Title
Risk Factors Associated with Chronic Kidney Disease of Unknown Etiology (CKDu): A Study of Patients from an Occupational Health Clinic in Rural Nicaragua

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Publication Date
2016

UNIVERSITY OF CALIFORNIA,
IRVINE

Risk Factors Associated with Chronic Kidney Disease of Unknown Etiology (CKDu): A Study of Patients from an Occupational Health Clinic in Rural Nicaragua

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedicine and Translational Science

by

Krystal A. Jimenez

Thesis Committee:
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2016

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ACKNOWLEDGMENTS

I would like to sincerely thank my thesis committee members, Professors Hoda Anton-Culver, John Billimek, and Argyrios Ziogas, for their guidance and mentorship throughout the development of this study. I would also like to thank the team of colleagues that, with great teamwork and collaboration, made this study possible. Thank you to Cristina Vargas, Cynthia Gonzalez, Sherry Firouzbakht, Alejandra Morales, Kyle Hersh, Lauren Van Woy, Athena Arias, Ana Ordaz Valencia, Pedro Alvarez, and Joel Johnson. I would also like to express my gratitude for the ability to work at UNAN-Leon amongst cutting-edge leaders in this field, including Dr. Donoso Peñalba and Dr. Marvin Gonzalez. A special thanks to the numerous Nicaraguan community activists and leaders that I had the honor of interacting with, along with the patients who provided the data for this study.

I would also like to acknowledge the Department of Epidemiology at the University of California, Irvine and the University of California, Irvine School of Medicine for sponsoring this study. I am also truly thankful for the Program in Medical Education for the Latino Community (PRIME-LC), which sponsored this degree and, above all, has provided me with an immense support system that continuously fuels my passion to serve medically underserved communities and address health inequities.

ABSTRACT OF THE THESIS

Risk Factors Associated with Chronic Kidney Disease of Unknown Etiology (CKDu): A Study of Patients from an Occupational Health Clinic in Rural Nicaragua
By

Krystal A. Jimenez

Master of Science in Biomedicine and Translational Science

University of California, Irvine, 2016

Professor Hoda Anton-Culver, PhD, Chair

Contrary to the conventional definition of CKD that is observed in developed countries, studies on CKD in developing countries demonstrate an atypical presentation of the disease, referenced as CKD of unknown origin (CKDu). CKD rates have been exponentially increasing in Nicaragua, particularly in sugarcane workers. This study assesses risk factors associated with this atypical presentation of CKD in patients from an occupational health clinic in rural Nicaragua.

This was a cross-sectional study that included 512 patient records (2009 to 2014). Records were randomly selected and transcribed into an electronic database. The data was analyzed with a case-control perspective comparing patients with CKD from those without the disease. A logistic regression analysis was performed in order to examine the personal and occupational risks associated with CKD.

Results of this study showed that patients with CKD were predominantly men, approximately ten years younger than patients without CKD, more commonly worked in agriculture, and had a lower prevalence of diabetes and hypertension. Regarding records of past medical history, there was poor agreement between physicians and patients.

Moreover, the logistic regression model demonstrated that agricultural work has a 24-fold increase in the risk of CKD, which is not confounded by known risk factors for CKD.

In conclusion, this study further characterizes the atypical presentation of CKD in Nicaragua. This study uniquely focuses on a specific population of workers that has not been previously studied. It also examines the association between particular occupational hazards and CKD, thus, furthering the understanding of CKD in Nicaragua.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health concern that contributes greatly to morbidity and mortality. The worldwide prevalence of CKD has been estimated to be as high as eight to sixteen percent (Jha, et al., 2013). The Global Burden of Disease Study 2010 reported that CKD rose on the list of top causes of total number of deaths worldwide from number 27 to 18 within the span of a decade. Such drastic movement up the list was only second to the trend seen with HIV and AIDS during that same decade (Lozano, et al., 2012). A subsequent Global Burden of Disease Study in 2013 reported a 36.9% increase in the age-standardized rate of death directly attributable to CKD worldwide between 1990 and 2013 (Vos, et al., 2015). In the United States alone, it is estimated that more than ten percent of adults have CKD, accounting for approximately 20 billion people (CDC National CKD Fact Sheet, 2014). Worldwide, roughly two million people currently are diagnosed with end-stage renal disease (ESRD), otherwise referred to as kidney failure.

Clinical Characteristics, Risk Factors, and Complications of CKD

According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI), CKD is internationally defined as the presence of kidney damage resulting in structural or functional kidney abnormalities (Levey, et al., 2007). Particularly, CKD can be solely diagnosed if the glomerular filtration rate (GFR) is less than 60 mL/min per 1.73 m^2 for three or more consecutive months, regardless of the presence of other markers of kidney damage. The spectrum of CKD is classified by five stages: CKD stage I, II, III, IV, and V; the latter three stages are characterized by irreversible damage to the renal tissue. CKD stage V (GFR less than 15 mL/min per 1.73 m^2) is considered ESRD, at which point dialysis or kidney transplant are warranted (Rosenberg, 2016).

CKD is commonly a sequela of long-standing illness or chronic use of nephrotoxic medications, both of which repetitively stress and damage the kidneys, thus leading to intrinsic renal disease. In the U.S., for example, hypertension and diabetes are responsible for up to two-thirds of all CKD cases annually, with diabetes being the leading cause of ESRD (National Kidney Foundation, 2015). It is estimated that approximately half of the patients diagnosed with type 2 diabetes will develop nephropathy, especially if proteinuria[1] is already present prior to the diagnosis of diabetes (McClellan and Flanders, 2003). In fact, diabetic nephropathy is the leading cause of CKD and ESRD worldwide, with hypertensive nephropathy as the second most common cause of CKD (Couser, et al., 2011). Moreover, cardiovascular disease, age greater than 60 years old, and family history of kidney failure are known risk factors for CKD. Some sources also suggest that chronic obesity may be a potential risk factor for CKD as well. (USRDS 2015 Annual Data Report).

Complications of CKD include CKD-associated anemia, hyperlipidemia, and metabolic bone disorders (Thomas, Kanso, and Sedor, 2008). Progression into ESRD is a complication in itself that accounts for increasing disability and mortality (Couser, et al., 2011). ESRD not only poses a threat against quality of life and productivity, but it also has been associated with increased all-cause mortality (Tonelli, et al., 2006; Go, et al., 2004). Mortality in patients with ESRD has been shown to be as high as 10 to 100-times greater than age-matched patients without kidney dysfunction (Couser, et al., 2011). Perhaps the

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[1] Outpouring of protein into the urine; a marker of kidney damage.

most significant complication of CKD, however, is the increased risk of developing cardiovascular disease as a comorbid condition (Sarnak, et al., 2003; Keith, 2004; Couser, et al., 2011; Rosenberg, 2016). According to the National Institute of Diabetes and Digestive and Kidney Diseases, the one-year mortality rate due to myocardial infarction was 51% in patients with CKD stage III to V compared to 36% in patients without CKD (NIDDK Kidney Disease Statistics for the U.S., 2008).

Atypical Presentations of CKD

CKD is largely due to complications of chronic disease, particularly diabetes and hypertension. However, certain regions of the world, demonstrate other less common etiologies of CKD, including kidney damage due to chemical exposures, low birth weight, and infectious diseases (Ayodele and Alebiosu, 2010). In Sub-Saharan Africa, for example, numerous renal disorders are associated with HIV infection, most commonly in the form of HIV-associated nephropathy (HIVAN). It is estimated that 1 to 3.5 million Africans are likely to develop ESRD from HIVAN (Gerntholtz, Goetsch, and Katz, 2006). In certain Asian countries, such as Malaysia, nephrolithiasis remains one of the leading causes of ESRD as well (Ayodele and Alebiosu, 2010). Furthermore, in the Balkan region of Europe, aristolochic acid nephropathy—stemming from the consumption of aristolochic acid infiltrating the wheat fields surrounding the Danube River—has been shown to progress to ESRD and is associated with an increased risk of developing urothelial cancer (Stefanovic, et al., 2009). Most notably, recent studies have reported an unusual presentation of CKD in low-income, agricultural communities, which has been designated as CKD of unknown etiology (CKDu).

CKDu has been observed in several regions worldwide, including Egypt, India, Sri Lanka, Southern Mexico, and Central America (Dominguez, Montoya Perez, and Jansa, 2006; Jha, 2009; Almaguer, Herrera, and Orantes, 2014). CKDu is characterized by its insidious onset and progression. It typically remains asymptomatic or undiagnosed until its late stages, at which point it progresses rapidly into ESRD. In contrast to the conventional pathophysiology of CKD, CKDu has not been attributed to hypertension or diabetes (Hoponick, et al., 2014). It uniquely presents in low-income, agricultural workers, particularly men between the ages of 20 and 50 (Almaguer, Herrera, and Orantes, 2014).

In response to the emerging epidemic of CKDu, numerous studies have proposed diverse hypotheses to explain its atypical presentation. Early studies regarding CKDu in Sri Lanka, for example, hypothesized that exposure to pesticides from agrichemicals was damaging to the kidneys and, thus, contributing to the pathogenesis of CKDu (Wanigasuriya, et al., 2007). Other reports from India hypothesized that the local water sources contained excessive amounts of metals that were potentially nephrotoxic and thus unsuitable for drinking (Reddy and Gunasekar, 2013). Some of the first studies of CKDu performed in Central America also agreed and hypothesized that agrichemicals and non-potable water could be responsible for the irreversible kidney damage (Trabanino, et al., 2002; Torres, et al., 2010;). Since then, however, the literature on CKDu[1] has been widely changing and providing a wide spectrum of speculations about agricultural risk factors contributing to renal impairment.

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[1] Since the underlying pathophysiology of CKDu has not been formally recognized, it shall be referred to simply as CKD for the remainder of this thesis.

Thesis Overview

The intent of this thesis is to contribute to this expanding school of thought by presenting a study that examines CKD through the lens of an occupational health clinic in Nicaragua that services a large population of patients with CKD. This study will investigate the risk factors associated with CKD, with a special focus on labor and occupational hazards.

The first chapter of this thesis will discuss the global burden of CKD and the health disparity that lies between developed and developing countries. This will serve as a foundation to further examine the CKD epidemic occurring in Nicaragua. Moreover, this will provide the groundwork for the rationale behind this thesis. Chapter 1 will conclude with the purpose and aims of this study.

Furthermore, in order to better understand the importance of studying CKD in Nicaragua, Chapter 2 will take a large step back from the focus of the study to provide a broad analysis of worldwide kidney disease trends among countries with differing incomes. This chapter will help put into perspective the CKD epidemic in Nicaragua as it compares to the rest of the world.

Chapter 3 will then regress to give an overview of the study in question. This chapter will describe the methodology and statistical analysis of the study. Consequently, Chapter 4 will present the results, which will be addressed with more detail in Chapter 5. This thesis will then conclude with a discussion of the significance and implications of the results.

Chapter 1: Background and Significance

This chapter will build upon the theme presented in the Introduction in order to expand on the topic of CKD, or the atypical presentation of CKD. As mentioned previously, the clinical presentation of CKD has been shown to differ between developed and developing nations. As such, this chapter will elaborate on the present understanding of CKD in developing countries. The chapter will then delve deeper into the discussion of CKD research in the developing nation of Nicaragua. The chapter will then conclude with an explanation of the significance and purpose for this study.

CKD in Developing Countries

The relationship between low socioeconomic status and prevalence of chronic diseases has been validated throughout numerous studies worldwide (WHO Global Status Report on Noncommunicable Diseases, 2014). In the U.S., results from the 2008 National Health and Nutrition Examination Survey (NHANES) demonstrated that individuals from lower socioeconomic status that have CKD are at greater risk of developing disability regardless of comorbid conditions (Plantinga, et al., 2012). Moreover, low income is also thought to play a similar role on the burden of CKD in developing countries. However, a diagnosis of CKD in these areas is assumed to be much more detrimental than in developed countries due to the scarcity of resources affecting the quality of care (Couser, et al., 2011). Unfortunately, it is estimated that 85% of the world lives in low- or middle-income countries, where the burden on CKD is hypothesized to be the greatest. Such burden of disease is expected to grow rapidly considering the growing rates of diabetes, hypertension, and cardiovascular disease currently being noted in low-income countries (Barsoum, 2006).

Aside from the burden of disease itself, another dilemma that developing nations face is the availability and accuracy of CKD data. Developed countries, such as the U.S., have relatively good kidney disease registries and are able to extrapolate data with more confidence than countries with suboptimal registries. For example, it is estimated that for every patient with ESRD in the U.S., there are more than 200 patients with CKD stage III or IV and more than 5,000 patients with CKD stage I and II. Although the exact numbers of patients within each stage of CKD is not certain, the reliability of the kidney disease registry in the U.S. allows for this projection of data. Such kidney registries, however, are not dependable in many developing countries due to lack of resources and infrastructure. Consequently, it is hypothesized that CKD and ESRD are being underreported in developing countries (Barsoum, 2006; Mills, et al., 2015). Since the absolute burden of CKD in developing countries cannot be determined if the data registries are deficient, it is therefore speculated that the prevalence of CKD are greater than reported.

The economic burden of CKD.

CKD is not only a public health threat, but it also places a financial strain on the individual as well as the health care system as a whole. In the U.S., for example, it is estimated that managing CKD costs more than $1,250 per month per patient, or more than $3,000 per month if the patient is also co-managing diabetes and heart failure (Collins, et al., 2010). Moreover, Medicare expenditures on CKD exceeded $60 billion in 2007, representing approximately 27% of the annual Medicare budget during that particular year (Collins, et al., 2010).

Such financial burden is not only seen in the U.S., but it is also observed in other developed and developing countries. Some developed nations spend up to three percent of their annual health care budget in order to provide treatment for ESRD, which only accounts for less than 0.03% of their total population (Levey, et al., 2007). Conversely, it is estimated that by 2030, more than 70% of the world's ESRD patients will be from developing countries, whose collective economies will account for only 15% of the world economy (Barsoum, 2006). Furthermore, a diagnosis of CKD—and more specifically ESRD—in a developing country is detrimental considering conventional management of CKD (with medications, dialysis, and ultimately kidney replacement therapy) is often unavailable or unaffordable. As a consequence, individuals with CKD die earlier than patients with CKD from a developed nation due to lack of appropriate therapy (Couser, et al., 2011). It is approximated that nearly one million people from developing nations die of ESRD each year (Barsoum, 2006). Thus, it is imperative to study CKD in developing countries in order to better understand the additional challenge that the disease poses on the these areas of the world. The next section will focus specifically on the disease burden of CKD in Nicaragua. It will provide a detailed history of CKD-related investigations from rural communities in or near Nicaragua

CKD Research in Nicaragua

Trabanino, et al. first observed this peculiar presentation of CKD along the Latin American Pacific Coast in 2002. Their study characterized each new patient on dialysis (1999 through 2000) from a hospital in a coastal town in El Salvador. The results of this study found that 33% of dialysis patients had an identifiable risk factor that had a well-established association to CKD. Of these known risk factors, diabetes, hypertension, and chronic non-steroidal anti-inflammatory use were the top three conditions identified within this group of patients. However, the remaining 67% of patients had a presentation of CKD without the presence of such underlying etiologies or risk factors. Moreover, Trabanino, et al. also showed that patients without typical risk factors of CKD were more commonly men (87%, compared to 48% of patients with typical risk factors), aged 40 to 59 years old (50%, compared to 34% of patients with typical risk factors), and worked in agriculture (63%, compared to 21% of patients with typical risk factors). Although this study did not include data analyses and, therefore, did not present statistically significant comparisons between the two groups of dialysis patients, it nonetheless served as a cornerstone to examining the association between agricultural work and CKD along the Latin American Pacific Coast. It undoubtedly instilled curiosity and concern within the scientific community regarding a new presentation of CKD that could possibly be related to occupational exposures.

CKD in Central America was repeatedly noted to have a disproportionate affect on individuals without a prior history of chronic illness and as early as in their third decade of life (Gracia-Trabanino, Dominguez, and Jansa, 2005). Moreover, CKD trends demonstrated exponential favoring of sugar cane workers along the Pacific Coast of Southern Mexico and Central America (Dominguez, Montoya Perez, and Jansa, 2006). The Nicaraguan Ministry of Health (MINSA) 1992-2002 reported that the national mortality rate of kidney disease increased from four to nine deaths per 100,000 inhabitants. Most notably, this change was concentrated in Northwestern Nicaragua, where kidney disease mortality increased from 13 to 36 deaths per 100,000 inhabitants with a male-to-female ratio of 5:1 during this same time frame (Cuadra, et al., 2006). In Chichigalpa, Nicaragua, a sugar cane-producing town in the Northwestern region, about 75% of male deaths ages 35 to 55 from 2002 to 2012 were attributed to CKD, the majority of which were sugar cane workers (La Isla Foundation, 2015). Therefore, it was evident that since then, CKD has been insidiously affecting the general state of the health of Nicaragua, both on a gross and individual level.

In 2008, in response to the overwhelming toll that CKD was posing on Nicaraguan rural communities, the World Bank funded a large, multi-factorial study in Chichigalpa, Nicaragua that was conducted by Boston University School of Public Health. This collaboration consisted of an extensive and broad six-part investigation, which included (1) an occupational hygiene assessment, (2) biochemical water testing, (3) interviews with physicians and pharmacists, (4) a pilot cohort study within a particular sugar cane plantation, (5) genetic analysis of biomarkers in laborers, and (6) analysis of urinary markers of kidney disease in healthy adolescents. The main results of this comprehensive study were that agrichemicals were not statistically shown to be associated with CKD, and that potable water did not contain sufficient amount of harmful chemicals to warrant suspicion for nephrotoxicity. Most notably, volume depletion from inadequate water intake in combination with daily muscle damage from strenuous labor was shown to be associated with higher serum markers of kidney damage. This observation was especially seen in sugar cane workers that performed the tasks of cane cutting and seeding (McClean, Amador and Laws, 2012). The results from this investigation served as the infrastructure for future studies in Nicaraguan agricultural workers. Not only did it conceptualize and quantify atypical CKD from various perspectives, but it also provided direction as to which factors should be considered for subsequent research.

Consequently, the First International Research Workshop on Mesoamerican Nephropathy (FIRWMN) met in 2012 to discuss the sociocultural, economic, and political implications of CKD in Nicaragua and the rest of Central America. During this congregation the term “Mesoamerican Nephropathy (MeN)” was coined in order to officially characterize abnormal kidney function[1] that is related to an unknown cause in agricultural workers throughout Central America (Elinder and Wernerson, 2016). Although the epidemic has only been examined within the past fourteen years or so, the association between CKD and agricultural labor has dated as far back as 1970 in Costa Rica according to a retrospective analysis (Cerdas et al., 2004). Though studies on the Nicaraguan epidemic have not dated that far back, it can be inferred that the CKD epidemic has been forthcoming for decades in Nicaragua as well. Thus, this epidemic has promoted a cascade of health disparities that have likely been deeply rooted for a prolonged amount of time.

Moreover, according to O’Donnell, et al., among 18-29 year-old study participants from the rural town of Quezalguaque, Nicaragua, 2.6% had reduced GFR compared to 0.2% of Americans as determined from NHANES 1999-2006 data. Similarly, 7.4% of 30-41 year-olds from Nicaragua had a reduced GFR, compared to 0.8% of the U.S. population (O’Donnell, et al., 2011). Moreover, Another study observed that people with CKD in Nicaragua did not commonly undergo dialysis despite the high prevalence of ESRD, perhaps due to the shorter duration of the disease secondary to a decreased probability of survival (Raines, et al., 2014). Consequently, as the agricultural labor force continues to become more vulnerable to CKD, this will further burden the country’s health care system. Overall, this results from such studies imply that CKD is a leading health concern not only for the affected individual, but also for the community at large.

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[1] Defined according to international standards of GFR as reported on page 1.

Purpose of this Study

This chapter described the atypical presentation of CKD in Nicaragua that has been extensively investigated since the identification of the disease over a decade ago. In turn, this literature review also serves to highlight the importance of recognizing the risk factors that have been associated with CKD in this population. Studies have shown evidence that such risk factors include male gender, agricultural work (particularly in sugar cane mills), inadequate water intake, and agrichemical exposure. This study, therefore, takes into consideration all of these factors in order to analyze the risk of CKD in a unique patient population of working-aged adults in Northwestern Nicaragua. In an effort to understand the etiology and risk factors that contribute to the development of CKD in this particular community, the intention of this study is to not only define the clinical and occupational characteristic of these patients, but to help guide the direction of future studies as well.

Specific Aims

The main objectives of this study are to (1) examine the demographic differences between patients with and without CKD; (2) assess the comorbid conditions associated with CKD as well as evaluate whether patient-reported comorbid conditions are consistent with clinician-diagnosed comorbid conditions; and most notably (4) determine if agricultural work and occupational hazards affect the risk of developing CKD. Ultimately, the goal of this study is to investigate whether any comorbid condition or occupational state can potentially contribute to the biological plausibility of CKD in this patient sample. Although numerous studies have already proposed various possible etiologies of this particular presentation of CKD, there still remains a definitive explanation. This study could provide further support to lean the working hypothesis in a particular direction.

Chapter 2: Worldwide Perspective of Kidney Disease

The main focus of this thesis is to describe and discuss the retrospective study that was introduced in the previous chapter. However, prior to focusing solely on the CKD epidemic in Nicaragua, it is crucial to first study the epidemiology of CKD worldwide. Recognizing worldwide CKD trends is necessary in order to understand the burden of disease on a global level. In turn, demonstrating a global perspective will help put into context the disease burden on Nicaragua in particular. Most importantly, the disparate distribution of kidney disease among countries of different incomes further highlights the need to study the underlying etiologies that cause the disease and, ultimately, the disparity. Therefore, this chapter will digress from the primary study of this thesis in order to exhibit mortality trends from an investigation of the World Health Organization (WHO) Mortality Database.

Mortality Study: The Worldwide Burden of Kidney Disease

In order to understand the full scope of this health issue, it is important to expand on the discussion of worldwide CKD trends by specifically examining mortality attributed to CKD. As described in Chapter 1, CKD is a progressively debilitating condition associated with increasing morbidity and mortality as the stage worsens. Unless interventions are introduced during the reversible stages of the disease, CKD will advance into ESRD, inevitably warranting renal replacement treatment, such as dialysis. Once on dialysis, the five-year survival rate is approximately 35% (United States Renal Data System, 2010). Thus, examining mortality data provides insight into the severity of the health issue. Moreover, studying mortality data can help identify the areas of the world that are experiencing the worst outcomes due to CKD.

WHO Mortality Database.

Mortality data was obtained from the WHO Mortality Database in order to examine CKD trends firsthand. This dataset includes comprehensive health data stratified by country and country income group. An advantage of utilizing this dataset is its significant sample size. Over 170 countries are accounted for in the WHO Mortality Database, including Nicaragua. Additionally, inclusion criteria guidelines were implemented in the selection of the national datasets that would comprise the WHO Mortality Database. This suggests that only those countries considered to have quality vital registries were included in the database (WHO, 2014). Moreover, data analysts included adjustments for specific causes of disease in order to account for over- or under-reporting of certain conditions. Thus, for the purpose of this study, the WHO Mortality Database is an appropriate resource to investigate mortality patterns.

A limitation of the WHO Mortality Database, however, is that it does not particularly discriminate mortality due to CKD. Instead, CKD is categorized under "kidney diseases," which is inclusive of all urogenital disease diagnoses except cancers of the urogenital tract, disorders affecting the prostate, gynecologic diseases, and urolithiasis (kidney stones). In fact, throughout the process of searching for a dataset for this study, it was very challenging to find a raw dataset of mortality attributable to CKD specifically. It was therefore decided that kidney disease mortality would suffice in order to support the objective of this investigation. Although the true mortality due to CKD cannot be extrapolated from the WHO Mortality Database, analyzing mortality due to kidney diseases as a whole can nonetheless yield valuable information.

Preparation of Mortality Data.

Mortality due to kidney diseases was compared to all-cause mortality at two different time points, 2000 and 2012. The data was further classified into income groups as defined by the World Bank Analytical Income of Economies for the fiscal year 2012 to match the latter time point (World Bank Data Team, 2012). The income categories are:

- Low income: $1,025 per capita or less
- Lower-middle income: 1,026-$4,035 per capita
- Upper-middle income: $4,036-$12,475 per capita
- High income: $12,476 per capita or more

Consequently, it was observed that the amount of data available (both for mortality due to kidney diseases and all-cause mortality) for low-income countries was substantially less than that of the other categories. This could in part be due to the unavailability of quality mortality registries in such developing countries. Therefore, the former two groups—low and lower middle income economies—were consolidated into one category deemed "lower income economies" in order to increase the sample size for this category. Thus, this consolidated category represents those countries with economies of $4,035 or less per capita, including Nicaragua. In turn, this will allow for better gross interpretation of the data.

Interpretation of Mortality Data.

Kidney disease mortality data was stratified by age group and compared among the three income groups. The age groups that were analyzed are consistent with the age groups provided by the WHO Mortality Database. Children under the age of fifteen were excluded on order to examine disease patterns in adult populations only.

Figure 2.1 below demonstrates all-cause worldwide mortality in 2012 as represented by age group and World Bank income level. The data is reported as the proportion of deaths in each age group compared to all deaths registered within that income group. It is apparent that mortality over the age of 70 years old increases as the country income level increases. Conversely, mortality at age 49 or younger is more apparent as the country income level decreases

Figure 2.1

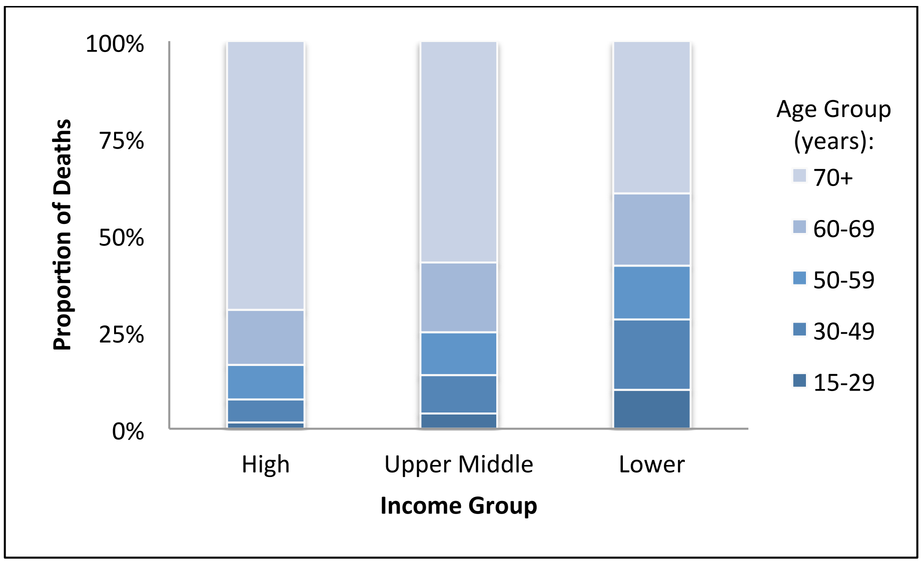

Figure 2.1: Worldwide all-cause mortality in 2012 by age and income group according to the World Health Organization (WHO Mortality Database, 2015).

The following Figure 2.2 now displays mortality attributed to kidney diseases during the same year. Similar to the all-cause mortality pattern (Figure 2.1), mortality due to kidney diseases appears to rise as age increases over the age of 70 consistently across all income groups. As the country income level decreases, however, the proportion of deaths due to kidney diseases in age groups under 59 years old is noticeably greater. In particular, there is a unique distribution of kidney disease mortality that differs from the all-cause mortality pattern. While all-cause mortality under the age of 69 years old shows a gradual incremental increase as income group decreases, kidney disease mortality displays a disparity between high income countries and upper middle and lower income countries. Figure 2.2 illustrates a noticeable upsurge in kidney disease deaths under the age of 69 years old that is inconsistent with the all-cause mortality pattern seen in Figure 2.1.

Figure 2.2

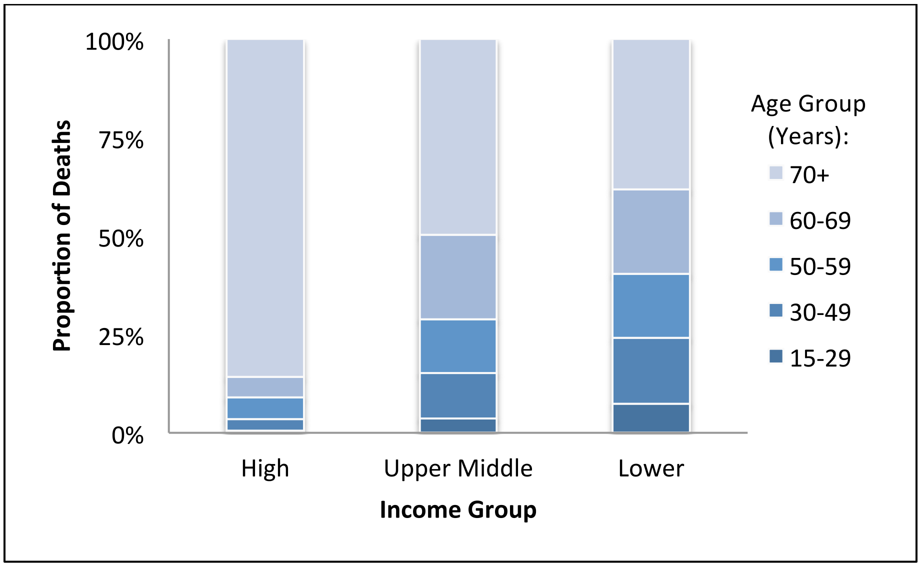

Figure 2.2: Worldwide deaths attributable to kidney diseases in 2012 stratified by age and income group according to the World Health Organization (WHO Mortality Database, 2015).

In order to better visualize the extend to which kidney diseases affect all-cause mortality, Figure 2.3 below illustrates the proportion of deaths attributable to kidney diseases in 2012. Although kidney disease deaths make up a relatively small part of all-cause mortality, there is nonetheless a visible disparity among income groups. In high income countries, kidney disease deaths comprise 1.55% of total mortality, in comparison to 1.22% and 2.14% in upper middle and lower income countries, respectively. Particularly, there is a 72% difference in deaths attributable to kidney diseases between high and lower income countries, the latter of which is most affected.

Figure 2.3

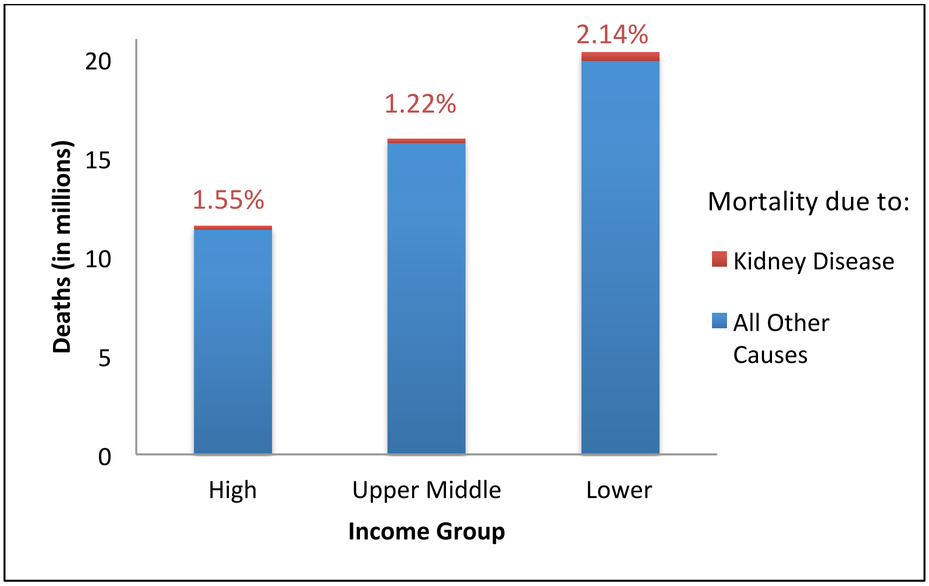

Figure 2.3: Proportion of deaths due to kidney diseases from all-cause mortality in 2012 stratified by income group according to the World Health Organization (WHO Mortality Database, 2015).

Moreover, in addition to demonstrating mortality differences by cause of death, it is also important to exhibit the rate of change of these mortality trends across the two time points, 2000 and 2012. The rate of change can help suggest whether an increase in cause-specific mortality is truly due to a disease epidemic or simply just a proportional increase in deaths overall. For upper middle income countries, the rate of change for kidney disease mortality is slower than the rate of change for all-cause mortality (0.3 and 1.2%, respectively). For high and lower income countries, however, the rate of change of kidney disease mortality is accelerated in comparison to the rate of change for all-cause mortality. In high income countries, kidney disease mortality rose 14.2% from 2000 to 2012, whereas all-cause mortality in high income countries increased by only 2.9%. Similarly, in lower income countries, kidney disease mortality rose 12.6%, whereas all-cause mortality for those countries increased by 8.1%. Consequently, it is crucial to examine the reasons behind such a discrepancy in the pattern of mortality attributable to kidney diseases.

Figure 2.4

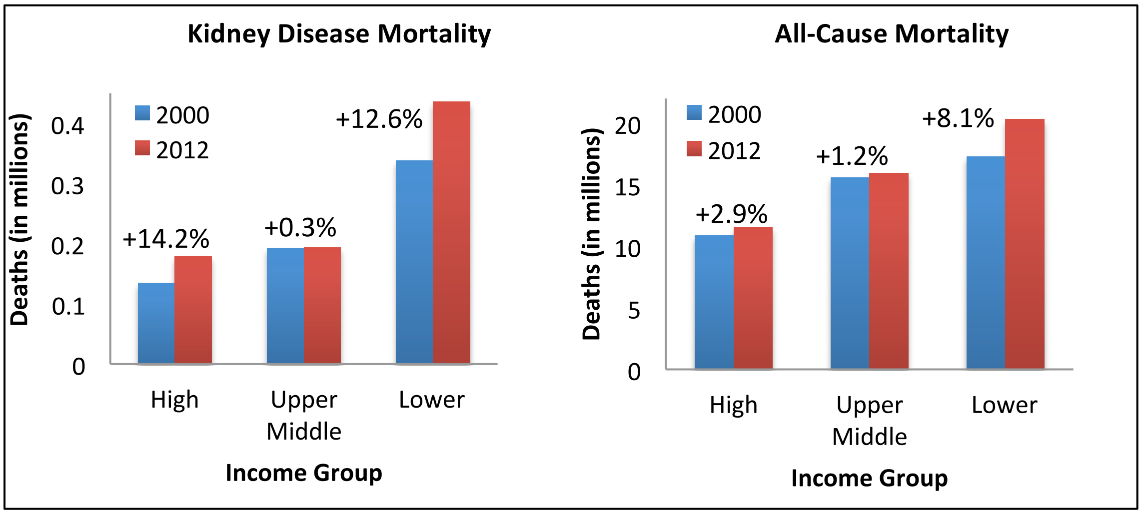

Figure 2.4: Rate of change of kidney disease and all-cause mortality between 2000 and 2012 stratified by age and income group according to the World Health Organization (WHO Mortality Database, 2015).

Change in Worldwide Mortality Patterns Attributed to CKD

In order to better understand the difference in kidney disease mortality patterns presented in the previous section, it is important to address the patterns of comorbid conditions that are associated with kidney disease. Unfortunately, the WHO Mortality Database does not report comorbid conditions that overlap with kidney disease mortality data. Instead, data from the Global Burden of Disease Study 2013 (GBD 2013) will be presented to provide a insight into the disparity in kidney disease mortality. Additionally, the focus of this section will move from examining kidney disease mortality among income groups to examining CKD mortality in Nicaragua specifically. Consequently, this will illustrate the gap in mortality data understanding and to convey the need to study the disparity of CKD deaths in lower income countries such as Nicaragua.

Mortality data from the GBD 2013 is presented via an interactive map that reports the probability of death from all-cause mortality and disease-specific mortality as well

(Global Burden of Disease Study 2013, 2014). This interactive application conveniently differentiates deaths due to CKD within the realm of kidney disease mortality. Furthermore, it sub-classifies deaths due to CKD by the etiology of CKD, such as diabetes mellitus and hypertension. Figures 2.5 and 2.6 demonstrate the global probabilities of death due to CKD that were attributable to diabetes and hypertension in 2013, respectively. Nicaragua, in particular, had a probability of death of 1.96% due to CKD attributable to diabetes and 0.49% due to CKD attributable to hypertension. Moreover, Figure 2.9 illustrates the probability of death due to CKD from all causes. Nicaragua had a notably high rise in the probability of death attributable to all-cause CKD (3.78%) compared to CKD due to diabetes and hypertension (Murray, et al., 2014).

Figure 2.5

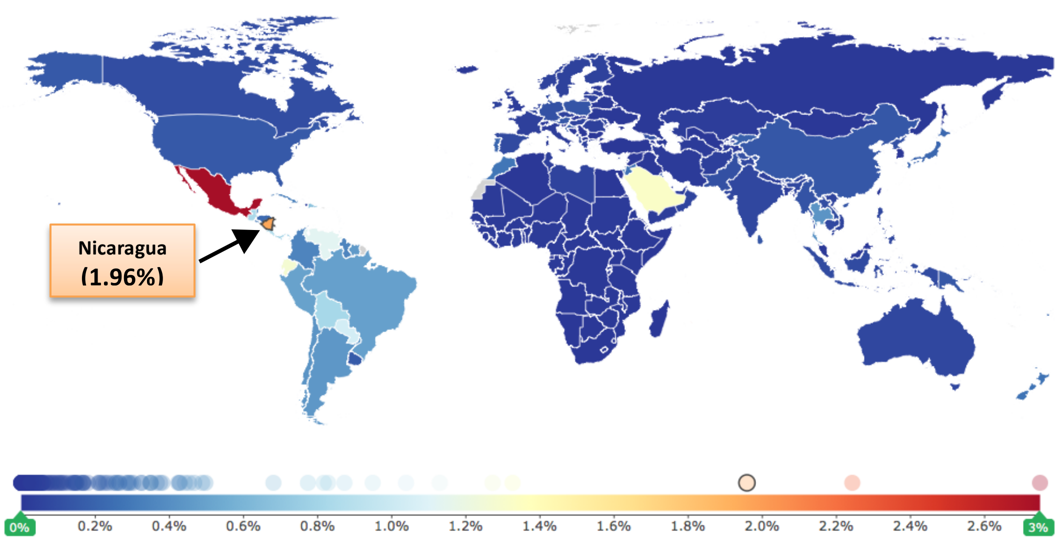

Figure 2.5: Worldwide probability of death due to CKD that is attributable to diabetes according to the Global Burden of Disease Study 2013 (Graph illustration of Life Expectancy and Probability of Death by the Institute for Health Metrics and Evaluation, 2014).

Figure 2.6

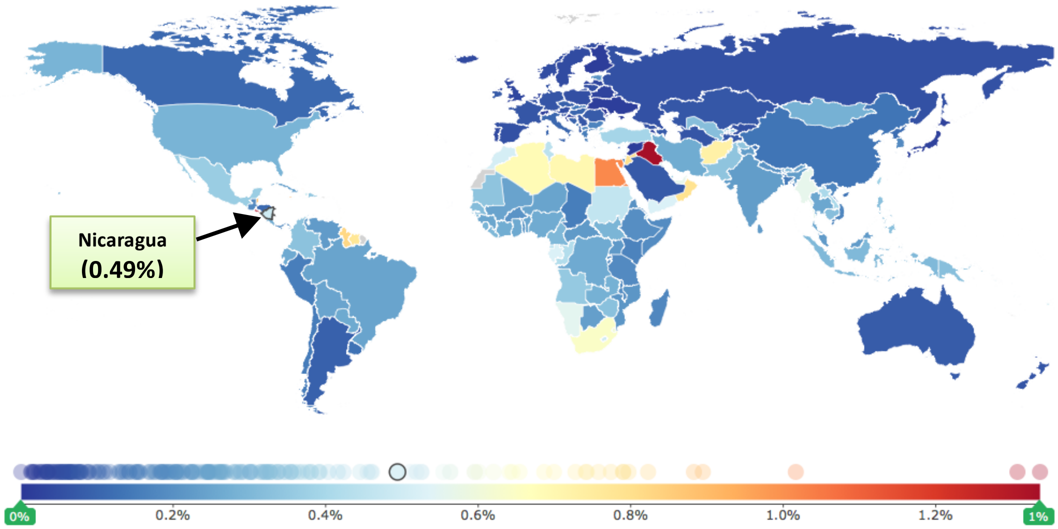

Figure 2.6: Worldwide probability of death due to CKD that is attributable to hypertension according to the Global Burden of Disease Study 2013 (Graph illustration of Life Expectancy and Probability of Death by the Institute for Health Metrics and Evaluation, 2014).

Figure 2.7

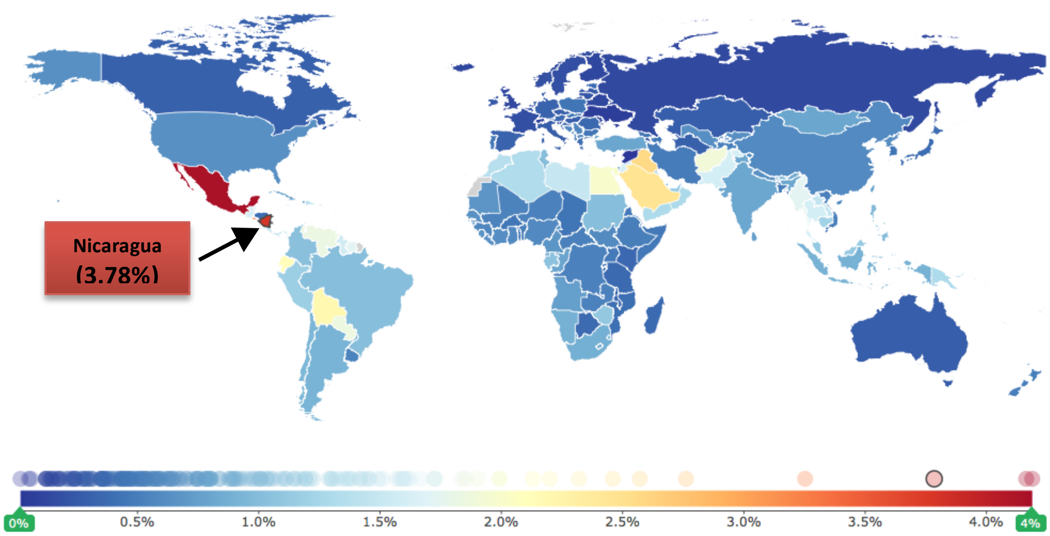

Figure 2.7: Worldwide probability of death due to CKD that is attributable to all-causes according to the Global Burden of Disease Study 2013 (Graph illustration of Life Expectancy and Probability of Death by the Institute for Health Metrics and Evaluation, 2014).

It would be expected that if CKD mortality attributable to all causes is increasing in Nicaragua, the most common etiologies of CKD—diabetes and hypertension—should also increase simultaneously. The GBD 2013 data, however, demonstrates that there is a disproportion in the probability of death of CKD from all-causes in Nicaragua, as compared to CKD caused by diabetes or hypertension. This suggests that other causes are leading to the development of CKD. Moreover, such causes are severe enough to lead to mortality. There is void in the understanding of CKD etiologies in Nicaragua; thus, this observation provokes further questioning of the underlying cause of CKD mortality in order to comprehend the root cause of the health disparity.

This chapter provides a basic presentation of global kidney disease trends in the context of overall mortality, thus shedding light on the issue at large concerning disparities in mortality trends among different income groups. Although there are several limitations of utilizing mortality databases—such as inconsistency of recording systems, lack of consideration for confounders, or multiple causes of mortality not accounted for (Lozano, et al., 2012)—this study nonetheless serves as a simple and broad foundation for the rest of this thesis. Taking this foundation forward, the next chapter will now revert to continue the discussion regarding the retrospective study in question. Chapter 3 will focus on the methodology used to examine the data from the study of medical records.

Chapter 3: Methods Used to Study Clinic Records

Study Overview

This is a retrospective, cross-sectional study that consisted of a medical record abstraction from the CISTA (*Centro de Investigacion en Salud Trabajo y Ambiente*) occupational health clinic, which is an affiliate of UNAN-Leon (*Universidad Nacional Autonoma de Nicaragua*) located in the Northwestern region of Nicaragua within the department of Leon. Since the study did not involve direct patient contact, it was granted exemption by the Institutional Review Board of the University of California, Irvine (Protocol HS# 2013-9539).

Study Participants

All data was obtained from adults over the age of 18 years old that permanently reside in Nicaragua. The CISTA clinic serves patients with occupational health issues from the Central and Northwestern regions of Nicaragua. CISTA patients are referred to the clinic by primary care providers, either community physicians or on-site physicians working at the place of employment. The purpose of this referral is mainly to assess the patient's needs and qualifications for public assistance programs in the setting of a work-related injury or illness. Such health issues could be related to a variety of occupations, including, but not limited to, agriculture, mining, teaching, clerical or administrative work, and specialty crafts.

Data Collection

Data was collected by two groups of medical student volunteers during the months of July 2013 and July 2014. A total of 512 medical records were included in this study. Data was obtained from the History and Physical (H&P) note (deemed by CISTA physicians as the *epicrisis*, or health summary) that were recorded between 2009-2014. Data was then transferred onto an electronic record within REDCap (Research Electronic Data Capture). Clinic records were translated from Spanish to English by the staff at CISTA as well as medical student volunteers, both of which are fluent in English and Spanish. All REDCap entries were de-personalized and given a record identification number in order to maintain patient confidentiality. Variables collected from the medical records included, but were not limited to general demographics (gender, age, region of residence, income), living conditions, past medical history, family history, substance use history, and occupational and work-related exposures (see Appendix 3.1). For patients that claimed working in agriculture, specific jobs and responsibilities (such as, seeding, crop burning, or irrigating) were also recorded, along with the estimated amount of time spent within that particular field of agriculture.

Medical records were chosen at random by blinded study volunteers. Charts were contained within envelopes that were only labeled by medical record number; patient data was not visible until the envelope was opened, at which point the medical record was then committed to the study. Not all of the medical records available at the clinic were transcribed; therefore, this study analyzes only a sample population of the patients seen at the CISTA clinic.

Data Preparation

Medical records were transcribed verbatim from the paper charts. Some items within the patient's chart were recorded as numeric variables; other items, however, were recorded as free-text. This resulted in numerous string variables composed of lengthy and verbose data. This posed a substantial problem because such variables were not standardized or appropriate for analysis. Data preparation, therefore, was an extensive and crucial component of this study. To view the syntax for a sample of the string variables that were cleaned and recoded, see Appendix 3.2.

Independent variables.

CKD was confirmed via serum levels of creatinine performed either by the referring physician or CISTA physician. Serum creatinine levels are available in the CISTA medical records; however, laboratory values were not utilized in this study since physician confirmation of CKD sufficed. Moreover, CKD status was defined by stage (I through V). For the primary analysis, CKD stages were recoded into a single variable (*dxCKD_any*) to represent all patients diagnosed with CKD, regardless of stage.

For the logistic regression analysis, the main independent variable that was observed was *Occupation*. The variable was recoded from the original item *Profession*, which was self-reported by the patient. Occupation was categorized into the most commonly reported trades (agriculture, machinery/electric, mining, and non-laborious/administrative jobs) or whether the patient was unemployed/retired. The variable was further dichotomized into agricultural work versus all other occupations. A limitation of this recoding system, however, is that the unemployed/retired group possibly includes patients that at one point did work in one of the aforementioned categories. Since the past occupation was not readily available for this group of patients, it was assumed that these patients were "non-agricultural workers" for the sake of the data analysis.

The other independent variables that were used as covariates for the logistic regression analysis included items from the past medical and occupational history portions of the H&P form. The variables used under past medical history, which were also the dependent variables in the primary analysis, are described in the section below. Occupational history included items regarding work-related hazards that the patients self-reported as well as a detailed labor history. The occupational hazards that were included in the logistic regression analysis are repetitive movements, uncomfortable positioning, excessive heat, heavy lifting, and chemical exposure (represented by the variables *RepMvmts*, *Position*, *Heat*, *Lifting, Chemical_exposure,* respectively)

Labor history was the most difficult variable to prepare for analysis. Labor history from patients that worked in agriculture was recorded in a free-text section in the original H&P form. Since medical records were transcribed verbatim into REDCap, labor history data consisted of lengthy entries that were separated by bullet points; thus, making the original variable inappropriate for analysis. The original string variable (*LaborHistory*) was deconstructed into sections from the bullet points and transferred into an Excel spreadsheet. On Excel, the labor history data was cleaned and recoded into the following new variables:

Table 3.1: Recoding of labor history data.

Variable Name	**Description**
Field	Agricultural field where the most time was spent working (e.g. sugar cane, banana, cotton)
Public_employer	Patient reported working with a public employer (e.g. Nicaraguan Sugar Estates Limited)
Private_employer	Patient reported working with a private employer
Time_months	Total agriculture exposure time (in months)
Time_years	If unsure of exposure time in months, total agriculture exposure timeframe (in years)
Irrigation	Job role of irrigation and drainage of crops
Planting	Job role of planting (i.e. seeding, sowing, and plowing) of the crop
Harvesting	Job role of harvesting (i.e. burning, cutting, processing) the crop
Pest_control	Job role of pest control (i.e. applying chemical insecticides)
Other	Other job roles or industries worked in

Once the labor history data was sufficiently prepared, it was merged back into the original database and these cleaned variables were then used for the logistic regression analysis.

Preparation of the variables for risk factors.

Items under the categories past medical history, social history, and occupational history were recoded into dichotomous variables. Past medical history included both clinician-diagnosed and patient self-reported history of disease, such as diabetes mellitus, hypertension, cardiovascular disease, and electrolyte/metabolic disorders. Considering that the H&P form that was transcribed from CISTA was from a newly established care visit, clinician diagnosis of disease depended on the patient's referral paperwork. For example, if the referral document stated that the patient was diagnosed with diabetes by the previous provider, the CISTA physician carried that information over to the CISTA H&P form under the item represented by the variable *DiagnosischoiceX* ("X" indicating the disease in question). For patient-reported medical history, however, the physician transcribed what the patient reported under the item represented by the variable *OtherPtDx*. Individual diseases recorded under *DiagnosischoiceX* and *OtherPtDx* were dichotomized and grouped into the respective organ system disease. For instance, chronic heart failure, myocardial infarction, and thromboembolism were grouped into cardiovascular diseases (represented by the variables *dxCVD* and *CV_disease* by physician and patient reports, respectively).

Table 3.2: Sample of the recoding of variables.

Variable Name	Coding	Description
dxCKD_any	0: no diagnosis 1: diagnosis	Diagnosis of any stage of CKD (I through V)
NicaDepts	1: Chinandega 2: Leon 3: Managua 4: Granada 5: Other/Unspecified	Nicaraguan department of residence
Occupation	1: Agriculture 2: Machinery/Electric 3: Mining 4: Non-labor/Administrative 5: Retired/Unemployed	Primary occupation at the time of H&P CISTA visit
dxDM	0: no diagnosis 1: diagnosis	Clinician-diagnosed diabetes mellitus
dxHTN	0: no diagnosis 1: diagnosis	Clinician-diagnosed hypertension
dxCVD	0: no diagnosis 1: diagnosis	Clinician-diagnosed cardiovascular disease
MD_lytes_any	0: no diagnosis 1: diagnosis	Clinician-diagnosed electrolyte or metabolic disorders
Diabetes	0: no diagnosis 1: diagnosis	Patient-reported history of diabetes
Hypertension	0: no diagnosis 1: diagnosis	Patient-reported history of hypertension
CV_disease		Patient-reported history of cardiovascular disease
fhxCKD	0: absent 1: present	Family history of CKD in at least one first-degree relative

Other variables.

The social history portion of the H&P includes a basic housing questionnaire as well as items regarding substance use. Housing data consists of average household size, average household monthly income, and location of residence. The variable *Residence*, also a string variable, was recoded into the categorical variable *NicaDepts* in order to represent the Nicaraguan departments (equivalent to states in the United States). The departments are illustrated in Appendix 3.3; the red stars indicate the four departments that the study patients resided in. In addition to residence, social history included other housing conditions, such as availability of drinking water at home (*DrinkingWater*). Furthermore, the social history also included items regarding substance use. Four items (*current_smoker*, *past_smoker*, *current_drinker*, and *past_drinker*) were dichotomized to represent whether the patient answered "yes" or "no" to the substance use questions.

Study Hypotheses

The following hypotheses were tested in this study:

- $H1_0$: There is no difference in demographics, comorbidities, and occupation in patients with CKD from those without CKD. It is hypothesized that patients with CKD are younger, predominantly male, do not have a proportional rate of comorbid conditions, and work in agriculture.
- $H2_0$: There is no difference in the comorbid conditions reported by physicians and patients. It is hypothesized that physicians and patients agree in regards to a past medical history of comorbid conditions.
- $H3_0$: The odds ratio of being diagnosed with CKD in patients that work in agriculture compared to patients that do not work in agriculture is 1; in other words, agricultural work does not increase the risk of CKD. It is alternatively hypothesized that patients who work in agriculture will have an increased risk of CKD even when adjusting for potential confounders.
- $H4_0$: There is no difference among agricultural workers in the prevalence of CKD between sugar cane workers and non-sugar cane workers. It is hypothesized that patients who reported predominantly working in the sugar cane industry have a higher prevalence of CKD.

Data Analysis

All data was analyzed using SPSS v. 23.0 (IBM Corp., Armonk, New York). Considering the primary aim of this study—to examine the risks associated with CKD—the data was approached with a case-control perspective. Approximately half of the study population has the diagnosis of CKD at any of the five stages (54%), whereas the other rough half of the population does not have the diagnosis of CKD (46%). A case-control approach allowed for the retrospective analysis of exposure to risk factors in patients with CKD compared to patients without CKD.

Examining differences between patients with and without CKD.

As stated in Chapter 1, the primary aims of this study were to examine the risk factors, including comorbid conditions and occupational exposures, associated with CKD in this particular patient population. Therefore, a bivariate analysis was conducted via a series of independent t-tests and Pearson chi-squared tests in order to compare demographic data, comorbidities, and occupation in patients with CKD from those without CKD (Hypothesis 1).

Regarding comorbid conditions, diabetes, hypertension, and cardiovascular disease were examined and compared between patients with and without CKD. The variables utilized for this analysis were recoded to include both patient and physician reported comorbidity (new variables: *DM_total, HTN_total, CVD_total*, respectively) in order to account for all of the cases that were not reported by patients but were reported by physicians, and vise versa. Moreover, another series of Pearson chi-squared tests were performed to examine clinician-diagnosed and patient-reported comorbid conditions using the original variables for physician and patient reported comorbidity (Hypothesis 2). The kappa statistic was calculated in order to assess the interrater reliability between the clinician and patient reports for the three conditions that both reporters agreed on: diabetes, hypertension, cardiovascular disease, and electrolyte/metabolic disorders.

Risk factors in agricultural workers.

A bivariate analysis was conducted in order to observe whether there was a difference in occupational hazards—including working conditions and biochemical exposures—between patients with and without CKD. Multivariate logistic regression analysis was then conducted to determine whether agricultural occupation had an effect on the risk of developing CKD (Hypothesis 3). Potential confounders were chosen according to the evidence provided by previous studies that examined risk factors associated with CKD. The relationship between CKD and the confounders was subsequently explored using Pearson's R correlation (see Appendix 3.4 for SPSS output). The confounders that were included in the logistic regression model were age, male gender, medical history of diabetes, hypertension, or cardiovascular disease, family history of CKD, and the top five most commonly reported occupational hazards.

Lastly, a supplemental bivariate analysis was performed to examine whether CKD status differs in patients with a detailed labor history, including field of work (Hypothesis 4). The items that were included in this analysis were private versus public employment status, specific job roles (irrigation, planting, harvesting, and pest control), and duration of exposure to agricultural work (see Table 3.1 for definitions of these variables).

Chapter 4: Study Results

Descriptive Statistics

All patients in the sample (N=512) were adults ranging between the age of 22 and 73, with a mean age of 43 years old. Approximately 86% of the patients were male. All patients that reported their location of current residence lived in four of the surrounding departments in Northwestern Nicaragua: Chinandega (56.8%), Leon (36.9%), Managua (1.0%), and Granada (0.2%; see Appendix 4.2 for a map of Nicaragua). Regarding current occupation, patients fell into one of the following categories: agriculture (58.2%), machinery/electric (6.5%), mining (6.7%), non-laborious/administrative work (14.5%), or currently retired or unemployed (14.1%). Household size ranged from one to six household members, with the average being two members per household. Average household income was C$4628 (US$161) and ranged between C$400 (US$14) to C$35,000 (US$1,220). [1] In terms of living conditions, most patients that completed this portion of the H&P form reported having access to electric lighting (90.9%) and drinking water at home (73.7%); however, only 26.9% reported having a sewage system installed at home.

Regarding past medical history, 13.9% of the study sample had a diagnosis of hypertension, whereas only 1.6% and 1.4% had a diagnosis of diabetes and cardiovascular disease, respectively. Moreover, 13.4% of patients reported current use of tobacco and an additional 30.9% reported prior chronic use of tobacco but quit more than a year prior to their medical visit. In addition, 17% reported current alcohol use, whereas 49.8% reported

[1] C$ represents Cordobas, the Nicaraguan currency. Exchange was calculated based on the rate of C$28.71 for every U.S. dollar (XE Currency Converter, 2016).

prior use of alcohol but have been sober for at least a year. Although frequency and duration of substance use was also documented in the medical record, it was not utilized in this study; only "yes" or "no" responses were examined (Table 4.1).

Table 4.1: Patient demographics (N=512).

Characteristic	Mean (SD)
Age (years)	43 (10.4)
Members in household	2 (1)
Household income*	C$4628 (C$288)**
	N/total (%)
Gender	
Male	438/510 (85.9)
Female	72/510 (14.1)
Residence	
Chinandega	281/495 (56.8)
Leon	196/495 (39.6)
Managua	5/495 (1.0)
Granada	1/495 (0.2)
Unknown	12/495 (2.4)
Current occupation	
Agriculture	294/505 (58.2)
Machinery/Electric	33/505 (6.5)
Mining	34/505 (6.7)
Non-laborious/Administrative	73/505 (14.5)
Retired/unemployed	71/505 (14.1)
Past medical history***	
Diabetes	8/512 (1.6)
Hypertension	71/512 (13.9)
Cardiac disease	7/512 (1.4)
Substance use	
Tobacco, current	68/508 (13.4)
Tobacco, ever	139/449 (31.0)
Alcohol, current	86/506 (17.0)
Alcohol, ever	216/434 (48.8)

*Patient-reported household incomes of C$0 (N=66) were excluded.
**Cordoba (C$) = Nicaraguan currency; equivalent to US$161 (US$10), respectively.
***Past medical history inclusive of physician and patient reports.

Bivariate Analysis of Patient Characteristics and CKD Status

As mentioned in the previous chapter, approximately half of the study population had a physician-confirmed diagnosis of CKD (53.7%) whereas the remaining approximate half (46.3%) did not have a diagnosis of CKD. Patients with CKD were approximately ten years younger (mean age of 38.5 years old) than non-CKD patients (mean age 48.6 years old). Although the study population as a whole was predominantly male, there was a significantly greater prevalence of men in the CKD group (92.0%) than the non-CKD group (78.7%). Moreover, the majority of CKD patients resided in the Northwestern-most department of Chinandega, whereas the majority of non-CKD patients live in Leon. Most of the patients who reported working in agriculture were also diagnosed with CKD (88.6%), whereas the majority of non-CKD patients worked in non-agricultural sectors.

Recall that medical history data for diabetes, hypertension, and cardiovascular disease reported by both physicians and patients was combined in order to include all cases with the respective diagnosis (refer to page 30). Diabetes and hypertension were therefore more prevalent in patients without CKD (2.6% and 17.3%, respectively) than in those with CKD (0.4% and 10.9%, respectively). There was no difference between the CKD and non-CKD groups with regards to a past medical history of cardiovascular disease. Furthermore, a family history significant for CKD in at least one first-degree relative was more prevalent in patients with CKD (10.2%) than in patients without CKD (1.3%). Lastly, prior use of tobacco and current use of alcohol was significantly higher in patients without CKD (37.3% and 25.6%, respectively) compared to patients with CKD (25.8% and 9.6%, respectively; see Table 4.2). Prior use of alcohol and current tobacco use were not shown to be significantly different between CKD and non-CKD patients.

Table 4.2: Comparison of demographics and medical history between patients with and without CKD.

Patient Characteristic	CKD	No CKD	P-value
Demographics			
Age in years, Mean (SD)	38.5 (9.9)	48.6 (8.0)	<.001*
Gender, N/total (%)			
Male	253/275 (92.0)	185/235 (78.7)	<.001**
Female	22/275 (8.0)	50/235 (21.3)	
Residence, N/total (%)			
Chinandega	250/271 (92.3)	31/224 (13.8)	<.001**
Leon	11/271 (4.1)	185/224 (82.6)	
Managua	1/271 (0.4)	4/224 (1.8)	
Occupation group, N/total (%)			
Agriculture	242/273 (88.6)	52/232 (22.4)	<.001**
All other	31/273 (11.4)	180/232 (77.6)	
Medical History			
Past Medical History, N/total (%)			
Diabetes	1/275 (0.4)	7/273 (2.6)	.018**
Hypertension	30/275 (10.9)	41/237 (17.3)	.037**
Cardiac disease	2/275 (0.7)	5/237 (2.1)	.179
Family history of CKD, N/total (%)	28/275 (10.2)	3/237 (1.3)	<.001**
Substance use, N/total (%)			
Tobacco, current	32/274 (11.7)	37/235 (15.7)	.196
Tobacco, past	64/248 (25.8)	75/201 (37.3)	.006***
Alcohol, current	26/272 (9.6)	60/234 (25.6)	<.001***
Alcohol, past	119/248 (48.0)	97/186 (52.0)	.223

*Significance based on a p-value less than 0.05 on a 2-sided independent t-test.
**Significance based on a p-value less than 0.05 on a 2-sided Pearson chi-squared test.
***Significance based on p-value less than 0.05 on a 2-sided Fisher's exact test.

Comparing Rates of Comorbid Conditions Reported by Clinicians and Patients

In order to compare the difference in reports of comorbid conditions between physicians and patients, the original variables for past medical history were utilized for this analysis (refer to page 30). Tables 4.3 and 4.4 demonstrate the most common comorbid conditions reported by clinicians and patients, respectively. As mentioned in the previous section, according to physician diagnosis, patients without CKD had a higher prevalence of hypertension (ratio of approximately 1:2) and diabetes (ratio of approximately 1:7).

However, there was no significant difference in the prevalence of hypertension or diabetes between CKD and non-CKD patients in the self-reported data. Electrolyte disturbances—whether unspecified, hypocalcemic, hyperuricemic, or azotemic—were more common in patients with CKD versus non-CKD patients in both the clinician reports (36% versus 0.4%) and patient reports (45.5% versus 1.3%). Moreover, there was a difference in the prevalence of asthma as reported by physicians and unspecified pulmonary diseases as reported by patients. Patients without CKD had a higher prevalence of such comorbidities. Additionally, gastrointestinal disease was found to be more prevalent in non-CKD patients according to patient reports.

Table 4.3: Most common *clinician*-reported comorbidities between CKD and non-CKD patients.

Comorbidity	CKD N/total (%)	No CKD N/total (%)	Ratio+	P-value
Hypertension	28/275 (10.2)	39/237 (16.5)	1:1.6	.048**
Diabetes Mellitus	1/275 (0.4)	7/273 (2.6)	1:6.5	.018**
Cardiovascular Disease	0/275 (0)	3/237 (1.3)	—	.061
Electrolyte/Metabolic Disturbance	99/275 (36)	1/237 (0.4)	90:1	<.001**
Unspecified	11/275 (4)	0/237 (0)	—	.002**
Hypocalcemia	27/275 (9.8)	1/237 (0.4)	24.5:1	<.001**
Hyperuricemia	81/275 (29.5)	0/237 (0)	—	<.001**
Cancer (unspecified type)	0/275 (0)	3/237 (1.3)	—	.061
Asthma	2/275 (0.7)	8/237 (3.4)	1:4.9	.031**

+Ratio of CKD:non-CKD cases with respective comorbidity.
**Significance based on a p-value less than 0.05 on a 2-sided Pearson chi-squared test.

Table 4.4: Most common *patient*-reported comorbidities between CKD and non-CKD patients.

Comorbidity, N/total (%)	CKD N/total (%)	No CKD N/total (%)	Ratio+	P-value
Hypertension	2/275 (0.7)	2/237 (0.8)	1:1.1	.881
Diabetes Mellitus	0/275 (0)	1/237 (0.4)	—	.281
Cardiovascular Disease	2/275 (0.7)	2/237 (0.8)	1:1.1	.881
Electrolyte/Metabolic Disturbance	125/275 (45.5)	3/237 (1.3)	35:1	<.001**
Azotemia	126/275 (45.8)	2/237 (0.8)	57.3:1	<.001**
Hyperuricemia	1/275 (0.3)	0/237 (0)	—	.353
Pulmonary Disease	0/275 (0)	6/237 (2.5)	—	.008**
Anemia	1/275 (0.4)	2/237 (0.8)	2:1	.478
Lipid Disorders	0/275 (0)	2/237 (0.8)	—	.127
Gastrointestinal Disease	2/275 (0.7)	8/237 (3.4)	1:4.9	.031**
Genitourinary Disease	12/275 (4.4)	5/237 (2.1)	2.1:1	.156

+Ratio of CKD:non-CKD cases with respective comorbidity.
**Significance based on a p-value less than 0.05 on a 2-sided Pearson chi-squared test.

Furthermore, interrater reliability testing was performed in order to assess the extent of agreement between physician and patient reports of comorbid conditions. Of the four comorbidities that physicians and patients reported in common, electrolyte/metabolic disturbances had the highest Cohen's kappa of .303 (Table 4.5). Diagnosis of diabetes had a kappa statistic of .220, whereas diagnosis of hypertension and cardiovascular diseases had negative kappa statistics (-.015 and -.007, respectively).

Table 4.5: Interrater reliability between *clinician*- and *patient*-reported comorbidities.

Disease	Kappa Statistic	Strength of Agreement*
Hypertension	-.015	Poor
Diabetes mellitus	.220	Fair
Cardiovascular disease	-.007	Poor
Electrolyte/Metabolic Disturbance	.303	Fair

*Adapted from Landis and Koch, 1977.

Differences in Occupational Hazards Among CKD and non-CKD Patients

Table 4.6 shows a chi-squared analysis of the occupational hazards reported by all patients. The working conditions that were more prevalent in CKD versus non-CKD patients were: repetitive movements (98.5% versus 94.5%, p=0.001), uncomfortable positions (97.8% versus 92.4%, p<.001), extreme heat (94.2% versus 59.1%, p<.001), and heavy lifting (89.8% versus 75.5%, p<.001). Conversely, the working conditions that were more prevalent in non-CKD patients versus CKD patients were: smoke inhalation (17.3% versus 5.2%, p<.001), humidity (8.4% versus 3.6%, p=.003), and poor ventilation (19.8% versus 1.5%, p<.001). Regarding biochemical exposures, the factors that were more prevalent in CKD versus non-CKD patients were exposure to chemicals and pesticides (58.4% versus 45.3%, p<.001) and insects (7% versus 2.3%, p=.006). Exposure to microorganisms (bacteria, viruses, and fungi), lead, and mercury were only reported by non-CKD patients (6.4%, 1.3%, and 0.4%, respectively).

Table 4.6: Occupational hazards reported by all patients (N=512).

Exposure	CKD	No CKD	P-value
Working Conditions, N/total (%)			
Repetitive movements	271/275 (98.5)	224/237 (94.5)	.001*
Uncomfortable positions	269/275 (97.8)	219/237 (92.4)	<.001*
Extreme heat	259/275 (94.2)	140/237 (59.1)	<.001*
Heavy lifting	247/275 (89.8)	179/237 (75.5)	<.001*
Smoke inhalation	11/213 (5.2)	31/179 (17.3)	<.001*
Humidity	10/275 (3.6)	20/237 (8.4)	.003*
Poor ventilation	4/275 (1.5)	47/237 (19.8)	<.001*
Excessive light	4/275 (1.5)	5/237 (2.1)	.072
Biochemical Exposures, N/total (%)			
Chemicals and pesticides	143/245 (58.4)	87/192 (45.3)	<.001*
Insects	15/213 (7.0)	4/172 (2.3)	.006*
Bacteria, Viruses, Fungi	0/204 (0)	11/171 (6.4)	.001*
Lead	0/275 (0)	3/237 (1.3)	.008*
Mercury	0/275 (0)	1/237 (0.4)	.035*

*Significance based on a p-value less than 0.05 on a 2-sided Pearson chi-squared test with Bonferroni correction.

Assessment of Agricultural Occupation on CKD Risk

A logistic regression was performed in order to further investigate the effects of agricultural occupation, age, male gender, past medical, family history of CKD, and occupational hazards on the risk of having a diagnosis of CKD. The bivariate model presented in Table 4.7 revealed that the odds of having CKD for patients who worked in agriculture were over 25 times greater than patients who did not work in agriculture. Additionally, male gender and family history of CKD were associated with over a 3-fold and 8-fold increased odds of CKD, respectively. Age was found to have a protective effect; the odds of developing CKD decreased by 10% for every one-year increase in age. Diabetes and hypertension were found to also decrease the odds of CKD by 88% and 41%, respectively. Moreover, all five of the most commonly reported occupational hazards significantly increased the odds of CKD. Most notably, exposure to extreme heat increased the odds of developing CKD by 11-fold. Heavy lifting, uncomfortable positions, and repetitive movements were found to have approximately a 2.9-, 3.7-, and 3.9-fold increased odds of CKD. Lastly, exposure to agrichemicals was associated with the lowest odds of CKD, but was nonetheless was found to increase the odds of developing CKD by 70%.

Table 4.7: Bivariate logistic regression model examining the risk of CKD.

Independent Variables	OR (95% CI)	P-value
Agricultural Occupation	25.6 (15.9-41.2)	<.001*
Age	.891 (.871-.911)	<.001*
Male gender	3.11 (1.82-5.31)	<.001*
Medical history		
Diabetes	.120 (.015-.982)	.048*
Hypertension	.585 (.353-.972)	.038*
Cardiovascular disease	.340 (.065-1.77)	.200
Family history of CKD	8.84 (2.65-2.95)	<.001*
Occupational hazards		
Extreme heat	11.2 (6.36-19.8)	<.001*
Heavy lifting	2.86 (1.75-4.67)	<.001*
Uncomfortable position	3.69 (1.44-9.44)	.007*
Repetitive movement	3.93 (1.26-12.2)	.018*
Chemical exposure	1.73 (1.18-2.52)	.005*

*Significance based on a p-value < .05

The aforementioned variables were consequently analyzed in a multivariate regression model shown in Table 4.8. Model 1 demonstrates the null logistic regression model without adjustment of potential confounders. When the covariates were added to the analysis (Model 2), the odds ratio of CKD in agricultural workers versus others only slightly decreased compared to Model 1 and remained statistically significantly high regardless of adjustment (OR=24.2, 95% CI: 13.9-42.0). Model 2 also shows that family history of CKD (OR=13.6, 95% CI: 2.49-73.9) and age (OR=.902, 95% CI: .858-.923) were the only variables that maintained a significant association with CKD after adjustment. Moreover, age (OR=.890, 95% CI: .858-.923) and family history of CKD (OR=52.7, 95% CI: 3.24-858) maintain this significant association with CKD even after adjusting for occupational hazards as well (Model 3). As for occupational hazards themselves, Model 3 shows that extreme heat (OR=18.1, 95% CI: 6.45-51.0) and chemical exposure (OR=3.27, 95% CI: 1.66-6.43) were also independently associated with CKD after adjustment.

Table 4.8: Comparison of hierarchical logistic regression models examining the risk of CKD.

Independent Variables	MODEL 1[a] OR (95% CI)	P-value	MODEL 2[b] OR (95% CI)	P-value	MODEL 3[c] OR (95% CI)	P-value
Main Independent Variable						
Agricultural Occupation	25.6 (15.9-41.2)	<.001*	24.2 (13.9-42.0)	<.001*	26.2 (13.2-52.2)	<.001*
Covariates						
Age			.902 (.876-.928)	<.001*	.890 (.858-.923)	<.001*
Male gender			1.53 (.721-3.22)	.270	.784 (.282-2.18)	.641
Medical history						
Diabetes			.517 (.048-5.63)	.588	.487 (.033-7.17)	.600
Hypertension			1.31 (.607-2.84)	.490	1.54 (.648-3.66)	.329
Cardiovascular disease			1.49 (.210-10.6)	.690	2.01 (.294-15.0)	.460
Family history of CKD			13.6 (2.49-73.9)	.003*	52.7 (3.24-858)	.005*
Occupational hazards						
Extreme heat					18.1 (6.45-51.0)	<.001*
Heavy lifting					1.57 (.596-4.13)	.362
Uncomfortable position					.219 (.040-1.19)	.079
Repetitive movement					5.41 (.615-47.6)	.128
Chemical exposure					3.27 (1.66-6.43)	.001*

*Significance based on a p-value < .05
a. Unadjusted (null) model.
b. Model 1+ adjustment for age, gender, medical history, and family history.
c. Model 2 + adjustment for top 5 occupational hazards.

Comparison of Labor History in CKD versus non-CKD Patients

Detailed labor history data was available for 181 out of the 294 patients who reported working in agriculture. Of these 181 patients, 137 (75.7%) worked in the sugar cane industry during the majority of their agricultural career. The remaining patients worked mostly in the banana (0.6%), cotton (0.6%), or shrimp (1.1%) industries or as a farmer for personally owned fields (1.1%). Table 4.9 shows a sub-analysis of labor history in these patients that reported working in agriculture. There was no difference in the mode of employment—whether the patient was employed by a large, public company, a smaller, privately owned company, or both—between sugar cane and non-sugar cane workers. Additionally, there was no difference between CKD and non-CKD patients in the total duration of time dedicated to that particular field. Occupation in the cotton industry was more prevalent in patients without CKD. There was no further difference in the prevalence of CKD in the other fields of labor, including the sugar cane industry. Lastly, the only job responsibility that was statistically different between CKD and non-CKD patients was planting; 29.9% patients who reported planting (sowing or seeding of product) had CKD versus only 6.8% of non-CKD patients reported this role. There was no significant difference in the job responsibilities of irrigation, harvesting, or pest control.

Table 4.9: Job characteristics of agricultural workers.

	CKD	No CKD	P-value
Labor demographics, N/total (%)			
Public employer	163/189 (86.2)	64/75 (85.3)	.848
Private employer	92/189 (48.7)	36/75 (48)	.921
Private and public employer	76/189 (40.2)	28/75 (37.3)	.666
Total duration (months), Mean (SD)	49.3 (54.7)	57.1 (59.5)	.450
Field of Labor, N/total (%)			
Sugar cane	144/189 (76.2)	59/75 (78.7)	.667
Banana	1/189 (0.5)	2/75 (2.7)	.195
Cotton	1/189 (0.5)	4/75 (5.3)	.024**
Tobacco	0/189 (0)	1/75 (1.3)	.284
Shrimp and Livestock	2/189 (1.1)	2/75 (2.7)	.320
Unspecified	41/189 (21.7)	7/75 (9.3)	.021**
Job responsibilities, N/total (%)			
Irrigation	47/147 (32.0)	20/56 (35.7)	.612
Planting	44/147 (29.9)	25/56 (44.6)	.048*
Harvesting	99/147 (67.3)	32/56 (57.1)	.174
Pest control	21/147 (14.3)	10/56 (17.9)	.527

*Significance based on a p-value less than 0.05 on a 2-sided Pearson chi-squared test.
**Significance based on p-value less than 0.05 on a 2-sided Fisher's exact test.

Chapter 5: Discussion and Conclusion

Discussion of Study Results

Differences in demographic data.

This study investigated the association between CKD and agricultural occupation. Additionally, this study examined the effect of age, gender, comorbid conditions, and occupational hazards on the risk of developing CKD. It was hypothesized that this study would demonstrate a difference in occupation, age, and gender between CKD cases and non-CKD controls. Results of this study revealed that agricultural occupation, younger age, and male gender were all more prevalent in patients with CKD compared to patients without CKD, thus further supporting the observations first reported by Trabanino, et al. in 2002 and confirmed by numerous studies thereafter (Brooks, 2009; Torres, et al., 2010; Orantes, et al., 2011; O'Donnell, et al., 2011). Moreover, bivariate analyses also showed a difference in family history between the two study groups. Patients with CKD had a higher prevalence of a family history significant for CKD, which also supports the results from other bivariate studies performed on similar agricultural communities (Orantes, et al. 2011; Orantes, et al., 2014).

Examination of comorbidities.

Regarding comorbid conditions, the study population as a whole had a low prevalence of diabetes and hypertension, which is an important result to emphasize given that diabetes and hypertension are the leading causes of CKD worldwide (Couser, et al., 2011). Moreover, this study did not demonstrate a difference in the prevalence of such comorbid conditions between patients with CKD and without CKD. This is also consistent with several studies showing that diabetes and hypertension are not associated with CKD in similar agricultural communities throughout Central America (Gracia-Trabanino, et al., 2005; O'Donnell, et al., 2010; Raines, et al., 2014). In particular, Raines, et al. showed that hemoglobin A1c levels[1] were not associated with reduced GFR[2]. Additionally, although patients with decreased GFR had higher systolic and diastolic blood pressures at the time of the data collection, a self-reported past medical history of hypertension was not common (Raines, et al., 2014). Thus, it can be presumed from this study that either (1) elevated blood pressure in the absence of a prior diagnosis of hypertension may be secondary to renal damage itself, or (2) individuals are unaware of an underlying diagnosis of hypertension, thus self-reported past medical history underestimates the prevalence of hypertension. This leads to a question of cause-and-effect. In other words, it is not clear whether renal disease is causing an elevation in blood pressure, or hypertension is causing renal disease. Considering that the Raines, et al. study was cross-sectional, it cannot establish such directionality. Likewise, this concept can be applied to the present study. Although blood pressure measurements were not obtained for this study, it would be interesting to note whether the study population had any discrepancies between actual blood pressure measurements and diagnosis of hypertension. Moreover, future studies with a longitudinal design could also explore whether blood pressure elevation occurs before or after a diagnosis of CKD.

The present study also examines the relationship between comorbid conditions and CKD with the additional perspective from physicians and patients themselves. Diabetes and

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[1] A measure of glycemic control and diagnostic criterion for diabetes.
[2] Defined in the study as a glomerular filtration rate less than 60 mL/min/1.73m^2.

hypertension were not as prevalent in CKD patients as they were in non-CKD patients according to physician diagnosis. However, there was a significant discordance between physician- and patient-reported comorbidities as evidenced from the interrater reliability testing. Although both physician and patient reports showed higher numbers of diabetes and hypertension in non-CKD patients compared to CKD patients, physicians reported a higher prevalence of diabetes and hypertension overall. Recall that CISTA clinicians transcribed diagnoses in accordance to the patient's medical record from the referring physician, thus, it can be assumed that this variable was consistent from physician to physician. If this assumption holds true, this could imply that there is lack of understanding on the patient's part of his or her medical history, resulting in an underestimation of comorbid conditions. Consequently, such discordance could have introduced errors throughout the remainder of the data analysis. However, in the hopes of reducing such error, comorbid conditions reported by both physicians and patients were combined prior to analysis to ensure that all conditions were accounted for in the event that a patient reported a comorbidity that the physician did not. Moreover, these results show that it is important for both clinicians and patients to have proper comprehension of a patient's past medical history, especially if such comorbidities might affect the likelihood of developing the disease in question (Redelmeier, et al., 2001; Ming, et al. 2004). In this study, recognition of a medical history of diabetes and hypertension were crucial in order to accurately assess the risk of CKD in this patient population.

Evaluating agricultural work as a risk factor for CKD.

Both the unadjusted and adjusted logistic regression models demonstrated that patients who worked in agriculture were drastically at increased odds (over 24-fold) of developing CKD compared to patients who did not work in agriculture, which further supports the hypothesis of this study. The odds ratio reported in this study is markedly high in comparison to the Raines, et al. study, which found agricultural workers to have four-fold increased odds of developing CKD only in the unadjusted model. Once the model was adjusted for age and male gender, the odds ratio was no longer significant, implying that age and gender were confounders for CKD risk in this study population (Raines, et al., 2014). Orantes, et al. also reported that agriculture was not a statistically significant risk factor for developing CKD in a multivariate logistic regression model, even though bivariate analyses did show a higher prevalence of CKD in agricultural workers (Orantes, et al., 2011).

The present study, however, does corroborate the results published by Sanoff, et al. in 2010, which showed that agricultural workers had 2.5-fold increased odds of developing CKD in Northwestern Nicaragua even after controlling for age and gender. The conflicting evidence among all of these studies, including the present one, could be due to differences in the patient populations that were studied. Raines, et al. and Orantes, et al. studied patient populations that reported a lower prevalence of agricultural occupations (35.6% and 40.6%, respectively). In contrast, the study populations of Sanoff, et al. and the present study consisted of 71% and 88.6% agricultural workers, respectively. If there is a true causation between agricultural work and CKD (which is yet unknown), such a skew in the distribution of occupations could have favored a greater association between CKD and agricultural work in the latter studies.

Regardless, this study demonstrated that agricultural occupation is a risk factor that increases the odds of having CKD. Considering that the odds ratio remained statistically significant and consistently greater than 24, this indicates that the effect of agricultural work was not confounded by the other variables that were controlled for. Of such results, it was most surprising that male gender was not a confounding variable, when the current literature has shown otherwise (Orantes, et al., 2011; Raines, et al. 2014). Conversely, it was not surprising that diabetes, hypertension, and cardiovascular disease were not confounders given that it was originally hypothesized that comorbid conditions would not have an effect on the risk of CKD in agricultural workers.

Moreover, this study showed that age was an independent predictor for CKD risk, although with an inverse relationship compared to other studies. Raines, et al. showed 2.5-fold increased odds of CKD in agricultural workers for every 10-year increase in age. Conversely, the present study showed that age was actually a protective factor that, when all other variables were controlled for, decreased the odds of CKD in agricultural workers by nearly 10% for every one-year increase in age. A possible explanation for this difference could be that there is inherent bias in the present study's patient population. Since the data was obtained from an occupational health clinic, the study sample consists of younger, working-age adults that are naturally at greater risk for developing work-related injuries and disease; thus, this is not representative of the general aging population.

Furthermore, family history of CKD was also an independent predictor of CKD. This has been previously validated in other studies, which have reported a 70 to 80% increased risk of CKD in agricultural workers with a positive family history[1] (Sanoff, et al., 2010; Orantes, et al., 2011). The present study, however, astonishingly showed 13-fold increased odds of developing CKD in agricultural workers with a family history of CKD in at least one first-degree relative. When this logistic regression model was controlled for occupational hazards, the odds further increased to over 50-fold. However, though both models showed odds ratios that were statistically significant, the confidence intervals were extremely wide, indicating uncertainty about the true effect that family history has on the odds of having CKD. A follow-up study with a larger patient sample would be necessary to formulate a more precise confidence interval.

It has been well studied that, although specific renal disease genes have yet to be identified, individuals with a family history of advanced nephropathy (including CKD and ESRD), are at high risk for developing kidney disease (Satko, et al., 2007). However, in the present study, it is difficult to differentiate whether such familial clustering of kidney disease is due to true genetic factors or environmental risks. From anecdotal experience of working at the CISTA clinic, individuals who worked in agriculture tended to come from households where multiple family members worked in agriculture, if not the same field or plantation. It was therefore not uncommon to witness multiple members of the same family who worked in agriculture and also had CKD at different stages. Future studies could consider focusing on familial clustering of CKD in agricultural communities in order to further assess the extent of the effect of genetic and environmental factors on the development of the disease.

Exploring specific occupational hazards.

This study also included an analysis of detailed agricultural labor history, including field of labor, duration of work, and work-related hazards. In the univariate analysis, employment in the sugar cane industry was not associated with a difference in the prevalence of CKD among agricultural workers; only employment in unspecified sectors had a greater prevalence of CKD. Although it is unknown which fields of agriculture are included in the unspecified group, it may be reasonable to assume that this group includes a large proportion of sugar cane workers given that sugar cane was the most commonly reported agricultural industry. Without making this assumption, though, these results ultimately do not support the hypothesis of this study that proposed that sugar cane workers would have a greater prevalence of CKD. Nonetheless, these results were surprising given the strong evidence that supports sugar cane work as a risk factor for developing CKD (Sanoff, et al., 2010; Raines, et al. 2014). In particular, Raines, et al. demonstrated that patients with a reduced GFR[1] spent significantly more lifetime days in sugar cane harvesting, most notably during the dry seasons.[2]

Although working in the sugar cane industry was not associated with CKD risk per se, four out of the eight reported occupational hazards that were positively associated with CKD are common to sugar cane work. For example, typical job responsibilities for a sugar cane worker include burning the sugar cane fields, extinguishing the crop fires, and immediately cutting the crop either manually or with machinery (Sugar Knowledge International, 2016). Sugar cane laborers perform repetitive movements, work in sustained uncomfortable positions, are required to lift the heavy crop, and expose themselves to chemicals and pesticides known to be nephrotoxic, all while performing these hazards under high temperatures on a daily basis. Understandably, such strenuous labor—often performed in continuous 12-hour shifts—poses a great health hazard on these workers.

[1] Defined by this study as a glomerular filtration rate less than 60 mL/min/1.73m^2.
[2] Dry season in Nicaragua lasts from December to April. Temperatures can reach as high as 95° Fahrenheit with approximately 60% humidity (Dall, 2007).

This further leads one to speculate whether extreme working conditions are the underlying contributors to kidney damage in young agricultural workers without significant medical comorbidities. Presently, the leading hypothesis regarding CKD risk in agricultural workers suggests that intense and physically demanding labor leads to insidious muscle damage, which in turn injures the renal tissue. This, in conjunction with insufficient water intake during working hours, places agricultural workers at risk for severe dehydration, thus adding further insult to the kidneys (Roncal-Jimenez, et al., 2016). Although the present study did not examine direct markers of muscle injury or water intake during labor, it does provide more insight as to which occupational hazards and working conditions could be contributing to the development of CKD in agricultural workers.

Study Limitations

Since this study was a retrospective, cross-sectional analysis, causality cannot be established from the results; thus, only associations were made. Additionally, the study sample was obtained from a very specialized clinic, thus limiting the applicability of these results. However, the aim of this study was to intentionally examine such an atypical presentation of CKD in this unique patient population from this clinic. Using medical records from a well established, academic institution therefore helped to focus on this target population. Nonetheless, this study excluded many working and non-working adults that did not seek medical care at the CISTA clinic. The study sample, therefore, does not accurately represent the general population of Northwestern Nicaragua that has been investigated by other studies that were actually performed within these communities (Brooks, 2009; O'Donnell, et al., 2011; McClean, et al., 2012; Raines, et al., 2014). Although the medical records used for the present study were obtained at random, the population where the medical records came from was inherently narrow compared to the study populations from the aforementioned studies. A study targeting the community at large would ensure a more random sampling of the study population.

A problem that this limitation poses is that this study sample consists only of patients with significant debilitation that warrants referral to an occupational specialist. This implies that other individuals, whether they worked in agriculture or not, who had early, not-yet-debilitating stages of CKD are not included in this analysis. Moreover, individuals at the opposite end of the spectrum who are too ill to see a doctor or are nearing the fatal phase of ESRD are also not included in this analysis. Therefore, the results of this study not only apply to the CISTA patient population, but specifically to patients with CKD that has been deemed debilitating enough to warrant medical attention but not severe enough to cause death. A more appropriate assessment of the risk factors associated with CKD should take into consideration all individuals with CKD within the community at large, regardless of stage, severity, or location of treatment.

Another limitation of this study is the presence of bias both from the physician and patients' perspectives. Since the data was collected from medical records, it depends on the accuracy of the history that was transcribed into the chart. In the presence of recall bias, this history data can be inaccurately misinterpreted. The poor interrater reliability of the comorbidity assessment between physicians and patients gives evidence to the affect of recall bias in this study sample. Moreover, since this study was performed in an occupational health clinic that is staffed by physicians specialized in work-related illness, there is also an element of observer bias. Since these physicians are trained to evaluate occupational hazards, they inherently will assess the patient's health with a different perspective than another physician without the supplemental training.

Lastly, another limitation of this study involves the dataset itself. Several variables were recorded into the original medical record as free text, thus, they were transcribed into the database as extensive string variables. As such, these variables required substantial pre-processing in order to standardize them in preparation for analysis. This introduces an element of observer bias considering that the recoding of these variables was dependent on subjective interpretation in order to designate the data into respective categories. This limitation was particularly noticeable when analyzing the labor history data, which was the most unstructured variable of them all. It would be beneficial for another observer to recode the labor history data in order to assess the interrater reliability of the data preparation. This would help detect any inconsistencies that could be affecting the data analysis.

Implications of This Study

Despite the study's limitations, it nonetheless has implications in clinical medicine and public health, both in Nicaragua and worldwide. First, occupation is a crucial factor to consider when assessing the risk of developing CKD. This study argues that a detailed social history with a comprehensive occupational history is just as relevant to the clinical picture as the patient's past medical history. Thus, clinicians working in similar rural communities must obtain appropriate information that includes type of occupation and specific work-related hazards in order to provide a thorough medical assessment and plan for the patient. Moreover, it is equally as important that patients themselves are well informed of their medical history and the conditions they are at risk for. This will ensure that patients not only maintain autonomy over their health, but also promote transparency between the provider and patient, thus helping to improve health outcomes.

Furthermore, Nicaragua is recognized as one of the top countries worldwide with the worst weather-related outcomes, including high morbidity and mortality due to extreme temperatures (Harmeling and Eckstein, 2012). In addition, Nicaragua's sugar cane production is expected to rise in the upcoming year, implying that the demand for agricultural workers will rise (CentralAmericaData.com, 2016). While climate is an occupational hazard that cannot be controlled for, other work-related hazards can be better regulated to ensure that workers are protected from CKD risk factors. For example, one study reported that adequate consumption of water, *bolis* (hydrating frozen treats replenished with electrolytes), and energy bars decreased the relative risk of developing CKD in agricultural workers. (Zepeda, 2007). Thus, an important implication of the present study is that proactive measures must be taken in order to provide therapeutic interventions that will alleviate the burden of occupational hazards in sugar cane workers.

Conclusion

The purpose of this study was to examine risk factors associated with CKDu in Nicaragua. The first two chapters served to lay the foundation for the rationale behind this study. As the worldwide mortality data analysis showed, deaths due to renal disease are disproportionately affecting lower income countries. In particular, Nicaragua is experiencing a rise in deaths attributable to CKD due to causes other than the most common etiologies of CKD, chronic hypertension and diabetes. Most importantly, the results from this study prove that CKD in Northwestern Nicaragua is indeed associated with agricultural occupation, younger age and a family history significant for CKD serving as independent predictors of CKD. Although this study did not find a significant association between CKD and sugar cane work in particular, the results nevertheless contribute to the expanding pool of CKD research in Nicaraguan agricultural communities and guide directions for future research.

The ultimate intention of this study is to further endorse the severity of the CKD epidemic in Nicaragua and similar developing nations. It not only is a public health dilemma; it is a worldwide socioeconomic disparity (Garcia-Garcia and Jha, 2015). CKD is a debilitating illness that leads to worse health outcomes if not treated promptly and efficiently (Couser, et al., 2011.). However, renal replacement therapy is expensive and not readily accessible in rural communities such as in Northwestern Nicaragua (Couser, et al., 2011; O'Donnell, et al., 2011; Weiner, et al., 2013). This further widening the health disparity, making it even more difficult to address. Social responsibility, therefore, calls upon the medical and scientific communities to intervene and take action against this pressing inequity.

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APPENDIX 3.1: REDCap data sheet

OSCIN Data Sheet

Please complete the survey below.

Thank you!

Date of record (00MON0000)	________________
Gender	○ Male ○ Female
City of residence	________________
Date of birth (00MON0000)	________________
Age	________________
Profession	________________
Diagnosis	☐ CKDI ☐ CKDII ☐ CKDIII ☐ CKDIV ☐ CKDV ☐ Hypoacussis ☐ Hyperuricemia ☐ Hypocalcemia ☐ Other
Type	____________________

Socioeconomic Conditions

Cooking	☐ Firewood ☐ Gas ☐ Electricity
Drinking water available in household?	○ Yes ○ No
Sewage system?	○ Yes ○ No
Electric lighting	○ Yes ○ No
# people in household that have a paying job	________________
Monthly household income (C$)	________________

Past Medical History

HTN (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

DM (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Epilepsy (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Cancer (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Asthma (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Cardiac Disease (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Parotiditis (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Malaria (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Dengue (years)
- ◯ Less than one year
- ◯ 1-3 years
- ◯ 4-6 years
- ◯ 7-10 years
- ◯ 11-13 years
- ◯ 14-16 years
- ◯ 17-20 years
- ◯ More than 20 years

Other (years) __________________________________

Medications

Medications

(Name, Dose, Frequency, Indication) __________________________________

Hospitalizations and Surgeries

Hospitalizations and Surgeries
(Date, Indication, Diagnosis, Complications) __________________________________

Family History

Family Hx: HTN

- ☐ Mother
- ☐ Father
- ☐ Brother(s)
- ☐ Sister(s)
- ☐ Maternal Uncle(s)
- ☐ Maternal Aunt(s)
- ☐ Maternal Grandmother
- ☐ Maternal Grandfather
- ☐ Paternal Uncle(s)
- ☐ Paternal Aunt(s)
- ☐ Paternal Grandmother
- ☐ Paternal Grandfather
- ☐ Other

HTN: other relatives

____

Family Hx: DM

- ☐ Mother
- ☐ Father
- ☐ Brother(s)
- ☐ Sister(s)
- ☐ Maternal Uncle(s)
- ☐ Maternal Aunt(s)
- ☐ Maternal Grandmother
- ☐ Maternal Grandfather
- ☐ Paternal Uncle(s)
- ☐ Paternal Aunt(s)
- ☐ Paternal Grandmother
- ☐ Paternal Grandfather
- ☐ Other

DM: other relatives

____

Family Hx: Epilepsy

- ☐ Mother
- ☐ Father
- ☐ Brother(s)
- ☐ Sister(s)
- ☐ Maternal Uncle(s)
- ☐ Maternal Aunt(s)
- ☐ Maternal Grandmother
- ☐ Maternal Grandfather
- ☐ Paternal Uncle(s)
- ☐ Paternal Aunt(s)
- ☐ Paternal Grandmother
- ☐ Paternal Grandfather
- ☐ Other

Epilepsy: other relatives

____

Family Hx: Cancer

- ☐ Mother
- ☐ Father
- ☐ Brother(s)
- ☐ Sister(s)
- ☐ Maternal Uncle(s)
- ☐ Maternal Aunt(s)
- ☐ Maternal Grandmother
- ☐ Maternal Grandfather
- ☐ Paternal Uncle(s)
- ☐ Paternal Aunt(s)
- ☐ Paternal Grandmother
- ☐ Paternal Grandfather
- ☐ Other

Cancer: other relatives ______________________________

Family Hx: Asthma

- ☐ Mother
- ☐ Father
- ☐ Brother(s)
- ☐ Sister(s)
- ☐ Maternal Uncle(s)
- ☐ Maternal Aunt(s)
- ☐ Maternal Grandmother
- ☐ Maternal Grandfather
- ☐ Paternal Uncle(s)
- ☐ Paternal Aunt(s)
- ☐ Paternal Grandmother
- ☐ Paternal Grandfather
- ☐ Other

Asthma: other relatives ______________________________

Family Hx: Other ______________________________

Daily Habits

Smoke tobacco?

- ○ Yes
- ○ No

Frequency of current tobacco use: ________________________

Ever smoked tobacco?

- ○ Yes
- ○ No

Frequency of previous tobacco use: ________________________

Quit how many years ago? ________________________

Drink alcohol?

- ○ Yes
- ○ No

Frequency of current alcohol use: ________________________

Ever drank alcohol?

- ○ Yes
- ○ No

Frequency of previous alcohol use: ______________________________

Quit how many years ago? ______________________________

Recreational drug use?
- ◯ Yes
- ◯ No

Frequency of recreational drug use: ______________________________

Exposures

Exposures
- ☐ Uncomfortable positions
- ☐ Repetitive movements
- ☐ Heavy lifting
- ☐ Heat
- ☐ Cold
- ☐ Loud Noise
- ☐ Vibration
- ☐ Poor ventilation
- ☐ Humidity
- ☐ Poor lighting
- ☐ Excessive lighting
- ☐ Mercury
- ☐ Lead

Chemicals
- ◯ Yes
- ◯ No

Type ______________________________

Dust
- ◯ Yes
- ◯ No

Type ______________________________

Smoke
- ◯ Yes
- ◯ No

Type ______________________________

Gas
- ◯ Yes
- ◯ No

Type ______________________________

Animals/insects
- ◯ Yes
- ◯ No

Type ______________________________

Viruses, bacteria, fungi
- ◯ Yes
- ◯ No

Type ______________________________

Other
- ◯ Yes
- ◯ No

Type ______________________________

Occupational History

Current occupation ________________

Main job responsibility ________________

Company ________________

Years worked in current occupation ________________

Shift worked
- ◯ Day
- ◯ Night
- ◯ Mixed

Hours worked per day ________________

Hours worked per week ________________

Overtime hours worked per week ________________

Labor History

____

Protective Measures

Protective measures
- ◯ Always
- ◯ Sometimes
- ◯ Never

Type ________________

Type ________________

Why ________________

Shower after work?
- ◯ Always
- ◯ Sometimes
- ◯ Never

Explanation of risks by employer prior to employment?
- ◯ Yes
- ◯ No

Explanation by employer of equipment usage?
- ◯ Yes
- ◯ No

Annual Hygiene and Safety Training completed?
- ◯ Yes
- ◯ No

Pre-employment physical exam completed?
- ◯ Yes
- ◯ No

Periodic physical exams?
- ◯ Yes
- ◯ No

How many? ________________

How often? ________________

Results ________________

APPENDIX 3.2: Sample of the recoding of string variables

```
RECODE  Residence ('Barrio Zaragoza, Leon'=2) ('Chchigalpa'=1) ('Chichi gala, chinandega'=1) ('Chichigalpa'=1)
   ('Chichigalpa, chinandega'=1) ('Chichiglapa'=1) ('Chichiglapa'=1) ('Chicogalpa'=1) ('Chinandega'=1) ('Chinandenga'=1) ('Chinendega'=1)
   ('Chingandega'=1) ('Corinto'=1) ('Diriomo, Granada'=5) ('El Jicaral'=2) ('El Realejo'=1) ('El Rialejo, Chinandega'=1)
   ('El Sauce, Leon'=2) ('El Veijo'=1) ('El viejo'=1) ('El Viejo'=1) ('EL Viejo'=1) ('EL VIEJO'=1) ('El Viejo (Ingenio Monte Rosa)'=1) ('El Viejo Chinandega'=1)
   ('El Viejo, chinandega'=1) ('El Viejo, Chinandega'=1) ('Guadalupe'=1) ('Jiquilillo, Chinandega'=1) ('La Paz Centro'=2) ('La Paz Centro, Leon'=2) ('La Quimora, Telica'=2)
   ('Lareynaga,Leon'=2) ('larreynaga'=2) ('Larreynaga'=2) ('Larreynaga, le��n'=2) ('larreynaga, leon'=2) ('Larreynaga, leon'=2) ('Larreynaga, Leon'=2) ('Le��n'=2) ('leon'=2)
   ('Leon'=2) ('LEON'=2) ('Leon, Leon'=2) ('Malpaisillo'=2) ('Malposillo'=2) ('Managua'=3) ('Mina de Limon'=2) ('Mina de Limon, Larreynaga, Le'=2) ('Mina el lim��n'=2)
   ('Mina el Lim��n, Larreynaga'=2) ('mina el limon'=2) ('Mina el limon'=2) ('Mina el Limon'=2) ('Mina El limon'=2) ('Mina El Limon'=2) ('Mina el Limon, larreynaga'=2)
   ('Mina el Limon, Larreynaga'=2) ('Mina El Limon, Larreynaga'=2) ('Mina el Limon, Larreynaga, Le'=2) ('Mina limon'=2) ('Mina Limon, Larreynaga'=2)
   ('Mina Limon, Larreynaga (Leon)'=2) ('Nagrote'=2) ('Posoltega'=1) ('Pozoltega, Chinandega'=1)
   ('Posoltega, chinandega'=1) ('Posoltega, Chinandega'=1) ('Puerto Moraz��n'=1) ('Puerto Morazan'=1)
   ('Puerto Sandino'=2) ('Quezalguaque, Leon'=2) ('San Jeronimo'=2) ('San Juan de Limay, Leon'=2) ('santa pancha'=2) ('Santa Pancha'=2) ('Santa Pancha, Larreynaga'=2)
   ('Santa Rosa del Pe��on, Le��n'=2) ('Santa Rosa del Penon, Leon'=2) ('STA. Pancha'=2) ('Cruca Santa Pancha'=2) ('Sutiaba, Leon'=2) ('Sutiava'=2) ('Telica'=2)
   ('Telica, LEon'=2) ('Tipitapa, Managua'=3) ('Villa Nueva'=1) ('Villa Nueva, chichandega'=1) ('Villa Nueva, Chinandega'=1) ('Villanueva'=1)
   ('Barrio Raul Ruiz'=9) ('Bo. Agosto Cesar'=9) ('Bo. Coyolar'=9) ('El Valle'=9) ('El Viejo, Leon'=9) ('Reparto Marco Antonio Medina'=9) INTO NicaDepts.
VALUE LABELS NicaDepts 1 "Chinandega" 2 "Leon" 3 "Managua" 4 "Granada" 5 "Unknown/uncategorized".
EXECUTE.

RECODE Profession ('Ag Laborer'=1) ('Ag laborer'=1) ('Ag worker'=1) ('Agricultural Laborer'=1)
   ('Agricultural Worker'=1) ('Agronomist'=1) ('Agricultural Workers'=1) ('Agricultural company wor'=1)
   ('Agricultural company workers'=1) ('Agricultural laborer'=1) ('Agricultural worker'=1) ('Field Worke'=1)
   ('Agriculture worker'=1) ('Cane cutter'=1) ('Cane cutter and pest con'=1) ('Cane cutter and pest '+
   'control'=1) ('Cotton Worker'=1) ('Irrigation worker'=1) ('Labor worker'=1) ('Laborer'=1) ('FIELD WORKER'=1)
   ('field worker'=1) ('Field Workers'=1) ('Field worker'=1) ('Fieldworker'=1) ('LABORER'=1) ('Agronomy engineer'=1)
   ('Sugar Cane Worker'=1) ('Sugar Cane Worker/ Unemp'=1) ('Sugar Cane Worker/ Unemployed'=1)
   ('Sugar cane cutter '=1) ('Sugar cane harvester (cu'=1) ('Sugar cane harvester (cutter)'=1) ('farm worker'=1)
   ('Sugarcane Worker'=1) ('Sugarcane worker'=1) ('Worker'=1) ('agricultural laborer'=1) ('Field Woker'=1)
   ('agricultural worker'=1) ('agriculture'=1) ('forestry '=1) ('laborer'=1) ('Field Worker'=1) ('sugar cane '+
   'worker'=1) ('worker'=1) ('Machine operator'=2) ('Machinist'=2) ('Machinist assistant'=2) ('Mechanic'=2)
   ('Industrial Electromechanic'=2) ('Industrial Mechanic'=2) ('Electric power plant worker'=2) ('(airplane) battery sealer'=2)
   ('Retired Drill Operator'=2) ('Conductor'=2) ('industrial electrician'=2) ('Factory worker'=2) ('Electrician'=2)
  ('Electromechanic'=2) ('Merchant/ Machinist'=2) ('mechanic'=2) ('ELECTRICIAN'=2) ('Machinery'=2)
   ('Welder'=2) ('Operador palo frontal'=2) ('tower operator'=2) ('Machinist Assistant'=2) ('conductor'=2)
   ('Machinery/Other'=2) ('Ex mine worker'=3) ('retired miner'=3) ('Miner/Machinist'=3) ('Ex miner'=3)
   ('Mine worker'=3) ('Miner'=3) ('Mining'=3) ('miner'=3) ('Underground engineer'=3) ('Retired'=5) ('Unemployed'=5) ('retired'=5)
   ('pension'=5) ('unemployed'=5) ('Pensioned'=5) (ELSE=4) INTO Occupation.
VALUE LABELS Occupation 1 "Agriculture" 2 "Mechanic/Electric" 3 "Mining" 4 "Non-labor" 5 "Retired/Unemployed".
EXECUTE.

RECODE OtherMDDx ("Hydroelectric disequilibrium secondary to erc"=1)  ("Hypokalemia, hypomagmesemia"=1) ("Hipomagnesemia"=1)
("Anemia  Hypokalemia   Eosinophilia"=1) ("hydroelectric dysequiibrium"=1) ("hyponatremia"=1) ("hydro-electric imbalance"=1) ("Hydroelectrolyte imbalance"=1)
("Anemia, Hydroelectrolyte imbalance"=1)
(ELSE=0)
INTO Lytes_Metab.
VARIABLE LABELS Lytes_Metab 'MD Dx of lytes disturbance'.
VALUE LABELS Lytes_Metab 1 "Yes" 0 "No".

RECODE OtherPtDx ("HTN"=1) ("HTN  UTI"=1) ("HTN  Morbid obesity"=1) ("-HTN  -Anemia"=1) ("HTN  Obesity grade 1"=1)
("-lumbalgia, Diabetes Type II, bronchial hyperreactivity, hypertension"=1)
("-Azotemia (2003)  -HTN, unknown"=1) ("-Azotemia (2009)  -Hyperuricemia, unknown yr of diag  -HTN, unknown yr of diag  -Anemia, unknow yr or diag"=1)
("-HTN   -Peptic ulcer   -Sinusitis  - Chronic lumbar pain"=1) ("hypertension"=1) (ELSE=0)
INTO Hypertension.
VARIABLE LABELS Hypertension 'Pt-reported hypertension'.

RECODE OtherPtDx ("- Azotemia (2010)  - Calcified Granuloma in the left superior lobule  - Os"=1) ("azotemia"=1) ("Azotemia, 2010"=1) ("azotemia 2007"=1)
("Azotemia (2009)"=1) ("-Azotemia (2007)"=1) ("Azotemia (2010)"=1) ("Azoemia (2009)"=1) ("azotemia 2009"=1)
("-Azotemia (2010)  -Fatigue due to heat: 8 occasions  -Contact with pesticides: 1 occasion"=1)
("- Azotemia, 2007"=1) ("azotemia 2010"=1) ("azotemia 2009"=1) ("azotemia 2010  heat stroke  pesticide intoxication"=1) ("-Azotemia (2003)  -HTN, unknown"=1)
("-Azotemia (2010)  -Syncope  -Fatigue due to heat"=1) ("Asotemia"=1) ("Azotemis (2005)"=1) ("Azotemia (7 years)"=1) ("Azotemia"=1)
("-Azotemia (2009)  -Hyperuricemia, unknown yr of diag  -HTN, unknown yr of diag  -Anemia, unknow yr or diag"=1) ("Azotemia (2010)"=1) ("Azotemia (2010)"=1)
("Azotemia 2007"=1) ("Azotemia (10 years)"=1) ("Azotemia (2007), vitiligo (2005)"=1) ("Azotemia"=1) ("azotemia 2010"=1) ("Azotemia (2009)"=1) ("Azotemia, 2011"=1)
("Azotemia 2010    heat stroke x2    heat exhaustion x2"=1) ("Azotemia, 2008"=1) ("azotemia 2011"=1) ("Contact with pesticides, heat exhaustion 5x, azotemia 2008"=1)
("Azotemia 2010"=1) ("Azotemia, 2008  Heat stroke x3"=1) ("Azotemia (2007)"=1) ("azotemia 2006"=1) ("azotemia 2002"=1) ("Azotemia 2009"=1)
("azotemia 2009"=1) ("Azotemia 2010"=1) ("azotemia 2012"=1) ("azotemia 2011"=1) ("Azotemia 2009  Heat exhaustion x 1"=1) ("Azotemia, 2011"=1)
("heat exhaustion  azotemia 2000"=1) ("Azotemia 2012  Heat exhaustion x 2"=1) ("Azotemia, (2011)"=1) ("azotemia 2008"=1) ("Azotemia 2012"=1) ("Azotemia, 2011"=1)
("Azotemia 2013"=1) ("Azotemia (2013)"=1) ("-Azotemia (2011)"=1) ("-Azotemia (2013)"=1) ("Azotemia 2008"=1) ("Azotemia 2013"=1) ("Azoremia 2010"=1)
("Azotemia 2011"=1) ("-Azotemia (2003)"=1) ("-Azotemia (2013)"=1) ("-Azotemia (2009)"=1) ("Azotemia (2011)"=1) ("Azotemia 2005"=1)
(ELSE=0) INTO Azotemia.
VARIABLE LABELS Azotemia 'Pt-reported azotemia'.

RECODE FamilyHxOther ('Brother-CKD'=1) ('Father- CKD'=1) ('-CKD, brother'=1) ('-CKD (brother)'=1)
   ('CKD (brothers)'=1) ('-CKD (father)'=1) ('CKD - brother'=1) ('CKD (mother & father)'=1) ('CKD: Dad and grandfather'=1)
   ('CKD-brothers'=1) ('Father CKD'=1) ('CKD'=1) ('CKD, brother'=1) ('IRC: father'=1) ('ERC, brother'=1)
   ('-CKD, father'=1) ('CKD (brothers)'=1) ('Erc - father'=1) ('CKD father'=1) ('father: CKD'=1) ('CKD- father'=1)
   ('- CKD- brother'=1) ('CKD (brother)'=1) ('CKD'=1) ('father: CKD'=1) ('-Father, CKD'=1) ('ERC-father'=1)
   ('ERC father'=1) ('CKD - Brother'=1) ('ERC (son)'=1) ('CKD father'=1) (ELSE=0) INTO fhxCKD.
VARIABLE LABELS  fhxCKD 'FamHx CKD in first degree relative'.
VALUE LABELS fhxCKD 1 "Yes" 0 "No".
EXECUTE.
```

APPENDIX 3.3: Departments of Nicaragua

https://hast-spanish.wikispaces.com/Nicaragua

APPENDIX 3.4: SPSS output of the exploratory analysis for potential confounders

Correlations

		MD Dx CKD of any stage	Age (continuous)	Male Gender	DM_total	HTN_total	CVD_total	Family Hx CKD in first degree relative	Heat	Lifting	Position	RepMvmts	Chemical (pesticide) exposure (numeric)
MD Dx CKD of any stage	Pearson Correlation	1	-.488**	.190**	-.104*	-.092*	-.059	.186**	.422**	.191**	.128**	.112*	.135**
	Sig. (2-tailed)		.000	.000	.018	.037	.180	.000	.000	.000	.004	.011	.005
	N	512	508	510	512	512	512	512	512	512	512	512	435
Age (continuous)	Pearson Correlation	-.488**	1	-.180**	.123**	.133**	.083	-.155**	-.209**	-.092*	-.094*	-.028	.058
	Sig. (2-tailed)	.000		.000	.005	.003	.061	.000	.000	.037	.034	.529	.229
	N	508	508	508	508	508	508	508	508	508	508	508	434
Male Gender	Pearson Correlation	.190**	-.180**	1	.006	-.032	-.001	.032	.332**	.306**	.136**	.029	.109*
	Sig. (2-tailed)	.000	.000		.895	.469	.990	.465	.000	.000	.002	.508	.022
	N	510	508	510	510	510	510	510	510	510	510	510	435
DM_total	Pearson Correlation	-.104*	.123**	.006	1	.132**	.121**	.034	.029	.057	.028	.023	-.007
	Sig. (2-tailed)	.018	.005	.895		.003	.006	.442	.512	.201	.528	.598	.887
	N	512	508	510	512	512	512	512	512	512	512	512	435
HTN_total	Pearson Correlation	-.092*	.133**	-.032	.132**	1	.099*	-.007	-.004	.029	.062	.011	.044
	Sig. (2-tailed)	.037	.003	.469	.003		.025	.873	.919	.511	.160	.799	.363
	N	512	508	510	512	512	512	512	512	512	512	512	435
CVD_total	Pearson Correlation	-.059	.083	-.001	.121**	.099*	1	-.030	.022	.008	.026	.022	-.046
	Sig. (2-tailed)	.180	.061	.990	.006	.025		.500	.618	.858	.556	.622	.335
	N	512	508	510	512	512	512	512	512	512	512	512	435
Family Hx CKD in first degree relative	Pearson Correlation	.186**	-.155**	.032	.034	-.007	-.030	1	.017	-.061	.018	-.044	.033
	Sig. (2-tailed)	.000	.000	.465	.442	.873	.500		.707	.167	.692	.316	.494
	N	512	508	510	512	512	512	512	512	512	512	512	435
Heat	Pearson Correlation	.422**	-.209**	.332**	.029	-.004	.022	.017	1	.277**	.328**	.138**	.052
	Sig. (2-tailed)	.000	.000	.000	.512	.919	.618	.707		.000	.000	.002	.278
	N	512	508	510	512	512	512	512	512	512	512	512	435
Lifting	Pearson Correlation	.191**	-.092*	.306**	.057	.029	.008	-.061	.277**	1	.271**	.267**	-.003
	Sig. (2-tailed)	.000	.037	.000	.201	.511	.858	.167	.000		.000	.000	.952
	N	512	508	510	512	512	512	512	512	512	512	512	435
Position	Pearson Correlation	.128**	-.094*	.136**	.028	.062	.026	.018	.328**	.271**	1	.423**	.058
	Sig. (2-tailed)	.004	.034	.002	.528	.160	.556	.692	.000	.000		.000	.226
	N	512	508	510	512	512	512	512	512	512	512	512	435
RepMvmts	Pearson Correlation	.112*	-.028	.029	.023	.011	.022	-.044	.138**	.267**	.423**	1	-.035
	Sig. (2-tailed)	.011	.529	.508	.598	.799	.622	.316	.002	.000	.000		.470
	N	512	508	510	512	512	512	512	512	512	512	512	435
Chemical (pesticide) exposure (numeric)	Pearson Correlation	.135**	.058	.109*	-.007	.044	-.046	.033	.052	-.003	.058	-.035	1
	Sig. (2-tailed)	.005	.229	.022	.887	.363	.335	.494	.278	.952	.226	.470	
	N	435	434	435	435	435	435	435	435	435	435	435	435

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).