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Relevance of heat stress and dehydration to chronic kidney disease (CKDu) in Sri Lanka

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A R T I C L E I N F O

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A B S T R A C T

Chronic kidney disease in the absence of hypertension and diabetes is a growing problem among agricultural laborers in tropical and subtropical regions. It is unclear if heat stress and dehydration are risk factors for this form of chronic kidney disease (CKDu). To investigate this relationship, agricultural workers in four villages (n = 261) in North Central Province, Sri Lanka completed the US National Institute for Occupational Safety and Health (NIOSH) health hazard evaluation of heat stress, translated into Sinhalese (July 2017). We constructed a heat stress/dehydration index based on the frequency of 16 symptoms (range 0–32; reliability, 0.84). Workers provided a urine sample for dipstick assessment of urine albumin-creatinine ratio (ACR) and refractometer analysis of urine concentration. Of 261 respondents, 41 participants reported diabetes or chronic kidney disease. They scored higher on the heat stress-dehydration index (10.78 vs. 8.03, $p < .01$) and were more likely to have ACR > 30 (85.4% vs. 69.4%, $p < .05$). Among 216 non-pregnant agricultural workers without diabetes or kidney disease (mean age, 46.6; 37% male), villagers in the high-CKDu prevalence area were more likely to show signs of dehydration (for example, greater urine concentration, 1.015 vs. 1.012, $p < .05$, among males); however, the heat stress-dehydration index overall was not associated with ACR or urine concentration. Because an elevated ACR (proteinuria) is not a reliable marker of early CKDu, additional studies are needed to assess the association between heat stress-dehydration symptoms and risk of CKDu.

1. Introduction

Climate change has resulted in an overall rise in temperature of about 0.8^{0}C throughout the last century and will likely continue (IPCC, 2014). Adverse health effects related to extreme hot environments include chronic dehydration, heat exhaustion and heat stroke, kidney disease, increases in vector-borne diseases, malnutrition, and increasing effects of air pollution (Kjellstrom et al., 2009). Environmental factors such as ambient temperature, wind, humidity, ventilation, and direct exposure to sun influence the heat load on some occupations, especially outdoor industries such as agriculture, mining, road building, fisheries, and forestry (Nilsson and Kjellstrom, 2010). Workers in these occupations are more vulnerable to heat illness, often combined with dehydration, that may vary from heat cramps to fatal heat stroke (Crowe, n.d.). Both tropical and sub-tropical populations are vulnerable to increasing risk of occupational heat stress.

In Sri Lanka, a tropical country located close to the equator, occupational heat stress is most common in the North Central Province (NCP), where temperature and other environmental factors are thermally stressful (Tawatsupa et al., 2012; Siriwardhana et al., 2015). High temperatures are typical and range, on average, between 33.3 °C and 34.7 °C (Department of Meteorology, Sri Lanka, 2016). The total area of NCP is estimated to be 10,472 km^2, including 9741 km^2 of land and 731 km^2 of inland water bodies (Department of Survey, Sri Lanka, 2016). The majority of the NCP population is engaged in agriculture and related occupations (92% farmers) (Jayasekara et al., 2015).

While chronic kidney disease linked to hypertension and diabetes is recognized as a source of global disease burden, chronic kidney disease in the absence of hypertension and diabetes is a growing problem among farmers and agricultural laborers in tropical and subtropical regions, including Asia (Sri Lanka, Bangladesh, India), Africa (Egypt), and Mesoamerica (southern Mexico, Guatemala, El Salvador,

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Nicaragua, Honduras, and Costa Rica) (Jha et al., 2013; Lunyera et al., 2016). Morphological and biochemical analyses suggest similarities between CKDu in Central America and Sri Lanka, but conclusions about a common etiology are challenging because Sri Lankan cases demonstrate a mixed morphology and more interstitial inflammation and vascular changes (Wijkström et al., 2018).

In some affected Sri Lankan communities, a WHO study showed the population prevalence of this "chronic kidney disease of unknown etiology" (CKDu) may be as high as 15–20% (Jayatilake et al., 2013; WHO, 2016). However, the case definition used in the WHO study relied on the albumin-to-creatinine ratio ≥ 30, which has been challenged because early CKDu typically presents with minimal proteinuria (Redmon et al., 2014). Using hospital and outpatient records, we have determined that as much as 10% of the population of certain Grama Niladhari (GN) administrative divisions in the north central region of Anuradhapura have had medical care or hospitalization related to CKDu.

A recent national screening effort confirms the high prevalence of the disease. While no uniform definition of CKDu is available, mass screening using the urine albumin creatinine ratio (ACR > 30) in an early morning urine sample, serum creatinine with estimated glomerular filtration rate (eGFR), and blood pressure (excluding people with other kidney disease and related disorders), found a similar prevalence (Presidential Task Force on Prevention of Kidney Disease of Uncertain Etiology, n.d.; Anon, 2017). In Anuradhapura in 2014, 13,764 CKDu cases were identified in a screening sample of 96,521, a prevalence of 14.3%. In the first half of 2015, 906 cases were identified among 10,019 screened (9%). National statistics indicate high mortality associated with kidney disease. WHO data for 2012 suggest kidney disease is the seventh most common cause of death in Sri Lanka and may be increasing (WHO, 2012).

The etiology of the disease is unclear, but researchers have proposed that "heat stress nephropathy may represent one of the first epidemics due to global warming" (Glaser et al., 2016). In this research we examined one potential correlate of kidney disease, reported symptoms of heat stress and dehydration, and examined a number of its social and behavioral features. Chronic dehydration and inadequate water consumption may increase the risk of kidney damage. For example, risk factors for CKDu identified in a case-control study included daily exposure to heat (> 6 h) and low intake of water (< 3 l) (Siriwardhana et al., 2015). These exposures are also associated with dysuria and measures of volume depletion (hyperuricemia, hypokalemia), which have recently been linked to kidney injury (Laws et al., 2016; Roncal-Jimenez et al., 2015).

The purpose of this research study was to assess the prevalence of reported symptoms of chronic heat stress and dehydration in a community-based sample from Sri Lanka. Villages were selected to represent local variation in the prevalence of chronic kidney disease (CKD) in North Central Province. Participants completed a back-translated Sinhalese questionnaire developed by the US National Institute for Occupational Safety and Health (NIOSH) to elicit symptoms of heat stress and dehydration and also provided urine samples. Urine parameters assessed in the research included albumin, creatinine, ACR, and specific gravity (concentration). Analyses assessed (1) the prevalence of chronic heat stress and dehydration in villages grouped by regional CKD prevalence, and (2) correlates of chronic heat stress and dehydration, including urine parameters, sociodemographic factors, water consumption behavior, work environments, and medical status.

2. Methods

Communities participating in the research were located in the two main Divisional Secretariats (DS), Vilachchiya and Nachchaduwa, of Anuradhapura District, North Central Province (NCP), Sri Lanka. According to the NCP Provincial Directors of Health, the prevalence of CKDu is high in Vilachchiya DS (7%) and comparatively low in Nachchaduwa DS (1.5%). To capture this variation in CKDu, this cross-sectional study was conducted in four villages, Dematamalgama, Bogoda, and Ruwangama in the high-prevalence Vilachchiya DS, and Hidogama in the low-prevalence Nachchaduwa DS. Data collection for the field study was completed in July 2017, the start of the dry season. The NCP Provincial Directors of Health and University of Pittsburgh Human Research Protections Office reviewed the study protocol and approved the research.

2.1. Participants and assessments

Two hundred and sixty-one participants were recruited. Inclusion criteria included age 18+, current employment in outdoor labor (e.g., agriculture, road construction, water works), Sinhalese speaker, residence in one of the four villages, and able to provide informed consent. Potential participants were notified of the study in advance by provincial health service officers. Research assessments were timed to coincide when villagers gathered at local worksites (e.g., clearing land). People working outside villages, mostly males, were assessed when they returned to villages during weekends. Participation in this survey was voluntary, and 95% of participants who were approached, men and women, agreed to complete the survey and provide a urine sample.

Trained research assistants from Allied Health Sciences programs at Sir John Kotelwala Defense University explained the study, answered questions respondents may have had, and obtained consent. All were native Sinhalese speakers. Participants received incentives of 1000 Sri Lanka rupees (=$6) in kind (dal, milk powder, tea, etc.) for completing the study.

2.2. Measures

Wet Bulb Globe Temperature (WBGT ^{0}C) levels and environmental temperature were measured in each area between 11 am-noon using the WBGT HT30 instrument. Three measurements were taken and the average was calculated on the day of assessment. Four parameters were measured: WBGT C, Black Globe Temperature (BGT C), air temperature (AT C), and relative humidity (RH%).

For the self-report survey, we adapted the US National Institute for Occupational Safety and Health (NIOSH) health hazard evaluation of heat stress (HETA-2012) translated and then back translated into Sinhalese. This questionnaire assesses respondents' current jobs, work history, work practices, and medical history. Data included demographic information, history of agricultural and other outdoor work, secondary occupations, lifestyle-related information, medical history, and medication use. Detailed work histories were obtained, including land ownership, number of hours per day working in the field, resting hours, and water intake during working hours, both for agriculture and other types of work.

Self-reports of medical conditions were also collected. Respondents reported the presence of diabetes mellitus (DM), chronic kidney diseases (CKD), hypertension, chronic back or joint pain, thyroid disease, muscle diseases (e.g., rhabdomyolysis), and other diseases diagnosed by medical officers. When possible, we reviewed participants' personal medical records, i.e., clinic-issued booklets that patients take to physician visits and which record diagnoses and prescription medications.

The HETA questionnaire assesses the frequency (never, 1–2 days/week, 3+ days/week) of sixteen symptoms of potential heat stress and dehydration, including headache, "very dry mouth," trouble urinating, fever, low urine output, "exhaustion so that you had to lie down," nausea, muscle cramps, stomach/abdominal pain, dark urine, dizziness, "heart racing or fluttering," diarrhea, disorientation, confusion, and vomiting. Reported frequencies were summed to construct a scale of potential heat stress-dehydration symptoms, with a range of 0–32. We also elicited information about alcohol consumption, smoking, details of water sources, and knowledge of CKDu. Standing height and weight were obtained and body mass index (BMI) calculated. The HETA questionnaire is shown in Appendix A.

As a proxy for socioeconomic status, we asked participants if they would be willing to give up 5% of annual income for a 10% reduction in disease risk. We reasoned that people unwilling to make this tradeoff would have less disposable income and greater economic insecurity. We also asked participants if they knew people with CKDu and if they thought they might already have the disease despite absence of a physician diagnosis.

Participants provided a urine sample, which was analyzed in the field. Participants were given a collection cup for 25 ml of urine. Albuminuria was measured by dipstick (CYBOW™ 2 AC, DFI, S. Korea) (detection limit 10-150 mg/l) with urine creatinine (detection limit 10–300 mg/dl). The albumin to creatinine ratio (ACR) was calculated. Urine specific gravity, an indicator of potential dehydration, was measured by digital refractometer (PAL 10S, Serial No: P319450).

2.3. Analyses

All variables were inspected for means, variance, missing values, and potential outliers. We assessed the internal reliability of the heat stress-dehydration index using Cronbach alpha.

We estimated regression models to assess the association of the heat stress-dehydration index with risk factors for chronic kidney disease, including urine markers. First, we determined if people reporting diagnoses of kidney disease or diabetes had higher scores on the heat stress-dehydration index. Given small numbers, we combined the diabetes and kidney disease groups for this analysis. Next, we limited analyses to people who did not report diabetes or hypertension. We (i) compared mean heat stress-dehydration index scores in individuals grouped by residence in high versus low CKDu prevalence villages; and (ii) we assessed the relationship of reported heat stress to urine markers and socioeconomic indicators.

3. Results

Of the 261 respondents enrolled, 4 women were excluded because they were currently pregnant. 41 participants reported diabetes mellitus (DM) or chronic kidney disease (CKD). The distribution of participants by village is shown in Table 1. WBGT ranged from a high of 31.0^0 C (air temperature 45^0 C) in Dematamalgama to a low of 26.6^0 C in Hidogama.

Reliability of the heat stress-dehydration composite scale was adequate, with a Cronbach alpha of 0.84. In the full sample, the heat stress-dehydration index had a mean (sd) of 8.45 (5.92) and median of 7.0. It ranged from 0 to 29 (of a potential maximum score of 32).

3.1. Heat stress-dehydration in people reporting physician diagnoses of kidney disease or diabetes and people not reporting diagnoses

We compared the 41 participants reporting diabetes or kidney disease with the remaining 216 participants in the sample. (We excluded the 4 currently pregnant.) As shown in Table 2, patients with diabetes or kidney disease were more likely to have ACR > 30 (85.4% vs. 69.4%, p < .05). People with either of the two medical conditions reported a higher symptom score (10.78 vs. 8.03, p < .01). In a regression model that included age, gender, BMI, ACR, urine specific gravity, and diabetes-kidney disease status, the heat stress-dehydration score was significantly and independently associated with gender and diabetes-kidney disease status. Heat stress scores were 3.6 points higher for women and 3.3 points higher for people reporting diabetes or kidney disease.

Table 1
Villages assessed and agricultural worker status.

	Total (n)	Males (n)	CKD (n)	DM (n)	Pregnant (n)	WBGT (Air temp, C^0)
High prevalence CKDu villages						
Dematamalgama	69	18	7	1	3	31.0 (45)
Bogoda	86	25	11	8	1	29.7 (37)
Ruwangama	67	25	10	1	0	28.6 (40)
Low prevalence CKDu villages						
Hidogama	39	32	0	3	0	26.6 (31)
Total	261	100	28	13	4	

DM, diabetes mellitus; CKD, chronic kidney disease; WBGT, Wet Bulb Globe Temperature.

Table 2
Comparison of agricultural workers with and without reported CKD or DM.

	Agricultural workers, No CKD or DM (n = 216)	Workers reporting CKD or DM (n = 41)
Age (years)	46.59 ± 13.02	53.73 ± 11.20
Male, %	37	48
BMI	23.50 ± 4.47	24.23 ± 5.42
Total years worked as an agricultural worker	22.44 ± 14.44	30.15 ± 12.76
Urine SG	1.015 ± 0.008	1.012 ± 0.007***
ACR > 30, %	69.4	85.4*
Heat stress-dehydration index	8.03 ± 5.7	10.78 ± 6.6**

CKD, chronic kidney disease; DM, diabetes mellitus; SG, specific gravity, Excludes 4 pregnancies.
* p < .05.
** p < .01.
*** p < .001.

3.2. Heat stress-dehydration in people not reporting kidney disease or diabetes

Of the 216 agricultural workers without diabetes or kidney disease from the four villages, 37% were male and the mean age was 46.6. 10% were underweight (BMI < 20), 16% overweight (BMI > 25), and 10% (BMI > 30) obese. They reported a mean of 8 h of work per day and rested 2 h or less.

Among the heat stress and dehydration symptoms, headache and very dry mouth were reported 3+ days/week by over 30% of the population, and exhaustion, dizziness, and heart racing by over 20% among the population. The mean (± SD) for the health stress-dehydration scale was 8.03 ± 5.7.

Notably, sociodemographic factors were relevant for reported heat stress-dehydration. Women reported higher scores on the index (9.3 vs. 6.0, p < .001). Women also reported lower daily intake of water than men (2.6 vs. 3.5 l/day, p < .001).

Lower income was also associated with a higher heat stress-dehydration symptom score. When asked in a hypothetic elicitation if they would be willing to exchange 5% of income to reduce the risk of the disease by 10%, 25.7% said they would not. These people reported a trend toward more dehydration-heat stress symptoms (9.4 vs. 7.6, p = .07). Notably, they reported less stability in agricultural work as well. In this group, 44.4% reported they did not work the same plot or work for the same landowner each season compared to 27.6% in the group willing to make the tradeoff (p = .014).

Urine markers showed that over two thirds of the population fell within the microalbuminuria range (30–300 mg/g of creatinine). Most participants (50% of this group) were in the 30–100 range. Only 3% had macroalbuminuria (over 300 mg/dl). Specific gravity (SG) ranged from 1.005 to 1.060, and two thirds of participants had a dehydration concentrated urine (over 1.010), indicating decreased water intake. Only 2% of participants had a high risk of dehydration, as indicated by specific gravity (SG) over 1.030 and 0.8% with SG over 1.035.

Participants in high prevalence CKD villages (Dematamalgama,

Table 3
Comparison of high- and low-CKD prevalence villages, males without CKD or diabetes, n = 80.

	High prevalence villages (n = 51)	Low prevalence village (n = 29)
Demographics		
Age, yr	46.5 ± 13.0	47.3 ± 13.5
Agricultural worker, yr	22.1 ± 14.6	24.1 ± 13.9
Have second job, %	72.5	62.1
Work same plot yearly, %	56.9	62.1
Access to water in home, %	84.3	79.3
Willing to give up 5% income to reduce CKDu risk, %	56.9	79.3**
Health indicators		
BMI	23.7 ± 4.6	22.4 ± 3.5
Back pain, %	62.7	72.4
Cardiovascular disease, %	17.6	17.2
Thyroid disease, %	0.0	3.4
Using steroids, %	0.0	9.6
Using pain medications, %	31.4	55.2
Urine parameters		
Specific gravity	1.015 ± 0.008	1.012 ± 0.009*
ACR > 30, %	84.3	58.6**
Health behaviors and symptoms		
Daily water consumption, liters	3.8 ± 1.4	3.0 ± 1.1**
Alcohol drinker, %	37.3	37.9
Heat stress-dehydration symptom index, μ (sd)	6.4 ± 5.4	5.1 ± 3.2

BMI, body mass index.
* $p < .05$.
** $p < .01$.

Ruwangama, and Bogoda) were grouped and compared to participants in Hidogama, a village in the low prevalence region. Participants in the three villages from the high-prevalence CKD region were more likely to have ACR > 30 (72.2% vs. 55.6%, $p < .05$) and greater heat stress-dehydration symptoms (8.4 vs. 6.1, $p < .001$). Table 3 restricts this comparison to males (because of the few women in the low-prevalence CKDu village; see Table 2). Males in the high-prevalence villages (n = 51) showed greater urine concentration (1.015 vs. 1.012, $p < .05$), a higher proportion with ACR > 30 (84.3% vs. 58.6%, $p < .01$) increased water consumption (3.8 vs. 3.1 l/day, $p < .05$), and a higher level of heat stress symptoms (6.4 vs. 5.1, N.S.) than men in the low-prevalence village (n = 29). Notably, sociodemographic and health indicators did not differ between men in the two sets of villages, except for willingness to give up 5% of income to reduce the risk of CKDu (56.9% vs. 79.3%, $p < .01$).

We then assessed the association of reported heat stress-dehydration symptoms with urine parameters in the sample without hypertension or diabetes. The regression model adjusted for socioeconomic indicators. As shown in Table 4, the regression model did not show an association between symptoms of heat stress-dehydration and ACR (or urine concentration in a separate model). Significant correlates included female status (associated with 3.1 additional points on the index) and higher income (associated with 2.1 fewer points on the index).

Finally, participants were well aware of the high prevalence of CKDu in the region. Nearly all (92.3%) reported knowing someone with the disease, 19.4% thought they might already have the disease, and 43.1% were afraid they might develop the disease. Notably, people who thought they may already have CKDu (n = 42) reported higher scores on the heat stress-dehydration index (11.5 vs. 7.2, $p < .001$) and drank less liters of water daily (2.4 vs. 3.0, $p < .01$) than people who did not think they had the disease (n = 170).

4. Discussion

One question for research on CKDu is whether higher temperatures,

Table 4
Correlates of heat stress-dehydration symptom index.

	B
Constant	6.48*
Age (yr)	0.04
Female	3.12***
Average water intake (l)	−0.39
BMI	0.02
Income proxy	−2.1*
ACR > 30	−0.28

F = 4.4, df 201, $p < .001$, $R^2 = 0.12$. Income proxy, willingness to trade 5% of income for 10% reduction in kidney disease risk. ACR, albumin-creatinine ratio.
*** $p = .001$.
* $p < .05$.

inadequate water intake, and dehydration-heat stress may be related to the increasing incidence of the disease in tropical areas, or whether these factors are secondary to other environmental exposures, such as heavy metals in pesticides and fertilizer (Herath et al., 2018; García-Trabanino et al., 2015). It is also possible that some combination of factors is at work. For example, volume depletion increases the risk of toxicity from other nephrotoxins. The relative role of heat stress and other environmental exposures may also differ by region.

We sought to determine the relationship between symptoms of heat stress and dehydration and urine markers of kidney function that may be related to CKDu. We found greater heat stress and dehydration symptom burden among people reporting diagnoses of diabetes or kidney disease compared to people without. We also found greater heat stress and dehydration symptom burden in three villages from a high prevalence CKDu region compared to a village from a region with lower prevalence. However, we did not see an association between the symptom index and ACR in at-risk participants across the four villages.

A number of factors may be responsible for this absence of an association. Dipstick testing was not confirmed with a second test and not limited to early morning assessment, which may have introduced error (and may account for the very high proportion with ACR > 30). Also, as mentioned earlier, ACR is not a reliable marker of CKDu at early stages of the disease. Lack of an association between heat stress/dehydration symptoms and ACR is consistent with CKDu as a non-proteinuric glomerular disease.

An unexpected finding from the research was the greater heat stress-dehydration burden among women, which appears to be related to lower intake of water. This finding deserves attention and is consistent with research in the US showing lower daily fluid intake in low-socioeconomic status groups (Brooks et al., 2017). We also note the potential greater risk of CKDu associated with lower income. People unwilling to give up income for a lower risk of disease in a hypothetic elicitation reported greater heat stress-dehydration symptom burden and also more economic insecurity, as indicated by less stability in seasonal agricultural work. Finally, local perceptions of symptoms are relevant. People without diagnoses who thought they may already have kidney disease were more likely to report heat stress-dehydration symptoms.

One implication of these findings is the need to refine the heat stress-dehydration hypothesis for CKDu. Differences in this symptom burden may only be relevant for people already diagnosed or at higher risk. Symptoms of dehydration-heat stress appear to tap a more general dimension of health, making the measure less likely to be associated with urine parameters. This would account for the greater symptom burden among women, people with lower disposable income, and people who think they may already have kidney disease.

Findings from this research should be interpreted within the limits of the research design. Participants came from only a small swath of the CKDu region of Sri Lanka. While participation was high, we were only able to obtain limited self-report information and a single urine sample.

We were not able to obtain serum measures. The national CKDu screening program will allow more careful assessment of risk factors for CKDu. Also, research focusing on the course of CKDu will help establish factors associated with disease progression (Vlahos et al., 2018). While heat-related symptoms in agricultural workers were broadly related to disease status (as indicated by differences across diagnostic groups and in ecologic comparisons), we did not see a relationship between symptom reports and urine parameters (ACR) among agricultural workers without diagnosed disease.

Declaration of Competing Interest

The authors report no conflict of interest.

Funders had no role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

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Appendix A

Adapted HETA Questionnaire (Translated into Sinhalese).
During the last agricultural season, how often did you have …

	Never	1–2 days/week	3+ days/week
Headache	0	1	2
Very dry mouth	0	1	2
Trouble urinating	0	1	2
Fever	0	1	2
Very little urine	0	1	2
Exhaustion so that you had to lie down	0	1	2
Nausea	0	1	2
Muscle cramps	0	1	2
Stomach/abdominal pain	0	1	2
Dark urine	0	1	2
Dizziness	0	1	2
Heart racing/fluttering	0	1	2
Diarrhea, loose stools	0	1	2
Disorientation, confusion	0	1	2
Vomiting	0	1	2
Fainting	0	1	2

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