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Highlights

- The association of occupational heat exposure with CKDu remains debated.
- kidney function of individuals in three occupational groups, farmers, fisherfolk and plantation workers in Sri Lanka was assessed.
- CKDu risk was lowest in occupational group with highest heat exposure.
- CKDu risk was higher among farmers and workers with low to moderate heat exposure.
- Heat stress does not appear to be the main driver of CKDu.

Research article

Occupational heat exposure alone may not explain chronic kidney disease of uncertain aetiology (CKDu) in Sri Lanka

P. Mangala C. S. De Silva[1,*]chathura@zoo.ruh.ac.lk, E.M.D.V. Ekanayake[1,2], T. D. K. S. C. Gunasekara[1], W. A. K. G Thakshila[1], P.M.M.A. Sandamini[1], P.A. Abeysiriwardhana[1], K.G.D. Nishara[1], Akila Harishchandra[3], P.H. Chaminda De Silva[4], Nipuna Siribaddana[5], E. P. S. Chandana[6], S. S Jayasinghe[7], Sisira Siribaddana[8], Nishad Jayasundara[9]

[1]Department of Zoology, Faculty of Science, University of Ruhuna, Matara 81000, Sri Lanka

[2]Department of Biomedical Sciences, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND 58203, USA

[3]School of Marine Sciences, The University of Maine, ME 04469, USA

[4]Department of Meteorology of Sri Lanka, Colombo 00700, Sri Lanka

[5]Department of Parasitology, Faculty of Medical & Allied Sciences, Rajarata University, Saliyapura 50008, Sri Lanka

[6]Department of Biosystems Technology, Faculty of Technology, University of Ruhuna, Matara 81000, Sri Lanka

[7]Department of Pharmacology, Faculty of Medicine, University of Ruhuna, Galle, 80000, Sri Lanka

[8]Department of Medicine, Faculty of Medical & Allied Sciences, Rajarata University, Saliyapura 50008, Sri Lanka

[9]The Nicholas School of the Environment, Duke University, Durham, NC 27708, USA

[*]Correspondence: Prof. P. Mangala C. S. De Silva, Department of Zoology, Faculty of Science, University of Ruhuna, Matara 81000, Sri Lanka

Abstract

Aim: Chronic kidney disease of uncertain aetiology (CKDu) is an emerging health concern in tropical farming communities. The role ofoccupational heat exposure as a potential driver of CKDu remains debated. Our study examines occupational heat exposure kidney health in three occupational groups in Sri Lanka.

Methodology: We recruited participants from three occupational groups from three climatic zones; fisherfolk from the dry and intermediate zones (N=225), paddy farmers from the intermediate zone (N=180) and tea plantation workers from the wet zone (N=70). Serum creatinine, cystatin-C, urea and uric acid, estimated glomerular filtration rate and urinary albumin-creatinine ratio were used as diagnostic criteria of renal impairment.

Results: CKDu susceptibility was at the highest among farmers (13.33%), with a significant differentce compared to the fisherfolk (5.36%; p=0.0003). Among the plantation workers, CKDu susceptibility was 5.71%, and it was not significantly different compared to the farmers (p=0.087) and the fisherfolk (p=0.427). Despite higher exposure to heat stress and dehydration, as indicated by the highest simplified wet bulb globe temperature (sWBGT) in the work environments, fisherfolk reported the lowest CKDu susceptibility, while farmers and workers with low to moderate heat exposure showed an increased incidence of abnormal renal function. Further, a multivariable regression analysis identified a significant effect of occupation (p=0.005), agrochemical exposure (p=0.001) and age (p=0.001) on the likelihood of CKDu susceptibility while the sWBGT in the working environments showed no significant effect (p=0.227).

Conclusion: With the evidence from our findings, heat exposure alone does not appear to be the leading driver of CKDu in Sri Lanka, suggesting that the nephropathy is more likely to be associated with occupational risks such as agrochemical exposures.

Keywords

Heat stress, Dehydration, CKDu, kidney injury, Cystatin-C, Sri Lanka.

1. Introduction

Over the last two decades, a novel form of chronic kidney disease (CKD) emerged in Mesoamerica and tropical Asia, with no distinct association with common risk factors such as hypertension, diabetes mellitus and glomerulonephritis. The exact cause for this remains unknown. Hence it is referred to as CKD of uncertain cause (CKDu) [1] or in some instances asMeso-American nephropathy (MEN) or chronic interstitial nephritis in agricultural communities (CINAC). The histopathological and socioeconomic attributes of CKDu vulnerable populations are similar across the global hotspots. [2].

While the leading causes of CKDu are still highly debated, current studies indicate a role for exposure to environmental toxicants such as heavy metals[3], agrochemical residues [3], fluoride and sodium and calcium imbalance in water [4], and genetic susceptibility [5]. Heat stress is also discussed as a likely driversof this disease, where the currently known global hotspots of CKDu, are predominantly located in tropical regions [6] with higher temperatures prevailing throughout the year (Figure 1).

A close association between the high environmental temperature and CKDu has deemed the heat stress dehydration hypothesis as a potential cause for CKDu in Mesoamerica [7]. Rodent studies have shown that recurrent daily heat exposure and dehydration potentially cause chronic tubulointerstitial disease with fibrosis and inflammation. Similar observations have been made in renal biopsies of individuals affected with Mesoamerican nephropathy [8]. Dehydration causes reversible kidney failure (stage 1 pre-renal failure). This renal injury can be prevented via rehydration during heat exposure [9]. Prolonged exposure to solar heat causes dehydration with increased plasma osmolality and renal damage may occur through a cascade of effects (Figure 2).

Increased plasma osmolarity induces the activation of aldose reductase in the proximal tubule leading to the endogenous production of fructose from glucose. Fructose metabolism by fructokinase mediates inflammation and tubular injury [10]. Consumption of fructose-containing sugary beverages instead of water while working has commonly been observed among Mesoamerican sugarcane workers, which may intensify the damage [9]. Supporting this, laboratory rats with heat-mediated dehydration showed increased renal impairment when rehydrated with sugary beverages instead of water [11]. Importantly, consumption of fructose-containing drinks while working in the field is less common among farmers in Sri Lanka. Dehydration-mediated hyperosmolarity induces vasopressin, which has been shown to accelerate the CKD under experimental conditions [12]. Vasopressin results in vasoconstriction and acts on the collecting duct to increase fluid retention. Vasoconstriction may develop hypoxia resulting in tubular damage. Increased water retention may concentrate urine, increasing the risk of urinary crystallization and associated complications [13].

Heat stress accompanied by volume depletion can result in hypokalemia, causing intrarenal vasoconstriction and hypoxia leading to tubulointerstitial injury [14]. Hypokalemia is commonly observed among sugarcane workers with CKD [15]. Strenuous work under the heat can also result in subclinical or clinical rhabdomyolysis [16]. Hence, heat stress and rhabdomyolysis are significant risk factors for repeated episodes of acute kidney injury, and in turn, it may undergo progression towards chronic kidney disease [17]. Dehydration also results in hyperuricemia and uricosuria, with elevated uric acid levels in the urine leading to crystallization. Crystallization is a sign of dehydration, and crystalluria has also been reported frequently among sugarcane workers [18].

Since CKDu may be a type of heat stress nephropathy, the disease may be emerging in different regions in the where people are involved in strenuous manual labor under hotter conditions. Although such a distribution has not been reported, it is likely that CKDu prevalence may be influenced by global warming [19], and similar epidemics could occur among individuals involved in outdoor exhaustive activities. Environmental health research employs various methods to measure heat exposure and its apparent effects.

The Wet Bulb Globe Temperature (WBGT) is considered a measure of the heat stress in direct sunlight, and the temperature, humidity, wind speed, sun angle and cloud cover (solar radiation) are considered in WBGT determination.. As expressed by the National Weather Service (NWS), USA, the physiological effects of environmental WBGT on human health is summarized in Table 1 [20]. Despite the significance of heat stress on human health and increasing global temperatures, to date little attention has been given to heat exposure and its potential links with CKDu in Sri Lanka.

Table 1: Wet Bub Globe temperature (WBGT)-based assessment of environmental heat exposure and the associated physiological effects of heat exposure and precautionary actions during work or exercise in direct sun light

WBGT / F (^{0}C)	**Time to develop heat stress or other physiological effects of heat stress**	**Precautionary actions (Each hour, a break in shade at least for)**
<80 (26.7)		
80-85 (26.7-29.4)	45 minutes	15 minutes
85-88 (29.4-31.1)	30 minutes	30 minutes
88-90 (31.1-32.2)	20 minutes	40 minutes
>90 (32.2)	15 minutes	45 minutes

Source: National Weather Service (NWS), USA

Since the early 1990s, chronic kidney disease of uncertain aetiology (CKDu), predominantly affecting poor middle-aged males in agricultural communities, has been a foremost health issue in Sri Lanka [21]. Sri Lanka has three climatic zones (wet, intermediate and dry zones), and CKDu is common among dry zone farming communities where they experience a significant level of occupational heat exposure, as illustrated in Figure 2. However, the northern region in Sri Lanka is not affected by CKDu, where high temperatures and harsh climatic conditions prevail. Instead, the disease seems to be localized around the highly agricultural areas. As a first step to understand the potential role of heat stress as a driver of CKDu in Sri Lanka, here we examined kidney health in individuals involved in strenuous labor from all three climatic zones and qualitatively compared with their heat exposure over the last five years.

2. Materials and Methods

2.1. Research Design and participants

A cross-sectional study was performed on three occupational groups; fisherfolk, farmers and tea plantation workers. The geographical regions represented dry, intermediate and wet zones in Sri Lanka. Fisherfolk was recruited from districts of Mannar (dry zone; Northern Province) and Matara (intermediate zone; Southern Province), sugarcane farmers from Moneragala (dry zone, Uva

Province) and paddy farmers from Matale (intermediate zone; Central Province) and tea plantation workers from Nuwara Eliya (upcountry wet zone; Central Province) (Figure 3).

We identified one Grama Niladhari division (GND) with more than 50 % of inhabitants involved in selected occupations in each district's Divisional Secretariat Division (DSD). The detailed administrative structure and strategy for selection of study areas are given in Table 2.

Table 2: Strategy for the selection of study areas.

District	Selected DSD	Selected GND for the study
Mannar district (5)†	Mannar (49) □	Panankaddukoddu West
Matara district (16)†	Dickwella (48) □	Kottegoda
Moneragala district (11)†	Buttala (28) □	Rahathangama
Matale district (11)†	Wilgamuwa (39) □	Thoppalapitiya
Nuwara-Eliya district (5)†	Walapane (125) □	Mahakudugala

DSD: Divisional secretariat divisions. GND: Grama Niladhari division. † Denotes the number of DSDs within the respective district, □ Denotes the number of GNDs within the respective DSD.

The Formula; $n = [(z^2) P (1-P)]/d^2$ was used for the determination of the minimum sample size for a particular study group [22]. The standard normal variate (z) was taken as 2.58 at 1 % type 1 error ($P < 0.01$) and the absolute error (d) was assumed to be 5% ($d = 0.05$). The prevalence of CKD in CKDu endemic North Central Province has been estimated as 2.35%, in the most recent epidemiological study by Ranasinghe et al., 2019 [23]. Hence the highest possible prevalence of CKDu in our study groups, was considered as 2.35 % ($P=0.0235$) for estimation of sample size. As per the calculations from above formula, the minimum sample size per study group was 61. Males and females involved in the three occupations, fishing, farming and tea plantations for ten years or more, were invited into the study. A total of 847 participants fulfilled the inclusion criteria, and 400 individuals from the three occupational groups participated in the study, including 225 fisherfolk (103 from Mannar and 122 from Dickwella), 180 farmers (104 paddy farmers from Wilgamuwa and 76 sugarcane workers from Buttala) and 70 plantation workers from Walapane. All the participants provided informed consent before interviews and sample collection.

2.2. **Data and sample collection**

The first void morning urine sample was collected into a sterile container, and a non-fasting blood sample was obtained into a plain vacutainer tube. A medical examination was carried and resting blood pressure was measured using a sphygmomanometer. The height and weight of the participants were measured using a portable stadiometer and a digital weighing scale. Healthcare professionals conducted the medical examination and blood sampling. An interviewer-administered structured questionnaire was used to collect the demographic data. Individuals who studied up to grade 11 are included in the primary education category. Individuals who have studied advanced level or above (degree/ diploma) were included in the secondary education category. Details on potential risk factors of CKDu such as current health status, medical history, lifestyle, daily working schedules, farming practices and agrochemical usage were collected.

2.3. Sample preparation, analysis and determinations

Blood samples were allowed to clot for 30 minutes at 37 °C. The tubes were centrifuged at 3500 rpm for 15 minutes, and the supernatant serum was pipetted for analysis of serum creatinine (SCr), Serum Cystatin C (SCysC), Serum Uric Acid (SUA) and Blood Urea Nitrogen (BUN). Urine samples were centrifuged at 1000 RCF for 10 min, and the supernatant was used for measuring urinary creatinine (UCr) and urinary microalbumin (UMalb). The biochemical analysis of serum and urine samples was performed using an automated biochemistry analyser (HumaStar 100, Human mbH, Germany) in the Department of Zoology, Faculty of Science, University of Ruhuna Sri Lanka. Urinary albumin creatinine ratio (ACR) was determined using creatinine and microalbumin concentrations of urine samples, and estimated glomerular filtration rate (eGFR) was determined using CKD-EPI creatinine-cystatin C equation, 2021 [24].

2.4. Assessment of heat exposure

The simplified wet bulb globe temperature (sWBGT) was calculated based on Dunne et al. [25], as a proxy of heat exposure (cumulative effect of temperature and humidity) of the occupational groups in their work environments. The sWBGT calculation is a simplified version of the wet bulb globe temperature that can be estimated using reanalysis [26] and climate model data [27]. In this study, we used European Center for Medium-Range Weather Forecast 5th Generation Reanalysis data (ECMWF ERA5 at two-meter air temperature (t2m), two-meter dew point temperature (d2m), and surface pressure (sp)) to calculate sWBGT following the method presented by Li et al. [26]. ERA5 hourly t2m and d2m data (0.25° grid resolution) on single levels (4) were downloaded from Copernicus Climate Data Store (CDS - https://cds.climate.copernicus.eu/) between 5-10N and 79-82E geographical region for 2014 to 2018 period. Based on the climate data, the following equations were used for determination of sWBGT.

$$sWBGT = 0.7Tw + 0.3Ta$$

Here, Tw is the isobaric wet bulb temperature and Ta is the dry air temperature at two-meter (t2m). To calculate hourly Tw, we used the Python code provided by Li et al. 2020 [26] and ERA5 t2m, d2m, and sp data. The calculation was conducted in the University of Maine cluster computing environment. Then, sWBGT was calculated in MATLAB (Mathworks Inc., USA) substituting Tw and t2m data into the above equation. sWBGT data between 0600 and 1800 were extracted and averaged to calculate the effective daily heat exposure of the target communities in their working environments. We used oceanic atmospheric data to calculate the sWBGT for the fishing groups and the terrestrial atmospheric data to calculate sWBGT for the other occupational groups. Monthly and annual sWBGT of the respective regions were calculated using the daily sWBGT data. The ERA5 data grid location map was generated using m_map, a mapping toolbox in the MATLAB environment.

2.5. Diagnostic criteria and data analysis

CKD was diagnosed using ACR and eGFR. Participants with eGFR < 60 mL/min/1.73m^2 and or urinary ACR ≥ 30 mg/g were considered CKD susceptible cases according to KDIGO guidelines [28]. CKD cases in the absence of diabetes mellitus, hypertension and other identifiable cause of CKD were classified as CKDu according to CKDu case definition guidelines in Sri Lanka [29]. Participants with venous glucose concentrations above 100 mg/dL were considered as patients with diabetes. In contrast, the participants with elevated systolic blood pressure (SBP) above 140 mmHg and diastolic blood pressure (DBP) above 90 mmHg were considered hypertensive [30]. Obesity was defined as BMI > 30 kg/m^2 according to the guidelines of the World Health Organization [31].

2.6. Statistical analysis

The distributions of clinical data were assessed for normality using Shapiro–Wilk test. Normally distributed continuous variables were expressed as mean with standard error of mean (SEM) while the parameters with non-normal distributions were expressed as median with inter quartile range (IQR). Intergroup comparison of the parameters with non-normal distributions was performed with the

Kruskal-Wallis test followed by Dunn's multiple comparison, while one-way ANOVA followed by Turkey's multiple comparison was adopted to compare normally distributed parameters. Comparison of the parameters expressed as proportions between the groups, was performed with Chi-squared test.A multivariable logistic regression was carried out to assess the effect of age, gender, sWBGT, occupation, hypertension, diabetes mellitus and agrochemical exposure on the likelihood of the incidence of CKDu susceptibility. Statistical analysis was performed using IBM SPSS Statistics 26.0 (IBM INC., New York, USA) and GraphPad Prism 9.0 (GraphPad Software LLC, USA).

2.7. Ethical Clearance

The study was conducted according to the declaration of Helsinki and with the approval of the Ethics Review Committee (Ref. No: 09.03.2016:3.2) of the Faculty of Medicine, University of Ruhuna, Sri Lanka. Participants were explained about the study and written, or a thumbprint consent (Appendix 3) was obtained from each individual for participation, collection, storage and analysis of biological samples.

3. Results

3.1. Population characteristics

The study included 475 individuals from fishing, farming and plantation worker communities. The primary sociodemographic data of the study groups are shown in Table 3.

Table 3: Sociodemographic characteristics of the study participants.

Parameter	**Farmers (FAR) (N=180)**	**Fisherfolk (FSH) (N=225)**	**Plantation workers (PLW) (N=70)**
Participants number (Male %)	122 (67.8)	183 (81.3)	35 (50.0)
Age in years Median (IQR)	47.0 (37.0-60.3)	44.0 (35.3-58.0)	47.5 (25.7-57.6)
Level of Education			
No school education (%)	12 (6.7)	47 (20.9)	10 (14.3)
Basic education (%)	141 (78.3)	148 (65.8)	60 (85.7)
Secondary education (%)	27 (15.0)	30 (13.3)	0

No school education FSH vs PLW; X^2 =10.14; P<0.01 Basic education FAR vs FSH; X^2 =16.14; P<0.0001 Secondary education FAR vs PLW; X^2 =10.33; P<0.01 FSH vs PLW; X^2 =11.72; P<0.01

Majority of the fisherfolk was males and female occupancy was comparatively low in the study group. Education of the participants showed substantial differences among the occupational groups. The overall level of education was higher among farmers and fisherfolk compared to the plantation workers.

3.2. Renal function

Different measurements of renal function of the participants in the three groups, are presented in Table 4.

Table 4: Renal function

Renal function	**Farmers (N=180)**	**Fisherfolk (N=225)**	**Plantation workers (N=70)**	**Comparison**
SCr (mg/dL)	0.90 (0.70 – 1.10)	0.74	0.70	**FAR vs FSH: p<0.0001** FSH vs PLW: p=0.151

Median (IQR)		(0.54 – 0.95)	(0.50-0.80)	**FAR vs PLW: p<0.0001**
SCys-C (mg/L) Median (IQR)	0.76 (0.60 – 0.96)	0.74 (0.62 – 0.85)	0.81 (0.71-0.99)	FAR vs FSH: p=0.364 **FSH vs PLW: p=0.003** FAR vs PLW: p=0.105
eGFR (Cr)[1] (mL/min/1.73m^2) Median (IQR)	99 (81 - 113)	111 (91 - 125)	113 (99 - 122)	**FAR vs FSH: p<0.0001** FSH vs PLW: p>0.99 **FAR vs PLW: p<0.0001**
eGFR (Cys-C)[2] (mL/min/1.73m^2) Median (IQR)	114 (81 - 125)	114 (100 - 126)	103 (78 - 118)	FAR vs FSH: p=0.179 **FSH vs PLW: p=0.0003** **FAR vs PLW: p=0.0443**
eGFR (Cr-Cys-C)[3] (mL/min/1.73m^2) Median (IQR)	110 (88 - 123)	116 (102 - 131)	113 (91 - 125)	**FAR vs FSH: p=0.0003** FSH vs PLW: p=0.216 FAR vs PLW: p=0.910
ACR/(mg/g) Median (IQR)	4.15 (2.02 – 8.81)	4.00 (3.00 – 9.00)	5.13 (3.02-10.10)	FAR vs FSH: p>0.99 FSH vs PLW: p=0.736 FAR vs PLW: p=0.345
BUN (mg/dL) Median (IQR)	13.6 (9.2 – 23.7)	21.9 (17.7 – 25.9)	24.1 (20.4 - 29.2)	**FAR vs FSH: p<0.0001** **FSH vs PLW: p=0.033** **FAR vs PLW: p<0.0001**
SUA (mg/dL) Median (IQR)	4.38 (3.53 – 5.49)	4.65 (4.01 – 5.50)	4.43 (3.44-5.49)	**FAR vs FSH: p=0.032** FSH vs PLW: p=0.203 FAR vs PLW: p>0.99
Renal function and disease susceptibilities				
Elevated ACR (≥ 30 mg/g) Cases (%)	21 (11.67)	19 (8.44)	0 (0.00)	FAR vs FSH: p=0.269 FSH vs PLW: p=0.462 FAR vs PLW: p=0.157
Declined eGFR (≤60 mL/min/1.73m^2) Cases (%)	23 (12.77)	1 (0.44)	5 (7.14)	**FAR vs FSH: p<0.0001** **FSH vs PLW: p=0.009** FAR vs PLW: p=0.206
CKD/ CKDu incidence Cases (%)	31 (17.22)	20 (8.89)	5 (7.14)	**FAR vs FSH: p=0.0122** FSH vs PLW: p=0.6467 **FAR vs PLW: p=0.0419**
CKD incidence Cases (%)	7 (3.88)	12 (5.33)	1 (1.43)	FAR vs FSH: p=0.4932 FSH vs PLW: p=0.1656 FAR vs PLW: p=0.3236
CKDu incidence Cases (%)	24 (13.33)	8 (3.56)	4 (5.71)	**FAR vs FSH: p=0.0003** FSH vs PLW: p=0.4274 FAR vs PLW: p=0.0869

Clinical parameters with non-normal distributions are expressed as median (IQR) and the intergroup statistical significance is expressed per the Kruskal-Wallis test followed by Dunn's multiple comparison. The prevalence of risk factors and disease susceptibility is given as a proportion of the total size of the respective occupational group, and intergroup statistical significance is expressed as implied by the Chi-squared test. eGFR calculated by;[1]CKD-EPI creatinine equation (2021), [2]CKD-EPI cystatin C equation (2012), [3]CKD-EPI creatinine-cystatin equation (2021). Abbreviations; FAR: farmers, FSH: fisherfolk, PLW: plantation workers, IQR: interquartile range, SCr: serum creatinine, SCys-C: serum cystatin-C, eGFR: estimated glomerular filtration rate, ACR: albumin creatinine ratio, BUN: blood urea nitrogen, SUA: serum uric acid, CKD: Chronic kidney disease of uncertain etiology, CKDu: CKD of uncertain etiology.

The farming group showed significantly higher median serum creatinine levels and low blood urea nitrogen levels than the two occupational groups. The distribution of clinical data within study groups is shown in figure 4.

ACR showed no significant variation across the three occupational groups, but eGFR significantly varied across the groups (Figure 5).

3.3. Heat exposure assessment

Environmental heat exposure of the three occupational groups were quantified using the simplified wet bulb globe temperature (sWBGT) and the annual variation in the working environments of the occupational groups is shown in the figure 6.

The highest mean sWBGT was in the oceanic environment of the fisherfolk and it was significantly higher ($p<0.0001$) compared to those of the farmers and plantation workers. Plantation workers experienced the lowest sWBGT with significant differences ($p<0.0001$) compared to the other two groups. Self-reported average daily water consumption and the length of work shifts showed no significant differences among the three occupational groups (Table 5).

Table 5: Environmental and lifestyle related risk factors associated with kidneyhealth, in the three occupational groups.

Parameter	**Farmers** (FAR) (N = 180)	**Fisherfolk** (FSH) (N = 225)	**Plantation workers** (PLW) (N = 70)	**Significance**
Environmental risk factors				
sWBGT / ^{o}C Mean (SEM)	24.10 (0.01)	25.74 (0.08)	21.01 (0.08)	**FAR vs FSH: p<0.0001** **FSH vs PLW: p<0.0001** **FAR vs PLW: p<0.0001**
heat exposure / (hours/day) * Median (IQR)	5.2 (5.0 – 5.5)	8.8 (7.0 – 10.0)	4.1 (4.0 – 4.7)	FAR vs FSH: p=0.0502 FSH vs PLW: p=0.0596 FAR vs PLW: p>0.9999
Agrochemical exposure* Cases (%)	117 (65.0)	0	65 (92.9)	**FAR vs FSH: p<0.0001** **FSH vs PLW: p<0.0001** **FAR vs PLW: p<0.0001**
Lifestyle- related risk factors				
Type 2 Diabetes Cases (%)	7 (3.9)	29 (12.9)	3 (4.3)	**FAR vs FSH: p=0.0016** **FSH vs PLW: p=0.044** FAR vs PLW: p=0.886
Hypertension Cases (%)	44 (24.4)	94 (41.7)	37 (52.8)	**FAR vs FSH: p=0.0003** FSH vs PLW: p=0.103 **FAR vs PLW: p <0.0001**
Obesity (BMI $\geq 30kg/m^2$) Cases (%)	6 (3.3)	32 (14.2)	6 (8.6)	**FAR vs FSH: p=0.0002** FSH vs PLW: p=0.079 FAR vs PLW: p=0.223
Smoking* Cases (%)	48 (26.7)	74 (32.9)	18 (25.7)	FAR vs FSH: p=0.177 FSH vs PLW: p=0.257 FAR vs PLW: p=0.872
Alcohol consumption* Cases (%)	59 (32.8)	113 (50.2)	26 (37.1)	**FAR vs FSH: p=0.0004** FSH vs PLW: p=0.056 FAR vs PLW: p=0.520
Water intake/ (L/day) * Median (IQR)	3.6 (3.1 – 3.7)	2.9 (2.7 – 3.0)	3.4 (3.2 -3.6)	FAR vs FSH: p=0.1965 FSH vs PLW: p=0.2781 FAR vs PLW: p>0.9999
Untreated Drinking water consumption* (%)	125 (69.4)	0	70 (100)	**FAR vs FSH: p<0.0001** **FSH vs PLW: p<0.0001**

				FAR vs PLW: p<0.0001

Parameters with non-normal distributions are expressed as median (IQR) and the normally distributed parameters are expressed as mean (SEM). Intergroup statistical significance for the parameters with non-normal distributions, is expressed per the Kruskal-Wallis test followed by Dunn's multiple comparison while it is given as per the one-way ANOVA followed by Turkey's multiple comparison for normally distributed parameters. The prevalence of risk factors and disease susceptibility is given as a proportion of the total size of the respective occupational group, and the statistical significance is expressed as implied by the Chi-squared test. * Denotes self-reported data. Abbreviations; IQR: inter quartile range, SEM: standard error of mean, BMI: body mass index, sWBGT: simplified wet bulbe globe temperature, ACR: albumin creatinine ratio, eGFR: estimated glomerular filtration rate, CKD: chronic kidney disease, CKDu: chronic kidney disease of uncertain etiology.

The effect of heat exposure was at the highest for fisherfolk with the highest sWBGT and the most prolonged duration of heat exposure compared to the other two groups. CKD incidence among the fisherfolk (5.3%), farmers (3.9%), and plantation workers (1.4%) showed no significant difference. The highest incidence of CKDu was reported in the farming group (13.3%), and 77.4% of the total CKD cases in the group were CKDu. Further, CKDu incidence in the farming group (13.3%) was significantly high compared to that of the fishing group (3.6%). The incidence of CKDu among fisherfolk (3.6%) and plantation workers (5.7%) revealed no significant difference. 40.0 % and 80 % of the CKD cases among fisherfolk and plantation workers were identified as CKDu, indicating that a higher proportion of CKD cases tends to be CKDu among those involved in agricultural activities. The prevalence of Type 2 diabetes was highest among the fisherfolk compared to farmers and plantation workers. Further, the incidence of hypertension among fisherfolk and plantation workers was higher than the farmers.

A multivariable logistic regression was carried out to assess the effect of age, gender, heat index, occupation, hypertension, diabetes mellitus and agrochemical exposure on the likelihood of CKDu susceptibility. The overall model was statistically significant when compared to the null model, ($\chi 2(7) = 56.85$, $p < 0.001$), explained 29.5 % of the variation of CKDu susceptibility (Nagelkerke R^2) and correctly predicted 93.5 % of CKDu susceptible cases. The effects of occupation (p=0.005), age (p=0.001) and agrochemical exposure (p=0.001) were significant, while sWBGT (p=0.227), gender (p=0.493), diabetes mellitus (p=0.997) and hypertension (p=0.995) showed no significant association.

4. Discussion

Globally, millions of people are experiencing occupational heat exposure depending on their occupation, geographical area and the microenvironment. Compared to the temperate of polar regions, high temperature and humidity of surface air in the tropical regions can lead to heat stress and dehydration. Heat stress and dehydration are linked to chronic kidney disease of uncertain cause (CKDu or CINAC), especially among sugarcane workers in Mesoamerica.

Biopsy-confirmed CKDu is reported from central America, Sri Lanka and the Uddanam area in South India [32]. In addition, it is known to be prevalent in several other regions including, El Minia Governorate of Egypt, Goa, Maharashtra, and Odisha in India, Northeastern Thailand, the Tabuk region in Saudi Arabia, Southern Sudan, Mexico (Tierra Blanco), and California Central Valley in the United States [7]. The increased prevalence of CKDu in warm tropical countries has added credence to the hypothesis of heat stress and dehydration as the leading cause of kidney disease. Some authors have named this global-warming nephropathy and describe CKDu as the first epidemic caused by global warming [7,33]. However, this hypothesis is still controversial, and the current scientific knowledge does not establish a strong link between heat stress and CKDu. Notably, the effect of heat exposure, exercise and exertion and the associated renal outcomes have not been thoroughly investigated in occupational, cultural and regional settings to develop a comprehensive understanding of the association of heat exposure and CKDu.

In the present study, we assessed the renal function of adults from three occupational groups with exhaustive outdoor activity regimens from different climatic zones. The fisherfolk and farmers are from the dry zone and plantation workers from the wet zone. When assessed based on albuminuria equal to or greater than 30mg/g and eGFR of less than 60ml/min/1.73m^2, the incidence of possible CKD among the fisherfolk, farmers and plantation workers did not significantly differ. However, the highest incidence CKDu was observed among farmers and the lowest incidence among fisherfolk. The incidence of CKDu among plantation workers showed no significant difference compared to the other groups. Here, we used simplified Wet Bulb Globe Temperature (sWBGT) as a measure of the heat stress mediated by occupational heat exposure within working environments. The sWBGT in the working environment of the fisherfolk was significantly higher than that for the farmers and plantation workers. The nature of the occupations and the working schedules showed noteworthy differences among the three groups. Typically, fisherfolk participating in this study worked in the day trawlers. On a typical working day, they leave early morning to the sea on trawler boats and return in the evening. Hence, the whole day, they are exposed to the sun without any shade or cover.

Further, the average water consumption of fisherfolk was also comparatively low. On the contrary, farmers do not have long and daily working schedules in the field. Notably, during the plantation and harvesting season, farmers are highly exposed to the sun, but they are not equally exposed to the sun throughout the year as the fisherfolk [34]. The average daily solar exposure of fisherfolk was significantly higher than that of the farmers. Tea plantation workers exhibited lower exposure to the sun with a low sWBGT. Analysis of the environmental heat index and working hours show that the fisherfolk have the highest exposure to the sun and, in turn, the most increased tendency for heat stress-dehydration among the three occupational groups. Importantly, fisherfolk have the same routine in their occupation almost throughout the year, experiencing regular heat stress and dehydration compared to the farmers and plantation workers. Nevertheless, CKDu was significantly low among the fisherfolk compared to the farmers and plantation workers, indicating that heat exposure may not be driving renal health outcomes in our study populations

Furthermore, we selected plantation workers from Walapane in Nuwara-Eliya district, one of the coldest regions in the wet zone in Sri Lanka. The sWBGT in Nuwara-Eliya was 21.01 ^{o}C, and it was significantly lower than that for the Mannar and Dondra from where fisherfolk were recruited. The incidence of CKDu susceptible cases among plantation workers was not significantly different from that for the fisherfolk. If the heat stress was the leading driver of CKDu, these workers should be safe from CKDu, as their heat exposure is extremely low with the cold, rainy and misty climate in hilly Nuwara-Eliya.

In Sri Lanka, there are three agro-climatic zones; wet, intermediate and dry zones with distinct climates. Considering the distribution of CKDu in Sri Lanka (Figure 3), the most affected regions (i.e., North Central Province) are located in the dry zone, in intensely cultivated areas. The temperature profile and sWBGT do not differ dramatically across CKDu prevalent and non-prevalent areas within the dry zone. If the heat stress-dehydration hypothesis is the leading driver of CKDu, disease prevalence is likely to be more homogeneous across the region. However, only a patchy distribution of the disease is observed, and furthermore CKDu is not reported widely from communities in regions with very harsh and warm climates, such as Mannar and Jaffna.

The first CKDu cases were identified in the early 1990s among paddy farmers in the North Central Province (NCP), where the highest CKDu burden is still observed. Also, the records on CKDu among sugarcane workers emerged in Mesoamerica in parallel with the discoveries in Sri Lanka. If so, CKDu cases might have been reported in higher numbers even before 1990. Further, if the heat was the leading driver, CKDu cases would have also been reported from tropical regions other than Central America and Sri Lanka, although the same could be said for agrochemical exposure where they are used widely across the world without equal CKDu prevalence. Therefore,it is possible that this increase in temperature contributes to CKDu, while agrochemical exposure is an initiator of the disease. It is also possible that the actual burden may be underestimated in most regions of the world due to the lack of medical facilities, community studies and biopsy-assisted CKD diagnosis. However, given the current high alert on CKDu among communities and the availability of free clinic and testing facilities in Sri Lanka, it is unlikely that CKDu is under reported within the country. Therefore, under-reporting is highly unlikely to explain the patchy distribution of CKDu across communities exposed to similar sWBGT profiles.

Early renal injury in the absence or very little heat exposure has been identified in children, adolescents and females in CKDu affected regions. A study among 2880 school children in North Central Province in Sri Lanka [35]. Further, recent studies have revealed renal injury among children and adolescents in CKDu affected regions in Nicaragua [36], El Salvador [37] and Mexico [38]. Additionally, several studies have demonstrated the incidence of CKDu among females in affected communities, where they are minimally exposed to heat stress in the working fields [39]. It is possible that in the absence of medical interventions, the early renal injury may progress towards chronic conditions following exposure to both heat and nephrotoxins in their environment.

In the leading CKDu hotspots in Mesoamerica, multiple studies used elevated SCr, BUN, serum uric acid and declined eGFR to indicate declined renal function in sugarcane workers across the day work shift [40]. The same decline in renal function was observed among sugarcane workers across the harvest season when measured by conventional urinary biomarkers (increased SCr and decreased eGFR) and emerging biomarkers in urine (elevated NGAL, IL-18 and N-acetyl-β-d-glucosaminidase) [41]. Heat exposure potentially mediates alterations in renal function across the day and harvesting period. However, it is not evident whether these alterations in renal function are persistent and undergo progression towards CKD or CKDu.

A variety of environmental risk factors such as agrochemical exposure (pesticides and fertilizers) and heavy metal exposure (lead, cadmium, arsenic) via contaminated food and water [42], excessive fructose intake, liquor consumption and smoking [43] are considered as potential risk factors of CKDu in global hotspots. Our results indicate a clear linkage of CKDu with agrochemical usage and consumption of untreated or contaminated water. Importantly, most plantation workers in Walapane used natural springs or surface water as their water source for drinking. These water sources near tea plantations are likely contaminated with weedicides like glyphosate and other agrochemicals. Details gathered from the survey revealed that most plantation workers in the hill country depend on such springs, but no study was carried out to assess the water quality of natural springs. More than 40% of paddy and sugarcane farmers consume untreated water from surface and tube wells near paddy fields and sugarcane plantations. Recently water projects in Wasgamuwa and Buttala have started providing treated water for the villages. As a result, most participants were using treated water in those locations. However, most of the participants consumed treated water only for their drinking purpose because of the limited treated water supply. Therefore, further studies are necessary to identify a role for drinking water contaminants, although the critical need for provision of treated water to the people living in CKDu affected areas is evident from past studies [44].

Several studies on CKDu that have been done in Sri Lanka have identified heat exposure and associated dehydration tendencies in agricultural workers in CKDu affected regions in Sri Lanka. A recent study with 261 agricultural workers in four villages in North Central Province (NCP) assessed the renal outcomes associated with heat stress. Participants from three villages with high burden of CKDu, reported significantly higher incidence of heat stress/ dehydration symptoms and albuminuria (ACR > 30 mg/g) compared to the participants from one village with low prevalence of CKDu. Further, 41 participants had diabetes or CKD and significantly higher heat stress and dehydration index [45]. Another study with 475 participants from villages in the NCP reported the highest mean heat stress index among agricultural workers in CKDu endemic regions compared to the non-agricultural workers in CKDu endemic regions and agricultural workers in CKDu non-endemic regions. Additionally, high urinary neutrophil gelatinase-associated lipocalin (NGAL) levels were seen among agriculture workers in endemic areas suggesting an association between heat stress and renal damage among agricultural workers [46]. Both studies above, merely produced evidence for the presence of heat stress and related symptoms in agricultural works along with indications of potential renal injury with elevated ACR and NGAL. Importantly, none of these studies examined the participants for the persistence of these dehydration symptoms or elevated renal health markers, thus provide no evidence for the association of heat stress and the onset or progression of nephropathies leading to CKDu. Similar dehydration symptoms along with elevated ACR, and urinary KIM-1 and NGAL levels have been observed in Mesoamerican sugarcane workers across daily and harvest season work shifts.

A potential drawback of our study is the selection of the site for participants, where the choice of districts to the GN division was based on sampling convenience, but the selection of participants from the GN division was based random sampling. Although occupation was carefully scrutinized, other sites could have been selected with the probability-based selection of the sampling unit (GN division). The other main drawback was the single point estimation of SCr and SCys-C to calculate eGFR and measurement urinary ACR. The kidney disease susceptibility was diagnosed based on a single measure. This resembles a cross sectional study and does not evaluate the persistence of altered renal function and longitudinal variations in biomarker expression in the participants. According to KDIGO criteria, chronicity (more than three months) or radiological evidence is necessary for precise determination of CKD [28]. Also, likely that our inclusion criteria of 10 years of continuous occupation might have resulted in exclusion of currently unoccupied CKDu patients due to their illness who used to be involved in one of the three occupations. Further, although we reached the calculated minimum sample size, the total participation was 475 individuals from 847 who were eligible for participation. The busy working schedules of the occupational groups may have led the relatively high rate of absence. Future studies targeting a larger population will be required to account for absent participants for more precise conclusions[47].

As our findings imply, a high incidence of primary risk factors of CKD, hypertension and diabetes mellitus were common among fisherfolk. On the contrary, the incidence of the above two risk factors, was lowest among paddy farmers. Plantation workers reported the highest incidence of hypertension and the second-highest incidence of diabetes mellitus. If heat stress is the leading cause of CKDu, the incidence of CKDu should be the highest among fisherfolk, as they are exposed to heat throughout the day. Sugarcane and paddy farmers are exposed to less heat as their workload varies with cultivation schedules. Plantation workers experienced the lowest heat stress due to the cold climate, and their tendency to get dehydrated is also rare. However, the incidence of CKDu among plantation workers showed no significant difference compared to fisherfolk and farmers.

In this study, we used the sWBGT calculation to assess the occupational heat exposure. It incorporates multiple environmental factors such as temperature, humidity, wind speed, sun angle and cloud cover (solar radiation), and considered as an accurate measure of heat stress [25]. Importantly, we used meteorological data of the oceanic environment for estimation of sWBGT, providing a more accurate assessment of the heat stress of the fisherfolk during their work hours. In overall analysis, the present study has produced plausible evidence to say that the heat stress is not the leading driver of CKDu. Further, our study indicates comparatively high incidence of CKDu in communities exposed to agrochemicals. Hence, the etiology appears to be more biased towards a toxic nephropathy.

5. Conclusion

We observed the highest incidence of CKDu among paddy farmers, despite their heat exposure likely being more moderate compared to fisherfolks. Even under a significantly high heat exposure and longer working hours under the sun, CKDu susceptibility was at the lowest among fisherfolk. Our findings indicate that, heat stress and dehydration are unlikely to be the leading drivers of CKDu in Sri Lanka. Considering that agrochemical exposure was high among the farmers. Heat exposure may act synergistically with other risk factors in causation and progression of CKDu. However, these associations require validations through in-depth studies and ongoing research is underway to quantify heat stress data at a higher resolution to account for thermal extremes as well as to precisely measure environmental contaminant levels in CKDu impacted areas.

Statements and Declarations

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Author Contributions

DSPMCS: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, writing of the original draft, review and editing; EMDVE: data curation, formal analysis, investigation, software, visualization, writing of the original draft; TDKSCG: data curation, formal analysis, investigation, software, visualization, writing of the original draft, review and editing. WAKGT: data curation, formal analysis, and investigation; PMMAS: data curation and investigation; PAA: data curation and investigation; KGD: data curation and investigation; AH: data curation, software and investigation; PHCDS: data curation and investigation; EPSC: resources, supervision, validation, review and editing; SSJ: resources, supervision, validation, review and editing; SS: resources, supervision, validation, review and editing; NS: resources, supervision, validation, review and editing; NJ: conceptualization, project administration, resources, supervision, validation, review and editing.

Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Review Committee of the Faculty of Medicine, University of Ruhuna (Reference No: 09.03.2016:3.2)

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study for collection, analysis and storage of samples, and publication of research findings per the institutional review board guidelines.

Author Agreement Statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs Signed by all authors as follows:

P. Mangala C. S. De Silva

E.M.D.V. Ekanayake

T. D. K. S. C. Gunasekara

W. A. K. G Thakshila

P.M.M.A. Sandamini

P.A. Abeysiriwardhana

K.G.D. Nishara

Akila Harishchandra

P.H. Chaminda de Silva

E. P. S. Chandana

S. S Jayasinghe

Sisira Siribaddana

Nipuna Siribaddana

Nishad Jayasundara

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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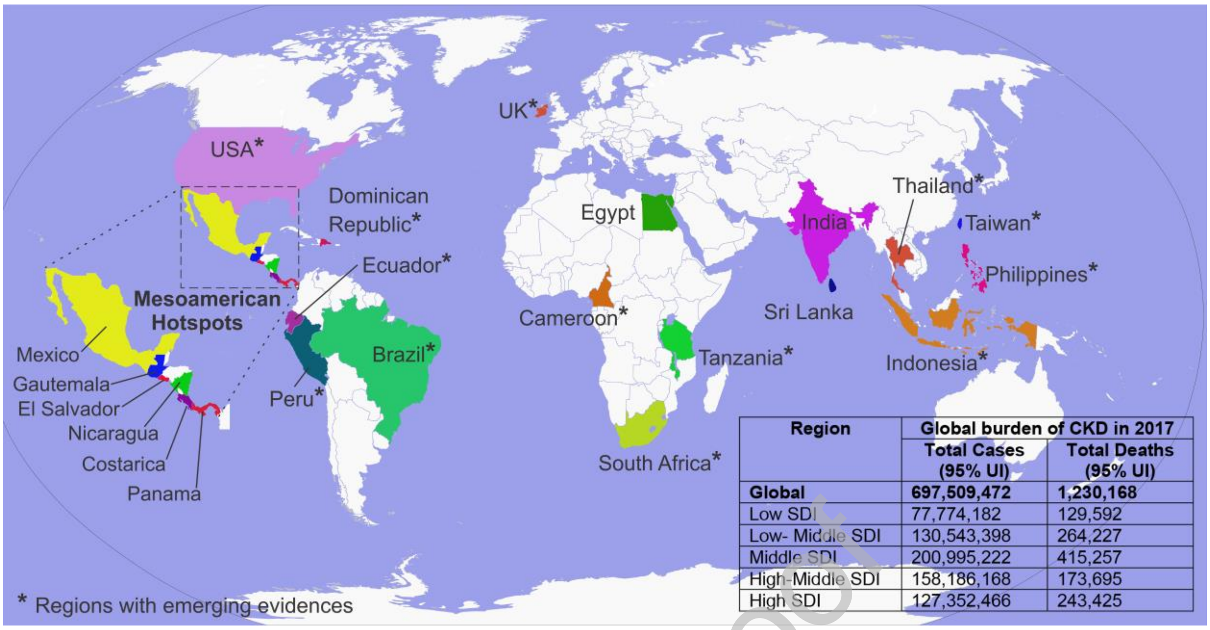
Figure Captions



Region	Global burden of CKD in 2017	
	Total Cases (95% UI)	Total Deaths (95% UI)
Global	**697,509,472**	**1,230,168**
Low SDI	77,774,182	129,592
Low- Middle SDI	130,543,398	264,227
Middle SDI	200,995,222	415,257
High-Middle SDI	158,186,168	173,695
High SDI	127,352,466	243,425

Figure 1: Global CKDu hotspots and burden of all forms of CKDs. The affected countries are shown in colors and *denotes countries with emerging evidence for the presence of CKDu. In the table, global burden is illustrated as all forms of CKD, including CKDu in countries stratified based on SDI, according to Bikbow et al., 2020 [6]. CKD: Chronic kidney disease, CKDu: CKD of uncertain etiology, SDI: Socio demographic Index, UI: uncertainty interval.

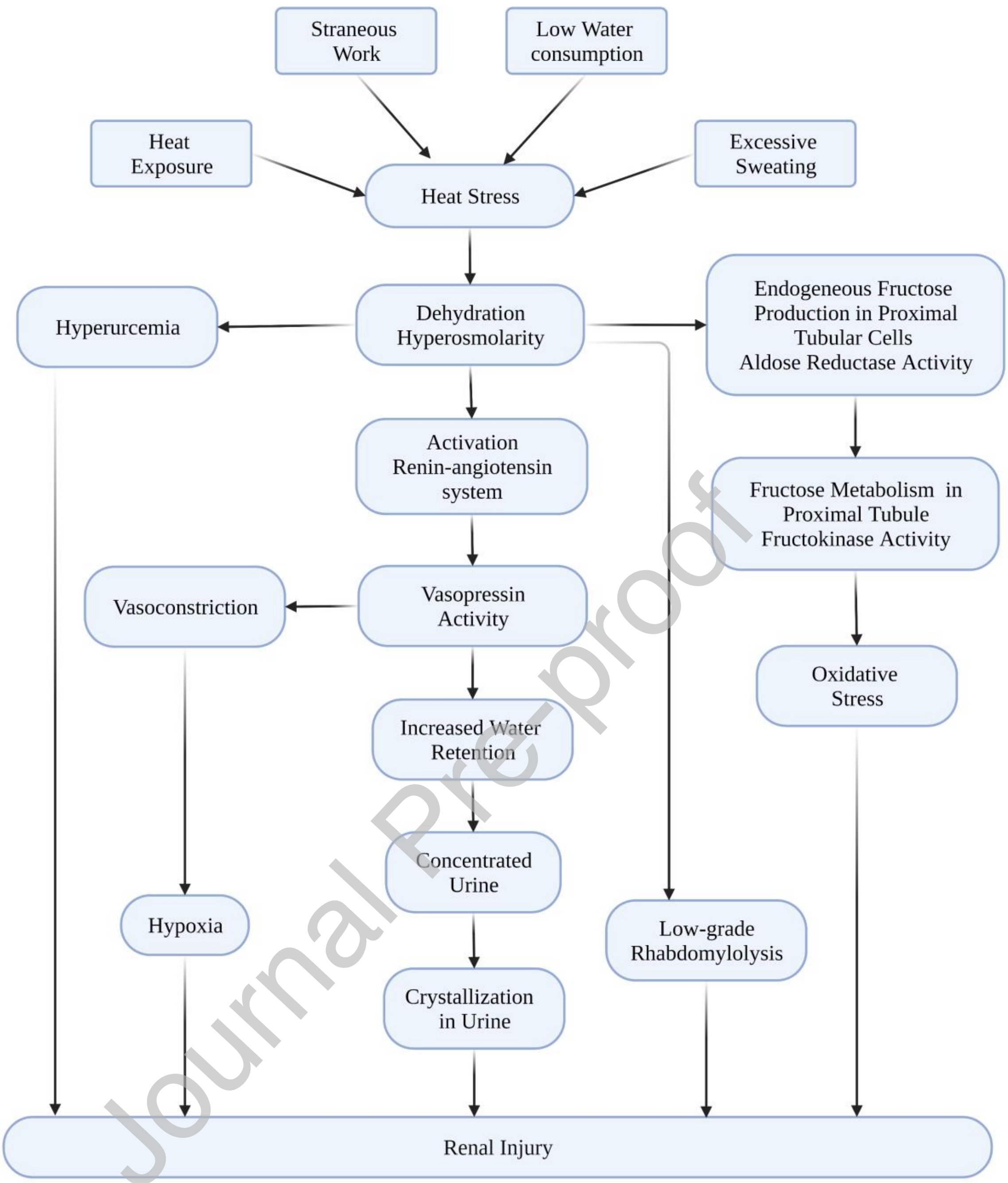


Figure 2: An overview of the potential pathways of renal injury, mediated by heat exposure and dehydration. The figure was exported under a paid subscription with BioRender.

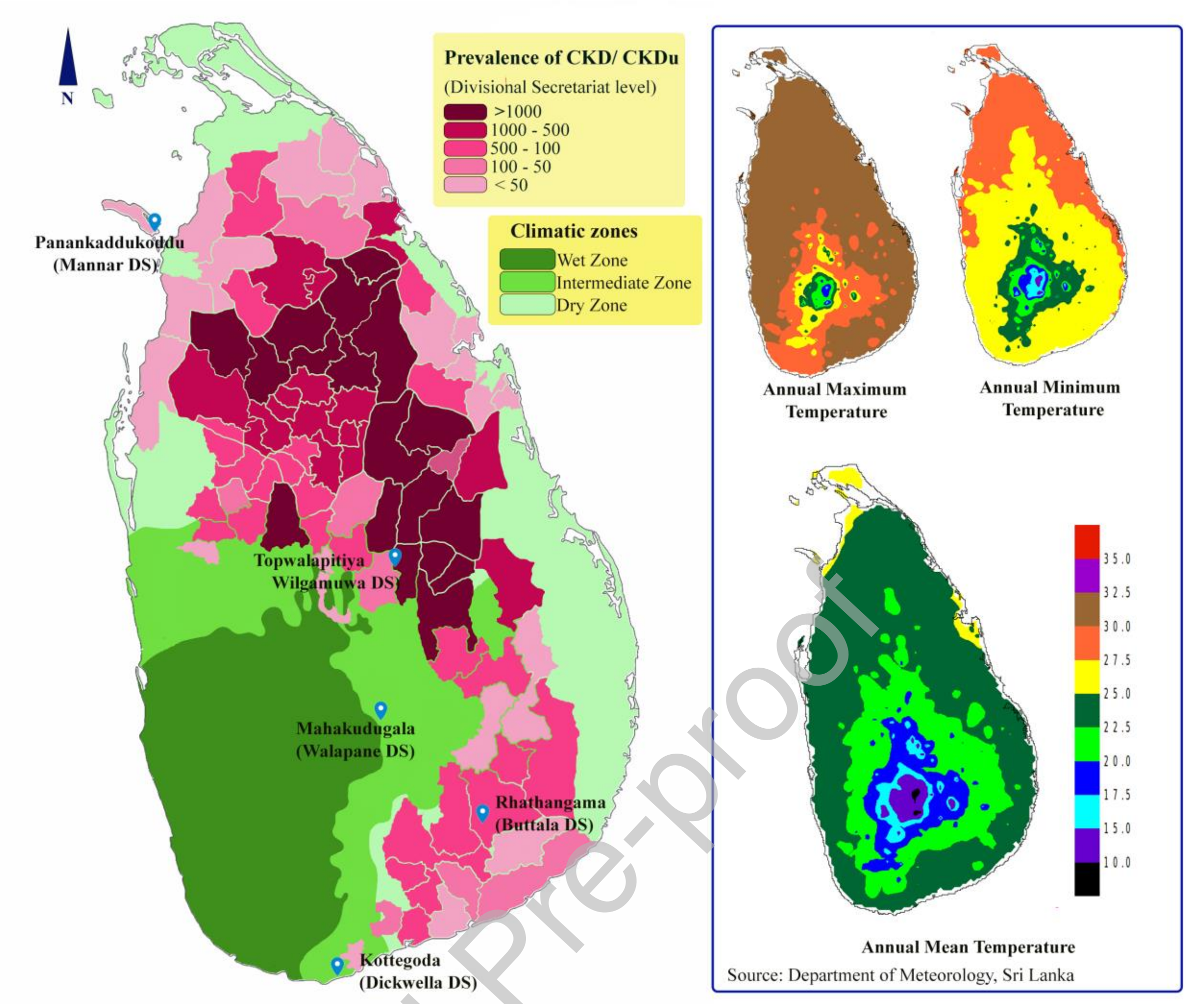


Figure 3: Study locations in the climatic zones and the prevalence of CKDu in Sri Lanka. The prevalence of CKDu is expressed as the number of reported cases in each Divisional Secretariat area in the country. Mannar and Dickwella represent fisherfolk, Buttala and Wilgamuwa represent farmers. Workers in tea plantations were selected from Nuwara Eliya. The graphs show the variation in annual minimum and maximum temperatures in the respective agroclimatic zones Source: Department of Meteorology of Sri Lanka

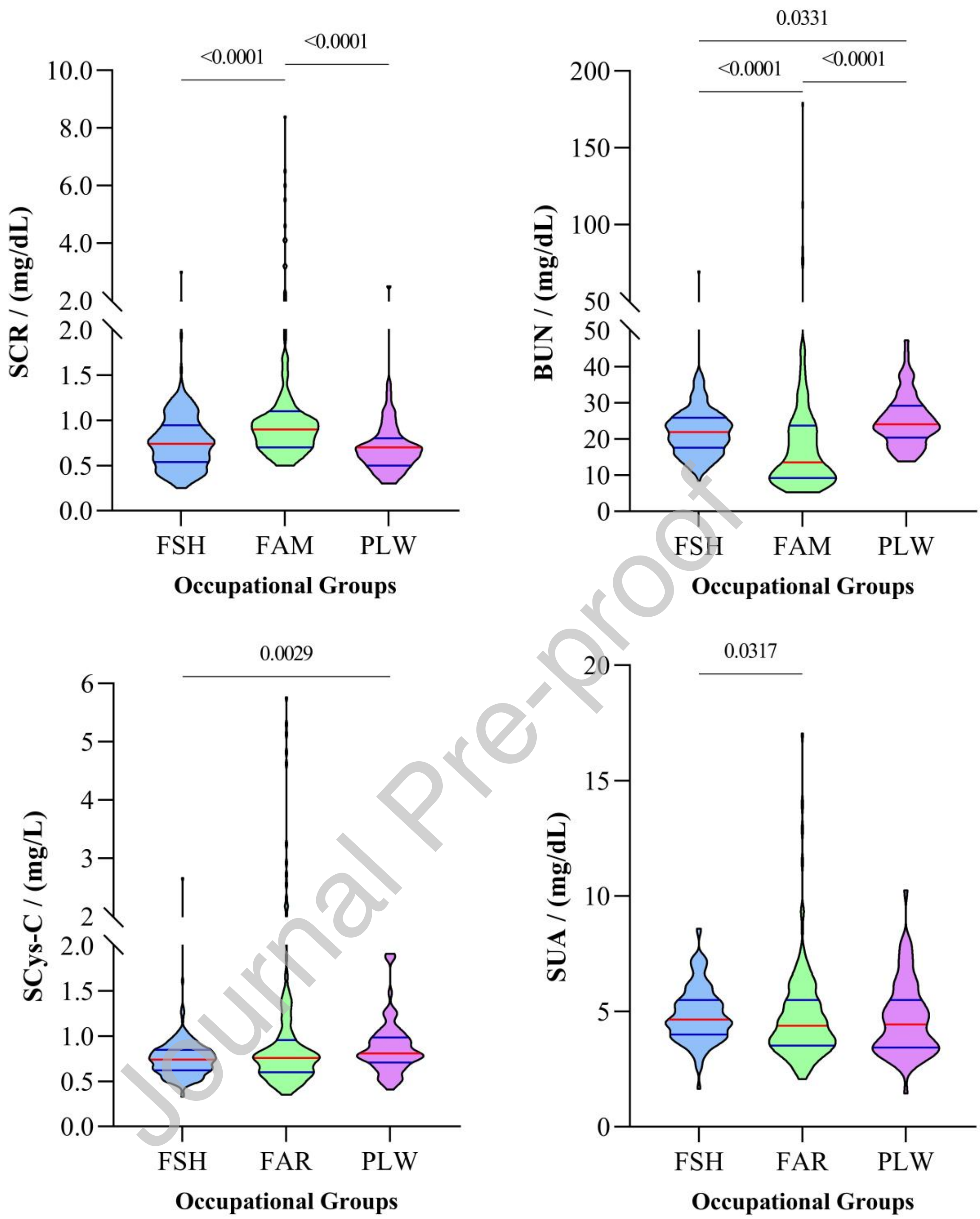


Figure 4: Renal function among the occupational groups. The plots represent distribution with median and interquartile ranges. Inter-group statistical significance is shown with p values from the Kruskal-Wallis test followed by Dunn's multiple comparison test. Occupational groups; FSH: fisherfolk, FAR: farmers and PLW: plantation workers. SCr: serum creatinine, BUN: Blood urea nitrogen, SUA: serum uric acid, SCys-C: serum Cystatin-C.

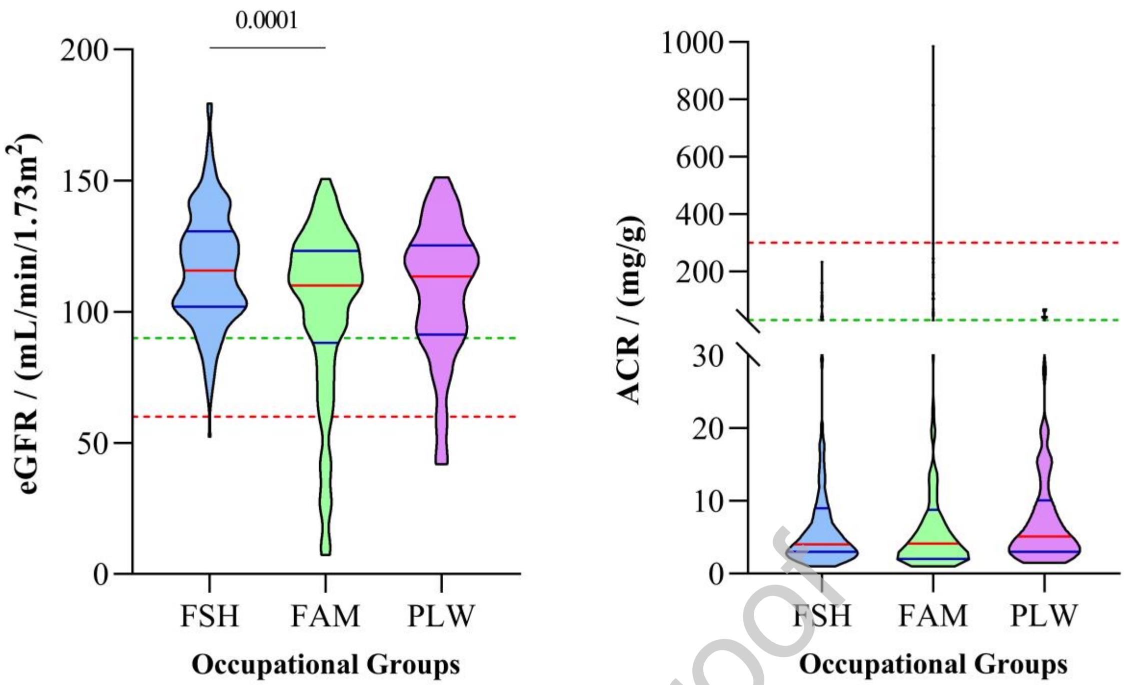


Figure 5: Renal function, ACR and eGFR, estimated by CKD-EPI creatinine-Cystatin-C equation 2021. The plots represent distribution with median and interquartile ranges. Inter-group statistical significance is shown with p values from the Kruskal-Wallis test followed by Dunn's multiple comparison test. FSH: fisherfolk, FAR: farmers and PLW: plantation workers, ACR: albumin creatinine ratio, eGFR: estimated glomerular filtration rate.

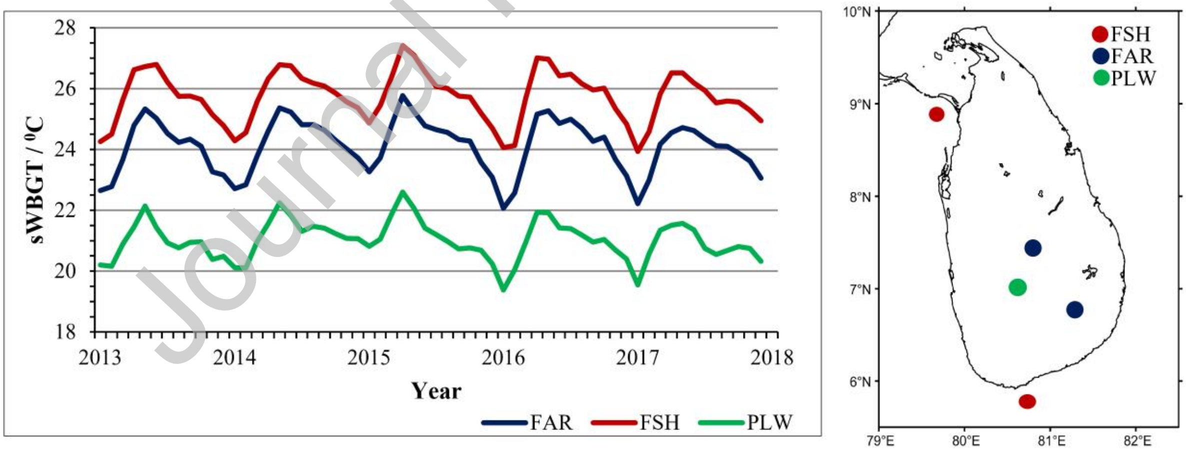


Figure 6: Annual variation of the simplified Wet Bulb Globe Temperature (sWBGT) in the work environments of the occupational groups. sBWGT was calculated using the European Center for Medium Range weather Forecasting- Reanalysis V5 (ECMWF-ERA5) hourly atmospheric temperature at two meters, dew point temperature at two meters and surface pressure data (Li et al., 2020) [26]. Occupational groups; FSH: fisherfolk, FAR: farmers and PLW: plantation workers.