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Risk factors for endemic chronic kidney disease of unknown etiology in Sri Lanka: Retrospect of water security in the dry zone

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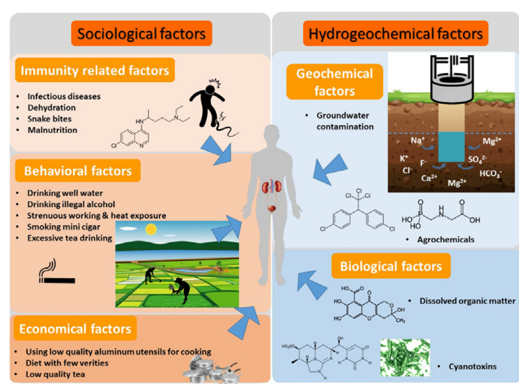
HIGHLIGHTS

- Hydrogeochemical, behavioral and sociological risk factors related to CKDu are reviewed.
- More than 98% of CKDu patients consumed groundwater as their primary water source.
- High F^-, HCO_3^- and total dissolved solids are unique in the CKDu endemic areas.
- Evaporation signal is prominent groundwater in the CKDu areas than non-CKDu areas.
- Water-rock interaction in CKDu prevailing areas is gaining considerable attention.

GRAPHICAL ABSTRACT



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ABSTRACT

The prevalence of chronic kidney disease of unknown etiology (CKDu) is receiving considerable attention due to the serious threat to human health throughout the world. However, the roles of geo-socio-environmental factors in the prevalence of the CKDu endemic areas are still unknown. Sri Lanka is one of the countries most seriously affected by CKDu, where 10 out of 25 districts have been identified as the areas with the high prevalence of CKDu (10–20%). This review summarizes the geographical distribution of CKDu and its probable geochemical, behavioral, sociological, and environmental risk factors based on research related to hydrogeochemical influences on CKDu in Sri Lanka. More than 98% of CKDu patients have consumed groundwater as their primary water source in daily life, indicating the interactions of geogenic contaminants (such as F^-, total dissolved solids, Hofmeister ions) in groundwater is responsible for the disease. Apart from the hydrogeochemical factors, mycotoxins, cyanotoxins, use of some herbal medicines, dehydration, and exposure to agrochemicals were alleged as risk factors. Sociological factors, including poverty, living habits and anthropogenic activities, may also provoke the emergence of CKDu. Therefore, the interaction of geo-socio environmental risk factors should be sociologically and scientifically considered to prevent the prevalence of CKDu. Future in-depth studies are required to reveal the individual role of each of the postulated etiological factors, possibly using machine learning and advanced statistics.

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1. Introduction

The emergence of a new form of chronic kidney disease (CKD) of unknown cause has received global attention since the mid-1970s due to impaired kidney function; this was named 'chronic kidney disease of unknown etiology' (CKDu) by the World Health Organization (Dharma-Wardana et al., 2015). CKDu is responsible for tens of thousands of deaths every year globally, and it has become a significant burden on public health and health care systems. However, the country-by-country prevalence of the disease is uncertain.

The increased health burden of CKDu has been observed not only in Asian countries but also in other parts of the world, including Central America, the Balkan Peninsula, and Egypt (Pearce et al., 2019). Milestones in the prevalence of unique CKDs around the world are shown in Fig. 1. CKDu is known by different names such as *itai-itai*, Balkan endemic nephropathy (BeN), Mesoamerican nephropathy (MeN), etc., in each country where the disease is diagnosed. The root causes of *itai-itai* disease in Japan and Balkan endemic nephropathy (BeN) in the Balkan Peninsula were confirmed as cadmium (Cd) exposure (1968) and ingestion of flour contaminated with *Aristolochia clematitis* (1993) seeds, respectively (Gifford et al., 2017). Sri Lanka is one of the countries most seriously affected by CKDu, where 10 out of 25 districts have been identified as the areas with the high prevalence of CKDu (10–20%). However, the exact etiology for CKDu is still controversial in countries like Sri Lanka (Gifford et al., 2017; Makehelwala et al., 2019).

In Sri Lanka, CKDu first manifested in the early 1990s, and patients were confined to a specific geographical area, predominantly North Central Province (NCP) which belongs to the dry zone of the country (Abeysekera et al., 1996; Wimalawansa, 2016). The incidence of CKDu increased up to 2016 and decreased slightly in 2017, which may have been due to increased community awareness and the use of community-based water supply schemes (Ranasinghe et al., 2019a). Since 1992, Sri Lanka has reported the highest incidence of CKDu in the South Asian region, including approximately 180,000 suffering from the disease and approximately 50,000 reported deaths (Wimalawansa and Wimalawansa, 2016). The Sri Lanka government spends approximately $19.7 million/year for the management of CKDu patients (Wimalawansa, 2019).

People affected by CKDu are mostly from underprivileged farming communities, who make a strong contribution to the economy of Sri Lanka. Adults from 30 to 50 years of age affected by CKDu can die due to disease progression and the lack of health care facilities in their geographical areas (Rajapakse et al., 2016). Also, most deaths from CKDu occur within three years of diagnosis, whereas the survival rate is five years (Rajapakse et al., 2016). Interestingly, most CKDu patients are males from families that were relocated as part of the Accelerated Mahaweli Development project in the 1980s. Additionally, it is known that they consumed groundwater as the primary source of drinking water, either from dug wells or tube wells (Chandrajith et al., 2011b; Dissanayake and Chandrajith, 2017). However, these patients claim that they used to drink water from the streams adjacent to paddy fields (de Alwis and Panawala, 2019).

The root factor(s) for the prevailing catastrophic health condition of CKDu in Sri Lanka is yet to be identified. Based on existing evidence, it has been postulated that multiple agents may contribute to the progression of CKDu, as evidenced by the large number of research publications related to CKDu (Fig. S1). Previous studies on CKDu in Sri Lanka have spanned various disciplines, including medical science (Anand et al., 2019), molecular biology and microbiology (Liyanage et al., 2016c; Wanigasuriya et al., 2008), water chemistry (Bandara et al., 2011; Jayasumana et al., 2014; Paranagama et al., 2018), geochemistry (Balasooriya et al., 2019; Cooray et al., 2019), and social sciences (Pinto et al., 2020; Redmon et al., 2014), etc. Many research efforts have focused on geo-environmental factors being potentially causative of CKDu because of its unique geographic distribution (Chandrajith et al., 2011b). In particular, the current literature suggests groundwater as a significant contributor to the etiology of the genesis and progression of CKDu (Weragoda and Kawakami, 2017; Chandrajith et al., 2011b), with some proposed risk factors including chronic exposure to toxic trace metals (Cd, lead (Pb), arsenic (As)), fluoride (F^-), and cyanobacterial toxins through contaminated drinking water (Jayasumana et al., 2014; Wimalawansa, 2016; Liyanage et al., 2016c; Dharma-wardana, 2018). However, the predominant factors leading to CKDu are still needed to be identified.

The hydrogeochemistry of groundwater consumed by people in the CKDu endemic areas is of significant interest (Balasooriya et al., 2019). The focal points of hydrogeochemical research are on the F^- content, ionicity, and the hardness of drinking water (Dharma-Wardana et al., 2015; Dissanayake and Chandrajith, 2017; Dissanayake and Chandrajith, 2019). Interestingly, gene expression has revealed that oxidative stress induced by external sources, such as environmental conditions, is high in the affected population (Sayanthooran et al., 2016). In addition, social behavior, such as living habits and economic status, also affects the prevalence of CKDu (Wanigasuriya et al., 2011; Wimalawansa, 2019; Wimalawansa and Dissanayake, 2020). Therefore, we hypothesized geochemical, sociological, and environmental factors may be interacted each other and systematically control the emergence of CKDu. Although few reviews have been published on CKDu, these have focused on the causative factors, epidemiology, and clinical and histopathological aspects (Weaver et al., 2015; Rajapakse et al., 2016; Lunyera et al., 2016; Wanigasuriya, 2012). No attempts have been made to assess the contribution of geo-socio-environmental risk factors. For example, very few attempts have been made to assess the exposure of people in the endemic area to pesticides and cyanotoxin in

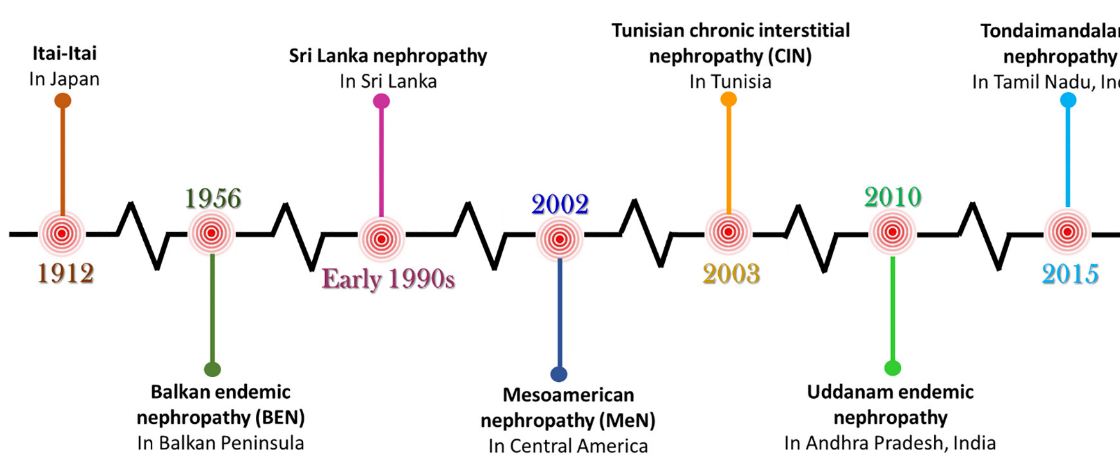

Fig. 1. Milestones in the prevalence of unique chronic kidney diseases worldwide.

groundwater (Jayasumana et al., 2014; Jayasumana et al., 2015b; Liyanage et al., 2016c; Madhushankha et al., 2013). Consequently, there is a need for a comprehensive study on the roles of geo-socio-environmental factors in the prevalence of the CKDu endemic areas in Sri Lanka.

Therefore, the objectives of this study are to 1) review geographic distribution and prevalence of CKDu in Sri Lanka, 2) evaluate geochemistry of water-rock interaction in CKDu endemic areas, and 3) build a scientific bridge by investigating and consolidating probable geochemical, behavioral, sociological and environmental risk factors based on literature related to hydrogeochemical influences on CKDu in Sri Lanka.

2. Geographical distribution of CKDu

The global CKDu epidemic has emerged predominately in agricultural communities (paddy, sugarcane, and cotton) of low-income countries near the equator (Wijkström et al., 2013; Wimalawansa and Wimalawansa, 2016). Though the causes of rapidly progressive CKDu in Central America, India, and Sri Lanka are not yet fully understood, heat exposure and dehydration, pesticides, and heavy metal–contaminated water intake are hypothesized as common etiologic risk factors that are associated with the behavioral influences of farming communities (Fernando et al., 2019a; Almaguer et al., 2014; Wimalawansa and Dissanayake, 2020).

2.1. Worldwide prevalence and population characteristics

As shown in Fig. 2, CKDu has been reported in both tropical and subtropical regions, including several Central American countries (El Salvador, Nicaragua, and Costa Rica), the dry zone of Sri Lanka, some states in India (Andhra Pradesh, Tamil Nadu, and Puducherry), European countries (Croatia, Herzegovina, Serbia, and Bosnia), and some regions in African continent such as the Al-Minya Governorate in Egypt and Nigeria (Lunyera et al., 2016; Balasooriya et al., 2019; Jayasekara et al., 2019; Abeyagunawardena and Shroff, 2021; Aguilar and Madero, 2019; Ajayi et al., 2021). Considering the geographical characteristics of CKDu endemic regions, mostly rural areas are affected, and coastal agricultural communities in lowlands along the Pacific coast in Central America also exhibit a high risk of disease (Weiner et al., 2013). Chronic renal failure in these Mesoamerican regions is identified as MeN (Campese, 2016). Central American countries such as Nicaragua (Torres et al., 2010), El Salvador (Peraza et al., 2012; Gracia-Trabanino et al., 2005; Orantes Navarro et al., 2015; Trabanino et al., 2002), Guatemala (Cusumano et al., 2005), Honduras and Costa Rica (Cerdas, 2005; Harhay et al., 2016; Cusumano et al., 2006) have shown an elevated mortality rate due to CKDu during the last two decades within sugarcane agricultural workers, especially among young males. Similar kidney disease was recorded in North American regions, including California, Florida, and eastern and southern Mexico, among agricultural workers (Aguilar and Madero, 2019).

Areas that have been widely studied for CKDu among agricultural communities include Egypt (El Minshawy, 2011), Nigeria (Ajayi et al., 2021), Balkan countries, Southeast Asian regions including Bangladesh, the northern region of Isan in Thailand, Andhra Pradesh, Tamil Nadu, and Puducherry regions of India (John et al., 2019; Tatapudi et al., 2019; Parameswaran et al., 2020), and the north-central region of Sri Lanka (Athuraliya et al., 2011; Jayatilake et al., 2013; Chandrajith et al., 2011b). BeN is the term used to identify the unique CKDu occurring in rural villages in Balkan countries along the Danube River, such as Croatia, Herzegovina, Bulgaria, Serbia, Romania, and Bosnia (Gifford et al., 2017; Stefanovic et al., 2006; Stiborová et al., 2016). The disease mostly prevails in the coastal and inland rural cashew nut, coconut, jackfruit, and rice farming areas in the Andhra Pradesh region and rice, peanut, and sugarcane farming areas in Tamil Nadu, and Puducherry regions of India (Reddy and Gunasekar, 2013; Abraham et al., 2019; Tatapudi et al., 2019; Parameswaran et al., 2020). Interestingly, only rural inland communities in Egypt, Nigeria, and Sri Lanka are affected (El Minshawy, 2011; Athuraliya et al., 2011). Also, it has been reported that Chena farmers (vegetables and other crops) in Sri Lanka are at higher risk than rice farmers (Jayatilake et al., 2013).

The gender distribution of CKDu differs in different regions. For BeN, females and males are equally affected. In contrast, the male population has a higher prevalence of renal failure than the female population in Central America, India, and Egypt. However, in Sri Lanka, there is a

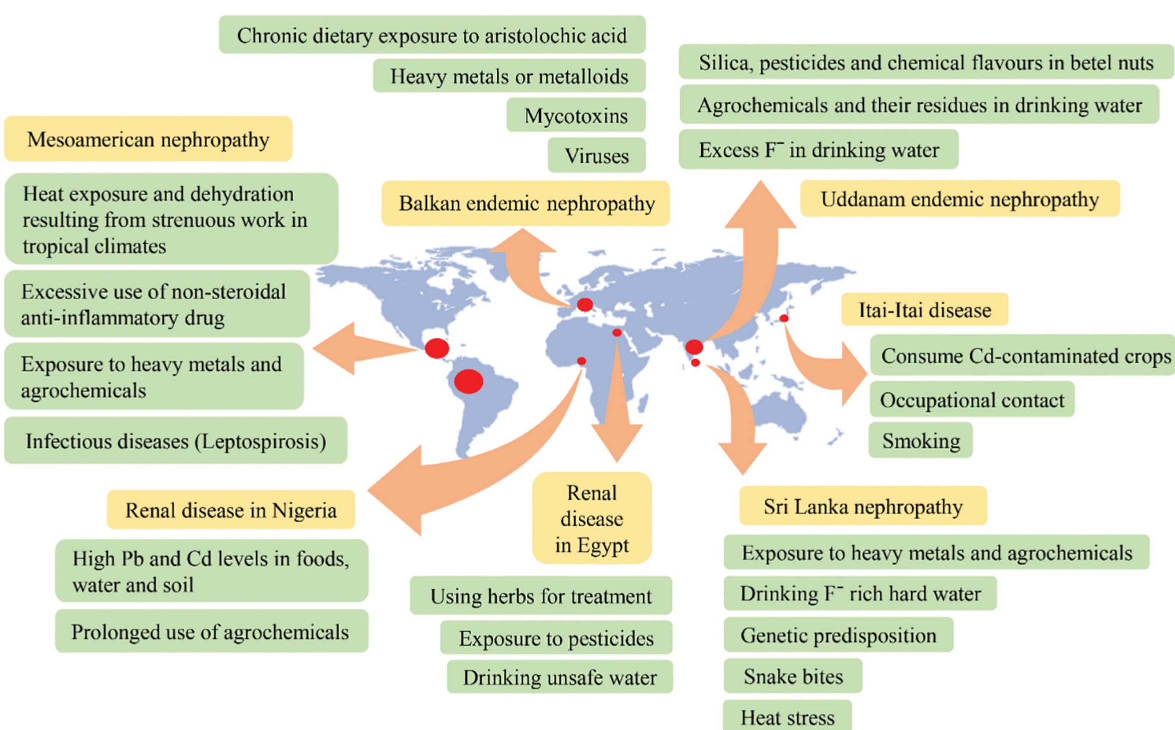

Fig. 2. Worldwide distribution of CKDu and possible causative factors in each region.

higher overall prevalence of CKDu in females than in males, although a higher prevalence of the final stages of CKDu can be seen in the male population (Weaver et al., 2015).

2.2. Disease characteristics

The leading pathological feature of renal failure in Central America is chronic tubulointerstitial nephropathy and secondarily vascular and glomerular damage (López-Marín et al., 2014). The BeN is commonly associated with upper urothelial cancer. In India, the leading pathological feature of CKDu is chronic tubulointerstitial nephritis, while in Sri Lanka, the leading pathological features of CKDu are interstitial inflammation, interstitial fibrosis, and tubular atrophy of varying degrees (Wijetunge et al., 2013). Basically, in Sri Lanka, CKDu progresses slowly with minimal proteinuria, while minor or no proteinuria occurs in Central America and India.

In Sri Lanka, case identification mainly depends on proteinuria, while serum creatinine and urine dipstick have been used in Central America (Weaver et al., 2015). Peritoneal dialysis is commonly undertaken in Central American regions for end-stage renal disease (ESRD). In Latin American countries such as Brazil, Puerto Rico, Venezuela, Chile, Argentina, and Uruguay, renal replacement is usually practiced (Cusumano et al., 2006). The characteristics of different ESRDs in the world are summarised in Table 1.

2.3. Possible causative or risk factors: a worldwide overview

Various hypotheses have been suggested for chronic renal failure due to its undefined etiology in affected countries, as shown in Fig. 2 and Table 1. Heat exposure and dehydration are challenges faced by agricultural field workers in hot climates and are considered major causative factors in some regions, including Mesoamerican countries and

Table 1
Worldwide distribution of CKDu, characteristics, and the suggested hypothesis.

Country	Region	Characteristics of the affected population			Hypotheses	Characteristic clinical features	References
		Occupation	Gender	Age			
Sri Lanka (Sri Lanka nephropathy)	Clusters in Uva, Central, North Central, and North-Western Provinces (Dehiattakandiya, Padaviya, Girandurukotte, Kabithigollawa, Medawachchiya, Medirigiriya, and Nikawewa)	Low-income agricultural workers (paddy, Chena)	Predominantly males	Majority 30–50	Heat stress, agrochemical exposure, heavy metal exposure, genetic predisposition, illegal alcohol/betel/tobacco, cyanotoxins, high F^{-} content with hardness in drinking water	Asymptomatic until end-stage renal failure Sterile urine Dysuria	Chandrajith et al. (2011b), Dharma-Wardana et al. (2015), Weaver et al. (2015)
India (Uddanam endemic nephropathy)	Andhra Pradesh (Odisha, Goa, Maharashtra, Nellor)	Rural cashew nut, coconut, and rice farmers	Both males and females are affected equally	50–60	Water-born agrochemicals, silica/pesticides/chemical flavors in betel nuts, high fluoride content in drinking water	Asymptomatic until end-stage renal failure	Ganguli (2016), Abraham et al. (2016)
India (Tondaimandalam nephropathy)	The states of Tamil Nadu, and Puducherry	Rice, groundnut and sugarcane farmers, animal herders	Predominantly males	40–50	Work related to farming, poor socioeconomic status	Asymptomatic early-stages Reduced or absent proteinuria Small kidneys	Parameswaran et al. (2020)
Central America (Mesoamerican nephropathy; MeN)	El Salvador, Nicaragua, Mexico (Tierra Blanca), Costa Rica	Sugarcane cutters (agricultural workers from communities along the Pacific coast)	Predominantly males	40–50	Heat exposure and dehydration resulting from strenuous work in tropical climates, excessive use of nonsteroidal anti-inflammatory drugs, infectious diseases (leptospirosis), other nephrotoxic medications, heavy metals (Pb, Cd, As, Hg & U), and agrochemicals	Asymptomatic until end-stage renal failure Cystitis (sterile urine, dysuria, frequency)	Ramirez-Rubio et al. (2013), Wesseling et al. (2013), Crowe et al. (2013)
Balkan Peninsula (Balkan endemic nephropathy-BeN)	Bosnia-Herzegovina, Croatia, Macedonia, Serbia, Bulgaria, and Romania	Rural farmers (residents of rural farming villages located along tributaries of the Danube River)	Both males and females are affected, with a slight female predominance	50–60	Chronic dietary exposure to aristolochic acid (AA), mycotoxins, heavy metals or metalloids, viruses, trace-element insufficiencies	Tubular acidosis Tubular proteinuria Weakened concentrating capacity	Gifford et al. (2017), Stiborová et al. (2016)
Egypt	Al-Minya governorate	Rural farmers	–		Drinking unsafe water, exposure to pesticides, using herbs for treatment	–	Kamel and El Minshawy (2010)
Japan (Itai-Itai disease)	Jinzu river basin, Toyama	–	Predominately older women	–	Consuming contaminated crops, smoking	Waddling gait Bone pain in postmenopausal women	Gifford et al. (2017)
Nigeria	Nguru, Komadugu-Yobe, Gashua, Bursari	Farmers and herders (agrarian communities situated close to River Kumadugu)	Predominantly female	50	Cd and Pb in the soil, water, goats, and fish, exposure to pesticides, herbicides, and fertilizer	Hypertensive nephrosclerosis and chronic glomerulonephritis	Ajayi et al. (2021), Sulaiman et al. (2018)

India (Peraza et al., 2012; Aguilar and Madero, 2019). Heat exposure along with long-term toxic exposure to heavy metals (Pb, Cd, As, mercury (Hg) and uranium (U)) and agrochemicals (pesticides) is also suggested as one of the major risk factors for sugarcane harvesters in endemic MeN areas (Torres et al., 2010) and coconut and cashew farms in Andhra Pradesh, India (Tatapudi et al., 2019).

Heavy metal exposure is a causative factor for ESRD in numerous cases. Lead-containing paints used in Queensland, Australia, caused Pb poisoning and resulted in ESRD of the adult population (Weaver et al., 2015). *Itai-itai* disease in Japan was caused by the ingestion of rice irrigated with industrially Cd-polluted water; this high exposure to Cd resulted in renal failure (Gifford et al., 2017). CKDu prevailing in Nigeria has a hypothesized causative factor related to Pb and Cd toxicity, and elevated levels of these metals have been recorded in foods, water, and soil (Sulaiman et al., 2018). Ecological studies on renal disease conducted in Taiwan noted the correlation of elevated mortality rates with moderate-high As levels in water sources. However, the Cd and As levels reported in water sources in CKDu endemic regions in Sri Lanka are much lower than those of high-risk regions identified in various ecologic studies worldwide (Chiu and Yang, 2005; Weaver et al., 2015; Wickramarathna et al., 2017). Additionally, high F^{-} concentration in drinking water is hypothesized to be a causative factor in some regions such as Uddanam, India (Abraham et al., 2016). Additionally, drinking water contamination by agrochemicals and F^{-} and exposure to silica, pesticides, and infections are proposed as causative factors for Uddanam endemic nephropathy in India (Ganguli, 2016), while drinking unsafe water is proposed to be a causative factor in Egypt (Kamel and El Minshawy, 2010).

Other than the heat exposure and unsafe water use, infectious diseases such as leptospirosis, and nephrotoxic medicine use, have also been considered as possible risk factors for CKDu (Torres et al., 2010; Ordunez et al., 2018). Interestingly, some research suggested dietary exposure to aristolochic acid and mycotoxins as causative factors for BeN (Stiborová et al., 2016); subsequently, the causative factor for BeN was identified as aristolochic acid containing in herbal species (Gifford et al., 2017). The combined effect of physically demanding occupations and heat stress as the cause of a renal disease has received more attention in Central America than in India and Sri Lanka, with increased chemical monitoring frequently reported in Sri Lanka (Jayatilake et al., 2013). Gender could also be an influencing factor because the disease shows a pattern of more frequent prevalence in males than in females (Gifford et al., 2017). However, there is a similarity in the hypothesized causative factors, to a certain extent, in some regions such as India, Sri Lanka, and Mesoamerican countries. For example, some of the causative factors are related to the occupational environment of the affected people, while some factors are related to the drinking water quality.

3. Prevalence of CKDu in Sri Lanka

3.1. Distribution of CKDu in Sri Lanka

The NCP of Sri Lanka is considered as the CKDu endemic region, where 10% of the adult population is affected by CKD/CKDu, and 27% of these cases have unknown etiology (Paranagama et al., 2018). Most of the NCP population depends on paddy cultivation, with more than 70% of paddy cultivation in Sri Lanka taking place in NCP. The remainder of the population relies on vegetable crops and related industries. Alongside NCP, the North Western, Uva, Eastern and Northern Provinces are identified as CKDu prevalent regions (Kafle et al., 2019). However, CKDu is not evenly distributed throughout NCP and occurs as clusters. As shown in Fig. 3, the high-prevalence CKDu areas identified in the country are Padaviya, Sripura, Girandurukotte, Medawachchiya, Nikawewa, Dehiattakandiya, Kabithigollawa, Polpithigama, Wilgamuwa, Giribawa, Mahiyanganaya, Rideemaliyadda, Welioya, Mahawa, Tantirimale, Horowpathana, Gomarankadawala, and Medirigiriya (Chandrajith et al., 2011b; Fernando and Sivakumaran, 2018; Balasooriya et al., 2019). According to Kafle et al. (2019), CKDu patients have also been reported in many other districts such as Anuradhapura, Matale, Vavuniya, Ampara, Trincomalee, Polonnaruwa, Badulla, Mullaittivu, Monaragala, and Kurunagala.

3.2. Hypothesized etiological factors

Researchers have proposed etiological factors for chronic kidney disease related to occupational exposure to chemicals, food and water consumption habits, and environmental conditions (Table S1). The most studied causative factors for CKDu in Sri Lanka are hydrogeochemical factors (high fluoride–concentration drinking water), common mycotoxins (ochratoxins), use of herbal medicines (aristolochic acid and nephrotoxic drugs), dehydration, exposure to agrochemicals (organophosphate pesticides, and high levels of As and Cd released from fertilizers and agrochemical application) and continuous low-dose exposure to heavy metals (Chandrajith et al., 2011a; de Silva et al., 2017; de Silva et al., 2016).

It has been hypothesized that toxins and pollutants could significantly contribute to CKDu by their ingestion through food, direct ingestion of toxins, and chronic exposure to toxins and pollutants through drinking water (Liyanage et al., 2016c). Toxins produced by animals, plants, and microorganisms could be ingested directly or through drinking water and could affect the function of kidneys, causing the disease (Table S1). Snake bites are common in these areas, and the snake toxins may cause chronic kidney failure in rural communities (Jayatilake et al., 2013). Most of the external factors suggested by researchers as causing kidney malfunctions are possibly associated with drinking water. Certain cyanobacteria have the potential to produce toxins that may affect human health. As cyanobacteria are ubiquitous in the environment and may occur in wells, tanks and reservoirs, the quality of drinking water could be affected by the toxins they produce. Research conducted in the dry zone of Sri Lanka, specifically in chronic kidney disease regions, has shown the presence of these cyanobacteria in drinking water bodies (Liyanage et al., 2016c). Surface water bodies could contain cyanobacteria and algae, while springs did not (Fernando and Sivakumaran, 2018). Areas where spring water was consumed had a lower prevalence of the disease.

Groundwater is the main water source in the dry zone community, with tank and reservoir water being consumed and used for irrigation purposes (Wickramarathna et al., 2017). The farming community is more vulnerable to CKDu because they mostly depend on their surrounding natural environment and drink more groundwater when working under humid conditions (de Silva et al., 2017). Numerous publications have proposed that toxic elements found in agrochemicals are the possible reason for the development of toxicity in groundwater of the area (Wimalawansa, 2016; Bandara et al., 2011) (Table S1). Jayasumana et al. (2015a) proposed that the continuous, long-term application of chemical fertilizers containing heavy metals and metalloids may result in their accumulation in drinking water sources, and ongoing use of water with high ionicity may contribute to CKDu by a protein denaturing mechanism in the kidney. However, few attempts have been made to identify the agrochemical residues in environmental water and groundwater in CKDu endemic regions. The increased levels of toxic trace elements in drinking water resulting from pesticides such as As were suspected as causative of CKDu (Jayasumana et al., 2014). However, according to the results from previous studies, the correlation between As levels and CKDu is not significant (Weaver et al., 2015). High Cd concentration in the dry zone drinking water was also a suspected causative factor for the disease. However, the difference in Cd concentrations measured in drinking water from CKDu non-prevalent and prevalent areas was minor, suggesting that drinking water Cd was not a causative factor (Diyabalanage et al., 2017; Fernando and Sivakumaran, 2018).

The environmentally induced causative factor for CKDu most studied is high F^{-} concentration in drinking water. According to previous

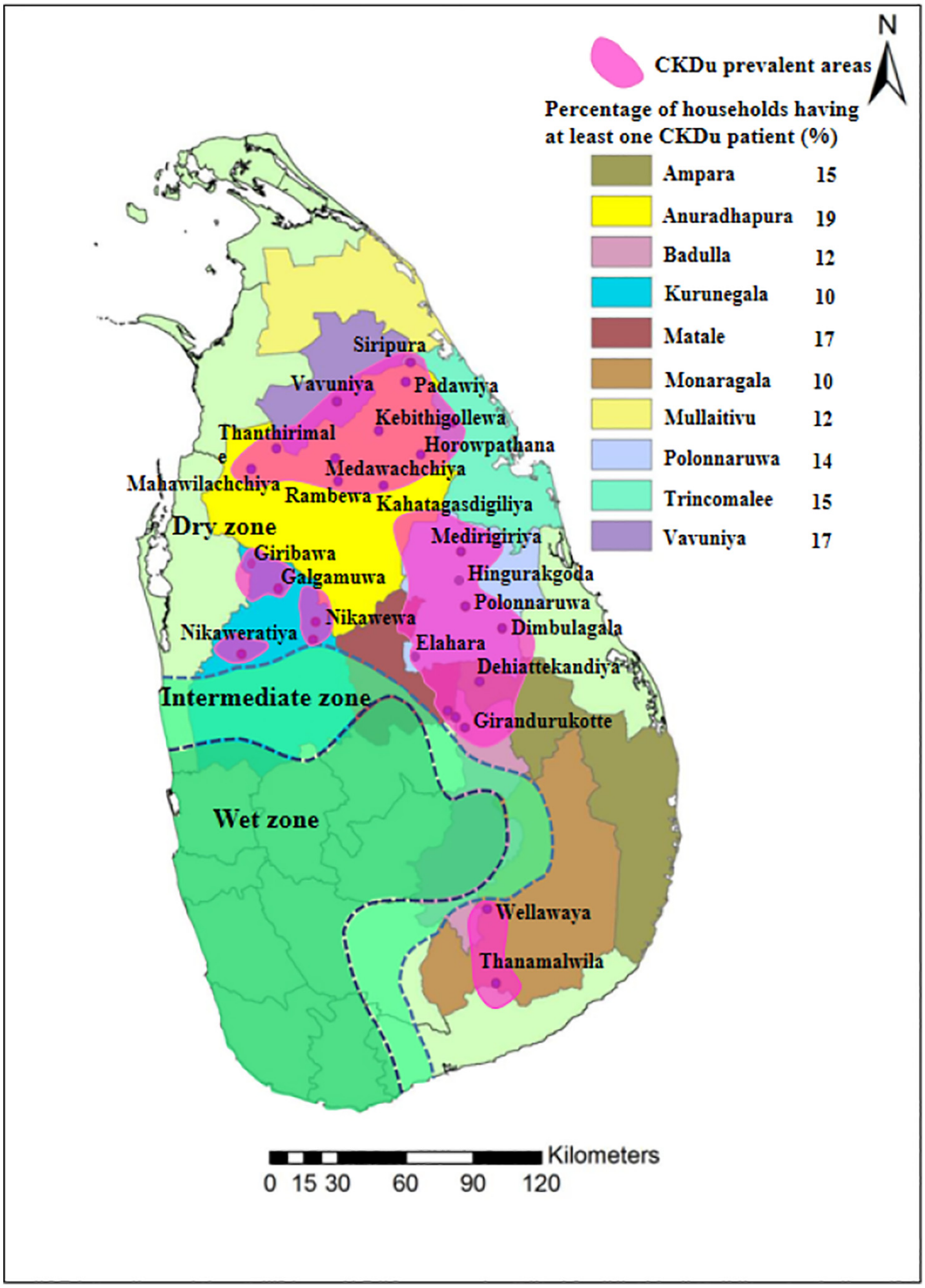

Fig. 3. CKDu prevalence areas in Sri Lanka. Percentage data source: Kafle et al. (2019).

studies, high F^- concentration may cause renal tubular damage. Fluoride may not act in isolation because some high F^- zones are not CKDu prevalent areas. Indeed, the effect of F^- may strongly depend on calcium (Ca^{2+}) and sodium (Na^+) activity. However, the F^- concentration of drinking water may contribute to chronic renal failure alone, at least to some extent (Chandrajith et al., 2011a). Furthermore, Dunuweera et al. (2017) suggested that dental and skeletal fluorosis, mostly in the North Western and North Central areas where CKDu is prevalent, could indicate a direct relationship between CKDu and F^- concentration in drinking water. High hardness alongside high F^- concentration in drinking water may contribute to CKDu because this environmental factor is related to tubular reabsorption (Balasooriya et al., 2019; Dunuweera et al., 2017). Aluminum fluoride is another proposed causative factor for CKDu: Ileperuma et al. (2009) identified that using aluminum utensils for cooking under acidic conditions could increase the leaching of aluminum (Al) as the F^- concentration of the water increased. All of the ions dissolved in drinking water in CKDu endemic areas may contribute to denaturing glomeruli basement proteins and, thereby, the ionicity of the drinking water could be a causative factor for chronic renal failure (Dharma-Wardana et al., 2015).

According to Senevirathna et al. (2012), direct exposure to sunlight and dehydration may contribute to kidney failure for male farmers working in the field. In BeN, aristolochic acid produced by *Aristolochia* plant genes was suggested as a causative factor for kidney disease (Gifford et al., 2017). In Sri Lanka, *Aristolochia clematitis* is used as ayurvedic medicine. Studies show that this medication produces nephrotoxic effects on patients; however, this medicine contains very low contents of aristolochic acid (Fernando and Sivakumaran, 2018; Weaver et al., 2015). Therefore, this acid cannot be considered as a causative factor for CKDu. A timeline of all the proposed hypotheses and national responses to CKDu in Sri Lanka is shown in chronological order in Fig. 4.

4. Geochemistry of water-rock interactions in CKDu endemic areas

In Sri Lanka, the geology of the dry zone is not distinctly different from that of the wet zone. Therefore, the hydrological and climatic conditions must play an essential role in the geochemistry of CKDu causative factors (Chandrajith et al., 2020). The groundwater in CKDu-affected areas occurs in high-grade metamorphic regolith aquifers, loosely arranged weathered or partially weathered soils or rocks. Studies on the CKDu endemic area in Girandurukotte showed that the subsurface is underlaid by charnockite and granitic gneiss, while the non-endemic CKDu area in the flat region near Ginnoruwa is underlaid by fluvial sediments (Balasooriya et al., 2019). Depending on the geology and the climate of an area, the groundwater type of the area can differ.

4.1. Groundwater types in CKDu endemic/non-endemic areas

In CKDu prevalent areas of Sri Lanka's dry zone, such as Padaviya, Nikawewa, Girandurukotte, and Medawachchiya, groundwater mostly consists of HCO_3^-, Ca^{2+} and Na^+ ions, and Ca-HCO_3 type is predominant. However, Wellawaya and Huruluwewa are CKDu non-endemic regions with Na^+-K^+ non-dominant anion type water as the common groundwater type. The Hambantota area, which is considered as a non-endemic region, has predominately Na/K-Cl type groundwater (Chandrajith et al., 2011a). CKDu non-endemic regions have predominantly Na-Cl/Ca-Mg-Cl, Ca-HCO_3, and then Ca-Na-HCO_3, together with Na^+, K^+, and Ca^{2+} as dominant cations and HCO_3^- and Cl^- as dominant anions. Na-Cl/Ca-Mg-Cl mixed groundwater types are due to seawater intrusion, and Ca-HCO_3 and Ca-Na-HCO_3 types are due to calcite and dolomite dissolution (Chandrajith et al., 2016). Weathering of silicate minerals present in aquifer materials is the reason for this kind of chemical

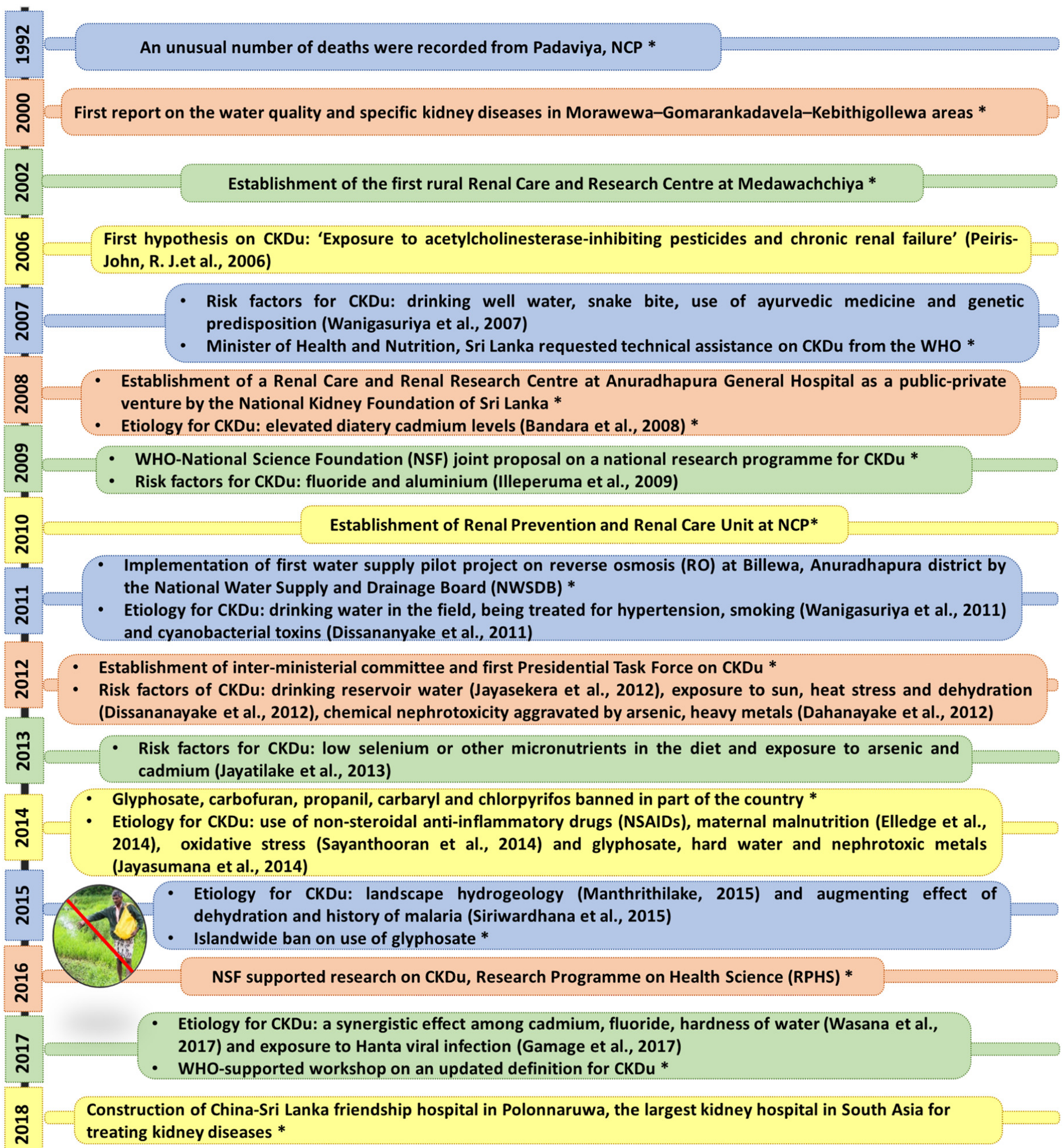

Fig. 4. Timeline of published hypotheses and national responses to CKDu in Sri Lanka. Data from de Alwis and Panawala (2019). National responses are marked with *.

composition. The main feature of groundwater in CKDu prevalent areas is elevated F^- associated with higher hardness than in CKDu non-dominant regions (Wickramarathna et al., 2017).

Prevalence of CKDu is categorized as high in Medawachchiya, Padaviya, Kahatagasdigiliya and Kebithigollawa, moderate in Nochchiyagama, Thalawa, and Mihintale, and low in Palagale and Galnewa, showing that the predominant groundwater types are Ca-HCO_3 type, Mg-HCO_3 type and non-dominant Ca-HCO_3 type, respectively. Results from CKDu non-endemic regions in Monaragala and Kandy districts showed Na^+ as the most available cation and Cl^- as the most available anion (Cooray et al., 2019). According to the study by Udeshani et al. (2020), Monaragala, with a high prevalence of endemic CKDu, had Ca-Mg-HCO_3 type alkaline water taken from shallow and deep groundwater in hard rock aquifers, including HCO_3^- as the major anion and Na^+ and Ca^{2+} as the major cations (Dissanayake et al., 2020). However, in the last decade water contaminated with F^- has emerged as a causative risk factor for the prevalence of CKDu. Therefore, understanding the pathways of F^- leaching into water is crucial.

4.2. Weathering of fluoride-bearing rocks

Fluorine is one of the most available elements in the lithological environment, and F^- is the most distributed ionic form of fluorine in natural water (Ali et al., 2016). Rocks are the main source of groundwater F^-, which comes through rock-water interactions (Ranasinghe et al., 2019b). Fluoride is leached from common rock-forming fluoride-bearing minerals such as apatite, mica, sphene, fluorite, hornblende, amphibole, and pyroxene with high F^- content (Chandrajith et al., 2011a). Silicate minerals present in the earth's crust typically contain about 650 mg/kg of F^- (Adriano, 2001). Also, fluorapatite, fluorspar, tourmaline, topaz, and cryolite—which have high contents of fluoride—contribute to the geochemical cycle of F^- in the environment (Ali et al., 2016; Chandrajith et al., 2020; Dissanayake and Chandrajith, 2019); high-grade metamorphic rocks (gneiss) and granitic rocks consist of these minerals. According to Dharmagunawardhane and Dissanayake (1993), the F^- content of various metamorphic rock types in Sri Lanka varies between 95 and 1440 mg/kg. Additionally, the F^- concentration of deep groundwater taken from biotite gneiss, calc-gneiss, charnockitic gneiss, and granulite rock aquifers was higher than that in groundwater taken from crystalline limestone and quartzite rock aquifers (Dharmagunawardhane and Dissanayake, 1993). This difference in F^- concentration between groundwater was caused by various mineral components in the aquifer rocks and their F^- dissolution capability into groundwater. Furthermore, longer resident times in fractured crystalline rock aquifers leave deep groundwater to interact with fluoride-bearing minerals and lead to the accumulation of dissolved F^- (Chandrajith et al., 2020; Balasooriya et al., 2019).

The enhanced weathering of rocks under tropical climatic conditions and the low dilution of water caused by higher evaporation during high temperatures result in high F^- leaching into aqueous media, thereby increasing the F^- concentration in groundwater (Chandrajith et al., 2011a). Additionally, the chemical properties of groundwater, such as alkali and alkaline earth metal content, hardness, HCO_3^-, alkalinity, and pH, determine the F^- mobility into groundwater (Saxena and Ahmed, 2003; Guo et al., 2014). Chandrajith et al. (2011a) suggested that the geochemical cycling of F^- in groundwater could be more highly influenced by the climate and the hydrology of the dry zone than by the rocks and mineral types. In wet climatic zones, extreme rainfall results in low F^- concentration by washing away excess F^-, while evaporation due to high temperatures in dry climatic zones causes the enrichment of groundwater F^- (Mukherjee and Singh, 2020; Dissanayake, 1996).

Fluoride-bearing minerals, such as fluorite, can be dissociated by favorable groundwater conditions: near neutral pH to alkaline pH (pH 7.6–8.6) with moderate specific conductivity. These factors are significant in governing F^- dissociation from rocks (Chandrajith et al., 2011a; Saxena and Ahmed, 2003). Additionally, sodium-rich alkaline groundwater can result in the dissociation of F^- from minerals (Chae et al., 2007).

4.3. Desorption of fluoride

The desorption of F^- on mineral surfaces has an important impact on F^- in groundwater (Chandrajith et al., 2020). Generally, there is a positive correlation between groundwater F^- and pH in Sri Lanka (Fig. 5a), with a correlation coefficient of 0.48 ($p < 0.01$). A slightly higher correlation coefficient was observed in CKDu areas (0.59) than that in non-CKDu areas (0.41). Due to the similar geochemical properties of F^- and OH^-, OH^- in a solution can easily displace F^- on the surface of sediments (Chandrajith et al., 2020). Accordingly, pH is an important factor that affects the desorption of F^- (Saxena and Ahmed, 2003). Studies have shown that the pH of groundwater in CKDu-affected areas is higher than that in non-CKDu areas (Balasooriya et al., 2019) and is usually weakly alkaline (Cooray et al., 2019). In weakly alkaline conditions, the surface charge of minerals is normally neutral or negative, which would inhibit the adsorption of F^- and result in the replacement of the adsorbed F^- on the surface by OH^- from groundwater (Jacks et al., 2005). Higher F^- concentrations were observed in CKDu areas (0.04 to 6.0 mg/L; median 0.90 mg/L) than those in non-CKDu areas (0.01–6.1 mg/L; median 0.67 mg/L) (Fig. 5).

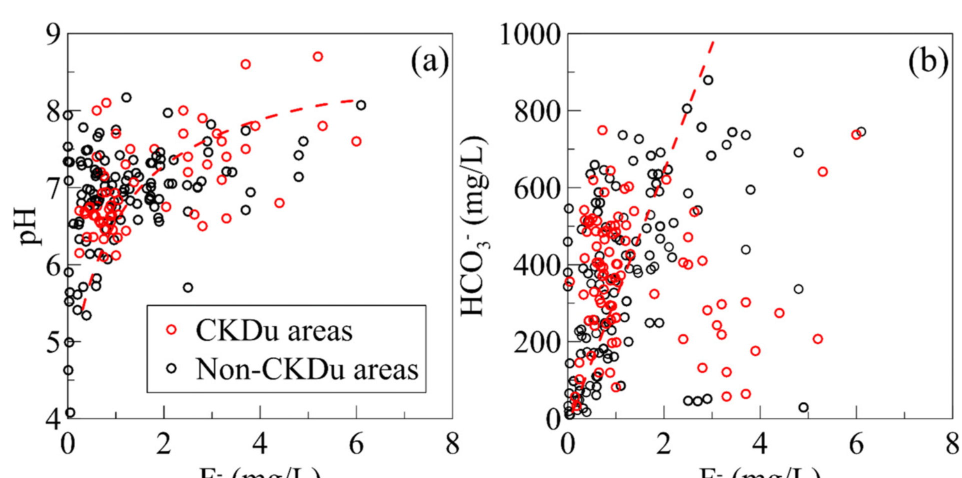

Fig. 5. (a) Groundwater F^- versus pH ($R = 0.48$; $p < 0.01$) and (b) HCO_3^- concentrations ($R = 0.21$; $p < 0.01$) in Sri Lanka. Data from: Abeywickarama et al. (2016), Balasooriya et al. (2019), Cooray et al. (2019), Imbulana et al. (2020), Nikagolla et al. (2020), Udeshani et al. (2020), Wickramarathna et al. (2017), Senarathne et al. (2020).

In addition to OH^-, HCO_3^- also strongly competes with F^- for adsorption sites. This is evidenced by the positive correlation between groundwater F^- and HCO_3^- ($R = 0.21$; $p < 0.01$) (Fig. 5b), indicating that HCO_3^- can replace the adsorbed F^- on the surface of solids (Singaraja et al., 2018; Mao et al., 2016). In Sri Lanka, HCO_3^- is the main groundwater anion in CKDu-affected areas (Chandrajith et al., 2011b; Cooray et al., 2019), which may lead to desorption of F^- from sediment surfaces. In the dry zone of Sri Lanka, the alkaline groundwater with high HCO_3^- concentrations enhances F^- desorption into groundwater (Saxena and Ahmed, 2003). In contrast, in the wet zone, the slightly acidic groundwater limits F^- dissolution (Rubasinghe et al., 2015).

4.4. Cation exchange

Cation exchange is also involved in influencing the geochemical routes of F^-. Na^+ and Ca^{2+} are generally found in various concentrations in groundwater, and these variations can affect the availability of CKDu risk factors such as F^- (Thilakerathne et al., 2015). According to Jacks et al. (2005) and Saxena and Ahmed (2003), groundwater can be evaporated significantly depending on the tropical climatic conditions. This increases the Na^+/Ca^{2+} ratio by decreasing Ca activity and finally increases F^- levels in groundwater. The Na^+/Ca^{2+} ratios of groundwater in CKDu endemic and non-endemic areas differ greatly: in CKDu endemic areas, Ca^{2+} ions have more affinity than Na^+ ions for F^- (Chandrajith et al., 2011a).

Cation exchange mainly occurs at the interface of groundwater and aquifer sediments, during which Ca^{2+} and Mg^{2+} in groundwater are adsorbed into aquifer sediments, and Na^+ and K^+ are desorbed into groundwater. Because carbonate mineral dissolution and silicate weathering can provide groundwater containing HCO_3^- and SO_4^{2-}, cation exchange is calculated by subtracting equivalent concentrations of HCO_3^- and SO_4^{2-} from Ca^{2+} and Mg^{2+} ((Ca^{2+} + Mg^{2+}) - (HCO_3^- + SO_4^{2-})). Na^+ that comes from desorption is calculated by subtracting an equivalent concentration of Cl^- from Na^+ (Na^+-Cl^-) because precipitation contributes identically to groundwater Na^+ and Cl^- (Wei et al., 2016). All groundwater samples were plotted near the line with a slope of −1.0, indicating that cation exchange affects groundwater quality in both CKDu and non-CKDu areas (Fig. S2). However, the regression line between ((Ca^{2+} + Mg^{2+})-(HCO_3^- + SO_4^{2-})) and (Na^+-Cl^-) in samples collected from CKDu areas had a slope of −0.9, which is slightly different from that from non-CKDu areas (−1.0). In addition, the median of (Na^+-Cl^-) in samples collected from CKDu areas (0.63) is higher than that from non-CKDu areas (0.55), meaning that cation exchange in CKDu prevalent areas is more evident than that in non-CKDu areas.

4.5. Evaporation

The Gibbs plot (Gibbs, 1970) is widely used to recognize the relationship between aquifer lithological characteristics and groundwater composition. These are based on the ratios of either $Cl^-/(Cl^- + HCO_3^-)$ or $(Na^+ + K^+)/(Na^+ + K^+ + Ca^{2+})$ as a function of total dissolved solids (TDS) to distinguish between three different fields: rock-water interaction dominance, precipitation dominance and evaporation dominance (Magesh et al., 2013). According to the Gibbs plot interpretation of water quality data from the Monaragala region, the groundwater of the area fell under rock-water interaction dominance and evaporation dominance fields by indicating that the water infiltrating into the subsurface was modified by rock-water interactions (Udeshani et al., 2020).

As shown in Fig. 6, most of the plots representing CKDu prevalent areas contained higher concentrations of TDS than the plots representing non-CKDu areas. This indicates that evaporation and concentration make greater contributions to the chemical compositions of groundwater in CKDu areas compared with groundwater in non-CKDu areas.

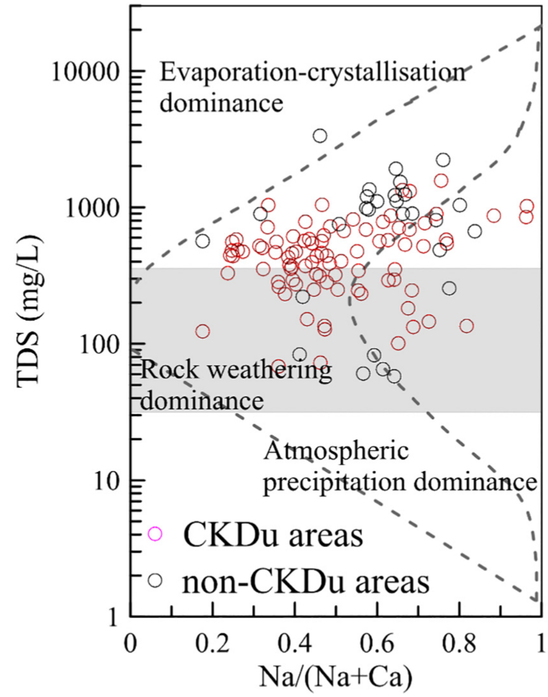

Fig. 6. Gibbs diagram of groundwater samples from CKDu prevalent areas and non-CKDu areas. Data from: Cooray et al. (2019), Imbulana et al. (2020), Senarathne et al. (2019).

In addition to Gibbs diagrams, $\delta^{18}O$ and δ^2H values in groundwater can also reflect the effect of evaporation on its chemical composition (Dansgaard, 1964). Groundwater values from both CKDu prevalent (with a regression line of $\delta^2H = 5.56\ \delta^{18}O - 2.82$; $r^2 = 0.92$) and non-CKDu areas (with a regression line of $\delta^2H = 6.32\ \delta^{18}O + 1.19$; $r^2 = 0.92$) deviated from the Local Meteoric Water Lines (LMWL: $\delta^2H = 7.71\ \delta^{18}O + 10.04$; (Chandrajith et al., 2013)), indicating that they were recharged from surface water and suffered from evaporation before infiltration (Fig. S3) (Wickramarathna et al., 2017). In Fig. S3, groundwaters from CKDu prevalent areas are located to the right and above groundwaters from non-CKDu prevalent areas, suggesting the stronger evaporation of groundwater from CKDu areas. This is in line with groundwater ionic composition results, showing that the effect of evaporation on the groundwater chemical composition is stronger in CKDu areas.

5. Water as a risk factor

5.1. Hydrogeochemical quality of waters

Most villagers in CKDu affected areas utilize different types of drinking water sources, including dug wells, tube wells, springs, and reservoirs. This shows that groundwater from shallow regolith aquifers is a very important source of freshwater in rural regions. Groundwater has stronger interactions with subsurface rocks and minerals than surface water due to water level fluctuations during dry and wet seasons. Hydrogeological conditions and the chemical composition of groundwater are important factors that can lead to the deterioration of water quality. In addition to natural influences, hydrogeochemical characteristics can also be affected by anthropogenic factors.

5.1.1. Physicochemical quality

Up to date, the average pH values of water samples in CKDu affected areas are neutral to alkaline, from pH 6.63 to 8.70 (Balasooriya et al., 2019; Wanasinghe et al., 2018; Wickramarathna et al., 2017; Nikagolla et al., 2020). Cooray et al. (2019) did not observe an apparent difference in the pH of water samples between the wet (7.85) and dry (7.30) seasons in the Anuradapura district. Additionally, the electrical conductivity (EC) values of shallow and medium dug well water was found to range from 315 to 2590 µS/cm (Wickramarathna et al., 2017; Wanasinghe et al., 2018), while surface water in the area showed low EC values (79.50 – 806.33 µS/cm), suggesting that these surface water bodies may regularly blend with surface runoff or infiltrated rainwater (Balasooriya et al., 2019).

In CKDu endemic regions, high water hardness is attributed to the Ca-HCO_3 type groundwater, while non-endemic regions have Na type groundwater attributed with high hardness (Chandrajith et al., 2011a). The total hardness of groundwater in CKDu prevalent areas in NCP was found to range from 122 to 454 mg/L, indicating the moderately hard to very hard nature of the water (Wickramarathna et al., 2017; Dissanayake and Chandrajith, 2017; Nikagolla et al., 2020). This increased water hardness could be the reason for the reported high EC values. In the contrast, surface water bodies had low water hardness (31.2 mg/L) (Jayasumana et al., 2015b). According to a study by Dharma-wardana (2018), kidneys can be intoxicated by Mg^{2+} and F^- from hard water due to the development of $(MgF)^+$ paired ions. However, calcium-rich hard water does not appear to have the same effect. Generally, lower alkalinity values were observed in wells and surface water bodies located in non-CKDu endemic areas compared to wells in CKDu endemic areas (Balasooriya et al., 2019).

Elevated levels of dissolved organic carbon (DOC) in drinking water appear to increase the prevalence of CKDu (Makehelwala et al., 2019). DOC is a mixture of various organic compounds, including fulvic acid, humic acid, and humus, which can frequently be found in aquatic ecosystems (Makehelwala et al., 2019). Makehelwala et al. (2019) observed that groundwater in CKDu high-risk zones in the Anuradhapura district was enriched in more aromatic DOC. However, there has been little attention to the interaction between DOC and di- or trivalent ions present in shallow hard groundwater in CKDu endemic zones. Some general groundwater quality parameters from published literature are summarised in Table 2. Although many studies have assessed the water quality in different CKDu prevalent areas, there has been a lack of attention on general water physicochemical parameters even though these parameters can provide a rapid indication of water quality.

5.1.2. Toxic trace metals

Another potential etiology of CKDu in major farming areas is exposure to trace metals during irrigation. As depicted in Table 3, the most frequently and intensively studied trace metals in relation to CKDu have been Cd, Pb, Al, zinc (Zn), As, iron (Fe), nickel (Ni), and copper (Cu), which have all shown potential nephrotoxic effects. Bandara et al. (2008) found slightly elevated concentrations of dissolved Cd, Fe, and Pb, which ranged from 0.03 to 0.06, 0.2 to 1.28, and 0.01 to 0.03 mg/L, respectively, in five reservoirs in CKDu prevalent areas. They were believed to be the etiological agents for the genesis of the CKDu. Furthermore, they found eight heavy metals (Cd, cobalt (Co), chromium (Cr), Cu, Fe, manganese (Mn), Pb, and Zn) in the storage rhizome of *Nelumbo nucifera* (lotus plant) in dry zone reservoirs, which is a popular vegetable among villagers (Bandara et al., 2008). For instance, it was estimated that 4.53 mg of Cd could be ingested by consuming 100 g of lotus root (Bandara et al., 2008). In contrast, most of the toxic elements—such as Cd, As, and Pb—were found to be present in low concentrations in water of CKDu-affected areas and generally did not exceed the permissible levels stipulated by the World Health Organization (WHO); this suggested that these metals were not causal factors of CKDu (Rango et al., 2015; Paranagama et al., 2013; Nanayakkara et al., 2014; Nikagolla et al., 2020). Additionally, a study conducted by Nanayakkara et al. (2014) confirmed that nephrotoxic heavy metals (i.e. Cd and As) did not provide evidence to the pathogenesis of CKDu in Sri Lanka. Due to these contrasting reports, there is doubt about the involvement of trace metals in the genesis of the CKDu (Chandrajith et al., 2011b; Jayatilake et al., 2013). The combined effect of some trace metals with ions in water can result in much higher toxicity than if the trace metals were present alone (Wasana et al., 2016; Dharma-wardana, 2018). Dharma-wardana (2018) has suggested that the $(CdF)^+$ ion pair in potable water has a strong synergistic effect on kidney health. Additionally, the ion-pairing of Al^{3+} with F^- (i.e., AlF_3 and AlF_4^-) in drinking water increased when there was high F^- stress, which has also been proposed as a causative factor of CKDu (Ileperuma et al., 2009).

5.1.3. Hofmeister ions

High concentrations of major ions in the water contribute to the TDS present in the water. It is suspected that certain concentrations of these ions in water can activate the Hofmeister series effect leading to kidney damage in humans (Manthrithilake, 2015). In Sri Lanka, concentrations of F^- in groundwater in CKDu affected areas were significantly higher than those in areas where CKDu was uncommon (Dissanayake and Chandrajith, 2017; Udeshani et al., 2020; Nanayakkara et al., 2020). A recent study carried out by Wasana et al. (2016) showed that F^- concentrations in the groundwater of some villages in NCP were in the range of 0.41 to 1.34 mg/L, while Dissanayake and Chandrajith (2017) observed a range from 0.62 to 1.42 mg/L. However, Cooray et al. (2019) recorded excessive F^- values (~2.3 ± 0.2 mg/L) in drinking

Table 2
Summary of general groundwater quality parameters in some CKDu endemic areas of Sri Lanka (standard deviation mentioned with ± mark).

Location	General water quality						Reference
	Temperature (°C)	pH	EC (µS/cm)	TDS (mg/L)	Alkalinity (mg/L)	Hardness (mg/L)	
Ginnoruwa	29.1 ± 0.9	6.64 ± 0.37	376 ± 191	210 ± 98	161 ± 83	154 ± 71	Balasooriya et al. (2019)
Girandurukotte	–	6.88	330	–	–	217	Chandrajith et al. (2011a)
	–	6.63	429	–	168	150	Wickramarathna et al. (2017)
	–	–	–	–	–	226	Dissanayake and Chandrajith (2017)
Nikawewa	–	7.08	1008	–	–	336	Chandrajith et al. (2011a)
	–	7.39	885	–	493	422	Wickramarathna et al. (2017)
	–	–	–	–	–	426	Dissanayake and Chandrajith (2017)
Wilgamuwa	–	6.73	512	–	226	184	Wickramarathna et al. (2017)
Padaviya	–	6.94	834	–	–	443	Chandrajith et al. (2011a)
	–	7.2	872.2	–	282.2	280.2	Cooray et al. (2019)
	–	6.87	674.67	–	–	–	Nikagolla et al. (2020)
	–	–	–	–	–	454	Dissanayake and Chandrajith (2017)
Medawachchiya	–	7.23	852	–	–	324	Chandrajith et al. (2011a)
	–	7.14	1049.71	–	–	–	Nikagolla et al. (2020)
	–	–	–	–	–	324	Dissanayake and Chandrajith (2017)
Padavi-Sripura	–	–	465	–	–	125.9	Jayasumana et al. (2015b)
Mahiyanganaya	–	6.45	262.24	–	–	–	Nikagolla et al. (2020)
	–	9.2	–	1000	–	500.0	WHO maximum permissible limit

Table 3
Summary of the major trace metals concentrations of groundwater in some CKDu endemic areas of Sri Lanka (ND = not detected, standard deviation mentioned with ± mark).

Location	Trace metals (μg/L)										Reference
	As	Cd	Pb	Cr	Co	Ni	Cu	Fe	Al	Zn	
Ginnoruwa	0.17 ± 0.1	0.9 ± 1.68	0.15 ± 0.23	0.32 ± 0.27	0.29 ± 0.3	1.17 ± 0.7	1.46 ± 2.34	27.2 ± 23.5	10 ± 8.5	46 ± 58.4	Balasooriya et al. (2019)
Girandurukotte	< 0.15–0.827	0.0027–0.006	0.046–0.215	–	–	0.575–1.262	< 0.8	–	3.25–152.1	0.58–40.71	Chandrajith et al. (2011b)
	–	–	–	–	–	–	–	0.15	–	–	Chandrajith et al. (2011a)
Nikawewa	< 0.15–0.528	0.0027–0.004	0.046–0.046	–	–	0.634–1.58	< 0.8		1.53–4.56	0.59–92.81	Chandrajith et al. (2011b)
	–	–	–	–	–	–	–	0.23	–	–	Chandrajith et al. (2011a)
Padaviya	–	–	–	–	–	–	–	0.07	–	–	Chandrajith et al. (2011a)
	–	–	–	–	–	1.66	< 1	12.33	–	13.5	Nikagolla et al. (2020)
Medawachchiya	< 1	–	–	–	–	1.71	< 1	9.42	–	29.28	Nikagolla et al. (2020)
Padavi-Sripura	0.3	0.04	0.2	0.5	0.2	3.1	1.9	45.2	2.9	7.7	Jayasumana et al. (2015b)
Medirigiriya	ND	ND	0.672	ND	–	1.38	2.85	112	–	12.9	Levine et al. (2016)
Mahiyanganaya	< 1	–	–	–	–	1.71	< 1	16.42	–	26.85	Nikagolla et al. (2020)
	10	3	10	50	–	70	2000	–	200	3000	WHO maximum permissible level

water and, interestingly, there was no significant difference in F^- concentration in water collected in the wet and dry seasons. Most of the studies in NCP found high F^- values above the 0.5 mg/L level that is considered as permissible for drinking water in Sri Lanka (Chandrajith et al., 2012; Dissanayake and Chandrajith, 2017; Cooray et al., 2019). In contrast, Cl^-, NO_3^-, SO_4^{2-}, and PO_4^{3-} concentrations in drinking water were several-fold lower than the WHO recommended limits (Wickramarathna et al., 2017; Paranagama et al., 2018).

Hofmeister series cations were observed in most previous water quality studies in CKDu-affected areas (Table 4). Several studies have shown that CKDu endemic regions in NCP have comparatively lower concentrations of major cations such as K^+, Ca^{2+}, Na^+ and Mg^{2+} in drinking water (Nanayakkara et al., 2019; Wickramarathna et al., 2017; Chandrajith et al., 2011a; Nikagolla et al., 2020). Not many studies have assessed the antagonistic health effects of F^- in combination with other ions such as Mg^{2+}. However, the difference in mean Na^+/Ca^{2+} ratios between endemic and non-endemic areas has been identified as a promising factor to indicate major geochemical dissimilarities. A lower Na^+/Ca^{2+} ratio was observed in CKDu endemic areas compared to in CKDu non-endemic areas (Table S2) (Chandrajith et al., 2011a; Paranagama et al., 2018; Dissanayake and Chandrajith, 2017).

Some studies have observed slightly higher Na^+/Ca^{2+} ratios in the water of CKDu-affected regions than those identified in the study by Paranagama et al. (2018). This indicates that the ratio is not constant throughout the whole endemic region and is specific to a particular area. However, the ratio is strongly related to the F^- concentrations in groundwater (Chandrajith et al., 2011a; Rajapakse et al., 2016). Decreased Na^+/Ca^{2+} ratios in high CKDu incidence areas could be due to either the lower Na^+ activity or high Ca^{2+} activity. Calcium is the chief cation in water and is directly related to hardness, along with Mg^{2+}. The formation of NaF by complexation of F^- with Na^+ occurs rapidly when the Na^+ concentration is increased, leading to decreased F^- toxicity in the human body (Rajapakse et al., 2016). Conversely, low Na^+/Ca^{2+} ratios in conjunction with high F^- levels in water could aggregate the toxic effect of F^- on the human body (Rajapakse et al., 2016). However, there are limited findings that provide Na^+/Ca^{2+} ratios of both CKDu-affected and non-affected regions. Furthermore, high evaporation rates due to prevailing high ambient temperatures in

Table 4
Summary of the Hofmeister ion concentrations for groundwater in some CKDu endemic areas of Sri Lanka.

Location	Hofmeister ions (mg/L)									Reference
	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	F^-	NO_3^-	SO_4^{2-}	PO_4^{3-}	
Ginnoruwa	31.2 ± 14.9	0.6 ± 0.3	30.7 ± 17.9	15.1 ± 9.6	52.1 ± 18.7	0.92 ± 1.04	0.66 ± 0.56	21.2 ± 15	0.79 ± 0.42	Balasooriya et al. (2019)
Girandurukotte	22.8	1.37	13.8	19	25	0.64	2.77	12.7	1.41	Chandrajith et al. (2011a)
	21.5	0.71	35.2	13.6	42.1	0.76	0.7	11	0.34	Wickramarathna et al. (2017)
	22.8	–	13.8	19	–	0.64	–	–	–	Dissanayake and Chandrajith (2017)
Nikawewa	135	4.51	40.3	54.6	83	1.21	2.55	47.5	1.35	Chandrajith et al. (2011a)
	79	1.8	73.5	47.2	62	1.61	1.2	25.1	0.21	Wickramarathna et al. (2017)
	135	–	40.3	54.6	–	1.21	–	–	–	Dissanayake and Chandrajith (2017)
Wilgamuwa	32.4	0.66	30.7	24.1	63.6	1.4	0.8	24	0.54	Wickramarathna et al. (2017)
Padaviya	58.3	0.62	35	20.1	175	0.62	2.99	34.6	0.58	Chandrajith et al. (2011a)
	–	–	–	–	69.5	2.8	–	19.9	–	Cooray et al. (2019)
	52.32	0.66	49.33	31.03	46.55	0.67	1.38	19.98	–	Nikagolla et al. (2020)
	58.3	–	35	20.1	–	0.62	–	–	–	Dissanayake and Chandrajith (2017)
Anuradhapura	78.78	–	61.26	27.82	81.71	0.52	1.14	–	0.18	Paranagama et al. (2018)
Polonnaruwa	40.17	–	69.43	28.65	48.75	0.49	1.89	–	0.44	Paranagama et al., 2018
Medawachchiya	47.7	13.08	33.3	98	ND	1.42	6.19	39.5	0.36	Chandrajith et al. (2011a)
	65.53	1.45	86	36.91	111.64	0.68	1.03	22.4	–	Nikagolla et al. (2020)
	47.7	–	33.3	98	–	1.42	–	–	–	Dissanayake and Chandrajith (2017)
Padavi-Sripura	51.9	0.6	29	13	–	–	–	–	–	Jayasumana et al. (2015b)
Medirigiriya	39.8	2.84	55.4	20.5	–	0.6	–	–	–	Levine et al. (2016)
Mahiyanganaya	26.5	0.66	26.09	12.57	15.71	0.65	0.05	8.97	–	Nikagolla et al. (2020)
	200.0	–	200.0	150.0	600.0	1.5	50.0	600.0	–	WHO maximum permissible level

(ND = not detected, standard deviation mentioned with ± mark).

arid regions may further concentrate ions and elevate the already high electrical conductivity values in water (Cooray et al., 2019).

5.1.4. Stable isotope signals

It is crucial to investigate groundwater dynamics in CKDu endemic areas to identify any correlations with CKDu since groundwater is an important water source in CKDu affected areas. Although isotopic studies exist for CKDu endemic zones, these are flawed, and general knowledge is still scarce (Nikagolla et al., 2020). However, the first study that provided isotopic data in CKDu areas reported that the δ^2H and $\delta^{18}O$ values of groundwater in the dry zone of CKDu prevalent areas during the pre-monsoon period varied from −39.67 to −7.37‰ and from −6.46 to −1.20‰, respectively (Wickramarathna et al., 2017). These groundwater δ^2H and $\delta^{18}O$ values deviated from the LMWL for the dry zone, as defined by $\delta^2H = 7.71\ \delta^{18}O + 10.04$ ($r^2 = 0.950$); (Chandrajith et al., 2013), indicating that the groundwater was recharged from surface water or that evaporation occurred before infiltration (Wickramarathna et al., 2017). Groundwater isotope signatures that are located on the LMWL suggest that the groundwater is directly from meteoric water, without any modification (Wickramarathna et al., 2017).

Additionally, according to the study by Edirisinghe et al. (2017) in Dehiaththakandiya, Padaviya, Medirigiriya, and Nikawewa—which are in the dry zone of Sri Lanka—different mechanisms were responsible for the recharge of groundwater in each area during and after the monsoon rain. Most of the shallow and deep wells in the Dehiaththakandiya, Padaviya, and Nikawewa areas were recharged directly by infiltration of rainwater. Most of the wells in non-CKDu areas were recharged from nearby surface water bodies (Edirisinghe et al., 2017). This suggested that water in the wells of CKDu-affected areas were not impacted by surface water inputs and remained unchanged, infiltrated rainwater. All shallow and deep wells in the Medirigiriya area were replenished by infiltrated rainwater and surface water (Edirisinghe et al., 2017). Replenished shallow water is characterized by enriched heavy isotope composition, similar to surface water. This finding indicated that groundwater recharged from local rainwater and surface water was not contributing to the prevalence of CKDu in Medirigiriya. Therefore, groundwater originating from highland rain flowed through quartzite bands combined with localized limestone structures, dissolving geogenic elements along the flow path, could be associated with CKDu in the Medirigiriya area (Edirisinghe et al., 2017).

Interestingly, a study by Edirisinghe et al. (2017) suggested that the consumption of deep groundwater could be an etiological factor for CKDu. Furthermore, Nikagolla et al. (2020) conducted a study to identify the water source origin by utilizing environmentally stable isotopes of $\delta^{18}O$, δ^2H, and dissolved inorganic carbon ($\delta^{13}C_{DIC}$) values in the Mahiyanganaya, Padaviya, Medawachchciya, and Rambewa areas. It was found that δ^2H ranged from −13.7 to −37.7‰ and $\delta^{18}O$ ranged from −2.12 to −5.99‰ (Nikagolla et al., 2020); these results were consistent with the findings of Wickramarathna et al. (2017). Nikagolla et al. (2020) observed two distinct types of groundwater based on the isotopic results in the regions: some wells contained groundwater that had been recharged by local rainfall and with isotopically depleted waters that had not been exposed to evaporation; others had isotopically enriched waters that had been subject to evaporation (Nikagolla et al., 2020).

5.1.5. Agrochemicals

Since the early 1980s, farmers have relied on agrochemicals to increase profits. Agrochemicals like glyphosate, toxaphene, organochlorine, organophosphate pesticides, etc., are in high demand among farmers (Wimalawansa, 2016; Gunatilake et al., 2019; Babich et al., 2020). Apart from the aforementioned components, fertilizers, which are used in the field to enhance crop production, contain phosphate and nitrate (Wimalawansa, 2015). Therefore, field workers are exposed to a high dose of chemicals for long durations due to limited self-protection (Kulathunga et al., 2019). Interestingly, to date, there have been scarce data to support agrochemical contamination in tube well water, even though people who drink tube well water are susceptible to CKDu (Wimalawansa, 2016).

According to Bandara et al. (2008), the Cd concentration of untreated soils in the NCP area is not high. However, continuous and excessive application of low-grade triple superphosphate fertilizer (TSP) over a long period may introduce large concentrations of trace elements into agricultural soils (Bandara et al., 2008). Excessive levels of Cd (>5 μg Cd/L) in reservoirs within the irrigated agricultural area in NCP were observed (Bandara et al., 2011). Furthermore, considerable quantities of phosphate and nitrate from fertilizer accumulating in the water of CKDu endemic areas facilitate algal blooms and cyanobacterial growth (Wimalawansa, 2015). During the past few decades, glyphosate—the leading herbicide in the CKDu endemic area—has been considered as an agent of CKDu due to its ability to form stable complexes with many divalent and trivalent metallic cations including Ca^{2+} and Mg^{2+} in hard water and to act as a carrier for metals into the kidney (Jayasumana et al., 2014). It has been suggested that even if such glyphosate complexes do form, they are insoluble in water and thus minimally absorbed by organisms (Wimalawansa, 2014; Dharma-Wardana et al., 2015). However, Babich et al. (2020) suggested that even 'safe' levels of chemical mixtures could have potential impacts on kidney dysfunction via mitochondrial impairment. Jayasumana et al. (2015b) found a strong positive relationship between farmers suffering from CKDu and history of glyphosate spraying (Jayasumana et al., 2015b). Unfortunately, due to the lack of scientific data, it has not been possible to verify that glyphosate is associated with CKDu (Chandrajith et al., 2011b; Wimalawansa, 2014).

5.2. Biological factors

5.2.1. Dissolved organic matter

DOC can be used as a carbon source for microorganisms, thereby affecting biogeochemical processes (McDonough et al., 2020). Generally, microorganisms preferentially use organic matter with short carbon chains and good bioavailability (Mao et al., 2018), causing the accumulation of high molecular weight, refractory organic matter in the aquatic environment. Compared with non-CKDu areas, DOC in groundwater in CKDu affected areas is mainly refractory fulvic acid with high aromaticity and low molecular weight, which indicates that strong microbial activity has occurred (Makehelwala et al., 2020). Because natural organic matter can control the migration and transformation of heavy metals by interactions such as complexation and competitive adsorption (Hoffmann et al., 2013; Makehelwala et al., 2019; Makehelwala et al., 2020), the increase of aromatic and refractory organic matter can enhance the release of heavy metals from sediments into groundwater. The elevation of heavy metals in groundwater can damage kidney tissues and result in CKDu (Wanigasuriya et al., 2011; Nanayakkara et al., 2019; Wickramarathna et al., 2017). Although nephrotoxic elements such as As, Cd, Pb, and U cause functional and structural damage in the proximal tubule cells of the kidney, some previous studies eliminate the interactions of those nephrotoxicants to CKDu cases in Sri Lanka (Rango et al., 2015).

5.2.2. Cyanobacteria and cyanotoxins

Due to eutrophication and rising temperatures, cyanobacteria in freshwater in Sri Lanka have increased significantly over the last century (Kulasooriya, 2017; de Figueiredo et al., 2004). Previous studies have reported that cyanobacteria are present in reservoirs in CKDu-affected areas (Dissananyake et al., 2011). Surface water in reservoirs is often used for irrigation by residents, affecting the biological composition of groundwater receiving the recharge from irrigation water.

Additionally, phosphate concentration in non-CKDu areas was lower than that in CKDu affected areas (Balasooriya et al., 2019). This means that conditions are more favorable for the growth of cyanobacteria in

CKDu affected areas, as these have more abundant nutrients. Cyanobacteria can produce cyanotoxins, which can damage human kidney tissue (Liyanage et al., 2016c). Therefore, the presence of cyanobacteria in groundwater, as found by a recent study (McDonough et al., 2020), may be one potential etiological factor for CKDu.

The hypothesized link between cyanotoxin formation from algal blooms/cyanobacteria is considered an essential risk factor in the etiology of CKDu (Manage, 2019; Liyanage et al., 2016c). The recent increase in cyanobacterial blooms in surface water systems has been attributed to anthropogenic eutrophication caused by fertilizer runoff in CKDu endemic areas (Dharma-Wardana et al., 2015; Magana-Arachchi and Liyanage, 2012; Liyanage et al., 2016a). Different cyanobacterial strains have the potential to produce different types of cyanotoxins, such as microcystins (MCs), cylindrospermopsins (CYNs), and nodularins (NODs), and most of these have been detected in freshwater reservoirs of CKDu endemic areas (Liyanage et al., 2016c; Liyanage et al., 2016a). Such toxins are capable of causing numerous health impacts, including acute and chronic illnesses (Carmichael et al., 2001). Cyanobacterial species with the potential to produce MCs and CYNs identified from the well waters in Giradurukotte are shown in Fig. S4. It was found that these different cyanobacterial species belonged to four orders: Chroococcales, Nostocales, Oscillatoriales, and Stigonematales, which were identified as potential MC and CYN generators (Liyanage et al., 2016c; Liyanage et al., 2016b). Furthermore, *Phormidium* spp. (56%) were the predominant in the drinking water of CKDu prevalent area, Giradurukotte, and are potent MC and neurotoxin producers (Liyanage et al., 2016c). Other cyanobacterial species, including *Anabaena* (9%), *Raphidiopsis* (5%), and *Lyngbya* (11%), were also notable in well water samples and are also known to produce potent hepatotoxins, cytotoxins, and neurotoxins that can cause kidney damage (Runnegar et al., 2002; Liyanage et al., 2016c). It has been suggested that toxin ingestion through drinking water is unlikely because most villagers utilize groundwater for drinking and cooking (Wanigasuriya, 2012).

In addition to cyanobacterial toxins, fungal toxins such as ochratoxin A (OA), which has carcinogenic and nephrotoxic properties, could contaminate many food items (Manage, 2019). Wanigasuriya et al. (2008) showed that OA content ranged from 0.3 to 3.2 g/kg among food commodities like maize (*Zea mays*), raw and parboiled rice (*Oryza sativa*) and legumes [mung (*Vigna radiate*), cowpea (*Vigna unguiculata*), millet (*Eleusine corocana*), soya bean (*Glycine* max) and undu (*Vigna mungo*)] that are grown in CKDu-affected areas. However, there have been limited studies to identify cyanobacterial diversity or cyanotoxin producers in water bodies used for human consumption (Liyanage et al., 2016b).

6. Sociological factors

Despite the lack of scientific evidence, many consider sociological factors like immunity, economic influence, and several social behaviors and activities as potential risk factors for CKDu. These hypotheses need further investigation (Wimalawansa, 2014; Wanigasuriya et al., 2007; Ileperuma et al., 2009). However, the combination of these suspected risk factors can cause a markedly increased burden on kidneys ultimately leading to CKDu.

6.1. Immunity

Limited studies have investigated the history of infectious diseases such as malaria, hantavirus, and Japanese encephalitis as possible risk factors for the development of CKDu in Sri Lanka (Yoshimatsu et al., 2019; Sarathkumara et al., 2019; Siriwardhana et al., 2015). For example, repeated cases of malaria (~5–6 times) were suggested as increasing susceptibility to CKDu (Siriwardhana et al., 2015). Furthermore, antimalarial drugs have been shown to produce nephrotoxic effects on humans and cause structural and functional kidney damage (Adaramoye et al., 2008). Consequently, recurrent use of antimalarial drugs may act as a provoking factor for the development of CKDu in affected individuals (Siriwardhana et al., 2015). Some investigators have speculated that dehydration from working in agricultural fields for long periods under hot temperatures may contribute to the pathogenesis of CKDu by dropping the immunity (Redmon et al., 2014; Jayasekara et al., 2019; Siriwardhana et al., 2015). The majority of people in CKDu endemic areas are of low economic status and therefore, consume high-carbohydrate and high-salt diets daily, contributing to kidney malfunction (Senevirathna et al., 2012). Additionally, some researchers ponder whether genetic conditions can result in an extra burden on the kidneys (Friedman and Luyckx, 2019). Furthermore, it has been postulated that a history of snakebite could be associated with CKDu as snake venom can increase the level of nephrotoxic constituents in the body (Nanayakkara et al., 2014; Senevirathna et al., 2012).

6.2. Economic influence

Some research has identified the poor economic status of the farming community as one of the contributing factors to CKDu (Wimalawansa, 2016; Wimalawansa, 2019; Wimalawansa and Dissanayake, 2020). Due to poverty, most people in the dry zone of Sri Lanka are used to consuming only a few varieties of food instead of a balanced diet and so get limited nutrients. Therefore, eating a nutrient-deficient diet increases the possibility of malnutrition and, consequently, can affect kidney health (Senevirathna et al., 2012; Wimalawansa, 2015; Ileperuma et al., 2009). For example, repetitive consumption of a high-calorie diet deficient in protein and other micronutrients over long periods might result in chronic exposure to the toxic elements found in those foods (Ananda Jayalal et al., 2019). Interestingly, Fernando et al. (2019b) found unique features of anemia among CKDu patients in Sri Lanka compared to the already described anemia that occurs in CKD.

It has been argued that the rural lifestyle of residents in CKDu affected areas might be one of the causal factors to trigger CKDu (Senevirathna et al., 2012; Ananda Jayalal et al., 2019). Ileperuma et al. (2009) have suggested that aluminum (Al) leaching from inferior quality aluminum utensils could form toxic complexes (AlF_x) by combining with F^- present in the potable water and could act as a causal factor for chronic renal failure. Most affected individuals died at home without accessing Western medical treatment due to its unaffordability and poverty-associated travel difficulties (Wimalawansa and Dissanayake, 2020).

6.3. Social behavior

6.3.1. Living habits

Microalbuminuria in urine has been identified as an early indicator of renal damage (Wanigasuriya et al., 2011). Accordingly, Wanigasuriya et al. (2011) found that high microalbuminuria levels were likely to be detected in people who had consumed water from field wells and had previously smoked. Importantly, Kafle et al. (2019) carried out an interesting and full-scale study based on self-reports of clinical diagnoses by over 8000 households of residents diagnosed with kidney disease in the decade to 2018. It was found that more than 98% of households in CKDu prevalent districts in Sri Lanka had used groundwater for at least five years as their primary source for drinking and cooking purposes (Kafle et al., 2019). Even though it was speculated that of these 83.11% of households in districts that consume groundwater, since 2009, no CKDu affected patients have been reported (Kafle et al., 2019). The food habits and frequent consumption of tea may need to be considered as the crops are grown in affected areas might affect CKDu. Frequent tea consumption during fieldwork could result in high F^- accumulation because tea, in general, is enriched in F^-. Furthermore, habitual smoking of homegrown tobacco and drinking locally-brewed illegal alcohol has been postulated as a potential cause of CKDu (Wimalawansa, 2014; Wanigasuriya et al., 2011; Pry et al., 2019; Gobalarajah et al., 2020). Interestingly, it was found that regulating such behaviors had an approximately 2% effect on alleviating CKDu (Wimalawansa, 2019).

Regular exposure to sun heat for extended periods (occupational heat stress) during the strenuous work of farmers in the hot, dry climatic zone has been considered a co-factor for kidney malfunction (Chandrajith et al., 2011b; Jayasekara et al., 2019). For example, Siriwardhana et al. (2015) reported that exposure to heat for more than 6 h per day might be a predisposing factor for CKDu (Siriwardhana et al., 2015; Ruwanpathirana et al., 2019). Jayasekara et al. (2019) identified that CKDu is common among male farmers who work in sunlight. Similarly, according to the study based on self-reports of clinical diagnoses, 71% of males and 69% of females were CKD-symptomatic across the ten affected districts (Kafle et al., 2019). Additionally, it was common to observe people attempting to diminish the societal stigma associated with the deadly disease of CKDu by concealing their real symptoms (Wimalawansa and Dissanayake, 2020). In summary, all these factors may be intricately interconnected to contribute to individual vulnerability to CKDu.

6.3.2. Anthropogenic activities

Despite the existing environmental regulations and escalating environmental pollution, there is a visible lack of enforcement of laws relating to environmental protection in many developing countries, including Sri Lanka (Wimalawansa and Dissanayake, 2020). Therefore, anthropogenic pollution, such as leachates from septic tanks, discharge of untreated sewage, emissions from coal-powered plants, and the use of agrochemicals—especially the abuse of poor-quality agrochemicals during the Green Revolution in the 1970s—may have accumulated, caused severe damage to the local hydro-environment and possibly induced CKDu.

The possible pathways for over-dosed heavy metals—such as Pb, As, and Cd in local irrigation systems—include emissions of burnt coal, improper treatment of industrial discharge, and application of unqualified agrochemicals (Bandara et al., 2008). Burning coal enriched in F^- has aggravated the high F^- conditions derived from the weathering of fluoride-bearing minerals. Additionally, heavy metals could also enter the atmosphere and, subsequently, the hydro-system through rainfall. Reported abuse of unqualified agrochemicals and inadequate disposal of industrial chemicals has led to the continuous introduction of heavy metals into local aqueous systems. For example, the Sri Lankan agricultural sector utilized 15,300 kg of phosphate fertilizer in 1974 and 36,200 kg in 1984. The total amount of P_2O_5 used since 1973 is 957,200 kg (M.O.A., 2006). The TSP used by Sri Lankan farmers carried 71.739 mg Cd/kg of P_2O_5. At this contamination level, at least 68.9 kg Cd has been added to agricultural land since 1973 (Bandara et al., 2008). The overuse of phosphate-containing fertilizers has introduced PO_4^{3-} and Ca^{2+} into hydrological systems, which has further decreased Na^+/Ca^{2+} ratios in CKDu endemic regions.

Due to the uneven terrain, animal farming can be ubiquitous in the central highlands of Sri Lanka. Leachates of livestock excreta and solid waste mix into the River Mahaweli and distributed into natural water bodies (Mahees and Silva, 2011; Hitihamu and Epasinghe, 2015). Together with domestic wastewater and septic tank leachates, this could result in excessive NO_3^- nitrogen, PO_4^{3-}, and DOC being introduced into the dry zone hydro-environment.

7. Concluding remarks

As most of the studies on CKDu have proposed independent hypotheses—either from sociological or scientific perspectives—the exact cause of CKDu is still unknown. Although most previous studies have been based on the general water quality status, the findings have been insufficient to support any postulated hypothesis. Groundwater in the endemic regions of CKDu is rich in F^-, alkalinity, total dissolved solids, and hardness, however, with low cation exchange. Detailed studies that address the groundwater chemistry, dynamics, recharge processes, and the interaction between different elements are needed. Even though heavy metals, such as As in fertilizers, are considered a critical etiological factor for CKDu, no adequate studies exist on trace element contents in fertilizers that are commonly used among agricultural communities. However, some previous studies have clearly eliminated the interaction of heavy metals which are nephrotoxicants such as As, Cd, Pb, and U to CKDu in low doses as risk factors for the emergence of CKDu. Further, a greater attention has been devoted to the potential role of Hofmeister ions including F^- in contributing to kidney disease. Recently, a great diversity of cyanobacteria with the potential to produce cyanotoxins were identified from the drinking wells in CKDu prevalent areas. These were postulated to induce renal damage. There are gaps in knowledge about the pathways of cyanotoxin uptake in the human body. Although the Sri Lankan governments have installed many reverse osmosis (RO) plants, they failed to address the need for a treatment process for the waste 'brine', which is often released back into the same environment or the irrigation canals. Therefore, a socio-economic analysis regarding the potential effects of such temporary solutions is required. Importantly, genetics could also play an important role in the prevalence of CKDu, and intensive studies should be conducted to identify whether there is a genetic susceptibility to the condition. The causative factors for CKDu remain unconfirmed. A combination of machine learning and advanced statistics would be cooperative in delineating the most influential factors for CKDu. Future studies need collaborative efforts and in-depth synergistic studies that consider all those socio-economic environmental risk factors for CKDu, including natural and anthropogenic influences, to understand the interaction and role of each of the postulated etiological factors.

CRediT authorship contribution statement

Oshadi Hettithanthri: Data curation, Formal analysis, Writing – original draft. **Sandun Sandanayake:** Formal analysis, Writing – review & editing. **Dhammika Magana-Arachchi:** Conceptualization, Writing – review & editing. **Rasika Wanigatunge:** Conceptualization, Writing – review & editing. **Anushka Upamali Rajapaksha:** Conceptualization, Writing – review & editing. **Xianjiang Zeng:** Data curation, Formal analysis, Writing – original draft. **Qiutong Shi:** Data curation, Formal analysis, Writing – original draft. **Huaming Guo:** Conceptualization, Funding acquisition, Writing – review & editing. **Meththika Vithanage:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

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