), banana/sugarcane (100-300 m), fishing (0-100 m), services (0-100 m), and coffee (200-675 m); 479 men and 617 women (83% response).

Predictor or Factor: Village; participant sex, age, and occupation; conventional chronic kidney disease risk factors.

Outcomes: Serum creatinine (SCr) values greater than laboratory reference range for sex, estimated glomerular filtration rate <60 mL/min/1.73 m^2, proteinuria stratified in the low (dipstick protein excretion, 30-300 mg/dL) and high (>300 mg/dL) range.

Results: Prevalences of abnormal SCr levels: 18% (of all men) and 5% (of all women); in the mining/subsistence farming village, 26% and 7%; banana/sugarcane, 22% and 6%; fishing, 13% and 4%; services, 0% and 1%; and coffee, 7% and 0%. Prevalences of estimated glomerular filtration rate <60 mL/min/1.73 m^2: 14% (of all men) and 3% (of all women); in the listed villages, 19% and 5%, 17% and 4%, 10% and 2%, 0% and 0%, and 7% and 0%, respectively. Proteinuria, predominantly in the low range, affected 14% and 11% of all men and women without marked differences between villages. By occupation, abnormal SCr levels occurred in 31% and 24% of male and female agricultural workers at 100-300 m above sea level, but not at higher altitudes, and also was high in male artisans (43%), construction workers (15%), and miners (14%). In logistic regression models, for the banana/sugarcane and mining/subsistence farming villages, high blood pressure and age were significant predictors of abnormal SCr levels in men, and for mining/subsistence farming, age in women.

Limitations: Causality is not addressed.

Conclusions: In some Nicaraguan villages and population segments, men in particular show a high prevalence of decreased kidney function of unknown origin, possibly environmental or occupational.

Am J Kidney Dis 55:485-496.

INDEX WORDS: Serum creatinine; chronic kidney disease (CKD); glomerular filtration rate (GFR); prevalence; Central America; occupation; agriculture.

Chronic kidney disease (CKD) is a worldwide public health problem with increasing numbers of patients in need of renal replacement therapy.[1-7] Knowledge regarding the prevalence or incidence of early-stage CKD nonetheless is scarce. Epidemiologic studies from industrialized countries have identified primarily aging, diabetes, hypertension, and use of nephrotoxic drugs as CKD risk factors.[1,4,5,7-10] Although some developing countries show similar patterns,[11,12] others have identified occupational and environmental causes.[13,14] The natural substances aristolochic acid and ochratoxin A have been related to CKD outbreaks,[15-19] and long-term exposures to heavy metals have been revealed as causes of renal damage.[20-24]

Nicaragua recently has witnessed an increasing number of renal replacement therapy patients

From the [1]Research Centre on Health, Work and Environment, National Autonomous University of Nicaragua at León, León, Nicaragua; [2]Occupational and Environmental Medicine, Department of Medical Sciences, Uppsala Universitet, Uppsala; [3]Department of Occupational and Environmental Medicine, Lund University, Lund; [4]Department of Renal Medicine, Karolinska University Hospital, Sweden; and [5]Central American Institute for Studies on Toxic Substances, Universidad Nacional, Heredia, Costa Rica.

Received August 3, 2009. Accepted in revised form December 2, 2009. Originally published online as doi:10.1053/j.ajkd.2009.12.012 on February 1, 2010.

Address correspondence to Cecilia Torres, MD, CISTA, Campus Médico, UNAN-León, León, Nicaragua. E-mail: ceciliatorreslacourt@yahoo.com

0272-6386/10/5503-0012$36.00/0
doi:10.1053/j.ajkd.2009.12.012

and CKD mortality. Data from the Nicaraguan Ministry of Health (MINSA) show that in 1992-2002, the crude national mortality rate increased from 4 to 9 deaths/100,000 inhabitants. Most affected is the Northwest Pacific region, where mortality increased from 13 to 36 deaths/100,000 inhabitants, with a male-to-female ratio of 5:1.[25] Unpublished studies in Nicaragua[26-28] and other studies from Central America[14,25,29,30] have suggested increased risks for agricultural workers, in particular, sugarcane workers, and have noted that kidney disease decreases at higher altitudes.

The available information is insufficient to understand the extent of this public health threat or its causes. The aim of this study is to investigate the prevalence of decreased kidney function in men and women of 5 villages of Northwestern Nicaragua, differentiated by their main economic profiles and occupations of their inhabitants. We investigated the extent to which conventional CKD risk factors may explain the prevalence of decreased kidney function and tried to substantiate or decrease the likelihood of agricultural work as a risk indicator and high altitude as a protective indicator for renal damage.

METHODS

Setting and Study Population

This cross-sectional survey established the prevalence of decreased kidney function in populations aged 20-60 years of 5 villages in Northwest Nicaragua. The villages were selected by convenience, with a maximum of 800 inhabitants to be manageable, and represent distinct economic profiles and locations at different altitudes: gold mining and subsistence farming (200-300 m above sea level), large-scale banana and sugarcane production (100-200 m above sea level), small-scale fishery near the Pacific Ocean (0-100 m above sea level), small-scale coffee farming (at 675 m above sea level and a minor part at 200 m above sea level), and services (0-100 m above sea level). The study was approved by the Ethical Committee for Biomedical Research of the National Autonomous University of Nicaragua at León (UNAN-León).

Data were collected from September to December 2007 on weekends to guarantee maximum participation. University personnel with village representatives performed a census in each village, registering members of each household independently of being in the village or not. All houses were georeferenced. Two weeks after the census, a survey was carried out using a questionnaire and clinical measurements, lasting 2-5 weekends. Participants were contacted in their houses and, if not at home, revisited at the end of the data collection in their village. All participants signed an informed consent.

Variables, Data Sources, and Measurements

We used serum creatinine (SCr) level greater than the laboratory reference range as an indicator for decreased kidney function: >1.2 mg/dL for men and >0.9 for women. In addition, we estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 based on the isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[31]

Trained medical we agree, the change is acceptable students visited every house applying the questionnaire covering demographic information, lifestyle, diseases, and medications. Subsequently, participants went to a mobile laboratory located in the health center, community house, or a village leader's home. Here, we measured blood pressure using a previously calibrated digital sphygmomanometer and weight and height using a calibrated clinical scale and obtained blood and urine samples.

Participants gave a morning random urine sample (50 mL) in a sterile collector and a nonfasting blood sample (20 mL) in 2 tubes, 1 with and 1 without anticoagulant. Two laboratory technicians performed within 30 minutes tests for glucosuria (glucose levels ≥100 mg/dL considered positive) and 2 different degrees of proteinuria (protein excretion >30 and >300 mg/dL) using reactive strips for chemical analyses (Urine-10; Cypress Diagnostics, www.diagnostics.be/frame_cl_uri.html). Blood samples without anticoagulant were centrifuged within the hour. Serum was transferred to 2 separate tubes, placed in an icebox, transported at the end of the day to the laboratory at UNAN-León, frozen, and kept at −20°C. Within 7 days, 1 of the serum sample tubes was transported on ice to the Central Laboratory of MINSA, where SCr was measured using Cobas Integra 400 (Roche Diagnostics, www.labsystems.roche.com/content/products/integra_400plus/introduction.html), automated equipment, using the Jaffé compensated method.[32-34] The remaining serum and full blood samples, as well as part of the urine samples, were stored for future analyses of nephrotoxins (heavy metals and pesticides). For quality control, 10% of the urine samples handled by each of the 2 technicians were reanalyzed by the other, with 97% of samples coinciding in all test parameters. For SCr measurements, every day an intralaboratory control was performed on the automated equipment according to its own reference values, and in addition, each batch of samples transferred to the MINSA laboratory included at least 2 spiked samples. Deviations were at all times within 1 standard deviation. The MINSA laboratory takes part in an international interlaboratory quality control program.

Hypertension was defined as either systolic blood pressure ≥140 mm Hg, diastolic pressure ≥90 mm Hg, or self-reported medical history. Diabetes mellitus was defined as glucosuria (glucose excretion ≥100 mg/dL) using a urine stick or self-reported medical history of diabetes mellitus. Obesity was defined as body mass index ≥30 kg/m^2. Urinary and renal illness was limited to self-reported medically diagnosed urinary tract infections in the previous year and history of renal lithiasis versus no such conditions. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) was defined as consuming at least 1 NSAID in the previous year for >7 consecutive days combined with a self-reported history of chronic joint pain.

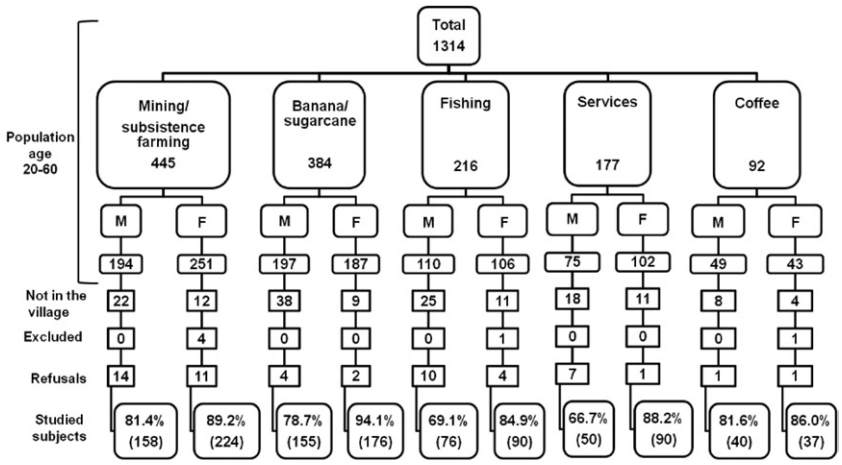

Figure 1. Study flow diagram of participation rates and reasons for nonparticipation. Overall participation was 83.1% (1,096 total participants), including 76.6% of men and 89.6% of women.

Current occupation was classified into primary, secondary, and tertiary sectors and economically inactive population. The primary sector included categories of agriculture (farmers, farm laborers, and forest workers), fishing (fishermen and women), and mining (extraction and support workers). The secondary sector included categories of artisan manufacturing (food, furniture, and metal objects), construction (only men), and other occupations of the secondary sector, mostly machinery and equipment installation and repair workers. The tertiary sector was kept as 1 category that included office workers, teachers, health personnel, vendors, taxi drivers and other transport workers, security guards and police officers, tourist workers, domestic workers, and other services. The economically inactive population included persons receiving disability benefits, housewives (only women), students, and unemployed, although the latter in a strict sense are part of the economically active population.

Statistical Methods

Descriptive parameters for SCr levels (median, minimum, maximum, and interquartile range) were calculated as indicators of renal function. All analyses were stratified by sex and village. The prevalence of abnormal SCr levels was calculated according to age and occupational category as an indicator of decreased kidney function. In addition, prevalences of low- (protein excretion, 30-300 mg/dL) and high-range (protein excretion >300 mg/dL) proteinuria and eGFR <60 mL/min/1.73 m^2 were computed. χ^2 tests were used for crude comparisons between groups. Multiple logistic regression models examined whether the village of residency predicted SCr levels greater than the laboratory reference range after individual adjustment for conventional risk factors. Predictors were hypertension, diabetes, obesity, urinary tract infections, renal lithiasis, use of NSAIDs, age, sex, and village of current residency. To be able to run the models with at least 5 participants in each category, populations of the fishing, services, and coffee villages were pooled as the reference group; age was analyzed as a continuous variable in women; and diabetes and renal lithiasis were excluded from these models. All analyses were performed using SPSS, version 16.0 (SPSS Inc., www.SPSS.com).

RESULTS

Of 1,314 inhabitants aged 20-60 years, 1,096 were included in the analyses, with an overall response rate of 83% (75% of men, 88% of women), ranging from 67% of men in the services village to 94% of women in the banana/sugarcane village. Six women from 3 villages were excluded for not providing blood and urine samples. Refusals were <10% for each village. Nonparticipation was caused mostly by migration for work according to information provided by family members (Fig 1). Most nonresponders were aged <40 years and worked currently in agriculture and construction both in and outside Nicaragua.

Differences between villages with regard to known CKD risk factors were small (Table 1). The coffee village population was slightly older and somewhat leaner. The fishing village population had lower prevalences of hypertension and history of urinary tract infections. All villages had a low prevalence of diabetes. Women more often were obese than men and more often reported use of NSAIDs. A high proportion of participants reported a history of medically diagnosed urinary tract infections, particularly women, but also men in the mining/subsistence farming, banana/sugarcane, and services villages. For urinary tract infections, there was a clear difference between villages for men, but not women.

SCr values varied widely with sex and villages (Table 2). Median values for men living in mining/subsistence farming, banana/sugarcane, and

Table 1. Risk Factors of Study Populations by Village Type and Elevation

Risk Factor	Sex	Mining/Subsistence Farming (200-300 masl)	Banana/ Sugarcane (100-200 masl)	Fishing (0-100 masl)	Services (0-100 masl)	Coffee (200-675 masl)	Total (0-675 masl)	P[a]
Age, mean (y)	M	34.9 ± 11.4	33.8 ± 10.5	35.1 ± 11.2	33.6 ± 12.0	36.1 ± 10.3	34.5 ± 11.0	0.7
	F	34.4 ± 10.6	35.9 ± 10.9	33.5 ± 11.0	34.7 ± 11.1	37.2 ± 10.6	34.9 ± 10.8	0.3
Hypertension	M	35 (22.2)	32 (20.6)	12 (16.4)	9 (18.0)	7 (17.9)	95 (20.0)	0.9
	F	56 (25.0)	46 (26.1)	12 (13.6)	22 (24.4)	9 (24.3)	145 (23.6)	0.2
Diabetes mellitus	M	2 (1.3)	1 (0.6)	2 (2.7)	0	1 (2.5)	6 (1.3)	0.8
	F	11 (4.9)	5 (2.8)	4 (4.4)	3 (3.4)	2 (5.4)	25 (4.1)	0.8
Obesity	M	23 (14.6)	22 (14.4)	10 (13.2)	13 (26.0)	5 (12.5)	73 (15.2)	0.3
	F	85 (37.9)	51 (29.0)	24 (26.7)	27 (30.0)	9 (24.3)	196 (31.8)	0.2
Use of nonsteroidal anti-inflammatory drugs	M	21 (13.3)	11 (7.1)	7 (9.2)	6 (12.0)	3 (7.5)	48 (10.0)	0.4
	F	49 (21.9)	28 (15.9)	10 (11.1)	15 (16.7)	8 (21.6)	110 (17.8)	0.2
History of diagnosed urinary tract infections	M	51 (32.2)	50 (32.2)	11 (14.5)	15 (30.0)	7 (17.5)	134 (28.0)	<0.01
	F	114 (50.9)	91 (51.7)	33 (36.7)	36 (40.0)	17 (45.9)	291 (47.2)	0.2
History of renal lithiasis	M	7 (4.4)	6 (3.9)	1 (1.3)	6 (12.0)	1 (2.5)	21 (4.4)	0.1
	F	10 (4.5)	2 (1.1)	2 (2.2)	4 (4.4)	3 (8.1)	21 (3.4)	<0.01

Abbreviation: masl, meters above sea level.
[a] χ^2 test for differences between villages.

fishing villages were higher, with wider interquartile ranges than for men in the coffee and services villages. The prevalence of SCr level greater than the upper laboratory reference range was highest for men in the mining/subsistence farming and banana/sugarcane villages at 26% and 22%, followed by the fishing village with a prevalence of 13% for men, respectively. The prevalence of abnormal SCr levels for women also was higher in these villages, although considerably lower than for men (7%, 6%, and 4%, respectively). SCr levels in the services and coffee villages were low for both sexes, with no men in the services and no women in the coffee village having SCr levels exceeding the laboratory reference range. The prevalence of eGFR <60 mL/min/1.73 m^2 followed a pattern very similar to that for increased SCr levels. The prevalence of proteinuria in men was not markedly different between villages.

Table 3 lists prevalences of no, low-range (30-300 mg/dL), and high-range (>300 mg/dL) proteinuria for eGFRs >60 and <60 mL/min/1.73 m^2. High-range proteinuria was seen mainly in men with an eGFR <60 mL/min/1.73 m^2. In men and women with an eGFR <60 mL/min/1.73 m^2, low-range proteinuria was more common than high range in groups with sufficient numbers, that is, the mining/subsistence farming and banana/sugarcane villages. Overall prevalences of proteinuria (protein excretion >30 or >300 mg/dL) were 12% and 38% for men with an eGFR >60 and <60 mL/min/1.73 m^2 and 11% and 33% for women, respectively.

The mining/subsistence farming and banana/sugarcane villages, at intermediate altitudes of 100-300 m above sea level, showed the highest prevalences of individuals, particularly men, with abnormal SCr values. The lowest prevalences were in the services village at sea level and the high-altitude coffee village, whereas the fishing village at sea level showed an intermediate prevalence. The 3 persons with abnormal SCr levels in the coffee village lived in the lowest part located at 200 m above sea level.

As expected, the percentage of populations with SCr levels greater than the reference range increased with increasing age categories. The prevalence of individuals with increased SCr levels was higher for men than women in all age groups in all villages except for the services village, where no men had abnormal values. Prevalences for men aged <40 years in the mining/subsistence farming and banana/sugarcane villages were 19% and 16% versus 6%, 0%, and 4% in the fishing, services and coffee villages, respectively (Fig 2).

Occupational activities were markedly gendered, with men concentrating in the primary sector and women being mainly housewives (Table 4). The prevalence of abnormal SCr levels in men working in agriculture was 25%. Stratifying agricul-

Table 2. SCr, eGFR, and Proteinuria Measurements in Study Population by Village Type and Elevation

		SCr (mg/dL)			SCr > Reference Range[a]		eGFR <60 mL/min/1.73 m^2		Proteinuria ≥30 mg/dL	
	No.	Median	Minimun-Maximum	IQR	%	*P*[b]	%	*P*[a]	%	*P*[b]
Mining/subsistence farming (200-300 masl)										
M	158	0.93	0.61-7.66	0.40	26.0	<0.01	18.5	<0.01	15.9	0.4
F	224	0.65	0.37-4.01	0.15	6.7		4.9		12.0	
Banana/sugarcane (100-200 masl)										
M	155	0.85	0.20-7.86	0.43	21.9	<0.01	17.1	<0.01	18.1	0.7
F	176	0.56	0.35-2.40	0.15	5.7		4.0		16.5	
Fishing (0-100 masl)										
M	76	0.93	0.48-3.92	0.33	13.2	0.04	10.5	0.06	14.5	<0.01
F	90	0.60	0.37-1.73	0.19	4.4		2.2		3.3	
Services (0-100 masl)										
M	50	0.77	0.44-1.09	0.17	0.0	0.9	0.0	—	16.0	0.6
F	90	0.54	0.32-0.95	0.14	1.1		0.0		13.3	
Coffee (200-675 masl)										
M	40	0.75	0.59-1.73	0.20	7.5	0.3	7.5	0.51	7.5	0.9
F	37	0.60	0.35-0.78	0.14	0.0		0.0		5.4	
Total										
M	479	0.87	0.20-7.86	0.34	18.3	<0.01	14.2	<0.01	13.8	0.06
F	617	0.61	0.32-4.01	0.16	4.9		3.2		11.2	
P[c]										
M	479					<0.01[c]		0.01[c]		0.6[c]
F	617					0.2[c]		0.20[c]		0.02[c]

Note: Conversion factors for units: SCr in mg/dL to μmol/L, ×88.4; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviation: eGFR, estimated glomerular filtration rate; IQR, interquartile range; masl, meters above sea level; SCr, serum creatinine.

[a]Men >1.2 mg/dL; women >0.9 mg/dL.

[b]χ^2 test for differences between men and women.

[c]χ^2 test for differences between villages.

tural occupation by village, male agricultural workers most often showed increased SCr levels in the mining/subsistence farming (41%) and banana/sugarcane (25%) villages compared with 7.5% in the coffee village. Of 21 women working in agriculture, 4 (19%) had abnormal SCr values, all of them from the banana/sugarcane village (Table 5).

Prevalences of abnormal SCr levels in men working in artisan manufacturing, construction, and mining also were high (43%, 15%, and 14%, respectively), but based on small numbers. Fishermen had an intermediate prevalence of 8%. Of 26 men unemployed or on disability benefits, 27% showed abnormal SCr values.

In logistic regression models, the adjusted odds ratios of the conventional risk factors for SCr levels greater than the laboratory reference range showed that age and high blood pressure related significantly to abnormal SCr levels in men. Living in the mining/subsistence farming or banana/sugarcane village also was related significantly to abnormal SCr levels in men (Table 6). For women, adjusted risk estimates were similar, although not always statistically significant. In both sexes, obesity was related to de-

Table 3. Prevalence of No, Low-, and High-Range Proteinuria by Category of eGFR for Study Participants by Village Type and Elevation

	eGFR (mL/min/1.73 m^2)	No.	No Proteinuria	Low-Range Proteinuria (30 to <300 mg/dL)	High-Range Proteinuria (≥300 mg/dL)
Mining/subsistence farming (200-300 masl)					
Men	≥60	135	120 (88.9)	14 (10.4)	1 (0.7)
	<60	23	13 (56.5)	6 (26.1)	4 (17.4)
Women	≥60	214	190 (88.8)	23 (10.7)	1 (0.5)
	<60	10	7 (70.0)	3 (30.0)	0 (0)
Banana/sugarcane (100-200 masl)					
Men	≥60	128	110 (85.9)	17 (13.3)	1 (0.8)
	<60	27	17 (63.0)	7 (25.9)	3 (11.1)
Women	≥60	170	144 (84.7)	24 (14.1)	2 (1.2)
	<60	6	3 (50.0)	2 (33.3)	1 (16.7)
Fishing (0-100 masl)					
Men	≥60	68	60 (88.2)	8 (11.8)	0 (0)
	<60	8	5 (62.5)	3 (37.5)	0 (0)
Women	≥60	88	85 (96.6)	3 (3.4)	0 (0)
	<60	2	2 (100)	0 (0)	0 (0)
Services (0-100 masl)					
Men	≥60	50	42 (84.0)	8 (16.0)	0 (0)
	<60	0	0 (0)	0 (0)	0 (0)
Women	≥60	90	78 (86.7)	12 (13.3)	0 (0)
	<60	0	0 (0)	0 (0)	0 (0)
Coffee (200-675 masl)					
Men	≥60	38	35 (92.1)	3 (7.9)	0 (0)
	<60	2	2 (100)	0 (0)	0 (0)
Women	≥60	37	35 (94.6)	2 (5.4)	0 (0)
	<60	0	0 (0)	0 (0)	0 (0)
Total					
Men	≥60	419	367 (87.6)	50 (11.9)	2 (0.5)
	<60	60	37 (61.7)	16 (26.7)	7 (11.7)
Women	≥60	599	532 (88.8)	64 (10.7)	3 (0.5)
	<60	18	12 (66.7)	5 (27.8)	1 (5.6)

Note: Values expressed as number (percentage). Conversion factor for GFR in in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: eGFR, estimated glomerular filtration rate; masl, meters above sea level.

creased risk of abnormal SCr level, reaching statistical significance for only women. Because hypertension can be both a cause and an effect of kidney damage, we also ran the models without hypertension, but this did not produce a notable change in odds ratios for the remaining variables.

DISCUSSION

A single determination of SCr and a dipstick for proteinuria in a single spot sample is not sufficient for the diagnosis of CKD on an individual basis. However, the finding of high prevalences of abnormal SCr levels in specific segments of the population in a population-based study with extensive coverage is highly worrying. In the banana/sugarcane and mining/subsistence farming villages, about a quarter of the men had abnormal SCr values indicative of decreased kidney function, and ~18% had an eGFR <60 mL/min/1.73 m^2. The prevalence of CKD of such severity in the general population of the United States and Europe is <5%,[35,36] as were our findings in the services and coffee villages. Adjustment for known risk factors for CKD did not attenuate the overall findings.

The prevalence of decreased kidney function in male agricultural workers, artisan manufacturers, construction workers, and miners also was higher than for other workers, with the lowest prevalence in the service sector. The pattern of decreased kidney function in women with regard to occupation was not totally consistent with

men. However, both male and female agricultural workers at an altitude of 100-300 m above sea level had increased SCr values, whereas agricultural workers at a higher altitude did not. In 2 villages, 1 at sea level and 1 at almost 700 m above sea level, there was no increased prevalence of increased SCr values.

A cross-sectional survey cannot address causality. However, this was a first critically needed exploration of the extent and characteristics of a severe emerging public health threat in a developing country. Although based on a convenience sample of distinct villages, one of the strengths of this study is that it included the total adult population in each village, together forming a rather large study population with >1,000 examined participants. The censuses were rigorously performed in the participating villages just before data collection, allowing a complete register of the adult populations. These characteristics favor valid and precise comparisons.

Migration to other villages and neighboring countries in search of work decreased the participation rate, especially for men. People who migrate for work tend to be healthier than those remaining, which could have resulted in an overestimation of decreased kidney function prevalence. However, because kidney damage often is asymptomatic until advanced stages of disease, it is not likely that renal function in the absent migrant workers was very different from our examined subset. Moreover, any overestimation

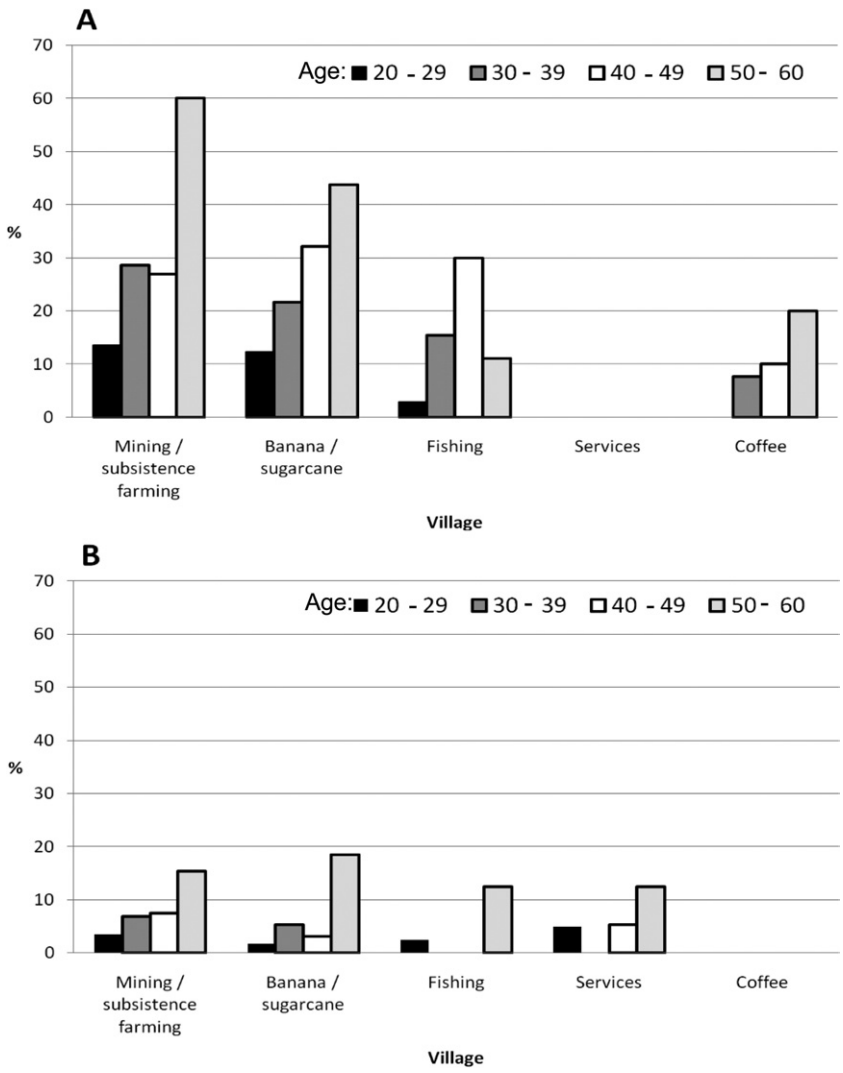

Figure 2. The prevalence of serum creatinine levels greater than the laboratory reference range (>1.2 mg/dL for men, >0.9 mg/dL for women) by age categories and village type for (A) men and (B) women.

Table 4. Current Occupational Sector of Study Populations by Village Type and Elevation

	Mining/Subsistence Farming (200-300 masl)	Banana/ Sugarcane (100-200 masl)	Fishing (0-100 masl)	Services (0-100 masl)	Coffee (200-675 masl)	Total (0-675 masl)	*P*[a]
Occupational sector for men							<0.01
Primary	61 (38.6)	130 (83.9)	51 (67.1)	4 (8.0)	39 (97.5)	285 (59.5)	
Secondary	60 (38.0)	9 (5.8)	6 (7.9)	15 (30.0)	0 (0)	90 (18.8)	
Tertiary	13 (8.2)	12 (7.7)	17 (22.4)	28 (56.0)	1 (2.5)	71 (14.8)	
Economically inactive	24 (15.2)	4 (2.6)	2 (2.6)	3 (6.0)	0 (0)	33 (6.9)	
Occupational sector for women							<0.01
Primary	0 (0)	17 (9.7)	3 (3.3)	1 (1.1)	4 (10.8)	25 (4.1)	
Secondary	8 (3.6)	6 (3.4)	5 (5.6)	4 (4.4)	0 (0)	23 (3.7)	
Tertiary	27 (12.1)	17 (9.7)	15 (16.7)	24 (26.7)	0 (0)	83 (13.5)	
Economically inactive	189 (84.4)	136 (77.3)	67 (74.4)	61 (67.8)	33 (89.2)	486 (78.8)	

Note: Values expressed as number (percentage).
Abbreviation: masl, meters above sea level.
[a] χ^2 test for differences between villages.

should be limited, taking into account that the overall participation rate was 83%.

One reason for refusing to participate was fear of job loss in the mining/subsistence farming and banana/sugarcane villages, where companies offering temporary jobs systematically exclude workers with high SCr values. The latter should tend to diminish the proportion of men with

Table 5. Cases of SCr Levels Greater Than Upper Limit of Laboratory Reference Range by Current Occupation

	Men		Women	
Sector of Current Occupation	Population	No. (%)	Population	No. (%)
Agriculture	236	60 (25.4)	21	4 (19.0)
Mining/subsistence farming village	61	25 (41.0)	—	—
Banana/sugarcane village	128	32 (25.0)	17	4 (23.5)
Fishing village	7	0 (0)	—	—
Services village	1	0 (0)	—	—
Coffee village	39	3 (7.5)	4	0 (0)
Fishery	48	4 (8.3)	4	0 (0)
Mining	43	6 (14.0)	1	1 (100)
Artisan manufacturing	7	3 (42.9)	21	1 (4.8)
Construction	20	3 (15.0)	—	—
Other occupations, secondary sector	15	0	1	0
Tertiary sector (services)	74	5 (6.8)	83	4 (4.8)
Unemployed	13	4 (30.8)	5	0 (0)
On disability benefits	13	3 (23.1)	1	0 (0)
Housewives	—	—	472	20 (4.2)
Students	7	0	8	0 (0)

Note: Upper limit of laboratory reference range for SCr is >1.2 mg/dL (men) and >0.9 mg/dL (women).
Abbreviation: SCr, serum creatinine.

Table 6. Multiple Logistic Regression Models With Predictors of SCr Values Greater Than the Upper Limit of the Reference Range in the Pooled Study Population

	Men			Women		
Covariable	SCr > Reference Range No. (%[a])	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	SCr > Reference Range No. (%[a])	Crude OR (95% CI)	Adjusted[c] OR (95% CI)
Hypertension	28 (29.5)	2.23 (1.32-3.75)	1.90 (1.07-3.37)	12 (8.3)	2.27 (1.06-4.82)	1.47 (0.62-3.45)
Obesity	14 (19.2)	1.06 (0.56-2.01)	0.71 (0.35-1.47)	5 (2.6)	0.41 (0.16-1.10)	0.29 (0.10-0.79)
Urinary tract infections	28 (20.9)	1.25 (0.60-2.07)	1.24 (0.72-2.12)	14 (4.8)	0.98 (0.47-2.04)	0.72 (0.33-1.59)
Use of nonsteroidal anti-inflammatory drugs	10 (20.8)	1.19 (0.57-2.49)	0.65 (0.28-1.50)	11 (10.0)	2.85 (1.32-6.18)	1.91 (0.78-4.67)
Age (y)						
20-29	18 (8.9)	Reference group		6 (2.6)	—	—
30-39	23 (19.7)	2.51 (1.29-4.89)	2.56 (1.29-5.10)	8 (4.4)		
40-49	26 (25.5)	3.52 (1.82-6.79)	4.06 (2.01-8.22)	5 (4.1)		
50-60	21 (36.8)	5.99 (2.91-12.36)	7.16 (3.26-15.70)	11 (13.9)		
All	—	—	—	30 (4.9)	1.06 (1.03-1.10)	1.05 (1.01-1.09)
Village type						
Fishing/services/coffee	13 (7.8)	Reference group		5 (2.3)	Reference group	
Mining/subsistence farming	41 (25.9)	4.12 (2.11-8.05)	4.20 (2.09-8.45)	15 (6.7)	3.04 (1.09-8.52)	3.48 (1.20-10.06)
Banana/sugarcane	34 (21.9)	3.31 (1.67-6.54)	3.39 (1.67-6.91)	10 (5.7)	2.55 (0.86-7.61)	2.42 (0.79-7.44)

Abbreviations: CI, confidence interval; OR, odds ratio; SCr, serum creatinine.
[a]Percentage of participants in the covariable category.
[b]All covariates are adjusted for each other.
[c]All covariates are adjusted for each other; age is treated as a linear variable.

decreased kidney function in miners and agricultural workers employed at banana and sugarcane plantations. However, such practice could influence workers with kidney damage to move into other occupations, possibly resulting in the high prevalence observed in subsistence farmers, artisan manufacturers, and construction workers, as well as in workers receiving disability benefits and the unemployed. Clearly, the lifetime occupational history of our participants must be explored further.

Some of our results are consistent with previous published and unpublished studies from Central America,[25-28,30] which reported kidney disorders to be more common in men than women, more common in agricultural workers than other occupations, and frequent in young people. New findings in our study were high prevalences of decreased kidney function in male artisan manufacturers, construction workers, and miners and female agricultural workers.

The influence of altitude, as hypothesized earlier in Central America,[29,37] is unclear from these data. Although agricultural work seemed strongly related to decreased kidney function in the villages at 100-300 m above sea level, it did not appear so in the coffee village at a higher altitude. This agrees with a study from El Salvador that did not observe increased kidney disorders (measured using proteinuria) in men in a coffee village at about the same altitude, whereas a high prevalence of proteinuria was observed in men in a sugarcane village at sea level.[37] In our study, there was no indication of an increased presence of decreased kidney function in the services village at sea level. Thus, low altitude does not seem to be a risk factor in itself.

Proteinuria and in particular high-range proteinuria occurred in a minority of individuals with a low eGFR. This suggests that proteinuria in the examined populations, in contrast to most endogenous renal diseases (such as chronic glomerulonephritis and diabetic nephropathy), is a secondary effect from kidney damage, rather than a starting point. It should be kept in mind that a positive result from a paper stick, as used, is a sensitive marker of albuminuria, but not tubular proteins, such as β_2-microglobulin, which typically are increased in urine in interstitial kidney disorders. Thus, tubulointerstitial kidney disease may be the cause of the CKD. More detailed analysis of urinary proteins in future studies may be helpful in elucidating the cause of the endemic kidney impairment.

With regard to conventional risk factors for CKD, it seems unlikely that misclassification, for example, because of participants not reporting hypertension or diabetes, explains their low predictive value for decreased kidney function. People have good accessibility to the health system at the village level and in general were aware of common chronic diseases because of a countrywide control program. Most drugs in Nicaragua can be bought over the counter and many ailments often are self-diagnosed and self-treated. We included in the models the use of NSAIDs, restricting the definition to >7 consecutive days during the last year combined with a self-reported history of chronic joint pain (referred to as "arthritis" by the Nicaraguan population), which we believe is the definition that will cause the least misclassification. It is unlikely that omission of other nephrotoxic drugs affected the results because they cause acute rather than chronic kidney disease. Phenacitin is the exception. This compound was used in Central America until 2002. Although we were unable to clarify the frequency of its use in Nicaragua, there are no reasons to believe that use differed between villages. The prevalence of self-reported medically treated urinary tract infections appeared high, but was not significantly associated with decreased kidney function in multivariate analyses.

In summary, this study provides new evidence regarding kidney disorder as a true public health threat in Nicaragua. The nature of the renal disease needs to be clarified. The low prevalence of proteinuria hints to an interstitial, not a glomerular, origin; however, our present data are not sufficient for far-reaching conclusions. Clearly, the absence of strong relations between decreased kidney function and conventional risk factors makes it necessary to look for new associated factors. Heavy workload in a hot climate leading to chronic dehydration has emerged as one hypothesis.[25] The impact of tropical temperatures on kidney function of workers in different production systems at different altitudes has not been studied. Other causal hypotheses can be thought of. Almost nothing is known about environmental pollutants in drinking water in the area (ie, heavy metals and pesticides), and possibly people who work under the hardest conditions sweat more and hence consume more water. Although we cannot pinpoint a specific factor, our findings strongly indicate that some of the examined populations, in particular men in some villages, are exposed to an unknown environmental or occupational hazard that makes them prone to kidney damage. For poor people in Nicaragua, this is disastrous because severe CKD often progresses to end-stage renal disease, and renal replacement therapy is only marginally available. In addition, decreased GFR is not merely a risk factor for end-stage renal disease, but also increases the risk of cardiovascular morbidity and mortality.[36,38] Considering the seriousness of CKD, far-reaching analytical studies to clarify the nature of the disease and causal factors are urgently needed to understand which preventive measures can be taken.

ACKNOWLEDGEMENTS

We thank all students and technicians at UNAN-León and UNAN-Managua (Milton Vallejos, Ergin Rodríguez, Efrén Altamirano, Eduardo Centeno, Sara Cárdenas, Yanitcia Blandón, Bayardo Castillo, Indira Valladarez, José Ramón Parajón, Yorling Maryorga, Armando Bravo, and Ervin Baca) who assisted in the difficult field work and Ministry of Health Laboratory (Alcides González, Consuelo Vega, Harold García, and Margarita Brenes) and Marcos Vanegas and the administrative team of the Research Centre on Health, Work and Environment for invaluable assistance. This study was performed in the context of the Program on Work and Health in Central America (SALTRA).

Support: This study was financed by the Swedish International Agency for Development Cooperation (Sida), through the SAREC project of Bilateral Research Cooperation with UNAN-León and the Sida-Health supported SALTRA.

Financial Disclosure: The authors report that they have no relevant financial interests.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Prevalence of chronic kidney disease and associated risk factors—United States, 1999-2004. *MMWR Morbid Mortal Wkly Rep*. 2007;56(8):161-165.

2. Arogundade FA, Barsoum RS. CKD prevention in Sub-Saharan Africa: a call for governmental, nongovernmental, and community support. *Am J Kidney Dis.* 2008;51(3):515-523.

3. Cusumano AM, Gonzalez Bedat MC. Chronic kidney disease in Latin America: time to improve screening and detection. *Clin J Am Soc Nephrol.* 2008;3(2):594-600.

4. Eknoyan G, Lameire N, Barsoum R, et al. The burden of kidney disease: improving global outcomes. *Kidney Int.* 2004;66(4):1310-1314.

5. Hamer RA, El Nahas AM. The burden of chronic kidney disease. *BMJ.* 2006;332(7541):563-564.

6. Hossain MP, Goyder EC, Rigby JE, El Nahas M. CKD and poverty: a growing global challenge. *Am J Kidney Dis.* 2009;53(1):166-174.

7. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet.* 2005;365(9456):331-340.

8. Durante-Mangoni EGA, Utili R, Falagas ME. Do we still need the aminoglycosides? *Int J Antimicrob Agents.* 2008;Oct 29. 33(3):201-205.

9. Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. *Am J Epidemiol.* 2000;151(5):488-496.

10. Martínez-Salgado CL-HF, López-Novoa JM. Glomerular nephrotoxicity of aminoglycosides. *Toxicol Appl Pharmacol.* 2007;223(1):86-98.

11. Zhang L, Zhang P, Wang F, et al. Prevalence and factors associated with CKD: a population study from Beijing. *Am J Kidney Dis.* 2008;51(3):373-384.

12. Amato D, Alvarez-Aguilar C, Castaneda-Limones R, et al. Prevalence of chronic kidney disease in an urban Mexican population. *Kidney Int Suppl.* 2005;97:S11-17.

13. Wanigasuriya KP, Peiris-John RJ, Wickremasinghe R, Hittarage A. Chronic renal failure in North Central Province of Sri Lanka: an environmentally induced disease. *Trans R Soc Trop Med Hyg.* 2007;101(10):1013-1017.

14. Cerdas M. Chronic kidney disease in Costa Rica. *Kidney Int Suppl.* 2005;97:S31-33.

15. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int.* 2008;74(2):158-169.

16. Grollman A P, Shibutani S, Moriya M, et al. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A.* 2007;104(29):12129-12134.

17. Hassen W, Abid S, Achour A, Creppy E, Bacha H. Ochratoxin A and beta$_2$-microglobulinuria in healthy individuals and in chronic interstitial nephropathy patients in the centre of Tunisia: a hot spot of ochratoxin A exposure. *Toxicology.* 2004;199(2-3):185-193.

18. Lai MN, Lai JN, Chen PC, et al. Increased risks of chronic kidney disease associated with prescribed Chinese herbal products suspected to contain aristolochic acid. *Nephrology (Carlton).* 2009;14(2):227-234.

19. Tanaka A, Nishida R, Yoshida T, Koshikawa M, Goto M, Kuwahara T. Outbreak of Chinese herb nephropathy in Japan: are there any differences from Belgium? *Intern Med.* 2001;40(4):296-300.

20. Bandara JM, Senevirathna DM, Dasanayake DM, et al. Chronic renal failure among farm families in cascade irrigation systems in Sri Lanka associated with elevated dietary cadmium levels in rice and freshwater fish (tilapia). *Environ Geochem Health.* 2008;30(5):465-478.

21. Barbier O, Jacquillet G, Tauc M, Cougnon M, Poujeol P. Effect of heavy metals on, and handling by, the kidney. *Nephron Physiol.* 2005;99(4):105-110.

22. Hellstrom L, Elinder CG, Dahlberg B, et al. Cadmium exposure and end-stage renal disease. *Am J Kidney Dis.* 2001;38(5):1001-1008.

23. Lin JL, Lin-Tan DT, Hsu KH, Yu CC. Environmental lead exposure and progression of chronic renal disease in patients without diabetes. *N Engl J Med.* 2003;348(4):277-286.

24. Yu CC, Lin JL, Lin-Tan DT. Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. *J Am Soc Nephrol.* 2004;15(4):1016-1022.

25. Cuadra S, Jakobsson K, Hogstedt C, Wesseling C. *Chronic Kidney Disease in Central America. Chronic Kidney Disease: Assessment of Current Knowledge and Feasibility for Regional Research Collaboration in Central America*, Section 1, vol 2. Heredia, Costa Rica: SALTRA; 2006.

26. Callejas L, Alonso CD, Mendoza B. Insuficiencia renal crónica: una prioridad en salud pública, en la zona de la costa del pacífico de Nicaragua, Mayo-Septiembre 2003. In: SALTRA, ed. *Chronic Kidney Disease: Assessment of Current Knowledge and Feasibility for Regional Research Collaboration in Central America,* Section 1, vol 2. 1st ed. Heredia, Costa Rica: Salud y Trabajo en América Central; 2006:26-27.

27. Callejas L, Alonso CD, Mendoza B. Insuficiencia renal crónica (IRC) en trabajadores de caña de azúcar, El Viejo, Chinandega. In: SALTRA, ed. *Chronic Kidney Disease: Assessment of Current Knowledge and Feasibility for Regional Research Collaboration in Central America,* vol 2. 1st ed. Heredia, Costa Rica: Salud y Trabajo en América Central; 2006:25-26.

28. Marín J, Berroterán J. Insuficiencia renal crónica: Cuadro clínico y situación epidemiológica en Nicaragua. In: SALTRA, ed. *Chronic Kidney Disease: Assessment of Current Knowledge and Feasibility for Regional Research Collaboration in Central America,* Section 1, vol 2. 1st ed. Heredia, Costa Rica: Salud y Trabajo en América Central; 2006:18-21.

29. Domínguez J, Montoya Pérez C, Jansá J. Análisis de prevalencia y determinantes de la insuficiencia renal crónica de la costa del Océano Pacífico: Sur de México, Guatemala, El Salvador y Honduras. In: SALTRA, ed. *Chronic Kidney Disease: Assessment of Current Knowledge and Feasibility for Regional Research Collaboration in Central America,* Section 1, vol 2. 1st ed. Heredia, Costa Rica: Salud y Trabajo en América Central; 2006:23-24.

30. Trabanino RG, Aguilar R, Silva CR, Mercado MO, Merino RL. [End-stage renal disease among patients in a referral hospital in El Salvador]. *Rev Panam Salud Publica.* 2002;12(3):202-206.

31. Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247-254.

32. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: evaluation, classification, and stratification. *Am J Kidney Dis.* Feb 2002; 39(2 suppl 1):S1-266.

33. Roche Diagnostics. *Creatinine Jaffé Gen.2, Compensated Method for Serum and Plasma.* Vol V 1 ES. Mannheim, Germany; Roche Diagnostics; 2006.

34. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. *Physiol Rev.* 2000;80(3):1107-1213.

35. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007; 298(17):2038-2047.

36. Hallan SI, Coresh J, Astor BC, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol.* 2006;17(8): 2275-2284.

37. Gracia-Trabanino R, Dominguez J, Jansa JM, Oliver A. [Proteinuria and chronic renal failure in the coast of El Salvador: detection with low cost methods and associated factors]. *Nefrologia.* 2005;25(1):31-38.

38. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004; 351(13):1296-1305.