Spring 4-2020

Identifying Risk Factors For Chronic Kidney Disease Of Unknown Origin In Six Central American Countries And Houston, Texas

Erika Figueroa-Solis
UTHealth School of Public Health

IDENTIFYING RISK FACTORS FOR CHRONIC KIDNEY DISEASE OF UNKNOWN ORIGIN IN SIX CENTRAL AMERICAN COUNTRIES AND HOUSTON, TEXAS

by

ERIKA FIGUEROA-SOLIS, BS, MPH

APPROVED:

Lawrence W. Whitehead

LAWRENCE W. WHITEHEAD, PHD

GEORGE L. DELCLOS, MD, MPH, PHD

DAVID GIMENO RUIZ DE PORRAS, PHD

DEAN, THE UNIVERSITY OF TEXAS SCHOOL OF PUBLIC HEALTH

DEDICATION

To Dina Bermea, Ethan Figueroa, Ellie F. Solis, and Jose D. Solis

IDENTIFYING RISK FACTORS FOR CHRONIC KIDNEY DISEASE OF UNKNOWN ORIGIN IN SIX CENTRAL AMERICAN COUNTRIES AND HOUSTON, TEXAS

by

ERIKA FIGUEROA-SOLIS
BACHELOR OF SCIENCE, Texas A&M University, 2011
MASTER OF PUBLIC HEALTH, Texas A&M University, 2014

Presented to the Faculty of The University of Texas

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PUBLIC HEALTH

THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH
Houston, Texas
April 15, 2020

ACKNOWLEDGEMENTS

I would like to thank my family for proving their never-ending support. This has been a long road, full of personal obstacles that hindered my trajectory, but I am glad that with your care, I have finally made it to the end of this journey. I would also want to thank my committee, Dr. Delclos, Dr. Gimeno, and Dr. Whitehead, who have guided me through this doctoral process. Without their mentorship, I would not be completing this professional degree.

Data analysis for Aim 1 and Aim 2 were partially supported by Grant IL-29677-16-75-K-48 from the United States Department of Labor (USDOL). The study described in Aim 3 was funded by the Centers for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH) Education and Research Center Grant (No. 5T42OH008421) to the Southwest Center for Occupational and Environmental Health (SWCOEH) at The University of Texas Health Science Center at Houston (UTHealth) School of Public Health.

IDENTIFYING RISK FACTORS FOR CHRONIC KIDNEY DISEASE OF UNKNOWN ORIGIN IN SIX CENTRAL AMERICAN COUNTRIES AND HOUSTON, TEXAS

Erika Figueroa-Solis, BS, MPH, DrPH
The University of Texas
School of Public Health, 2020

Dissertation Chair: George L. Delclos, MD, MPH, PHD

Chronic kidney disease (CKD) is a public health problem that is recognized worldwide. The type of CKD in Central America does not fit the "usual" CKD encountered in countries with upper middle-income economies, and is also often referred to as CKD of undetermined cause (CKDu). Evidence suggests that CKDu is a disease of occupational origin that can be brought on by a combination of exposures: hot environments, high physical job demands, inadequate hydration protocols, and effects of other nephrotoxic agents. Many gaps remain in knowledge related to CKDu and its putative risk factors, geographic distribution, distributions of renal function in certain demographics and countries as well as regarding feasibility of data collection and analytic methods. To address some of these gaps, I 1) estimated the prevalence and geographic distribution of potential CKDu risk factors among industry sectors in the six Spanish-speaking countries of Central America; 2) mapped the geographic variations of temperature patterns in relation to suspected CKDu risk factors and work-related CKD in the same countries; and 3) field tested the Disadvantaged Populations estimated Glomerular Filtration Rate (eGFR) Epidemiology (DEGREE) study

protocol, outdoor point-of-care (POC) testing for serum creatinine, and a new risk factor module on CKDu for future use in U.S. outdoor Hispanic workers.

A national representative survey titled The Second Central American Survey of Working Conditions and Health (II ECCTS by its Spanish acronym) was administered to a minimum of 1,500 workers per country, of both sexes, formal and informal workers, and in both urban and rural settings. The data from the II ECCTS were used to estimate the prevalence of CKDu risk factors and CKD risk. Overall descriptive statistics, prevalence of possible CKD and work-related CKD, and prevalence of CKDu risk factors and their distribution were calculated for the overall Central American region, and stratified by economic sector. Secondly, data collected from the II ECCTS were also used to better characterize the climate patterns and the geographic distribution of suspected CKDu risk factors in order to create a weather map to identify possible new "hot spots" in Central America. Finally, we conducted a pilot study of 50 Hispanic outdoor workers in Houston, where they completed the DEGREE and CKDu questionnaires, had anthropometrics and paired blood samples obtained for POC and laboratory assays of renal function at two different points in time (fall and spring).

Findings from the national representative survey II ECCTS supplement the prior literature, demonstrating a high prevalence of self-attributed work-related CKD among 30 to 49-year-old mestizo males who worked in the primary and secondary sectors, and had physically demanding jobs. Geographically, most work-related CKD was concentrated in the central to western region of Central America associated with warm temperatures and also overlapped with persons reporting two or more CKDu risk factors. Moreover, there were several geographic areas of CKDu risk factors with no reported work-related CKDu, possibly reflecting as yet-undiscovered clusters of the disease. Implementation of the DEGREE and the new CKDu module was straightforward and well understood. The POC device performed well in the field, with some adjustment in methods when temperature readings were out of range. A combination of these methods can allow researchers to further explore CKDu and its risk factors both in new parts of Central America as well as in the U.S. among similar worker populations. This knowledge is needed so that preventive measures and interventions can be designed and implemented to prevent future cases of CKDu.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

BACKGROUND

Literature Review

A.1. Chronic kidney disease

Chronic kidney disease (CKD) is a public health problem that is recognized worldwide. According to the Kidney Disease Improving Global Outcomes (KDIGO), CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73m^2, for three months or more, irrespective of cause (Levey et al. 2005). Although most epidemiologic studies have identified certain lifestyle-related risk factors associated with CKD, such as diabetes and hypertension, there has been an increase in unidentified risk factors from environmental and occupational exposures largely growing in different parts of the world, especially developing countries (Torres et al. 2010). Studies have reported that men are more affected than women in both number and severity (Ranasinghe et al. 2019). It is predicted that this disease has caused thousands of deaths, and has increasingly reduced the life expectancy of young adults in Mesoamerica, South Asia and other tropical regions of the world (Gonzalez-Quiroz et al. 2019). For example, in Central America (Figure 1), a largely silent epidemic of chronic renal failure has been killing thousands of men over the past couple of decades (Brooks et al. 2012; Johnson et al. 2019; Lunyera et al. 2016).

Figure 1.Map of Central America. Source: Schroeder, 1978.

A.1.1. Chronic kidney disease in Central America

The type of CKD cases described in Central America does not fit the "usual" CKD encountered in countries with upper middle-income economies. These cases predominantly affect male agricultural workers, often in their 30s and 40s, and are associated with high mortality (Torres et al. 2010) (Ramirez-Rubio et al. 2013). About 20% to 40% of male employment in Central America is in agriculture (Institute 2016). The age structure of the labor force in Central America ranges from 15 to 65 years old (Bank 2012). The CKD prognosis is poor due to delays in diagnosis and the limited availability of renal replacement therapy (i.e., dialysis or renal transplantation) in their countries.

During a workshop in 2012 hosted in Costa Rica, where healthcare professionals from Nicaragua, Costa Rica, and El Salvador promoted awareness of the problems CKD had imposed in their communities, this type of CKD was given the name "Mesoamerican nephropathy"

(MeN) (Correa-Rotter and García-Trabanino 2019; Flores et al. 2016; Wijkström et al. 2013). However, it is also often referred to as CKD of undetermined cause (CKDu), or of non-traditional cause (CKDnT). The vast majority of the agricultural workforce in the United States is composed of immigrants from both Mexico and Central America; however, most of the studies examining kidney injury in agricultural workers have been performed in Central America (Mix et al. 2017).

In Central America, CKDu is hypothesized to be associated with occupational and environmental exposures affecting young men working in lowland agricultural settings in Central America, most notably sugarcane harvesters (Lozier et al. 2016; Said and Hernandez 2015; Weaver et al. 2015; Wesseling et al. 2020). Agricultural activity is relatively high in Central America; basic grains (maize, beans and rice), on average account for near 40%, and export-oriented crops (coffee, sugar cane, oil palm, banana and pineapple) about 45% of the cultivated land (Pomareda 2013).

Although mechanized agriculture is growing in Central America, manual agriculture prevails due to productivity constraints affected by low finances and agroecological conditions (Institute 2016). A study conducted in El Salvador concluded that the prevalence of decreased estimated GFR (eGFR) in men was 18% in the coastal communities compared to 1% in the communities at higher altitude that worked in the production of sugarcane (Peraza et al. 2012; Wijkström et al. 2013). Another study conducted by Laws et al. found that eGFR varied by category in sugarcane workers, and decreased during the harvest in seed cutters, irrigators, and cane cutters, as compared to factory workers (Laws et al. 2015). It was determined that the decline in kidney function during the harvest and the differences by job category and employment duration provide evidence that one or more risk factors of CKDu are occupational (Laws et al. 2015).

In addition, both El Salvador and Nicaragua have conducted cross-sectional studies of populations in Central America and used serum creatinine to confirm the increased prevalence of CKD in certain types of rural populations. These studies have demonstrated that males were more likely to be affected than females, and these men tended to be employed in the agricultural work industry performing hard labor (Wijkström et al. 2013). As a result, many of the individuals that already suffer from an apparent but undiagnosed severe form of CKD can develop terminal kidney failure, and due to the fact that dialysis or kidney transplants are in limited quantities in these countries, mortality rates are high (Gonzalez-Quiroz et al. 2019; Wijkström et al. 2013). These epidemiologic studies have also helped understand that people working at lower altitudes, with high ambient temperature levels, are more likely to develop and have CKDu than those living at higher elevations (Brooks et al. 2012; Johnson et al. 2019). Comparative studies are scarce in the other Central American countries.

More recently, a prospective study conducted in Guatemala evaluated kidney function in sugarcane workers over the 6-month harvest and found that a kidney function decline (percent change in eGFR) occurred in 36% of the participants. Moreover, relevant risk factors associated with this kidney decline included working at a particular plantation mill, being a local area worker compared with being a highland worker, and being a current smoker. Nevertheless, BMI, hypertension, pesticide or insecticide application, among other potential risk factors were not significant (Butler-Dawson et al. 2018). Moreover, there has also been increased interest on the effect on the kidney during short-term physiological changes of intense work in hot and humid environments. One study assessing heat stress and dehydration as well as pre-shift renal damage of sugarcane cutters in El Salvador observed high prevalence of reduced eGFR, and cross-shift changes consistent with recurrent dehydration from intense workload (García-Trabanino et al. 2015). Another study found that factory workers exposed to heat stress had a greater decline in estimated glomerular filtration rate compared to controls over one work shift (-13 ± 11 vs. -5 ± 7 mL/min; $p < 0.01$) (Nerbass et al. 2019). Furthermore, prevalence of CKD is significant in brick workers (12.1%, n= 27), suggesting that CKDu can be found in other occupations (Gallo-Ruiz et al. 2019).

The droughts and floods that occur due to naturally occurring phenomena of high spatial and temporal variability distinguish the six Spanish-speaking countries of interest in Central America (Guatemala, Honduras, Nicaragua, El Salvador, Costa Rica, and Panama) (Hidalgo et al. 2013). Recent advances in the geographic information system (GIS) field have allowed agriculture sectors to estimate conditions that affect both human and environmental systems, especially those that can affect water availability and drought frequency (Bouroncle et al. 2016; Hidalgo et al. 2013). Consistent projections of increased temperatures as well as dry seasons affect both crop and worker productivity. Working under hot, dry, and humid conditions can cause agriculture workers to become dehydrated and increase their chance of developing heat stress, if fluids and minerals are not adequately replenished. Prolonged conditions of this environment can decrease the worker’s kidney function, thus allowing for the potential of developing kidney disease, which can start as acute but progress to chronic (Johnson et al. 2019; Tawatsupa et al. 2012).

A.1.2. The Disadvantaged Populations Estimated Glomerular Filtration Rate Epidemiology Study (DEGREE)

As these studies conducted in Nicaragua, El Salvador, and Guatemala emerged, there has been growing interest in implementing similar studies in the U.S. in the major agricultural states. A study recently conducted found that approximately 12% of 295 agricultural workers in the Central Valley of California had cross-shift increases in serum creatinine consistent with the KDIGO criteria for acute kidney injury (AKI), a risk factor for CKD (Moyce et al. 2016). The KDIGO AKI criteria are based on defined increases in serum creatinine over defined time periods, or acute drops in urine output. Similarly, another study from Florida reported that approximately 53% of 192 agricultural workers were dehydrated pre-shift and 81% post-shift on each workday, and about 33% of participants had AKI on at least one workday (Mix et al. 2017). As is the case in Central America, these workers did not have the risk factors more commonly associated with CKD (i.e., diabetes or hypertension). This suggests that some agricultural workers in the U.S., who are predominantly Hispanic, could be sustaining similar renal injury as that observed in CKDu in Central America.

The hallmark measurement for renal failure is the GFR, which is usually estimated (eGFR) from the serum creatinine level, obtained in whole blood samples. Creatinine is a waste product that comes from the normal wear and tear on muscles of the body, and is measured in the blood stream (Foundation 2017). This alone is not the most reliable way to check kidney health – the level of creatinine in your blood is affected by age, race, gender, and body size. The best way to determine kidney health is GFR. There is a lack of characterization of the distribution of *normal* eGFR in affected populations. The degree of bias in GFR estimates is affected by ethnicity and body weight/muscle mass, with ethnicity-adjusted equations still being highly variable around the world (Caplin et al. 2017). There is very little information, though, on the variation of eGFR internationally, especially in developing nations with multiple race and ethnic groups. If such data were accurate and available, they could permit both better international comparisons and early detection of new clusters of CKDu through ecological and other epidemiological studies.

An important new initiative, designed to facilitate international comparisons of eGFR, was the recent launch of the Disadvantaged Populations Estimated Glomerular Filtration Rate (eGFR) Epidemiology Study (DEGREE) (Caplin et al. 2017). Its goal is to determine the worldwide distribution of both normal and reduced eGFR, especially in low and middle-income countries (LMICs), by encouraging researchers to follow a standardized protocol consisting of obtaining a minimum core of demographic data and standardized measurement of serum creatinine, based on a whole blood sample, analyzed using isotope dilution mass spectrometry (IDMS) in a laboratory. The protocol is designed for use both in general populations and in more focused studies of specific occupational groups. More recently, a follow-up study termed the "CO-DEGREE" focused on the lack of studies that have considered risk factors for early kidney damage in CKDu (Gonzalez-Quiroz et al. 2019). Thus, a new generic cohort protocol was proposed to characterize the decline in kidney function over time and conduct etiological research in those at risk of developing CKDu (Gonzalez-Quiroz et al. 2019).

A.1.3. The Central American Survey of Working Conditions and Health

There is an opportunity to examine other work sectors that may harbor CKDu, based on national surveys of working conditions and health in Central America. The First Central American Survey of Working Conditions and Health (I ECCTS by its Spanish acronym) was conducted in 2011, and included the six Spanish-speaking countries in Central America (i.e., all but Belize), where over 12,000 workers were interviewed in their homes. Data collection included worker and family demographics, employment conditions, occupational risk factors, self-perceived health, and access to social protections (Benavides et al. 2014). However, it did not include questions specifically directed at suspected risk factors for CKDu (i.e., exposure to heat, hydration status, physical exertion, NSAID use, etc.) nor a specific question on pre-existing kidney disease. A second round of the survey, the II ECCTS, funded in part by a cooperative agreement with the U.S. Department of Labor (USDOL), was administered in the same six countries, with full data collection completed in May 2018. Improvements were made to the original I ECCTS survey instrument, including a supplemental "Heat/Kidney Disease" module that now includes items specifically targeting the suspected CKDu risk factors. This new module could allow the identification of new clusters of CKDu in both Central America as well as in targeted populations of Hispanic workers in the U.S. The II ECCTS questionnaire is in Appendix A.

Public Health Significance

B. Public Health Significance in CKDu

Despite evidence suggesting that CKDu is a disease of occupational origin – largely due to a combination of exposure to hot environments, high physical job demands, inadequate hydration protocols, and possible added effects of other nephrotoxic agents (e.g., high use of nonsteroidal anti-inflammatory agents) – important questions remain. Although recent literature has suggested the involvement of multiple etiological factors, a systematic search has been futile on identifying a main causative agent (Herath et al. 2018). Although most studies of CKDu have centered on sugar cane and other agricultural workers, it is likely that there are other occupations with similar exposures which remain unnoticed. These hot environments can also occur in men working near furnaces, ovens, smelters, and boilers in kitchens; steel plants; foundries; automobile industries; and glass manufacturing units (Nerbass et al. 2019). Thus, there is a need for studies to examine renal function in other occupations with similar exposures, capable of causing CKDu, in both Central America and the U.S.

Furthermore, there is a relative lack of knowledge of what the baseline levels of renal function in the Central American population are, given that the normal range for these values are dependent on race and ethnicity. Screening tests for CKDu are essential in endemic-prone areas (Herath et al. 2019). Renal failure, central to the diagnosis of CKDu, is defined based on eGFR, which in turn depends on accurate measurement of serum creatinine. Until recently, there was a lack of protocols using standardized creatinine measurements in the field and laboratory. The DEGREE protocol addresses this shortcoming, but there are questions regarding the feasibility of implementing it in resource-limited countries (Caplin et al. 2019). Among these, transporting blood specimens obtained in remote areas to a central laboratory for analysis may be difficult; using Point-of-Care (POC) measurements that can be immediately analyzed in the field are an attractive alternative, but their accuracy outside of healthcare settings has not been established.

POC testing is defined as a medical diagnostic test that, instead of being performed in a clinical laboratory, is done near the patient with near-immediate real time results. It often can be performed by non-laboratory personnel, and usually requires only a small sample of blood or urine. POC has the advantage of immediate results that do not require transport of specimens and which can enable medical decision-making. Although the gold standard for serum creatinine analysis is IDMS in a central laboratory, this requires obtaining and transporting a whole blood sample within a hospital, taking about 30 minutes or longer to complete. POC measurements for creatinine have recently become available. These handheld devices are capable of providing quantitative data on a patient's renal function within minutes that could be useful in certain healthcare settings, such as emergency units and outpatient clinic settings, or even in the home (Martínez Lomakin and Tobar 2014). Recent studies have used the same type of POC device, and reported favorable findings towards kidney injury or disease. For example, in a recent study the POC i-STAT (Abbott Laboratories, Abbott Park, IL, USA) device was used to measure changes in serum creatinine from preshift and postshift work in Californian agricultural workers related to heat strain (Moyce et al. 2017). Overall, accuracy between POC devices and reference standards (clinical laboratory procedures) has been found to range between moderate and excellent, with 95% limits of agreement often lying between ±35.4 mmol/L (±0.4 mg/dL) (Gbinigie et al. 2015; Martínez Lomakin and Tobar 2014). However, most accuracy testing of POC creatinine has been done in indoor, usually climate-controlled settings. There have not been any studies that compare POC values, obtained in the field where conditions of temperature and humidity are different from indoor settings, with those of the gold standard IDMS.

Hypothesis, Research Question, Specific Aims or Objectives

C. Specific Aims

As discussed above, many gaps remain in knowledge related to CKDu and its putative risk factors, geographic distribution, distributions of renal function in certain demographics and countries as well as regarding feasibility of data collection and analytic methods. In this dissertation, I analyzed data on CKDu risk factors from the II ECCTS survey and, separately, conducted a pilot study of Hispanic outdoor workers in Houston, in order to:

Aim 1: Estimate the prevalence and geographic distribution of potential CKDu risk factors by industry sectors in Central America;

Aim 2: Map the geographic variations of climate and temperature patterns in relation to potential CKDu risk factors and work-related CKD in Central America;

Aim 3: Test the feasibility of implementing the DEGREE protocol and determine the accuracy of POC measurement and analysis obtained in outdoor environments in a sample population of Hispanic outdoor workers in Houston, TX as a precursor for future studies of renal function in both Central America and the U.S.

D. Hypotheses

Hypothesis 1: The putative CKDu risk factors among industry sectors in Central America will be more widely distributed geographically than previously reported in other studies; this could uncover more cases and clusters of CKDu than previously known.

Hypothesis 2: There will be a larger number of regions at risk for CKDu in hotter and more humid settings than previously recorded in CKDu studies.

Hypothesis 3: The DEGREE protocol will be a feasible instrument in identifying the distribution of both normal and reduced eGFR in this population. The POC will be a practical and accurate device in outdoor settings to measure blood chemistries (hemoglobin, serum creatinine, and serum BUN) when compared to IDMS.

METHODS

E. Methods

E.1. Methods for Aim 1

Aim 1: Estimate the prevalence and geographic distribution of potential CKDu risk factors by industry sectors in Central America.

E.1.1. Sample selection

The I ECCTS questionnaire was based on validated international instruments (Benavides et al. 2014); it included 78 items on demographics, employment conditions, labor rights, working conditions, and health and well-being indicators. The II ECCTS includes items specifically targeting the suspected CKDu risk factors. The questionnaire features measures of physical demands of work, exposure to heat and humidity, hydration methods, use of analgesics and exposure to other potential workplace risk factors, all presumed to increase the risk of CKDu in this region.

The survey field work of the II ECCTS was conducted in the six Spanish-speaking countries of Central America, administered to a minimum of 1,500 workers per country (n=9,032), of both sexes, formal and informal workers, and in both urban and rural settings. As in the I ECCTS (Benavides et al. 2014), to correct for differences between the sample and the source population of each country and the region as a whole, each individual included in the sample was weighted by sex, age (18–30, 31–50 and 51–65), industry sector (primary (mainly, agricultural), secondary (mainly, manufacturing and construction), tertiary (mainly, services)) and country (Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, and Panama).

Data were collected by interview at the home of the consenting adult participant between February and May of 2018. The interviewers entered the participants' responses in the field into hand-held computerized devices, which allowed for instant capture of data that were transmitted daily to a secure database repository, with backup copies stored in a separate secure location. A coding manual was prepared to guide data entry and variables coding.

E.1.2. Variable selection

For Aim 1, we extracted the following variables from the II ECCTS, as shown in Table 1: *Location: zone; Filter Questions: age; General Conditions of Employment: occupation; length of employment; Company/Business/ Establishment Characteristics: industry, location of job, commute time, means of transportation to and from work; Socio-Demographics: gender, education level, ethnic group, income level; and Module of CKDu Suspected Risk Factors: exposure to heat, humidity, physical demands, analgesics, agrochemicals, hydration protocols.* Table 1 below contains the question and answers choices for the chosen variables. All questions have the option "Do not know" or "Refuses" if the respondent spontaneously says that response.

Table 1. Study variables (from the II ECCTS Questionnaire)

Category	Question Number	Question	Answer options	Variable	Variable Categories
Location	N/A	Zone	a) Urban b) Rural	Zone	Urban Rural
Filter Question	PF1	How old are you in years?	a) Numbers	Age	18-29 30-49 50-64 65+
General Conditions of Employment / Occupational History	A4	How long have you been working in your main job?	a) Number of years b) Number of days c) Number of months	Length of Employment	Less than 1 year Up to 5 Years 6 to 10 years 11 to 15 years 16 years and above
Company/Business/ Establishment Characteristics	B23	In your main job, what is the main economic activity of the company, business, institution or organization where you work or of the job you do? Please describe the activity.	Open ended coded; later defined to a derivative of on CIIU-3.1 Classification of 2 digits: a) Agriculture b) Manufacturing c) Services d) Construction e) Sales f) Transport g) Education and Healthcare	Industry Sector	Primary Secondary Tertiary

			h) Public Administration and Defense		
	B27	Where is your main job located?	a) At your house b) At another house c) Building d) Country e) Street f) Means of transportation g) Other. Specify:	Location	At your house At another house Building Country Street
	B28	On a typical working day, how long does it approximately take for you to go from your house to your job and vice versa? (Specify hours and minutes)	a) Number of hours b) Number of minutes	Commute (minutes)	0 1-5 5-10 11-20 >21
	B29	What means of transportation do you usually use to go from your house to your job and vice versa?	a) On foot b) Bicycle c) Motorcycle d) Public transportation, e.g., bus, train, metro/subway e) Taxi f) Private car g) Company transportation h) Other. Specify:	Transportation	On foot Bicycle Motorcycle Public transportation Taxi Private car Company transportation

Socio-demographic Characteristics	F79	What is the sex of the person interviewed?	a) Woman b) Man	Sex	Female Male
	F80	What is the last year or grade level or level of education that you passed or completed?	a) I did not go to school / without school b) Elementary (grade 1, 2, 3, 4, 5 or 6) c) Middle school (grade 7, 8, 9, 10, 11, 12) d) University (years 1, 2, 3, 4, 5 o 6)	Education (years of schooling)	No schooling Elementary (Grades 1-6) Middle School (Grades 7-12) University (years 1-6)
	F83	Which ethnic group do you belong to?	a) Indigenous b) Mixed race c) White d) Black e) Mulatto f) Other	Ethnicity	Indigenous Mestizo White Black Mulatto
	F87	What has been your average monthly income over the last three months?	a) No more than $200 b) $201 to $300 c) $301 to $500 d) $500 to $1000 e) More than $1000	Household Monthly Income	No more than $200 $201 to $300 $301 to 500 $501 to $1000 More than $1000
Module: Kidney Disease	G96	Over the last 12 months, how often were you exposed, in your job, to high temperatures that made you feel uncomfortable?	a) Frequently b) Sometimes c) Rarely d) Never	Exposure to heat	Yes No

	G98	How often did you drink water at your job last week?	a) Every 30 minutes or with more frequency b) Every hour c) Every hour and a half d) Every two hours e) Every four hours. a) I did not drink water at work	No water intake	Yes No
	G99	What is the general level of humidity at your workplace?	a) Dry b) Pleasant and desirable c) A little humid f) Very humid and muggy	Exposure to humidity	Yes No
	G102	When you are at work, which of the following situations is more similar to the physical effort or the work intensity that you are carrying out?	a) Very easy b) Easy c) Strong d) Very strong d) So strong that I have to take breaks	High physical demands	Yes No
	G104	How thirsty do you get doing your job?	a) I'm not thirsty b) I'm a little thirsty c) I'm very thirsty	High thirst	Yes No
	G107	Over the last week, how many times did you take any pain killers?	c) Number of times	Use of analgesics	Yes No

	G108	Over the last 12 months, have you used or have you had direct contact with agrochemicals at your job? (Choices listed)	a) Never b) Seldom (1 to 4 times) c) Regularly (5 to 12 times) d) Frequently (more than 12 times)	High exposure to agrochemicals	Yes No

E.1.3. Statistical analysis for Aim 1

Prepared datasets and initial quality control checks were first completed through the survey vendor in Central America. The analysis was performed using the Stata statistical package (StataCorp 2017). The main analyses for Aim 1 consisted of the following: 1) weighted prevalence of the sociodemographic variables (sex, ethnicity, education, monthly income), location variable (zone), filter variable (age), occupational history (employment time), establishment characteristics (industry sectors), CKD, self-attributed work-related CKD, and each of the suspected CKDu risk factors (exposure to high heat, humidity, physical demands, agrochemicals, no water intake, use of analgesics, and high thirst; 2) logistic regression analysis to estimate the association of CKD and work-related CKD with other variables. All the analyses were completed for the Central American region as a whole (i.e., the combined sample of the six surveyed countries), and stratified by industry sector.

E.2. Methods for Aim 2

Aim 2: Map the geographic variations of climate and temperature patterns in relation to potential CKDu risk factors and work-related CKD in Central America.

E.2.1. Sample selection

This dissertation also used the self-attributed work-related and CKDu risk factor data collected from the II ECCTS questionnaire to better characterize the climate patterns and the geographic distribution of suspected CKDu risk factors. Average annual temperature readings for the year 2018 were collected from the websites National Oceanic and Atmospheric Administration (NOAA) and Time and Date under verified weather stations ((NOAA) and Information 2019; TimeandDate.com 2019). Latitude and longitude Global Positioning System (GPS) coordinates were recorded from administered surveys in both rural and urban areas as a quality control measure by the survey vendor. These GPS coordinates were used as the initial estimated location of the participant in relation to his or her workplace. The location of the participant's workplace was estimated from a combination of the following questions in the II ECCTS questionnaire: mean of transportation (II ECCTS B29), how long it takes to arrive at the job (II ECCTS B28), and the type of place where the work is located, for example, at a house, building, country, etc. (II ECCTS B27). A buffer zone of 10 miles was created from the original location coordinate to the estimated distance of the workplace location. Choosing a buffer smaller than 10 miles did not render differences between the original location coordinate and the estimated workplace location.

E.2.2. Geographic Information System (GIS)-derived data

Weather maps at different periods of time can be superimposed and removed for analysis and visualization of weather developments (Saseendran S. A. et al. 2009). Static (i.e., non-interactive or real-time) GIS weather maps were created to demonstrate the weather pattern as well as the geographic location of suspected CKDu risk factors (i.e., physical demands, heat and humidity on the job), work-related CKD, and buffer zone of the participants' workplace. Weather maps were created using ArcGIS® software by Esri (Esri 2018).

First, GPS coordinates for participants of self-attributed work-related CKD were added as "x y" data and displayed under the coordinate input system of World Geodetic System (WGS) 1984. Vector points were generated in the six countries of Central America (Guatemala, Nicaragua, Honduras, Costa Rica, El Salvador, and Panama), and saved as a layer titled "Work-related CKD". Moreover, GPS coordinates for participants who reported "yes" to any two literature-reviewed CKDu risk factors (high temperature, high humidity, and high physical demands) were added as "x y" data and also displayed under the same coordinate input system, WGS 1984. Vector points were also generated in the six countries, and saved as a layer titled "Any 2 Risk Factors (High Temperature, High Humidity, High Physical Demands). A shapefile containing vector data outlining the boundaries of the six Central American countries was added to better define the geographic location parameters of the vector points layers. Buffer analysis was completed for both work-relayed CKD and CKDu risk factor layers. Finally, weather station annual temperature readings with "x y" data were incorporated under the WGS 1984 coordinate input system, and formed vector points for the locations of the verified weather stations. Due to the lack of weather stations found in Central America, an interpolation technique called inverse distance weighted (IDW) had to be completed in order to create geographical weather patterns. The interpolation of the annual temperature readings was saved as a layer titled "2018 Annual Temperature ˚F Ranges". Thus, three different GIS layers were created: 1) work-related CKD, 2) suspected CKDu risk factors, and 3) annual temperature. Once finalized, the weather map was exported as an image. This image helped provide details about possible "hot spots" or clusters of self-attributed work-related CKD and selected CKDu risk factors found under each of the six

Central American countries by creating a geographical construct that could be identified, visualized and explored.

E.3. Methods for Aim 3

Aim 3: Test the feasibility of implementing the DEGREE protocol and determine the accuracy of POC measurement and analysis obtained in outdoor environments in a sample population of Hispanic outdoor workers in Houston, TX as a precursor for future studies of renal function in both Central America and the U.S.

E.3.1. Heat/Kidney Disease questionnaire module and DEGREE protocol

The same "Heat/Kidney Disease" module, along with the Disadvantaged Populations Estimated Glomerular Filtration Rate (eGFR) Epidemiology Study (DEGREE) protocol and Point of Care (POC) serum creatinine testing, was administered in a pilot study of Houston-based day laborers funded by Grant No. 5T42OH00842109 from the National Institute for Occupational Safety and Health (NIOSH) / Centers for Disease Control and Prevention (CDC) to the Southwest Center for Occupational and Environmental Health (SWCOEH), a NIOSH Education and Research Center (ERC) in UTSPH. The data were collected in the field in the fall of 2017 and spring of 2018. The purpose of this pilot study was to field test the DEGREE protocol, POC testing for serum creatinine, and the Heat/Kidney Disease module of the II ECCTS (see Table 1 above) in U.S. Hispanic workers, for use in a larger study of outdoor workers subject to high heat and humidity conditions, in both Central America and the U.S. The DEGREE study intends to determine the worldwide distribution of both normal and reduced eGFR. Concurrent serum creatinine sample were analyzed with POC testing as well as IDMS. These POC handheld devices are capable of providing quantitative data within minutes on a patient's renal function that could be useful in certain healthcare settings (Martínez Lomakin and Tobar 2014). However, this type of POC testing has never been implemented in an outdoor setting. To date, there have been very few international studies on the distribution and causes of CKDu. Most of the literature has described local experiences in different parts of the world, with comparisons limited by differences in case definition, study design, sampling approach, and/or methods.

E.3.2. Sample collection

A cross-sectional study design was implemented using a convenience sample of 50 Houston-based Hispanic outdoor workers, recruited from the Houston Area Safety Council (HASC) facility in Pasadena, Texas. This study began in late fall 2017, after approval by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects. HASC is a fully staffed medical and worker training facility serving contractors in the greater Houston area. Employers send their workers to HASC for various pre- employment and post-placement activities, such as: a) required and periodic medical evaluations, including laboratory testing; b) drug testing; c) respirator medical evaluations and fit testing; and d) mandated worker training sessions. A large proportion of the several hundred workers seen each day at HASC are Hispanic and work outdoors, primarily in construction. The facility is open Monday through Friday, from 6am to 6pm. HASC agreed to use their facility to: a) approach potential participants, and b) use their facility (including their parking lot) for participant interviews and collection of samples. Since time spent at the HASC facility is paid by the employers, participants were only approached while they are in waiting areas and/or on a day when they are not on their employer’s time.

The field team consisted of three members: two graduate student data collectors and a trained phlebotomist. All members were proficient in both English and Spanish. A table, chairs, blood drawing area/portable exam table, and refreshment area was set up outside of the HASC facility. Ambient temperature and humidity were measured outdoors with a standard anemometer station (TSI Q-Trak Plus Model 8554, St. Paul, MN), and recorded at hourly intervals.

Participants were approached in the HASC waiting areas, the study was explained to them, and, if interested, they were screened for eligibility criteria: 1) 18 years old and older ; 2) performing manual labor outdoors for a minimum of 20 hours a week (e.g. construction, landscaping, etc.).; 3) Hispanic; 4) no prior diagnosis of kidney injury or disease; 5) no disease associated with CKD (e.g. diabetes, hypertension, glomerulonephritis); and 6) not taking any medications to treat kidney injury, hypertension, cardiovascular disease.

Informed consent, interviewer-administered questionnaires and collection of a urine sample were completed indoors. The single blood sample, height, weight, and blood pressure were obtained outdoors, in a designated area of HASC. The sample was to be obtained and analyzed outdoors in order to test the performance of the POC device in hot environments, which was compared to standard IDMS analysis by a certified laboratory.

Eligible participants were administered two questionnaires by a member of the research team: the DEGREE protocol data collection form and the II ECCTS Heat/Kidney module. After completing the questionnaire, participant height (in stocking feet) and weight were recorded using a stadiometer and digital scale. Three resting blood pressures were obtained in the supine position using an electronic blood pressure monitor (OmronTM Digital Blood Pressure monitor with cuff; this device is programmed to take three consecutive blood pressure measurements). This is in accordance with the DEGREE protocol. Participants were also asked to provide a clean urine specimen in order to obtain a dipstick analysis using a digital analyzer (McKesson 120 Urine Analyzer), and results recorded. The HASC indoor bathroom facilities were used for collection of the urine specimen. Nevertheless, if the participant was unable or not comfortable providing a urine sample or did not complete this portion of the data collection, this section was omitted for the participant.

Next, a single blood sample of approximately 10 cc, or two teaspoons, was obtained by an experienced phlebotomist from a forearm vein, with the participant in the supine position, and the specimen was placed in one lavender, one red, and one green top tube, each labelled with the participant's study ID. The lavender and red top tubes were prepared for transport to a local LabCorpTM laboratory, as per their instructions, for measurement of hemoglobin and a basic metabolic panel analysis (i.e., creatinine, blood urea nitrogen (BUN)), using IDMS, as per the DEGREE protocol. Following the manufacturer's procedure, blood from the green top tube was used for the POC creatinine measurement obtained with the i-STAT® Chem 8+ Point of Care Handheld Analyzer (Model 04J60-20), and results were immediately recorded. Participants were then provided a cool refreshment, and monitored for five minutes to ensure there was no bleeding from the forearm site. Each participant was given a $20 gift card to Walmart, thanked for their participation and released. The total estimated participant time was 20 to 30 minutes.

E.3.3. Statistical Analysis of Aim 3

Most items in the DEGREE protocol questionnaire and the “Heat/Kidney Disease” module have the advantage of a response frequency scale, but others have only a dichotomous Yes/No response. For the iSTAT device readings, the comparison standard was defined as the LabCorp-obtained values for creatinine, BUN, electrolytes and eGFR (creatinine: 0.76 – 1.27 mg/dL; BUN: 6 – 20 mg/dL; eGFR: >59 mL/min/1.73m^2).

Scatter plots of paired lab and POC values were plotted and a line of equality drawn. The Pearson correlation coefficient (r) between the two methods was calculated in order to determine the linear correlation between the two methods. Correlation quantifies the degree to which two variables are linearly related, but does not assess or imply the agreement or differences between the measurements taken by the two methods. Bland-Altman plots were generated to assess agreement with the percent differences and means between both methods (Bland and Altman 1986). The Bland Altman plot is a scatter plot XY, in which the Y axis shows the difference between the two paired measurements (A-B) and the X axis represents the average of these measures ((A+B)/2) (Giavarina 2015). The plot demonstrates the percentage difference of the two paired measurements against the mean of the two measurements, and suggests that 95% of the data points should lie within ± 2s of the mean difference or the agreement limits (Giavarina 2015). This can help show when there is an increase in variability of the differences as the magnitude of the measurement increases, and can highlight anomalies and reveal overestimates or underestimates of one method over the other (Giavarina 2015). A mean difference of zero would indicated no bias between the two methods. When the mean difference is not zero and is a negative value, it indicates that on average the second method (B) measures more than the first method (A). When the mean difference is a positive value, it indicates that on average the first method (A) measures more than the second method (B). For this analysis, the first method was IDMS and the second method was i-STAT POC. The Stata statistical package (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) was used for the analyses.

JOURNAL ARTICLE

Prevalence and geographic distribution of self-reported chronic kidney disease and potential risk factors in Central America

International Archives of Occupational and Environmental Health.

ABSTRACT

Objectives: To estimate the prevalence and geographic distribution of self-reported work-related chronic kidney disease of undetermined origin (CKDu) and potential CKDu risk factors by industry sector in the six Spanish-speaking countries of Central America.

Methods: In 2018, the Second Central American Survey of Working Conditions and Health (II ECCTS) interviewed 9,032 workers in Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, and Panama. We calculated the prevalence and distribution of self-reported CKD, work-related CKD, and suspected CKDu risk factors. The distribution of suspected CKDu risk factors was mapped to both work-related CKDu and to GIS weather maps, using average temperatures in Central America.

Results: The primary and secondary industry sectors showed the highest prevalences of males, suspected CKDu risk factors, and work-related CKD. Age (group 30-49: OR, 2.38, 95% CI 1.03 to 5.51), ethnicity (mestizo: OR, 7.44, 95% CI 2.14 to 25.82), and exposure to high physical demands (OR, 2.45, 95% CI 1.18 to 5.09) were significantly associated with work-related CKD. The majority of work-related CKD GPS coordinates were located in the western parts of Honduras and Nicaragua, while risk factors for CKDu were more commonly reported in Guatemala, El

Salvador, and Honduras, and along coastal areas. Most work-related CKDu overlapped with areas with a high density of CKDu risk factors, with a few exceptions in central Nicaragua. Finally, there were areas that clustered CKDu risk factors without any work-related CKD points, mainly in the western part of Guatemala. Annual average temperatures in 2018 were cooler in the northern parts of Central America (67.0˚F–74.9˚F), while the highest annual average temperatures (79.0˚F-83.9˚F) were along the coastal regions of Nicaragua and Panama. Most work-related CKD coordinates were located in warm temperature regions, although suspected CKDu risk factors were present across all temperature ranges.

Conclusion: Our findings supplement the prior literature, demonstrating a high prevalence of self-reported work-related CKD among 30 to 49-year-old mestizo males who worked in the primary and secondary sectors, and had physically demanding jobs. Odds were nearly three-fold increased for those laboring in humid environments, although this did not reach statistical significance. Likewise, work in high heat and increased thirst also had nonsignificant elevated odds for work-related CKDu. Geographically, most work-related CKD was concentrated in the central to western region of Central America associated with warm temperatures and also overlapped with persons reporting two or more CKDu risk factors. Moreover, there were several geographic areas of CKDu risk factors with no reported work-related CKD in our study. Further research is needed to identify if locations with CKDu risk factor clusters represent industries and sectors not currently associated with the risk of CKDu.

Key Words: annual temperature; industry sector; CKDu; workers

INTRODUCTION

Chronic impairment of kidney function not associated with known risk factors or a specific histological diagnosis has been termed “chronic kidney disease (CKD) of undetermined origin” (CKDu) or “CKD of non-traditional cause” (CKDnt) (Caplin et al. 2017; Chicas et al. 2019; Flores et al. 2016; Wijkström et al. 2013). In Central America, CKDu is hypothesized to be associated with occupational and environmental exposures mainly affecting young men working in lowland agricultural settings, most notably sugarcane harvesters (Said and Hernandez 2015) (Wesseling et al. 2020). It is more prominent in men who have worked in such settings for two or more seasons, are between 20 and 50 years old, are asymptomatic, and have normal or only slightly elevated blood pressure and normal blood glucose levels (Johnson et al. 2019). By the year 2012, an estimated 20,000 deaths were attributed to CKDu (Ramirez-Rubio et al. 2013). Cases for CKDu are increasing and presenting in specific disease hotspots, most often located in rural agricultural communities (Correa-Rotter and García-Trabanino 2019). This disease hotspot concept creates a geographical construct that can be identified, visualized and explored using geographic information systems (GIS) and spatial analysis methods (McLafferty 2015).

Other undescribed industries that share similar risk factors could conceivably also harbor CKDu (Al-Bouwarthan et al. 2019; Gallo-Ruiz et al. 2019; Gifford et al. 2017; Nerbass et al. 2019; Nerbass et al. 2017). There is a great need for standardized tools to estimate potential kidney disease prevalence. For exploratory or hypothesis-generating purposes, data derived from national surveys of working conditions and health could serve to identify clusters of self-reported renal disease and/or its risk factors. Any such clusters could then warrant further investigation. The First Central American Survey of Working Conditions and Health (I ECCTS by its Spanish acronym) was conducted in 2011, and included its six Spanish-speaking countries (from North to South: Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, and Panama), where over 12,000 workers were interviewed in their homes. Data collection included worker and family demographics, employment conditions, occupational risk factors, self-perceived health, and access to social protections (Benavides et al. 2014). However, it did not include questions specifically directed at suspected risk factors for CKDu (i.e., exposure to heat, hydration status, physical exertion, nonsteroidal anti-inflammatory drug (NSAIDS) use, etc.) nor a specific question on pre-existing kidney disease. A second round of the survey, the II ECCTS, was administered in 2018 in the same six countries to over 9,000 workers. As was the case in the I ECCTS, the study population consisted of large, nationally representative samples of the working population. This newer survey, however, featured a supplemental "Heat/Kidney Disease" module that included self-reported items specifically targeting the suspected CKDu risk factors, as well as a question on kidney disease.

Linking survey data to their geographic location, including meteorological data, could add an element of validation to self-report as well as supplemental information on the identification and distribution of possible clusters of CKDu and its risk factors. Recent advances in the GIS field have allowed agriculture sectors to estimate conditions that affect both human and environmental systems, especially those involving water availability and drought frequency (Bouroncle et al. 2016; Hidalgo et al. 2013). The consistency of increased temperatures as well as dry seasons affect both crop and worker productivity. Working under hot, dry, and humid conditions, involving tasks characterized by high physical demands, can cause workers to become dehydrated and increase their chance of developing heat stress, if fluids and minerals are not adequately replenished (Sorensen and Garcia-Trabanino 2019). Repeated exposure to this type of environment can affect renal function, possibly through repeated episodes of acute kidney injury (AKI) that can potentially lead to chronic disease (Tawatsupa et al. 2012).

Using data from the II ECCTS and GIS linkages, we estimated the prevalence and geographic distribution of CKD and work-related CKD as well as suspected CKDu risk factors and mapped the geographic variations of temperature patterns in relation to CKDu in Central America. Completing this analysis could lead to detecting industry sectors, other than agricultural, that may share a similar prevalence of potential CKDu risk factors, harboring as yet undetected disease.

METHODS

The II ECCTS survey was administered to a nationally representative sample of 1500 workers per country (9,032 overall, from 1500 in Nicaragua to 1510 in Guatemala), and included both sexes, formal and informal workers, and both urban and rural settings. The sampling method design used to recruit participants was the same as for the I ECCTS (Benavides et al. 2014). Results were weighted by country, age, sex and industry sector: primary (mainly, agricultural), secondary (mainly, manufacturing and construction), tertiary (mainly, services). Grouping of the industry sectors can be found on supplemental Table A. Data collection was performed between February and June 2018.

Based on the I ECCTS questionnaire (Benavides et al. 2014), which included standard questions used in previous international surveys and sections on demographics, employment conditions, labor rights, working conditions, and health and well-being indicators , the II ECCTS added new items on CKDu and its suspected risk factors. The outcome of CKD was measured by a Yes/No response to the question: "*In the last month, have you experienced the following? [T] Chronic kidney disease (kidneys).*" If answered yes, participants were asked about whether or not they thought their disease was work-related (self-attributed work-related CKD). Suspected risk factors included the following: physical demands of work: measured by asking about the physical effort or the work intensity carried out at work using a visual aid and 5-point Likert scale: *very easy, easy, strong, very strong*, and *so strong that I have to take breaks*; exposures to heat (high temperatures at the workplace that made you feel uncomfortable) and humidity (general level humidity at the workplace), both of them measured using a 4-point Likert scale (*frequently, sometimes, rarely, never*); water intake measured using a 6-point Likert scale (*every 30 minutes or with more frequency, every hour, every hour and a half, every two hours, every four hours,* and *I did not drink water at work)*; being highly thirsty at the jobsite measured using a 3-point Likert scale (*not thirsty, somewhat thirsty, and highly thirsty*); use or direct contact with agrochemicals over the last 12 months measured using a 4-point Likert scale (*frequently, sometimes, rarely, never*); and use of analgesics over the last week was an open-ended response.

Statistical Analysis

We calculated the weighted prevalence of the sociodemographic variables (sex: male, female; age: 18-29, 30-49, 50-64, 65+; ethnicity: indigenous, mestizo, white, black, mulatto; education: no schooling, elementary, middle school, university; monthly income: no more than $200, $201 to $300, $301 to $500, $501 to $1000, more than $1000; employment time: less than one year, up to five years, six to ten years, 11 to 15 years, 16 years and above; zone: urban, rural; sector: primary, secondary, tertiary), self-reported CKD (answers: yes, no), self-attributed work-related CKD (answers: yes, no), and each of the six suspected CKDu risk factors: high physical job demands (responses "*strong," "very strong," and "so strong I have to take breaks"* coded as "Yes"); exposure to heat/high temperatures (i.e., answers "*frequently"* coded as "Yes") and humidity (i.e., answer "*very humid and muggy"* coded as "Yes"); no water intake (i.e., answer "*I don't drink water at work"* coded as "Yes"); high thirst (i.e., answer *"I'm very thirsty"* coded as "Yes"); use of agrochemicals (i.e., answer *"frequently"* coded as "Yes"); and use of analgesics (responses indicating using one or more analgesics). Logistic regression was used to estimate the association of CKD and work-related CKD with other variables. Regression models were built applying Hosmer and Lemeshow model-building strategy (Hosmer et al. 2013) as follows: First, two separate bivariate models were built between each of the outcome variables (CKD and work-related CKD) and all the other variables. Second, two separate multivariate models (one model for the outcome variable CKD and the second model for outcome variable work-related CKD) were performed by incorporating all the variables for which their association in the bivariate analyses with the corresponding outcome had a p-value < 0.2. Hosmer-Lemeshow goodness-of-fit tests were run to determine models' fit, which is indicated by a p-value greater than 0.5 (Fagerland and Hosmer 2012). All statistical analyses were performed using Stata IC-64 v.16 (StataCorp 2017).

For the generation of static GIS weather maps to show the link of weather patterns with work-related CKD, suspected CKDu risk factors and geographic buffer zone location of the workplace reported by the participants, we used ArcGIS® (Esri 2018). We first linked the de-identified survey data to GIS weather maps by GPS coordinates to characterize the climate patterns and the geographic distribution of CKD and CKDu risk factors. Average annual temperature readings were collected from the National Oceanic and Atmospheric Administration (NOAA) and

Time and Date under verified weather stations websites ((NOAA) and Information 2019; TimeandDate.com 2019). Interpolation was completed using the weather station readings in order to estimate the average annual temperature of the participant's outdoor work environments. In order to estimate workplace locations, location coordinates were measured and compared to the survey questions asking for means of transportation, how long it takes to arrive at the job, and the type of place where the work is located, for example, at a house, building, country, etc. in order to calculate distance traveled. A buffer zone of 10 miles was created from the original location coordinate to the estimated distance of the workplace location. Well-documented literature-reviewed CKDu risk factors, such as physical demands, heat and humidity on the job, were selected (Correa-Rotter and García-Trabanino 2019; Wesseling et al. 2020). A map was created for using the answers coded as "yes" to any two CKDu risk factors.

RESULTS

In the weighted sample of workers in the total of Central America, there were more men than women (61% vs. 39%) (Table 1). The proportion of males was much larger in the primary sector than in the two other sectors. A high number of participants were in the 30 to 49-year age group, had a middle school education and earned less than $200 a month. The most frequently reported CKDu risk factors were high physical demands at work (49.0%) and use of analgesics (87.2%). In general, 4.4% of the participants reported a history of CKD (n= 370); 38% (n=141) of these were self-reported as work-related CKD. When comparing across industry sectors, workers in the primary sector reported higher percentages for middle school education, earning less than $200 a month, and five CKDu risk factors (high physical demands, exposure to heat, exposure to humidity, high use of agrochemicals and having high thirst). The majority of workers in the secondary and tertiary sectors reported a university education, earning at least $500 a month, and one CKDu risk factor (no water intake). Close to half of the workers across all sectors had been employed at least five years in their current job.

The CKD and work-related CKD groups had an elevated prevalence of high physical demands (63% and 75%, respectively) and use of analgesics (78% and 71%, respectively) (Table 2). Workers in the primary and secondary sectors who reported CKD and work-related CKD had higher percentages of high physical demands, exposure to heat, exposure to humidity, high use of agrochemicals and high thirst than those in the tertiary sector. For both CKD and work-related CKD, high analgesic use and no water intake at work were higher in the tertiary sector.

Bivariate logistic regression analysis identified the following variables for selection into the multivariate analysis ($p<0.20$): CKD: age, education, monthly income, length of employment, zone, and sector of economy, high physical demands, exposure to heat and humidity, high thirst, no water intake, use of analgesics; work-related CKD: sex, age, ethnicity, monthly income, economic sector, high physical demands, exposure to humidity, no water intake (Table 3). Six CKDu risk factors (except high use of analgesics) were included in the multivariate analysis for both CKD and work-related CKD models for consistency across both dependent variables.

Table 4 summarizes the final multivariate models for both CKD and work-related CKD. Exposure to high humidity (OR, 2.08, 95% CI 1.07 to 4.06), no water intake (OR, 1.93, 95% CI 1.05 to 3.57), and high thirst (OR, 1.89, 95% CI 1.25 to 2.86) were significantly associated with CKD. The 30 to 49-year age group (OR, 2.38, 95% CI 1.03 to 5.51), ethnicity (mestizo: OR, 7.44, 95% CI 2.14 to 25.82), and exposure to high physical demands (OR, 2.45, 95% CI 1.18 to 5.09) were significantly associated with work-related CKD; high humidity had a two-fold elevated OR (2.31), although it did not reach statistical significance [95% CI 0.57-9.37]. Goodness of fit tests for both fully adjusted models showed a good fit ($p>0.05$).

The static GIS weather map, and its linkages to work-related CKDu and persons with two or more CKDu risk factors for Central America are shown in Figure 1. The majority of work-related CKD GPS coordinates were located in the western parts of Honduras and Nicaragua. Risk factors for CKDu (exposure to heat, exposure to humidity, and high physical demands) were more commonly reported in Guatemala, El Salvador, and Honduras, and along coastal areas. Most work-related CKDu overlapped with areas with a high density of CKDu risk factors. However, there were a few work-related CKD coordinates that did not have this overlap, primarily in central Nicaragua and isolated instances, along its Atlantic coast. Conversely, there were areas that clustered CKDu risk factors without any work-related CKD points, chiefly in the western part of Guatemala.

Annual average temperatures in 2018 were cooler in the northern parts of Central America (67.0˚F–74.9˚F), while the highest annual average temperatures (79.0˚F-83.9˚F) were along the coastal regions of Nicaragua and Panama. Most work-related CKD coordinates were located in warm temperature regions (75.0˚F and above). The CKDu risk factors were present across all temperature ranges, but more so in relatively cool areas (67.0˚F–74.9˚F) or very warm areas (70.0˚F-81.9˚F).

DISCUSSION

To our knowledge, this represents the first epidemiological large-scale, population-based study of CKDu and its risk factors in Central America. Young men without common risk factors or underlying conditions, such as diabetes or hypertension, leading to CKD but who work in physically demanding jobs under conditions of high heat and humidity are at high risk of CKDu (Chicas et al. 2019; Johnson et al. 2019). Our findings, using data from nationally representative samples of workers in Central America, supplement the prior literature, demonstrating a high prevalence of self-attributed work-related CKD among 30 to 49-year-old males who worked in the primary and secondary sectors, and had physically demanding jobs. Odds were nearly three-fold increased for those laboring in humid environments, although this did not reach statistical significance. Likewise, work in high heat and increased thirst also had nonsignificant elevated odds for work-related CKDu. Geographically, most work-related CKD was concentrated in the central to western region of Central America associated with warm temperatures and also overlapped with persons reporting two or more CKDu risk factors. These areas, which include Nicaragua, El Salvador and Costa Rica, are well described in the literature as focal areas of CKDu (Correa-Rotter and García-Trabanino 2019; Gallo-Ruiz et al. 2019; Gifford et al. 2017; Laws et al. 2015; Lunyera et al. 2016; Minnings et al. 2015; Wesseling et al. 2015; Yih et al. 2019). However, there are less well-known areas, such as the central part of the Region, particularly Honduras, where cases are less often described, and should be further studied. Moreover, there were several geographic areas of CKDu risk factors with no reported work-related CKD in our study. Among these were central Guatemala, as well as the coastal areas of Panama and southern Costa Rica. This latter group represents an opportunity for further follow-up with studies that include measurement of renal function to identify as yet undeclared clusters of CKDu cases.

We observed that work-related CKD was associated with sociodemographic variables, mainly sex, age and ethnicity. This is consistent with the target population: middle-aged men between 30 to 50 years old (Correa-Rotter and García-Trabanino 2019; Friedman 2019; Wesseling et al. 2020; Yih et al. 2019). Although the mestizo ethnicity was also significantly associated with work-related CKD, previous studies have yet to find CKD-risk to be ethnicity-specific to the mestizo population (González-Quiroz et al. 2017; Perez-Gomez et al. 2018). The term “mestizo” is used to identify populations who have an extensive admixture of Native American, European and African ancestry (Wang et al. 2008). Two ethnicity-specific genes have been associated with end-stage renal disease of unknown etiology in other populations: apolipoprotein L1 (APOL1) gene in African Americans, and Glutathione S-transferase Mu 1 (GSTM1) null phenotype in the Mexican population (Freedman and Sedor 2008; Gutiérrez-Amavizca et al. 2013; Sayanthooran et al. 2016). This evidence has caused the authors of these studies to suggest the possible association of genetic factors or variants with the mestizo population. However, no studies have addressed this to any great extent in the mestizo population in Central America to verify this assumption. Thus, further studies are needed to better understand the role of ethnicity in CKDu (Lunyera et al. 2016; O'Donnell et al. 2010; Perez-Gomez et al. 2018).

High humidity, no water intake, and high thirst were significantly associated with those participants that reported CKD, while high physical demands were significantly associated with work-related CKD. All four of these occupational risk factors are well documented as having a role in CKDu (García-Trabanino et al. 2015; Lucas et al. 2015; Wesseling et al. 2016). In the majority of research done in Central America, age, male sex, low altitude, high ambient temperatures, and dietary history have been positively associated with CKDu (Lunyera et al. 2016;

Nerbass et al. 2017). We found high humidity and no water intake to be associated with CKD. In a detailed recent review, Wesseling and colleagues concluded working-age men exposed to heat, humidity, intensive labor, and without proper hydration, are more susceptible to developing CKDu in Central America (Wesseling et al. 2020). Use of analgesics was found to be not significant with either CKD group. This finding is in accordance with the lack of evidence from epidemiological studies (González-Quiroz et al. 2017; Lunyera et al. 2016; Pearce and Caplin 2019). Exposure to agrochemicals was not significant in the bivariate analysis and was not included in the multivariate analysis for either renal disease outcome. Although not significant in our study, some studies have found agrochemical use to possibly have a role in the development of CKDu due to high mortality rates in both men and women (Herrera Valdés et al. 2015; Ordunez et al. 2018). Agrochemical exposure by husbands who are pesticide applicators has been proposed as a possible explanation for women to be exposed to harmful chemicals who do not work directly in agriculture. Overall, however, findings related to the role of agrochemicals in CKDu have been inconsistent, with most not finding evidence of a link (Lunyera et al. 2016). The strong relationship we found between CKD and established risk factors for CKDu may also indicate that some of these CKD cases are occurring in persons who have yet to recognize its work-relatedness.

Creating the weather map allowed us to visualize where self-reported work-related CKD cases are located in relation to CKDu risk factors in Central America. Most of the work-related CKD was located in the central to western parts of the region, with very few cases along the Caribbean coast. We selected the most widely referenced CKDu risk factors (exposure to heat, exposure to humidity, and high physical demands) and chose any combination of two or more of them to add more specificity to the measure, since there is a high prevalence of each of these variables when taken individually (Correa-Rotter and García-Trabanino 2019). Risk factors for CKDu were more clustered along the Pacific coast. Several studies of CKDu conducted in Guatemala have involved the Escuintla region, located in the country's coastal lowland region, where sugarcane harvest is common, along with conditions of high humidity, heat and heavy physical demands (Butler-Dawson et al. 2018; Butler-Dawson et al. 2019; Griffin et al. 2018; Sorensen et al. 2019). Similar conditions are found along the coastal areas of El Salvador, Nicaragua and the Guanacaste region of Costa Rica (Laws et al. 2015; Peraza et al. 2012; Wesseling et al. 2015).

However, we also observed clusters of CKDu risk factors together with work-related CKD in geographic areas that are less often described; specifically, western Honduras and the Pacific coasts of lower Costa Rica and Panama. Some CKDu cases have been reported in these two areas, but to a much lesser degree (Ordunez et al. 2018). Some of the industries in these areas are also associated with elevated temperature/humidity or jobs with high physical demands. In Honduras, the northern coastal region along the Caribbean and the surrounding land by the Gulf of Fonseca is arable land used primarily for cultivation of crops, such as bananas, coffee, corn, tobacco, and cotton (Wehner et al. 2018). In the lower Costa Rican coast, there is a large palm industry, with harvest being done under very humid environments since workers perform their jobs under the low-laying palm tree canopy (Barcelos et al. 2015; Myzabella et al. 2019). In Panama, the coastal area has large fishing and banana harvest industries that are essential to their economy (Martín-Cleary and Ortiz 2014). Banana harvesting is also typically performed under conditions of high physical demand and humid conditions. Targeted follow-up studies of workers in these areas, with surveys and measurement of renal function, would serve to identify the degree to which CKDu is an issue there.

We also encountered a few work-related CKD reports that did not overlap with CKDu risk factors, primarily in central Nicaragua. Most CKDu studies conducted in Nicaragua have reported CKD in working-age men (Gifford et al. 2017; Kupferman et al. 2016; Torres et al. 2010). Agricultural regions for coffee, cotton, and sugarcane in Nicaragua are consistent with our work-related CKD cluster findings. However, the absence of overlying CKDu risk factors in these few cases could either be spurious or suggest that some work-related CKDu could be associated with different occupational risk factors, or not be work-related given the limitations of self-report.

Lastly, we identified areas that clustered CKDu risk factors but in the absence of any work-related CKD. This occurred mainly in the western part of Guatemala, coastal areas of Panama and southern Costa Rica. The rationale for lower Costa Rica (on both the Atlantic and Pacific sides) and Panama possibly being of interest for further study is described above. In addition, in western Guatemala, although we had no self-report of work-related CKD, a high risk of AKI and decline in kidney function have been described in this area (Butler-Dawson et al. 2018; Butler-Dawson et al. 2019; Sorensen et al. 2019).

These areas that feature CKDu risk factor clusters, in the absence of work-related CKD should be further studied. Our findings may be pointing to industry sectors, other than agricultural, harboring workers susceptible to the development of CKDu. Previous studies have found high CKD mortality in the Guanacaste and Limon Province, along the coasts (Wesseling et al. 2015). Our map identified CKDu risk factors in those regions along with a few work-related CKD points. However, CKDu risk factors were also noted in the southern region of Costa Rica, Parrita to

Dominical, which is rich in palm oil plantations. Additional, more focused research in these areas might help uncover as yet undetected new foci of CKDu.

A major strength of this study is the large sample size, representative of the working population in Central America, which increases the generalizability of findings. Inclusion of both informal and formal sector workers also makes it possible to search for CKDu in populations that often escape official registries, despite being more vulnerable and likely exposed to more hazardous working conditions (Benavides et al. 2014; Garbanzo et al. 2016). Because of the study population size and sampling frame, we were also able to expand our study of renal disease and its risk factors to different industry sectors, going beyond agriculture. In fact, the prevalence of self-reported CKD and work-related CKDu in the secondary and tertiary sectors was not trivial. Recent studies of nonagricultural workers who may share similar work exposures such as high heat and physical demands have identified other occupations, such as construction workers or brickmakers, with CKDu (Gallo-Ruiz et al. 2019; Yih et al. 2019). Linkages of our GIS weather maps to survey responses added more objectivity to self-reports of exposure to high temperatures and humidity.

There are also some limitations to consider when interpreting our findings. First, all data was self-reported, making it susceptible to recall bias. This bias can both underreport or overreport both risk factors and renal disease prevalence. Participants without a clinical diagnosis of renal disease are less likely to know or suspect they have CKD, leading to underreporting of disease. On the hand, among those with diagnosed CKD, its relationship with work could be overreported or underreported. Self-reporting could inflate causal attribution since sick participants may have a higher tendency to attribute their health condition to their work (McCaughey et al. 2013). The nonsignificant, yet elevated, odds of high humidity as a risk factor for work-related CKD may have been due to underpowering for this association; however, previous studies have confirmed humidity is a contributing risk factor for CKDu (García-Trabanino et al. 2015; Wesseling et al. 2020) and the increased odds ratio we found is consistent with this literature. It is possible that using the heat index as a measure of heat exposure would have yielded different results, as it reflects the combined effect of temperature and relative humidity. However, heat index data were not available in the 2018 weather station readings, limiting the ways in which we could examine the effects of temperature on self-reported renal disease ((NOAA) 2019). Integrating heat index readings to our annual temperature data might have allowed a more accurate representation of the temperature workers are actually exposed to. However, heat index is more useful in warm seasons (spring and summer), and agencies use to different algorithms to calculate heat index, which may cause readings to not be comparable (Anderson et al. 2013). It is also important to note that the annual temperatures for heat demonstrated in the map may not affect all workers continuously year-round. For example, sugarcane workers only work during harvesting seasons, which can last for 6 months. Once the harvesting season is over, agricultural workers pursue work opportunities in jobs that may or may not be outdoors. Thus, constant year-round exposure to heat and humidity in the agriculture sector cannot be measured accurately. Nonetheless, continuous day-to-night exposure to heat among other suspected CKDu risk factors for a period of 6 months can accelerate the symptoms for AKI, which can later progress to CKDu (Kupferman et al. 2018; Lewington et al. 2013; Wesseling et al. 2013; Wijkström et al. 2018).

Our study results merely provide a bird's eye view of population-based prevalence of chronic kidney disease and its associations with putative occupational risk factors. Findings from our GIS analysis are more aligned with an ecological design, and thus serve more as hypothesis-generating, identifying opportunities for more targeted and more rigorously designed studies. Next steps in this direction could include studies that couple survey results with objective, blood-based measurement of renal function, such as obtaining baseline levels of estimated glomerular filtration rates (eGFR). One such approach could be to apply the Disadvantaged Populations eGFR Epidemiology (DEGREE) protocol to Central America, as it includes both questionnaire and laboratory measurements (Caplin et al. 2017). This would lead to a population-based examination of the distribution of average renal function in the region, establishing reference values and possibly allowing the detection of significant geographic variation in renal function. This, in turn, could be linked to both sociodemographic and occupational risk factor data from the survey (Al-Bouwarthan et al. 2019; Caplin et al. 2017; Caplin et al. 2019). There is also a need for better weather data collection from existing Central American weather stations. Finally, expanding this epidemiological approach to other Hispanic worker populations, including those in the U.S., subject to similar meteorological conditions, occupations and physical demands, and across all industry sectors, could lead to the detection of new clusters of CKDu (Aguilar and Madero 2019). Detection of new disease is the first step in identifying opportunities for the design of preventive interventions aimed at reducing the burden of CKDu in these workers.

Table 2. Demographics of participants in II ECCTS (n=9,032) for Central America.
Journal Article Table 1. Demographics of participants in II ECCTS (n=9,032) for Central America.

	Primary Sector+ N (%)*	Secondary Sector+ N (%)*	Tertiary Sector+ N (%)*	Total
Sex				
Male	812 (84.4%)	1,015 (58.9%)	2,735 (41.7%)	4,562 (61.3%)
Female	146 (15.6%)	605 (41.1%)	3,719 (58.3%)	4,470 (38.7%)
Age (years)				
18-29	200 (27.9%)	403 (38.5%)	1,831 (42.5%)	2,434 (36.4%)
30-49	395 (37.5%)	766 (39.6%)	2,871 (36.9%)	4,032 (38.0%)
50-64	245 (23.1%)	350 (16.4%)	1,350 (15.3%)	1,945 (18.2%)
65+	118 (11.6%)	101 (5.5%)	402 (5.3%)	621 (7.4%)
Ethnicity				
Indigenous	198 (30.3%)	202 (25.4%)	639 (21.0%)	1,039 (25.5%)
Mestizo	506 (48.2%)	806 (50.2%)	3,347 (53.3%)	4,659 (50.6%)
White	104 (10.5%)	286 (11.0%)	1,348 (12.4%)	1,738 (11.3%)
Black	24 (1.5%)	63 (1.2%)	270 (1.7%)	357 (1.4%)
Mulatto	25 (1.8%)	41 (1.1%)	226 (1.4%)	292 (1.4%)
Other/ Do not know / Refused	101 (7.7%)	222 (11.2%)	624 (10.2%)	947 (9.7%)
Education (years of schooling)				
No schooling	37 (3.8%)	147 (9.1%)	1,391 (18.8%)	1,575 (10.7%)
Elementary (Grades 1-6)	175 (18.1%)	75 (5.9%)	249 (4.5%)	499 (9.4%)
Middle School (Grades 7-12)	562 (56.1%)	641 (41.0%)	1,868 (30.1%)	3,071 (42.2%)
University (years 1-6)	184 (22.0%)	756 (44.0%)	2,942 (46.5%)	3,882 (37.7%)
Do not know / Refused	0 (0.0%)	1 (0.0%)	4 (0.1%)	5 (0.0%)
Household Monthly Income				
No more than $200	496 (55.8%)	396 (32.3%)	1,608 (33.5%)	2,500 (40.3%)
$201 to $300	187 (18.6%)	355 (27.2%)	1,357 (25.6%)	1,899 (24.2%)
$301 to 500	130 (16.1%)	405 (25.2%)	1,606 (24.4%)	2,141 (22.0%)
$501 to $1000	60 (3.9%)	288 (9.8%)	1,064 (9.4%)	1,412 (7.8%)
More than $1000	23 (1.4%)	92 (2.5%)	386 (2.5%)	501 (2.2%)
Do not know / Refused	62 (4.2%)	84 (2.9%)	433 (3.6%)	579 (3.6%)
Length of Employment				
Less than 1 year	90 (7.6%)	198 (11.7%)	919 (14.5%)	1,207 (11.3%)
Up to 5 Years	244 (31.4%)	617 (44.6%)	2,947 (51.4%)	3,808 (42.6%)
6 to 10 years	144 (14.4%)	289 (16.5%)	1,054 (14.7%)	1,487 (15.2%)
11 to 15 years	108 (13.0%)	138 (7.6%)	515 (6.7%)	761 (9.0%)
16 years and above	360 (32.7%)	364 (18.9%)	937 (11.4%)	1,661 (20.8%)
Do not know / Refused	12 (0.9%)	14 (0.7%)	82 (1.3%)	108 (1.0%)
Zone				
Urban	194 (21.0%)	1,084 (64.2%)	4,698 (71.8%)	5,976 (52.8%)
Rural	764 (79.0%)	536 (35.8%)	1,756 (28.2%)	3,056 (47.2%)
CKDu Risk Factors				
High physical demands of work	659 (66.3%)	891 (49.9%)	2,243 (31.6%)	3,793 (49.0%)
Exposure to heat	274 (30.1%)	398 (22.1%)	1,106 (16.3%)	1,778 (22.7%)
Exposure to humidity	66 (4.8%)	61 (2.1%)	163 (1.3%)	290 (2.7%)
High thirst	449 (39.8%)	569 (31.1%)	1728 (22.5%)	2746(31.0%)
No water intake	19 (2.1%)	56 (2.9%)	298 (4.5%)	373 (3.2%)
Use of analgesics	785 (86.6%)	1,315 (88.3%)	5,037 (86.6%)	7,137 (87.2%)
High exposure to agrochemicals	488 (50.5%)	98 (3.9%)	363 (3.5%)	949 (18.9%)

CKD				
Responded Yes	64 (5.4%)	60 (4.5%)	246 (3.5%)	370 (4.4%)
Believe CKD to be work-related^	35 (41.4%)	27 (41.2%)	79 (27.5%)	141 (37.5%)

[*] Weighted Percentage.
[+] Industry sector: primary (mainly, agricultural), secondary (mainly, manufacturing and construction), tertiary (mainly, services).
[^] Percentage is out of the total of self-reported CKD

Table 3. CKD risk factors by industry sectors between CKD and work-related CKD for Central America.
Journal Article Table 2. CKD risk factors by industry sectors between CKD and work-related CKD for Central America.

	CKD (N=370)				Work-related CKD (N=141)			
Sectors	**Primary Sector+ N (%)***	**Secondary Sector+ N (%)***	**Tertiary Sector+ N (%)***	**Total**	**Primary Sector+ N (%)***	**Secondary Sector+ N (%)***	**Tertiary Sector+ N (%)***	**Total**
CKD Risk Factors								
High physical demands of work	47 (75.0%)	35 (61.7%)	121 (45.3%)	203 (62.6%)	30 (90.4%)	17 (69.1%)	47 (53.2%)	94 (74.8%)
Exposure to heat	22 (43.4%)	16 (27.0%)	56 (18.1%)	94 (31.1%)	13 (35.4%)	11 (42.9%)	21 (22.5%)	45 (35.7%)
Exposure to humidity	7 (7.2%)	3 (4.6%)	7 (2.1%)	17 (5.0%)	4 (9.3%)	2 (6.2%)	5 (5.9%)	11 (7.4%)
High thirst	38 (58.4%)	23 (43.5%)	92 (36.7%)	153 (47.5%)	22 (66.1%)	11 (44.9%)	33 (38.7%)	66 (52.5%)
No water intake	3 (2.0%)	5 (5.2%)	22 (8.1%)	30 (4.7%)	1 (2.3%)	1 (0.5%)	6 (6.4%)	8 (2.5%)
Use of analgesics	43 (74.9%)	43 (78.1%)	190 (82.8%)	276 (78.1%)	23 (70.5%)	16 (65.0%)	61 (84.3%)	100 (71.2%)
High exposure to agrochemicals	29 (50.7%)	2 (3.9%)	19 (7.0%)	50 (23.2%)	20 (67.0%)	1 (4.4%)	5 (4.6%)	26 (30.9%)

* Weighted Percentage.
+ Economic sector: primary (agricultural), secondary (manufacturing and construction), tertiary (services).

Table 4. Bivariate logistic regression analysis of associations between CKD and work-related CKD.

Journal Article Table 3. Bivariate logistic regression analysis of associations between CKD and work-related CKD sociodemographic characteristics. II ECCTS, Central America.

	CKD (n=370)		**Work-Related CKD (n=141)**	
Variables	OR [95% CI]	P-Value	OR [95% CI]	P-Value
Sex				
Female	Ref		Ref	
Men	1.00 [0.69-1.43]	0.98	2.39 [1.22-4.66]	0.01
Age (years)				
18-29	Ref		Ref	
30-49	1.17 [0.73-1.88]	0.52	1.97 [0.82-4.74]	0.20
50-64	1.71 [1.01-2.91]	0.05	1.47 [0.55-3.93]	0.44
65+	1.45 [0.69-3.04]	0.33	0.77 [0.23-2.65]	0.68
Ethnicity				
Indigenous	Ref		Ref	
Mestizo	1.10 [0.64-1.88]	0.74	4.17 [1.26-13.79]	0.02
White	0.85 [0.39-1.84]	0.68	1.41 [0.30-6.59]	0.66
Black	0.79 [0.31-2.04]	0.63	2.76 [0.41-18.44]	0.29
Mulatto	0.51 [0.15-1.71]	0.28	2.51 [0.26-24.02]	0.43
Other	0.64 [0.30-1.35]	0.24	2.02 [0.43-9.50]	0.37
Education				
No schooling	0.52 [0.25-1.07]	0.07	1.05 [0.28-3.95]	0.94
Elementary	Ref		Ref	
Middle School	0.70 [0.37-1.34]	0.28	1.47 [0.48-4.57]	0.50
University	0.66 [0.34-1.29]	0.22	1.24 [0.38-4.06]	0.72
Monthly Income				
No more than $200	Ref		Ref	
$201 to $300	0.97 [0.60-1.56]	0.90	0.76 [0.32-1.79]	0.53
$301 to 500	0.66 [0.42-1.04]	0.07	1.84 [0.76-4.42]	0.17
$501 to $1000	0.28 [0.16-0.48]	0.29	0.88 [0.32-2.47]	0.81
> $1000	0.38 [0.11-1.30]	0.12	0.16 [0.02-1.11]	0.06
Length of Employment				
Less than 1 year	Ref		Ref	
≤ 5 Years	1.08 [0.64-1.82]	0.78	0.92 [0.32-2.61]	0.87
6 to 10 years	1.53 [0.88-2.66]	0.14	1.39 [0.46-4.24]	0.56
11 to 15 years	1.31 [0.68-2.52]	0.42	1.18 [0.33-4.28]	0.80
≥16 years	1.12 [0.65-1.94]	0.69	1.04 [0.35-3.10]	0.95
Zone				
Urban	Ref		Ref	
Rural	1.44 [1.00-2.05]	0.05	1.08 [0.55-2.13]	0.83
Sector				
Primary	Ref		Ref	
Secondary	0.82 [0.51-1.33]	0.42	1.00 [0.40-2.48]	0.98
Tertiary	0.63 [0.43-0.93]	0.02	0.54 [0.26-1.12]	0.10
High Physical Demands of Work				
No	Ref		Ref	
Yes	1.81 [1.26-2.58]	0.00	2.23 [1.13-4.40]	0.02

Exposure to Heat				
No	Ref		Ref	
Yes	1.56 [1.01-2.41]	0.04	1.36 [0.60-3.08]	0.46
Exposure to Humidity				
No	Ref		Ref	
Yes	2.07 [1.06-4.06]	0.03	2.95 [0.74-11.79]	0.13
High Thirst				
No	Ref		Ref	
Yes	2.11 [1.46-3.05]	0.0	1.48 [0.74-2.99]	0.27
No Water Intake				
No	Ref		Ref	
Yes	1.53 [0.88-2.64]	0.13	0.40 [0.13-1.22]	0.11
Use of Analgesics				
No	Ref		Ref	
Yes	0.51 [0.34-0.75]	0.00	0.57 [0.27-1.20]	0.74
High Exposure to Agrochemicals				
No	Ref		Ref	
Yes	1.33 [0.80-2.23]	0.27	1.81 [0.67-4.85]	0.24

Table 5. Multivariate logistic regression analysis of associations between CKD and work-related CKD.

Journal Article Table 4. Multivariate logistic regression analysis of associations between CKD and work-related CKD selected sociodemographic characteristics. II ECCTS, Central America.

	CKD (n=370)		Work-Related CKD (n=141)	
Variables	OR [95% CI]	P-Value	OR [95% CI]	P-Value
Sex				
Female	Ref	--	Ref	
Men	--	--	1.83 [0.88-3.81]	0.11
Age (years)				
18-29	Ref.		Ref	
30-49	1.17 [0.69-1.98]	0.57	2.38 [1.03-5.51]	0.04
50-64	2.08 [1.23-3.52]	0.01	0.93 [0.31-2.82]	0.90
65+	1.74 [0.80-3.78]	0.16	0.71 [0.20-2.52]	0.60
Ethnicity				
Indigenous	Ref	--	Ref	
Mestizo	--	--	7.44 [2.14-25.82]	0.00
White	--	--	2.24 [0.36-14.06]	0.39
Black	--	--	5.56 [0.48-65.01]	0.17
Mulatto	--	--	3.01 [0.06-155.01]	0.58
Other	--	--	4.77 [0.97-23.41]	0.06
Education				
No schooling	1.21 [0.49-2.99]	0.66	--	--
Elementary	Ref		Ref	
Middle School	0.90 [0.45-1.83]	0.78	--	--
University	1.12 [0.48-2.62]	0.79	--	--
Monthly Income				
No more than $200	Ref		Ref	
$201 to $300	1.04 [0.62-1.74]	0.88	0.54 [0.22-1.28]	0.16
$301 to 500	0.65 [0.40-1.06]	0.09	1.45 [0.51-4.10]	0.49
$501 to $1000	0.27 [0.15-0.48]	0.00	1.09 [0.37-3.19]	0.88
> $1000	0.36 [0.11-1.18]	0.09	0.16 [0.01-2.05]	0.16
Length of Employment				
Less than 1 year	Ref		Ref	
≤ 5 Years	1.18 [0.70-2.00]	0.54	--	--
6 to 10 years	1.45 [0.80-2.60]	0.22	--	--
11 to 15 years	1.18 [0.59-2.35]	0.64	--	--
≥16 years	0.76 [0.42-1.38]	0.37	--	--
Zone				
Urban	Ref		Ref	
Rural	1.29 [0.85-1.97]	0.23	--	--
Sector				
Primary	Ref		Ref	
Secondary	1.10 [0.60-2.04]	0.75	1.15 [0.41-3.22]	0.80
Tertiary	0.93 [0.54-1.60]	0.79	0.49 [0.19-1.26]	0.14
High Physical Demands of Work				
No	Ref		Ref	
Yes	1.44 [0.95-2.18]	0.09	2.45 [1.18-5.09]	0.02
Exposure to Heat				
No	Ref		Ref	

Yes	1.16 [0.74-1.83]	0.51	1.37 [0.57-3.30]	0.48
Exposure to Humidity				
No	Ref		Ref	
Yes	2.08 [1.07-4.06]	0.03	2.31 [0.57-9.37]	0.24
No Water Intake				
No	Ref		Ref	
Yes	1.93 [1.05-3.57]	0.04	0.48 [0.08-2.69]	0.40
High Thirst				
No	Ref		Ref	
Yes	1.89 [1.25-2.86]	0.00	1.25 [0.60-2.63]	0.55
Use of Analgesics				
No	Ref		Ref	
Yes	0.51 [0.34-0.76]	0.00	0.86 [0.40-1.85]	0.69

$^{+}$Hosmer-Lemeshow goodness-of-fit (CKD), p=0.36; $^{+}$Hosmer-Lemeshow goodness-of-fit (work-related CKD), p=0.26

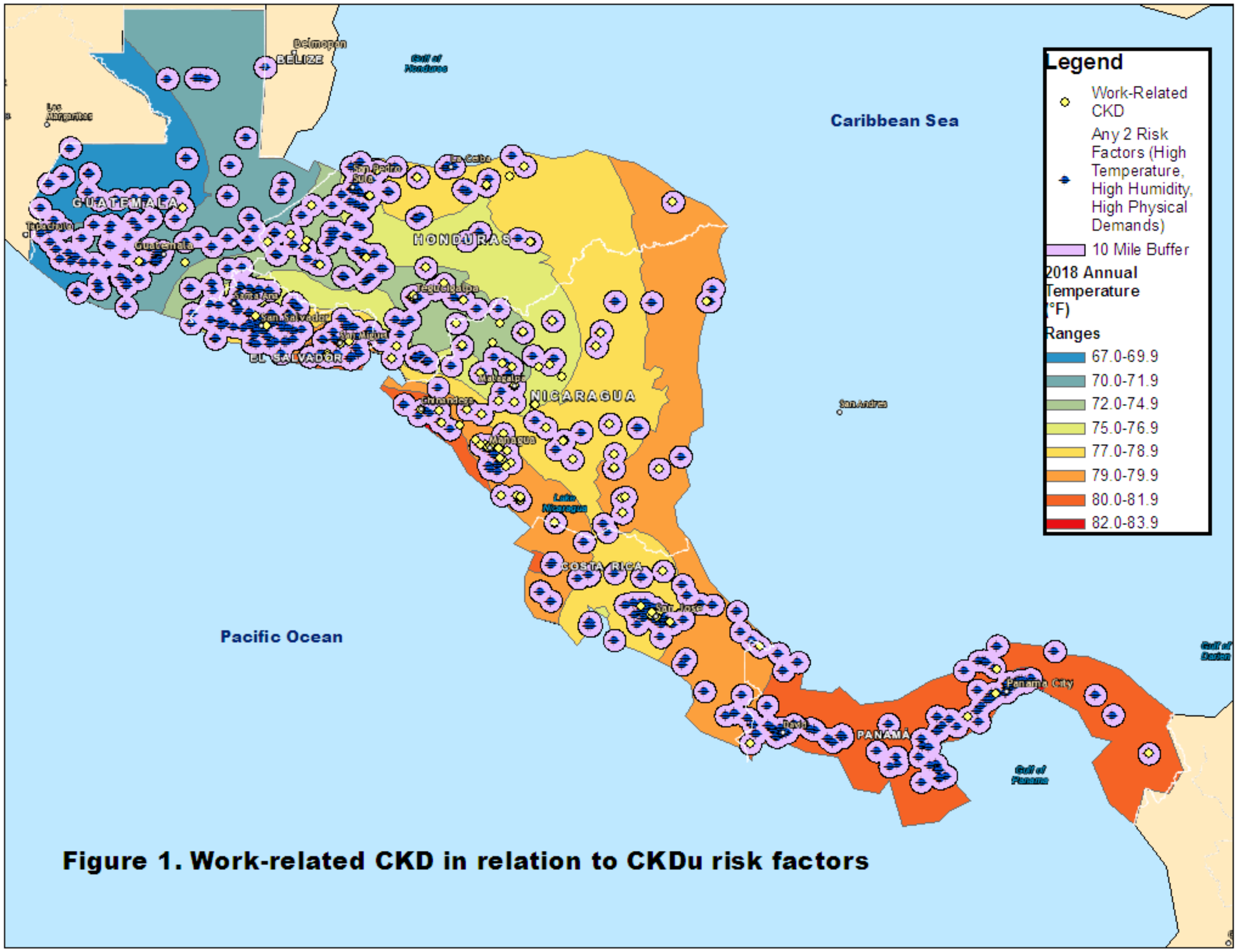


Figure 1. Work-related CKD in relation to CKDu risk factors

Figure 2. Overlap of work-related CKD and CKDu risk factors.

REFERENCES

(NOAA) NOaAA, Information NCfE (2019) Find a Station. https://www.ncdc.noaa.gov/data-access/land-based-station-data/find-station. Accessed November 1 2019

(NOAA) UDoCaNWS (2019) Heat Index. www.weather.gov/safety/heat-index. Accessed October 10 2019

Aguilar DJ, Madero M (2019) Other Potential CKD Hotspots in the World: The Cases of Mexico and the United States Seminars in Nephrology 39:300-307 doi:https://doi.org/10.1016/j.semnephrol.2019.02.008

Al-Bouwarthan M, Quinn MM, Kriebel D, Wegman DH (2019) Assessment of Heat Stress Exposure among Construction Workers in the Hot Desert Climate of Saudi Arabia Annals of Work Exposures and Health 63:505-520 doi:10.1093/annweh/wxz033

Anderson GB, Bell ML, Peng RD (2013) Methods to calculate the heat index as an exposure metric in environmental health research Environ Health Perspect 121:1111-1119 doi:10.1289/ehp.1206273

Barcelos E et al. (2015) Oil palm natural diversity and the potential for yield improvement Front Plant Sci 6:190-190 doi:10.3389/fpls.2015.00190

Benavides FG, Wesseling C, Delclos GL, Felknor S, Pinilla J, Rodrigo F (2014) Working conditions and health in Central America: a survey of 12 024 workers in six countries Occupational and Environmental Medicine 71:459-465 doi:10.1136/oemed-2013-101908

Bouroncle C, Pablo I, Rodríguez-Sánchez B, Medellín C, Martinez Valle A, Laderach P (2016) Mapping climate change adaptive capacity and vulnerability of smallholder agricultural livelihoods in Central America: ranking and descriptive approaches to support adaptation strategies Climatic Change 141 doi:10.1007/s10584-016-1792-0

Butler-Dawson J et al. (2018) Risk Factors for Declines in Kidney Function in Sugarcane Workers in Guatemala J Occup Environ Med 60:548-558 doi:10.1097/JOM.0000000000001284

Butler-Dawson J et al. (2019) Evaluation of heat stress and cumulative incidence of acute kidney injury in sugarcane workers in Guatemala International Archives of Occupational and Environmental Health 92:977-990 doi:10.1007/s00420-019-01426-3

Caplin B et al. (2017) International Collaboration for the Epidemiology of eGFR in Low and Middle Income Populations - Rationale and core protocol for the Disadvantaged Populations eGFR Epidemiology Study (DEGREE) BMC Nephrology 18 doi:10.1186/s12882-016-0417-1

Caplin B et al. (2019) The International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology: Report of the working group on approaches to population-level detection strategies and recommendations for a minimum dataset Kidney International 95:4-10 doi:10.1016/j.kint.2018.08.019

Chicas R, Mix J, Mac V, Flocks J, Dickman NE, Hertzberg V, McCauley L (2019) Chronic Kidney Disease Among Workers: A Review of the Literature Workplace Health & Safety 67:481-490 doi:10.1177/2165079919843308

Correa-Rotter R, García-Trabanino R (2019) Mesoamerican Nephropathy Seminars in Nephrology 39:263-271 doi:https://doi.org/10.1016/j.semnephrol.2019.02.004

Esri (2018) Esri. Environmental Systems Research Institute, Redlands, CA
Fagerland MW, Hosmer DW (2012) A Generalized Hosmer–Lemeshow Goodness-of-Fit Test for Multinomial Logistic Regression Models The Stata Journal 12:447-453 doi:10.1177/1536867x1201200307
Flores S, Rider AC, Alter HJ (2016) Mesoamerican nephropathy: a novel case of kidney failure in a US ED The American Journal of Emergency Medicine 34:1323.e1325-1323.e1326 doi:10.1016/j.ajem.2015.11.048
Freedman BI, Sedor JR (2008) Hypertension-Associated Kidney Disease: Perhaps no More Journal of the American Society of Nephrology 19:2047-2051 doi:10.1681/asn.2008060621
Friedman DJ (2019) Genes and environment in chronic kidney disease hotspots Current Opinion in Nephrology and Hypertension 28:87-96 doi:10.1097/mnh.0000000000000470
Gallo-Ruiz L et al. (2019) Prevalence and Risk Factors for CKD Among Brickmaking Workers in La Paz Centro, Nicaragua American Journal of Kidney Diseases 74:239-247 doi:10.1053/j.ajkd.2019.01.017
Garbanzo MR, Benavides FG, Gimeno D (2016) P251 Psychosocial risk exposure and musculoskeletal pain among formal and informal workers in central america Occupational and Environmental Medicine 73:A205-A205 doi:10.1136/oemed-2016-103951.567
García-Trabanino R et al. (2015) Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador – A cross-shift study of workers at risk of Mesoamerican nephropathy Environmental Research 142:746-755 doi:https://doi.org/10.1016/j.envres.2015.07.007
Gifford FJ, Gifford RM, Eddleston M, Dhaun N (2017) Endemic Nephropathy Around the World Kidney International Reports 2:282-292 doi:https://doi.org/10.1016/j.ekir.2016.11.003
González-Quiroz M, Pearce N, Caplin B, Nitsch D (2017) What do epidemiological studies tell us about chronic kidney disease of undetermined cause in Meso-America? A systematic review and meta-analysis Clinical Kidney Journal 11:496-506 doi:10.1093/ckj/sfx136
Griffin BR et al. (2018) Unadjusted point of care creatinine results overestimate acute kidney injury incidence during field testing in Guatemala PLoS One 13:e0204614-e0204614 doi:10.1371/journal.pone.0204614
Gutiérrez-Amavizca BE et al. (2013) Contribution of GSTM1, GSTT1, and MTHFR polymorphisms to end-stage renal disease of unknown etiology in Mexicans Indian J Nephrol 23:438-443 doi:10.4103/0971-4065.120342
Herrera Valdés R et al. (2015) Clinical characteristics of chronic kidney disease of non-traditional causes in women of agricultural communities in El Salvador Clin Nephrol 83:56-63 doi:10.5414/cnp83s056
Hidalgo HG, Amador JA, Alfaro EJ, Quesada B (2013) Hydrological climate change projections for Central America Journal of Hydrology 495:94-112 doi:https://doi.org/10.1016/j.jhydrol.2013.05.004
Hosmer DW, Lemeshow S, Sturdivant RX, Hosmer DW, Jr. (2013) Applied Logistic Regression. John Wiley & Sons, Incorporated, New York, UNITED STATES

Johnson RJ, Wesseling C, Newman LS (2019) Chronic Kidney Disease of Unknown Cause in Agricultural Communities New England Journal of Medicine 380:1843-1852 doi:10.1056/NEJMra1813869

Kupferman J et al. (2016) Characterization of Mesoamerican Nephropathy in a Kidney Failure Hotspot in Nicaragua American Journal of Kidney Diseases 68:716-725 doi:https://doi.org/10.1053/j.ajkd.2016.06.012

Kupferman J et al. (2018) Acute Kidney Injury in Sugarcane Workers at Risk for Mesoamerican Nephropathy American Journal of Kidney Diseases 72:475-482 doi:10.1053/j.ajkd.2018.04.014

Laws RL et al. (2015) Changes in kidney function among Nicaraguan sugarcane workers International Journal of Occupational and Environmental Health 21:241-250 doi:10.1179/2049396714Y.0000000102

Lewington AJP, Cerdá J, Mehta RL (2013) Raising awareness of acute kidney injury: a global perspective of a silent killer Kidney international 84:457-467 doi:10.1038/ki.2013.153

Lucas RAI et al. (2015) Heat stress and workload associated with sugarcane cutting - an excessively strenuous occupation! Extrem Physiol Med 4:A23-A23 doi:10.1186/2046-7648-4-S1-A23

Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW (2016) CKD of Uncertain Etiology: A Systematic Review Clinical journal of the American Society of Nephrology : CJASN 11:379-385 doi:10.2215/CJN.07500715

Martín-Cleary C, Ortiz A (2014) CKD hotspots around the world: where, why and what the lessons are. A CKJ review series Clinical Kidney Journal 7:519-523 doi:10.1093/ckj/sfu118

McCaughey D, DelliFraine JL, McGhan G, Bruning NS (2013) The negative effects of workplace injury and illness on workplace safety climate perceptions and health care worker outcomes Safety Science 51:138-147 doi:https://doi.org/10.1016/j.ssci.2012.06.004

McLafferty S (2015) Disease cluster detection methods: recent developments and public health implications Annals of GIS 21:127-133 doi:10.1080/19475683.2015.1008572

Minnings K et al. (2015) Chronic kidney disease prevalence in Rivas, Nicaragua: Use of a field device for creatinine measurement Clinical Biochemistry 48:456-458 doi:https://doi.org/10.1016/j.clinbiochem.2015.01.005

Myzabella N, Fritschi L, Merdith N, El-Zaemey S, Chih H, Reid A (2019) Occupational Health and Safety in the Palm Oil Industry: A Systematic Review Int J Occup Environ Med 10:159-173 doi:10.15171/ijoem.2019.1576

Nerbass FB, Moist L, Clark WF, Vieira MA, Pecoits-Filho R (2019) Hydration Status and Kidney Health of Factory Workers Exposed to Heat Stress: A Pilot Feasibility Study Annals of Nutrition and Metabolism 74(suppl 3):30-37 doi:10.1159/000500373

Nerbass FB, Pecoits-Filho R, Clark WF, Sontrop JM, McIntyre CW, Moist L (2017) Occupational Heat Stress and Kidney Health: From Farms to Factories Kidney International Reports 2:998-1008 doi:https://doi.org/10.1016/j.ekir.2017.08.012

O'Donnell JK et al. (2010) Prevalence of and risk factors for chronic kidney disease in rural Nicaragua Nephrology Dialysis Transplantation 26:2798-2805 doi:10.1093/ndt/gfq385

Ordunez P, Nieto FJ, Martinez R, Soliz P, Giraldo GP, Mott SA, Hoy WE (2018) Chronic kidney disease mortality trends in selected Central America countries, 1997–2013: clues to an epidemic of chronic interstitial nephritis of agricultural communities Journal of Epidemiology and Community Health 72:280-286 doi:10.1136/jech-2017-210023

Pearce N, Caplin B (2019) Let's take the heat out of the CKDu debate: more evidence is needed Occupational and Environmental Medicine 76:357-359 doi:10.1136/oemed-2018-105427

Peraza S et al. (2012) Decreased Kidney Function Among Agricultural Workers in El Salvador American Journal of Kidney Diseases 59:531-540 doi:10.1053/j.ajkd.2011.11.039

Perez-Gomez MV, Martin-Cleary C, Fernandez-Fernandez B, Ortiz A (2018) Meso-American nephropathy: what we have learned about the potential genetic influence on chronic kidney disease development* Clinical Kidney Journal 11:491-495 doi:10.1093/ckj/sfy070

Ramirez-Rubio O, McClean MD, Amador JJ, Brooks DR (2013) An epidemic of chronic kidney disease in Central America: an overview Postgraduate Medical Journal 89:123-125 doi:10.1136/postgradmedj-2012-201141rep

Said S, Hernandez GT (2015) Environmental Exposures, Socioeconomics, Disparities, and the Kidneys Advances in Chronic Kidney Disease 22:39-45 doi:10.1053/j.ackd.2014.09.003

Sayanthooran S, Magana-Arachchi DN, Gunerathne L, Abeysekera TDJ, Sooriyapathirana SS (2016) Upregulation of Oxidative Stress Related Genes in a Chronic Kidney Disease Attributed to Specific Geographical Locations of Sri Lanka Biomed Res Int 2016:7546265 doi:10.1155/2016/7546265

Sorensen C, Garcia-Trabanino R (2019) A New Era of Climate Medicine — Addressing Heat-Triggered Renal Disease New England Journal of Medicine 381:693-696 doi:10.1056/NEJMp1907859

Sorensen CJ et al. (2019) Risk Factors and Mechanisms Underlying Cross-Shift Decline in Kidney Function in Guatemalan Sugarcane Workers J Occup Environ Med 61:239-250 doi:10.1097/JOM.0000000000001529

StataCorp (2017) StataCorp. StataCorp LP, College Station, TX

Tawatsupa B, Lim LLY, Kjellstrom T, Seubsman S-a, Sleigh A, Thai Cohort Study T (2012) Association between occupational heat stress and kidney disease among 37,816 workers in the Thai Cohort Study (TCS) Journal of epidemiology 22:251-260 doi:10.2188/jea.je20110082

TimeandDate.com (2019) Weather. https://www.timeanddate.com/. Accessed November 1 2019

Torres C et al. (2010) Decreased Kidney Function of Unknown Cause in Nicaragua: A Community-Based Survey American Journal of Kidney Diseases 55:485-496 doi:10.1053/j.ajkd.2009.12.012

Wang S et al. (2008) Geographic patterns of genome admixture in Latin American Mestizos PLoS Genet 4:e1000037-e1000037 doi:10.1371/journal.pgen.1000037

Wehner L, Mcgaffey L, Spilling M (2018) Honduras. Cavendish Square Publishing LLC,

Wesseling C et al. (2016) Heat stress, hydration and uric acid: a cross-sectional study in workers of three occupations in a hotspot of Mesoamerican nephropathy in Nicaragua BMJ open 6:e011034-e011034 doi:10.1136/bmjopen-2016-011034

Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH (2013) The Epidemic of Chronic Kidney Disease of Unknown Etiology in Mesoamerica: A Call for

Interdisciplinary Research and Action American Journal of Public Health 103:1927-1930 doi:10.2105/ajph.2013.301594
Wesseling C et al. (2020) Chronic kidney disease of non-traditional origin in Mesoamerica: a disease primarily driven by occupational heat stress Rev Panam Salud Publica 44:e15-e15 doi:10.26633/RPSP.2020.15
Wesseling C, van Wendel de Joode B, Crowe J, Rittner R, Sanati NA, Hogstedt C, Jakobsson K (2015) Mesoamerican nephropathy: geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica Occupational and Environmental Medicine 72:714-721 doi:10.1136/oemed-2014-102799
Wijkström J et al. (2018) Morphological and clinical findings in Sri Lankan patients with chronic kidney disease of unknown cause (CKDu): Similarities and differences with Mesoamerican Nephropathy PLoS One 13:e0193056-e0193056 doi:10.1371/journal.pone.0193056
Wijkström J et al. (2013) Clinical and Pathological Characterization of Mesoamerican Nephropathy: A New Kidney Disease in Central America American Journal of Kidney Diseases 62:908-918 doi:10.1053/j.ajkd.2013.05.019
Yih WK et al. (2019) Investigating Possible Infectious Causes of Chronic Kidney Disease of Unknown Etiology in a Nicaraguan Mining Community The American journal of tropical medicine and hygiene 101:676-683 doi:10.4269/ajtmh.18-0856

SUPPLEMENTAL TABLES

Table 6. Industry Sector Grouping* by Economic Sector.

Journal Article Table A. Industry Sector Grouping* by Industry sector (n=9,032)

Sectors	Primary	Secondary	Tertiary	Total
Industry Sector Groups*				
Agriculture	958 (100%)	0 (0.0%)	0 (0.0%)	956 (10.6%)
Manufacturing	0 (0.0%)	1,150 (71.0%)	0 (0.0%)	1,150 (12.7%)
Services	0 (0.0%)	0 (0.0%)	2,646 (41.0%)	2,646 (29.3%)
Construction	0 (0.0%)	470 (29.0%)	0 (0.0%)	470 (5.2%)
Sales	0 (0.0%)	0 (0.0%)	2,555 (39.6%)	2,555 (28.3%)
Transport	0 (0.0%)	0 (0.0%)	328 (5.1%)	328 (3.6%)
Education and Healthcare	0 (0.0%)	0 (0.0%)	650 (10.1%)	650 (7.2%)
Public Administration and Defense	0 (0.0%)	0 (0.0%)	275 (4.3%)	275 (3.0%)

* Industry sector groups were a derivative of on CIIU-3.1 Classification of 2 digits

JOURNAL ARTICLE

Feasibility of implementing the Disadvantaged Populations eGFR Epidemiology Study (DEGREE) protocol, point-of-care field measurements and a new module on risk factors for chronic kidney disease of unknown origin in Hispanic outdoor workers

International Archives of Occupational and Environmental Health.

ABSTRACT

Objective: To field test the Disadvantaged Populations eGFR Epidemiology (DEGREE protocol, outdoor point-of-care (POC) testing for serum creatinine, and a new risk factor module on chronic kidney disease of undetermined origin (CKDu) in U.S. outdoor Hispanic workers.

Methods: Fifty workers were interviewed in Houston (TX). DEGREE and CKDu questionnaires were completed indoors. Anthropometrics and paired blood samples for POC and laboratory assay were completed outdoors over two periods (November-December 2017, April-May 2018).

Results: Administration of DEGREE and CKDu questionnaires averaged 10 and 5 minutes, respectively, with all questions easily understood. We observed high correlations between POC and IDMS creatinine (r=0.919) and BUN (r=0.974). The POC device would disable testing when outdoor temperatures were above 85°F or below 65°F; this was adjustable.

Conclusions: Implementation of DEGREE and the new CKDu module was straightforward and well understood. The POC device performed well in the field, with some adjustment in methods when temperature readings were out of range.

Key Words: CKDu, DEGREE, Hispanic, workers

BACKGROUND

Chronic kidney disease (CKD) is a global health problem that can be caused by diabetes, hypertension, glomerulonephritis, congenital abnormalities or obstruction of the urinary tract (Caplin et al. 2017).The hallmark measurement for renal failure is the glomerular filtration rate (GFR), which is usually estimated (eGFR) from the serum creatinine level, obtained in whole blood samples. Based on the eGFR, a CKD case definition has been established by the 'Kidney Disease: Improving Global Outcomes CKD Work Group', which categorizes CKD into five stages (G1-G5) and two substages (G3a and G3b) based on eGFR. Categories G3a-G5 correspond to decreased eGFR (i.e., eGFR < 60 ml/min/1.73m^2) (Lozier et al. 2016). CKD cases identified in high-income countries are typically associated with lifestyle-related risk factors, such as type II diabetes and hypertension(Torres et al. 2010). However, over the past 10-15 years, CKD cases have been described in low- and middle-income countries that do not fit this "usual" CKD pattern. These unusual cases predominantly affect male agricultural workers, often in their 30s and 40s, and are associated with high mortality (Butler-Dawson et al. 2018; Ramirez-Rubio et al. 2013; Torres et al. 2010). Their prognosis is poor due to delays in diagnosis and limited availability of therapy (i.e., dialysis or renal transplantation).

This chronic impairment of kidney function not associated with known risk factors or a specific histological diagnosis has been termed "CKD of undetermined cause" (CKDu), "CKD of non-traditional cause" (CKDnt) or "Mesoamerican nephropathy" (MeN), given the initial description of CKDu in Central America (Wijkström et al. 2013). Clusters of a similar CKD have also been reported in Sri Lanka, India, Saudi Arabia, Egypt, Senegal, and, more recently, in the

United States (U.S.) (Caplin et al. 2017; Flores et al. 2016; Lunyera et al. 2016). In Central America, CKDu is hypothesized to be associated with occupational and environmental exposures affecting young men working in lowland agricultural settings, most notably sugarcane harvesters (Said and Hernandez 2015). To date, at least for Central American CKDu, suspected causes include a combination of exposure to high heat and humidity, inadequate hydration, high physical demands and, possibly, concomitant use of nephrotoxic nonsteroidal anti-inflammatory agents. Although attention has focused primarily on the sugarcane industry, there are other at-risk occupations and industrial industry sectors characterized by similar exposures reported in Central America (Gallo-Ruiz et al. 2019; Herath et al. 2018).

Most of the literature has described local experiences in different parts of the world, but differences in case definition, study design, sampling approach, and/or methods with limit study comparisons. Additionally, there is lack of characterization of the distribution of *normal* eGFR in the affected populations, which is likely to vary regionally. Moreover, the degree of bias in GFR estimates is affected by ethnicity and body weight/muscle mass, with ethnicity-adjusted equations still being highly variable around the world (Caplin et al. 2017; Weaver et al. 2015). Designed to facilitate international comparisons of eGFR, the 'Disadvantaged Populations Estimated Glomerular Filtration Rate (eGFR) Epidemiology Study' (DEGREE) was launched to determine the worldwide distribution of both normal and reduced eGFR through the use of the same protocol. DEGREE was especially aim to researchers in low- and middle-income countries, encouraging them to follow a standardized protocol consisting of a minimum core of demographic data and standardized measurement of serum creatinine analyzed using isotope dilution mass spectrometry (IDMS) in a laboratory (Caplin et al. 2017). To date, DEGREE has not been tested in either Central

America, where most cases of CKDu have been reported, or in similar collectives of workers in the U.S.

Although DEGREE uses central laboratory analysis of creatinine, there may be a need for testing in remote geographic areas in hot/humid outdoor environments where obtaining and transporting biological specimens may be excessively cumbersome or subject to specimen deterioration. Thus, having a reliable real-time measure of renal function could be useful. Point-of-care (POC) testing is defined as a medical diagnostic test done near the patient with near-immediate real time results. This blood sample can be taken from a fingerprick or venipuncture. Although the gold standard for serum creatinine analysis is IDMS in a central laboratory, this requires obtaining and transporting a whole blood sample, taking 30 minutes or longer to complete. POC has the advantage of immediate results that do not require transport of specimens and which can enable fast medical decision-making. POC devices provide quantitative data on a patient's renal function within minutes, which is useful in healthcare settings like emergency units and outpatient clinic settings, or even in the home (Gbinigie et al. 2015). Although recent studies have used POC devices to measure renal function, and reported promising results when comparing the accuracy of kidney function values, (Gbinigie et al. 2015; Martínez Lomakin and Tobar 2014; Moyce et al. 2017) POC devices have yet to be tested outdoors. Were the POC device provide accurate outdoor measurements, its usefulness for field studies of outdoor workers would increase.

Finally, despite the suspected strong role of occupational factors as determinants of CKDu in Hispanic worker populations, which typically are collected by means of questionnaires, there is a lack of survey questions available for researchers. However, the Second Central American Survey of Working Conditions and Health (II ECCTS by its Spanish acronym) conducted in

2018/19 among 9,000 formal and informal workers in all six Spanish-speaking countries in Central America (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama) developed a supplemental “Heat/Kidney Disease” module that included items specifically targeting the suspected CKDu risk factors. This module has not been tested among other groups of Hispanic workers that may be at risk for CKDu, such as Hispanic outdoors workers in the U.S.

In brief, the aim of this study was to examine the feasibility of implementing the DEGREE protocol, in combination with outdoor POC testing for serum creatinine and the application of a new module on risk factors for CKDu in Hispanic outdoor workers in order to determine their feasibility in the field and the usability for future research.

METHODS

A cross-sectional study was conducted in a convenience sample of 50 Houston-based Hispanic outdoor workers, recruited from the Houston Area Safety Council (HASC) facility in Pasadena, Texas. This study began in late fall 2017, after approval by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects. HASC is a fully staffed medical and worker training facility serving contractors in the greater Houston area to where employers send their workers for various pre- employment and post-placement activities, such as: a) required and periodic medical evaluations, including laboratory testing; b) drug testing; c) respirator medical evaluations and fit testing; and d) mandated worker training sessions. A large proportion of the several hundred workers seen daily at HASC are Hispanic and work outdoors, primarily in construction. HASC allowed the authors to use their facility to approach potential participants, and for participant interviews and sample collection.

The team consisted of two Spanish-speaking research members, and a trained phlebotomist. A table, chairs, blood drawing area/portable exam table, and refreshment area were set up outdoors in the facility parking area. Ambient temperature and humidity were measured outdoors with a standard anemometer station (Model 8552/8554 Q-Trak Plus IAQ Monitor, TSI Incorporated, Shoreview, MN) and readings were recorded at hourly intervals.

Participants were approached in the HASC waiting areas, the study was explained to them and, if interested, they were screened for eligibility criteria: 1) 18 years old and older; 2) performing manual labor outdoors for a minimum of 20 hours a week (e.g., construction, landscaping, etc.); 3) Hispanic; 4) no prior diagnosis of kidney injury or disease; 5) no disease associated with CKD (e.g., diabetes, hypertension, glomerulonephritis); and 6) not taking any medications to treat kidney injury, hypertension, or other cardiovascular disease.

Informed consent and interviewer-administered questionnaires were completed indoors. Eligible participants were administered two questionnaires (either in English (n=44, 89%) or in Spanish (n=6, 11%)) by a member of the research team: the DEGREE protocol data collection form and the II ECCTS Heat/Kidney module. After completing the questionnaire, participants were escorted outside to have height (in stocking feet) and weight recorded using a stadiometer and digital scale. Three resting blood pressures were obtained in the supine position using an electronic blood pressure monitor (Omron™ Digital Blood Pressure monitor with cuff, Bannockburn, Illinois; this device is programmed to take three consecutive blood pressure measurements) in accordance with the DEGREE protocol.

A single blood sample was also obtained outdoors, in order to test the performance of the POC device in hot environments, with results compared to standard isotope dilution mass spectrometry (IDMS) analysis by a certified commercial laboratory (LabCorp™, Pasadena, TX). In order to avoid testing discrepancies between blood samples, and drawing blood from the participant from two different locations, all blood samples were obtained venipuncture. The blood sample (approximately 10 cc, or two teaspoons) was obtained by an experienced phlebotomist from a forearm vein, with the participant in the supine position, and the specimen was placed in one lavender, one red, and one green top tube, each labelled with the participant's study ID. The lavender and one red top tube were prepared for transport to a local commercial laboratory (LabCorp™), as per their manual of procedures, for measurement of hemoglobin and kidney function indicators (creatinine, blood urea nitrogen (BUN)), using IDMS, as per the DEGREE protocol. Both tubes were stored in an empty cooler and taken to the lab at the end of each recruitment day. Results were ready for review between one and two business days. Blood from the green top tube was used for the POC creatinine measurement with a single-use cartridges handheld analyzer (i-STAT® Chem 8+ Point of Care Handheld Analyzer, Model 04J60-20, Abbott Laboratories, Abbott Park, Illinois), following the manufacturer's procedure, and results were immediately recorded. The total estimated participant time for all components (questionnaires, anthropometrics, and lab draw) was about 25 minutes.

Most items in the DEGREE protocol questionnaire and the "Heat/Kidney Disease" module have the advantage of a response frequency scales, but others have only a dichotomous Yes/No response. For the POC device readings, the gold standard was defined as the central laboratory-obtained values for creatinine, electrolytes and eGFR.

Statistical Analysis

Scatter plots of paired lab and POC values were plotted and a line of equality drawn. The Pearson correlation coefficient (*r*) between the two methods was calculated in order to determine the linear correlation between the two methods, which quantifies the degree to which two variables are related, but does not assess or imply the agreement between the two methods. Therefore, Bland-Altman plots were generated to assess agreement with the percent differences and means between both methods (Bland and Altman 1986). These plots help show when there is an increase in variability of the differences as the magnitude of the measurement increases, and can highlight anomalies and reveal overestimates or underestimates of one method over the other (Giavarina 2015). For this analysis, the IDMS was used as the gold standard. The Stata statistical package (Stata Corp, College Station, TX) was used for the analyses (StataCorp 2017).

RESULTS

Recruitment was divided between two time periods. The first 29 participants were recruited in November and December 2017, referred to as the "colder period" (outside temperature range from 59.7°F to 86°F, with an average relative humidity of 64.9%, and an average heat index of 76.6°F), and a second group of 26 participants in April and May 2018, referred to as the "hotter period" (73.2°F to 89.8°F, with an average relative humidity of 69.3%, and an average heat index of 88.3°F). When calculating for heat index using the recorded temperatures and relative humidity, the highest reported heat index was 106°F.

We invited these 55 participants to complete the DEGREE protocol and CKDu module, and undergo core measurements. However, five participants did not complete the blood testing. The age of the final sample ranged from 19 to 60 years, with an average age of 29 years. The most common occupation was scaffold builder (n=12). The majority of men had a high school education, while less than 6% had a college or professional degree (Table 1). Administration of the DEGREE and core measurements, excluding blood draw, averaged 10 minutes. All questions were straightforward and easily understood by the participants. Administration of the "Heat/Kidney Disease" module averaged five minutes, and all questions were answered without any difficulty, need for clarification or reluctance to answer.

Table 2 compares the anthropometric and physical measures dictated on the DEGREE protocol by season. Overall, average BMI was 31.26 (SD = 6.745) and average blood pressure was 132 mm Hg for systolic and 85 mm Hg for diastolic (SD = 11.70, 10.58). When measurements were separated to distinguish those from the colder period (n=24) and the hotter period (n=26), there were no differences in BMI. However, average blood pressure was lower for those participants recruited during the hotter period than the colder period (p-value = 0.016 diastolic; p-value = 0.0001 for systolic).

Regarding the comparison between POC and IDMS measurements, we found that measurements of creatinine and blood urea nitrogen (BUN) correlated well across the range of temperatures (Table 3). Hemoglobin measurements also correlated strongly during the coldest outdoor temperatures and the hottest temperatures. Strong correlations were observed for hemoglobin, serum creatinine, and BUN (r = >0.850).

The Bland-Altman plot for hemoglobin demonstrated a bias of -3.58% and an agreement range of -11.43% to 4.27%, suggesting that, on average, the POC provides measurements 3.58% higher than those obtained from the IDMS analysis. Serum creatinine indicates a near negligible bias of -0.18%. Serum BUN has a bias of -0.72% that is constant for lower averages of BUN (compared to a -1.59% bias with all 50 samples). The hemoglobin plot was the only plot to show no evident trend (Figure 1).

The POC device generally worked well outdoors, with one exception. The POC would disable cartridge testing when outdoor temperatures were high (above 85°F) or low (below 65°F). However, this would quickly resolve once the POC was brought inside the clinic for a few minutes to cool the device.

DISCUSSION

Implementation of the DEGREE protocol and CKDu module was straightforward and well understood; completion rate for both surveys was above 98%. Participants had no difficulty understanding the questions or procedures that needed to be completed (i.e., blood pressure, blood draw), in either English or Spanish. We did not encounter any major problems with POC testing for renal function or hemoglobin measurements. Results for BUN, creatinine and hemoglobin correlated well with those obtained from IDMS.

One major strength from our study is that all blood samples were collected from the same site, i.e., the forearm. Thus, all three blood vials collected from each participant contained the same whole blood source for simultaneous POC and IDMS testing. Executing this also avoided drawing blood from the participant two different times from two different places (forearm and finger). One recent study did report POC testing overestimated creatinine by 22% compared to laboratory testing using a distinct method of blood sample collection (fingerprick for POC and venipuncture for IDMS) under tropical field conditions (Griffin et al. 2018). Thus, an adjustment factor of 0.7775 was applied to all POC creatinine values for a later study analyzing cross-shift percent change in eGFR from 105 sugarcane workers in Guatemala (Sorensen et al. 2019). There may be an advantage to using a venipuncture blood sample rather than a fingerstick sample due to blood volume and testing efficiency. Recently, a study performed analytical and clinical comparability of POC devices with a central laboratory reference for creatinine and found that the i-STAT device showed the highest clinical concordance with the reference standard (Kappa: 0.94) and had the smallest average analytical error (6%) for creatinine when using a whole blood sample (Minnings et al. 2015).

There were some limitations. Since all blood samples completed by venipuncture, we did not examine accuracy of venipuncture versus fingerprick results when using a POC device. The POC allows for both fingerstick and venipuncture blood testing. Studies that have used POC testing rely on a fingerprick for the POC device and venipuncture for laboratory testing. A study done in Nicaragua found POC testing for creatinine demonstrated acceptable repeatability, excellent sensitivity (100%) and modest specificity (79%) using blood samples from two different sources (forearm for Jaffe kinetic method with a Roche Cobas Integra 400 analyzer and finger for POC) (van der Heijden et al. 2019). However, there are no available studies that compare the accuracy of solely using fingerprick capillary blood for comparable POC and IDMS results. Nevertheless, if future studies can find the accuracy of using fingerprick blood, it may be a preferable method over venipuncture due to lower cost of equipment, faster laboratory testing, and a less invasive blood draw.

Only a few of the outdoor temperature ranges were as warm or hot as those expected in the Central American agricultural fields. Central America has a tropical humid climate with no real winter; even the coldest month averages above 64.4°F, with summers of 80.6°F to 89.6°F, with a relative humidity between 75% and 85%. When using the heat index to measure the heat index temperature, the temperature in the agricultural areas can increase significantly. A temperature in Central America of 90°F with a relative humidity of 80% can result in a heat index temperature of 113°F ((NOAA) 2019). The highest reported heat index for this study was 106°F. Thus, it may be useful to retest the POC at heat indices that are closer to 113°F. This is important given that cartridge testing with the POC we used was only possible within a range of outdoor temperatures between 65°F and 85°F. However, only a few minutes were needed to cool the device and reinstate the testing function, with no reading bias observed after this was done. Certainly, more studies are needed to determine what obstacles can be encountered with POC devices in outside settings (e.g., to test if readings are stable and accurate despite long term exposure to heat) and what remedies can be developed to overcome those issues. For instance, repeating our study by supplementing the POC sensor with a small cooler in order to cool down the POC sensor, would help determine the effectiveness of the POC device in the field and in hotter temperatures.

In addition, it may be beneficial to conduct more research studies with a larger sample population to better determine the feasibility of using the DEGREE protocol, POC testing, and "Heat/Kidney Disease" module. Given the extremely high mortality and morbidity reported with this disease, efforts to identify baseline of normal and reduced eGFRs, faster in-field serum measurement testing that circumvents the need for specimen preservation and transport to an offsite laboratory, and common risk factors associated with CKDu can help researchers prevent future cases and provide care for those affected. Future studies should also focus on testing the comparability of POC and laboratory testing using only one type of blood source.

Table 7. DEGREE Protocol social demographics by season.
Journal Article Table 1. DEGREE Protocol social demographics by season.

Demographics	**Colder Period (n=24)** N (%)	**Hotter Period (n=26)** N (%)
Age (years)		
19-29	14 (58.3%)	16 (61.5%)
30-39	6 (25.0%)	7 (26.9%)
40-49	3 (12.5%)	1 (3.9%)
50-59	0 (0%)	2 (7.7%)
60 +	1 (4.2%)	0 (0%)
Occupation		
Boilermaker	3 (12.5%)	1 (3.9%)
Carpentry	0 (0.0%)	0 (0.0%)
Certified mechanic	1 (4.2%)	1 (3.9%)
Construction	1 (4.2%)	0 (0.0%)
Electrician	1 (4.2%)	2 (7.7%)
Foundation Repair	0 (0.0%)	1 (3.9%)
Industrial painter	0 (0.0%)	4 (15.4%)
Insulation	3 (12.5%)	2 (7.7%)
Ironworker	0 (0.0%)	2 (7.7%)
Pipefitter	2 (8.3%)	2 (7.7%)
Refineries	3 (12.5%)	1 (3.9%)
Scaffold builder	6 (25.0%)	6 (23.1%)
Skilled worker	0 (0.0%)	1 (3.9%)
Technician	1 (4.2%)	0 (0.0%)
Welder	0 (0.0%)	2 (7.7%)
Other	1 (4.2%)	1 (3.9%)
Education		
Less than high school		
High School	4 (16.7%)	1 (11.5%)
Some College	9 (37.5%)	14 (53.9%)
College Degree / Professional	9 (37.5%)	8 (30.8%)
Degree	2 (8.3%)	1 (3.9%)
Household Income		
< $30,000	0 (0.0%)	0 (0.0%)
$30,000 - $50,000	3 (12.5%)	0 (0.0%)
$50,000+	3 (12.5%)	0 (0.0%)
Did not answer	18 (75.0%)	26 (100.0%)
Interview language		
English	22 (91.7%)	22 (84.6%)
Spanish	2 (8.3%)	4 (15.4%)

Table 8. DEGREE Protocol Core Physical Measurements by season.

Journal Article Table 2. DEGREE Protocol Core Physical Measurements by season.

	Colder Period (n=24)				Hotter Period (n=26)			
Measurements	**Mean**	**SD**	**Range**	**p-Value**	**Mean**	**SD**	**Range**	**p- Value**
Temperature (°F)	74.5	8.3	(59.7-86)	0.0002	82.1	4.8	(73.2-89.60.9)	<0.0001
Height (cm)	176.3	6.6	(164-187)	0.56	175.5	7.4	(155.5-191)	0.58
Weight (kg)	97.9	25.0	(61.7-152.4)	0.39	93.4	18.5	(62.1-140.2)	0.23
BMI	31.4	7.3	(20.0-50.3)	0.47	30.3	5.5	(20.7-45.2)	0.32
Systolic BP (mmHg)	134.0	12.0	(111.0-161.3)	0.087	129.6	8.7	(115.3-147.3)	0.016
Diastolic BP (mmHg)	88.7	9.6	(63.7-108.0)	0.0005	80.8	9.0	(65.7-104.0)	0.0001

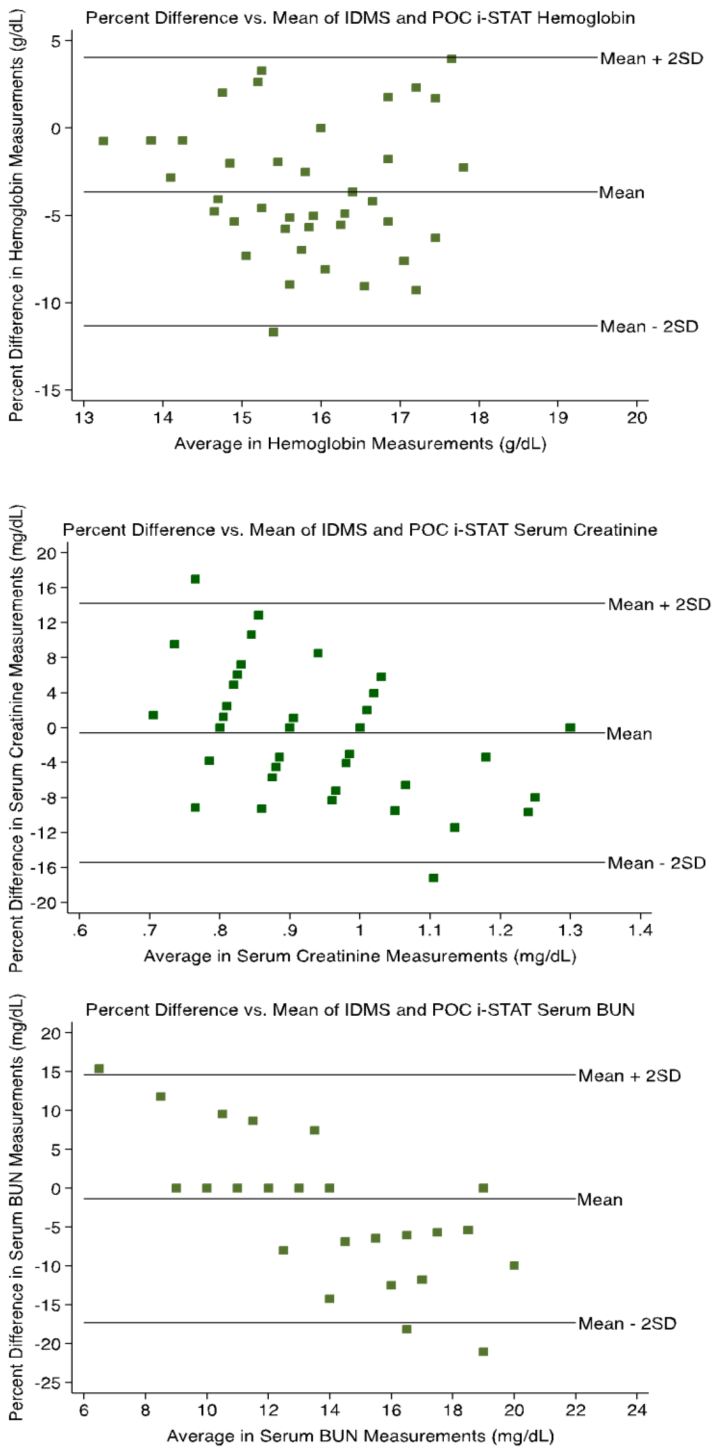
SD = Standard deviation; BMI = Body Mass Index; BP = Blood pressure.

Table 9. Comparison of IDMS measurements and Point-of-Care i-STAT CHEM8+ measurements by season.

Journal Article Table 3. Comparison of IDMS measurements and Point-of-Care i-STAT CHEM8+ measurements by season.

Blood chemistries	**Colder Period (n=24)**			**Hotter Period (n=26)**		
	IDMS	**iSTAT**		**IDMS**	**iSTAT**	
	Mean (SD)	**Mean (SD)**	***r***	**Mean (SD)**	**Mean (SD)**	***r***
Hemoglobin (g/dL)	16.03 (1.21)	16.86 (1.12)	0.878	15.47 (1.220)	15.85 (1.221)	0.868
Creatinine (mg/dL)	0.88 (0.13)	0.89 (0.15)	0.896	0.95 (0.1361)	0.965 (0.1788)	0.914
BUN (mg/dL)	12.83 (3.82)	13.25 (4.34)	0.964	13.46 (3.08)	13.81 (3.86)	0.986
eGFR (ml/min/1.73m^2)	114.00 (15.18)	--	--	105.81 (18.21)	--	--

IDMS = isotope dilution mass spectrometry; SD =Standard deviation; BUN = Blood urea nitrogen; eGFR = estimated glomerular filtration rate; *r*= *Pearson's* correlation coefficient.



Journal Figure 1. Bland-Altman plot for measurements of POC vs. IDMS (n=50).

Figure 3. Bland-Altman plot for measurements of POC vs. IDMS (n=50).

REFERENCES

(NOAA) UDoCaNWS (2019) Heat Index. www.weather.gov/safety/heat-index. Accessed October 10 2019

Bland M, Altman D (1986) Statistical methods for assessing agreement between two methods of clinical measurement Lancet 327:307-310 doi:https://doi.org/10.1016/S0140-6736(86)90837-8

Butler-Dawson J et al. (2018) Risk Factors for Declines in Kidney Function in Sugarcane Workers in Guatemala J Occup Environ Med 60:548-558 doi:10.1097/JOM.0000000000001284

Caplin B et al. (2017) International Collaboration for the Epidemiology of eGFR in Low and Middle Income Populations - Rationale and core protocol for the Disadvantaged Populations eGFR Epidemiology Study (DEGREE) BMC Nephrology 18 doi:10.1186/s12882-016-0417-1

Flores S, Rider AC, Alter HJ (2016) Mesoamerican nephropathy: a novel case of kidney failure in a US ED The American Journal of Emergency Medicine 34:1323.e1325-1323.e1326 doi:10.1016/j.ajem.2015.11.048

Gallo-Ruiz L et al. (2019) Prevalence and Risk Factors for CKD Among Brickmaking Workers in La Paz Centro, Nicaragua American Journal of Kidney Diseases 74:239-247 doi:10.1053/j.ajkd.2019.01.017

Gbinigie O, Price CP, Heneghan C, Van den Bruel A, Plüddemann A (2015) Creatinine point-of-care testing for detection and monitoring of chronic kidney disease: primary care diagnostic technology update The British journal of general practice : the journal of the Royal College of General Practitioners 65:608-609 doi:10.3399/bjgp15X687613

Giavarina D (2015) Understanding Bland Altman analysis Biochemia medica 25:141-151 doi:10.11613/BM.2015.015

Griffin BR et al. (2018) Unadjusted point of care creatinine results overestimate acute kidney injury incidence during field testing in Guatemala PLoS One 13:e0204614-e0204614 doi:10.1371/journal.pone.0204614

Herath C, Jayasumana C, De Silva PMCS, De Silva PHC, Siribaddana S, De Broe ME (2018) Kidney Diseases in Agricultural Communities: A Case Against Heat-Stress Nephropathy Kidney International Reports 3:271-280 doi:https://doi.org/10.1016/j.ekir.2017.10.006

Lozier M, Turcios-Ruiz R, Noonan G, Ordunez P (2016) Chronic kidney disease of nontraditional etiology in Central America: A provisional epidemiologic case definition for surveillance and epidemiologic studies Rev Panam Salud Publica 40:294-300

Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW (2016) CKD of Uncertain Etiology: A Systematic Review Clinical journal of the American Society of Nephrology : CJASN 11:379-385 doi:10.2215/CJN.07500715

Martínez Lomakin F, Tobar C (2014) Accuracy of point-of-care serum creatinine devices for detecting patients at risk of contrast-induced nephropathy: A critical overview Critical Reviews in Clinical Laboratory Sciences 51:332-343 doi:10.3109/10408363.2014.937794

Minnings K et al. (2015) Chronic kidney disease prevalence in Rivas, Nicaragua: Use of a field device for creatinine measurement Clinical Biochemistry 48:456-458 doi:https://doi.org/10.1016/j.clinbiochem.2015.01.005
Moyce S, Mitchell D, Armitage T, Tancredi D, Joseph J, Schenker M (2017) Heat strain, volume depletion and kidney function in California agricultural workers Occupational and environmental medicine 74:402-409 doi:10.1136/oemed-2016-103848
Ramirez-Rubio O, McClean MD, Amador JJ, Brooks DR (2013) An epidemic of chronic kidney disease in Central America: an overview Postgraduate Medical Journal 89:123-125 doi:10.1136/postgradmedj-2012-201141rep
Said S, Hernandez GT (2015) Environmental Exposures, Socioeconomics, Disparities, and the Kidneys Advances in Chronic Kidney Disease 22:39-45 doi:10.1053/j.ackd.2014.09.003
Sorensen CJ et al. (2019) Risk Factors and Mechanisms Underlying Cross-Shift Decline in Kidney Function in Guatemalan Sugarcane Workers J Occup Environ Med 61:239-250 doi:10.1097/JOM.0000000000001529
StataCorp (2017) StataCorp. StataCorp LP, College Station, TX
Torres C et al. (2010) Decreased Kidney Function of Unknown Cause in Nicaragua: A Community-Based Survey American Journal of Kidney Diseases 55:485-496 doi:10.1053/j.ajkd.2009.12.012
van der Heijden C, Roosens L, Cluckers H, Van Craenenbroeck AH, Peeters B (2019) Analytical and clinical performance of three hand-held point-of-care creatinine analyzers for renal function measurements prior to contrast-enhanced imaging Clinica Chimica Acta 497:13-19 doi:https://doi.org/10.1016/j.cca.2019.06.025
Weaver VM, Fadrowski JJ, Jaar BG (2015) Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and/or occupational nephropathy? BMC nephrology 16:145-145 doi:10.1186/s12882-015-0105-6
Wijkström J et al. (2013) Clinical and Pathological Characterization of Mesoamerican Nephropathy: A New Kidney Disease in Central America American Journal of Kidney Diseases 62:908-918 doi:10.1053/j.ajkd.2013.05.019

CONCLUSIONS

The overall findings of this dissertation address some of the gaps in knowledge of CKDu, by identifying other industries and areas with similar exposures that may be at risk for the CKDu, the feasibility of protocols to obtain baseline renal function, and the accuracy of POC testing in outdoor settings. First, nationally representative data for the working population in Central America collected by the II ECCTS demonstrated a high prevalence of work-related CKD among working age males in the primary and secondary sectors, and had physically demanding jobs. Second, the GIS weather maps displayed clusters of work-related CKD and CKDu risk factors, together and separately, in areas where research studies have been limited. Third, in our small pilot study, we found implementation of the DEGREE protocol and CKDu module to be straightforward and well understood by Hispanic outdoor workers in either English or Spanish. Finally, POC testing for renal function and hemoglobin measurements had high accuracy and correlated well with those obtained from IDMS analysis. These pilot study findings demonstrate the feasibility of conducting larger studies using these methods in outdoor workers in the U.S.

We identified other industry sectors that may harbor CKDu, based on a nationally representative survey of working conditions and health in Central America. The analysis uncovered workers in the primary and secondary industry sectors who reported CKD and work-related CKD had higher percentages of high physical demands, exposure to heat, exposure to humidity, high use of agrochemicals and high thirst than those in the tertiary sector. The multivariate analysis for both CKD and work-related CKD identified significant associations with different sociodemographic and CKDu risk factors across industry sectors (CKD: exposure to high humidity, no water intake, and high thirst; work-related CKD: 30 to 49-year age group;

mestizo ethnicity, and exposure to high physical demands). Exposure to high humidity, heat, and thirst were also found to have elevated odds ratios in the multivariate models, but did not demonstrate statistical significance. Thus, the hypothesis for Aim 1 was confirmed because CKDu risk factors among workers in Central America appear to be distributed among more industry sectors than previously reported in other studies.

The second hypothesis focused on finding selected CKDu risk factors and work-related CKD in Central America in relation to geographic variation in climate and temperature. The weather map uncovered other sectors at risk for CKDu risk factor exposure and development of CKD related to work in locations that lack epidemiological studies, such as Honduras and Panama. It also identified very few areas that clustered work-related CKD but in the absence of any CKDu risk factors, such as central Nicaragua. More importantly, areas that featured CKDu risk factor clusters in the absence of work-related CKD were observed in areas such as southern Costa Rica and coastal Panama that could be associated with other economic activities harboring workers susceptible to the development of CKDu. As a result, the second hypothesis for Aim 2 was also considered true since we found a larger number of areas with hot and humid conditions than previously described that might be at risk for CKDu.

Finally, the third hypothesis was to examine the feasibility of using the DEGREE protocol to identify the distribution of both normal and reduced eGFR in Houston outdoor workers, and to assess the practicality and accuracy of POC testing in outdoor settings when compared to IDMS analysis. Implementation of the DEGREE protocol and CKDu module surveys was successful, with a completion rate above 98%. Participants had no difficulty understanding the questions or procedures that needed to be completed. The outdoor POC testing for BUN, creatinine and hemoglobin was feasible, with results showing POC correlated well and accurately with IDMS analysis. Thus, the third hypothesis for Aim 3 was also demonstrated, indicating the DEGREE protocol and POC testing of renal function are feasible for use in larger studies of CKDu in outdoor working populations in the U.S.

Further steps and recommendations are to conduct future research studies that allow for the better identification of other non-agricultural industries, locations, and populations susceptible to the development of CKDu, both in Central America and the U.S. This could help uncover new clusters of working populations at risk of exposure to established CKDu risk factors in advance of disease development, allowing the possibility of implementing preventive measures to offset their effects. Moreover, studies that include measurement of renal function and national representative surveys are needed to better ascertain the distribution of renal function, both normal and abnormal, in Central America and in at-risk populations such as those of mestizo ethnicity. It is also necessary to expand research of at-risk populations and of renal function to other regions or countries, which is one of the objectives of the global DEGREE project. Many Hispanic outdoor workers in Texas are migrants from Central America and, until recently, represented the fastest growing group of immigrant workers to the U.S. (Obinna and Field 2019). Many of these workers are mestizo and perform a variety of outdoor manual jobs in different parts of the U.S. Repeating our pilot study in a larger population of Hispanic outdoor workers in other parts of Texas and the U.S. would be valuable to assess the practicality of a nationwide deployment of the study. Although measurement of renal function by IDMS still represents the gold standard, there may be barriers to this approach when studies are completed in remote, rural locations in Central America (or possibly even in the U.S.). For example, if maintenance of cold chain or transportation of blood specimens to a central laboratory for analysis poses a challenge, POC testing can be a viable alternative. POC testing for renal function and hemoglobin is quick and can be performed using the same method we used in our pilot study. Additional studies using this method could be expanded to agriculture-rich regions in the United States, such as those in California and Florida, where previous studies have found decreases in eGFR, associated with heat stress-related CKDu risk factors (Aguilar and Madero 2019; Mix et al. 2017; Moyce et al. 2016; Moyce et al. 2017). It might be even more useful in resource-poor developing countries around the world with problems in transportation infrastructure.

Although there remain many unknowns regarding the causes of CKDu, the literature strongly supports the role of occupational and environmental factors in working age males with decreased eGFR: high heat, high humidity, and high physical demands. This dissertation reaffirms these findings in the Central American population, and points to new areas and activities that could also be CKDu hot spots. Thus, next steps following these outcomes are to conduct larger scale studies of the DEGREE protocol, use of POC testing for renal function, epidemiological studies that combine renal function blood chemistry testing with the II ECCTS Kidney module.

Results from this dissertation add to the body of knowledge of CKDu, its causes and should be useful in future research. These findings, coupled with greater efforts to determine the distribution of both normal and reduced eGFR worldwide, faster in-field testing of kidney function, and the application of population-based, nationally representative epidemiological approaches to the study of CKDu research are important steps. This knowledge is needed so that more preventive measures and interventions can be designed and implemented to prevent future cases of CKDu.

REFERENCES

(NOAA) NOaAA, Information NCfE (2019) Find a Station. https://www.ncdc.noaa.gov/data-access/land-based-station-data/find-station. Accessed November 1 2019

(NOAA) UDoCaNWS (2019) Heat Index. www.weather.gov/safety/heat-index. Accessed October 10 2019

Aguilar DJ, Madero M (2019) Other Potential CKD Hotspots in the World: The Cases of Mexico and the United States Seminars in Nephrology 39:300-307 doi:https://doi.org/10.1016/j.semnephrol.2019.02.008

Al-Bouwarthan M, Quinn MM, Kriebel D, Wegman DH (2019) Assessment of Heat Stress Exposure among Construction Workers in the Hot Desert Climate of Saudi Arabia Annals of Work Exposures and Health 63:505-520 doi:10.1093/annweh/wxz033

Anderson GB, Bell ML, Peng RD (2013) Methods to calculate the heat index as an exposure metric in environmental health research Environ Health Perspect 121:1111-1119 doi:10.1289/ehp.1206273

Bank W (2012) Better Jobs in Central America. The Role of Human Capital (Rep.). http://www.worldbank.org/content/dam/Worldbank/document/Better%20Jobs%20in%20Central%20America.pdf. Accessed August 1, 2018

Barcelos E et al. (2015) Oil palm natural diversity and the potential for yield improvement Front Plant Sci 6:190-190 doi:10.3389/fpls.2015.00190

Benavides FG, Wesseling C, Delclos GL, Felknor S, Pinilla J, Rodrigo F (2014) Working conditions and health in Central America: a survey of 12 024 workers in six countries Occupational and Environmental Medicine 71:459-465 doi:10.1136/oemed-2013-101908

Bland M, Altman D (1986) Statistical methods for assessing agreement between two methods of clinical measurement Lancet 327:307-310 doi:https://doi.org/10.1016/S0140-6736(86)90837-8

Bouroncle C, Pablo I, Rodríguez-Sánchez B, Medellín C, Martinez Valle A, Laderach P (2016) Mapping climate change adaptive capacity and vulnerability of smallholder agricultural livelihoods in Central America: ranking and descriptive approaches to support adaptation strategies Climatic Change 141 doi:10.1007/s10584-016-1792-0

Brooks DR, Ramirez-Rubio O, Amador JJ (2012) CKD in Central America: A Hot Issue American Journal of Kidney Diseases 59:481-484 doi:10.1053/j.ajkd.2012.01.005

Butler-Dawson J et al. (2018) Risk Factors for Declines in Kidney Function in Sugarcane Workers in Guatemala J Occup Environ Med 60:548-558 doi:10.1097/JOM.0000000000001284

Butler-Dawson J et al. (2019) Evaluation of heat stress and cumulative incidence of acute kidney injury in sugarcane workers in Guatemala International Archives of Occupational and Environmental Health 92:977-990 doi:10.1007/s00420-019-01426-3

Caplin B et al. (2017) International Collaboration for the Epidemiology of eGFR in Low and Middle Income Populations - Rationale and core protocol for the Disadvantaged Populations eGFR Epidemiology Study (DEGREE) BMC Nephrology 18 doi:10.1186/s12882-016-0417-1

Caplin B et al. (2019) The International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology: Report of the working group on approaches to population-level detection strategies and recommendations for a minimum dataset Kidney International 95:4-10 doi:10.1016/j.kint.2018.08.019

Chicas R, Mix J, Mac V, Flocks J, Dickman NE, Hertzberg V, McCauley L (2019) Chronic Kidney Disease Among Workers: A Review of the Literature Workplace Health & Safety 67:481-490 doi:10.1177/2165079919843308

Correa-Rotter R, García-Trabanino R (2019) Mesoamerican Nephropathy Seminars in Nephrology 39:263-271 doi:https://doi.org/10.1016/j.semnephrol.2019.02.004

Esri (2018) Esri. Environmental Systems Research Institute, Redlands, CA

Fagerland MW, Hosmer DW (2012) A Generalized Hosmer–Lemeshow Goodness-of-Fit Test for Multinomial Logistic Regression Models The Stata Journal 12:447-453 doi:10.1177/1536867x1201200307

Flores S, Rider AC, Alter HJ (2016) Mesoamerican nephropathy: a novel case of kidney failure in a US ED The American Journal of Emergency Medicine 34:1323.e1325-1323.e1326 doi:10.1016/j.ajem.2015.11.048

Foundation TNK (2017) Creatinine: What is it? https://www.kidney.org/atoz/content/what-creatinine. Accessed August 25, 2018

Freedman BI, Sedor JR (2008) Hypertension-Associated Kidney Disease: Perhaps no More Journal of the American Society of Nephrology 19:2047-2051 doi:10.1681/asn.2008060621

Friedman DJ (2019) Genes and environment in chronic kidney disease hotspots Current Opinion in Nephrology and Hypertension 28:87-96 doi:10.1097/mnh.0000000000000470

Gallo-Ruiz L et al. (2019) Prevalence and Risk Factors for CKD Among Brickmaking Workers in La Paz Centro, Nicaragua American Journal of Kidney Diseases 74:239-247 doi:10.1053/j.ajkd.2019.01.017

Garbanzo MR, Benavides FG, Gimeno D (2016) P251 Psychosocial risk exposure and musculoskeletal pain among formal and informal workers in central america Occupational and Environmental Medicine 73:A205-A205 doi:10.1136/oemed-2016-103951.567

García-Trabanino R et al. (2015) Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador – A cross-shift study of workers at risk of Mesoamerican nephropathy Environmental Research 142:746-755 doi:https://doi.org/10.1016/j.envres.2015.07.007

Gbinigie O, Price CP, Heneghan C, Van den Bruel A, Plüddemann A (2015) Creatinine point-of-care testing for detection and monitoring of chronic kidney disease: primary care diagnostic technology update The British journal of general practice : the journal of the Royal College of General Practitioners 65:608-609 doi:10.3399/bjgp15X687613

Giavarina D (2015) Understanding Bland Altman analysis Biochemia medica 25:141-151 doi:10.11613/BM.2015.015

Gifford FJ, Gifford RM, Eddleston M, Dhaun N (2017) Endemic Nephropathy Around the World Kidney International Reports 2:282-292 doi:https://doi.org/10.1016/j.ekir.2016.11.003

Gonzalez-Quiroz M et al. (2019) Rationale and population-based prospective cohort protocol for the disadvantaged populations at risk of decline in eGFR (CO-DEGREE) BMJ Open 9:e031169 doi:10.1136/bmjopen-2019-031169

González-Quiroz M, Pearce N, Caplin B, Nitsch D (2017) What do epidemiological studies tell us about chronic kidney disease of undetermined cause in Meso-America? A systematic review and meta-analysis Clinical Kidney Journal 11:496-506 doi:10.1093/ckj/sfx136

Griffin BR et al. (2018) Unadjusted point of care creatinine results overestimate acute kidney injury incidence during field testing in Guatemala PLoS One 13:e0204614-e0204614 doi:10.1371/journal.pone.0204614

Gutiérrez-Amavizca BE et al. (2013) Contribution of GSTM1, GSTT1, and MTHFR polymorphisms to end-stage renal disease of unknown etiology in Mexicans Indian J Nephrol 23:438-443 doi:10.4103/0971-4065.120342

Herath C, Jayasumana C, De Silva PMCS, De Silva PHC, Siribaddana S, De Broe ME (2018) Kidney Diseases in Agricultural Communities: A Case Against Heat-Stress Nephropathy Kidney International Reports 3:271-280 doi:https://doi.org/10.1016/j.ekir.2017.10.006

Herath N et al. (2019) Normality data of eGFR and validity of commonly used screening tests for CKD in an area with endemic CKD of unknown etiology; need for age and sex based precise cutoff values BMC Nephrology 20:298 doi:10.1186/s12882-019-1477-9

Herrera Valdés R et al. (2015) Clinical characteristics of chronic kidney disease of non-traditional causes in women of agricultural communities in El Salvador Clin Nephrol 83:56-63 doi:10.5414/cnp83s056

Hidalgo HG, Amador JA, Alfaro EJ, Quesada B (2013) Hydrological climate change projections for Central America Journal of Hydrology 495:94-112 doi:https://doi.org/10.1016/j.jhydrol.2013.05.004

Hosmer DW, Lemeshow S, Sturdivant RX, Hosmer DW, Jr. (2013) Applied Logistic Regression. John Wiley & Sons, Incorporated, New York, UNITED STATES

Institute IFPR (2016) Increasing agricultural mechanization in Latin America will take more coordination, investment. http://www.ifpri.org/blog/increasing-agricultural-mechanization-latin-america-will-take-more-coordination-investment. Accessed August 1, 2018

Johnson RJ, Wesseling C, Newman LS (2019) Chronic Kidney Disease of Unknown Cause in Agricultural Communities New England Journal of Medicine 380:1843-1852 doi:10.1056/NEJMra1813869

Kupferman J et al. (2016) Characterization of Mesoamerican Nephropathy in a Kidney Failure Hotspot in Nicaragua American Journal of Kidney Diseases 68:716-725 doi:https://doi.org/10.1053/j.ajkd.2016.06.012

Kupferman J et al. (2018) Acute Kidney Injury in Sugarcane Workers at Risk for Mesoamerican Nephropathy American Journal of Kidney Diseases 72:475-482 doi:10.1053/j.ajkd.2018.04.014

Laws RL et al. (2015) Changes in kidney function among Nicaraguan sugarcane workers International Journal of Occupational and Environmental Health 21:241-250 doi:10.1179/2049396714Y.0000000102

Levey AS et al. (2005) Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO) Kidney International 67:2089-2100 doi:10.1111/j.1523-1755.2005.00365.x

Lewington AJP, Cerdá J, Mehta RL (2013) Raising awareness of acute kidney injury: a global perspective of a silent killer Kidney international 84:457-467 doi:10.1038/ki.2013.153

Lozier M, Turcios-Ruiz R, Noonan G, Ordunez P (2016) Chronic kidney disease of nontraditional etiology in Central America: A provisional epidemiologic case definition for surveillance and epidemiologic studies Rev Panam Salud Publica 40:294-300

Lucas RAI et al. (2015) Heat stress and workload associated with sugarcane cutting - an excessively strenuous occupation! Extrem Physiol Med 4:A23-A23 doi:10.1186/2046-7648-4-S1-A23

Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW (2016) CKD of Uncertain Etiology: A Systematic Review Clinical journal of the American Society of Nephrology : CJASN 11:379-385 doi:10.2215/CJN.07500715

Martín-Cleary C, Ortiz A (2014) CKD hotspots around the world: where, why and what the lessons are. A CKJ review series Clinical Kidney Journal 7:519-523 doi:10.1093/ckj/sfu118

Martínez Lomakin F, Tobar C (2014) Accuracy of point-of-care serum creatinine devices for detecting patients at risk of contrast-induced nephropathy: A critical overview Critical Reviews in Clinical Laboratory Sciences 51:332-343 doi:10.3109/10408363.2014.937794

McCaughey D, DelliFraine JL, McGhan G, Bruning NS (2013) The negative effects of workplace injury and illness on workplace safety climate perceptions and health care worker outcomes Safety Science 51:138-147 doi:https://doi.org/10.1016/j.ssci.2012.06.004

McLafferty S (2015) Disease cluster detection methods: recent developments and public health implications Annals of GIS 21:127-133 doi:10.1080/19475683.2015.1008572

Minnings K et al. (2015) Chronic kidney disease prevalence in Rivas, Nicaragua: Use of a field device for creatinine measurement Clinical Biochemistry 48:456-458 doi:https://doi.org/10.1016/j.clinbiochem.2015.01.005

Mix J et al. (2017) Hydration Status, Kidney Function and Kidney Injury in Florida Agricultural Workers J Occup Environ Med 60 doi:10.1097/JOM.0000000000001261

Moyce S, Joseph J, Tancredi D, Mitchell D, Schenker M (2016) Cumulative Incidence of Acute Kidney Injury in California's Agricultural Workers Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 58:391-397 doi:10.1097/JOM.0000000000000668

Moyce S, Mitchell D, Armitage T, Tancredi D, Joseph J, Schenker M (2017) Heat strain, volume depletion and kidney function in California agricultural workers Occupational and environmental medicine 74:402-409 doi:10.1136/oemed-2016-103848

Myzabella N, Fritschi L, Merdith N, El-Zaemey S, Chih H, Reid A (2019) Occupational Health and Safety in the Palm Oil Industry: A Systematic Review Int J Occup Environ Med 10:159-173 doi:10.15171/ijoem.2019.1576

Nerbass FB, Moist L, Clark WF, Vieira MA, Pecoits-Filho R (2019) Hydration Status and Kidney Health of Factory Workers Exposed to Heat Stress: A Pilot Feasibility Study Annals of Nutrition and Metabolism 74(suppl 3):30-37 doi:10.1159/000500373
Nerbass FB, Pecoits-Filho R, Clark WF, Sontrop JM, McIntyre CW, Moist L (2017) Occupational Heat Stress and Kidney Health: From Farms to Factories Kidney International Reports 2:998-1008 doi:https://doi.org/10.1016/j.ekir.2017.08.012
O'Donnell JK et al. (2010) Prevalence of and risk factors for chronic kidney disease in rural Nicaragua Nephrology Dialysis Transplantation 26:2798-2805 doi:10.1093/ndt/gfq385
Obinna DN, Field LM (2019) Geographic and Spatial Assimilation of Immigrants from Central America's Northern Triangle International Migration 57:81-97 doi:10.1111/imig.12557
Ordunez P, Nieto FJ, Martinez R, Soliz P, Giraldo GP, Mott SA, Hoy WE (2018) Chronic kidney disease mortality trends in selected Central America countries, 1997–2013: clues to an epidemic of chronic interstitial nephritis of agricultural communities Journal of Epidemiology and Community Health 72:280-286 doi:10.1136/jech-2017-210023
Pearce N, Caplin B (2019) Let’s take the heat out of the CKDu debate: more evidence is needed Occupational and Environmental Medicine 76:357-359 doi:10.1136/oemed-2018-105427
Peraza S et al. (2012) Decreased Kidney Function Among Agricultural Workers in El Salvador American Journal of Kidney Diseases 59:531-540 doi:10.1053/j.ajkd.2011.11.039
Perez-Gomez MV, Martin-Cleary C, Fernandez-Fernandez B, Ortiz A (2018) Meso-American nephropathy: what we have learned about the potential genetic influence on chronic kidney disease development* Clinical Kidney Journal 11:491-495 doi:10.1093/ckj/sfy070
Pomareda DC (2013) Tropical Agriculture Platform (TAP) Innovations in the Agriculture of Central America: Progress, Institutional Capacity and Policy Needs CIAT-FAO.
Ramirez-Rubio O, McClean MD, Amador JJ, Brooks DR (2013) An epidemic of chronic kidney disease in Central America: an overview Postgraduate Medical Journal 89:123-125 doi:10.1136/postgradmedj-2012-201141rep
Ranasinghe AV et al. (2019) The incidence, prevalence and trends of Chronic Kidney Disease and Chronic Kidney Disease of uncertain aetiology (CKDu) in the North Central Province of Sri Lanka: an analysis of 30,566 patients BMC Nephrology 20:338 doi:10.1186/s12882-019-1501-0
Said S, Hernandez GT (2015) Environmental Exposures, Socioeconomics, Disparities, and the Kidneys Advances in Chronic Kidney Disease 22:39-45 doi:10.1053/j.ackd.2014.09.003
Saseendran S. A., Harenduprakash L., S. RL, V. SS (2009) A GIS application for weather analysis and forecasting. Geospatial World
Sayanthooran S, Magana-Arachchi DN, Gunerathne L, Abeysekera TDJ, Sooriyapathirana SS (2016) Upregulation of Oxidative Stress Related Genes in a Chronic Kidney Disease Attributed to Specific Geographical Locations of Sri Lanka Biomed Res Int 2016:7546265 doi:10.1155/2016/7546265
Sorensen C, Garcia-Trabanino R (2019) A New Era of Climate Medicine — Addressing Heat-Triggered Renal Disease New England Journal of Medicine 381:693-696 doi:10.1056/NEJMp1907859
Sorensen CJ et al. (2019) Risk Factors and Mechanisms Underlying Cross-Shift Decline in Kidney Function in Guatemalan Sugarcane Workers J Occup Environ Med 61:239-250 doi:10.1097/JOM.0000000000001529

StataCorp (2017) StataCorp. StataCorp LP, College Station, TX
Tawatsupa B, Lim LLY, Kjellstrom T, Seubsman S-a, Sleigh A, Thai Cohort Study T (2012) Association between occupational heat stress and kidney disease among 37,816 workers in the Thai Cohort Study (TCS) Journal of epidemiology 22:251-260 doi:10.2188/jea.je20110082
TimeandDate.com (2019) Weather. https://www.timeanddate.com/. Accessed November 1 2019
Torres C et al. (2010) Decreased Kidney Function of Unknown Cause in Nicaragua: A Community-Based Survey American Journal of Kidney Diseases 55:485-496 doi:10.1053/j.ajkd.2009.12.012
van der Heijden C, Roosens L, Cluckers H, Van Craenenbroeck AH, Peeters B (2019) Analytical and clinical performance of three hand-held point-of-care creatinine analyzers for renal function measurements prior to contrast-enhanced imaging Clinica Chimica Acta 497:13-19 doi:https://doi.org/10.1016/j.cca.2019.06.025
Wang S et al. (2008) Geographic patterns of genome admixture in Latin American Mestizos PLoS Genet 4:e1000037-e1000037 doi:10.1371/journal.pgen.1000037
Weaver VM, Fadrowski JJ, Jaar BG (2015) Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and/or occupational nephropathy? BMC nephrology 16:145-145 doi:10.1186/s12882-015-0105-6
Wehner L, Mcgaffey L, Spilling M (2018) Honduras. Cavendish Square Publishing LLC,
Wesseling C et al. (2016) Heat stress, hydration and uric acid: a cross-sectional study in workers of three occupations in a hotspot of Mesoamerican nephropathy in Nicaragua BMJ open 6:e011034-e011034 doi:10.1136/bmjopen-2016-011034
Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH (2013) The Epidemic of Chronic Kidney Disease of Unknown Etiology in Mesoamerica: A Call for Interdisciplinary Research and Action American Journal of Public Health 103:1927-1930 doi:10.2105/ajph.2013.301594
Wesseling C et al. (2020) Chronic kidney disease of non-traditional origin in Mesoamerica: a disease primarily driven by occupational heat stress Rev Panam Salud Publica 44:e15-e15 doi:10.26633/RPSP.2020.15
Wesseling C, van Wendel de Joode B, Crowe J, Rittner R, Sanati NA, Hogstedt C, Jakobsson K (2015) Mesoamerican nephropathy: geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica Occupational and Environmental Medicine 72:714-721 doi:10.1136/oemed-2014-102799
Wijkström J et al. (2018) Morphological and clinical findings in Sri Lankan patients with chronic kidney disease of unknown cause (CKDu): Similarities and differences with Mesoamerican Nephropathy PLoS One 13:e0193056-e0193056 doi:10.1371/journal.pone.0193056
Wijkström J et al. (2013) Clinical and Pathological Characterization of Mesoamerican Nephropathy: A New Kidney Disease in Central America American Journal of Kidney Diseases 62:908-918 doi:10.1053/j.ajkd.2013.05.019
Yih WK et al. (2019) Investigating Possible Infectious Causes of Chronic Kidney Disease of Unknown Etiology in a Nicaraguan Mining Community The American journal of tropical medicine and hygiene 101:676-683 doi:10.4269/ajtmh.18-0856