Multi-pronged research on endemic chronic kidney disease of unknown etiology in Sri Lanka: a systematic review

Dinushi Arambegedara1 · Saroj Jayasinghe2 · Preethi Udagama1

Received: 30 August 2021 / Accepted: 27 October 2021 / Published online: 19 November 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract
Increasing prevalence of endemic chronic kidney disease of unknown etiology (CKDu) in Sri Lanka is a major health problem since the 1990s. Despite numerous studies on CKDu, research groups have been unable to develop a comprehensive approach to mitigate the disorder, and thereby to identify research gaps. We conducted a systematic literature review of 119 publications on CKDu in Sri Lanka from Pubmed, Google Scholar, and Scopus, published until end September 2020. A higher CKDu prevalence in the working population of the North Central Province was reported with recent studies indicating patients from non-endemic regions as well. A majority were etiological studies that recorded conflicting and inconclusive evidence on CKDu etiology. Studies on clinico-pathological, diagnostic, biochemical, and molecular biological aspects of CKDu, studies analyzing CKDu symptom burden, anthropological, and behavioral impacts of CKDu, were reviewed as well. A dearth of research exists on nutritional, demographical, immunological, and microbial aspects of CKDu. The overview of the reviewed literature indicated the absence of a comprehensive plan of action to mitigate this situation. Hence, we propose the “One Health” approach with a systems dynamics model as a potential way forward to alleviate the CKDu epidemic in Sri Lanka. This enables the representation of multiple causative agents (and interactions thereof) among environmental, animal, and human systems, in concert with the “exposome” that provides the totality of exposure the individual has undergone since birth.

Keywords Sri Lanka. CKDu epidemic · One Health approach · Systems dynamics model · Exposome

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| CKD          | Chronic kidney disease |
| CKDu         | Chronic kidney disease of unknown etiology |
| NCP          | North Central Province |
| CINAC        | Chronic interstitial nephritis in agricultural communities |
| NCR          | North Central Region |
| PRISMA       | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| eGFR         | Estimated glomerular filtration rate |
| UACR         | Urinary albumin creatinine ratio |
| F            | Fluoride |
| Cd           | Cadmium |
| Pb           | Lead |
| Na           | Sodium |
| Ca           | Calcium |
| Mg           | Magnesium |
| As           | Arsenic |
| V            | Vanadium |
| SNP          | Single nucleotide polymorphism |
| Se           | Selenium |
| Cr           | Chromium |
| Zn           | Zinc |
| Fe           | Iron |
| HRQOL        | Health-related quality of life |
| TIN          | Tubulointerstitial nephritis |
| SLSON        | Sri Lanka Society of Nephrology |
| S.Cr         | Serum creatinine |
| S.Cys        | Serum Cystatin C |
| KIM-1        | Kidney Injury Molecule 1 |
| A1M          | Alpha 1 Microglobulin |
| RBP4         | Retinol Binding Protein 4 |
| OPN          | Osteopontin |

Responsible Editor: Lotfi Aleya

* Preethi Udagama
preethi@zoology.cmb.ac.lk

1 Department of Zoology and Environment Sciences, Faculty of Science, University of Colombo, Colombo 3, Sri Lanka
2 Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Colombo 8, Sri Lanka
IGFBP1  Insulin Like Growth Factor Binding Protein 1
GCLC  Glutamine cysteine C subunit
GSTM1  Glutathione S Transferase Mu 1
FN1  Fibronectin 1
IGFBP3  Insulin like Growth Factor Binding Protein 3
KLK1  Kallikrein 1
FA  Fluctuating Asymmetry
TSH  Thyroid stimulating hormone
PTH  Parathyroid hormone
SGPT  Serum glutamic pyruvic transaminases
ALT  Alanine amino transferase
SGOT  Serum glutamic oxaloacetic transaminases
AST  Aspartate transaminase
GGT  Gamma-glutamyl transferase
LDH  Lactic acid dehydrogenase
BMI  Body mass index
LAMB2  Laminin Beta2
KCNA10  Potassium voltage-gated channel sub family A member 10
SLC13A3  Sodium-dependent dicarboxylate transporter member 3
FGF23  Fibroblast growth factor-23
NLRP3  NLR family pyrin domain containing 3
EIF2  Eukaryotic Initiation Factor 2
mTOR  Mammalian target of rapamycin
Cdc42  Cell division cycle 42
RhoA  Ras homolog family member A
μUNPD  Micro-urate nanoparticle detection.

Background

The global increase of chronic kidney disease (CKD) is mainly attributed to the well-known associated risk factors, i.e., diabetes mellitus, long-standing hypertension, and chronic glomerulonephritis (Codreanu et al. 2006). Sri Lanka too experienced an increasing prevalence of a form of CKD sans the manifestation of these known risk factors. This was initially observed in the 1990s in geographically discrete areas in the North Central Province (NCP), which encompasses the island’s dry zone (Chandrajith et al. 2011a). Hence, this novel renal disease was termed “Chronic Kidney Disease of unknown etiology” (CKDu) (Paranagama et al. 2011). Distinction of CKDu from other CKDs in Sri Lanka was based mainly on its relatively low proteinuria, a bland urinary sediment and the absence of diabetes or hypertension. This was initially observed in the 1990s in geographically discrete areas in the North Central Province (NCP), which encompasses the island’s dry zone (Chandrajith et al. 2011a). Hence, this novel renal disease was termed “Chronic Kidney Disease of unknown etiology” (CKDu) (Paranagama et al. 2011). Distinction of CKDu from other CKDs in Sri Lanka was based mainly on its relatively low proteinuria, a bland urinary sediment and the absence of diabetes or hypertension. The latter when present was mild and considered its consequence rather than the cause (Selvarajah et al. 2016).

Across the globe, CKDu has achieved an escalating prevalence and is seen in epidemic proportions (Jha et al. 2013). Developing nations of South Asia (Sri Lanka, Bangladesh, and India), Africa (Egypt), and Mesoamerica (El Salvador, Nicaragua, Guatemala, Honduras, Costa Rica, and Southern Mexico) are affected by CKDu (Jha et al. 2013; Lunyera et al. 2016; Weaver et al. 2015). This mainly afflict the rural farming communities, with a male preponderance, and is prevalent in tropical and sub-tropical countries with a hot climate throughout the year (Bello et al. 2017). The topography of the CKDu localized regions globally, are flat and the ground conditions are harsh with little rain and prolonged dry periods (Wimalawansa 2014).

In the early 21st century, the term CKDu was first used in El Salvador for a disease that predominantly affected the agricultural communities of large scale plantations (Trabacino et al. 2002). Other names proposed include CINAC (chronic interstitial nephritis in agricultural communities) (Jayasumana et al. 2016) and chronic agrochemical nephropathy (Jayasinghe 2014). The CKDu epidemic witnessed in El Salvador, Nicaragua, and Costa Rica reported renal pathological and epidemiological characteristics similar to the Sri Lankan CKDu (Jayasumana et al. 2017).

Comparison of CKDu in Central America (Mesoamerican Nephropathy) and in Sri Lanka suggests morphological and biochemical similarities (Jayasumana et al. 2018). Pathology can be described as chronic tubulointerstitial nephritis with interstitial fibrosis as the predominant lesion and a variable distribution of tubulointerstitial and glomerular abnormalities (Gunawardena et al. 2021).

CKDu results in progressive deterioration of renal function, where patients remain asymptomatic until the late stages (Jayatilake et al. 2013). Histopathology of the affected kidneys include tubular atrophy, interstitial mononuclear cell infiltration, and interstitial fibrosis (Nanayakkara et al. 2012a). These features are indicative of a toxic etiology (Jayatilake et al. 2013; Waniagasekara et al. 2007 & Waniagasekara et al. 2011).

The Sri Lankan CKDu patient cohort includes both men and women between 17 and 70 years of age where the majority include men aged between 30 and 60 years (Athuraliya et al. 2009; Chandrajith et al. 2011a, 2011b). This evidently demonstrates that CKDu affects the working population in their productive age (Cooray et al. 2019).

In 2017, the Epidemiology Unit, Ministry of Health, Sri Lanka reported that either all or a few of the Divisional Secretariat Divisions of 11 districts of the 25 administrative districts of the country are at risk of the occurrence of CKDu: namely, Anuradhapura, Polonnaruwa, Kurunegala, Ampara, Trincomalee, Badulla, Mullaitivu, Vavuniya, Matale, Monaragala, and Hambantota displayed in Figure 1. A total of 70% CKD patients in the NCP were diagnosed with CKDu (Jayasekara et al. 2015) with a 9.1% in Hambantota (Athuraliya et al. 2011). A percentage of 54% of patients attending the Nephrology Unit, Kandy suffered from CKDu (Athuraliya et al. 2009).

The number of CKDu patients has gradually increased (Elledge et al. 2016), a majority of these patients being...
reported from the NCP and North Western Province; a significant number of patients have also been reported from Uva, Eastern and Northern Provinces (Chandrajith et al. 2011a, 2011b).

Epidemiological data has indicated three high prevalent areas within the North Central Region (NCR), namely, Medawachchiya, Padaviya, and Girandurukotte. In addition, Medirigiriya and Nikawewa were identified as two smaller foci. Emergence of new foci can be predicted while the older foci remain static (Jayasekara et al. 2013). These foci are distributed in a mosaic pattern since endemic villages are located a few kilometers away from non-endemic villages (Chandrajith et al. 2011a, 2011b). Yet, within an endemic village, some households manifest the disease, while others have never reported a case. This suggests that both environmental and genetic factors may contribute to the etiology and progression of the disease (Chandrajith et al. 2011a, 2011b).

The Presidential Task Force established for the prevention of CKDu in Sri Lanka confirms that approximately 20,000 patients are admitted to government hospitals causing 2,000 deaths annually. The actual number of deaths may exceed since deaths occurring in private homes are not accounted for. Prevalence of CKDu is also believed to be underreported due to the lack of reliable epidemiological studies (Kafle et al. 2019).

The Institute of Policy Studies of Sri Lanka reports that care for CKDu consumes 4-5% of the total healthcare budget due to the high cost of dialysis and renal transplant (Wanigasuriya et al. 2007). In many patients, CKDu will progress to the end stage renal disease, which in rural communities can be lethal since renal replacement therapy is limited or not affordable (Bello et al. 2017; Chandrajith et al. 2011a, 2011b). These regions also lack access to safe drinking water, modern medical facilities, and effective healthcare (Wimalawansa 2019).

CKDu prevention actions include education campaigns to prevent environmental pollution, enhancing nationwide awareness, educating the farmers regarding the responsible
usage of agrochemicals, and providing safe potable water (Elledge et al. 2016; Wimalawansa 2014).

In this systematic review, we compiled research studies reported by Sri Lankan scientists on endemic CKDu up until September 2020 with no restrictions going back in time. The status of publications on prevalence, etiology, histopathological, and clinical aspects alongside molecular biological, sociological, and symptomatic studies were reviewed in the context of Sri Lankan CKDu research. The results are used to propose a progressive way forward to elucidate the known unknowns of this disease.

Main text

Literature search

The literature search was conducted using Pubmed, Google Scholar, and Scopus databases in September 2020 to explore potential scientific publications by Sri Lankan researchers on endemic CKDu carried out in Sri Lanka. The keywords used for the search were as follows: “CKDu” OR “CKD-U” OR “Chronic Kidney Disease” AND “Sri Lanka.”

Fig. 2 Search process illustrated in a PRISMA flowchart for the systematic review

Study selection

Studies were included if (i) the focus of the research was CKDu, (ii) described results from an original study, (iii) published in English, (iv) the study showed a clear distinction between CKD and CKDu, and (v) the study was conducted by Sri Lankans or was a collaborative research that included Sri Lankan researchers. No time restriction on the publishing date was considered. The studies were included first based on the title and next on the abstract. Exclusion criteria were as follows: (i) editorials, reviews, letters, case reports, brief reports, and abstracts, and (ii) studies that analyzed water quality or kidney injury without direct reference to CKDu.

Figure 2 illustrates the literature search and selection of studies according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The search showed 1856+ citations; duplicates were removed and 1324+ citations were excluded based on the title/abstract. A total of 216+ citations were pooled from the three separate literature searches of which 89+ citations were excluded based on the exclusion criteria, reducing the number of included citations/full text articles to be 127+.

These were assessed for eligibility. From the full text review,
8 publications were considered irrelevant resulting in 119 publications to be included in this review.

Analysis

Peer-reviewed original articles on endemic CKDu observed in Sri Lanka conducted by Sri Lankan researchers were included in this systematic review. Relevant information on the aim, objectives, and the findings of different studies was extracted, summarized, and were categorized under appropriate subheadings. This categorization will help in providing a clear view on the major research lapses that exist in the Sri Lankan CKDu research scenario, with a suggested holistic approach, as the way forward.

Studies on prevalence and demography

Individuals with low estimated glomerular filtration rate (eGFR) thereby suffering from CKD in the absence of hypertension, diabetes, and heavy proteinuria are in reality, victims of CKDu (Ruwanpathirana et al. 2019). In 2011, 84% of CKD patients from NCP, with unknown etiology, indicated the prevalence of CKDu. A total of 70% of CKD patients in the NCP were diagnosed with CKDu in 2015 (Jayasekara et al. 2015).

Many studies focused on determining the CKDu prevalence. The point prevalence of population over 18 years of age was 2 to 3% (Chandrajith et al. 2011a, 2011b) and more prevalent in the age group over 40 years with a mean age of 54.7 ± 8 years (Jayasekara et al. 2013). However, CKDu patients are relatively younger than CKD patients (Jayasekara et al. 2015). The onset of renal damage leading to CKDu may set in at a very early age due to exposure to environmental toxins (Orantes-Navarro et al. 2017); CKDu has been reported in 10-15 years old children in the NCP (Jayasekara et al. 2013), with an estimated 8.7% of children manifesting elevated urinary albumin creatinine ratio (UACR).

The prevalence of low eGFR along with elevated UACR (which indicated early renal damage) proves that CKDu in this area has a very early onset (Agampodi et al. 2018).

Population screening conducted in 2011 indicated the female: male ratio of CKDu to be 1:1.13 (Chandrajith et al. 2011a, 2011b) which reportedly increased to 1:2.4 by 2012 (Jayasekara et al. 2013). A 16.9% prevalence of CKDu in females and a 12.9% prevalence in males was reported in 2013 (Jayatilake et al. 2013), contradicting most other studies where a male preponderance was observed (Kafle et al. 2019). Although CKDu prevalence in females was higher, the more severe stages of CKDu were often observed in males (Jayatilake et al. 2013). This is plausible because the male sex is a risk factor in progressing to end stage renal disease (Lipworth et al. 2012). A study conducted in 2015 re-established the male preponderance of CKDu with 1:2.6 female: male ratio (Jayasekara et al. 2015). Latest statistics revealed a threefold higher CKDu prevalence in males (11.2%) than in females (3.7%) (Ruwanpathirana et al. 2019).

CKDu incidence approximately doubles every four to five years; hence, currently, >150,000 individuals are affected by the disease where approximately 3% lose their lives, annually (Sunil 2015). An average of 13 people die prematurely of CKDu on a daily basis (Wimalawansa 2014).

It was recorded that 54% of patients attending the Nephrology Unit, Kandy suffered from CKDu, while up to 82% was recorded at the Renal Clinic, Anuradhapura (Athuraliya et al. 2009). Percentage of CKDu patients that have contributed to CKD prevalence was considerably higher (84%) at Medawachchiya (NCP) compared to 2.9% and 9.1% observed in Yatinuwara (Central province) and Hambantota (Southern province), respectively (Athuraliya et al. 2011).

A cross-sectional study that explored CKDu cases in non-endemic Hambantota reported a 0.43% CKDu prevalence in 2011 (Athuraliya et al. 2011); whereas a study conducted in 2016 reported a prevalence of 6%. Since, Hambantota which is also a part of the dry zone shares a similar socio-economic background and identical farming practices as NCP, and there is a looming possibility of CKDU emergence also in Hambantota (De Silva et al. 2016a, 2016b).

A CKDu prevalence of 9.5% was detected in a 200 patient cohort at the National Hospital, Sri Lanka (Wijewickrama et al. 2011), while another study reported an overall prevalence of 7.5% CKDu patients in the island (Wimalawansa and Wimalawansa 2014). While hospital statistics on morbidity and mortality due to CKDu is underestimated, the disease prevalence and deaths are increasing annually (Ellledge et al. 2016; Wimalawansa 2014).

Etiologic studies

The risk factors of CKDu are surmised to be occupational and environmental. Sri Lankan studies on determining the etiology of CKDu were mainly focused on heavy metals (e.g., Cd, As, and Pb) (Ananda Ananda Jayalal et al. 2019), effects of groundwater (Rango et al. 2015), trace elements (Chandrajith et al. 2011a, 2011b), dehydration alongside with heat stress (Nanayakkara et al. 2020a, 2020b), infections (Gamage et al. 2017), and usage of agrochemicals (Jayasumana et al. 2015a, 2015b, 2015c).

Fluoride (F⁻) exposure via drinking water and its gradual accumulation in the body is nephrotoxic (Fernando et al. 2019a, 2019b, 2019c; Nanayakkara et al. 2020a, 2020b; Perera et al. 2020; Thammitiyagodage et al. 2017). The synergistic influence of F⁻ and water hardness can enhance CKDu (Balasooriya et al. 2019; Wickramarathna et al. 2017), particularly when high elevated levels of...
Mg$^{2+}$ contribute to water hardness (Dharmawardana 2017; Wickramarathna et al. 2017). Positive correlation of F$^-$ to CKDu was also proven to be triggered by water hardness and cadmium (Cd). It may also be attributed to synergetic effect of F$^-$, water hardness and Cd (Wasana et al. 2015a, 2015b). Decreased Na/Ca ratio can aggravate the damage caused by F$^-$, thus, increasing CKDu incidence (Chandrajith et al. 2011a, 2011b). Apart from these, the combination of Na$^+$ and F$^-$ and the secondary combination of Mg$^{2+}$ and F$^-$ in water require further investigation (Paranagama et al. 2018). Aluminofluoride complexes play a significant role in causing CKDu (Ileperuma et al. 2009); however, controversial results were seen when an environmental study concluded F$^-$, aluminum, and aluminofluoride complexes as non-etiological agents of CKDu (Nanayakkara et al. 2014; Wasana et al. 2015a, 2015b). Even though long term Cd exposure is widely suggested to be the main cause of CKDu (Ananda Ananda Jayalal et al. 2019; Bandara et al. 2008; Jayatilake et al. 2013; Perera et al. 2020; Wanasinghe et al. 2018), an equal number of studies exclude Cd as a causative factor (Ayala Herath et al. 2018; Chandrajith et al. 2011a, 2011b; Diyabalanage et al. 2017; Nanayakkara et al. 2014 & Nanayakkara et al. 2019; Wickramarathna et al. 2017). Exploratory studies have found a potential link between CKDu and As toxicity (Amarasinghe et al. 2013). Almost all agrochemicals, especially phosphate fertilizers used by farmers in the NCP, are contaminated with As and provide a strong source of this heavy metal (Jayasumana et al. 2015a, 2015b, 2015c). Chronic lead (Pb) exposure could cause CKDu especially in the presence of other nephrotoxins (Ananda Ananda Jayalal et al. 2019; Levine et al. 2015; Perera et al. 2020). The etiological heavy metal agent, if applicable, still remains inconclusive since several studies indicated that As would not cause CKDu (Ananda Ananda Jayalal et al. 2019; Ayala Herath et al. 2018; Diyabalanage et al. 2017; Nanayakkara et al. 2014 & Nanayakkara et al. 2019; Wickramarathna et al. 2017). Also, a few other studies rule out the hypothesis of Pb as an etiological agent (Ayala Herath et al. 2018; Nanayakkara et al. 2014; Wickramarathna et al. 2017). A novel study analyzing human bone samples of individuals who died of CKDu indicated a higher chronic Pb exposure where the F$^-$ content was also high. This led researchers to conclude that Pb exposure reduced the GFR and at a certain threshold of low GFR, F$^-$ excretion will be impaired. This F$^-$ accumulation in blood may exacerbate nephrotoxicity which can further trigger GFR deterioration (Bulathge et al. 2020). A high number of CKDu patients were detected in areas with elevated concentrations of soil vanadium (Jayawardana et al. 2015). The hypothesis of chromium (Cr) as an etiological agent of CKDu was also ruled out (Ayala Herath et al. 2018). Ions such as zinc (Zn), iron (Fe), and selenium (Se) are capable of suppressing the toxicity caused by Cd, F, and As (Dharmawardana 2017).

The safe levels of heavy metals in drinking water in endemic areas can indeed cause kidney dysfunction due to its unique hydrogeochemistry resulting in CKDu. Hence, use of spring water is encouraged at least for drinking purposes (Babich et al. 2020; Chandrajith et al. 2011; Jayasekara et al. 2015). Consumption of untreated well water and history of drinking water from an abandoned well were found to be causative factors for CKDu (Balasubramanya et al. 2020; de Silva et al. 2017; Dharmawardana 2017; Jayasumana et al. 2014 & Jayasumana et al. 2015a, 2015b, 2015c). Origin, recharge mechanism, and the flow pattern of groundwater with the geological conditions that can cause groundwater contamination are suggested as the main etiological factors for CKDu (Wijayawardane et al. 2018). Drinking water also is likely to be a contributory factor towards the progression of CKDu (Siriwardhana et al. 2018). However, yet another study concluded that due to the lack of correlation of trace element concentrations between urine and water samples, it is highly unlikely for drinking water to be an etiological agent of CKDu and that food or tobacco could be the non-water sources of the toxic chemicals (Rango et al. 2015). It is also implausible that water supplied by the irrigation projects of Mahaweli river to be directly related to CKDu etiology (Diyabalanage et al. 2015; Weeraratna and Wimalawansa 2015).

Agrochemicals are assumed to be a very prominent causative factor for CKDu. Intensive agrochemical usage was a result of government agricultural resettlement policies with the introduction of mechanized monocrop agriculture instead of the organic multi crop agriculture (de Silva et al. 2017).

CKDu is associated with farmers spraying pesticides (ex: glyphosate) with minimal use of personal protective equipment (Jayasumana et al. 2014; Ileperuma et al. 2009). Specifically, bispyribac-sodium (a weedicide), organophosphate compounds (in insecticides), and monocozeb (a broad-spectrum, contact fungicide) increase CKDu risk (Jayasumana et al. 2014; Peiris-John et al. n.d.). CKDu supports a toxicological origin but it is onerous to localize a single nephrotoxin; hence, it may be concluded that the synergistic effects of agrochemicals and heavy metals in concert may cause CKDu (Jayasumana et al. 2015a, 2015b, 2015c). In addition to excessive fertilizer usage, conduits moving fertilizer to NCP via irrigation systems increase the ionicity of water. It has been suggested that usage of water with a high ionicity to play a major etiological role in CKDu (Dharmawardana et al. 2015). However, neonicotinoids were eliminated as a causative agent (Kabata et al. 2016).

A study claims that dehydration is likely to contribute to CKDu development (Siriwardhana et al. 2015). Conversely, another report refutes this hypothesis (Jayasekara et al.
yet, dehydration seems to have an indirect effect in CKDu pathogenesis. This may be so, as tubular epithelial cells are exposed to a higher concentration of environmental toxins due to the formation of concentrated urine (Nanayakkara et al. 2020a, 2020b). Hantavirus was hypothesized as a possible risk factor for CKDu (Gamage et al. 2017). Another study hypothesized both hantavirus and leptospirosis as causative agents (Gamage and Sarathkumara 2016). However, individuals with hantavirus exposure were exclusively found to be at a higher risk of CKDu (Sarathkumara et al. 2019; Sunil-Chandra et al. 2020). A past leptospirosis infection was not associated with the etiology of CKDu (Sunil-Chandra et al. 2020). An association was established between CKDu disease progression and hypertension (Seneviratna et al. 2012). Furthermore, past history of malaria is likely to contribute to CKDu development (Siriwardhana et al. 2015).

Selenium deficiency along with nephrotoxin exposure can be a predisposition to CKDu (Levine et al. 2015). Genetic susceptibility coupled with environmental exposure, lifestyle, and behavior can result in CKDu (Levine et al. 2015; Wanigasuriya et al. 2007). Neither the food consumption pattern nor ochratoxin A in food commodities were proven to be etiological agents (Siriwardhana et al. 2014; Wanigasuriya et al. 2008).

Most of these studies, based on small sample sizes, explored a single hypothesized causative factor. Complex interactions between the etiological agents were disregarded, yet the stand remains inconclusive with no single etiological factor implicated for CKDu (Vlahos et al. 2019). The absence of a clear approach to elucidate the etiology of this disease has left vulnerable citizens with a high degree of concern on the risks of farming.

Despite efforts to understand the epidemiology and etiology of CKDu, several other queries remain unresolved or with the need of further explanations that include pathological and clinical features (Anand et al. 2019) and the symptom burden of CKDu (Senanayake et al. 2017).

Table 1 summarizes the aforementioned studies categorized according to etiological agent/factor tested, type of study carried out (in vitro/human/in vivo animal), and the potential role in the etiology of CKDu.

CKDu = chronic kidney disease of unknown etiology; F = fluoride; Cd = cadmium; Pb = lead; Na = sodium; Ca = calcium; Mg = magnesium; As = arsenic; V = vanadium; SNP = single nucleotide polymorphism; Se = selenium; Cr = chromium

**Studies on CKDu symptoms**

A majority (95%) of the CKDu patients reported at least a single symptom while 55.8% manifested five or more (Abeywickrama et al. 2020). Difficulty in keeping legs still, bone/joint pain, feeling irritable, muscle cramps, loss of appetite, and lack of energy were the most common reported symptoms among CKDu patients (Abeywickrama et al. 2020; Senanayake et al. 2017). Depression and psychological distress contributed to the psychological symptom burden. The high physical and psychological symptom burden and the inferior socio-economic status were associated with a low health-related quality of life (HRQOL) of CKDu patients (Senanayake et al. 2020).

**Clinico-pathological studies**

The predominant histopathological forms of CKDu are mostly compatible with chronic tubulointerstitial nephritis (TIN) (Selvarajah et al. 2016), which is caused due to environmental toxic exposure (Nanayakkara et al. 2012a, 2012b). Among the other dominant histopathological observations were interstitial fibrosis (the earliest detectable pathological change), tubular atrophy, and glomerular sclerosis (Nanayakkara et al. 2012a, 2012b; Selvarajah et al. 2016; Wijetunge et al. 2013). Interstitial inflammation has a definitive role in CKDu progression (Wijetunge et al. 2013). Glomerular collapse, interstitial infiltration, and vascular pathological features such as fibrous intimal thickening and arteriolar hyalinosis are also common (Nanayakkara et al. 2012a, 2012b; Selvarajah et al. 2016). CKDu is associated with less arterial stiffening than CKD (Gifford et al. 2016). When a study correlated the aforementioned prominent histopathological changes with clinical stages of CKDu put forward by the National Kidney Foundation, based on the individual eGFR values, the following were reported (Table 2) (Wijetunge et al. 2015).

Accordingly, a significant proportion of these patients were asymptomatic at all clinical stages (Wijetunge et al. 2015).

Acute episodes of interstitial nephritis observed in healthy individuals of CKDu endemic areas are followed by a pathological process that leads to CKDu. Therefore, these symptomatic healthy individuals must undergo periodic surveillance for early CKDu detection (Badurdeen et al. 2016). Therefore, validating approaches for proper clinical diagnostics is crucial.

**Diagnostic studies**

A 3-level case definition published by the Ministry of Health in November 2016 to identify CKDu in Sri Lanka was refined and updated by the Sri Lanka Society of Nephrology (SLSN). Accordingly, CKDu in Sri Lanka consists of 3 tiers of diagnosis:

(i) Suspected CKDu—relevant for the primary care level
(ii) Probable CKDu—for epidemiologic surveillance
### Table 1: Compilation of Sri Lankan research studies on etiological factors of CKDu

| Etiological agent (s) or factor (s) | Type of study (in vitro/human/animal) | Potential role in etiology | Reference |
|-----------------------------------|--------------------------------------|---------------------------|-----------|
| F⁻ | Human | Nephrotoxic | (Fernando et al. 2019a, 2019b, 2019c; Nanayakkara et al. 2020a, 2020b) |
| F⁻ and water hardness | Animal (Wistar rats) | Possibly etiological | (Thammitiyagodage et al. 2017) |
| F⁻, water hardness, and Cd (synergistic effect) | Human | Enhance CKDu | (Wickramarathna et al. 2017) |
| F⁻ and other ions in hard water | Human | Etiological | (Wasana et al. 2015a, 2015b) |
| F⁻, Cd, and Pb | Human | F⁻—nephrotoxic, Cd—etiological, Pb—etiological | (Dharmawardana 2017) |
| Na/Ca ratio aggravate the damage caused by F⁻ | Human | Etiological | (Chandrajith et al. 2011a, 2011b) |
| F⁻-Na combination and the secondary combination of F⁻ and Mg | Human | Need further investigation | (Paranagama et al. 2018) |
| F⁻, aluminum, and aluminofluoride complexes | Human | Non-etiologial | (Wasana et al. 2015a, 2015b) |
| Cd | Human | Etiological | (Bandara et al. 2008; Wanasinghe et al. 2018) |
| Cd, Pb, and As | Human | Cd—main cause of CKDu, Pb—etiological, As—non-etiological | (Ananda Ananda Jayalal et al. 2019) |
| Cd and As | Human | Non-etiologial | (Diyabalanne et al. 2017; Nanayakkara et al. 2019) |
| Cd, Pb, As, and Cr | Human | Non-etiologial | (Ayala Herath et al. 2018) |
| As toxicity | Human | Potential link to CKDu | (Amarasinghe et al. 2013) |
| V | Human | High number of CKDu patients in areas with high V content in soil | (Jayawardana et al. 2015) |
| Cd, As, Pb, and genetic susceptibility | Human | Cd, As, Pb—non-etiological, Major genetic susceptibility for SNP in SLC13A3 | (Nanayakkara et al. 2014) |
| Cd, Se deficiency, and genetic susceptibility | Human | Cd—major etiological role, Se deficiency, genetic susceptibility—predisposing factors for CKDu | (Jayatilake et al. 2013) |
| Genetic susceptibility and environmental exposure | Human | Etiological | (Wanigasuriya et al. 2007) |
| Drinking water | Human | Etiological | (Siriwardhana et al. 2018) |
| Metals in drinking water | Animal (zebra fish—Danio rerio) | Cause kidney dysfunction | (Babich et al. 2020) |
| Unique hydrogeochemistry of drinking water | Human | Etiological | (Chandrajith et al. 2011a, 2011b) |
| High water ionicity | Human | Major etiological role | (Dharmawardana et al. 2015) |
| Natural spring water | Human | Reduce CKDu risk | (Jayasekara et al. 2015) |
| Water from Mahaweli River | Human | No direct etiologial role | (Weeraratna and Wimalawansa 2015) |
| History of drinking water from an abandoned well, glyphosate, other pesticides | Human | Etiological | (Jayasumana et al. 2015a, 2015b, 2015c) |
| Drinking water, food, tobacco | Human | Drinking water—no etiological role, Food, tobacco—sources of toxic chemicals | (Rango et al. 2015) |
| Staple food, food consumption pattern | Human | Non-etiologial | (Siriwardhana et al. 2014) |
The ideal method to diagnose CKDu is via analyzing renal tissue, yet obtaining biopsies is invasive, expensive, and unsuitable for initial screening (Kumar and S. S. 2002). The initial tool for screening CKDu is the semi-quantitative dipstick proteinuria which can detect macro albuminuria in late CKDu stages. This biomarker is not optimal to detect early stage CKDu (Jayasekara et al. 2015). Serum creatinine (S.Cr) and UACR (renal damage marker) appear to be more sensitive than dipstick proteinuria. Cystatin C was found to be the most sensitive and specific but costly. UACR, individually, has inferior sensitivity. This study also suggests lowering of the current UACR cutoff limit below 30 mg/g to improve CKDu detection (Ratnayake et al. 2017).

Also, the three clinical characteristics—age, urine dipstick proteinuria, and serum albumin—jointly could predict the likelihood of CKDu (Anand et al. 2019).

Biomarker discovery is becoming increasingly important in medicine because of the potential for early screening and for facilitating a more personalized approach to medical care (Wasung et al. 2015).

Urine is considered an excellent source for biomarkers since markers resulting from the pathophysiological processes in the kidney are released into urine (Fernando et al. 2019a, 2019b, 2019c). Urinary KIM-1 (kidney injury molecule) is a good predictor for renal injury prior to detectable eGFR changes (Ichimura et al. 1998). This can be used as a biomarker for early CKDu detection (De Silva et al. 2016a, 2016b). While the marker combination of A1M (alpha 1 microglobulin), KIM1, and RBP4 (retinol binding protein 4) can differentiate all CKD categories (CKD + CKDu) from healthy controls, the marker combination OPN (osteopontin), KIM1, and RBP4 can distinguish CKDu patients from CKD (Fernando et al. 2019a, 2019b, 2019c). Fibrinogen and β-2 microglobulin are also suggested as potential tools for CKDu screening but need further validation (Wanigasuriya et al. 2017).

Since kidney injury is initiated with the induction of molecular level changes, identification of molecular markers can be much promising (Wasung et al. 2015). A
panel consisting of IGFBP1 (insulin like growth factor binding protein 1), KIM1, GCLC (glutamine cysteine C subunit), and GSTM1 (glutathione S transferase mu 1) genes could be used in combination for early screening of CKDu whereas these genes alongside FN1 (fibronectin 1), IGFBP3 (insulin-like growth factor binding protein 3), and KLK1 (kallikrein 1) could be used to monitor the progression of CKDu. Nevertheless, these biomarkers must be validated using larger populations prior to clinical use (Sayanthooran et al. 2017).

Hypothetically, if both environmental and genetic predisposition to CKDu are factual, this may be associated with epidermal ridge formation thereby leading to both digital and palmar dermatoglyphic asymmetry which can be used as a non-invasive CKDu diagnostic tool (Thilanga et al. 2020). Mechanisms responsible for the fluctuating asymmetry (FA) observed in CKDu patients may be associated with mechanisms responsible for CKDu development. A diagnostic tool based on FA could be developed for predicting the risk for CKDu prior to its development (Thilanga et al. 2020).

**Biochemical studies**

Hitherto, very few studies focused on identifying specific biochemical manifestations of CKDu. However, several studies on clinical features outlined some of the related key biochemical parameters.

In CKDu patients, the median level for sodium, potassium, calcium, phosphorous, urea, uric acid, total protein, albumin, and bicarbonate within the body was normal and within the reference intervals except for elevated serum creatinine, amylase, alkaline phosphatase, and decreased vitamin D and hemoglobin levels. The level of C-reactive protein was normal while thyroid stimulating hormone (TSH), parathyroid hormone (PTH), ferritin, and calcium remained normal. Liver disease markers, serum glutamic pyruvic transaminases/alanine aminotransferase (SGPT/ALT), serum glutamic oxaloacetic transaminases/aspartate transaminase (SGOT/AST), gamma-glutamyl transferase (GGT), and lactic acid dehydrogenase (LDH) had an inverse correlation with the advancement of the disease indicating subclinical liver disease (Fernando et al. 2020).

Disease severity of CKDu is associated with the prevalence of anemia. The crucial etiological factor for a majority of the patients is iron deficiency while the rest remains unexplained which needs further elucidation (Warnakulasuriya et al. 2019). Furthermore, low BMI may increase the risk of developing CKDu. This condition can compromise the ability in repairing their damaged kidneys and their tolerance to illness (Kulathunga et al. 2020).

**Molecular biological studies**

Familial clustering of CKDu observed among the patients suggests the possibility of genetic susceptibility to the disorder (Nanayakkara et al. 2012a, 2012b; Wanigasiriya et al. 2007). However, CKDu is multifactorial disease, supporting the hypothesis that pathogenesis occurs in genetically susceptible individuals exposed to environmental toxins (Majewski et al. 2011).

Three genetic variants in LAMB2 (Laminin beta2) and a single variant in KCNA10 (potassium voltage-gated channel sub family A member 10) can be observed exclusively among CKDu cases (Nanayakkara et al. 2015). Also, a significant SNP (single nucleotide polymorphism) in SLC13A3 (sodium-dependent dicarboxylate transporter member 3) gene indicates a major genetic susceptibility to CKDu. Therefore, further research is necessary to elucidate the link of SNP rs6066043 with CKDu (Nanayakkara et al. 2014). Moreover, unraveling the expression patterns of genes in CKDu endemic populations will pave the path for a better understanding of the disease (Sayanthooran et al. 2016).

Upregulation of genes related to oxidative stress, such as FGF23 (fibroblast growth factor-23), NLRP3 (NLR family pyrin domain containing 3), GCLC, and GSTM1, is observed in CKDu and CKD patients with a greater than threefold and twofold upregulation of GCLC and GSTM1, respectively. This is indicative of the higher influence of external sources in causing oxidative stress in CKDu patients (Sayanthooran et al. 2016).

Activation of the molecular processes such as innate immune responses, interferon signaling, and inflammasome signaling pathways and the decreased activity of EIF2 (Eukaryotic Initiation Factor 2) signaling and mTOR (mammalian target of rapamycin) signaling can be witnessed in CKDu, clearly indicating the presence of a viral infection. Activation of pathways linked to fluoride toxicity, G-protein activation, cell division cycle 42 (Cdc42) signaling, Rac signaling, and RhoA (Ras homolog family member A) signaling in CKDu patients confirm of possible fluoride toxicity. Cell death, cell movement, and anti-microbial responses are among the biological functions activated whereas mitochondrial dysfunction, oxidative stress, and apoptosis are the toxicological functions activated in CKDu patients (Sayanthooran et al. 2018).

**Studies on new inventions and possible interventions**

Eradicating CKDu through proper disease prevention programs, medicine, and healthcare collectively with efficient diagnosis is crucial (Chung et al. 2015; Wimalawansa 2019). CKDu can be eradicated within 15 years by implementing a
focused chronic disease prevention plan and by using essential interventions (Wimalawansa 2019).

According to aforementioned reasons, diagnosis of CKDu in rural areas is challenging due to the lack of highly sensitive and specific techniques that can be applied in rural settings. A semi-automated, point of care technique, “micro-urine nanoparticle detection” (μUNPD), presented in 2015, was facilitated using a hand-held magnetic device. Markers of kidney injury such as KIM-1 and Cystatin C were detected up to 0.1 ng/ml and 20 ng/ml concentrations, respectively (Chung et al. 2015).

Resorting to organic agriculture which can sustain the health of soils, ecosystems, and people, has been identified as a sustainable solution to the prevention/reduction of the CKDu disease (Ranasinghe 2016). The importance of organizing an agricultural development program based on ecological sustainability, agricultural diversification, and social justice for the landless farmers in the Sri Lankan dry zone has been highlighted (de Silva et al. 2017).

Biomedical interventions are used in the hospitals for CKDu disease management, community programs to conduct mass blood surveys and well water testing, and in the food and health education programs carried out in the village health communities. These approaches enlighten the public via media which is identified as bio-media citizenship (de Silva 2018).

Traditional Sri Lankan medical treatment can be considered as an alternative, cost effective, and an efficient approach since it does have a significant effect in controlling CKDu progression (Kumarasinghe et al. 2019).

**Anthropological and sociological studies**

CKDu research by Sri Lankan scientists has been largely undertaken from epidemiological and biomedical perspectives. Additional studies that address social and behavioral needs of CKDu patients must be conducted. Anthropological studies on health and disease depict the knowledge, beliefs, and practices of a community, and how such information could probably be used to improve provision of health care (Kleinman et al. 2006).

Media reports on biomedical, epidemiological, and sociocultural research into CKDu etiology have strengthened the specific perspective in society that polluted water has a direct relationship to CKDu. This belief has changed the behavior of residents of CKDu endemic zones towards water consumption (de Silva 2019).

Societal issues such as inappropriate agricultural and water policies, poor governance, and limited access to clean municipal water supplies exist. There are also economic implications such as loss of human capital and families losing assets to pay for their health issues. The study highlighted the need for implementing a water quality management strategy, educational programs, and health monitoring programs in the region (Pinto et al. 2020).

**Discussion**

This compilation of research studies on CKDu in Sri Lanka has explored the probable causative agents of the disease, yet present conflicting conclusions on CKDu etiology. Thus, relevant, well planned, high quality research studies are critically warranted. However, the research findings reported here, it may be hypothesized that CKDu is a multifactorial disease linked to the environment, agricultural practices, and genetic predispositions.

Apart from etiological studies, clinico-pathological studies evaluating the renal tubular functions in CKDu patients, studies suggesting non-invasive and alternative ways of CKDu diagnosis instead of the gold standard-renal biopsy, alternative therapies of treatment, molecular biological, biochemical, and sociological studies were performed. Molecular biological studies have advanced to studying the expression patterns of genes in CKDu endemic populations paving the way for a better understanding of the disease. Nevertheless, further in-depth research is vital to elucidate the genetic predisposition to CKDu. The focus on anthropological perspectives of CKDu, to a certain extent, has been fulfilled.

Despite these studies, major deficits exist in the Sri Lankan CKDu research scenario. Links to low BMI and malnutrition require further study. Research to examine potential ethnicity and genetic links, illicitly brewed alcohol consumption (kasippu), health, and diet surveillance, is justified. Immunological and microbial aspects of CKDu need a significant focus but remain largely unexplored. Exposure to different environments influences changes in an individual’s microbiome, which may correlate with the changes in the immunology of CKDu. These aspects, thus far, have not been investigated.

There were previous attempts to collate the research done at regional and local levels (Abraham et al. 2019; WHO 2016). However, they lack a comprehensive framework to understand the range of studies and do not provide a conceptual base to propose future directions for research. Our approach has been to place the research work using a One Health approach in a system dynamics framework and integrate with a novel tool available to understand the roles of the aetiological factors, namely, exposomes.

Future research, quantifying interactions between the different etiological factors and unique features related to CKDu using methods such as systems dynamics modeling which can conceptualize the complex causative agents, is warranted, rather than the traditional statistical analyses which assume the presence of independent factors.
influencing the disease outcome in a linear fashion (Jayasinghe and Zhu 2020).

A more detailed system dynamics model encompassing the One Health approach was developed by the first author using the conclusions based on published studies in Figure 3. This attempts to capture the complex systems existing between the environment, animals, and the human society (One Health approach) in relation to CKDu epidemic in Sri Lanka (Conrad et al. 2013).

The “One Health Approach” is an important concept which focuses on the inter-relationships and inter-connections among humans, animals, and the environment. The health and well-being of humans are intimately linked with the health of animals and their environment (Kahn 2011). Instead of the individual or disease centered approach promoted currently, One Health promotes an integrated community-based concept (Conrad et al. 2013). Evidence exists for feasibility of integration from across all 3 sectors of human, animal, and environmental health (Buttke 2011). Collaborative research on CKDu would be more beneficial and sustainable, thereby focusing on all the general aspects instead of the finer details of a solitary factor (Conrad et al. 2013).

A single, One Health focused survey was conducted for a pilot case control study in Sri Lanka to evaluate the relationships between key demographic, cultural, behavioral, and occupational variables as risk factors for CKDu. The study suggested future research to be focused on practices associated with chewing betel, potential animal interactions including pests in the home and pets and risk factors associated with water. This study, however, did not include extensive details on genetic, nutritional, and microbial aspects (Pry et al. 2021). Yet, the One Health approach has been successfully used in eradicating chronic and zoonotic diseases worldwide.

For example, Hendra virus (HeV), a zoonotic paramyxovirus (for which natural reservoirs are bats), infected humans who had a strong epidemiologic link to similarly affected horses. Even if no human case was attributed to direct spill-over from bats, being the natural reservoirs of the virus, eradication of bat populations was discussed. This is despite their crucial roles in the environment and the development of a vaccine for horses had the potential to interrupt the HeV transmission chain from bats to horses to human. This is an application of One Health approach is not just in terms of interconnected human and animal but also with respect to animal health (Middleton et al. 2014). Nonetheless, targeting humans, animals, and the environment separately can be inadequate when utilizing the One Health approach (Gao

Fig. 3 A system dynamics model of the Sri Lankan CKDu epidemic

© Springer
Wild first introduced the exposome concept in 2005, which includes total environmental exposures within an individual’s lifetime (Wild 2005). Hence, the idea is to capture the diverse chemical, biological, and physical stressors in the environment and their induced physiological responses (Vermeulen et al. 2020). The diverse stressors can be either general external (climate, education, financial status, urban, or rural environment), specific external (chemicals, radiation, physical activity, diet, occupation, and infections), and internal (metabolism, gut microbiota, inflammation, and epigenetics) environments. Longitudinal environmental exposure from conception to death can also be considered (Wild 2012). Identifying the exposome affecting CKDu together with all variables from effects to results via research can be difficult; hence, the general goal of exposome studies is to capture the stressors to the greatest degree possible to reflect the holistic impact (Gao 2021). Due to the increasing recognition of non-genetic factors of CKDu, it is necessary to characterize the exposome in addition to the genome (Li et al. 2019).

Though both the “One Health” and the “exposome” are broad concepts, they provide promising integrated approaches to investigate the complex environment (Jiang et al. 2018). The current COVID-19 pandemic illustrates the significance of studying the relationships between human and animal health regarding their biological stressors and related exposure pathways (Tiwari et al. 2020). If the SARS-CoV-2 virus was discovered earlier on by the exposome approach and the COVID-19 zoonotic disease gave an early warning by the abnormal behavior of animals, researchers would have had more time to develop therapeutic and vaccine plans before the pandemic outbreak (Gao 2021). Exposome approach on CKDu can provide significant insight into identifying what exposures need to be evaluated further under One Health.

Assessing the risk for One Health should be carried out to estimate the impact on human, animal, and environmental health due to the exposure to environmental stressors in the exposome such as agrochemicals, pests, microbiota, and genetics. The concept of multiple stressors of the exposome and numerous receptors in One Health is ideal to gain a comprehensive, holistic risk assessment of CKDu (Gao 2021). Integrating the concepts of one health and the exposome should include species, stressors, pathways, and interactions for a given environment and assess the risks that fit into the goals of One Health.

Current technological developments such as next generation sequencing and high resolution mass spectrometry which can identify the numerous stressors in exposome and receptors in “One Health” make it possible to understand our environment better, thereby to efficiently fight against chronic diseases. Therefore, investigating the combined effects of the multiple stressors present across multiple species within the concepts of one health and exposome would be the best as shown in Figure 4.

Conclusions

This review exclusively focused on studies on the CKDu epidemic in Sri Lanka conducted with links to Sri Lankan institutions or researchers. This exposition included all research publications up until September 2020.

Research on CKDu thus far has targeted etiologic factors in silos. We propose using the One Health approach collectively with the exposome on the CKDu epidemic, thereby quantifying interactions between the environmental, animal, human systems, and the totality of exposures the individual undergoes since birth (Abraham et al. 2019).

Acknowledgements The authors profusely thank Mr. Praneeth Ratnayake, Research Assistant, Department of Zoology and Environment Sciences, Faculty of Science, University of Colombo, for preparing Figures 1 and 4.

Author contribution DA reviewed the literature, performed the analysis, and drafted the manuscript. PU conceptualized the paper, significantly contributed on the concepts of One Health and Exposome, helped writing the manuscript, and revised the final manuscript. SJ contribute on the concept of systems dynamic models, read, and revised the final manuscript. All authors read and approved the final manuscript.

Data Availability Data was not generated nor analyzed in this review. All material used for the study are listed under references.
Declarations

Ethics approval and consent to participate  Not applicable.

Consent for publication  Not applicable.

Competing interests  The authors declare no competing interests.

References

Abeywickrama HM, Wimalasiri S, Koyama Y, Uchiyama M, Shimizu U, Kakihara N et al. (2020) Quality of life and symptom burden among chronic kidney disease of uncertain etiology (CKDu) patients in Girandurukotte, Sri Lanka. Int J Environ Res Public Health 17(11):1–16. https://doi.org/10.3390/ijerph17114041

Abraham G, Agarwal SK, Gowrishankar S, Vijayan M. (2019) Chronic kidney disease of unknown etiology: hotspots in India and other Asian countries. Semin Nephrol 39(3):272–277. https://doi.org/10.1016/j.semnephrol.2019.02.005

Agampodi SB, Amarasinghe GS, Naotunna PGCR, Jayasumana CS, Siribaddana SH. (2018) Early renal damage among children living in the region of highest burden of chronic kidney disease of unknown etiology (CKDu) in Sri Lanka. BMC Nephrol 19(1):1–8. https://doi.org/10.1186/s12882-018-0911-8

Amarasinghe MD, Lanka S, Lanka S, Hospital G, Lanka S, Hospital DG et al. (2013) Possible link of chronic arsenic toxicity with chronic kidney disease of uncertain etiology in Sri Lanka. J Nat Sci Res 3(1):64–73

Anand S, Montez-Rath ME, Adasooriya D, Ratnatunga N, Kambham N, Wazil A et al. (2019) Prospective biopsy-based study of CKD of unknown etiology in Sri Lanka. Clin J Am Soc Nephrol 14(2):224–232. https://doi.org/10.2215/CJN.07403618

Ananda Ananda Jayalal TB, Jayaruan Bandara TWMA, Mahawithanage STC, Wansapala MAJ, Galapaththi SPL. (2019) A quantitative analysis of chronic exposure of selected heavy metals in a model diet in a CKD hotspot in Sri Lanka. BMC Nephrol 20(1):1–14. https://doi.org/10.1186/s12882-019-1371-5

Athuraliya NTC, Abeysekera TDJ, Amerasinghe PH, Kumarasiri R, Bandara P, Karunarathne U, Jones AL. (2011) Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. Kidney Int 80(11):1212–1221. https://doi.org/10.1038/ki.2011.258

Athuraliya TN, Abeysekera DT, Amerasinghe PH, Kumarasiri PV, Disanayake V. (2009) Prevalence of chronic kidney disease in two tertiary care hospitals: high proportion of cases with uncertain aetiology. Ceylon Med J 54(1):23–25. https://doi.org/10.4038/cmj.v54i1.471

Ayala Herath HMS, Kawakami T, Nagasawa S, Serikawa Y, Motoyama A, Tushara Chaminda GG, Amarasooriya AAG (2018) 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 16(2):212–222. https://doi.org/10.2166/wh.2018.070

Babich R, Ulrich JC, Ekanayake EMV, Massarsky A, De Silva PMCS, Manage PM et al. (2020) Kidney developmental effects of metal-herbicide mixtures: implications for chronic kidney disease of unknown etiology. Environ Int 144(March). https://doi.org/10.1016/j.envint.2020.106019

Badurdeen Z, Nanayakkara N, Ratnatunga NVI, Wazil AWM, Abeysekera TDJ, Rajakrishna PN et al. (2016) Chronic kidney disease of uncertain etiology in Sri Lanka is a possible sequel of interstitial nephritis! Clin Nephrol 86:106–109. https://doi.org/10.5414/CNP86S115

Balasooriya S, Munasinghe H, Herath AT, Diyabalanage S, Ileperuma OA, Manthrihilake H et al. (2019) Possible links between groundwater geochemistry and chronic kidney disease of unknown etiology (CKDu): an investigation from the Ginnoruwa region in Sri Lanka. Expo Health 0123456789. https://doi.org/10.1007/s12403-019-00340-w

Balasubramanya S, Stiefel D, Hornbulyk T, Kafle K. (2020) Chronic kidney disease and household behaviors in Sri Lanka: historical choices of drinking water and agrochemical use. Econ Hum Biol 37. https://doi.org/10.1016/j.ehb.2020.100862

Bandara JMR, Senevirathna DMAN, Dasanayake DMRSB, Herath V, Bandara JMRP, Abeysekara T, Rajapaksha KH. (2008) Chronic renal failure among farm families in cascade irrigation systems in Sri Lanka associated with elevated dietary cadmium levels in rice and freshwater fish (Tileapia). Environ Geochem Health 30(5):465–478. https://doi.org/10.1007/s10653-007-9129-6

Bello AK, Levin A, Tonelli M, Okpechi IG, Fearhally J, Harris D et al. (2017) Assessment of global kidney health care status. JAMA 317(18):1864–1919. https://doi.org/10.1001/jama.2017.4046

Bulathge T, Ananda Jayalal A, Thushara S, Mahawithanage C. (2020) Evidence of selected nephrotoxic elements in Sri Lankan human autopsy bone samples of patients with CKDu and controls. BMC Nephrol 21(1):1–14. https://doi.org/10.1186/s12882-020-02049-4

Buttke DE. (2011) Toxicology, environmental health, and the “One Health” concept. J Med Toxicol 7(4):329–332. https://doi.org/10.1007/s13181-011-0172-4

Chandrajith R, Disanayake CB, Ariyaratna T, Herath HMMJK, Padmasri JP. (2011a) Dose-dependent Na and Ca in fluoride-rich drinking water -another major cause of chronic renal failure in tropical arid regions. Sci Total Environ 409(4):671–675. https://doi.org/10.1016/j.scitotenv.2010.05.046

Chandrajith R, Nanayakkara S, Itai K, Aturatiya TNC, Disanayake CB, Abeysekera T et al. (2011b, September) Chronic kidney diseases of uncertain etiology ( CKDu ) in Sri Lanka : geographic distribution and environmental implications. Environ Geochim Health 33:267–278. https://doi.org/10.1016/j.s10653-010-9339-1

Chung HJ, Pellegrini KL, Chung J, Wanigasuriya K, Jayawardene I, Lee K et al. (2015) Nanoparticle detection of urinary markers for chronic kidney disease and household behaviors in Sri Lanka. PLoS One 10(7):1–11. https://doi.org/10.1371/journal.pone.0133417

Codreanu I, Perico N, Sharma SK, Schieppati A, Remuzzi G. (2006) Prevention programmes of progressive renal disease in developing nations. 11, 321–328. https://doi.org/10.1111/j.1440-1797.2006.00587.x

Connor PA, Meek LA, Dumit J. (2013) Operationalizing a One Health approach to global health challenges. Comp Immunol Microbiol Infect Dis 36(3):211–216. https://doi.org/10.1016/j.cimid.2013.03.006

Cooray T, Wei Y, Zhong H, Zheng L, Weragoda SK, Weerasooriya R. (2019) Assessment of groundwater quality in CKDu affected areas of Sri Lanka: implications for drinking water treatment. Int J Environ Res Public Health 16(10). https://doi.org/10.3390/ijerph16101698

de Silva MWA (2018) Bio-media citizenship and chronic kidney disease of unknown etiology in Sri Lanka. Med Anthropol Cross Cult Stud Health Illness 37(3):221–235. https://doi.org/10.1080/01459740.2017.1311886

de Silva MWA (2019) Drinking water and chronic kidney disease of unknown aetiology in Amuradhapura, Sri Lanka. Anthropol Med 26(3):311–327. https://doi.org/10.1080/13648470.2018.1446822

de Silva MWA, Albert SM, Jayasekara JMKB (2017) Structural violence and chronic kidney disease of unknown etiology in Sri Lanka. Soc Sci Med 178:184–195. https://doi.org/10.1016/j.soscimed.2017.02.016
De Silva PMCS, Mohammed Abdul KS, Eakanayake E. B. K.-1 and N. for D. of C. K. D. of U. E. (CKDu) among A. C. in S. L. M. D. V., Jayasinghe, S. S., Jayasumana, C., Asanthi, H. B., … Siribaddana, S. H. (2016a). 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, 10(9), 1–17. https://doi.org/10.1371/journal.pntd.0004979

Dharmawardana MWC (2017) Chronic kidney disease of unknown etiology and the effect of multiple-ion interactions. Environ Geochim Health 40(2):705–719. https://doi.org/10.1007/s10653-017-0017-4

Dharmawardana MWC, Amarasiri SL, Dharmawardene N, Panabokke CR (2015) Chronic kidney disease of unknown aetiology and ground-water iontotoxicity: study based on Sri Lankan. Environ Geochim Health 37(2):221–231. https://doi.org/10.1007/s10653-014-9641-4

Diyabalalage S, Abeekoon S, Watanabe I, Watai C, Ono Y, Wijesekara S et al (2015) Has irrigated water from Mahaweli River contributed to the kidney disease of uncertain etiology in the dry zone of Sri Lanka? Environ Geochim Health 38(3):679–690. https://doi.org/10.1007/s10653-015-9749-1

Diyabalalage S, Fonseka S, Dasanayake DMSNB, Chandrajith R (2017) Environmental exposures of trace elements assessed using keratinitized matricies from patients with chronic kidney diseases of uncertain etiology (CKDu) in Sri Lanka. J Trace Elem Med Biol 39:62–70. https://doi.org/10.1016/j.jtemb.2016.08.003

El Nahas AM, Bello AK (2005) Chronic kidney disease: the global challenge. Lancet 365(9456):331–340

Elledge MF, Redmon JH, Levine KE, Wickremasinghe RJ, Waniagasariya KP, John, R. J. P.-. (2016) Chronic kidney disease of unknown etiology in Sri Lanka: quest for understanding and global implications - RTI Press Research Brief - NCBI Bookshelf. Environ Monit Assess 188(10):1–16. https://doi.org/10.1007/s10653-014-0007-1405

Fernando BNTW, Alli-shaik A, Hemage RKD, Badurdeen Z, Het-tiarachchi TW, Abey sundara HTK, Abeysekara TDJ (2019a) Pilot study of renal urinary biomarkers for diagnosis of CKDu of uncertain etiology. Kidney Int Rep. https://doi.org/10.1016/j.ekir.2019.07.009

Fernando BNTW, Sudeshika TSH, Hettiarachchi TW, Badurdeen Z, Abeysekara TDI, Abey sundara HTK et al (2020) Evaluation of biochemical profile of chronic kidney disease of uncertain etiology in Sri Lanka. PLoS One 15(5):1–14. https://doi.org/10.1371/journal.pone.0232522

Fernando WBNT, Nanayakkara N, Gunarathne L, Chandrajith R (2019b) Serum and urine fluoride levels in populations of high environmental fluoride exposure with endemic CKDu: a case–control study from Sri Lanka. Environ Geochim Health 42(5):1497–1504. https://doi.org/10.1007/s10653-019-00444-x

Fernando WBNT, Hettiarachchi TW, Sudeshika T, Badurdeen Z, Abey sundara H, Ranasinghe S et al (2019c) Snap shot view on anaemia in chronic kidney disease of uncertain aetiology. Nephrology 24(10):1033–1040. https://doi.org/10.1111/nep.15345

Gamage CD, Sarathkumara YD (2016) Chronic kidney disease of uncertain etiology in Sri Lanka : are leptospirosis and hantaviral infection likely causes ? Med Hypotheses 91:16–19. https://doi.org/10.1016/j.mehy.2016.04.009

Gamage C, Yoshimatsu K, Sarathkumara YD, Kalendiran T (2017) Serological evidence of hantavirus infection in Girandurukotte, an endemic area for chronic kidney disease of unknown aetiology ( CKDu ) in Sri Lanka hantavirus infections. Int J Infect Dis (March). https://doi.org/10.1016/j.ijid.2006.09.12291

Gao P (2021) The expanse in the era of One Health. Environ Sci Technol 55(5):2790–2799. https://doi.org/10.1021/acs.est.0c00703

Gifford F, Kimmitt R, Herath C, Webb DJ, Melville V, Siribaddana S et al (2016) Arterial stiffness and Sri Lankan chronic kidney disease of unknown origin. Sci Rep 6:1–6. https://doi.org/10.1038/srep32599

Gunawardena S, Dayaratne M, Wijesinghe H, Wijewickrama E (2021) A systematic review of renal pathology in chronic kidney disease of uncertain etiology. Kidney Int Rep 6(6):1711–1728. https://doi.org/10.1016/j.ekir.2021.03.089

Ichimura T, Bonventre JV, Bailly V, Wei H, Hession CA, Cate RL, Sanicola M (1998) Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem 273(7):4135–4142. https://doi.org/10.1074/jbc.273.7.4135

Ipeperuma OA, Dharmagunawardhane HA, Herath KPRP (2009) Dissolution of aluminium from sub-standard utensils under high fluoride stress: a possible risk factor for chronic renal failure in the North-Central Province. JNatSciFoundation Sri Lanka 37(3):219–222. https://doi.org/10.4038/jnsfsr.v37i3.1217

Jayasekara JM, Dissanayake MD, Adhikari SB, Bandara P (2013) Geographic distribution of chronic kidney disease of unknown origin in North Central Region of Sri Lanka. Ceylon Med J 58(1):6–10. https://doi.org/10.4038/cmj.v58i1.5356

Jayasekara JMKB, Dissanayake MD, Sivakanesan R, Ranasinghe A, Karunarathna RH, Priyanthu Kumara GWG (2015) 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 25(4):275–280. https://doi.org/10.2188/jea.JE20140074

Jayasekara KB, Kulaseoriya PN, Wijayasiri KN, Rajakapakse ED, Dulshika DS, Bandara P et al (2019) Relevance of heat stress and dehydration to chronic kidney disease (CKDu) in Sri Lanka. Prev Med Rep 15(April):100928. https://doi.org/10.1016/j.pmedr.2019.100928

Jayasinghe S (2014) Chronic kidney disease of unknown etiology should be renamed chronic agrochemical nephropathy. MEDICC Review 16(2):72–74

Jayasinghe S, Zhu Y (2020) Chronic kidney disease of unknown etiology ( CKDu ) using a system dynamics model to conceptualize the multiple environmental causative pathways of the epidemic. Sci Total Environ 705. https://doi.org/10.1016/j.scitotenv.2019.135766

Jayasumana C, Dassanayake R, Priyawardane N, Elinder C, Wernerson A (2018) Morphological and clinical findings in Sri Lankan patients with chronic kidney disease of unknown cause ( CKDu ) : similarities and differences with Mesoamerican Nephropathy. PLoS One 13(3):1–19. https://doi.org/10.1371/journal.pone.0193056

Jayasumana C, Fonseka S, Fernando A, Jayalath K, Amarasinghe M (2015a) Phosphate fertilizer is a main source of arsenic in areas affected with chronic kidney disease of unknown etiology in Sri Lanka. Springerplus 4(1):1–8. https://doi.org/10.1186/s40064-015-0868-z

Jayasumana C, Gunatilake S, Senanayake P (2014) Glyphosate, hard water and nephrotoxic metals : are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka ? Int J Environ Res Public Health 11(2):2125–2147. https://doi.org/10.3390/ijerph110202125

Jayasumana C, Gunatilake S, Siribaddana S (2015b) Simultaneous exposure to multiple heavy metals and glyphosate may contribute to Sri Lankan agricultural nephropathy. BMC Nephrol 16(1). https://doi.org/10.1186/s12882-015-0109-2

Jayasumana C, Orantes C, Herrera R, Almaguer M, Lopez L, Silva LC et al (2016) Chronic intestinal nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. Nephrol Dial Transplant 32(2):234–241. https://doi.org/10.1093/ndt/gfw346
Jayasumana C, Paranagama P, Agampodi S, Wijewardane C, Gunatilake S (2015c) Drinking well water and occupational exposure to herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka. 1–10

Jayatilake N, Mendis S, Maheepala P, Mehta FR et al (2013) Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. BMC Nephrol 14(1). https://doi.org/10.1186/1471-2369-14-180

Jayawardana DT, Pitawala HMTGA, Ishiga H (2015) Geochemical evidence for the accumulation of vanadium in soils of chronic kidney disease areas in Sri Lanka. Environ Earth Sci 73(9):5415–5424. https://doi.org/10.1007/s12665-014-3796-2

Jha V, Garcia-garcia G, Iseki K, Li Z, Naicker S, Plattner B et al (2013) Global kidney disease 3 chronic kidney disease: global dimension and perspectives. Lancet 382(9888):260–272. https://doi.org/10.1016/S0140-6736(13)60687-X

Jiang C, Wang X, Li X, Inlora J, Wang T, Liu Q (2018) Dynamic human environmental exposome revealed by longitudinal personal monitoring. Cell 175(1):277–291. https://doi.org/10.1016/j.cell.2018.08.060

Kalke K, Balasubramanya S, Horbulak T (2019) Prevalence of chronic kidney disease in Sri Lanka: a profile of affected districts reliant on groundwater. Sci Total Environ 694(August):133767. https://doi.org/10.1016/j.scitotenv.2019.133767

Kahn LH (2011) The need for one health degree programs. Infect Ecol Epidemiol.1. https://doi.org/10.3402/iee.v1i0.7919

Kleinman A, Eisenberg L, Good B (2006) Culture, illness, and care: clinical lessons from anthropologic and cross-cultural research. Focus 4(1):140–149. https://doi.org/10.2907/foc.4.1.140

Kulathunga MRDL, Wijayawardena MAA, Naidu R, Wimalawansa SJ, Wijeratne AW (2020) Association between body mass index and estimated glomerular filtration rate in patients with chronic kidney disease of uncertain aetiology in Sri Lanka. Environ Geochem Health 42(9):2645–2653. https://doi.org/10.1007/s10661-019-00472-7

Kumar M, S. S. (2002) Biomarkers of diseases in medicine. Curr Trends Sci 403–417

Kumarasinghe N, Suriyakumara V, Aslam F, Gunaratne EDL et al (2019) Follow up study on Sri Lankan traditional medicine treatment on diagnosed chronic kidney disease of unknown etiology patients in Kebithigollewa, North Central Province (NCP), Sri Lanka. J Nephropathol 5(1). https://doi.org/10.14722/jnep.2019.10075

Levine KE, Redmon JH, Elledge MF, Wanigasuriya KP, Smith K, Munoz B et al (2015) Quest to identify geochemical risk factors associated with chronic kidney disease of unknown etiology (CKDu) in an endemic region of Sri Lanka—a multimedia laboratory analysis of biological, food, and environmental samples. Environ Monit Assess 188(10). https://doi.org/10.1007/s10661-016-5524-8

Li J, Li X, Zhang S, Snyder M (2019) Gene-environment interaction in the era of precision medicine. Cell 177(1):38–44. https://doi.org/10.1016/j.cell.2019.03.004

Lipworth, L., Mumma, M. T., Cavanaugh, K. L., Edwards, T. L., Ikizler, T. A., E. Tarone, R., ... Blot, W. J. (2012). Incidence and predictors of end stage renal disease among low-income blacks and whites. PLoS ONE, 7(10), 1–7. https://doi.org/10.1371/journal.pone.0048407

Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD (2016) Article CKD of uncertain etiology : a systematic review. Clin J Am Soc Nephrol 11:379–385. https://doi.org/10.2215/CJN.07500715

Majewski J, Schwartzentruber J, Lalonde E, Montpetit A, Jabado N (2011) What can exome sequencing do for you? J Med Genet 48(9):580–589. https://doi.org/10.1136/jmedgenet-2011-100223

Middleton D, Pallister J, Klein R, Feng Y, Haining J, Arkinstall R et al (2014) Hendra virus vaccine , a One Health approach to protecting horse, human, and environmental health. Emerg Infect Dis 20(3):372–379. https://doi.org/10.3201/eid2003.131159

Nanayakkara I, Dissanayake RK, Nanayakkara S (2020a) The presence of dehydration in paddy farmers in an area with chronic kidney disease of unknown etiology. Nephrology 25(2):156–162. https://doi.org/10.1111/nep.13605

Nanayakkara S, Komiya T, Ratnatunga N, Seneviratna STMLD, Harada KH, Hitomi T et al (2012a) Tubulointerstitial damage as the major pathological lesion in endemic chronic kidney disease among farmers in North Central Province of Sri Lanka. Environ Health Prev Med 17(3):213–221. https://doi.org/10.1007/s12199-011-0243-9

Nanayakkara S, Seneviratna S, Harada KH, Chandrajith R, Hitomi T, Abeysekera T et al (2019) Systematic evaluation of exposure to trace elements and minerals in patients with chronic kidney disease of uncertain etiology (CKDu) in Sri Lanka. J Trace Elem Med Biol 54:206–213. https://doi.org/10.1016/j.jtemb.2019.04.019

Nanayakkara S, Seneviratna STMLD, Abeysekera T, Chandrajith R, Ratnatunga N, Gunaratne EDL et al (2014) An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the North Central Regional of Sri Lanka. J Occup Health 56(1):28–38. https://doi.org/10.1539/joh.13-0712-OA

Nanayakkara S, Seneviratna STMLD, Harada KH, Chandrajith R, Nanayakkara N, Naizumi A (2020b) The influence of fluoride on chronic kidney disease of uncertain aetiology (CKDu) in Sri Lanka. Chemosphere 257. https://doi.org/10.1016/j.chemosphere.2020.12718

Nanayakkara S, Seneviratna STMLD, Karunaratne U, Chandrajith R, Harada KH, Hitomi T et al (2012b) 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 17(2):109–117. https://doi.org/10.1007/s12199-011-0224-z

Nanayakkara S, Seneviratna STMLD, Parahitiyawwa NB, Abeysekera T, Chandrajith R, Ratnatunga N et al (2015) 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 20(5):354–369. https://doi.org/10.1007/s12199-015-0475-1

Orantes-Navarro CM, Herrera-Valdés R, Almaguer-López M, López-Marín L, Vela-Parada XF, Hernandez-Cuchillas M, Barba LM (2017) Toward a comprehensive hypothesis of chronic interstitial nephritis in agricultural communities. Adv Chronic Kidney Dis 24(2):101–106. https://doi.org/10.1053/j.ackd.2017.01.001

Paranagama DGA, Bhuiyan MA, Jayasuriya N (2018) Factors associated with chronic kidney disease of unknown aetiology (CKDu) in North Central Province of Sri Lanka: a comparative analysis of drinking water samples. Appl Water Sci 8(6). https://doi.org/10.1007/s13201-018-0792-9

Perera WPT, Dayananda MDNR, Liyanage JA (2020) Exploring the root cause for chronic kidney disease of unknown etiology (CKDU) via analysis of metal ion and counterion contaminants in drinking water: a study in Sri Lanka. J Chemother 2020. https://doi.org/10.1155/2020/8679974

Pinto U, Thoradeniya B, Maheshwari B (2020) Water quality and chronic kidney disease of unknown aetiology (CKDu) in the dry zone region of Sri Lanka: impacts on well-being of village communities and the way forward. Environ Sci Pollut Res To 27(4):3892–3907. https://doi.org/10.1007/s11356-019-06669-8

Pry J, Jackson W, Rupasinghe R, Lishanthine G, Badurdeen ZAT et al (2021) A pilot case-control study using a One Health approach to evaluate behavioral , environmental , and occupational risk
factors for chronic kidney disease of unknown etiology in Sri Lanka. One Health Outlook 3(4). https://doi.org/10.1186/s42522-020-00034-3

Ranasinghe H (2016) Organic agriculture as a sustainable solution to chronic kidney disease unidentified (CKDu). Int J Curr Multidiscip Stud 3(2):71–77. https://doi.org/10.4038/ijms.v3i2.9

Rango T, Jeuland M, Manthrihitake H, McCormick P (2015) Nephrotoxic contaminants in drinking water and urine, and chronic kidney disease in rural Sri Lanka. Sci Total Environ 518–519:574–585. https://doi.org/10.1016/j.scitotenv.2015.02.097

Ratnayake S, Badurdeen Z, Nanayakkara N, Abeysekera T (2017) Screening for chronic kidney disease of uncertain aetiology in Sri Lanka: usability of surrogate biomarkers over dip-stick proteinuria. BMC Nephrol 18. https://doi.org/10.1186/s12882-017-0610-x

Kabara R, Shanika N, Senevirathna STMLD, Kouji H, Harada, Rohana Chandrathith, Toshiaki Hitomi5, Tilak Abeysekera, T. and A. K. (2016) Neonictinoid concentrations in urine from chronic kidney disease patients in the North Central Region of Sri Lanka. J Occup Health 58(1):128–133

RJ Petris-John, JKP Wanigasuriya, Wickremasinghe AR, W. D. and A. H. (n.d.). Exposure to acetylcholinesterase-inhibiting pesticides and chronic renal failure. 42–43

Ruwanpathirana T, Senanayake S, Gunawardana M, Munasinghe A, Ginige S, Gamage D et al (2019) 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 19(763):1–12. https://doi.org/10.1186/s12889-019-7117-2

Sarathkumara YD, Gamage CD, Lokupathirage S, Muthushingse DS, Nanayakkara N, G. L. et al. (2019). Exposure to hantavirus is a risk factor associated with kidney diseases in Sri Lanka : a cross sectional study. Viruses, 11(8), 700. https://doi.org/10.3390/v11080700

Sayanthooran S, Gunerathne L, Abeysekera TDJ, Magana-Arachchi DN (2018) Transcripome analysis supports viral infection and fluoride toxicity as contributors to chronic kidney disease of unknown etiology (CKDu) in Sri Lanka. Int Urol Nephrol 50(9):1667–1677. https://doi.org/10.1007/s11255-018-1892-z

Sayanthooran S, Magana-arachchi DN, Gunerathne L, Abeysekera T (2017) Potential diagnostic biomarkers for chronic kidney disease of unknown etiology ( CKDu ) in Sri Lanka : a pilot study. BMC Nephrol 18. https://doi.org/10.1186/s12882-017-0440-x

Sayanthooran S, Magana-arachchi DN, Gunerathne L, Abeysekera TDJ, Sooryapathiranna SS (2016) Uregulation of oxidative stress related genes in a chronic kidney disease attributed to specific geographical locations of Sri Lanka. Biomed Res Int. 2016. https://doi.org/10.1155/2016/7546265

Selvarajah M, Weeratunga P, Sivayoganthan S, Rathnathunga N, Raja-pakse S (2016) Clinico-pathological correlates of chronic kidney disease of unknown etiology in Sri Lanka. Indian J Nephrol 26(5):357–363. https://doi.org/10.4103/0971-4065.167280

Senanayake S, Gunawardena N, Palihawadana P,Bandara P, Hanifra R (2017) Symptom burden in chronic kidney disease ; a population based cross sectional study. BMC Nephrol 18(1). https://doi.org/10.1186/s12882-017-0638-y

Senanayake S, Gunawardena N, Palihawadana P,Senanayake S, Karunarathna R, Kumara P, Kularatna S (2020) Health related quality of life in chronic kidney disease; a descriptive study in a rural Sri Lankan community affected by chronic kidney disease. Health Qual Life Outcomes 18(1). https://doi.org/10.1186/s12955-020-01369-1

Senevirathna L, Abeysekera T, Nanayakkara S, Chandrathith, R Natunanga N, Harada KH et al (2012) Risk factors associated with disease progression and mortality in chronic kidney disease of uncertain etiology: a cohort study in Medawachchiya, Sri Lanka. Environ Health Prev Med 17(3):191–198. https://doi.org/10.1007/s12199-011-0237-7

De Silva PMCS, Shameek K, Abdul M, Eakanayake MD, Eakanayake V, Jayasinghe SS, Jayasumana C (2016b) 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 10(9):1–17. https://doi.org/10.1371/journal.pntd.0004979

Sriwardhana EARIE, Perera PAJ, Sivakanesan R, Abeysekara T, Nugegoda DB, Weerakoon K, Sriwardhana DAS (2018) Diminished disease progression rate in a chronic kidney disease population following the replacement of dietary water source with quality drinking water: a pilot study. Nephrology 23(5):430–437. https://doi.org/10.1111/nep.13051

Sriwardhana E, Perera P, Sivakanesan R, Abeysekara T, Nugegoda D (2015) Dehydration and malaria augment the risk of developing chronic kidney disease in Sri Lanka. Indian J Nephrol 25(3):146–151. https://doi.org/10.4103/0971-4065.140712

Sriwardhana ERI, Perera PA, Sivakanesan R, Abeysekara T, Nugegoda DB, Weerakoon KG (2014) Is the staple diet eaten in Medawachchiya, Sri Lanka, a predisposing factor in the development of chronic kidney disease of unknown etiology? - a comparison based on urinary β2-microglobulin measurements. BMC Nephrol 15(1):1–9. https://doi.org/10.1186/1471-2369-15-103

Sunil-Chandra NP, Jayaweera JAAS, Kumbukgolla W, Jayasundara MVML (2020) Association of hantavirus infections and leptospirosis with the occurrence of chronic kidney disease of uncertain etiology in the North Central Province of Sri Lanka: a prospective study with patients and healthy persons. Front Cell Infect Microbiol 10:1–10. https://doi.org/10.3389/fcimb.2020.55737

Sunil JW (2015) Agrochemicals and chronic kidney disease of multi-factorial origin: environmentally induced occupational exposure an occupational exposure disease. Int J Nephrol Kidney Failure 8(4):390/4103. https://doi.org/10.4038/jnkf.v8i4.3907

Thammitayagodge MG, Gunatillaka MM, Ekanayaka N, Rathnayake C, Horadagoda NU, Jayathissa R et al (2017) Ingestion of dug well water from an area with high prevalence of chronic kidney disease of unknown etiology (CKDu) and development of kidney and liver lesions in rats. Ceylon Med J 62(1):20. https://doi.org/10.4038/emj.v62i1.8428

Thilanga B, Wijerathne B, Meier RJ, Salgado SS (2020) Quantitative and qualitative dermatoglyphics of chronic kidney disease of unknown origin ( CKDu ) in Sri Lanka. J Physiol Anthropol 39(1). https://doi.org/10.1186/s40101-019-0207-0

Tiwari R, Dham A, Shanur K, Ishq Yato M, Malik YS, Singh R et al (2020) COVID-19: animals, veterinary and zoonotic links. Vet Q 40(1):169–182. https://doi.org/10.1007/s00125-020-00627-x

Trabanino RG, Aguilar R, Silva CR, Ortiz M, Leiva R, El NT (2002) Nefropatía terminal en pacientes de un hospital de referencia en El Salvador. Pan Am J Public Health 12(3):202–206

Vermeulen R, Schymanski EL, Barabási AL, Miller GW (2020) The exposome and health: where chemistry meets biology. Science 367(6476):392–396

Vlahos P, Schensul SL, Nanayakkara N, Chandrathith, R Haider L, Anand S et al (2019) Kidney progression project (KiPP): protocol for a longitudinal cohort study of progression in chronic kidney disease of unknown etiology in Sri Lanka. Glob Public Health 14(2):214–226. https://doi.org/10.1080/17441692.2018.1508480

Wanasinhe WCS, Gunaratna MHJP, Herath HMPIK, Jayasinghe GY (2018) Drinking water quality on chronic kidney disease of unknown aetiology (CKDu) in Ulagalla Cascade, Sri Lanka. Sabaragamuwa Univ J 16(1):17. https://doi.org/10.4038/suslj.v16i1.7714
Wanigasuriya K, Jayawardene I, Amarasiriwardena C, Wickremasinghe R (2017) Novel urinary biomarkers and their association with urinary heavy metals in chronic kidney disease of unknown aetiology in Sri Lanka: a pilot study. Ceylon Med J 62(4):210–217. https://doi.org/10.4038/cmj.v62i4.8568

Wanigasuriya KP, Peiris- John RJ, Wickremasinghe R (2011) Chronic kidney disease of unknown aetiology in Sri Lanka: is cadmium a likely cause? BMC Nephrol 12(1):32. https://doi.org/10.1186/1471-2369-12-32

Wanigasuriya KP, Peiris- John RJ, Wickremasinghe R, Hittarage A (2007) Chronic renal failure in North Central Province of Sri Lanka: an environmentally induced disease. Trans R Soc Trop Med Hyg 101(10):1013–1017. https://doi.org/10.1016/j.trstmh.2007.05.006

Wanigasuriya KP, Peiris H, Ileperuma N, Peiris- John RJ, Wickremasinghe R (2008)Could ochratoxin A in food commodities be the cause of chronic kidney disease in Sri Lanka? Trans R Soc Trop Med Hyg 102(7):726–728. https://doi.org/10.1016/j.trstmh.2008.04.007

Wasana HMS, Aluthpatabendi D, Kularatne WMTD, Wijekoon P, Weerasooriya R, Bandara J (2015a) Drinking water quality and chronic kidney disease of unknown etiology (CKDu): synergic effects of fluoride, cadmium and hardness of water. Environ Geochem Health 38(1):157–168. https://doi.org/10.1007/s10653-015-9699-7

Wasana HMS, Perera GDRK, De Gunawardena PS, Bandara J (2015b) The impact of aluminum, fluoride, and aluminum–fluoride complexes in drinking water on chronic kidney disease. Environ Sci Pollut Res 22(14):11001–11009. https://doi.org/10.1007/s11356-015-4324-y

Wasung, M. E., Chawla, L. S., & Madero, M. (2015). Biomarkers of renal function, which and when? Clin Chim Acta, 438(1), 350–357. https://doi.org/10.1016/j.cca.2014.08.039

Weaver VM, Fadrowski JJ, Jaar BG (2015) Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and / or occupational nephropathy? BMC Nephrology. (August). https://doi.org/10.1186/s11361-015-0155-6

Weeraratna S, Wimalawansa SJ (2015) A major irrigation project (Accelerated Mahaweli Programme) and the chronic kidney disease of multifactorial origin in Sri Lanka. Int J Environ Agric Res 1(6):16–27

WHO (2016) International Expert Consultation on Chronic Kidney Disease of Unknown Etiology

Wickramarathna S, Balasooriya S, Diyabalalage S, Chandrajith R (2017) Tracing environmental aetiological factors of chronic kidney diseases in the dry zone of Sri Lanka—a hydrogeochemical and isotope approach. J Trace Elem Med Biol 44:298–306. https://doi.org/10.1016/j.jtemb.2017.08.013

Wijayawardane RL, Manthrihalke H, Pitawala HMTGA (2018) 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 chronic kidney disease of unknown etiology (CKDu) endemic. Isot Environ Health Stud 54:244–261. https://doi.org/10.1080/10256016.2017.1377704

Wijetunge S, Ratnatunga NVI, Abeysekera TDJ, Wazil AWMM, Selvarajah M (2017) Endemic chronic kidney disease of unknown etiology in Sri Lanka: correlation of pathology with clinical stages. Indian J Nephrol 25(5):274–280. https://doi.org/10.4103/0971-4065.145095

Wijetunge S, Ratnatunga NVII, Abeysekera DTDJJ, Wazil AWMM, Selvarajah M, Ratnatunga CN (2013) Retrospective analysis of renal histology in asymptomatic patients with probable chronic kidney disease of unknown aetiology in Sri Lanka. Ceylon Med J 58(4):142–147. https://doi.org/10.4038/cmj.v58i4.6304

Wijewickrama ES, Gunawardena N, Jayasinghe S, Herath C (2019) CKD of unknown etiology (CKDu) in Sri Lanka: a multilevel clinical case definition for surveillance and epidemiological studies. Kidney Int Rep 4(6):781–785. https://doi.org/10.1016/j.ekir.2019.03.020

Wijewickrama ES, Weerasinghe D, Sumathipala PS, Horadagoda C, Laranrolle RD, Sheriff RMH (2011) Epidemiology of chronic kidney disease in a Sri Lankan population: experience of a tertiary care center. Saudi J Kidney Dis Transplant An Official Pub Saudi Center Organ Transplant Saudi Arabia 22(6):1289–1293

Wild CP (2005) Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. 14(August), 1847–1851. https://doi.org/10.1155/2005/118610

Wild CP (2012) The exposome: from concept to utility. Int J Epidemiol 41(January):24–32. https://doi.org/10.1093/ije/dyr236

Wimalawansa SA, Wimalawansa SJ (2014) Impact of changing agricultural practices on human health: chronic kidney disease of multi-factorial origin in Sri Lanka. Wudpecker J Agricult Res 3(5):110–124

Wimalawansa SJ (2014) Escalating chronic kidney diseases of multifactorial origin in Sri Lanka: causes, solutions, and recommendations. Environ Health Prev Med 19(6):375–394. https://doi.org/10.1007/s12199-014-0395-5

Wimalawansa SJ (2019, August) Public health interventions for chronic diseases: cost–benefit modelizations for eradicating chronic kidney disease of multifactorial origin (CKDmfo/CKDu) from tropical countries. Helyion 5(10):e02309. https://doi.org/10.1016/j.helyion.2019.e02309

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.