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CLINICAL RESEARCH

Rationale and Design of the International Prospective Study of CKD of Uncertain Etiology in Agricultural Communities

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Introduction: There has been an alarming increase in the incidence of a chronic kidney disease (CKD) of unknown etiology primarily affecting young individuals engaged in agricultural activities in Mesoamerica and South Asia. Despite extensive research over the past 2 decades, causes remain unclear. The disease is characterized by progressive loss of kidney function with the absence of heavy proteinuria and hematuria. The International Prospective Study of CKD of Unknown Etiology in Agricultural Communities (CURE study) aims to do the following: (i) identify factors associated with kidney function decline among individuals with or at risk for CKD of uncertain etiology (CKDu); (ii) better characterize the clinical phenotypes of individuals with CKDu and differentiate them from other forms of CKD; (iii) employ advanced laboratory and data analysis methods to conduct discovery science related to risk factors, biomarkers, and causal mechanisms; and (iv) establish a biorepository for future research.

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Methods: The CURE study is a prospective cohort study of up to 3600 participants from 7 sites in Central America and India aged 18 to 45 years with estimated glomerular filtration rate (eGFR) ≥ 20 ml/min per 1.73 m^2, no evidence of diabetes, and no other known causes of CKD. Biological samples and questionnaire data are collected from participants during 4 visits at 8-month intervals.

Results: Blood, urine, and hair will be analyzed for kidney function biomarkers, trace elements, pesticides and other contaminants, untargeted metabolomics, and genetic assays. Environmental samples, collected from a subset of study participants, will be analyzed for trace elements, agrochemicals, and burning exposures.

Conclusion: This study will provide novel information about CKDu etiology and clinical phenotypes across distinct geographies.

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Over the past 2 decades, a form of CKD with unknown cause has increasingly been recognized as a major global public health concern. The disease appears to be unrelated to more common causes of CKD, such as diabetes and hypertension, and is characterized by the relative absence of conventional markers of kidney damage such as heavy proteinuria and/or hematuria, with biopsy studies showing tubulointerstitial nephritis. To date, clinicians and researchers have observed the disease most commonly among young socioeconomically disadvantaged individuals mainly engaged in agricultural work, though no clear etiology has been identified.[1,2] Although various names have been used to describe the disease or diseases, we will refer to it as CKDu in this report.[3] CKDu has been most clearly documented in Central America, India, and Sri Lanka, where the disease has become a leading cause of premature death and disability, and emerging evidence suggests that other countries may also be affected.[2,4–8] Research to-date has primarily focused on heat stress in Central America and agrochemicals and metals in South Asia.[9] Recent studies have suggested the potential contribution of these and other risk factors, including infectious agents, nephrotoxic medications (e.g., certain nonsteroidal antiinflammatory drugs and traditional medicines), low birthweight, and genetic susceptibility.[3] Poverty and other social determinants of health are fundamental drivers of exposure to virtually all the suspected causes.[2]

Rationale for the CURE Consortium Study

Although some progress has been made over the past 2 decades, basic questions remain concerning the main drivers of CKDu development and progression and even its definition.[3] It is also unclear whether the causes, and even the disease itself, are the same or differ by geographic region. In 2021, 3 institutes of the National Institutes of Health, namely the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Environmental Health Sciences, and the Fogarty International Center funded the CURE research consortium to bring together a broad range of expertise in kidney disease, environmental science, and epidemiology to enable discovery science to identify the causes of CKDu and disease progression across and within geographic regions with evidence of endemic disease. The CURE consortium builds on previous research and knowledge that has provided important, but limited, insights given that the majority of published studies used a cross-sectional design, enrolled only prevalent cases, had modest sample size, and had limited exposure assessment on only 1 or 2 factors.[4–7] Importantly, differences in the identification of affected and at-risk individuals, as well as variability in sampling and analytical methods, have hampered meaningful aggregation or comparison of results across these prior studies.

We expect that many of these limitations will be addressed by the CURE consortium through a large prospective multicountry cohort study that includes affected and unaffected individuals residing in a geographic area with a high incidence of disease. The protocol uses a largely hypothesis-agnostic approach to the collection of demographics, clinical information, biospecimens, and environmental samples. The primary goals of the CURE study are the following: to (i) identify causes of decline in kidney function; (ii) better characterize the clinical phenotype(s) of individuals with CKDu and differentiate them from other forms of CKD; (iii) employ advanced laboratory and data analysis methods to conduct discovery science related to risk factors, biological markers, and causal mechanisms; and (iv) establish a biorepository for future research. We will accomplish these goals through interdisciplinary research in partnership with investigators in CKDu-affected communities.

Table 1. Locations and Institutions of the CURE consortium

Academic Partners	Countries and affiliate institutions	Locations
Boston University	El Salvador Agency for Agricultural Development and Health (AGDYSA)	Bajo Lempa Region in the District of Jiquilisco in the Department of Usulután
	Nicaragua Centro Medico del Pacifico (CENMED Pacifico, S.A.)	Municipalities of Chichigalpa and El Viejo in the Department of Chinandega
Columbia University	India The George Institute for Global Health	Uddanam Region in the State of Andhra Pradesh
University of North Carolina-Chapel Hill	Costa Rica Universidad de Costa Rica	"Cantones" (Counties) of Bagaces, Cañas, Carrillo and Liberia in the Province of Guanacaste
Universidad Nacional de Costa Rica	Costa Rica Universidad Nacional de Costa Rica	"Cantones" (Counties) of Bagaces and Cañas in the Province of Guanacaste
	Guatemala Universidad de San Carlos Guatemala from Guatemala, along with Wuqu' Kawoq Maya Health Alliance	Municipality of La Democracia in the Department of Escuintla
	Panamá Universidad de Panamá	Provinces of Coclé, Herrera, and Los Santos

AGDYSA, Agency for Agricultural Development and Health; CURE, International Prospective Study of Chronic Kidney Disease of Unknown Etiology in Agricultural Communities.

Study Organization

The CURE consortium is a cooperative network that includes the following: (i) a scientific data coordinating center that provides overall management of the study protocol, coordinates sample logistics, and conducts data quality assurance and data analysis; (ii) a renal science core that provides expertise in planning, biological samples analysis, and interpretation related to clinical phenotyping, kidney pathology, and discovery science; and (iii) 4 field epidemiology site (FES) awardees, which comprise experts in clinical care and/or the study of CKDu, and represent 7 geographic research sites across 6 countries. The FES are responsible for local ethics reviews, participant recruitment, enrollment, collection of data and biological and environmental samples, and all other interactions with study participants, such as return of results and referral to medical care. The research sites are all located in rural areas with previous evidence of high CKDu burden (Table 1, Figure 1).[10-12] The National Institutes of Health Human Health Exposure Analysis Resource laboratories are working with the CURE consortium to provide extensive consultation and technical guidance regarding sample collection and handling, and will complete laboratory analyses for environmental exposure assessment in both biological and environmental samples.[13]

Guided by a steering committee and multiple topic-specific working groups, consortium members develop and implement all aspects of the study. Additional information about the participating institutions and FES is available on the consortium website: https://ckducureconsortium.org/.

METHODS

Study Design

The CURE study is a prospective cohort study that aims to enroll 3600 individuals; one-third of participants will be enrolled in the 1 India site and the remaining two-thirds from the Central American sites. Eligible individuals must be aged 18 to 45 years with eGFR $\geq$ 20 ml/min per 1.73 m^2 as determined at local laboratories at the time of screening, have no evidence of diabetes by structured interview and glycated hemoglobin level, and no other known causes of CKD. The complete list of eligibility criteria is shown in Table 2.

Given the interest in both new cases of CKDu and progression among those with CKDu, the enrollment plan aims to achieve proportional representation across 3 categories of eGFR (30–59, 60–89, and $\geq$ 90 ml/min per 1.73 m^2). Owing to the difference by sex in reported prevalence of CKDu across study regions, we also set the enrollment target at $\geq$ 80% and $\geq$ 60% men within each eGFR stratum for Central America and India, respectively. To avoid highly imbalanced age distributions, the target for each eGFR stratum is no more than two-thirds of individuals aged either 18 to 30 or 31 to 45 years.

The overall protocol follows STROBE guidelines and is the same across research sites, with minor adjustments to accommodate variations in research regulations, policies, and practices among different countries.[14] Protocols and informed consent forms are approved by a single institutional review board in the United States and institutional review boards or local ethics committees in each country.

In the current phase of the study, participants will be followed-up for up to 2 years with visits at 8-month intervals. Acknowledging that additional data on histology and dehydration may be useful in achieving study aims, selected cohort members may participate in small substudies that focus on kidney biopsy and physiology of sodium and water handling under conditions of occupational heat stress.

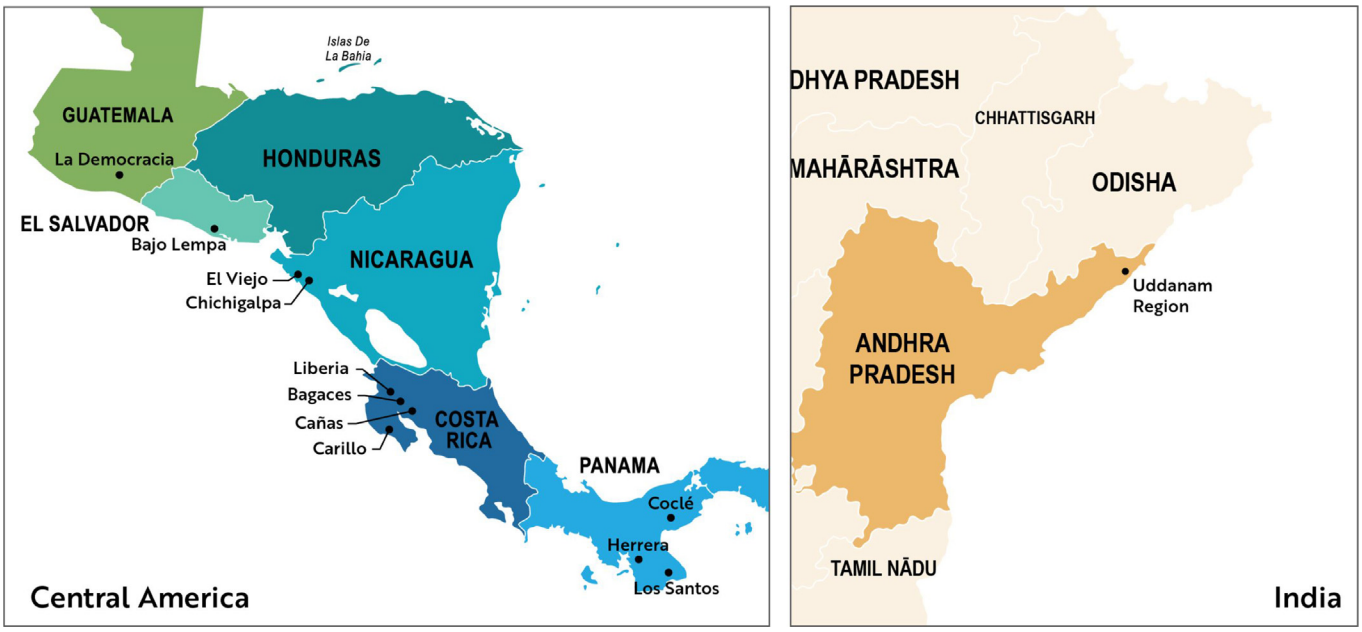

Figure 1. Geographic locations of research activities of the CURE consortium.

Study Recruitment and Visits

The FES' employ a range of recruitment strategies based on local conditions and knowledge from previous studies. The strategies are influenced by the goal of enrolling participants balanced across the spectrum of eGFR and include home visits, referrals provided by residents and formal and informal community leaders, community and workplace screening events, identification of affected individuals at clinics that treat patients with CKD, and participants identified in previous CKDu studies.

Identified individuals are screened by structured interview, urine dipstick, and analysis of serum creatinine and glycated hemoglobin. Individuals identified during the screening visits as needing medical attention are referred to the appropriate health care services. Eligible individuals who are within recruitment strata that have not yet been filled are invited to participate. The informed consent process includes a description of potential benefits and risks of the study and a description of the main study protocol, including environmental sampling. In some sites the storage of samples in a biobank and use of samples for future research is included within overall study consent; in other sites, individuals have the option to opt out of biobanking and use of their specimens for future research. Consenting individuals are enrolled within 6 weeks of the screening. To minimize participant burden and excessive blood collection at a single time point, baseline questionnaires and biological sample collection are split across 2 study visits, 1 to 3 months apart. Subsequent follow-up visits occur at approximately 8-month intervals.

The schedule of data and specimens collected by visit is shown in Table 3. The questionnaires in Spanish

Table 2. Participant inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Resident of study area for at least past 12 mo and no plans to relocate permanently in the next 12 mo • Willingness to attend study visits and provide biospecimens during the study • Aged 18–45 yrs as determined by self-report • eGFR ≥ 30 ml/min per 1.73 m^2 based on serum creatinine by local laboratory testing[c] • Albumin: urine dipstick = absent, trace, 1+for all values of eGFR; 2+ acceptable for eGFR < 60 ml/min per 1.73 m^2 • Heme urine dipstick[e]: = absent, trace, or 1+	• Evidence of diabetes mellitus (self-report, HbA1c ≥ 6.5% by local laboratory measurement and/or glucose ≥200 mg/dl by point-of-care device) • Pregnancy, as determined by self-report at screening[a] • Previous diagnosis of other forms of kidney disease[b] • Currently receiving hemodialysis or peritoneal dialysis treatment, or history of kidney transplant[b] • Solitary kidney or kidney size dimorphism (> 1.5 cm difference)[b] • Cystic kidney disease[b,d] • Kidney stones requiring surgery[f]

eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.
[a]Women who become pregnant during the study continue to be followed.
[b]In the absence of medical record information, if self-report is "no" or "unknown," the potential participant is not excluded for any of these conditions.
[c]All local laboratories are using Isotope Dilution Mass Spectrometry (IDMS) standardization method to quantify serum creatinine.
[d]If ultrasound is performed, criteria are as follows: presence of at least 3 (unilateral or bilateral) cysts among people age 18–39 or presence of at least 2 cysts in each kidney (total = 4+) among people age 40–45 yrs.
[e]Attempts are made to screen women at a time that avoids menstruation.
[f]If ultrasound or medical record is available, criteria are as follows: obstructing stone(s), single stone > 10 mm; multiple stones > 5 mm in either or both kidneys.

Table 3. Schedule of participant evaluations

Data topic or sample type	Screening	Visit 1 (study entry)	Visit 2	Visit 3	Visit 4	Visit 5
Number of mo after study entry	N/A	0	3	11	19	27
Screening consent	X					
Full informed consent		X				
Questionnaires						
Sociodemographic		X				
Personal medical history, health care access, medication		X	X	X	X	X
Family medical history		X				
Behavioral (diet, illicit drug use, alcohol use, hydration practices)		X	X	X	X	X
Occupational (job categories and tasks, manual labor)			X	X	X	X
Environmental exposures (e.g., water source, pesticide exposure)		X	X	X	X	X
Targeted physical exam						
Blood pressure and anthropometry		X	X	X	X	X
Biological sample collection						
Urine	X	X	X	X	X	X
Serum	X	X	X	X	X	X
Plasma		X	X	X	X	X
Whole blood[a]		X	X	X	X	X
Hair		X		X		
Environmental sample collection (from a subset of participants)						
Water, dust wipes, soil, and wristbands		2 time points representing distinct seasons across 5 study visits				

N/A, not available; X, collected.
[a]RNA and DNA are only collected at visits 1 and 3.

(at Central American sites) and Telegu (at the India site) assess family structure; individual demographics; medical history (including family history of kidney disease); recent medical visits; and medication use; occupational and environmental exposures, including workload, heat, hydration, water source, and use of agrochemicals; and diet and alcohol and tobacco use. Each FES pilot-tested the instruments and their linguistic adaptation and provided feedback to the scientific data coordinating center on any required changes. Blood and urine samples are obtained from all participants at all study visits, and a hair sample is obtained at visits 1 and 3. Residential drinking water, dust wipes, and silicone wristbands are collected from a subset of participants twice; once during the dry season and once during the rainy season. A smaller subset of participants will also provide a single soil sample from around their homes. Additional details about environmental sampling and analysis are provided in Gonzalez-Quiroz.[15]

Serum samples from each study visit are analyzed at a Clinical Laboratory Improvement Amendments–certified laboratory in the US using the Isotope Dilution Mass Spectrometry–traceable creatinine assay, with serum from visit 1 used to establish the baseline eGFR. Serum, plasma, and whole blood are used to measure markers of kidney function, trace elements, untargeted metabolomics, and for extraction of DNA for genetic and epigenomic assays. Urine samples are used for measurement of kidney biomarkers, untargeted metabolomics, trace elements, pesticide metabolites, and for pathogen analysis. Specific analyses for hair samples will focus on exposures that are determined to provide the greatest scientific benefit. Water, dust wipes, and silicone wristbands are being analyzed for environmental exposures, including pesticides, trace elements, and semivolatile organic compounds. On-site analysis of nitrate, conductivity, chlorine, iron, and coliforms (*Escherichia coli*) in water samples will be conducted.

Outcomes

Outcomes related to development and progression of kidney disease focus principally on the following: (i) slope of decline in eGFR over the course of the study, and (ii) occurrence of a significant decline in eGFR (defined as $> 30\%$ decline in GFR). Time to stage 5 CKD (eGFR < 15 ml/min per 1.73 m^2 or kidney replacement therapy) and death because of kidney disease will also be considered in statistical analyses, separately and as a combined composite outcome. Secondary outcomes include empirically derived eGFR trajectories; urinary and plasma biomarkers of kidney tubular injury, inflammation, and fibrosis; and other kidney function indicators discovered during the study.

Data and Specimen Management

The flow of data and specimens is shown in Figure 2. Deidentified participant-level questionnaire data are entered in the field using electronic tablets linked to a central electronic database. The scientific data coordinating center uses this database to track study progress and to produce datasets for statistical analyses. The FES staff can access their site's questionnaire and laboratory

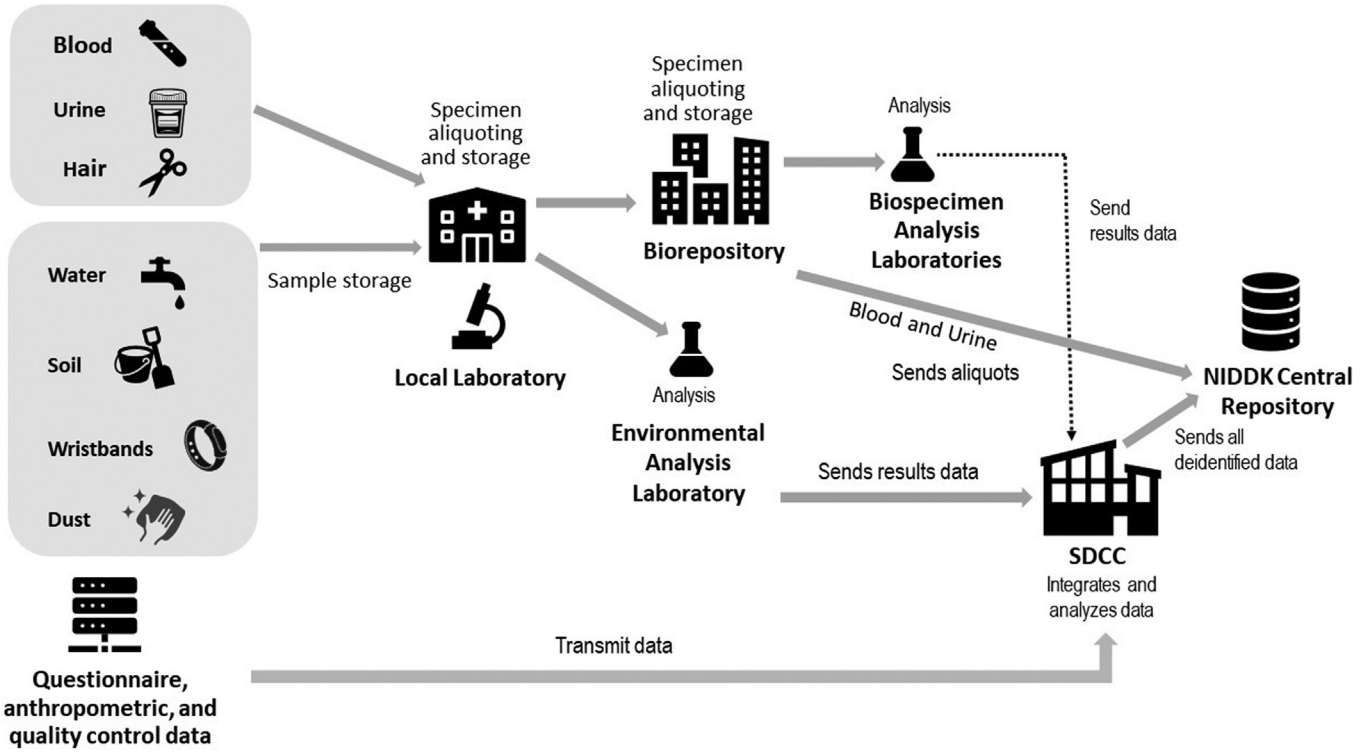

Figure 2. Flow of data and sample collection, analysis, and data storage and disposition. NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; SDCC, scientific data coordinating center.

process data in real-time through the database and standard reports. Only FES staff have access to site-specific participant personal information and GPS coordinates at the highest available level of precision for each participant's residence.

To ensure specimen quality and harmonization of processes across FES, the consortium developed Biospecimen and Environmental Sample Standard Operating Procedures, which specify the methods of sample collection, processing, local storage and shipping, biorepository storage and laboratory analysis, quality assurance and quality control, and data analysis. Local field teams reviewed and piloted the procedures before the study to ensure quality and feasibility.

Blood and urine are collected at each study visit. Blood and urine are centrifuged in the field or at a nearby local laboratory within prespecified time limits. Once processed and aliquoted, all samples are first stored at FES laboratories within appropriate temperature ranges according to standardized storage procedures. They are then batch shipped on dry ice to a central study biorepository in the US, where they are stored temporarily before being further aliquoted and shipped to appropriate laboratories throughout the US for analysis.

For the environmental sample collection, a lead field team visited each site to train and supervise the local field team for the initial implementation. Local field teams then independently complete the remaining collection for each season and manage local storage and shipment of environmental samples, maintaining communication with the lead team and other consortium investigators. Collected environmental samples are then shipped directly from the sites to laboratories in the US designated for environmental analyte testing.

Analyte data from biological samples and environmental samples collected from the participants and their homes will be linked to their questionnaire data in the main study database for statistical analyses.

At the end of the study, participants who consented to use of their samples for future analyses will have 20% volume of all blood and urine samples shipped to the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository. Researchers may access data and stored samples after review and approval of a research proposal following the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository's standard controlled access procedures.

RESULTS

Return of Results

The CURE consortium is committed to returning study results to participants, because of the potential clinical implications of findings. The consortium has developed a standard operating procedure for returning results of local laboratory tests that are clinically relevant to

individual participants (e.g., serum creatinine and glycated hemoglobin, complete blood cell count, urine dipstick results, and physical measures such as body mass index and blood pressure). The return of results occurs in real time or as soon as possible after assays are completed, and in a manner consistent with local regulations and in line with community expectations. The consortium FES' have established protocols to provide referrals, where appropriate, to specialized care when abnormal laboratory results or measures are identified. Results of analyses of interpretable and validated kidney biomarkers, genetics, agrochemicals, metals and results of on-site water analysis will be shared with participants by FES staff when available. In addition to reporting individual test results and reference values or ranges (using the World Health Organization, US Environmental Protection Agency and/or local guidelines), each site provides information about potential associated health risks and recommendations for reducing and preventing future exposures. Local results are returned as soon as possible; results for analytes measured in the US laboratories can be returned to participants approximately 6 months after samples are available in the laboratory. Study staff will deliver results in-person using templates adapted from other studies. Results of exploratory analyses of urinary or blood biomarkers will be shared in aggregate (i.e., not individually) because clinical interpretation of individual-level results for novel biomarkers may still be under development at the time results become available.

In addition to returning results to individual participants, CURE will share aggregated data with appropriate entities, such as community organizations, health facilities, and local or national government bodies. The consortium steering committee will provide overall guidance but ultimately defer to FES in determining how best to share local results, including providing culturally appropriate explanations about potential sources and health risks, recommendations to reduce or avoid exposures, and a local contact for questions.

Statistical Analysis Overview

To support the overarching goal of identifying risk factors for CKDu, including complex relationships and interactions while controlling for known confounders, associations between an individual risk factor and each of the study outcomes will be initially estimated via models that include only each single risk factor as the exposure with control for confounders. Promising associations will then be investigated by combining multiple risk factors in the same model based on a review of biologic plausibility and similarity of the measure, including interactions and nonlinear relationships. For instance, arsenic levels measured in water and hair would not be placed in the same model together because they would be expected to be highly correlated and have similar relationships. However, arsenic measured in hair could be placed in a model with nonsteroidal antiinflammatory drug use because these could have different mechanisms of action.

All analyses will be performed overall and stratified by geographic region, age category, and sex to investigate possible effect modification or interaction and further elucidate mechanisms underlying these associations. Confounders will be identified *a priori* through a literature review and confirmatory correlation analyses and will be reviewed for inclusion in specific analyses, such as evaluation of risk factors pertaining to disease onset or initiation among groups with baseline eGFR of 60 to 89 and $\geq$ 90 ml/min per 1.73 m^2 and risk factors pertaining to disease progression among the baseline eGFR $<$ 60 ml/min per 1.73 m^2 group. Change in eGFR over time, which is the primary outcome of interest, will be modeled using a generalized linear mixed model or its extensions if dichotomized.[16] All models will include fixed effects for time elapsed and confounders as well as a random subject effect to account for the within-person correlation of multiple measurements. Along with the overarching modeling strategy, the specific models used for each outcome are summarized in Table 4.

In exploratory analyses, generalized additive mixed effects models using penalized splines of the hypothesized predictor will be used to identify possible complex nonlinear relationships between risk factors and eGFR.[17] The methods described here can be fitted using restricted maximum likelihood or Bayesian approaches, both of which can be implemented using standard statistical software. We will consider supervised and unsupervised machine learning tools to account for the

Table 4. Summary of outcomes and analysis methods

Outcome	Analysis methods
Continuous eGFR at baseline	Linear regression
Categorical eGFR at baseline	Logistic regression
Change in eGFR over study	Linear mixed model (with random effect for subject)
Sustained decline in eGFR over study	Logistic regression
Acute kidney event	Logistic regression by baseline eGFR category
Time to sustained decline in eGFR over study	Kaplan-Meier graph; Cox proportional hazards model
CKDu status (determined at end of study)	Logistic regression
Urine/plasma KIM-1, urine NGAL, urine ACR at baseline and over study	Descriptive Statistics; Linear Regression

ACR, albumin-to-creatinine ratio; CKDu, chronic kidney disease of uncertain etiology; eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule -1; NGAL, neutrophil gelatinase-associated lipocalin.

correlation and high dimensionality of certain exposures. We will use machine learning tools, such as tree-based methods, to investigate interactions between environmental risk factors (e.g., random forests).[18]

Although we recognize the potential for identifying spurious associations because of the large number of risk factors being investigated, all associations will be scrutinized for biologic plausibility and whether related risk factors show similar associations. Because this study's goals are primarily exploratory to identify leading risk factors or risk factor combinations, any significant associations will be validated.

For a sample size of 3600, an exposure prevalence of 0.1, and a SD of eGFR of 18 ml/min per 1.73 m^2, the CURE study will have 90% power to detect a difference of 2.2 ml/min per 1.73 m^2 in the eGFR slope over 2 years. This assumes a dropout rate of 15% and no multiplicity adjustments. Adjusting for 50 comparisons, we can still detect a difference of 3.1 ml/min per 1.73 m^2 in average eGFR slope between exposed and unexposed groups during that time frame.

Additional Infrastructure to Support the Research

The CURE consortium benefits from a wide range of existing research expertise and on-the-ground experience that is being leveraged to evaluate the quality and feasibility of study procedures, update the protocol as more research comes to light, interpret results, and disseminate research findings to appropriate audiences within affected communities and the broader research community. Each of the committees and working groups described in Table 5 includes representatives from the FES, the scientific data coordinating center, the renal science core, and the National Institutes of Health.

Table 5. Working groups and committees of the CURE consortium

Scientific planning committee	• Discusses questions related to protocol implementation, including any amendments that the Consortium deems necessary
Data and specimens quality working group	• Oversees evaluation of the quality of the data, specimens, and procedures associated with the study • Monitors quality metrics, for example, distribution of enrollment across recruitment categories, completeness of data reporting, participant retention over time, and sample quality, to ensure scientific rigor in study implementation.
Publications and presentations committee	• Discusses potential publication topics and determines target journals and co-authorship responsibilities, ensuring that all researchers have equal opportunities to contribute to resulting publications and presentations • Actively encourages early-stage researchers to take the lead on papers
Ancillary studies committee	• Reviews applications to conduct research using CURE study data for purposes other than those specified in the specific aims
Exposures and Omics working groups	• Reviews questions related to measurement of exposures of interest and interpretation of results from questionnaire data, and environmental, metabolomic, and genetic analyses

CURE, International Prospective Study of Chronic Kidney Disease of Unknown Etiology in Agricultural Communities.

DISCUSSION

Challenges

The CURE consortium endeavors to overcome numerous challenges encountered in previous research efforts on CKDu. Compared with the few longitudinal studies that have been conducted, the CURE study is much larger, allowing for more precise estimates and more in-depth analyses, and incorporates data from India and 6 countries from Central America.[19-21] We will be able to conduct a wide range of analyses of biological and environmental samples at laboratories that employ the most recent analytical approaches and techniques. In addition, we will be able to conduct targeted physiology, biopsy, and genetic substudies that will add further depth to the assessment of both potential causes of CKDu occurrence and progression and to a better understanding of the characteristics of the disease. A standardized protocol and procedures ensure consistency in data and sample collection and facilitate comparability across study sites. In addition to laying the groundwork for a broadly applicable definition of CKDu, the work of the consortium will provide new insights into the causes of the disease and understanding of the mechanisms of disease progression.

Nevertheless, several challenges can be foreseen. First, in common with other longitudinal cohort studies of chronic diseases where relevant exposure can precede disease by years, ascertainment of past exposure generally must be obtained by questionnaire. The CURE study has included several questions that elicit historical information; however, we recognize that recall will be imperfect. Second, the reliance on eGFR equations based on serum biomarkers introduces imprecision in categorizing CKD stages, and determinants that do not affect GFR, such as diet and muscle mass, may differ across participants and across populations. This limitation is particularly pronounced in populations not represented during equation development. We are mitigating this concern by having all assays done at a single laboratory and using eGFR slope as one of the primary outcomes, because these factors do not affect intraindividual variability over time. Third, current biomarkers lack sensitivity and specificity in detecting early tubulointerstitial damage, a hallmark of CKDu, necessitating the identification of novel biomarkers that can provide specificity to CKDu diagnosis.[22]

In addition, the study faces practical challenges related to the assessment of recurrent, subclinical acute kidney injury as a potential contributor to CKDu occurrence and progression, particularly in outpatient settings where systematic biological sample collection over short time frames is challenging.[23] Factors such as internal and external migration of participants, compounded by seasonal variations in environmental exposures such as heat stress, pose logistical hurdles that can affect cohort integrity and data quality, which we will address in statistical analyses. Moreover, conducting research in low-resource and rural settings complicates the implementation of standardized protocols and the collection of detailed exposure data and biospecimens. However, this has been greatly mitigated by incorporating input into protocol and implementation development from the FES, most of whom have had substantial previous experience in conducting studies in the region. In addition, the consortium has conducted extensive training and feasibility evaluation, frequent meetings among consortium committees and working groups with simultaneous language translation and accommodations for people in multiple time zones, and development of a system for rapid feedback regarding enrollment as well as data and sample collection and quality.

Vision for the Future

Ultimately, the CURE Consortium strives to enhance global scientific and clinical understanding of CKDu. By addressing critical gaps in knowledge and fostering innovation, the consortium aims to alleviate the burden of CKDu and improve the quality of life for individuals affected by this debilitating condition worldwide. The CURE Consortium is committed to enhancing research expertise at all sites, fostering ongoing investigation, and translating findings into actionable insights for treatment and prevention strategies in the study's CKDu-endemic regions.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

As a study protocol only at this stage, no data sharing statement applies.

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