IMPROVING OUTCOMES

FOR NONCOMMUNICABLE DISEASES IN LOW- AND MIDDLE-INCOME COUNTRIES

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CHAPTER 7

Deciphering Chronic Kidney Disease of Unknown Etiology in Sri Lanka

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Introduction and Background

Geographic Setting

Sri Lanka is an ethnically, culturally, and geographically diverse island nation located in the northern Indian Ocean off the coast of India. Although the country has many urban areas, the vast majority of its 20 million people reside in rural settings. Sri Lanka has recently transitioned from a low- to a middle-income nation and is undergoing a significant demographic shift. It has a large young population, but it also has one of the largest elderly populations in the developing world. The average life expectancy is now greater than 75 years and rising.

Sri Lanka maintains one of the strongest public health systems in developing Asia. The system is built on a foundation of community-based medical doctors, a network of mobile midwives and environmental health officers, and a commitment to investing in public health research and training. Similar to other recently established middle-income countries, the disease pattern has shifted away from infectious, maternal, and childhood concerns toward noncommunicable diseases (NCDs).

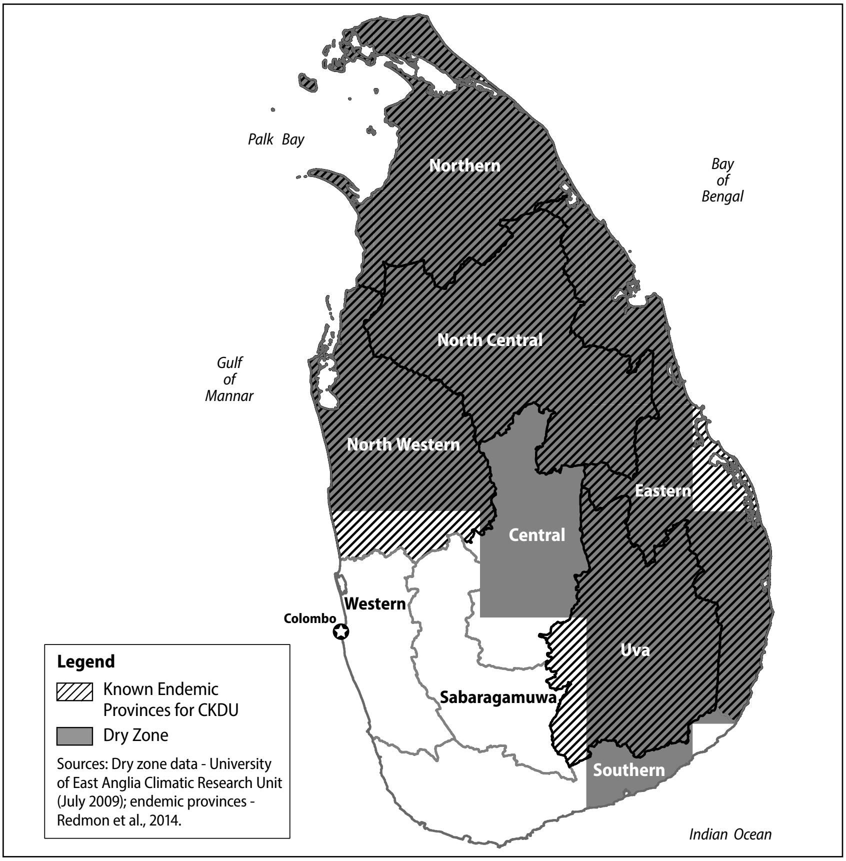
Noncommunicable Disease Burden

NCDs currently account for nearly 90 percent of the overall disease burden in Sri Lanka.[1] An increasing proportion of the Sri Lankan population is affected by NCDs attributable to several suspected factors; these include a rapidly changing age distribution, economic development, urbanization, reduced levels of physical activity, a decline in healthy eating patterns, and tobacco, alcohol, and substance use and abuse. NCDs are often perceived to be associated with affluent lifestyles, but they are also a burden for more impoverished areas of Sri Lanka. The prevalence of hypertension, for example, does not show a significant difference between the lowest and highest wealth groups.

The Chronic Kidney Disease of Unknown Etiology Epidemic

A rapidly growing facet of the NCD disease burden is chronic kidney disease (CKD). What is particularly perplexing is that CKD of unknown etiology (CKDu) is causing a public health epidemic in Sri Lanka and other developing countries with rural agriculture. These cases are concentrated in the North Central Province but are found throughout Sri Lanka's dry zone, which gets approximately 3.6 to 50 mm of precipitation annually (Figure 7.1).

Figure 7.1 Provinces in the dry zones of Sri Lanka are affected by chronic kidney disease of unknown etiology



Since the early 1990s, the number of CKDu cases has risen appreciably; about 2,000 new patients seek treatment annually in Sri Lanka. Overall, approximately 20,000 to 22,000 individuals are affected. Approximately 8,000 CKDu patients are under treatment in endemic areas.[2,3]

Diagnosing CKDu

Patients diagnosed with CKDu have CKD with a typical HbA1C below 6.5 percent (not diabetic), blood pressure below 160/100 mm Hg untreated or below140/90 mm Hg on up to two antihypertensive medications (not hypertensive), and no history of snake bite or other known risk factors associated with traditional CKD.[4] The consensus is that CKDu in Sri Lanka is asymptomatic in early stages but slowly progresses until late stages, when symptoms appear and the disease is characterized by renal tubular and interstitial damage. CKDu is present among both sexes, but more patients are men (especially those aged 30 to 60 years), the majority of late-stage cases are observed in men, and men appear to have the most severe cases.[5-7]

Searching for CKDu Risk Factors

The causes of CKDu genesis and progression are likely multifaceted. Potential risk factors hypothesized or reported include environmental exposure to nephrotoxins, agricultural work, diet and nutrition, dehydration, lifestyle factors, and genetic susceptibility.[8,9] The disease is slowly progressive and takes many years for symptoms such as fatigue, panting, nausea, anemia, and severe pain to develop. Upon diagnosis, the impact is traumatic for patients and their families, who are often unable to pay the high direct and indirect costs of the renal dialysis treatments necessary to prolong life.[10]

Within endemic areas, CKDu has affected primarily people of lower socioeconomic status who reside in agricultural areas or engage directly in farming. The World Health Organization (WHO) estimates that 15 percent of the region's population of 2.5 million is at risk. CKDu is requiring an increasingly larger proportion of limited health care budgets, and the potential risk factors associated with it are not yet understood well enough for educational awareness and prevention efforts to be effective.[2,3] Furthermore, the number of individuals with CKDu is likely underreported because of the lack of symptoms prior to advanced stages, the high costs associated with medical care, and the limited number of dialysis clinics.

CKDu Hot Spots Around the Globe

Geographical hot spots of CKDu have emerged in numerous countries spanning the globe. Rural inhabitants of Central America, including those in localized geographical areas within El Salvador, Nicaragua, and Mexico, have experienced a rapidly expanding CKDu epidemic since 2000.[11-14] CKDu in Central America is prevalent among young male agricultural workers engaged in sugarcane or cotton farming under very hot conditions. Patients experience a progressive, asymptomatic decline in kidney function, as measured by estimated glomerular filtration rate (eGFR).[15-18] Other important hot spots include India, where the disease pattern appears similar to that observed in Central America, and Tunisia, Serbia, Bulgaria, Croatia, and other localized areas within the Balkan Peninsula, where thousands of people have been affected.[19-22]

Project Collaboration Background

The size and scope of this emerging Sri Lankan health crisis prompted Professor Ananda Rajitha Wickremasinghe from the University of Kelaniya's Department of Public Health to initiate contact with RTI and formally ask whether RTI's advanced analytical skills and instrumentation could be used to obtain laboratory analytical results for biological and environmental samples that had already been collected in selected CKDu-endemic areas of Sri Lanka. A cross-disciplinary team of RTI technical staff collaborated to evaluate how the current sample repository could be analyzed at RTI; the data were subsequently used to characterize further potential CKDu risk factors and provide additional insight into the necessary structure of a more comprehensive follow-up study on CKDu.

Based on the research reviewed and regional geochemical analysis study, we explored recommendations for developing a more comprehensive and definitive way to identify CKDu risk factors in a subsequent study. We also identified how CKDu could be mitigated once the risk factors are more clearly established.

Methods

Baseline Literature Review

The RTI team first conducted a comprehensive literature review on CKDu in Sri Lanka to identify data gaps. The review included evaluating both focused studies that hypothesized that a single risk factor may be related to CKDu and a broader study that made an effort to approach the causes of the CKDu epidemic in Sri Lanka from a multifactorial standpoint.

The emerging CKDu crisis in Sri Lanka prompted a variety of investigations to determine the scope and causes of the disease. The broad research topics studied thus far include fertilizers with metal contaminants; pesticides, including organophosphates and glyphosate; mycotoxins, including ochratoxin A; hydrogeochemistry, including fluoride in water; and cookware and cooking practices. Our summary describes the findings of both highly focused studies and more broadly focused studies.

Focused Studies

In an effort to determine both the extent and potential risk factors of CKDu in Sri Lanka's North Central Province, researchers have recently conducted several etiological studies.[3] Cadmium is a known nephrotoxin and has caused environmental contamination resulting from the application of some inorganic, phosphate-based fertilizers.[25,26] Studies have reported renal tubular dysfunction following environmental exposure to cadmium elsewhere in Asia.[27,28] As rice and freshwater fish are important components of the Sri Lankan diet,[29] several studies explored cadmium levels in these media obtained from endemic area irrigation and drinking waters.[30-33] Other investigations have explored potential CKDu linkages with exposure to acetylcholinesterase (AChE)-inhibiting organophosphate pesticides or metal-chelating glyphosate broad-spectrum herbicides.[34,35]

The historic use of arsenic-containing pesticides has also prompted studies on the potential exposure to this element and the genesis of CKDu.[36] Other laboratory studies estimated the presence of nephrotoxic mycotoxins, including ochratoxin A, in food and CKDu patients within the endemic area or the deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme protecting against oxidative stress.[8,37] Ayurvedic medicines have also been cited as a potential factor in the genesis and progression of CKDu because of their high prevalence in Sri Lanka.[38]

In addition to its potential exposure from agrochemical-based nephrotoxins, Sri Lanka's CKDu-endemic area is within the country's dry zone (see Figure 7.1), which is characterized by a unique, complex hydrogeochemistry. Alternating wet and dry cycles can affect soil redox potential and other physiochemical characteristics (e.g., organic matter, pH, conductivity, cation exchange capacity) that determine heavy metal mobility and bioavailability. Also within the endemic area are regions with moderate to highly elevated fluoride content in their groundwater.[39] This phenomenon has prompted some investigators to speculate that elevated levels of this analyte, in combination with other factors, including the leaching of aluminum from low-grade cookware, can contribute to the genesis of CKDu.[40,41]

The tubulointerstitial progression of CKDu and its prevalence in the agricultural dry zone of Sri Lanka spurred many narrowly focused investigations seeking to identify population susceptibility or the presence of one or more environmental nephrotoxins, specifically agrochemical contaminants. However, because most studies focused on one potential CKDu risk factor, many studies involved small sample sizes, dated field collection or laboratory analytical methods, or incomplete media studied (e.g., biological, environmental, food). Study conclusions are therefore often difficult to replicate, resulting in more questions than answers.

Broader Study

The most comprehensive study undertaken on the CKDu issue in Sri Lanka was the product of a collaborative effort between the Ministry of Health (MoH) and WHO. This case-control study was conducted from 2009 through 2012 and sought to determine the prevalence and risk factors of CKDu in the endemic area; it featured heavy metal, pesticide, and biochemical measurements of biological and environmental samples. The biological sample types included urine, blood serum, hair, and nails. The environmental sample types included water, food (e.g., rice, vegetables, and fish), fodder (e.g., pasture, weeds), tobacco, pesticides, and fertilizer. Although the investigators collected samples for each of these sample media, the number of samples varied by media type. As an example, biological samples included 733 CKDu cases, but between 57 and 495 individuals were chosen for urine, serum, hair, and nail samples; most individuals were tested only for three heavy metal constituents. The environmental samples also varied in collection size and analysis procedures. For example, 119 food samples were collected from endemic areas and 32 were collected from nonendemic areas, whereas 88 soil samples were collected from endemic areas and 41 samples from nonendemic areas.

This study reached two conclusions. First, chronic exposure to low levels of cadmium through the consumption of contaminated food and water is a risk factor in how CKDu develops. Second, selenium deficiency and genetic susceptibility may also be predisposing factors.[42]

Although the MoH and WHO collaborative study represented an early multifaceted effort to identify the risk factors of CKDu in Sri Lanka, the findings have been controversial, and many questions remain unanswered.[41] Based on the critical analysis of the Sri Lankan MoH-WHO study, we recommended (in a previously published paper[23]) doing the following:

1. Further evaluate the CKDu case definition and refine medical testing procedures, as needed.
2. Geospatially link biological and environmental samples.
3. Provide more comprehensive information on the overall study design and field protocols.
4. Provide more comprehensive information on the laboratory protocols.
5. Publish additional studies on CKDu in Sri Lanka and integrate the findings.

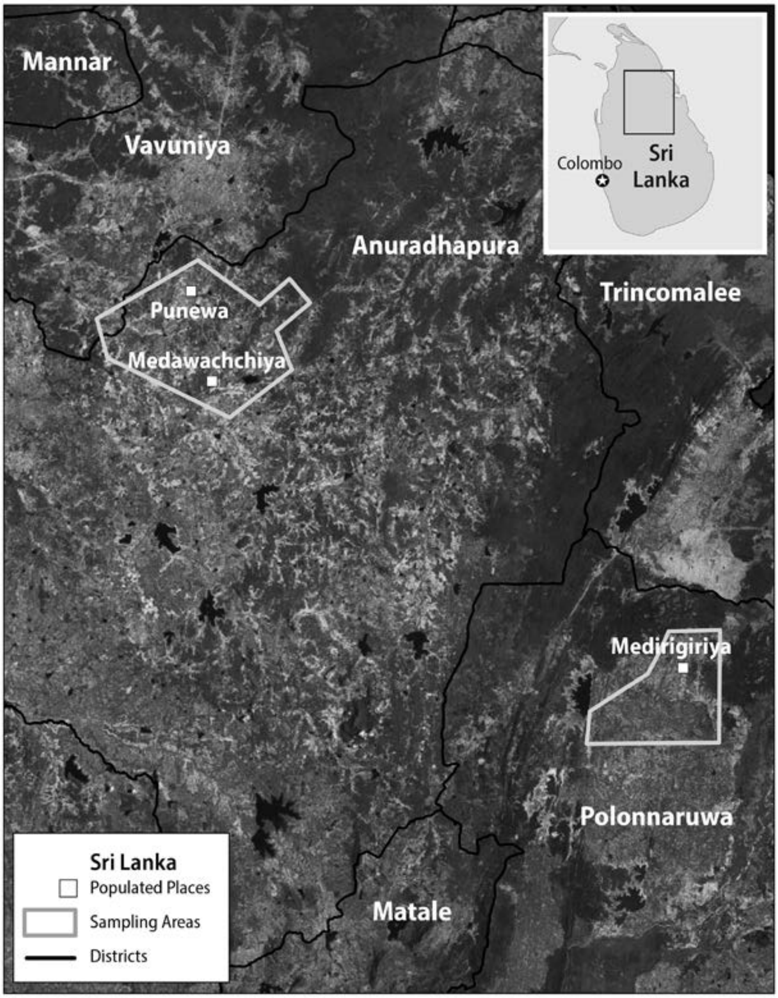
These critical analyses identified several potentially significant study design flaws.[23] Some observers have claimed that the conclusions were "predetermined" in response to enormous political and economic pressure applied by the agrochemical industry.[43]

Data Gathering and Partnership

Before RTI's involvement, field research design, brief participant interviews, and sample collection had been completed in 2012 and 2013 through a partnership between the Faculty of Medicine, University of Kelaniya (Sri Lanka); the Faculty of Medical Sciences, University of Sri Jayewardenepura (Sri Lanka); the University of Alabama at Birmingham's Department of Epidemiology (USA); and the Sri Lanka Atomic Energy Authority. The Sri Lankan collaborators conducted field design and completed sample collection in 2012 and 2013.

The Institutional Review Board of the University of Kelaniya approved informed consent and study protocols. The investigators collected a repository containing biological samples, including blood and hair, and supporting environmental media, including regional freshwater fish, locally harvested rice, drinking water, and soil samples, from CKDu cases and non-CKDu controls in endemic areas. The towns of Medawachchiya and Medirigiriya were the study sites within the North Central Province endemic area (Figure 7.2).

Figure 7.2 Sampling areas in two endemic dry zone regions of Sri Lanka



In response to the scope of the CKDu crisis and the lack of consensus concerning the MoH-WHO collaborative study findings, RTI and Sri Lankan collaborators formed a partnership in late 2013.[24] RTI personnel subsequently traveled to Sri Lanka for a data-gathering trip with university partners; the main goals were to gather general insight on the current knowledge of CKDu in the population and to arrange for transport of the sample repository and associated data to RTI International in Research Triangle Park, North Carolina, USA, for subsequent laboratory analysis.

The study collected biological samples from men ages 29 to 62 living in the North Central Province region. Environmental samples came from the environs of the study participants' residences, and local rice farmers and fishermen in the general north Central Province region provided food samples. Some individuals were undergoing ongoing medical treatment for CKDu; the diagnosis was confirmed in living patients by small, echogenic kidneys, elevated serum creatinine levels, and the presence of proteinuria via dipstick urine test without hypertension, diabetes, or other renal disease at the time of diagnosis. Controls were individuals living within the study areas but who had no biochemical evidence of CKDu.

Laboratory and Data Analysis

Following sample transport, RTI completed the advanced, blinded laboratory analyses at its headquarters in Research Triangle Park, North Carolina, between November 2013 and March 2014. The RTI Institutional Review Board approved the protocol.

The sample repository included three media types: environmental (soil and water), biological (blood), and food (rice and fish). RTI scientists analyzed the samples for targeted analyte concentrations using an array of state-of-the-art instrumentation; we sought to determine the concentration of a suite of heavy metals and additional trace elements and ions linked with CKDu in literature reports and other elements of interest. Appropriate quality control samples were processed along with study samples to ensure a high level of data quality. Collection of scientifically defensible data is critical because many published reports on this topic have been challenged on the grounds of irreproducible data and inadequate protocols. Additionally, RTI laboratories have extensive experience with measurement equipment that is not available to CKDu researchers in Sri Lanka.

We used a sensitive, broad-panel metallomics and mineralomics approach to generate geochemical laboratory analytical data. These data allowed us to determine whether the regional mean and maximum levels of these constituents in the CKDu endemic area are of potential concern in comparison with risk screening levels or published mean and maximum values. These advanced laboratory analyses addressed some of the controversial nephrotoxin findings in the MoH-WHO collaborative effort. Specifically, the analyte suite included up to 18 metals and minerals, including cadmium, arsenic, selenium, and fluoride. We used advanced sample preparation (cleanroom facility and high-purity reagents) and analysis instrumentation. These techniques included inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma optical emission spectrometry (ICP-OES), ion chromatography (IC), and combustion atomic absorption spectrometry (CAAS).

Staff analyzed several laboratory QC samples with a sample batch. Method blank data consistently indicated that analyte background contribution from the employed reagents and procedures was not significant.

Results

We conducted a regional geochemical analysis of the RTI laboratory analytical data by conducting basic statistics that identify the constituent concentration mean, minimum, and maximum values for the multimedia samples collected. We compared these values against other publicly available risk screening data (e.g., for soil and water) or published values (e.g., for blood). We also reviewed the data gaps in the current sample repository and recommended the completion of a comprehensive multimedia and georeferenced sample collection with associated survey information in a follow-up study.

The objective of this limited geochemical laboratory analysis was to determine the concentration of metals and trace element nutrients in biological samples (human whole blood and hair), food samples (fish and rice), and environmental samples (drinking water and soil). We quantified the geochemical concentrations in biological and environmental media and subsequently used basic statistical measurements to compare media against applicable benchmark values, such as US soil screening levels. Laboratory analytical findings for the biological, food, and environmental study samples from Levine et al.[24] include the following findings:

- **Blood:** Cadmium and lead blood concentrations exceeded mean US reference values from healthy nonsmokers for 68.7 percent and 89.2 percent of the samples, respectively.
- **Hair:** Mercury levels in hair exceeded US mean reference values in 60.7 percent of the samples.
- **Rice:** The maximum measured cadmium concentration in rice is below the Codex Alimentarius Commission reference level and maximum allowable concentration for Chinese rice.

- **Fish:** Observed concentrations were similar to or lower than other recent literature reports.[33,42] However, this sample size was limited and not directly linked to consumption habits.
- **Soil:** Arsenic, chromium, copper, iron, mercury, manganese, nickel, lead, and selenium concentrations exceeded mean background US soil concentrations. Within the limited number of soil samples, arsenic levels were determined to be above initial risk screening and mean background concentration reference levels.
- **Drinking Water:** Fluorine, iron, manganese, sodium, and lead exceeded applicable drinking water standards in some cases. Analyses revealed elevated fluorine levels, and many samples had “hard” or “very hard” water.

These biological data suggest that the population within the North Central Province is subject to chronic low-level exposure to cadmium, lead, and mercury. Analysts did not find that food samples exceeded reference values or standards. However, rice and freshwater fish are both important components of the Sri Lankan diet. Thus, given the relatively small number of samples collected from this limited study and the amount of these dietary food staples ingested, chronic exposure to cadmium could act as an environmental nephrotoxin. Accordingly, we recommend ongoing monitoring of these and other food staples in any subsequent laboratory analytical analysis designed to capture data that can be used to evaluate potential CKDu risk factors.

Environmental samples exceeded reference values and risk screening standards in certain cases, including arsenic, chromium, copper, iron, mercury, manganese, nickel, lead, and selenium in soils, and fluorine, iron, manganese, sodium, and lead in water. Overall, data collected from study drinking water samples reflected the unique hydrogeochemistry of the region, including elevated levels of several elements (e.g., fluorine and iron) and the prevalence of hard or very hard water.

We presented our findings at the US Environmental Protection Agency’s National Institute of Environmental Health Sciences at Research Triangle Park. We also provided educational awareness, a critique of the MoH-WHO study, and a summary of our laboratory analytical results in three separate papers.[10,23,24]

Discussion

Studies to date have focused on a variety of potential risk factors for CKDu in Sri Lanka and other CKDu hot spots. The goals of our limited regional geochemical analysis study were twofold: (1) to complete broad panel element analyses of biological (human whole blood and hair), food (rice and freshwater fish), and environmental (soil and drinking water) samples collected from the CKDu-endemic area in Sri Lanka's North Central Province and (2) to use the data from this regional geochemical analysis to inform future multifactorial investigations regarding CKDu risk factors.

Our team focused on publishing a study analyzing a limited set of multimedia biological and environmental samples. Our aim was to identify whether metals or fluoride may be present above average levels based on standard health benchmarks and population averages. Given the relatively small sample size of this study, we could not definitively identify any single hydrogeochemical condition, environmental nephrotoxin, biochemical parameter, or other regional geochemical risk factor that could be linked to CKDu.

This preliminary screening identified that specific constituents may be present above levels of concern, but it did not compare results against specific kidney toxicity values or cumulative risk related to a multifactorial disease process. The data from this limited investigation are intended to be used in the subsequent study design of a comprehensive and multifactorial etiological study of CKDu risk factors that includes sample collection, individual surveys, and laboratory analyses to comprehensively evaluate the potential environmental, behavioral, genetic, and lifestyle risk factors associated with CKDu.

The complex nature of the unfolding CKDu health crisis in Sri Lanka and the significant remaining data gaps necessitate a multidisciplinary large-scale study. The etiology of CKDu is likely related to multiple risk factors including genetic predisposition, nutritional, behavioral and lifestyle factors, and exposure to one or more environmental nephrotoxins.

Conceptual Model

In Figure 7.3, we present a potential conceptual study model based on research conducted to date. This framework is organized by source; release, fate, and transport mechanisms; exposure media; exposure route; and human receptors.

Figure 7.3 Potential conceptual study model for CKDu risk factors

Potential Source	Potential Release, Fate and Transport Mechanisms	Potential Exposure Media	Potential Exposure Route	Potential Human Receptors
Agrochemical Application (e.g. potential heavy metal content within fertilizer or pesticide) Other Environmental Factors (e.g. industrial emissions, naturally occurring metals)	Particulate Emissions or Volatilization	Air	Inhalation	Agricultural Workers (e.g. middle-aged males)
	Dispersion and Deposition	Soil	• Ingestion • Dermal Contact	
	Uptake or Bioaccumalation	Food	Ingestion	
	Leaching	Groundwater	Ingestion	
	Runoff	Surface Water	• Ingestion • Dermal Contact	
	Erosion	Sediment	Ingestion	
Low Quality Cookware	Leaching	Food	Ingestion	Residents (e.g. children)
Traditional Ayurvedic Medicines (e.g. byproducts)	Medicinal Adminstration	Medicine		
Recreational Substances	Consumption	Alcohol or Tobacco		
Other Lifestyle Factors (e.g. over- and under-nutrition)	Variable	Variable		

This conceptual study model presents an example of the sources, media, and exposure pathways to consider. Nevertheless, it may change based on additional evaluation or new research findings. Researchers could evaluate potential mechanisms of action for CKDu genesis and progression based on the various risk-factor hypotheses. For example, metal nephrotoxins are often cited as potential concerns associated with agrochemical use, whereas generalized kidney stress may be related to lifestyle or behavioral factors such as dehydration and undernutrition.

A critical component of this approach is collecting data to obtain a better understanding of occupational, nutritional, hydration, and behavioral habits for agricultural workers and residents. In future studies, we also recommend including an in-depth survey questionnaire that considers demographic, lifestyle, and behavioral factors as potential additional exposure routes and media (e.g., tobacco use, vegetable consumption, and potential occupational exposures). Doing so will create a more robust informational dataset linked to laboratory analyses and let investigators consider cumulative exposures more fully.

Georeferenced Study Location and Receptor Population

To maximize the impact of robust data and appropriate interpretation, we propose two key actions: (1) any subsequent investigation should be conducted at "hot spot" locations within the endemic area in Sri Lanka, and (2) control groups should ideally consist of both asymptomatic villages within the endemic area and villages from nonendemic areas. Additionally, studies should link all multimedia sample data directly to field questionnaire information by sample identification and georeferenced location. As noted in Redmon et al., an approach that includes multimedia sampling and analysis along with georeferencing allows for more rigorous comparative data analysis, multivariate linear regression modeling, and human health risk assessment that will decrease the overall uncertainty associated with the corresponding results.[23]

Further refining the CKDu case definition, developing an early diagnostic technique, and determining which geographic areas and hydrogeochemical parameters to include will also be critical in further differentiating endemic and nonendemic areas in the region. Lastly, efforts should be made to identify causal commonalities between CKDu in Sri Lanka and CKDu hot spots elsewhere in the world.

Quality Control

Another critical facet of future CKDu studies is early implementation of rigorous quality control procedures for both field sample and questionnaire data collection and laboratory analyses. Researchers should use both standardized protocols and advanced equipment and analytical methods to collect samples in the field and analyze them in the laboratory.

In studies to date, using inconsistent quality control procedures has complicated efforts to replicate study findings and has contributed to an atmosphere of distrust. Employing advanced sample preparation and analysis instrumentation with adequate sensitivity and resolution power to determine analytes of interest is critical, as are open and transparent quality-control procedures with a priori defined acceptance criteria. These protocols will bolster confidence in study findings within the scientific community and for the public at large.

Using a secondary, independent testing laboratory to prepare and analyze duplicate samples to compare analyte results is also important. Testing may focus on heavy metals, pesticide residues, genetic susceptibility, and biomarkers in biological and environmental samples. Implementing this step will provide further credibility to the results.

Data Evaluation

Laboratory analytical results and survey information should be evaluated using appropriate statistical analyses, which can include multivariate linear regression modeling if the sample size is sufficient. Additionally, a multimedia human health risk analysis could be conducted using concentration data obtained through field study collection and subsequent laboratory analysis and survey information about demographics, behaviors, and lifestyle factors. This knowledge base would enable investigators to model average and high health risk estimates associated with exposure to environmental nephrotoxins.

Similar studies could be implemented in other CKDu-affected countries to identify cross-country linkages. Ideally, a multicountry study could implement the same field collection, survey collection, and laboratory analytical techniques in CKDu-affected areas in two or more countries to identify and compare risk factors that contribute to CKDu incidence by country (Table 7.1).

Table 7.1 Post–field collection data evaluation and synthesis

• Conduct state-of-the-science laboratory analyses.
• Perform statistical analyses to identify linkages and conduct multimedia human health risk analysis.
• Perform similar CKDu studies in other affected countries.
• Based on results, provide educational awareness and occupational health and safety training.

Source: Adapted from Elledge et al. (2014).[10]

Educational Awareness and Training

Expanded CKDu education access and coverage are desperately needed to address fears and aid in early detection. Current programs designed to reach high-risk and endemic communities are now under-resourced. Far too many patients are unable to access care and treatment consistently. Building the capacity of both the public health system and supporting testing laboratories in terms of equipment and professional staff training will be crucial components in the ongoing struggle against CKDu.

Providing educational awareness and occupational health and safety training to residents and public health providers will be critical within the endemic area and across Sri Lanka once researchers have unequivocally identified CKDu risk factors. Educators can base informational materials and educational or occupational training programs in Sri Lanka on the findings of a comprehensive field study to pinpoint the risk factors associated with CKDu.

Identifying risk factors, encouraging better processes of diagnosis and treatment, and fostering improvement in health outcomes in endemic areas will require a robust decision-support approach, as well as working across health, agriculture, and environmental agencies. Effective educational awareness and occupational health and safety training about mitigating the risk associated with CKDu can also be extended to health workers in other countries with increasing CKDu prevalence once risk factors are more clearly identified.

Global Implications

Identifying commonalities between the CKDu epidemic in Sri Lanka and similar CKDu health crises across the world is important. Table 7.2 outlines key next steps in a global effort to deal with CKDu. Global health research

Table 7.2 Important next steps for research and program development globally

• Share information as a public service and for research purposes.
• Strengthen disease registries and surveillance reporting systems for cases of CKDu.
• Develop capacity in national environmental toxicology and epidemiological networks, including the expansion and harmonization of laboratory equipment, protocols, and training to ensure data quality.
• Prepare an economic evaluation of CKDu to model the costs and societal impact in Sri Lanka and elsewhere to support CKDu advocacy.
• Evaluate and recognize the societal and economic impacts on communities and the nation as a whole.

collaborations by professional and medical staff that would facilitate data exchange and provide training in countries affected by CKDu would benefit patients and public health systems in Sri Lanka, India, North Africa, Central America, and the Balkan Peninsula. Given the complexity of the CKDu issue, international multidisciplinary collaborations will be necessary to facilitate research and help to implement policy actions and community outreach designed to mitigate CKDu risks. To be successful, these collaborations must consider political sensitivities and complexities within the study county and seek to identify one or more in-country champions.

Conclusions

The present burden of CKDu on the economy, the public health system, and families within affected communities is tremendous. The complexity and multifaceted nature of the emerging CKDu health crisis in Sri Lanka requires an interdisciplinary approach to identify the risk factors associated with CKDu and subsequently to achieve tangible, lasting improvement in health outcomes.

Key Findings and Lessons Learned

- Based on our study results and a review of current literature, we postulate that exposure to one or more environmental factors, coupled with behavioral or lifestyle conditions and a genetic predisposition of susceptible populations, may ultimately be responsible for CKDu genesis and progression.
- Given the relatively small sample size of this study, we could not definitively identify any single hydrogeochemical condition, environmental nephrotoxin, biochemical parameter, or other regional geochemical risk factor that could be linked to CKDu.
- This preliminary screening identified that specific constituents may be present above levels of concern, but it did not compare results against specific kidney toxicity values or cumulative risk related to a multifactorial disease process.
- Our limited regional geochemical analysis was conducted to inform study design for a potential subsequent multifactorial investigation that will allow for more intensive statistical measurements, risk analysis, and modeling to improve the likelihood of identifying multiple CKDu risk factors.
- The complex, multifaceted nature of the unfolding CKDu health crisis in Sri Lanka and the significant remaining data gaps necessitate a multifaceted, large-scale comprehensive study.
- RTI is well positioned as a multidisciplinary nonprofit research institute to collaborate with in-country investigators, clinicians, and policy makers to conduct a follow-up comprehensive study to decipher the risk factors associated with CKDu, and then subsequently provide educational and international development support.

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