Received: 10 May 2021 | Revised: 29 September 2021 | Accepted: 16 October 2021
DOI: 10.1111/nep.13989

REVIEW ARTICLE

NEPHROLOGY WILEY

Two decades of chronic kidney disease of unknown aetiology (CKDu) research: Existing evidence and persistent gaps from epidemiological studies in Sri Lanka

Jennifer Pett[1,2] | Fahim Mohamed[3,4,5,6] | John Knight[1,2] | Christine Linhart[1] | Nicholas J. Osborne[1,7] | Richard Taylor[1]

[1]School of Population Health, University of New South Wales, Sydney, NSW, Australia
[2]The George Institute for Global Health, Sydney, NSW, Australia
[3]South Asian Clinical Toxicology Research Collaboration, Faculty of Medicine University of Peradeniya, Kandy, Sri Lanka
[4]Department of Pharmacy, Faculty of Allied Health, University of Peradeniya, Peradeniya, Sri Lanka
[5]Australian Kidney Biomarker Reference Laboratory, Department of Nephrology, Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia
[6]Faculty of Medicine and Health, Discipline of Biomedical Informatics and Digital Health, Clinical Pharmacology and Toxicology Research Group, The University of Sydney, Sydney, NSW, Australia
[7]School of Public Health, University of Queensland, Brisbane, Queensland, Australia

Correspondence
Nicholas J. Osborne and Christine Linhart, School of Population Health, University of New South Wales, Sydney, QLD, Australia.
Email: n.osborne@uq.edu.au and c.linhart@unsw.edu.au

Abstract

Background: Chronic Kidney Disease of unknown origin (CKDu) excludes known primary renal conditions or systemic disease (such as diabetes mellitus or hypertension). Prominence of CKDu has been noted for some decades in Sri Lanka, especially among men in particular rural areas, prompting many studies directed towards environmental causation. This article critically reviews relevant primary studies.

Methods: Articles for this literature review ($n = 86$) were found by searching Medline, Embase, Global Health and ProQuest databases over 2000–2020 utilizing a standard algorithm. Articles were critiqued according to criteria for diagnosis of CKDu, aetiological agents investigated, analytic methods employed and findings.

Results: Criteria for diagnosis of CKDu varied significantly, including pre-selection by proteinuria, eGFR and biopsy proven interstitial nephritis. Prevalence studies have been largely conducted in the North Central Province, with recent studies demonstrating the presence of CKDu in other regions. Aetiological factors investigated in primary studies included water source, use of agrochemicals, agricultural work, heavy metals, snake bites, ayurvedic medication, heat stress, infectious diseases and usage of tobacco and betel leaf. There is no conclusive evidence for any one aetiological agent despite consistent evidence of distal factors such as male sex, rural residence and farming.

Conclusions: The current body of evidence for any aetiological agent as the cause of CKDu in Sri Lanka is limited. Further research with stronger study designs is necessary to increase knowledge of aetiology of CKDu in Sri Lanka to identify and eliminate exposure to possible causative agent(s) prior to concluding that the disease is multifactorial.

KEYWORDS
environmental exposure/adverse effects, global health, nephritis, interstitial, enal insufficiency, chronic/epidemiology, Sri Lanka

SUMMARY AT A GLANCE

This review of 79 reports from the literature found no conclusive evidence linking CKDu in Sri Lanka to any single aetiological agent despite consistent association with male sex, rural residence, and the farming industry.

1 | INTRODUCTION

Chronic kidney disease of unknown aetiology is marked by declining renal function in the absence of any obvious attributable cause of renal failure such as diabetes mellitus (DM), glomerulonephritis, hypertension (HT) or structural abnormalities.[1] The twentieth century has witnessed several epidemics of chronic kidney disease of unknown origin (CKDu) including Itai-Itai disease in Japan (cadmium exposure),[2] Queensland lead nephropathy,[3] Chinese herbal nephropathy (Aristolochia exposure),[4] and Balkan endemic nephropathy (BEN).[5] Scientific consensus on the aetiology of BEN and Itai-Itai disease required extensive research spanning decades. At the end of the twentieth century, two new epidemics of CKDu were described in Sri Lanka and Mesoamerica.[6,7] In both regions, the disease is described as predominantly affecting male agricultural workers with histopathology showing tubulo-interstitial nephritis on biopsy.[8] There are reports of a similar CKDu also occurring in India, Mexico, Sudan, Tunisia, Tanzania and Egypt.[2,8–10] Research in both Sri Lanka and

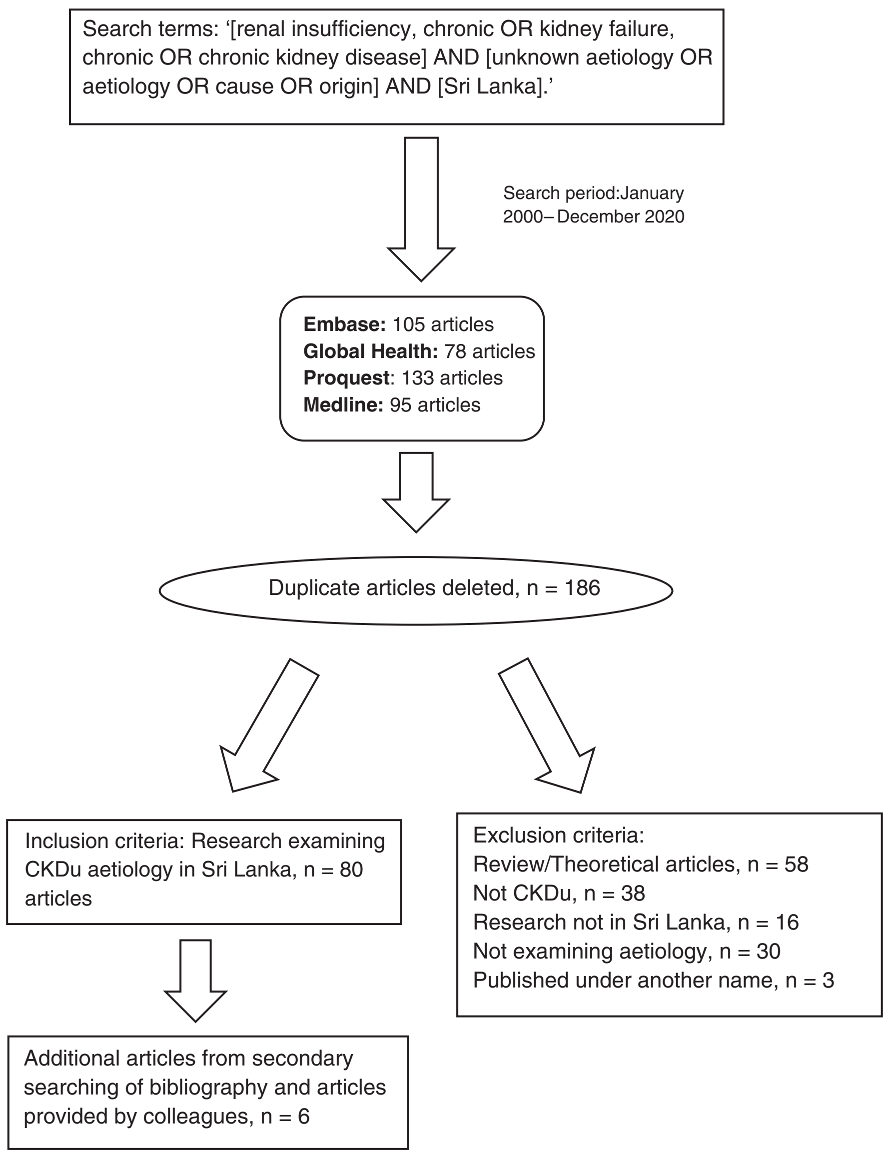

FIGURE 1 Inclusion criteria for review

Mesoamerica has failed, thus far, to reach a consensus on the aetiology. Difficulties in identifying potential exposures arise because CKDu may present after a considerable time following exposures, and be due to recurrent low dose chronic exposures.[11] CKD due to unknown or other causes (excluding hypertension, diabetes mellitus and glomerulonephritis) is estimated to have the highest age-standardized rate of disability adjusted life years of all causes of CKD globally.[12]

This article is a narrative review of the current knowledge, and limitations of empirical research, in understanding the aetiology of CKDu in Sri Lanka through consideration of the evidence for different risk factors that have been investigated in the published literature.

2 | METHODS OF REVIEW

Articles for this literature review were found by searching Medline, Embase, Global Health and ProQuest databases utilizing the following search terms '[renal insufficiency, chronic OR kidney failure, chronic OR chronic kidney disease] AND [unknown aetiology OR aetiology OR cause OR origin] AND [Sri Lanka]'. The article search period was from January 2000 to December 2020. The inclusion and exclusion criteria are summarized in Figure 1.

The aim is to examine the quality of the literature in the area to assess the progress made in the last 20 years and not to answer a single research question. Further, we aim to reduce a priori exclusion of a substantial number of studies through not limiting inclusion criteria to a particular methodology or CKDu criteria because of the diverse research methodologies and varied definitions of CKDu utilized by research studies in Sri Lanka. Thus, a systematic review methodology was not adopted. This approach enables a more comprehensive review of the existing literature and identification of the persistent gaps in epidemiological studies in Sri Lanka. Each reviewed article was classified by methodology, with the factors investigated and main findings summarized within the tables included in Supplementary

TABLE 1 Definitions of CKD and CKDu by different organizations

Reference	Criteria
Kidney Disease: Improving Global Outcomes (KDIGO). 2005, updated 2012	Duration over 3 months of: eGFR <60 ml/min/1.73 m^2, AND/OR Albuminuria—with an albumin creatinine ratio (ACR) ≥30 mg/g AND/OR Urinary sediment abnormalities e.g. red blood cell casts in proliferative glomerulonephritis, white blood cell casts in pyelonephritis, oval fat bodies or fatty casts in diseases with proteinuria AND/OR Electrolyte abnormalities, e.g. renal tubular acidosis, renal potassium wasting and renal magnesium wasting AND/OR Pathological abnormalities detected by histology or inferred, e.g. glomerular diseases, vascular diseases, tubulointerstitial diseases AND/OR Structural abnormalities detected by imaging, e.g. polycystic kidneys AND/OR History of renal transplantation
World Health Organization/Ministry of Health, Sri Lanka. 2013	Albumin-creatinine ratio ≥30 mg/g with no history of glomerulonephritis, pyelonephritis, renal calculi or snake bite, not on treatment for diabetes, HbA1c <6.5%, blood pressure <140/90 mmHg if on treatment for hypertension or <160/100 mmHg if not on treatment for hypertension
Sri Lankan Society of Nephrologists. 2018	**Suspected CKDu**: eGFR <60 ml/min/1.73 m^2 using CKD-EPI Equation OR albuminuria ≥30 mg/g creatinine OR proteinuria ≥150 mg/g creatinine *Without*: urine protein/creatinine ratio > 3000 mg/g creatinine diagnosed diabetes, on treatment for diabetes, or random capillary plasma glucose ≥200 mg/dl hypertension with untreated blood pressure > 160/100 mmHg, or on more than two antihypertensives previous acute kidney injury requiring dialysis age > 70 years **Probable CKDu**—repeat assessment after 12 weeks showing: eGFR <60 ml/min/1.73m^2 using CKD-EPI Equation OR albuminuria ≥30 mg/g creatinine OR proteinuria ≥150 mg/g creatinine *Without*: diabetes, as evidenced by fasting glucose ≥126 mg/dl, 2-h plasma glucose ≥200 mg/dl on oral glucose test, or HbA1c ≥6.5% Clinical, laboratory or ultrasound evidence of other known causes of CKD including polycystic kidney disease, congenital malformations, autoimmune disease, glomerular diseases, obstructive nephropathy, kidney stones and, unequal kidney sizes of greater than >1.5 cm **Confirmed CKDu**—as for suspected and probable CKDu and: Histopathological features of CKDu on biopsy OR Meeting all of the suspected and probable CKDu criteria and renal biopsy not possible

material. A summary review of the main findings is discussed in the article by identified aetiological risk factor.

2.1 | Definition of CKDU in Sri Lanka

The earliest official definition of CKDu in Sri Lanka (Table 1), formulated by the World Health Organization (WHO) and the Sri Lanka Ministry of Health (MoH) in 2013[13] defined CKDu by the presence of proteinuria, and did not include estimated glomerular filtration rate (eGFR). Studies have demonstrated that the sensitivity of proteinuria as a marker for CKDu is <30%.[14–17] The Sri Lankan Society of Nephrologists (SLSON) released an updated official case definition of CKDu in 2018[1] that classified cases as one of three stages and included eGFR (Table 1). Proteinuria remains as a diagnostic option which may encourage its usage as a low-cost option for screening, but may lead to potential inadequate capture of CKDu cases. The clinical parameters used to define CKDu in the empirical studies in Sri Lanka have varied extensively. The different definitions utilized (Table 2) limit the ability to compare and contrast studies; with the quality of many studies affected through the use of definitions that may fail to adequately identify CKDu cases.

2.2 | CKDU prevalence in Sri Lanka

An analysis by the Sri Lanka Medical Statistics Division found a CKD prevalence rate during 2000–2010 of 1.88 per 1000 population in the North Central Province (NCP), compared to 0.4 per 1000 in all other provinces.[18] Since then, research studies have considered the NCP to be the epicentre of CKDu in Sri Lanka. The lack of CKDu outside of the NCP may be due to lack of surveillance in other regions. Recent studies have demonstrated CKDu to be present in other areas of Sri Lanka, such as in the Southern and Uva Provinces.[18,19] A prevalence study published in 2011 found the proportion of CKD cases attributable to CKDu was as high as 84% in the endemic area of Medawachchiya, NCP.[20] The highest quality prevalence study, utilizing the Disadvantaged Populations eGFR Epidemiology Study (DEGREE) protocol, was conducted in 2017 across five Grama Niladhari (GN) divisions (smallest census unit in Sri Lanka) in the NCP; of these, two divisions were considered highly endemic for CKDu, two medium endemic and one low endemic.[21] CKDu was defined as eGFR <60 ml/min/1.73 m^2 in the absence of HT, DM or heavy proteinuria. From 3521 participants, 251 met CKDu criteria, with a calculated prevalence of 11.2% in males and 3.7% in females. There were no cases in males under the age of 30 years, with CKDu first recorded in males aged 31–40 years with a prevalence of 3.4%, increasing with age to 29.4% in males aged 51–60 years.[21]

Analysis of hospital data in the NCP from 2003 to 2017 demonstrated an increase in CKD incidence (CKDu was not distinguished) from 0.47 in Anuradhapura between 2003 and 2008 to 1.43 between 2013 and 2017.[22] It is unclear whether the increase in cases was due to the implementation of organized community screening programmes, and/or an increased exposure to an unidentified aetiological agent, or other influences. A subsequent decline in recorded cases in 2016–2017 was postulated to be due to the provision of safe drinking water.[22] This claim is uncorroborated by any available data, and other reasons should be considered, including: a decline in incidence following screening and identification of undiagnosed cases, changing diagnostic criteria, reduction in screening programmes, natural fluctuations in incidence and/or variation in exposure to an unidentified aetiological agent. The 5-year survival rate of CKD/CKDu cases in the NCP in one study was 71.2%, with 17.5% of cases dying within the first 3 years of diagnosis.[22]

TABLE 2 CKD and CKDu definitions utilized in the literature in Sri Lanka

Definition of CKD/CKDu	Number of studies
Unclear or undefined	14
ACR/dipstick proteinuria/microalbuminuria	13
Biopsy proven CKD/CKDu	9
Use of multiple diagnostic criteria	9
eGFR	7
Serum creatinine	5
Self-reported	2

2.3 | Sex

Male predominance of CKD in Sri Lanka is most prevalent in adults in younger age groups and decreases steadily with increasing age from 4.2:1 in the 35–39 years age group, to 2.2:1 in the >60 years age group.[18] Other epidemiological studies have found similar sexual dimorphism,[21,23] with only one study finding higher prevalence in females.[13] The higher risk associated with male sex is probably a consequence of sex-related exposures or behaviour such as occupation.

2.4 | Water

Fluoride in drinking water has been postulated to be an aetiological agent. Fluoride levels in groundwater are elevated, compared to national and international guidelines, across all areas of Sri Lanka, not only in CKDu endemic zones.[24] The absence of clinical signs of fluorosis, and higher levels of fluoride in drinking water in other countries where CKDu is not reported, imply that fluoride is unlikely to be a risk factor for CKDu in Sri Lanka.

A cross-sectional study, which identified CKDu through proteinuria, found an association between the use of shallow wells as a drinking water source and CKDu; odds ratio 5.5 (95% CI 3.5–8.7) compared to the referent group that used natural springs.[18] Geographic Information Systems (GIS) mapping has found that CKDu endemic villages tend to be located below the levels of reservoirs and canals, which may lead to drinking water being contaminated by drained irrigated water.[25]

Other studies, including the DEGREE prevalence study, found no association between CKDu and well water usage.[21] Conflicting results may be a consequence of difficulty in characterization and measurement of exposure, such as collection of water from more than one source, changing water sources, failure to adjust for social and economic status (SES), and potential for measurement bias through retrospective self-reported usage. Detailed data on the types of wells used, depth of wells, and whether they were designed for human consumption, or are adapted irrigations wells, is often lacking in studies.

Variation in measurement of heavy metals and fluoride in water, even locally, may be due to timing of specimen collection and calibration of measurement instruments.

Water hardness has also been suggested as a potential cause of CKDu, however, currently there is no conclusive evidence with one study demonstrating mixed results with high levels of water hardness also recorded in low prevalence areas.[26]

Governments and NGOs have endeavoured to provide safe drinking water and there have been anecdotal reports of subsequent decreases in CKDu.[27,28] Improved taste and appearance of drinking water may reduce fears held by individuals, leading to a potential positive impact through increased hydration.[29]

2.5 | Agricultural work

Male agricultural workers have been identified as the main group at risk of CKDu. Nanayakkara et al.,[30] in a case–control study, found the strongest association between farming and CKDu, with an odds ratio for farming of 9.2 (95% CI 4.2–20.0). Farmers were under-represented in study controls (70%), compared to cases (98%). Some studies which found an association with farming had limitations such as: hospital-based case–control design; measurement issues of exposure variables; lack of differentiation between CKD and CKDu; and failure to analyse sexes separately.[20,31–33] Evidence from outside of Sri Lanka has found CKDu in urban and non-agricultural occupations[10,34,35] and not all studies in Sri Lanka have shown a significant association with farming.[21] No study has separated farming into different subcategories based on socioeconomic status such as land owners or wage labourers who are exposed to different levels of labour and agrochemicals.[36] Simple occupation questions may also fail to capture agricultural exposures undertaken in home gardens by non-farmers.

2.6 | Agrochemicals

Increased usage of agrochemicals commencing during introduction of larger industrial style farming in the 1960s, has been postulated as a cause for CKDu.[37] Triple Super Phosphate fertilizer was suggested to be a potential aetiological agent, and a possible source of arsenic.[38] There is no evidence that the NCP utilizes more phosphate fertilizer than non-endemic CKDu areas of Sri Lanka.

Studies measuring agrochemical levels in CKDu cases have been limited, and generally of insufficient study size to derive robust conclusions. One study demonstrated higher levels of neonicotinoid insecticides in Japanese controls than Sri Lankan CKDu cases.[39] Another study found lower levels of blood acetyl choline esterase (AChE) in CKD farmers than controls, which can be due to exposure to AChE lowering pesticides.[40] AChE levels generally recover within 3 months of exposure to pesticides, while CKD may follow exposure by a number of years, or even decades; and, in addition, AChE levels may not be an accurate measure of kidney toxicity.

Various agrochemicals have been banned in parts of Sri Lanka at various times, with many reintroduced. No relationship has been documented between agrochemical bans and CKDu prevalence. The Northern Province experienced an extended ban (due to concerns of munition manufacture during the Civil War). CKDu has not been reported in the Northern Province, whether through lack of data or absence of cases, and current agrochemical usage between the NCP, NP and other provinces has not been compared.

Currently, no available studies have sufficient evidence to establish causality for agrochemical usage as a putative exposure for CKDu. A clear link between agrochemical usage and CKD has been demonstrated in other settings, with a recent review of NHANES data demonstrating an increased risk of kidney disease associated with both acute and chronic pesticide exposure.[41] Many existing studies in Sri Lanka are of limited utility in making conclusions due to possible bias in: timing of sample collection, selection of locations, recall self-report bias, failure to distinguish between different agrochemical usage, and failure to adequately capture usage of personal protective equipment (PPE). Differences in exposure measurement between studies may have contributed to some case–control and prevalence studies showing a strong association,[23,31,33] while others have shown a weak or no association.[13,20,21]

2.7 | Heavy metals

There is no conclusive evidence of heavy metals having a causative role in CKDu in Sri Lanka despite known associations in other epidemics. Extensive testing for chromium, arsenic, lead and cadmium in 1435 dug and tube wells from all provinces in Sri Lanka, as well as 67 rice samples from endemic areas, and 24 samples from non-endemic areas, did not demonstrate elevated levels of any tested heavy metals compared to Sri Lankan and WHO parameters.[42] Sampling of drinking water samples from CKDu endemic villages has demonstrated no elevated levels of lead, thallium, caesium, cadmium, molybdenum, strontium, rubidium, arsenic, zinc, carbon, nickel, cobalt, iron, manganese, chromium, vanadium and aluminium in water samples compared to WHO and United States Environmental Protection Agency guidelines.[30] Other biological measurements of heavy metals have shown urinary cadmium clearance to be higher in Japanese controls than both Sri Lankan cases and controls.[43] Renal biopsies have shown no localized distribution of cadmium in renal biopsies, and cadmium levels were higher in Australian controls than Sri Lankan CKDu cases.[44] Dietary sources of heavy metal have been suggested as a potential cause of CKDu, with one study finding elevated dietary intake of lead and cadmium.[45] However, no comparison was made to non-prevalent CKDu areas. Other potential sources of heavy metal which have been identified in other settings such as ayurverdic medication,[46,47] betel leaf[48] and household sources such as paint[49] have not been studied in relation to CKDu in Sri Lanka.

2.8 | Tobacco and betel

Associations between tobacco and CKDu have been proposed. Most studies[15,23] failed to analyse the sexes separately, or to control for sex and socio-economic status, despite large differences in daily smoking rates between males (19%) and females (0%),[50] and smoking being more prevalent among individuals of lower socio-economic status.[50] An association between CKDu and smoking has been reported on analysis of the sexes separately, with males OR 1.9 (95% CI 1.1–3.2).[21] Chewing of tobacco is also more common in males (36%) than females (4%).[50] No studies have considered the different types of tobacco chewing, such as that associated with betel nut use (areca nut, slaked lime, and betel piper leaf). Only one small case–control study has considered the relationship between betel nut use and CKDu, finding an OR of 5.95 (95% CI 1.9–18.9).[51] The authors do not mention if sex and socioeconomic confounders are controlled for in the analysis.

2.9 | Snake bites

Snakebite has the potential to cause acute and chronic renal injury. A clinical cohort study demonstrated that 37% of 54 patients presenting to hospital with AKI post snake bite in Sri Lanka, progressed to CKD within 1 year.[52] Biopsies of seven of the cases demonstrated interstitial nephritis with some glomerular sclerosis and tubular and cortical necrosis.[52] A community-based survey found the incidence of self-reported snake bite to be 398 per 100 000 per year.[53] Previous statistics based on hospital data, indicate that not everyone seeks medical attention after snake bite[53] suggesting that kidney injuries after snake bite may also be under-reported. Prevalence and case–control studies[30,32] have suggested CKDu may be associated with a history of a snake bite. The DEGREE prevalence study found an association between snake bite and CKDu, with a non-significant OR of 1.7 (95% CI 0.8–3.4, $p = .17$) for males, and an OR of 1.8 (95% CI 0.7–4.7, $p = .22$) for females.[21] Snake bite may also be a potential confounder due to association with rural living and outdoor work.

2.10 | Family history and genetics

Familial history of CKDu has been an identified risk factor which may be due to genetic influences, or common exposure to the same aetiological agent in the entire family group. Nanayakkara et al. found through whole exome-sequencing of eight cases and eight controls that gene variant rs34970857 on the KCNA10 gene was associated with CKDu.[54] While a genetic predisposition may explain why not everyone with the same risk factors develops CKDu, it does not explain which aetiological agent is responsible.

2.11 | Ayurverdic medication

Qualitative research has revealed that ayurverdic medication usage is common in rural areas in Sri Lanka, with villagers more likely to seek ayurvedic than allopathic medical treatment for symptoms which may indicate an acute kidney injury.[55] Ten medicinal recipes in the Sri Lanka Ayurveda Pharmacopoeia utilize *Aristolochia indica* as an ingredient.[56] CKD from aristolochia exposure has previously been associated with increased frequency of ureteral tumours; in the Chinese herbal nephropathy epidemic in Belgium almost half of the affected cohort developed comorbid urothelial tumours. Urothelial tumours have not been reported in Sri Lanka.[4,5]

2.12 | Heat stress

Heat stress can be due to environmental exposures, such as climatic conditions and lack of shade as well as impacted upon by other factors including water intake. There is currently no clear mechanism for heat stress to cause CKDu through hypotheses have been proposed, such as vasopressin increases and damage due to hyperuricemia.[57] Renal biopsies in heat stress patients generally show acute tubular necrosis in contrast to the tubulo-interstitial disease seen in CKDu in Sri Lanka.[58] Heat stress has been investigated less in Sri Lanka than in Mesoamerica. Measurement of heat stress in one cross-sectional and one case–control study[33,59] of CKDu in Sri Lanka were subject to recall bias, and provide low quality evidence for an association between heat stress and CKDu. Critics of the heat stress hypothesis in Sri Lanka point to the absence of reported CKDu in the agricultural Northern Province, which has hotter conditions than the NCP, as well as the absence of CKDu in other occupations exposed to high temperatures such as construction workers.[37,60,61] Heat, as measured by sun exposure time, was not found to be a risk factor for CKDu in the DEGREE Sri Lanka study.[21]

2.13 | Infectious diseases

Elevated levels of IgG antibodies for hantavirus have been found in a case–control study of 132 CKDu cases (54%), compared to 200 community controls (14%).[62] Recruitment of participants was not stated, and potentially unmatched controls for agricultural exposures may have biased results. Hantavirus is transmitted through contact with rodent urine, faeces and saliva. Leptospirosis has had known outbreaks in Sri Lanka,[63] and can cause acute kidney injury with tubulo-interstitial nephritis[64] and has been postulated to be a potential cause of CKDu.[65]

2.14 | Acute cases

Subclinical acute kidney injury (AKI), or recurrent injuries, have been postulated as potential precursors to CKDu in Sri Lanka. The

TABLE 3 Summary of published research findings, limitations and scope for future research

Study Types[a]	Cross-sectional ($n = 15$)	Case–Control ($n = 29$)	Case Series ($n = 15$)	Ecological/ Environmental ($n = 32$)	Other ($n = 3$)
Methods	Prevalence of CKDu/CKD by area, and by individual putative risk factors	Comparison of selected cases of CKDu/CKD with non-cases (controls)	Characteristics of cases of CKD/CKDu and acute renal injury, with follow-up in some instances	Measures of environmental risk factors with comparisons to guidance levels (not toxicity) and/or between areas	Qualitative study (1) Experimental studies in animals (2)
Findings	Identifies NCP as high prevalence area. Suggestive evidence of CKDu in other provinces. Some high-quality prevalence studies Examined: Farming, family history, drink well water, dehydration, pesticide spray, urinary glyphosate, tobacco	Examined family history, farming, work in heat, agrochemical, exposure, male, tobacco, drink well water, Ayurvedic medication, hantavirus antibodies, snake bite, As in hair/nails	Renal histopathology: tubulo-interstitial nephritis Acute kidney injury possible precursor to CKDu. Some data on disease progression and mortality	Analyses of water, food and soil for Cd, As, Pb, & other heavy metals, plus trace elements to compare to guidance levels (not toxicity) from Sri Lankan and WHO advice	Qualitative research offers perception of CKDu risk factors Experimental studies relate contaminated water source to CKD in rats
	Consistent evidence of influence of distal risk factors including rural residence, male sex and farming Identification of possible proximate/intermediate risk factors such as water source, agrochemicals, ayurverdic medication Lack of evidence for proximate causes e.g., environmental heavy metal contamination of water, soil or food				
Limitations of current research	Measures prevalence not incidence Lack of quality research in various provinces limit comparisons of prevalence and localized risk factors	Cases often not matched on demographic variables Cases and controls often hospital recruited	No comparison to non-cases Biopsies unable to demonstrate causative agent	Environmental samples assessed without explicit linkage to CKDu prevalence Possible issues with instrument calibration or timing of sample collection	Perception of risk factors may not relate to actual risk Animal studies may not relate to risk in humans
	Inconsistent definitions of CKD and CKDu and failure to distinguish between the two conditions Prevalent cases with uncertain period of exposure Inconsistent and/or undefined measures of exposure factors e.g. drinking water sources, agrochemical exposure Limitations of ability to relate exposures over time to CKDu diagnosis Non-random recruitment of participants in many studies Difficulties in capture of historical exposure, e.g., changing water sources and agrochemicals use over time Often only one measurement of renal function for inclusion as acute or chronic kidney disease				
Suggestions for future research	Random recruitment of participants High quality prevalence surveys to be conducted in all areas	Random community-based recruitment Cases and controls matched on demographic variables Measurement and comparison of further potential exposures, e.g., agrochemical levels in blood	Detailed case history interviews may provide further details on potential novel exposures for investigation	Linkage of population level data on CKDu prevalence to environmental samples in surveys of different high and low risk areas	Further qualitative research to identify novel risk factors for investigation by visits to high and low CKDu prevalence areas
	Usage of consistent and accepted definition of CKDu that is distinguished from CKD Improved and consistent definition of measured exposure factors such as agrochemical exposure, different types of farming and water sources Investigation of exposures that have been less well investigated, e.g., Ayurvedic medication Repeated measurement of renal function (e.g., 3 months apart) to ensure that disease is chronic Cohort studies ≥2 years would establish incidence and prevalence, and exposure measurement prior to clinical presentations, from periodic routine testing of the cohort for acute kidney injury AKIu and CKDu				

[a]If more than one study was published within the same article, each study was counted and reviewed separately for the purposes of critiquing the studies.

interconnectedness of acute and chronic kidney disease has been suggested elsewhere.[66] A case series of patients at Kandy Teaching Hospital, presenting with symptomatic AKI, found a mixture of acute and chronic tubulo-interstitial nephritis, and glomerular sclerosis, in renal biopsies.[67] The acute and chronic cases may be potentially linked because of occurrence in the same area, similarities in biopsy results, and parallel characteristics reported in both affected groups (predominantly males and agricultural workers).[67]

2.15 | Discussion

Currently there is no strong evidence for any one aetiological exposure to be the putative cause of CKDu. The lack of substantive proof for a particular exposure has led some research to conclude that CKDu is a consequence of multiple exposure factors although lack of evidence for a singular cause does not mean that the cause is multifactorial. Previous CKDu endemics such as Itai-Itai disease (cadmium) and Balkan endemic nephropathy (*Aristolochia*) required decades of research before scientific consensus was achieved on a singular cause. A number of studies have shown that there is a lack of effect for various possible causes, such as heavy metal exposures. Current studies show evidence of distal casual exposures such as rural residence, male sex and occupation in farming, albeit with some exceptions (Table 3 and supplementary tables). Further research is required to establish which proximate elements associated with these factors lead to increased risk for CKDu.

The DEGREE study,[21] conducted in the region of Anuradhapura, provides the current most robust evidence from a prevalence study investigating CKDu in Sri Lanka, by use of a standardized definition and research protocol. Strengths of the study include: a clear definition of CKDu and distinction from CKD; random selection of participants; and inclusion of both high and low prevalence areas within the same province. Limitations of the study include the estimation of exposure (measurement, and retrospective recall), and the calculation of association using prevalence data. These limitations are applicable to many other studies and have been summarized in Table 3. The study was also limited to one geographical area and was not able to contrast and compare potential exposures and prevalence between different regions. The majority of the studies undertaken to investigate CKDu in Sri Lanka have been affected by methodological issues, and gaps remain in understanding the aetiology of CKDu, which have been discussed throughout the article and summarized in Table 3. Some issues have arisen due to constraints of the research environment such as existing hospital datasets, lack of distinction between CKD and CKDu, difficulties associated with conducting field research, and costs associated with some potential research designs (e.g., cohort studies).

Areas of future research interest and ideas to close gaps in knowledge have been summarized in Table 3. The main areas of improvement for all future studies would be: the consistent application and usage of a recognized definition of CKDu separated from CKD; random community-based selection of participants; improved definitions of exposure factors including specific agrochemical exposure that considers duration of exposure and use of personal protective equipment; and ensuring high quality research in all provinces so that CKDu is recognized where it exists. Ideally, to move beyond the current understanding of CKDu in Sri Lanka the evidence base must move beyond the initial enquiries that have been undertaken (generally ecological, cross-sectional studies and case–control) which have not provided clear answers to the aetiology question. It appears a higher order methodologically stronger approach will be needed, such as long term appropriately funded cohort studies with clearly defined measures of exposures and outcomes.

3 | CONCLUSION

The current body of evidence for any aetiological agent as the proximate cause of CKDu in Sri Lanka is limited. The failure to find a definitive cause has led to several review papers concluding that the disease is multifactorial.[28,60,68,69] Previous CKDu epidemics, such as Itai-Itai disease in Japan (cadmium) required decades of research before a consensus on aetiology was achieved showing a singular aetiological agent.[2] Positive findings from research are that the disease is most common in male agricultural workers, that there may be exposures through some drinking water sources, and that there is probably a relation between acute episodes and chronic renal disease of unknown cause. There is also evidence of absence of effects of some exposures, such as heavy metals. Further in-depth research with stronger study designs is necessary to increase knowledge of aetiology of CKDu in Sri Lanka in order to identify and eliminate exposure to causative agent(s).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Jennifer Pett https://orcid.org/0000-0002-9272-1002

Nicholas J. Osborne https://orcid.org/0000-0002-6700-2284

REFERENCES

1. Wijewickrama ES, Gunawardena N, Jayasinghe S, Herath C. CKD of unknown etiology (CKDu) in Sri Lanka: a multilevel clinical case definition for surveillance and epidemiological studies. *Kidney Int Rep*. 2019;4(6):781-785. doi:10.1016/j.ekir.2019.03.020
2. Gifford FJ, Gifford RM, Eddleston M, Dhaun N. Endemic nephropathy around the world. *Kidney Int Rep*. 2017;2(2):282. doi:10.1016/j.ekir.2016.11.003
3. Emmerson BT. Chronic lead nephropathy. *Kidney Int*. 1973;4(1):1. doi:10.1038/ki.1973.73
4. Cosyns JP. Aristolochic acid and 'Chinese herbs nephropathy'—a review of the evidence to date. *Drug Saf*. 2003;26(1):33-48.
5. Jelaković B, Dika Ž, Arlt VM, et al. Balkan endemic nephropathy and the causative role of Aristolochic acid. *Semin Nephrol*. 2019;39(3):284-296. doi:10.1016/j.semnephrol.2019.02.007
6. Gooneratne I, Ranaweera A, Liyanarachchi N, Gunawardane N, Lanerolle R. Epidemiology of chronic kidney disease in a Sri Lankan

population. *Int J Diabetes Develop Countries*. 2008;28(2):60-64. doi:10.4103/0973-3930.43101
7. Trabanino RG, Aguilar R, Silva CR, Mercado MO, Merino RL. End-stage renal disease among patients in a referral hospital in El Salvador. Revista panamericana de salud publica = pan. *Am J Public Health*. 2002;12(3):202. doi:10.1590/s1020-49892002000900009
8. Johnson RJ, Wesseling C, Newman LS. Chronic kidney disease of unknown cause in agricultural communities. *N Engl J Med*. 2019; 380(19):1843. doi:10.1056/NEJMra1813869
9. Elledge MF, Redmon JH, Levine KE, Wickremasinghe RJ, Wanigasariya KP, Peiris-John RJ. Chronic kidney disease of unknown etiology in Sri Lanka: quest for understanding and global implications. *RTI Press Res Brief*. 2014. doi:10.3768/rtipress.2014.rb.0007.1405
10. Stanifer JW, Maro V, Egger J, et al. The epidemiology of chronic kidney disease in northern Tanzania: a population-based survey. *PLoS One*. 2015;10(4):e0124506. doi:10.1371/journal.pone.0124506
11. Kumaresan J, Seneviratne R. Beginning of a journey: unraveling the mystery of chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka. *Glob Health*. 2017;13(1):43. doi:10.1186/s12992-017-0268-y.
12. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2020; 395(10225):709-733. doi:10.1016/S0140-6736(20)30045-3
13. Jayatilake N, Mendis S, Maheepala P, Mehta FR. Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. *BMC Nephrol*. 2013;14(1):180. doi:10.1186/1471-2369-14-180
14. Herath N, Dassanayake R, Dissanayake M, et al. Normality data of eGFR and validity of commonly used screening tests for CKD in an area with endemic CKD of unknown etiology; need for age and sex based precise cutoff values. *BMC Nephrol*. 2019;20(1):298. doi:10.1186/s12882-019-1477-9
15. Selvarajah M, Weeratunga P, Sivayoganthan S, Rathnatunga N, Rajapakse S. Clinicopathological correlates of chronic kidney disease of unknown etiology in Sri Lanka. *Indian J Nephrol*. 2016;26(5):357–363. doi:10.4103/0971-4065.167280.
16. Anand S, Montez-Rath ME, Adasooriya D, et al. Prospective biopsy-based study of CKD of unknown etiology in Sri Lanka. *Clin J Am Soc Nephrol*. 2019;14(2):224. doi:10.2215/CJN.07430618
17. Redmon JH, Elledge MF, Womack DS, et al. Additional perspectives on chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka—lessons learned from the WHO CKDu population prevalence study. *BMC Nephrol*. 2014;15(1):125. doi:10.1186/1471-2369-15-125
18. Jayasekara KB, Dissanayake DM, Sivakanesan R, Ranasinghe A, Karunarathna RH, Kumara GW. Epidemiology of chronic kidney disease, with special emphasis on chronic kidney disease of uncertain etiology, in the north central region of Sri Lanka. *J Epidemiol*. 2015; 25(4):275-280. doi:10.2188/jea.JE20140074
19. De Silva PMCS, Abdul KSM, Eakanayake EMDV, et al. Urinary biomarkers KIM-1 and NGAL for detection of chronic kidney disease of uncertain etiology (CKDu) among agricultural communities in Sri Lanka. *PLoS Negl Trop Dis*. 2016;10(9):e0004979. doi:10.1371/journal.pntd.0004979
20. Athuraliya NTC, Abeysekera TDJ, Amerasinghe PH, et al. Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. *Kidney Int*. 2011;80(11):1212. doi:10.1038/ki.2011.258
21. Ruwanpathirana T, Senanayake S, Gunawardana N, et al. Prevalence and risk factors for impaired kidney function in the district of Anuradhapura, Sri Lanka: a cross-sectional population-representative survey in those at risk of chronic kidney disease of unknown aetiology. *BMC Public Health*. 2019;19(1):763. doi:10.1186/s12889-019-7117-2.
22. Ranasinghe A, Kumara G, Karunarathna RH, et al. The incidence, prevalence and trends of chronic kidney disease and chronic kidney disease of uncertain aetiology (CKDu) in the north Central Province of Sri Lanka: an analysis of 30,566 patients. *BMC Nephrol*. 2019;20(1): 338. doi:10.1186/s12882-019-1501-0.
23. Wanigasuriya KP, Peiris-John RJ, Wickremasinghe R. Chronic kidney disease of unknown aetiology in Sri Lanka: is cadmium a likely cause? *BMC Nephrol*. 2011;12:32. doi:10.1186/1471-2369-12-32
24. Cooray T, Wei Y, Zhong H, Zheng L, Weragoda S, Weerasooriya R. Assessment of groundwater quality in CKDu affected areas of Sri Lanka: implications for drinking water treatment. *Int J Environ Res Public Health*. 2019;16(10):1698. doi:10.3390/ijerph16101698.
25. Jayasekara JM, Dissanayake DM, Adhikari SB, Bandara P. Geographical distribution of chronic kidney disease of unknown origin in north central region of Sri Lanka. *Ceylon Med J*. 2013;58(1):6. doi:10.4038/cmj.v58i1.5356
26. Wasana H, Aluthpatabendi D, Kularatne W, Wijekoon P, Weerasooriya R, Bandara J. Drinking water quality and chronic kidney disease of unknown etiology (CKDu): synergic effects of fluoride, cadmium and hardness of water. *Off J Soc Environ Geochem Health*. 2016; 38(1):157-168. doi:10.1007/s10653-015-9699-7
27. Edirisinghe EANV, Manthrithilake H, Pitawala HMTGA, Dharmagunawardhane HA, Wijayawardane RL. Geochemical and isotopic evidences from groundwater and surface water for understanding of natural contamination in chronic kidney disease of unknown etiology (CKDu) endemic zones in Sri Lanka. *Isot Environ Health Stud*. 2018;54(3):244-261. doi:10.1080/10256016.2017.1377704
28. Wimalawansa S. Escalating chronic kidney diseases of multi-factorial origin in Sri Lanka: causes, solutions, and recommendations. *Environ Health Prev Med*. 2014;19:375-394. doi:10.1007/s12199-014-0395-5
29. DRR-Team. DRR-Team CKDU Scoping Mission Report; 2016.
30. Nanayakkara S, Senevirathna S, Abeysekera T, et al. An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by Tubulointerstitial damages in the north central region of Sri Lanka. *J Occup Health*. 2014;56(1):28-38. doi:10.1539/joh.13-0172-OA
31. Jayasumana C, Paranagama P, Agampodi S, Wijewardane C, Gunatilake S, Siribaddana S. Drinking well water and occupational exposure to herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka. *Environ Health*. 2015;14(1):6. doi:10.1186/1476-069X-14-6
32. 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. doi:10.1016/j.trstmh.2007.05.006
33. Siriwardhana EARIE, Perera PAJ, Sivakanesan R, Abeysekara T, Nugegoda D, Jayaweera JAAS. Dehydration and malaria augment the risk of developing chronic kidney disease in Sri Lanka. *Indian J Nephrol*. 2015;25(3):146-151. doi:10.4103/0971-4065.140712
34. Gallo-Ruiz L, Sennett CM, Sánchez-Delgado M, et al. Prevalence and risk factors for CKD among brickmaking workers in La Paz Centro. *Nicaragua Am J Kidney Dis*. 2019;74(2):239-247. doi:10.1053/j.ajkd.2019.01.017
35. Ghosh R, Siddarth M, Singh N, et al. Organochlorine pesticide level in patients with chronic kidney disease of unknown etiology and its association with renal function. *Environ Health Prev Med*. 2017;22(1): 49. doi:10.1186/s12199-017-0660-5
36. De Silva M, Albert S, Jayasekara J. Structural violence and chronic kidney disease of unknown etiology in Sri Lanka. *Soc Sci Med*. 2017; 178:184. doi:10.1016/j.socscimed.2017.02.016
37. Jayasinghe S. Chronic kidney disease of unknown etiology should be renamed chronic agrochemical nephropathy. *MEDICC Rev*. 2014;16(2):72.
38. Jayasumana C, Fonseka S, Fernando A, et al. Phosphate fertilizer is a main source of arsenic in areas affected with chronic kidney disease of unknown etiology in Sri Lanka. *Springerplus*. 2015;4(1):1-8. doi:10.1186/s40064-015-0868-z
39. Kabata R, Nanayakkara S, Senevirathna S, et al. Neonicotinoid concentrations in urine from chronic kidney disease patients in the north

central region of Sri Lanka. *J Occup Health*. 2016;58(1):128. doi:10.1539/joh.15-0140-BR
40. Peiris-John RJ, Wanigasuriya JKP, Wickremasinghe AR, Dissanayake WP, Hittarage A. Exposure to acetylcholinesterase-inhibiting pesticides and chronic renal failure. *Ceylon Med J*. 2006;51(1):42. doi:10.4038/cmj.v51i1.1382
41. Osborne N, Reid S, Karatela S, Assefa Y, Wan E-TG. 228Relationship of pesticide exposure with kidney function in NHANES: lessons from low level chronic exposure. *Int J Epidemiol*. 2021;50(Supplement_1):i182. doi:10.1093/ije/dyab168.517.
42. Herath HMAS, Kawakami T, Nagasawa S, et al. Arsenic, cadmium, lead, and chromium in well water, rice, and human urine in Sri Lanka in relation to chronic kidney disease of unknown etiology. *J Water Health*. 2018;16(2):212. doi:10.2166/wh.2018.070
43. Nanayakkara S, Senevirathna S, Karunaratne U, et al. Evidence of tubular damage in the very early stage of chronic kidney disease of uncertain etiology in the north Central Province of Sri Lanka: a cross-sectional study. *Environ Health Prev Med*. 2012;17(2):109-117. doi:10.1007/s12199-011-0224-z
44. Mott S, Hoy W, Gobe G, Satarug S, Abeysekera T. Assessment of cadmium load in renal biopsies from Sri Lankan people with chronic kidney disease of unknown origin. 49th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology; Brisbane, QLD Australia: Nephrology; 2013. p. 61.
45. Jayalal TA, Bandara TJ, Mahawithanage ST, Wansapala MJ, Galappaththi S. A quantitative analysis of chronic exposure of selected heavy metals in a model diet in a CKD hotspot in Sri Lanka. *BMC Nephrol*. 2019;20(1):208. doi:10.1186/s12882-019-1371-5.
46. Mikulski MA, Wichman MD, Simmons DL, Pham AN, Clottey V, Fuortes LJ. Toxic metals in ayurvedic preparations from a public health lead poisoning cluster investigation. *Int J Occup Environ Health*. 2017;23(3):187-192. doi:10.1080/10773525.2018.1447880
47. Lynch E, Braithwaite R. A review of the clinical and toxicological aspects of 'traditional' (herbal) medicines adulterated with heavy metals. *Expert Opin Drug Saf*. 2005;4(4):769-778. doi:10.1517/14740338.4.4.769
48. Al-Rmalli SW, Jenkins RO, Haris PI. Betel quid chewing elevates human exposure to arsenic, cadmium and lead. *J Hazard Mater*. 2011;190(1–3):69-74. doi:10.1016/j.jhazmat.2011.02.068
49. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. *Exe Suppl*. 2012;101:133-164. doi:10.1007/978-3-7643-8340-4_6
50. Gamlath L, Nandasena S, Padmal H, et al. Differentials in cardiovascular risk factors and diabetes by socioeconomic status and sex in Kalutara, Sri Lanka. Asia Pacific. *J Public Health*. 2017;29(5):401-410. doi:10.1177/1010539517709028
51. Pry JM, Jackson W, Rupasinghe R, et al. A pilot study of behavioral, environmental, and occupational risk factors for chronic kidney disease of unknown etiology in Sri Lanka. *BioRxiv*. 2019;837393. doi:10.1101/837393
52. Herath HMNJ, Wazil AWM, Abeysekara DTDJ, et al. Chronic kidney disease in snake envenomed patients with acute kidney injury in Sri Lanka: a descriptive study. *Postgrad Med J*. 2012;88(1037):138. doi:10.1136/postgradmedj-2011-130225
53. Ediriweera DS, Kasturiratne A, Pathmeswaran A, et al. Mapping the risk of snakebite in Sri Lanka—a National Survey with geospatial analysis. *PLoS Negl Trop Dis*. 2016;10(7):e0004813. doi:10.1371/journal.pntd.0004813
54. Nanayakkara S, Senevirathna S, Parahitiyawa N, et al. Whole-exome sequencing reveals genetic variants associated with chronic kidney disease characterized by tubulointerstitial damages in north central region, Sri Lanka. *Environ Health Prev Med*. 2015;20(5):354-359. doi:10.1007/s12199-015-0475-1
55. De Silva MWA. Drinking water and chronic kidney disease of unknown aetiology in Anuradhapura, Sri Lanka. *Anthropol Med*. 2018;1-17:311–327. doi:10.1080/13648470.2018.1446822.
56. Wijesinghe W, Pilapitiya S, Hettiarchchi P, Wijerathne B, Siribaddana S. Regulation of herbal medicine use based on speculation? A case from Sri Lanka. *J Tradit Complement Med*. 2016;7(2):269-271. doi:10.1016/j.jtcme.2016.06.009
57. Roncal-Jimenez C, Lanaspa MA, Jensen T, Sanchez-Lozada LG, Johnson RJ. Mechanisms by which dehydration may Lead to chronic kidney disease. *Ann Nutr Metab*. 2015;66(3):10-13. doi:10.1159/000381239
58. Herath C, Jayasumana C, De Silva PMCS, De Silva PHC, Siribaddana S, De Broe ME. Kidney diseases in agricultural communities: a case against heat-stress nephropathy. *Kidney Int Rep*. 2018;3(2):271. doi:10.1016/j.ekir.2017.10.006
59. Jayasekara J, Kulasooriya P, Wijayasiri KN, et al. Relevance of heat stress and dehydration to chronic kidney disease (CKDu) in Sri Lanka. *Prev Med Rep*. 2019;15:100928. doi:10.1016/j.pmedr.2019.100928
60. Jayasumana C, Orantes C, Herrera R, et al. Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. *Nephrol Dial Transplant*. 2017;32(2):234-241. doi:10.1093/ndt/gfw346
61. Rajapakse S, Shivanthan MC, Selvarajah M. Chronic kidney disease of unknown etiology in Sri Lanka. *Int J Occup Environ Health*. 2016;22(3):259-264. doi:10.1080/10773525.2016.1203097
62. Gamage CD, Yoshimatsu K, Sarathkumara YD, Kulendiran T, Nanayakkara N, Arikawa J. Serological evidence of hantavirus infection in Girandurukotte, an area endemic for chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka. *Int J Infect Dis*. 2017;57(C):77-78. doi:10.1016/j.ijid.2017.02.004
63. Ehelepola NDB, Basnayake BMLS, Sathkumara SMBY, Kaluphana KLR. Two atypical cases of hantavirus infections from Sri Lanka. *Case Rep Infect Dis*. 2018;2018. doi:10.1155/2018/4069862
64. Yang CW. Leptospirosis renal disease: understanding the initiation by toll-like receptors. *Kidney Int*. 2007;72(8):918-925. doi:10.1038/sj.ki.5002393
65. Yang CW. Leptospirosis renal disease: emerging culprit of chronic kidney disease unknown etiology. *Nephron*. 2018;138(2):129-136. doi:10.1159/000480691
66. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371(1):58-66. doi:10.1056/nejmra1214243
67. Badurdeen Z, Nanayakkara N, Ratnatunga NVI, et al. Chronic kidney disease of uncertain etiology in Sri Lanka is a possible sequel of interstitial nephritis! *Clin Nephrol*. 2016;86(13):106. doi:10.5414/CNP86S115
68. Jackson WA, Pry JM, Wickramasinghe S, et al. Utilizing a one health approach for identifying risk factors associated with an epidemic of chronic kidney disease of unknown etiology (CKDu) in the north central region of Sri Lanka. *Ann Glob Health*. 2016;82(3):575-576. doi:10.1016/j.aogh.2016.04.651
69. Wanigasuriya K. Update on uncertain etiology of chronic kidney disease in Sri Lanka's north-central dry zone. *MEDICC Rev*. 2014;16(2):61.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Pett J, Mohamed F, Knight J, Linhart C, Osborne NJ, Taylor R. Two decades of chronic kidney disease of unknown aetiology (CKDu) research: Existing evidence and persistent gaps from epidemiological studies in Sri Lanka. *Nephrology*. 2022;27(3):238-247. doi:10.1111/nep.13989