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Association Of Kidney Stones With Chronic Disease Among Adults In The United States: Considerations By Race-Ethnicity

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ASSOCIATION OF KIDNEY STONES WITH CHRONIC DISEASE AMONG ADULTS IN THE UNITED STATES: CONSIDERATIONS BY RACE-ETHNICITY

A Thesis

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by

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ABSTRACT

Background: Little research has been conducted to describe the relationship between kidney stones and risk of cardiovascular disease and stroke in individuals of different race ethnicities.

Purpose: The purpose of this study was to compare the prevalence of co-morbidities and to investigate whether there was a statistically significant association between kidney stone formers and increased odds of cardiovascular disease and stroke in race-ethnicity groups.

Methods: Data from the 2007-2012 cycles of the National Health and Nutrition Examination Survey (NHANES) were used. Survey and biological data used included kidney stone cases, hypertension, obesity, diabetes, chronic kidney disease, cardiovascular disease and stroke. Covariates in the analytic models included ratio of family income to poverty, age, gender, education, diet, smoking and tobacco use, poverty level, physical activity, and alcohol use.

Results: After adjusting for confounders, kidney stone participants had increased odds of obesity, hypertension, diabetes, cardiovascular disease, and stroke. Non-Hispanic black kidney stone formers, compared to other ethnic groups, had the highest prevalence of obesity (65.6%), hypertension (67.6%), diabetes (37.8%), and stroke (6.1%). However, Mexican American kidney stone formers had the highest prevalence of elevated cholesterol (38.2%), with non-Hispanic white kidney stone formers having the highest prevalence of cardiovascular disease (7.1%).

Conclusion: We observed a relatively strong association between kidney stones and various morbidities, with these observations not appearing to be moderated by race-ethnicity. However, when utilizing the Pooled Cohort Equations to predict 10-yr risk of a future ASCVD event,

kidney stones was only associated with future risk among non-Hispanic Black kidney stone formers

LIST OF ABBREVIATIONS AND SYMBOLS

AHA	American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
HR	Hazards Ratio
OR	Odds Ratio

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CHAPTER I

INTRODUCTION

Nephrolithiasis, or kidney stone events, affect approximately 10% of the U.S. population (The National Institute of Diabetes and Digestive and Kidney Diseases (NDDK, 2013). The number of Americans suffering from kidney stones between 2007 and 2010 nearly doubled from 1990s (Ferraro et al., 2013). Kidney stones are crystals formed in the kidney that become trapped in the urinary tract. The kidneys naturally produce crystal-promoting and inhibiting substances, which are carried in urine. Crystal inhibitors include: urine volume, citrate, magnesium, phylate, and pyrophosphate. Crystal promoters include: calcium, sodium, phosphorous, struvite, uric acid, and the amino acid cysteine. Kidney stones develop when an imbalance of crystal promoters and inhibitors exist due to lifestyle factors, genetics, or other conditions (University of Wisconsin-Madison, 2010).

Kidney stones can arise in a variety of areas including the renal tubules, ureters, or bladder. Stones can be asymptomatic or large enough, as in case of staghorn calculi, to cause urinary obstruction and serious kidney damage. The obstruction caused by kidney stones could lead to chronic kidney disease (CKD) that may progress to end-stage renal failure (ESRF) and replacement of the natural kidney function by dialysis or renal transplantation (Ahmed, Ahmed, & Khalil, 2012). Similarly, kidney stones could predispose individuals to urinary tract infections,

cystitis, or pyonephrosis. However, the latest findings have found associations with increased incidence of progressive CKD and ESRF (Hootan, 2003). Kidney stones cause a significant amount of pain and 50% of diagnosed patients experience high rates of reoccurrence (Lotan et al., 2012). Symptoms of kidney stones include: pain while urinating, blood in urine, sharp pain in the back, nausea, and vomiting (NDDK, 2013). The economic burden of kidney stones has increased since 2000, with reported medical costs of $5.3 billion in 2010 (Saucier et al., 2010).

Risk factors for kidney stones, cardiovascular disease and stroke overlap and are interrelated. Kidney stone events are more prevalent amongst people with hypercholestermia, hypertension, obesity, and diabetes (Daudon, Traxer, Conort, Lacour & Jungers, 2006; Hamano et al., 2005; Ramey, Franke, & Shelley, 2004; Saucier et al., 2010; Taylor et al., 2005). Non-Hispanic white men have been identified as having the highest risk for development of kidney stones and associated medical conditions, such as gout, diabetes, and gallstone disease (Akoudad et al., 2010). Although these findings are well established, little research has been conducted to describe the relationship between kidney stones and risk of cardiovascular disease (CVD) and stroke across race-ethnicities, even though minority populations have significant health disparities in relation to hypertension, obesity, type-2 diabetes, high cholesterol, cardiovascular disease, and stroke (Centers for Disease Control and Prevention, 2014a).

The non-Hispanic black population is thought to have a low prevalence of kidney stones when compared to the non-Hispanic white population (Akoudad et al., 2010; Ferraro et al., 2013) while not much is known about prevalence and incidence of kidney stones in the non-Hispanic black population and its association with other diseases. Significant health disparities are seen among other ethnic groups as well. In 2011, the age-adjusted percentage for diabetes in Mexican Americans was 10%, while non-Hispanic whites were at 5.9% (CDC, 2014b) and little is known

about the prevalence of kidney stones within these populations. The purpose of this study is to compare the prevalence of co-morbidities (obesity, hypertension, diabetes, cholesterol, cardiovascular disease, and stroke) within race-ethnicity groups, and to investigate whether there is a statistically significant association between kidney stone formers and increased odds of cardiovascular disease and stroke between race-ethnicity groups. A non-stone forming population for each ethnic group will be used for comparison purposes. The investigation of potential risk factors will include measures of obesity, diabetes, hypertension, total cholesterol, cardiovascular disease and stroke.

Significance of the Study

This study will the question of whether non-Hispanic black persons who form kidney stones (and other ethnic group kidney stone formers) have increased odds of experiencing cardiovascular disease or stroke event. This study also will provide insight of whether the relationship between kidney stones and an increased risk of cardiovascular disease found in other research studies is consistent across race-ethnicity groups. The findings could contribute to cardiovascular and public health research in the non-Hispanic black population, as they are known as having the highest risk of death from end-stage renal failure and cardiovascular disease. In addition, the findings could determine whether clinical protocol in urology and nephrology should be altered (e.g. increase health education for kidney stone formers) in order to prevent heart disease. There could be a need for heart disease prevention discussions for patients with kidney stones and biological factors should be considered (such as calcium deposition, biomarker screening, and management of morbidities such as, obesity, hypertension, and diabetes). Non-Hispanic black and other subpopulations with risk factors for kidney stones will benefit from this study, as these factors are related to cardiovascular disease.

Research Hypotheses

Hypothesis 1: I hypothesized kidney stone formers would have greater prevalence and greater odds of co-morbidities, and that non-Hispanic black kidney stone formers would have the greatest prevalence and greatest odds of co-morbidities when compared to other race-ethnicity groups. The non-stone forming population would have a lower prevalence of co-morbidities.

Hypothesis 2: Based on previous literature (Hamano et al., 2005; Torricelli et al., 2014), I hypothesized that total cholesterol would mediate the relationship between kidney stone presence and cardiovascular disease/stroke. Further, I hypothesized that hypertension and obesity will mediate the relationship between kidney stone presence, cardiovascular disease and stroke.

Hypothesis 3: I hypothesized that individuals with kidney stones and obesity, and those with kidney stones and hypertension would have a greater odds of having cardiovascular disease and stroke than those with just kidney stones, just obesity, and just hypertension.

CHAPTER II

REVIEW OF LITERATURE

Nephrolithiasis affects the middle aged adult population, more significantly adults 40 years or older (Mayo Clinic, 2014). It also significantly affects the non-Hispanic white population more than other racial-ethnic groups. Additional risk factors for nephrolithiasis include dehydration, family history of kidney stones, digestive surgeries, and diets high in protein, sugar, and sodium. The rate of kidney stones has increased significantly over the past two decades, and it is believed to be due to the increases in rates of diabetes and obesity (Ferraro et al., 2013). The causes of kidney stone events are multifactorial, but relationships have been found between type 2-diabetes (Daudon, Traxer, Conort, Lacour, & Jungers, 2006; West et al., 2008), obesity (Taylor et al., 2005; West et al., 2008), hypertension, (Cappuccio, Strazzullo, & Mancini, 1990; Dai, Zhao, Liu, You, & Wang, 2013; Ramey, S., Franke, W., & Shelley, M., 2004; West et al., 2008), high cholesterol levels (Hamano et al., 2005; Torricelli et al., 2014), and kidney stones. Previous research has also shown baseline kidney stone formers to have an increased risk of cardiac events such as myocardial infarction, fatal coronary heart disease, and coronary artery bypass surgery (Ferraro et al., 2013; Rule et al., 2010).

Obesity

Obesity is defined as a body mass index (BMI) greater than or equal to 30. Obesity affects approximately 34.9% of the U.S. adult population (CDC, 2014d). Approximately 37.9% of non-Hispanic black men and 57.6% of non-Hispanic black women are obese (CDC, 2015). In 2010, the adult obese population in the United States was approximately 72.5 million. Approximately 41% of obese adults had incomes at or above 350% of the poverty level, 39% had incomes between 130% and 350% of poverty level and 20% had incomes below 130% of the poverty level. Non-Hispanic black men and women with incomes between 130% and 350% of the poverty level had higher rates of obesity than non-Hispanic black men and women above the 350% mark or below the 130% mark. Additionally, Mexican American men with income at or above 130% suffer from greater rates of obesity than Mexican American men and women below 130% of poverty line. According to the NCHS Data Brief, there were no significant differences in the prevalence of obesity by poverty level in the non-Hispanic white men, but there were significant differences in non-Hispanic white women (Ogden, Lamb, Carroll, & Flegal, 2010).

Obese individuals are at an increased risk for many adverse conditions, such as hypertension, diabetes mellitus, cardiovascular disease, and even some cancers (Ogden et al., 2010). Larger body size and weight gain also increases the risk of kidney stone formation. Excessive nutritional intake increases the presence of lithogenic substances in the body, such as calcium, oxalate, and uric acid, which contribute to calcium, oxalate, and uric acid stones (Asplin, 2009). Obesity also causes irregular kidney function by raising blood pressure with increased renal tubular absorption (Hall et al., 2014) and causing kidney weight gain (Ahmed et al., 2012).

Research suggests that incidence of kidney stone disease is directly associated with weight and BMI. Curan, Willett, Rimm, Speizer, and Stampfer (1998) found the magnitude of the association between kidney stones and weight varies by gender. Assessing two large cohorts: The Nurses' Health Study (n = 89376 women) and the Health Professionals Follow-up Study (n = 51529 men), they found the incidence of kidney stones to be greater amongst women participants (n = 1078) when compared to men (n = 953), and found women to have higher BMIs. The relative risk of developing a kidney stone was 1.89 (1.51 to 2.36) in women and 1.19 (0.83 to 1.70) in men.

Siener, Glatz, Nicolay, and Hesse (2004) evaluated the prevalence of obese and overweight participants to determine the influence of weight on the risk of calcium oxalate stone disease. Their findings contradicted those of Curan et al. (1998); stone disease was more common in overweight and obese men (n = 363) than in overweight and obese women (n = 164). Stone events were also highest amongst overweight and obese men when compared to normal weight men (p = .028). This study found that increasing BMI was associated with a higher risk of calcium oxalate stone formation in both genders (p = .015) but the highest risk was for men with higher BMI (p = .047). In addition to high risk of stone formation, 49% of overweight men had one or more of the following: hypertension, cardiovascular disease, diabetes, gout, gallstone disease, and hyperuricemia. Seventy-four percent of the obese men had at least one of the co-morbidities. Forty-four percent of overweight women had at least one of the co-morbidities, while 59% of obese women had at least two of the co-morbidities. This study concluded that weight influenced calcium oxalate stone formation significantly because higher weight causes an increase of urinary crystal promoters and does not increase the urinary crystal inhibitors.

Therefore more opportunities for calcium oxalate crystal stone formation occur in those who are obese.

Urinary pH, especially a persistently low pH (< 5.5) has been shown to greatly contribute to the development of uric acid nephrolithiasis (Pak, Sakhaee, & Peterson, 2001). Maalouf et al. (2004) found an inverse association between urinary pH and elevated bodyweight after analyzing medical data derived from University of Texas Southern Medical Center (Texas group; n = 1130 men and 585 women) and The University of Chicago (Chicago group; n = 2121 men and 1047 women). The mean age for the Texas group was 43 years and the mean weight was 79kg (approximately 174.17 pounds). The mean age for the Chicago group was 44 years and the mean weight was 80kg (approximately 176.37 pounds). Urinary pH was lowest (< 5.84) for individuals that weighed more than 95kg (Dallas group; n = 285, Chicago group; n = 546). This study suggested that low urinary pH was associated with the effects of obesity, which may sometimes cause uric acid nephrolithiasis by producing excessive acids in urine caused by insulin resistance.

Zhou, Watts, Agalliu, DiVito and Hoenig (2013) conducted a study examining the medical records of 269 patients with urinary stones and found visceral fat area (a marker of visceral obesity) was significantly higher in uric acid stone formers when compared to non-uric acid stone formers (209.3 vs. 161.9 cm^2, $p = 0.001$). A high level of visceral fat was also reported as an independent risk factor for uric acid nephrolithiasis (OR 3.64, 95% CI 1.22-10.85, $p = 0.02$) when compared to the low level of visceral fat area. This study concluded that in addition to routine treatments for stones, other efforts should include lifestyle modifications to enhance weight loss in order to effectively treat obese kidney stone formers.

Semins et al. (2010) analyzed the Blue Cross Blue Shield database to assess the affects of BMI on the risk for kidney stone disease. They included more categories of obesity (BMI

greater than 40 kg/m^2) in addition to the lower categories of BMI. The 95,598 stone cases that were identified consisted of 54,572 women and 41,025 men. The likelihood of the development of a kidney stone was two times greater in men than in women and the likelihood also increased with age (OR 1.44 for participants age 35-44 to OR 2.44 for participants age 55-64). Obese participants (except for men with a BMI higher than 50 kg/m^2) were significantly more likely to develop a kidney stone than people with a BMI less than 30 kg/m^2. Overall, this study recognized that having a BMI that is considered "obese" increased the risk of kidney stone disease, but once the body mass index is greater than 30 kg/m^2 the level of risk stabilized. The authors suggest that this stabilization may be due to an increase in urinary excretion of elements that promote stone formation.

Hypertension

Hypertension or high blood pressure is defined as a systolic reading of 140mm Hg or higher and a diastolic reading of 90mm Hg or higher. The systolic reading measures the pressure in the arteries when the heart contracts and the diastolic reading measures the pressure in the arteries between contractions (American Heart Association, 2015). Hypertension is a common condition that causes damage to blood vessels and organs over time due to elevated pressure on arteries and vessels. Approximately 78 million U.S. adults have been diagnosed with hypertension and the number is expected to increase (American Heart Association, 2014a). Symptoms of hypertension could be asymptomatic; many adults do not know they have the disease until they visit a doctor or check their blood pressure.

Hypertension is considered to be a major risk factor for heart disease and kidney stones. High blood pressure causes significant damage to the kidneys due to the damaging of blood

vessels throughout the body, which makes it harder for the kidneys to remove waste and function properly (Medical College of Wisconsin, 2014). African Americans, or non-Hispanic blacks, are considered to have the highest risk for hypertension when compared to other ethnic groups (American Heart Association, 2014). Approximately 43% of African American men and 45.7% of African American women have high blood pressure. Mexican Americans are reported to have 27.8% of men and 28.9% of women with high blood pressure while Caucasians have 33.9% of men and 31.3% of women with high blood pressure (CDC, 2014b). African Americans also develop hypertension at an earlier age more often than other ethnic groups. African Americans are at least six times more likely to develop kidney complications due to hypertension than their Caucasian counterparts (CDC, 2014b).

Previous studies have found that a bidirectional relationship exists between hypertension and kidney stones. Kidney stone formers have an increased risk of hypertension and hypertensive individuals are at an increased risk for developing a kidney stone (Madore, Stampfer, Rimm, Curhan, 1998). Renal damage from kidney stones may contribute to hypertension, and hypertensive individuals may have higher concentrations of urinary calcium, which would cause calcium stone formation (Cappuccio, Strazzullo, & Mancini, 1990). Studies have also revealed significant gender differences in hypertensive kidney stone formers. Dai, Zhou, Liu, You, & Wang (2013) and Akoudad et al. (2010) found that men with a history of hypertension were more susceptible to developing kidney stones than women.

Cappuccio et al. (1990) examined 688 male hypertensive and normotensive individuals to test whether kidney stone disease was more prevalent in people that were hypertensive. Sixty-one participants were previously diagnosed with hypertension and were receiving treatment. In total, 118 participants were hypertensive and the untreated hypertensive participants were

recognized as hypertensive at the time of screening. The prevalence of a history of stone disease was 13.4% in the normotensive group, 20.3% in the untreated hypertension group, and 32.8% in the diagnosed hypertension group. Treated hypertensive participants were heavier and older than the other groups. After adjustments for age and BMI, the prevalence of kidney stones remained higher in the treated and diagnosed hypertensive participants (age, F = 4.54; p =.011, BMI, F = 4.58; p = 0.011). Overall, their results concluded that hypertensive participants had twice the risk of developing a kidney stone than normotensive participants (OR 2.63; 95% CI, 1.75 to 5.71).

Hall et al. (2001) assessed the risk factors of kidney stones in southern postmenopausal women using the Women's Health Initiative. Postmenopausal women from nine southern Women's Health Initiative Centers were enrolled for the study (n = 27,410). Of these women, 1,170 kidney stone formers were identified. When assessing the hypertensive women enrolled (n = 887), 485 women had both hypertension and kidney stones (41.5%), which was greater than the number of hypertensive women without a kidney stone (n = 402, 34.4%, p = 0.001). Therefore, this study identified hypertension to be a risk factor for kidney stones in postmenopausal women.

Madore, Stampfer, Rimm, & Curhan, (1998) conducted a similar study to determine whether normotensive women participants with a history of kidney stones were more likely to develop hypertension in the future compared to women participants with no history of kidney stones. The Health Professionals Follow-up study was used to assess 51,529 men that were 40 to 75 years old. A total of 4,111 participants reported a history of kidney stones and 11,623 participants reported being diagnosed with hypertension. Statistical analysis revealed an association between kidney stones and hypertension (age adjusted odds ratio, OR 1.31 95%

confidence interval, CI 1.30 to 1.32). Overall, their study concluded that having a kidney stone increases the risk of subsequent hypertension.

Diabetes

Diabetes is a condition caused by having high concentrations of glucose in the bloodstream due to the absence of insulin or insufficient use of insulin. Beta cells store and release insulin, which regulates glucose concentrations in the blood. The absence of beta cells and inadequate production of insulin from beta cells cause diabetes. Diabetes is diagnosed using hemoglobin A1C ("A" stands for adult type) blood test, which measures the average glucose in the blood up to 3 months. Individuals with A1Cs greater than or equal to 6.5% are considered diabetic. Plasma glucose levels greater than or equal to 200 mg/dL is also used to diagnose diabetes. Risk factors for diabetes include: physical inactivity, family history of diabetes, low HDL cholesterol, hypertension and obesity. In 2012, approximately 29.1 million people in the United States (9.3% of population) identified as having diabetes (American Diabetes Association (ADA), 2015). Non-Hispanic blacks are 1.7 times more likely to develop type 2 diabetes as compared to non-Hispanic whites. According to the ADA, approximately 7.6% of non-Hispanic whites are diabetic, 13.2% of non-Hispanic blacks are diabetic, and 13.9% of Mexican Americans are diabetic. Diabetes dramatically increases the risk for complications and diseases such as cardiovascular disease and kidney damage. High levels of glucose in blood vessels damage the filtering function of the kidneys and can lead to chronic kidney disease and end-stage renal failure (Mayo Clinic, 2014).

Research has shown type 2 diabetes to increase the risk of kidney stone formation due to associated damage to kidney function (Cameron, Maalouf, Adams-Huet, Moe & Sakhaee, 2006;

Meydan, Barutca, Calizkan, & Camsari, 2003; Taylor et al., 2005). The effects of diabetes elicit kidney stone formation by altering urine composition thus effecting ammonium production. It also causes elevated levels of plasma free fatty acids, which enters the urinary tract and interferes with glutamine utilization during the process of ammonium production (Taylor et. al, 2005). Insulin resistance contributes to the accumulation of acids such as ammonia, and significantly lowers pH, which favors uric acid stone formation (Daudon, Traxer, Conort, Lacour, & Jungers, 2006). Low urine pH itself has an impact on the urinary tract's ability to excrete acid, such as citrate, which increases the risk for calcium-containing kidney stones (Taylor et al., 2005).

Taylor et al. (2005) conducted a study to evaluate the relationship between a history of reported diabetes mellitus and the prevalence of kidney stones in men and women using the Nurses' Health Study (n = 121,700 older women, aged 30 – 55 years), the Nurse's Health Study II (n = 116,671 younger women, aged 25 – 42 years), and the Health Professionals Follow-up Study (51,529 men, aged 40-75 years). Of these participants, 1,473 older women, 949 younger women, and 1,568 men had a history of diabetes. After analysis, all three cohorts demonstrated a relationship between kidney stones and a history of diabetes mellitus. The relative risk of a kidney stone for individuals with diabetes compared to those without was 1.38 (95% CI 1.06 - 1.79) in older women, 1.67 (95% CI 1.28 - 2.20) in younger women, and 1.31 (95% CI 1.11 - 1.54) in men. The relative risk of kidney stones for individuals with diabetes compared to those without was 1.29 (95% CI 1.05-1.58) in older women, 1.60 (95% CI 1.16-2.21) in younger women, and 0.81 (95% CI 0.59-1.09) in men. The relative risk for incidence of diabetes in subjects with kidney stones compared to those without was 1.33 (95% CI 1.18-1.50) in older women, 1.48 (95% CI 1.14-1.91) in younger women, and 1.49 (95% CI 1.29-1.72) in men.

Therefore, this study concluded that diabetes mellitus was associated with an increased odds for the development of kidney stones.

Daudon et al. (2006) evaluated kidney stone types in people with and without type 2 diabetes, specifically comparing calcium and uric acid stones. A total of 40,718 stones were analyzed from the Laboratoire Crystal. Two thousand four hundred and sixty four of these were from 272 patients with type 2 diabetes. There were also 2192 stones that were analyzed from patients without diabetes. The proportion of uric acid nephrolithiasis was significantly higher (3 times higher) in stone formers with type 2 diabetes than in patients without diabetes ($p < 0.0001$). Also, the proportion of stone cases from patients with type 2 diabetes was higher amongst uric acid stone formers than calcium stone formers (27.8 versus 6.9%; $p < 0.0001$). Type 2 diabetes was recognized as a major factor independently associated with risk of uric acid stone formation (OR 6.9, 95% CI; 5.5 to 8.8). Researchers also noticed that the prevalence of uric acid stones rose with age and BMI.

Cameron et al. (2006) also performed an analysis of patients with type 2 diabetes to determine metabolic differences between stone formers and non-stone formers. Participants were from the University of Texas Southern Medical Center in Dallas Texas. The stone formers (n = 8), non -stone formers (n = 24), and normal volunteers (n = 59) had significant differences in pH levels. Urine pH was significantly lower in the stone forming population when compared to the non-stone forming patients ($p < 0.01$). Also, the stone forming population had a higher prevalence of obesity and hyperinsulinemia when compared to normal volunteers. Low urine pH was concluded to be the main risk factor for the development of kidney stones in people with type 2 diabetes.

Total Cholesterol and Combined morbidities (Metabolic syndrome)

In addition to research on hypertension, obesity, and diabetes, studies have found relationships between kidney stones and high cholesterol. High cholesterol levels occur when there are fatty deposits in blood vessels, which increase the risk of a heart attack or stroke. High cholesterol is defined as 240 mg/dL or greater (Mayo Clinic, 2015). Approximately 71 million American adults have high low-density lipoprotein (LDL) cholesterol, and only 1 out of every 3 adults have controlled cholesterol levels (CDC, 2015). Research has linked high levels of cholesterol with higher rates of kidney stones (Torricelli et al, 2014). In addition, Hamano et al. (2005) identified hypercholesterolemia as one of several coronary heart disease risk factors for calcium oxalate kidney stone formers. They conducted a case control study to examine 181 calcium oxalate stone formers and compared them to 187 control participants. The variables examined included body mass index (BMI), current alcohol use, smoking, hypertension, hypercholesterolemia, diabetes, and hyperuricemia. Multivariate logistic regression revealed statistical significance for smoking (OR 4.29, 95% CI; 2.68-6.86, $p < 0.0001$), hypertension (OR 3.57, 95% CI 2.11-6.07, $p < 0.0001$), and hypercholesterolemia (OR 2.74, 95% CI; 1.51-5.00, $p < 0.0001$). Those with kidney stones had 2.74 increased odds of having high cholesterol.

Metabolic syndrome (MS) is defined as the grouping of factors that increase the risk for heart disease (obesity, hypertension, increased serum triglyceride level, decreased serum high-density lipoprotein cholesterol level, and diabetes mellitus), and affects approximately 30% of the U.S. population (AHA, 2014b). Kohjimoto et al. (2013) examined whether the clustering of metabolic syndrome traits increased the severity of kidney stone disease in 11,555 patients. Overall, 61.7% had at least one trait, 65.2% had at least 2 traits, 69.3% had at least 3 traits, and 73.3% had at least 4 traits ($p < 0.001$). Their results showed that clustering of metabolic

syndrome traits (obesity, diabetes, hypertension, and dyslipidemia) is associated with increased risk of kidney stone formation. Participants of this study with four traits had a 1.8-fold greater odds of multiple and/or recurrent stones compared with patients with zero traits (OR 1.78; 95% CI, 1.22 - 2.66).

Sakhaee et al. (2012) measured whether calcium nephrolithiasis increased the risk of metabolic syndrome in 128 recurrent calcium stone formers from Dallas, Texas and 140 recurrent calcium stone formers from Bern, Switzerland (both were compared to 109 non-stone formers from Dallas Texas). They concluded that in non-stone formers, the risk of calcium nephrolithiasis increased with the number of features of MS. They also found that stone formers have a higher propensity for calcium oxalate nephrolithiasis, but the risk was not independently associated with increasing features of MS. West et al. (2008) reported history of kidney stones using The National Health and Nutrition Examination Survey III. Their results found that the prevalence of kidney stones was associated with metabolic syndrome and the number of metabolic syndrome traits increased the risk 7.5% if 3 traits were present and to 9.8% if 5 traits were present. Participants with four or more traits had a 2-fold increase in odds of reported kidney stones.

Cardiovascular disease and Stroke

Cardiovascular disease refers to a variety of conditions that contribute to the narrowing of blood vessels, which hinder blood flow to and from the heart. Conditions of cardiovascular disease include: coronary artery disease, atherosclerosis, heart arrhythmia, and congenital heart defects (Mayo Clinic, 2013). The symptomology of cardiovascular disease varies from chest pain discomfort or pain, shortness of breath, nausea or cold sweats. Having cardiovascular disease can

also result in heart attacks or sudden death. Cardiovascular disease is the leading cause of death for both men and women in the United States (CDC, 2013; Lee & Wildeman, 2013). In 2008, the percentage of deaths caused by heart disease for non-Hispanic whites was 25.1%; for non-Hispanic blacks, 24.5% of deaths, and for Hispanics, 20.8% of deaths. There is a greater prevalence of cardiovascular disease, stroke, myocardial infarction, and atherosclerosis in the non-Hispanic black community (Hollier, 2013). In 2013, non-Hispanic blacks 20 years or older had cardiovascular disease rates of 44.4% in men and 48.9% in women. Percentages for non-Hispanic blacks with coronary heart disease were 6.8% for men and 7.1% for women (AHA, 2013). In 2013, Mexican American adults age 20 years and older had cardiovascular disease rates of 33.4% for men and 30.7% for women. Percentages for Mexican Americans with coronary heart disease were 6.7% for men and 5.3% for women. Due to the higher prevalence of the disease and its risk factors, cardiovascular disease is considered a major health disparity for African Americans (Jackson Heart Study, 2013).

Similar to cardiovascular disease, strokes occur when there is an interruption of blood supply and narrowing blood vessels leading to the brain, leading to brain cell damage. Strokes can cause a variety of symptoms such as difficulty with speech, paralysis, blurred vision, headaches, and loss of coordination. Approximately 85% of strokes are ischemic strokes, which are caused by the narrowing of arteries that lead to the brain. Ischemic strokes are caused by blood clots; these blood clots consist of fatty deposits and lipid radicals. Risk factors that increase the risk of stroke include: obesity, high cholesterol, diabetes, physical inactivity, excessive alcohol use, or heart disease (Mayo Clinic, 2015).

According to the CDC, stroke is the fifth leading cause of death in the United States. The risk of stroke is twice as high for non-Hispanic blacks when compared to non-Hispanic whites.

Additionally, non-Hispanic blacks are more likely to die after stroke events than non-Hispanic whites. Following non-Hispanic blacks, Hispanics are also more likely to suffer from a stroke when compared to non-Hispanic whites (CDC, 2015a).

Previous studies have found significant associations between kidney stones and increased risk of cardiovascular disease and stroke. Rule et al. (2010) examined 4564 incident stone formers from Olmsted County, MN. They found kidney stone formers to have a 38% higher risk for myocardial infarction (HR 1.38; 95% CI 1.07-1.77). After adjustments for kidney disease, hypertension, diabetes, obesity, dyslipidemia, gout, alcohol dependence, and tobacco use, the increased risk remained (HR 1.31; 95% CI 1.02 to 1.69). A prospective study conducted by Ferraro et al. (2013) determined there was a higher risk of developing coronary heart disease in participants with a history of kidney stones after adjusting for high blood pressure, diabetes, elevated cholesterol, and BMI (Hazard Ratio (HR) for Nurses' Health Study I, 1.18 (95% CI 1.08 - 1.28); HR for Nurses' Health Study II, 1.42 (95% CI 1.07 - 1.90). Domingos and Serra (2011) examined the Portuguese National Health Survey and the prevalence of cardiovascular disease, hypertension, diabetes, obesity, and stroke in kidney stone formers. When compared to non-stone formers, there was a higher odds ratio of myocardial infarction (OR 1.338; 95% CI 1.003-1.786) and stroke (OR 1.330; 95% CI 1.015-1.743).

More recent studies, specifically meta-analyses and systematic reviews have also found significant associations between a history of kidney stones and coronary heart disease. Cheungpasitporn et al. (2014) examined four cohort studies and one cross-sectional study, which included 52, 791 kidney stone patients. Calculated pooled risk ratios demonstrated significant association between kidney stones and coronary heart disease (RR 1.24; 95% CI 1.10-1.40). The

results remained significant for females (RR 1.34; 95% CI 1.12-1.82) but not for males (RR 1.14; 95% CI 0.94-1.38).

CHAPTER III

METHODOLOGY

The primary objective for this study was to determine, among those with a reported history of kidney stones, which race-ethnicity group(s) had an increased odds of cardiovascular disease and stroke. Secondary objectives of this study was to 1) compare the prevalence of select co-morbidities (i.e., obesity, hypertension, diabetes, and chronic kidney disease) in kidney stone formers within race-ethnicity groups, while also comparing these co-morbidities in non-kidney stone formers, 2) explore biological mechanisms to explain the possible relationship between kidney stone presence and cardiovascular disease/stroke and 3) examine the potential combined effects of kidney stone presence, obesity and hypertension on the odds of having cardiovascular disease and stroke.

Participants

The sample used for this study included 20 – 79 year old men and women who participated in the 2007-2012 cycles of the National Health and Nutrition Examination Survey (NHANES). Race/ethnicities included: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race- including multi-racial persons. Notably, the ages 20-79 years were selected because only NHANES participants 20 and older were eligible for the

medical questionnaire used to assess the morbidities described herein, and participants 80 years and older were top-coded as "80" in the NHANES dataset; inclusion of those with a coded value of "80" years may induce biases related to residual confounding.

The University of Mississippi Institutional Review Board (IRB) requires review of research involving human participants. Although this research involved data collected from human participants, the IRB recognizes de-identified data that is publically available, such as data from NHANES, exempt from IRB review. The exemption would have been denied if this project merged multiple data sets that would enable the identification of human participants to be known, which was not the case (U.S. Department of Health & Human Services, 2010). The National Center for Health Statistics (NCHS) ethics review board protocol number for NHANES cycles 2007-2010 is #2005-06 and the protocol number for cycles in 2011-2012 is #2011-17 (CDC, 2012).

The *continuous* NHANES survey represents the total civilian, non-institutionalized population 2 months of age or older in the United States after 1999. The data collected in this survey includes questionnaires administered at home and from physical examinations in mobile examination centers (MECs). A complex, multistage, clustered probability sampling design was used to select a representative sample of the U.S. civilian population. Four-stages are employed in this design, including, 1) selection of the primary sampling units (PSUs), which consist of counties, 2) selection of segments, which consist of cities embedded within the county 3) random selection of households, and 4) random selection of individuals within households (average of 1.6 person per household). Beginning in 1999, the sample size collected each year was approximately 5,000 and they were from at least 15 geographic regions across the United States. Since then, the data has been released in 2 year intervals (e.g., 1999 - 2000, 2001 - 2002, etc.)

(CDC, 2014c). For the purposes of this study, data gathered from years 2007 - 2012 will be used, as these are the only NHANES cycles that collected kidney stone-related information.

Data Extraction

For this study, the primary outcomes of interest included kidney stone cases, hypertension, diabetes, cardiovascular disease, stroke, and measured obesity (BMI $\geq 30 kg/m^2$). In order to control for parameters that would influence kidney stone presence and the other evaluated morbidities, the following covariates were included in the analytic models: ratio of family income to poverty, age, education level, smoking status, alcohol use, kidney disease, and physical activity. The extraction and data verification process utilized to prepare for analyses consisted of a series of 11 steps.

1) Go to the Center for Disease Control Prevention website and the continuous NHANES homepage (http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm).
2) Locate variables relevant to hypotheses and analyses.
3) Download data files in a TEMP folder (because data is in SAS format).
4) Use Stata to open data files within the TEMP folder and save the data files in a "DATA" folder. This is the method used to transfer data from SAS format to a Stata format.
5) Examine data files and the associated codebooks to observe any changes or differences in the data that occurred from each year.
6) Sort data by SEQN (variable ID) and merge the data to the master data file and append the data across the cycles.
7) Identify missing data and recode values accordingly.

8) Define the variables descriptively by labeling them. For example, define race with numbers and description: 1=Mexican American 2= other Hispanic, etc.

9) Construct the 6-year sample weights (http://www.cdc.gov/nchs/tutorials/nhanes/SurveyDesign/Weighting/Task2.htm)

10) Perform various data treatment procedures, including the reconstruction of variables to create appropriate categories (e.g., use the two smoking questions to create four smoking groups: smokes every day, some days, former smoker, and never smoker).

11) Compute the statistical analyses using survey-specific commands.

Study Variables

As displayed in Table 1, study variables included various chronic diseases, behavioral, and demographic parameters. The chronic diseases, which were assessed from survey and biological data (see Table 1), included kidney stone cases, hypertension, obesity, diabetes, chronic kidney disease, cardiovascular disease and stroke. The behavioral and demographic variables (assessed via survey), which were used for descriptive purposes as well as covariates in the analytic models, included ratio of family income to poverty, age, gender, education, smoking and tobacco use, poverty level, physical activity, and alcohol use.

Sample Size Determination

In the 2007-2012 NHANES cycles, 16,486 participants were 20-79 years of age. Among these 16,486 participants, 15,716 provided data on the primary study variables (i.e., kidney stone obesity, hypertension, etc.). Among these 15,716 participants, 13,006 provided data on the

covariates (i.e., ratio of family income to poverty, age, gender, education, smoking status, alcohol, and physical activity). These 13006 participants constituted the analytic sample.

Analysis

All statistical analyses were computed in Stata Version 13 (StataCorp, College Station, TX). Statistical significance was set at $p < 0.05$ for all analyses. Post-hoc achieved power analysis was computed to examine the achieved statistical power for the analytical tests. Various regression-related calibration and diagnostic tests were be employed. For example, studentized residuals (a type of standardized residual) were examined to check for outliers; normality of residuals was assessed using Lawrence C. Hamilton's interquartile range procedure (e.g., non-normality of residuals being those points that are either 3 inter-quartile ranges below the first quartile or 3 inter-quartile ranges above the third quartile); heteroskedasticity was assessed using the Breusch-Pagan/Cook-Weisberg test; multicollinearity was assessed via variance inflation factors; model specification was assessed using the Stata linktest; and cell size was checked for each variable to prevent numerical problems.

Aim 1 was to compare the prevalence of co-morbidities (obesity, hypertension, diabetes, cardiovascular disease and stroke) in non-Hispanic Black kidney stone formers and kidney stone formers within other race-ethnicity groups, while also comparing non-kidney stone formers.

Hypothesis 1: I hypothesized that kidney stone formers would have a greater prevalence and greater odds of co-morbidities, and that non-Hispanic Black kidney stone formers would have the greatest prevalence of co-morbidities when compared to other race-

ethnicity groups. The non-stone forming population would have the lowest prevalence of co-morbidities.

Analysis 1: Univariate analyses were used to report proportions of the evaluated co-morbidities across the racial ethnicity groups. A chi-square test was used to determine if there were proportional differences between the co-morbidities and the race-ethnicity groups. Separate analyses were performed for each medical condition (e.g. race-ethnicity groups and obesity, racial –ethnicity groups and hypertension, etc.).

A multivariable logistic regression was used to examine the association between kidney stone presence (independent variable) and each comorbidity (dependent variable). A separate multivariable logistic regression model was used for each comorbidity. A multivariable logistic regression model was used to examine the association between kidney stone presence and multimorbidity (i.e., having at least 2 of the evaluated diseases). In order to assess whether race-ethnicity moderates the association between kidney stone presence and each comorbidity (e.g., obesity), multiplicative statistical interaction was employed by creating a cross-product term between the race-ethnicity and presence of kidney stone variables along their main effects in a multivariable logistic regression model. If the multiplicative statistical interaction variable was significant, effect modification models were then employed separately for each race-ethnicity.

For the regression analyses, both unadjusted and adjusted results were presented.

Aim 2 was to examine biological mechanisms to explain the potential relationship between kidney stone presence and cardiovascular disease and stroke.

Hypothesis 2: Based on previous literature (Torricelli et.al, 2014), I hypothesized that total cholesterol would mediate the relationship between kidney stone presence cardiovascular disease/stroke. Further, I hypothesized that hypertension and obesity would mediate the relationship between kidney stone presence, cardiovascular disease and stroke.

Analysis 3: Baron and Kenny mediational analysis, using bootstrapped confidence interval, was used to examine whether the above listed parameters mediated the relationship between kidney stone presence and the identified morbidity. The relative magnitude (effect size) of the indirect was be estimated by calculating the mediation ratio (P_M), which is the ratio of the indirect effect to the total effect: P_M=ab/(ab)+c, with 'a' being the slope linking kidney stone presence to the mediator, 'b' is the conditional slope linking the mediator to the outcome, and 'c' is the conditional slope linking kidney stone presence to the outcome variable. The ratio of indirect effect to the direct effect were calculated as: R_M=ab/c.

Aim 4 was to examine whether there was an additive combined effect of kidney stone presence and obesity, hypertension, diabetes and elevated cholesterol with cardiovascular and stroke.

Hypothesis 4: I hypothesized that individuals with kidney stones and obesity, and those with kidney stones and hypertension would have a greater odds of having cardiovascular disease and stroke than those with just kidney stones, just obesity, and just hypertension.

Analysis 4: To examine the potential combined effects of kidney stones and obesity and kidney stones and hypertension, a morbidity index variable was created by summing the number of morbidities they had (range 0-2). Two multivariable logistic regression analyses were computed, one model

included cardiovascular disease as the outcome variable and the other included stroke as the outcome. For both models, the morbidity index variable served as the independent variable with having 0 (vs. 1 and 2) morbidities serving as the referent group for the morbidity index variable

CHAPTER IV

RESULTS

Table 1 displays the characteristics of the study sample stratified by kidney stones status. Those with kidney stones, compared to those without kidney stones, were more likely to be male (56% vs. 48.6%), older (51.7 years vs. 45.2 years), and of non-Hispanic white origin (78.7% vs. 68.6%). Those with kidney stones when compared to those without kidney stones also had higher BMI (30.3 kg/m2 vs 28.73 kg/m2), higher blood pressure (51.1% vs. 33.3), and had a higher prevalence of diabetes (21.6% vs. 10.4%), high cholesterol (4.3% vs. 4.0%), kidney disease (4.0% vs. 1.7), cardiovascular disease (6.4% vs. 2.3%), and stroke (4.5% vs. 2.0%).

Aim 1 was to compare the prevalence of co-morbidities (obesity, hypertension, diabetes, cardiovascular disease and stroke) in non-Hispanic Black kidney stone formers and kidney stone formers within other race-ethnicity groups, while also comparing non-kidney stone formers. Table 2 displays the prevalence of comorbidities among race-ethnicity groups who have had a kidney stone. Non-Hispanic black kidney stone formers, compared to Mexican Americans, other Hispanic, and non-Hispanic white kidney stone formers, had the highest prevalence of obesity (65.6%), hypertension (67.6%), diabetes (37.8%), and stroke (6.1%). However, Mexican Americans had the highest prevalence of elevated cholesterol (38.2%), with non-Hispanic whites having the highest prevalence of cardiovascular disease (7.1%).

Aim 2 was to determine whether there was a statistically significant association between kidney stone formers and increased odds of the above-mentioned co-morbidities (obesity, hypertension, diabetes, cardiovascular disease and stroke), and compare associations across racial ethnicity groups. Table 3 displays the multivariable logistic regression results examining the association between kidney stones and the previously-described morbidities; results are also presented across race-ethnicity groups. Individuals with kidney stones (vs. no kidney stones) had statistically significant increased odds of having each of the evaluated morbidities, with the exception of elevated cholesterol. Specifically, kidney stone formers (vs. no kidney stones), had a 49% increased odds of obesity, 63% increased odds of hypertension, 86% increased odds of diabetes, 68% increased odds of cardiovascular disease, and 68% increased odds of stroke.

There was little evidence of effect modification by race-ethnicity regarding the kidney stone-morbidity relationship; significant associations between kidney stones and morbidity status was observed for each race-ethnicity group. With regard to non-Hispanic black kidney stone formers, they had a 97% increased odds of obesity, 60% increased odds of hypertension, and an 82% increased odds of diabetes. All models were adjusted for age, gender, physical activity, education, smoking, alcohol, total caloric intake, dietary protein intake, dietary calcium intake, and dietary sodium intake.

Aim 3 was to examine biological mechanisms to explain the potential relationship between kidney stone presence, cardiovascular disease, and stroke. The Barron and Kenny mediational analyses were computed to examine whether select potential mediators (total cholesterol and hypertension) mediated the relationship between kidney stones and cardiovascular disease/stroke; all mediational analyses controlled for the covariates described in the previous models. Mediation analyses indicated that the indirect effect of total cholesterol on

the relationship between kidney stones and cardiovascular disease was significant (β = .006; bootstrapped 95% CI: .01-.001; p <. 05), with a relatively small effect; the proportion of the total effect mediated was 7%. Similarly, the indirect effect of total cholesterol on the relationship between kidney stones and stroke was significant (β = .02; bootstrapped 95% CI: .001-.01; p < .05), with a relatively small effect; the proportion of the total effect mediated was 3.9%.

The indirect effect of hypertension on the relationship between kidney stones and cardiovascular disease was not significant (β = .01; bootstrapped 95% CI: -.0001-.001; p > .05), with a relatively small effect; the proportion of the total effect mediated was 15.3%. However, the indirect effect of hypertension on the relationship between kidney stones and stroke was significant (β = .01; bootstrapped 95% CI: .007-.02; p < .05), with a relatively modest effect; the proportion of the total effect mediated was 22.9%.

Aim 3 was to examine whether there was an additive combined effect of kidney stones with each of the morbidities (kidney stones and obesity, kidney stones and hypertension, kidney stones and diabetes and kidney stones and elevated cholesterol). We examined the impact of the combined effect on risk of cardiovascular disease and stroke. There was consistent evidence of a combined effect of kidney stones and the evaluated morbidities on cardiovascular disease (Table 4). Those with kidney stones and obesity (vs. not) had a 2.36 fold increased odds of having cardiovascular disease; and those with kidney stones and hypertension (vs. not) had an 85% increased odds of cardiovascular disease. In addition, those with kidney stones and obesity (vs. not) had a 57% increased odds of stroke; those with kidney stones and hypertension (vs. not) had a 2.08 fold increased odds of having stroke.

Pooled Cohort Equations

The main limitation of the previous analyses was the cross-sectional design, which precludes an inability to ascertain temporal sequence. For example, it is plausible to suggest that kidney stones may influence cardiovascular disease risk, but it is equally plausible to suggest that cardiovascular disease, or morbidities associated with cardiovascular disease (e.g., hypertension), may precipitate the development of kidney stones. In an effort to address this directionality issue, additional analyses were computed that examined the association of kidney stones on the predicted risk of cardiovascular disease within the next 10 years.

Predicted 10-yr risk for a first atherosclerotic cardiovascular disease (ASCVD) event for adults 40-79 years (age range equations derived from) was calculated using the Pooled Cohort Equations, developed by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines (Golf et al., 2013). These equations have demonstrated evidence of validity (Mutner et al., 2014; Park et al., 2014)

Pregnant women or participants on cholesterol medication or who had been told by a doctor or other health professional that they had congestive heart failure, coronary heart disease, angina, heart attack, or stroke were excluded from these ASCVD analyses, which resulted in a sample of 5,571 adults 40-79 years of age, free of cardiovascular disease. Separate equations were developed for black and white/other men and women, which included the following variables in the equations: age (yrs), concentration of total cholesterol (mg/dL) and HDL-cholesterol (mg/dL), treated or untreated systolic blood pressure (mmHg), diabetes status (defined here as physician diagnosis or A1C $\geq$ 6.5%), and self-reported smoking status (yes/no). Participants with an ASCVD score of $\geq$ 7.5% were considered to be at an elevated risk for

future cardiovascular events while participants with an ASCVD score of ≥20% were considered to be at high risk for future cardiovascular events.

After adjustments (same covariates as in previous models), having kidney stones was not associated with an increase odds of having an ASCVD event within the next 10-years (OR = 1.03; 95% CI: 0.58-1.82, $p = 0.91$). When stratified by race-ethnicity, results were also non-significant for Mexican Americans (OR = 1.35; 95% CI: 0.42-4.29), other Hispanic (OR 1.02; 95% CI: 0.21-4.85), and non-Hispanic whites (OR 0.81, 95% CI: 0.40-1.61). However, among non-Hispanic blacks, those with kidney stones had a 2.24 increased odds (OR 2.24; 95% CI: 1.08-4.66; $p = 0.03$) of having an ASCVD event within the next 10-years when compared to non-Hispanic blacks with no history of a kidney stone.

Table 1: Characteristics of the analyzed participants in the 2007-2012 National Health and Nutrition Examination Survey (N=13006)

Variables	Kidney stones (n=1,140)	No kidney stones (n=11,866)	*p* Value*
Gender (%)			
Male	56 (51.7-60.2)	48.6 (47.6-49.7)	.0023
Female	44 (39.8-48.3)	51.3 (50.3-52.4)	
Age (Years)	51.7 (50.8-52.6)	45.2 (44.4-45.9)	<.001
Race-ethnicity (%)			<.001
Mexican American	5.9 (3.6-8.2)	8.5 (6.3-10.6)	
Other Hispanic	5.1 (2.9-7.3)	5.3 (3.9-6.7)	
Non-Hispanic White	78.7 (73.8-83.6)	68.6 (64.5-72.7)	
Non-Hispanic Black	5.6 (3.7-7.5)	11.2 (9.1-13.3)	
Other Race	4.6 (2.6-6.6)	6.3 (5.3-7.4)	
Average # of times passed a stone	2.25	0	
BMI (kg/m^2) ≥ 30	30.3 (29.9-30.7)	28.7 (28.5-28.9)	<.001
Hypertension (%)	51.1 (47.3-54.8)	33.3 (31.7-34.8)	<.001
Diabetes (%)	21.6 (18.3- 24.9)	10.4 (9.7-11.4)	<.001
Total to HDL cholesterol Ratio[a]	4.3 (4.2-4.4)	4.0 (3.9-4.1)	<.001
Kidney Disease (%)	4.0 (2.7-5.4)	1.7 (1.3-2.1)	.001
Cardiovascular Disease (%)	6.4 (4.8-8.1)	2.3 (1.9-2.8)	<.001
Stroke (%)	4.5 (3.2-5.7)	2.0 (1.7-2.4)	<.001
Education (%)			.1006
High School or less	42.3 (37.9-46.8)	39.2 (36.5-41.9)	
Some college or more	57.7 (53.2-62.1)	60.8 (58.1-63.5)	
Alcohol use (%)[b]			<.001
Non-drinker	30.5 (26.5-34.5)	24.5 (22.7-26.2)	
Light to moderate drinker	38.9 (34.1-43.6)	35.3 (33.6-37.1)	
Heavy Drinker	30.6 (27.2-34.1)	40.2 (38.6-41.7)	
Smoking			.04
Smokes everyday	19.2 (15.9-22.5)	17.8 (16.2-19.4)	
Smokes some days	2.3 (1.4-3.2)	3.5 (3.0-4.0)	
Former Smoker	27.7 (23.9-31.5)	24 (22.5-25.4)	
Never smoked	50.8 (45.6-56.1)	54.7 (52.7-56.6)	
Physical Activity in past 30 days (Y/N)			
Moderate to vigorous work/recreational physical activity (YES)	69.2 (65.8-72.5)	74.1 (72.4-75.8)	.003
Energy (kcal)	2166.6 (2087.7-2245.5)	2216.48 (2188.9-2244.1)	.23
Calcium (mg)	944 (901.6-986.3)	1000.7 (981.6-1019.8)	.01
Sodium (mg)	3626.5 (3489.3-3763.8)	3628.5 (3581.5-3675. 5)	.97
Protein (g)	81.5 (78.4-84.6)	84.5 (83.4-85.7)	.0475

*P-Value <.05. An adjusted Wald test was used for continuous variables and a design-based likelihood ratio test was used to determine proportional differences for the categorical variables.

[a] Total cholesterol ratio was calculated by calculating the ratio of total to HDL cholesterol

[b] Light-to-moderate drinker defined as 1 alcoholic drink/day for women and 1-2 alcoholic drinks/day for men; heavy drinker defined as 2 or more alcoholic drinks/day for women and 3 or more alcoholic drinks/day for men

Table 2: Prevalence of morbidities in kidney stone formers stratified by race-ethnicity: 2007-2012 NHANES (N=1,164)

Race-ethnic groups with Kidney stones	Obesity (%)	Hypertension (%)	Diabetes (%)	Total Cholesterol (%)	CVD (%)	Stroke (%)
Mexican American	48 (39.3-56.6)	46.4 (38.4-54.5)	26.9 (19.5-34.3)	38.2 (28.5-47.8)	3.6 (1.1-6.2)	5.2 (1.6-8.8)
Other Hispanic	44.6 (339-55.2)	42.8 (32.3-53.3)	17.1 (11.3-23.0)	35.8 (27.0-44.5)	4.8 (2.0-7.5)	2.8 (.52-5.1)
Non-Hispanic White	44.2 (39.4-49)	50.3 (45.7-55)	19.3 (15.9-22.6)	35.6 (30.7-40.5)	7.1 (5.0-9.1)	4.6 (3.1-6.1)
Non-Hispanic Black	65.6 (58.9-72.3)	67.6 (59.7-75.6)	37.8 (11.4-44.2)	27.6 (17.7-37.6)	1.5 (-.30-3.2)	6.1 (2.8-9.4)

Table 3: Results of multivariate logistic regression examining the association between kidney stones and morbidities: 2007-2012 NHANES (N=13,006).

	OR (95% CI) Obesity	OR (95% CI) Hypertension	OR (95% CI) Diabetes	OR (95% CI) High Cholesterol	OR (95% CI) CVD	OR (95% CI) Stroke
Kidney stones vs. non-kidney stones – Entire Sample	1.49 (1.28-1.75)	1.63 (1.35-1.96)	1.86 (1.5-2.31)	1.12 (.95-1.32)	1.68 (1.16-2.45)	1.68 (1.15-2.45)
By Race-Ethnicity						
Mexican American	1.15 (.82-1.62)	1.89 (1.22-2.92)	1.71 (.96-3.03)	1.14 (.72-1.82)	1.95 (.77-4.91)	2.91 (1.19-7.12)
Other Hispanic	1.33 (.80-2.25)	1.68 (1.06-2.66)	.98 (.53- 1.83)	.93 (.59-1.47)	2.89 (1.26-6.63)	2.54 (.86-7.46)
NH-White	1.42 (1.13-1.80)	1.56 (1.24-1.96)	1.78 (1.38-2.29)	1.06 (.86-1.30)	1.70 (1.12-2.58)	1.79 (1.11-2.89)
NH-Black	1.97 (1.37-2.81)	1.60 (1.05-2.45)	1.82 (1.32-2.52)	1.62 (.68-1.98)	.56 (.144-2.16)	1.03 (.509-2.08)

Table 4: Association of kidney stones and presence of other morbidities on odds of having cardiovascular and cerebrovascular disease.

	OR (95% CI) Cardiovascular Disease	OR (95% CI) Stroke
Kidney Stones vs. No Kidney Stone	1.68 (1.16-2.45)	1.68 (1.15-2.45)
Kidney Stones & Obesity vs. Not	2.36 (1.54-3.63)	1.57 (.94-2.61)
Kidney Stones & Hypertension vs. Not	1.85 (1.11-3.08)	2.08 (1.32-3.29)
Kidney Stones & Diabetes vs. Not	3.83 (2.36-6.23)	1.83 (1.04-3.2)

CHAPTER V

DISCUSSION

The purposes of this study were to examine the interrelationships between kidney stones, cardiovascular disease and stroke, as well as various morbidities, such as obesity, hypertension, diabetes, and high cholesterol. Additionally, we were interested in examining potential parameters that may mediate the relationship between kidney stones and cardiovascular disease and stroke.

When comparing those who have had or have kidney stones to those without a history of kidney stones, kidney stone formers had statistically significant increased odds of all of the morbidities, with the exception of elevated cholesterol. Specifically, kidney stone formers had a 49% increased odds of obesity, 63% increased odds of hypertension, 86% increased odds of diabetes, 68% increased odds of cardiovascular disease, and 68% increased odds of stroke. Our cross-sectional analyses did not demonstrate non-Hispanic black kidney stone formers as having an increased odds of all morbidities when compared to the other races, but did demonstrate non-Hispanic Black kidney stone formers as having a 97% increased odds of obesity, 60% increased odds of hypertension, and an 82% increased odds of diabetes. Although our analyses did not demonstrate a strong moderation effect of race-ethnicity (i.e., other race-ethnicity groups were also significant), analyses via Pooled Cohort Equations revealed that non-Hispanic blacks, and no other ethnicity groups, had an increased risk of future cardiovascular disease. Specifically,

non-Hispanic black kidney stone formers had a 2.24 increased odds of having an ASCVD event within the next 10-years when compared to non-Hispanic blacks with no history of a kidney stone.

To our knowledge, this is the first study to comprehensively examine the interrelationships between kidney stones and various morbidities, while considering race-ethnicity specific effects. To date, there have been two meta-analyses that have examined the prospective relationship between kidney stones and cardiovascular disease. Liu et al. (2014) examined six cohort studies and, as supported by each of these six studies, determined that kidney stones conferred a higher risk for myocardial infarction and coronary revascularization.

Cheungasitporn et al. (2014) examined four cohort studies and one cross-sectional study with these studies showing that a history of kidney stones was associated with increased risk of coronary heart disease in females. Both meta-analyses included the prospective study conducted by Ferraro et al. (2013); their results demonstrated a higher risk of developing coronary heart disease in participants with a history of kidney stones after adjusting for high blood pressure, diabetes, elevated cholesterol, and BMI, suggesting that, perhaps, other non-cardiometabolic parameters may be mediating the relationship between kidney stones and future cardiovascular disease. Notably, however, the study by Ferraro and colleagues also reported a higher prevalence of obesity, hypertension, diabetes, and elevated cholesterol in those with kidney stones when compared to those without. Approximately 95% of the population employed in their prospective study identified as being "White", while the remainder of the population identified as "Non-White". Our study found that non-Hispanic White kidney stone formers had higher odds of morbidities, but the odds were not as high as other ethnicity groups, such as Mexican Americans and non-Hispanic Blacks.

When using the Framingham and Systematic Coronary Risk Evaluation equations, Ferraro and colleagues also found a higher 10-year risk of cardiovascular disease for kidney stone formers when compared to non-kidney stone formers. Our study assessed 10-year risk of an ASCVD event using the Pooled Cohort Equations in all ethnicity groups within NHANES; we found that only non-Hispanic black kidney stone formers had a higher ASCVD risk score when compared to non-Hispanic black non kidney stone formers. Taken together, our findings are in partial support of those by Ferraro et al. (2013) by demonstrating an association between kidney stones and various morbidities; however, our findings extend those of Ferraro et al. and other studies by showing that non-Hispanic blacks with kidney stones have an increased 10-year risk of an ASCVD event, as determined using the Pooled Cohort Equations.

Individuals with a history of kidney stones have a 50% chance of developing stones again (Lotan et al., 2012). Approximately 75% of reported kidney stones are composed of calcium/calcium oxalate. Calcium kidney stones have shown to be similar to vascular calcium plaque found in coronary vessels. The observed link that exists between kidney stones, cardiovascular disease, and stroke may be attributed to shared pathophysiological mechanisms. Vascular calcification (i.e. deposition of calcium into the blood vessel structures) occurs when there are abnormally high concentrations of calcium and phosphate, due to insufficient or defective calcification inhibitors (Lomashvili, Garg, Narisawa, Milan, & O'Niel, 2010). Similarly, kidney stones develop when there is an imbalance of crystal promoters and inhibitors (University of Wisconsin-Madison, 2010). Pyrophosphate, a phosphorous oxyanion, is an inhibitor of calcification and crystallization, and is present in both the heart and kidney, respectively. Insufficient or low concentrations of pyrophosphate cause arterial calcification and kidney crystallization (Lomashvili et al., 2010). Therefore those with kidney stones could have a

deficiency of inhibitors (crystal inhibitors include: urine volume, citrate, magnesium, phylate, etc.) from continued development of kidney stones, which would lead to subsequent cardiovascular disease and stroke.

Kidney stones, CVD, and stroke also share pathways such as vascular endothelial injury and endothelial dysfunction (Reiner et al., 2011). Hyperuricemia, or high uric acid levels, have been associated with both kidney stones and cardiovascular disease. Uric acid acts as a proinflammatory agent, ultimately increasing levels of C-reactive protein (CRP). Raised CRP levels are indicative of possible arterial damage and endothelial dysfunction, providing another potential mechanism explaining the kidney stone-CVD relationship as endothelial dysfunction is a major risk factor for CVD (Hadi, Carr, & Suwaidi, 2005). Uric acid also impairs renal nitric oxide levels, which effectively reduces hypertension and renal injury (Zoccali, Maio, Mallamaci, Sesti, & Perticone, 2006), both of which are also contributors to CVD (Weiner et al., 2004).

In addition to chronic kidney stone formation influencing CVD/stroke risk via insufficient inhibitors and endothelial injury, another possible mechanism is shared risk factors of kidney stone formers and those with cardiovascular disease and stroke. Lifestyle factors such as dietary habits, physical activity, and water intake are shared factors that influence development of morbidities, kidney stones, and cardiovascular disease/stroke (AHA, 2015). Individuals with kidney stones tend to have unhealthy profiles, including higher rates of obesity (Siener et al., 2004), higher rates of hypertension (Madore, Stampfer, Rimm, & Curhan, 1998), and diabetes (Taylor et al., 2005). Hypertension is recognized as the single most contributive factor of development of stroke and cardiovascular disease (World Heart Federation, 2015). It is possible that having a kidney stone increases risk of the development of hypertension via alterations in calcium metabolism.

According to the CDC, non-Hispanic Blacks tend to have higher rates of morbidities when compared to other race-ethnicities. A greater disparity is seen in the prevalence of hypertension. Approximately 43% of African American men and 45.7% of African American women have high blood pressure. Other ethnicities, such as Mexican Americans, have 27.8% of men and 28.9% of women with high blood pressure; Caucasians have 33.9% of men and 31.3% of women with high blood pressure (CDC, 2014b). Non-Hispanic blacks are also at least six times more likely to develop kidney complications due to hypertension than their Caucasian counterparts (CDC, 2014b). Currently, there is no definitive explanation of why non-Hispanic blacks in the United States have a higher prevalence of hypertension. Researchers speculate a combination of genetic factors, dietary factors, and environmental factors as possible contributors. According to the "slavery hypertension hypothesis", African Americans have a genetic predisposition for hypertension caused by salt deficiency in African slaves, the distress caused by the slave trade, and slavery conditions in the United States. Due to genetic predisposition, African slaves had an enhanced ability to conserve salts, which provided protection from salt-depletive diseases. Higher rates of hypertension are thus seen in African descendants, who now consume much higher sodium in American foods (Fuchs, 2011). Many find this hypothesis difficult to accept and difficult to refute because there have not been genetic racial differences between U.S. born African descendants and native Africans, when the hypothesis speculates a bottleneck occurred when slaves traveled via Middle Passage. Although researchers argue about the genetic disposition component of the hypothesis, salt sensitivity among African Americans are apparent; intakes of just half a teaspoon can cause a rise in blood pressure as much as five points (Armelagos, 2005). In addition, the chronic stress component of

the hypothesis is considered valid, as many researchers today identify chronic stress as a determinant of health disparities.

Recently, environmental factors, such as the anticipation of racial discrimination or harassment, have also been found to be associated with the hypertension prevalence seen in non-Hispanic blacks in the United States. This hyper-reactivity to stress from vigilance can activate the hypothalamic-pituitary response systems. Repeated activation over periods of time can cause elevated levels of cortisol and adrenocorticotrophic hormone even when the stressor is no longer present, which has been linked to hypertension. Stress also elicits endothelial dysfunction by activation of the sympathetic nervous system (SNS). Repeated activation of the SNS causes damage to tissues, which triggers hypertension (Hall et al., 2012). Hicken, Lee, Morenoff, House, & Williams (2014) found racism related vigilance to be positively associated with hypertension in non-Hispanic blacks, but not in non-Hispanic whites. For every reported increase in vigilance, there was 4% greater odds of hypertension (OR= 1.04; 95% CI=1.00-1.09). A significant association between hypertension and dimensions of discrimination (specifically, lifetime discrimination and greater burden of discrimination) was also found in an all non-Hispanic black prospective study (Sims et al, 2011). When comparing the highest to the lowest level of discrimination, hypertension was 8% to 9% higher amongst non-Hispanic blacks after adjusting for age, gender, and socioeconomic status (PR =1.08; 95% CI = 1.02- 1.15).

According to Hall et al. (2012), the role of renal excretion of water and electrolytes is a major part of blood pressure regulation. The two hormones, renin and aldosterone, both regulate mean arterial pressure by maintaining extracellular volume in the presence of salt. In this renal-body fluid feedback mechanism, renin activates a raise in blood pressure to restore pressure regulation in the kidneys. In cases of increased sodium intake and raised aldosterone levels in

proportion with renin levels, blood pressure becomes unregulated. The continued elevation of aldosterone causes an imbalance of pressure natriuresis, which causes hypertension. Elevated aldosterone levels also result in organ damage and changes in cardiac output. When considering race ethnicity, this hormone abnormality (low renin hypertension) is more prevalent among non-Hispanic blacks, thus possibly explaining differences in hormone regulation and how this regulation impacts mean arterial pressure in non-Hispanic blacks (Rifkin et al., 2014). We found non-Hispanic Black kidney stone formers to have a 60% increased odds of hypertension when compared to non-Hispanic Whites. The relationship that exists between hypertension and kidney stones could be the mechanism that explains why African American kidney stone formers had a higher risk of cardiovascular disease 10 years later.

Another possible mechanism that could explain why a relationship was found between kidney stones and higher risk of an ASCVD event in non-Hispanic blacks could be decreased vitamin D levels seen in non-Hispanic blacks. Vitamin D is a fat soluble vitamin that acts as a regulator of calcium and phosphorus; a risk factor for low vitamin D is darker skin pigmentation (melanin in skin inhibits UV (ultraviolet) penetration; UV penetration (sunlight) activates production of vitamin D). Non-Hispanic blacks are notorious for having vitamin D concentrations below doctor recommendations (between 20-30 ng/ml) (Harris, 2006). Reduced levels of vitamin D are contributive to both kidney stones and fatal cardiovascular consequences. Specifically, low vitamin D elevates calcium levels, which results in both kidney stones and endothelial dysfunction. Because calcium levels are unregulated, the concentration of calcium in the urinary tract increases, which results in calcium stones. Deficient concentrations of vitamin D also induce adhesion molecule expression and inference with endothelial-dependent contractions. Vitamin D receptors, present in cardiac muscle cells, regulate calcium levels in the cell. In mice

experiments, increased free calcium in cardiac muscle cells modified contractibility of the heart, cellular hypertrophy, and heart rate ratio (Nemerovski et al, 2009). Also, vitamin D deficiency is mediated by elevated plasma parathyroid hormone which directly targets endothelial cells (Muscogiuri et. al, 2012). Secondary hyperparathyroidism develops in result of inadequate levels of vitamin D, which directly impacts blood pressure and the contractibility of the heart.

Given our observed findings that those with kidney stones have increased odds of various morbidities, it is important for clinicians to consider introduction of prevention techniques (such as weight management and ways to prevent hypertension) for cardiovascular disease and stroke as a part of their protocol for kidney stone formers in order to prevent future disease. Additionally, biological factors, such as calcium deposition, biomarker screening, and management of other morbidities should be introduced to kidney stone patients in order to prevent chronic disease. Clinicians should also consider potential race-ethnicity effects among their kidney stone patients, as, for example, non-Hispanic blacks with a history of kidney stones had an increased predicted risk for a future ASCVD event.

Major strengths of this study include the utilization of a national sample and the comprehensive assessment of the interrelationships between kidney stones, morbidity, and future risk of an ASCVD event. However, despite these strengths, notable limitations included the inability to determine the type of stone and how long participants' had a history of kidney stones. Further, another limitation was the cross-sectional design employed in NHANES, rendering temporal sequence not possible. In an attempt to overcome this limitation, we utilized the Pooled Cohort Equations to predict future risk of an ASCVD event, which were developed from multiple prospective investigations (Goff et al., 2013; Kandula et al., 2014; Muntner et al., 2014; Park et al., 2014).

In conclusion, we observed a relatively strong association between kidney stones and various morbidities, including hypertension and self-report history of cardiovascular disease and stroke, with these observations not appearing to be moderated by race-ethnicity. However, when utilizing the Pooled Cohort Equations that were derived from prospective investigations to predict 10-yr risk of a future ASCVD event, kidney stones was only associated with future risk among non-Hispanic black kidney stone formers. In order to confirm our findings, future prospective studies examining the association of kidney stones with cardiovascular disease and stroke with broader race-ethnicity categories and age ranges are warranted.

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EDUCATION

M.S., Health Promotion, University of Mississippi, to be awarded August 2015
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RESEARCH EXPERIENCE

Research Assistant, 2014-2015
University of Mississippi,
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Department of Health, Exercise, and Recreation Management, University of Mississippi

Graduate School Fellowship, 2013-2015
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PUBLICATIONS and PRESENTATIIONS

Glover, L. Bass, M., Carither, T., & Loprinzi, P. (2015). Association of Kidney Stones with 10-Year Predicted Risk of an Atherosclerotic Cardiovascular Disease Event among Adults in the United States: Considerations by Race-Ethnicity. (In Progress)