

**THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND KIDNEY  
FUNCTION/CHRONIC KIDNEY DISEASE**

by

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# **THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND KIDNEY FUNCTION/CHRONIC KIDNEY DISEASE**

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**INTRODUCTION:** Chronic kidney disease is a serious public health concern because of the large physical and economic burden on society. Because of this large burden, it is important to determine what factors are associated with the development and progression of the disease, especially in early stages. Physical activity has been shown to be related to many risk factors for CKD; however, few studies have assessed its direct relationship with kidney function.

**METHODS:** Using data from NHANES, a nationally representative U.S., we described physical activity by various intensities, gender and race/ethnicity (paper 1). We then investigated the cross-sectional relationship between varying intensities of objectively assessed physical activity and kidney function in the same population (paper 2). Using data from the Strong Heart Study, an American Indian cohort at high risk for CKD, we investigated the relationship between subjectively assessed physical activity with kidney function prospectively (paper 3). **RESULTS:**

We showed that Mexican Americans were more physically active than whites and blacks at all levels of intensity, in contrast to findings using questionnaires. We also confirmed that light intensity activity made the largest contribution to total movement. In paper 2, we showed that objectively assessed light intensity physical activity was independently associated with kidney function while objectively and subjectively assessed moderate to vigorous physical activity was not. In paper 3 we showed that physical inactivity was associated with rapid declines and kidney

function over a five year period. Physical inactivity was also associated with development of kidney damage over a ten year period. **PUBLIC HEALTH SIGNIFICANCE:** The results of these three papers show that physical activity of various intensities are related to kidney function and that physical activity may also preserve kidney function over time in a high risk population. Previous recommendations for physical activity and health were unable to discuss the benefits of physical activity on kidney function because the paucity of evidence. This study is of public health significance because it adds to the growing body of evidence for which we can base our future recommendations.

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## 1.0 INTRODUCTION

Chronic kidney disease (CKD) is the progressive deterioration of renal function eventually leading to renal failure, also called End Stage Renal Disease (ESRD). CKD is of immense public health concern and expected to become a bigger problem in the coming decades. There are a number of reasons that CKD is an important public health concern: 1) the high prevalence of the disease 2) the disproportionate burden on certain age and ethnic groups 3) the high risk for adverse health outcomes 4) and the high economic cost. Despite these factors, CKD awareness and prevention efforts remain low in the US [1].

It is important to consider the number of people affected by this condition. Worldwide prevalence of CKD ranges from 4-16% in adults greater than 18 years of age [2-8]. A study of the US population using the National Health and Nutrition Examination Survey (NHANES) estimates that from 1999-2004, approximately 17% of adults greater than 20 years of age had CKD [9]. This was an increase of approximately 16% compared to NHANES data from 1988-1994. While the vast majority of individuals with CKD are in early stages of renal disease, the final stage of CKD is also growing in prevalence. In 2000, there were approximately 400,000 people with ESRD in the United States which is double the number of cases reported in 1991[10]. By 2030, the estimated prevalence of ESRD is projected to reach over 2 million people [11-13].

While the prevalence of CKD can be seen across all racial/ethnic and age groups the burden of the disease is not distributed equally across these groups. The prevalence of CKD is greater in older adults with approximately 40% of individuals greater than 65 years of age having CKD in the United States and internationally [2]. Similarly, ethnic minorities also experience a higher burden of CKD compared to non-Hispanic whites [9]. It has been reported that ethnic minorities represents half of the total ESRD population [10, 14].

Although improvements in survival have been seen in recent years, individuals with CKD are still at high risk for early mortality. Only 35% of the individuals on dialysis, a treatment for ESRD, can expect to live 5 years [15]. Currently, the Centers for Disease Control and Prevention (CDC) lists kidney disease as the ninth leading cause of death in the United States [16]. The mortality rates for CKD are likely higher considering it increases the risk of death from other causes. Individuals with ESRD experience a 10 to 30 fold increase risk of death from cardiovascular events such as coronary heart failure, myocardial infarction, and stroke compared to the general population [17]. Non-fatal cardiovascular events are also common in this population [18]. The National Kidney Foundation Task Force has recommended that individuals with CKD be regarded as having the highest risk for CVD [19, 20]. According to the United States Renal Data Systems (USRDS), patients with CKD have a 2 to 4 fold higher rates of stroke compared to the non-CKD population [21].

In addition to the physical toll that CKD places on individuals there is also a large economic cost associated with the disease. According to the USRDS, spending in 2006 on patients with ESRD reached \$23 billion which represented 6.4% of total Medicare spending despite the fact patients with ESRD represents only 1% of the Medicare population [21]. The cost of care for individuals with ESRD may reach 6 times the cost of an individual without

ESRD [22]. A population based study in Germany also indicated that the 10-year cost of CKD and its associated morbidities was 65% higher for individuals with CKD compared to individuals without CKD [23]. With the projected prevalence of ESRD expected to reach 2 million in the next two decades, the growing cost could represent a major problem to our economic and health care systems [13]. More effort needs to be directed at identifying individuals at early stages of the disease and identifying factors which can slow its progression.

It's worth restating that CKD is an enormous public health problem but the development of CKD is not inevitable and its rate of progression is highly variable. Studies have reported annual declines in GFR ranging from 2- 20 mL/min in patients with diabetic nephropathy [24-26]. The variability in the rate of CKD progression is what makes it important to identify all potentially modifiable factors for which intervention efforts can then be focused. There have been numerous intervention efforts which have focused on treating hypertension pharmacologically which have proven to be effective at reducing CKD outcomes [27-29]. In addition, obesity is another modifiable risk factor which has shown to be independently related to CKD [30-32]. Intervention efforts aimed at weight loss have proven to be effective at reducing albuminuria, systolic blood pressure, and preventing further decline in renal function [33]. Most of these studies however, focused on diet or surgical treatments to obesity with few including physical activity as part of a lifestyle approach [33]. The role of physical activity in reducing the risk of CKD has not yet been determined. Further investigation is needed to examine the effects of activity on the progression of the CKD.

## 1.1 PHYSICAL ACTIVITY AND CHRONIC KIDNEY DISEASE

Physical activity has been shown to have a positive effect on many chronic conditions such as cardiovascular disease and diabetes [34]. A survey of nephrologists at the World Congress on Nephrology also indicated a widespread belief that a sedentary lifestyle is an important risk factor in individuals with CKD [35]. Increasing levels of physical activity and reducing levels of inactivity continue to be two of our nation's health goals, as documented by Healthy People 2010 [36]. Despite this, physical activity levels are low in the general population and especially among individuals with CKD [37].

Population based studies of the US population have shown that individuals with CKD are less active than the general population [38]. A study by Stengel et al examined cross-sectional data from NHANES II and showed that physically inactive individuals had over twice the prevalence of CKD compared to very active individuals [39]. Studies internationally have found similar results, identifying low levels of physical activity among individuals with decreased renal function [40]. In patients with ESRD, physical activity levels may also be low due to the fact that their capacity for exercise may be reduced. In the Wave 2 of the Dialysis Morbidity and Mortality Study, less than half of the study participants on dialysis engaged in physical activities more than once per week and 75% reported limitations in their ability to engage in vigorous physical activity [41]. These reported limitations in their exercise capacity were associated with an increase risk for mortality in this population [42, 43]. Studies have also indicated that having a reduced capacity for exercise contributes to diminished health related quality of life [23, 44]. Even though exercise capacity is diminished in individuals with ESRD, it's important to note that exercise training has been shown to improve aerobic capacity, physical function, and health related quality of life in these individuals [45-49].

There is also some evidence to suggest that physical activity can be effective at preventing the development of CKD. The benefits of physical activity in preserving renal health may be related to its effect on important risk factors for CKD. Physical activity, along with dietary changes and weight loss, has been shown to prevent and or delay the onset of many chronic conditions such as diabetes, the leading cause of CKD [50]. In addition to preventing the development of diabetes in high risk individuals, physical activity may help individuals to better manage their diabetes through glucose control which is important for preventing diabetic complications such as CKD [51]. Blood pressure control is also key, especially among individuals with diabetes, in preventing CKD development and progression [52]. Physical activity has also been shown to reduce blood pressure, especially in individuals with hypertension [53]. Other potentially important factors in preventing CKD progression such as, improving lipid profiles and reducing levels of inflammation, may be achieved through increasing physical activity [54, 55].

While there is a lot of evidence supporting the relationship between physical activity and risk factors for CKD, few studies in humans have looked at the association between physical activity and markers of renal function. Animal models have provided biological plausibility for the relationship between physical activity and CKD. Several studies have shown that moderate physical activity reduces renal injury and slows the progression of CKD in rats [56-58]. Few studies have explored the relationship between physical activity and renal function in humans. The AusDiab study found that physical activity was associated with albuminuria (a marker for renal damage) at baseline but failed to find a longitudinal association between physical activity and estimated glomerular filtration rate (eGFR) over the five years of study follow-up [59]. In

contrast, results from the Cardiovascular Health Study (CHS) indicated that physical inactivity was associated with faster declines in renal function during follow-up [60].

One of the major limitations of the AusDiab and the CHS was the lack of racial diversity. Ethnic minorities experience a higher burden of CKD, and studies which examined the association between moderate activity and renal function in high risk minority populations are scarce [61]. In the current effort, we hope to add to the literature by examining the association between physical activity and CKD in two racially diverse populations (NHANES and SHS).

In addition to having a better understanding about the relationship between CKD and physical activity in minority populations, there needs to be a better understanding about the specific intensity levels required to affect renal function. In other words, must the activity be performed at a moderate to vigorous level or is light physical activity also important? Results from the AusDiab study using accelerometry have shown that light intensity physical activity is related to 2-hour fasting plasma glucose and overall metabolic risk (cluster of variables related to metabolic syndrome: HDL cholesterol, triglycerides, systolic and diastolic blood pressure, waist circumference, and fasting plasma glucose) independent of activities of moderate intensity [62, 63]. Due to the fact that metabolic risk factors are associated with CKD, it is possible that light physical activity may also be related to CKD [64]. Using data from NHANES which has incorporated accelerometers as part of their physical activity assessment, we will address questions about the level of intensity needed to effect renal function.

## 1.2 STUDY GOALS

The aim of this dissertation is to examine the relationship between subjectively and objectively assessed physical activity with CKD/renal function in both a nationally representative and a high risk minority population. Specifically we plan to use accelerometers to objectively assess physical activity, which have the ability to measure a range of intensities of physical activity. In manuscript 1 we plan to describe objectively measured physical activity by race/ethnicity and gender in a nationally representative sample (NHANES). We will then examine the association between the various intensities of physical activity and renal function in the same nationally representative sample (manuscript 2). In addition to examining the cross sectional relationship between physical activity and renal function in a nationally representative sample, we will also examine the longitudinal effects of physical activity on renal function in a high risk minority population. Using data from the Strong Heart Study (SHS), a study of 13 American Indian tribes from 3 geographical locations, we will assess the association between baseline levels of physical activity and the 10 year incident CKD (manuscript 3). Specific aims for each manuscript will be described in more detail below.

1. Describe various intensity levels of physical activity objectively by race/ethnicity and gender in a nationally representative sample (Manuscript 1).

Previous examinations using physical activity questionnaires have revealed low levels of physical activity especially among ethnic minorities such as black and Mexican Americans. Total physical activity which is most largely composed of activities of lower intensity, and unstructured activity may be relatively more important metabolically. To address questions related to total physical activity, an objective measure of physical activity

is needed as the ability to assess light physical activity by questionnaire is limited. Using data from the 2003-2004 NHANES study cycle, we will describe all intensities of physical activity (light, moderate to vigorous, total) and sedentary activities by race/ethnicity and gender. This will provide the background for additional investigations examining intensity of activity in NHANES and renal function.

2. Examine the association between objectively assessed physical activity and renal function in a nationally representative sample (manuscript 2).

To date, all of the studies examining the association between physical activity and renal function have used subjective questionnaires. As mentioned above, questionnaires have the ability to accurately assess activities of moderate to vigorous intensity but are limited in their ability to assess activities of lower intensity. The accelerometer has the ability to also capture light intensity physical activity which allows it to measure “total” physical activity (the combination of light and moderate to vigorous activity) better than the questionnaire. This analysis will examine the association between activities of light intensity, moderate to vigorous physical activity, and total physical activity, which is combination of both light and moderate to vigorous activity, with renal function in a nationally representative population. It is hypothesized that higher amounts of total physical activity (light and moderate to vigorous physical activity) are associated with higher renal function. In addition, higher amounts of sedentary activity will be associated with lower renal function.

3. To determine the association between subjectively assessed physical activity with the development of CKD in American Indians. Using data from the SHS, we will assess the association between baseline levels of subjectively assessed physical activity and the 10 year incidences of CKD. We will also examine the association between baseline (subjectively assessed) physical activity with change in renal function over the same time frame (manuscript 3).

Few studies have examined the association between physical activity and CKD or renal function prospectively. Even fewer have examined this association in minority populations such as Native Americans where risk of CKD development is high. The SHS is a longitudinal study of 13 American Indian tribes from three locations (Phoenix, Oklahoma, North and South Dakota) which was designed to examine cardiovascular morbidity, mortality and CVD risk factors. The SHS assessed physical activity subjectively with the Modifiable Activity Questionnaire and collected measures of renal function during examination visits (**Examination I**: 1989-1991; **Examination II**: 1993-1995; **Examination III**: 1998-1999, respectively). It is hypothesized that higher levels of baseline physical activity will be associated with lower odds of developing renal disease. Higher levels of baseline physical activity will also be associated with a slower decline in renal function.

### 1.3 PUBLIC HEALTH SIGNIFICANCE

Chronic kidney disease is of serious public health concern because of the large burden on society both physically and economically [65]. Because of the large burden of the disease, it is important to determine what factors are associated with CKD and renal function at early stages

of the disease. The benefits of physical activity to renal health have been demonstrated in a few studies but there are still questions which remain unanswered. One of the unanswered questions is related to the longitudinal effects of physical activity on renal function. The few studies which have sought to address this question in humans have revealed conflicting results [59, 60]. As the benefits of physical activity for preserving renal function are unproven, further examination is warranted. There are also few studies which have examined the association between physical activity and CKD in high risk minority groups. This current effort will examine this relationship in a minority group noted as being at high risk for developing CKD.

In addition to having a better understanding about the relationship between CKD and physical activity in minority populations, there needs to be a better understanding about the intensity level required to effect renal function. As a result of the incorporation of accelerometers to assess physical activity in NHANES, we are now able to measure activities of lower intensity and unstructured activities. This addition to the activity assessment in NHANES will allow us to examine the total volume of physical activity. It is likely that total physical activity, which is a combination of light and moderate to vigorous activity, is more related to renal function than moderate to vigorous physical activity alone. This current effort will describe all intensities of physical activity objectively in a nationally representative population and examine their association with renal function. This will provide us with more insight on how physical activity relates to CKD.

## **2.0 CHAPTER 2**

### **2.1 OVERVIEW OF RENAL FUNCTION**

The human body carries out an important process of breaking down material to be utilized for energy, maintaining cell structure, as well as other important functions. In this process of metabolism, waste products are generated that need to be removed from the body. The kidneys are two bean shaped organs located in the middle of the back just below the rib cage whose major function is to remove these wastes from the body. The kidney has other important functions which help to maintain chemical balance in the body through the secretion and degradation of enzymes and hormones, as well as regulating the body's fluid volume and electrolyte balance. The kidneys are involved with the secretion of erythropoietin and calcitriol (1,25 OH vitamin D), which has important functions in red blood cell formation and bone health [66]. The kidneys also have an important function for regulating blood pressure by secreting renin which activates the renin-angiotensin system (RAS). The body's fluid volume is regulated by controlling the amount of water and sodium that are excreted in the urine. The regulation of fluid volume and electrolyte balance (e.g. potassium and magnesium levels) have important implications for a number of the body's functions including, blood pressure, cardiac output, and cell membrane potentials and excitability.

The kidneys are highly vascular organs receiving 20% of resting blood volume. As plasma flows through and is filtered by the kidney, the rate of plasma clearance over a unit of time (glomerular filtration rate or GFR) can be used to assess kidney function [67]. In normal kidneys, the GFR is between 90-130 mL/min/1.73m<sup>2</sup>. After the age of 40, GFR decreases by approximately 8 mL/min/1.73m<sup>2</sup> a decade [68]. There are also other factors such as diabetes and hypertension which can hasten this decline in GFR that will be discussed in more detail later.

The functional units of the kidneys where filtration actually occurs are called nephrons. Each kidney has about one million nephrons, more than what the body needs to sustain normal filtration. The overall GFR is the sum of all of the single nephron GFR's. The nephrons consist of a glomerulus where filtration occurs and tubules, which play a role in secretion and reabsorption of molecules. The size/structure and ionic charge of the glomerular basement membrane help to control the filtration of water and smaller molecules and provides a barrier against filtration of larger molecules. If a larger molecule such as albumin is able to pass through this barrier, it may indicate a loss in the charge and/or size selectivity barrier. Not only can changes in filtration result from changes in membrane permeability it can also be the result of changes in pressure in the glomerulus. The pressure is controlled by constriction or dilation of the afferent and efferent arterioles. As nephrons become non-functional by disease, the response is to increase the pressure in the remaining nephrons. While this helps preserve overall GFR, in the long-term the increase in pressure leads to damage of the remaining nephrons. This contributes to progression of kidney disease [69].

As stated earlier, glomerular filtration is one of the key functions of the kidney and assessing the rate of that filtration has important clinical implications. Glomerular filtration rate can either be measured directly or indirectly by measuring the level of markers present in either

the urine or blood. Key to measuring GFR is the choosing of a marker that is not reabsorbed or secreted by the kidney, can pass through the glomerular membranes freely, and is not metabolized by the kidney. Inulin has all of these properties and is regarded as the ideal marker to directly measure GFR [70, 71]. Direct measures of inulin clearance involve continuous intravenous infusion of inulin which is then collected in the urine through bladder catheterization. This method is not practical in clinical or research settings which prompted other measures to be developed. Other widely used markers include  $^{125}\text{I}$ -iothalamate,  $^{99\text{m}}\text{Tc}$ -diethylenetriaminepenta-acetic acid, and  $^{51}\text{Cr}$ -ehylenediaminetetra-acid, which can be detected in the urine or blood to get a measure of GFR.

There are also indirect ways to estimate GFR that may be less accurate but more feasible in research and/or clinical settings. Measures of serum creatinine levels can be used to estimate GFR through the use of simple formulas. The formulas are necessary to account for differences in creatinine generation, due to differences in muscle mass. The Modification of Diet in Renal Disease study developed such an equation to estimate GFR:

$$\text{eGFR} = 186.3 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age}^{-0.203} (\times 0.742 \text{ for women}) (\times 1.21 \text{ for Non-Hispanic Black}) [72]$$

Another equation by Cockcroft-Gault estimates creatinine clearance with the following formula:

$$\text{Cc} = [(140 - \text{age}) \times \text{weight (kg)} (\times 0.85 \text{ if female}) / (72 / \text{serum creatinine})][73]$$

These equations are widely used because of their relative ease and inexpensiveness. Despite their popularity in clinical settings the use of creatinine based measures to assess renal

function is not without its shortcomings. For one, it's not the ideal marker because it is both filtered by the glomeruli and secreted by the renal tubules. Creatinine is also produced by muscles thus apparent changes in GFR may be more of a reflection changes in of muscle mass in some individuals. Despite its shortcomings, using a clearance creatinine based formula to estimate GFR is the most widely used clinical tool and has shown to be valid in those with renal impairment and may be useful in assessing renal function over time in these individual [72, 74, 75].

While no ideal endogenous markers of renal function have been identified, there are other markers of renal function, namely cystatin C, which are being investigated. Cystatin C is a non-glycosylated 13 kDa protein which is produced at a constant rate by all cells in the body [76]. Since cystatin C production is not dependent on muscle mass or diet, many suggest it may be a better estimator of GFR than creatinine [77]. While, the results from some studies have shown that cystatin C is more accurate at determining renal dysfunction than creatinine, other studies have shown no difference between the two measures. While cystatin C has been shown to be a better predictor of mortality than creatinine, there still are some questions as to whether it is relatively better at classifying CKD [78, 79]. As more studies are needed to determine the benefits of using cystatin C versus creatinine, some researcher have suggested that it is better to use both measures in equations to estimate GFR rather than either alone [80].

## **2.2 CHRONIC KIDNEY DISEASE**

The assessment of glomerular filtration is of immense importance because any deterioration in the kidney's ability to perform filtration and other vital functions can have serious consequences.

Deterioration of kidney function is generally the result of damage to the nephrons, the functional units of the kidney. Acute damage to the kidney can result from a variety of cause including immune disease, genetic disorders, infection, as well as trauma caused by injury or the use of some medications. The most common causes of renal deterioration are hypertension and diabetes, both of which will be discussed in more detail later in the literature review. While some of these causes can be acute, chronic kidney disease occurs through gradual deterioration in function.

The National Kidney Foundation has a classification system which indicates the stages of chronic kidney disease (see Table 2.1):

**Table 2.1 Chronic kidney disease classification**

	Glomerular Filtration Rate (mL/min/1.73 m <sup>2</sup> )	Description
Normal	>90	High risk (diabetes, hypertension, old age, positive family history, or a member of a high risk ethnic group)
Stage 1	>90 with evidence of kidney damage	Evidence of kidney damage (protein in urine)
Stage 2	60 – 89 with evidence of kidney damage	Kidney damage and mild decrease in renal function
Stage 3	30 – 60	Moderate decrease in renal function
Stage 4	15-29	Severe decrease in renal function
Stage 5	<15 or dialysis	Kidney Failure

Normal renal function is defined as having a GFR >90 mL/min/1.73 m<sup>2</sup> with no evidence of renal damage (albuminuria to creatinine ratio (ACR) <30 mg/g, no other urinary or radiologic evidence of renal damage). You may be considered at risk for CKD if you have other risk factors including diabetes, hypertension, older age, positive family history, or if you are a member of a high risk ethnic group. Stage 1 CKD is defined as having a GFR between 90-130

mL/min/1.73 m<sup>2</sup> + evidence of renal damage (A/C ratio >30 mg/g, most commonly). Stage 2 CKD is defined as having a GFR between 60-89 mL/min/1.73 m<sup>2</sup> with evidence of renal damage. Stage 3 CKD is defined as having a GFR between 30-60 mL/min/1.73 m<sup>2</sup>. Stage 3 can also be broken down further into early (3a) and late (3b) sub-categories [81]: Stage 3a CKD is defined as having a GFR between 46-59 mL/min/1.73 m<sup>2</sup> and Stage 3b is defined as having a GFR between 30 - 45 mL/min/1.73 m<sup>2</sup>. Stage 4 CKD is a severe decrease in kidney function defined as having a GFR between 15-29 mL/min/1.73m<sup>2</sup>. Stage 5 CKD is also called renal failure and is defined as having a GFR below 15 mL/min/1.73m<sup>2</sup>. If renal function falls to this level, the body needs help to keep up with the body's filtration needs which comes in the form of dialysis or transplant.

### **2.3 MARKERS OF RENAL DAMAGE**

As indicated by the National Kidney Foundation classification system, proteinuria is an early marker for renal damage even when GFR is normal. The size selective properties of the kidney prevent larger molecules, such as proteins, from being filtered through the glomeruli. Excess protein in the urine is a marker of deterioration of this size selective barrier. In normal adults, less than 130 mg of protein per day is found in urine [82]. Urinary protein levels above 130 mg/day can be both a marker and a progression promoter. Proteinuria can also promote CKD progression by stimulating protein reabsorption, which has pro-inflammatory and fibrogenic effects. Proteinuria also stimulates the activation of the local renin angiotensin systems (RAS) which can lead to increases in glomerular pressure [83].

Albumin is commonly used as a clinical manifestation of renal damage. Albumin excretion can either be determined in a timed urinary specimen (e.g. 12 or 24 hrs) or in a spot

urine collection. If the latter is used, the albumin is expressed per gram urinary creatinine to adjust for differences in urine concentration. Microalbuminuria is defined as an ACR between 30-300 mg/day (or 30-300 mg/g creatinine). An ACR value above 300 mg/day is the definition of macroalbuminuria. Studies have shown that albuminuria can serve as an early predictor of renal and cardiovascular events in individuals with diabetes, hypertension, and the general public [84-86]. This is of concern considering the high prevalence of albuminuria both in the US and worldwide, especially in individuals at high risk for CKD development. The Third National Health and Nutrition Examination survey study indicated that 28% of US adults with diabetes and 16% of individuals with hypertension had microalbuminuria compared to only 5.1% in healthy adults [87]. Microalbuminuria was also highly prevalent in older adults documented in nearly 20% of males and females over the age of 60, a group at increased risk for CKD.

Reducing albuminuria is a proposed target to decrease cardiovascular and renal outcomes [88, 89]. The Ramipril Efficacy in Nephropathy (REIN) study showed that high levels of proteinuria at baseline was associated with faster progression of CKD and subsequent reduction slowed the progression to ESRD in patients with non-diabetic nephropathy [90]. A study by Araki et al demonstrated the beneficial effects of reducing urinary albumin in individuals with diabetes by controlling for traditional risk factors (blood pressure, glucose, etc.). In this study, a reduction of albuminuria by 50% resulted in a decrease in renal or cardiovascular events by nearly 60% [91]. Additional studies have confirmed the clinical importance of reducing albuminuria, mainly using pharmacological treatments directed at the renin-angiotensin system. Whether reducing albuminuria by other measures translates into decreased progression of kidney disease is not yet proven. Lifestyle approaches such as increasing physical activity may potentially be effective in reducing urinary albumin.

## 2.4 RISK FACTORS/CAUSE OF CKD

### 2.4.1 Diabetes

Diabetes is the leading cause of chronic kidney disease and ESRD. CKD is present in 40% of individuals with a history of diabetes compared to 15% of individuals with no history of diabetes [10]. The United States Renal Data Systems also indicates that diabetes currently accounts for nearly half of the ESRD cases [21]. Studies have also shown that the progression of diabetic nephropathy is faster than non-diabetic nephropathy [92]. The course of CKD progression is similar among type 1 and type 2 diabetes patients, however, individuals with type 2 diabetes have traditionally been more likely to die of CVD prior to ESRD [92, 93]. With the worldwide prevalence of diabetes expected to reach well over 400 million by 2030, diabetic nephropathy is a major public health concern [94].

Although having diabetes puts individuals at increased risk for CKD development, it's important to note that not everyone who has diabetes develops diabetic nephropathy. Diabetic nephropathy develops in 35-40 % of individuals with type 1 and type 2 diabetes and the progression of the disease is also highly variable [95, 96]. Studies have reported annual declines in GFR ranging from 2- 20 mL/min [24-26]. Several factors are related to this varied development and progression of diabetic nephropathy that have been observed.

Blood pressure control has been identified as one of the key factors associated with development and faster progression of diabetic nephropathy [97]. A study by Hovid et al showed that the annual decline in renal function was more than double the rate in individuals with hypertension compared to individuals who were normotensive. The study also showed that achieving blood pressure control through anti-hypertensive treatment slowed the progression of

renal decline [98]. In addition to strict blood pressure control, tight glucose control has been identified as an important factor in the development of diabetic nephropathy [51, 99]. The Diabetes Control and Complications Trial and Epidemiology of Diabetes of Interventions and Complications (DCCT/EDIC) study showed that intensive glucose control decreased the risk of cardiovascular disease and lowered the risk for retinopathy and nephropathy in individuals with type 1 diabetes [100]. The benefit of glucose control in individuals with type 2 diabetes is less clear. Some studies have found that intensity of glucose control provided no extra benefit in reducing cardiovascular outcomes [101]. In the Steno-2 study, treatment of hypertension and dyslipidemia were found to be more important than glucose control in individuals with type 2 diabetes [102]. The data on later stages of kidney disease are still sparse and future studies are needed to investigate the benefits of glucose control in individuals with type 2 diabetes.

#### **2.4.2 Hypertension**

Hypertension is the second leading cause of CKD. Data from NHANES have shown that 16% of adults in the United States with hypertension have CKD compared to 5.1% of normotensive adults. Blood pressure control in individuals with CKD is often poor [103]. A study by Plantinga et al showed that 70% of individuals with CKD from 1999-2006 in the United States have uncontrolled blood pressures [104]. These numbers are alarming considering the strong evidence that poor blood pressure control is associated with rapid progression of the disease [105, 106]. Even marginal increases in blood pressure can result in worse outcome for individuals with CKD. A study by Hsu et al showed that even among those with pre-hypertension (systolic blood pressure of 130 to 139 mm Hg and diastolic blood pressure <90 mm Hg or diastolic blood pressure of 85 to 89 mm Hg and systolic blood pressure <140 mm Hg),

there was a near two fold increase in risk of ESRD development compared to those with normal blood pressure[107]. A study by Bakris et al also showed that every increase of 10 mmHg in baseline systolic blood pressure resulted in an increase risk of ESRD or death by 6.7% [29]. With the increasing risk for adverse outcomes being experienced with changes in blood pressure, even in the “normal” range, hypertensive therapy is of utmost importance in CKD management.

Recognizing the importance of aggressive treatment of hypertension in patients with CKD, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has recommended blood pressure goals of 130/80 mmHg. Pharmacological therapies such as angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocks (ARB) have been used to treat hypertension [108]. Several studies have shown that anti-hypertensive therapy slows the progression of kidney disease [109, 110]. The benefit of blood pressure reduction may be especially important in individuals who are obese. A 20-year follow-up study in Norway showed that obese individuals with pre-hypertension had nearly three times the risk for adverse outcomes compared to individuals with normal blood pressure. There was no increase risk for adverse events in individuals who were not obese [111]. Blood pressure treatments through ACE inhibitors or ARB’s have the added benefit of reducing proteinuria in addition to lower blood pressure [106] [112].

### **2.4.3 Race/ethnicity**

Ethnic minorities carry a disproportionate burden of CKD and the progression to ESRD. In 2004, it was reported that African Americans have the highest incidence of ESRD, which develops at a rate five times that of whites [113]. Although African Americans on dialysis may have a survival advantage over to whites on dialysis, they are more likely to die at earlier stages

of the disease compared to whites [114]. Other ethnic minorities including American Indians, Alaskan Natives, Asians, Pacific Islanders, and Hispanic also experience disparities in the prevalence of CKD [115, 116]. African Americans, Native Americans, and Asian/Pacific Islanders make up 29.6%, 1.6%, and 3.2% of the ESRD population despite making up smaller percentages of the general population [117, 118]. There has been an increasing disparity in the incidence of ESRD in African Americans compared to whites over the last twenty five years. A disparity in ESRD incidence is also seen in American Indians compared to white, however, that disparity has been decreasing in recent years.

One possible explanation for the decreasing incidence of ESRD in American Indians may be better diabetes management [14, 119]. Another explanation may be that American Indians are experiencing an increase in another chronic disease, such as heart disease that may be occurring prior to developing ESRD. Analysis of data from the Strong Heart Study by Howard et al. has shown that rates of coronary heart disease was nearly twice as high in American Indian participations of the SHS compared to individuals from a cohort of white and black participants (Atherosclerosis Risk in Communities Study) [120]. A report for the CDC in 2001 indicated that 36% of all deaths from heart disease in American Indians in the US were pre-mature (<65 years of age) [121]. Lastly, there may be an increase in the number of individuals self-reporting American Indian as their ethnicity in the later years which may bias the sample, making them their risk appear more similar to whites .

Addressing the ethnic disparities of CKD was an objective of Healthy People 2010 and will likely continue to be a goal in the future. Reasons for the disparities in CKD are multi-factorial including social, biological, and institutional factors.

One factor which is likely responsible for the excess prevalence of CKD in minority populations is the higher prevalence of diabetes in those minority groups. The prevalence of diabetes is nearly two times higher among African American, Mexican American, and Native Americans compared to whites (CDC). Management of diabetes in minority populations is also poor, which leads to a higher frequency of diabetic complications including CKD. Studies have indicated that minorities are more likely to have uncontrolled blood pressure and poorly controlled glucose levels compared to whites [103, 122-126]. Reasons for poor diabetes management and subsequent complications in minorities may be related to socio-economic and educational factors [127, 128]. There may also be some biological factors which influence the progression of diabetic nephropathy. A study by Goldschmid indicated that African Americans have a higher prevalence of microalbuminuria within 1 year of diabetes diagnosis independent of glucose control [129].

Hypertension, the second leading cause of ESRD, is also more prevalent in African Americans compared to whites. While lifestyle factors are important, increased salt sensitivity in African Americans may be an important biological factor [130]. Studies have shown that increases in salt intake raises blood pressure more in African Americans compared to whites [130]. The results of the DASH study indicated a greater drop in blood pressure with sodium restriction in African Americans [131].

In addition to the biological factors which lead to disparities of CKD, there are also social/behavioral factors which come into play. CKD progresses silently in early stages and there is a general lack of awareness both worldwide as well as in minority communities. The Jackson Heart Study was an observational study of African Americans in three Mississippi communities which assessed kidney disease through eGFR and the presence of albuminuria. The

study documented that only 16% of the individuals with CKD were aware of their condition. Even among those in stages 4-5 CKD, awareness was only around 65%, which was lower than their awareness of diabetes or hypertension [132]. A study by Waterman et al conducted a study of African Americans in 7 states across the United States and showed that over 40% of the sampled population had CKD, but less than 3% viewed it as a top concern [133]. The lack of concern and awareness about CKD may lead to African Americans missing opportunities for detection and subsequent medical intervention at earlier stages of the disease.

Lifestyle factors such as obesity and physical inactivity also influence disparities of CKD among ethnic minorities. There are higher rates of obesity among ethnic minorities, particularly African American females and Native Americans compared to whites. Also, among African American females and Native Americans, self reported physical inactivity has consistently been high in national surveillance studies.

#### **2.4.4 Age**

Normal renal function in adults is typically around  $125 \text{ mL/min/1.73m}^2$ . As we age, glomerular filtration steadily decreases. After the age of 40, GFR decreases about  $8 \text{ mL/min/1.73m}^2$  a decade. This perpetual decline in GFR places older adults at greater risk for CKD development [134-136]. The prevalence of CKD is greater in older adults with approximately 40% of individuals >65 years of age having CKD in the United States. These results are consistent with rates of CKD in older adults around the world. Older adults with CKD experience an increase risk for morbidity and mortality (USRDS). With the aging of our population, CKD will continue to pose a problem.

### **2.4.5 Gender**

Many studies have indicated that male gender is associated with faster progression of renal disease. Males, more frequently than females, develop ESRD at all ages [10]. The MDRD study also showed that males have more rapid decline of GFR than females, which was explained by higher urinary protein excretion, mean arterial pressure, and HDL cholesterol at baseline [137]. Other studies have indicated that genetic differences between males and females may explain the differences in renal outcomes. In individuals with diabetes, females have been shown to have better renal endothelial function than males, which may influence progression of diabetic nephropathy [138]. In animal models, male mesangial cells produced greater pro-inflammatory activity compared to females [139].

### **2.4.6 Dyslipidemia**

Individuals with CKD are at increased risk for adverse CVD outcomes. Part of that increased risk may be due to the high prevalence of traditional risk factors for CVD, such as dyslipidemia. An abnormal lipid profile including elevated triglycerides, low density LDL particles, very low density lipoproteins (VLDL), and low levels of HDL cholesterol, is both a promoter of and consequence of CKD [140]. Secondary dyslipidemia in CKD patients is the result of abnormalities in key proteins that regulate lipid metabolism [141]. The reduced expression of lipoprotein lipase by skeletal muscle and adipose tissue leads in reduced plasma clearance of VLDL and chylomicrons which results in elevated triglyceride levels[142]. There is also increased synthesis and decreased catabolism of LDL by the liver when CKD is accompanied by albuminuria [143, 144]. Increased oxidative stress and inflammation are also consequences of

abnormal lipid levels leading to damage to endothelial cells, increased atherosclerosis, and faster progression of the CKD [145]. The use of statins may not only reduce lipid levels, but may also reduce inflammation and slow progression of the CKD.

It is important to note that the lipid profile of a CKD patient will vary depending on the stage of the disease and level of proteinuria. In individuals without proteinuria, LDL is typically normal or mildly elevated. There is an increase in triglycerides and decrease in HDL. In proteinuric patients, LDL levels can be very high. Reverse epidemiology between total cholesterol and mortality has been documented in dialysis patients. Multiple observational studies have shown that in patients on dialysis, those with hypocholesterolemia (<100 mg/dl) had an increase risk of mortality compared to individuals with high cholesterol (200 – 250 mg/dl) [146, 147]. Hypocholesterolemia in dialysis patients may be a marker for inflammation since the hypocholesterolemia is associated with elevated levels of C-Reactive Protein (CRP) and in the subset of individuals on dialysis who do not have markers of inflammation, the usual pattern of elevated cholesterol being associated with mortality is seen [148].

#### **2.4.7 Smoking**

Smoking status is a known risk factor for CKD. A study by Hallan et al showed that current smokers had a relative risk of 1.52 for having CKD in the NHANES population [40]. A study by Shankar et al showed that former and current smokers had a 1.12 and 1.97 odds of developing CKD over those who never smoked [149]. This risk was increased 5 fold in those with heavy alcohol consumption. Smoking has also been shown to be a significant predictor of advanced stage CKD. In a study by Yamagata et al, current smokers had a 1.13 and 1.16 higher risk of

developing CKD (Stage 3 or higher) compared to non-smokers in men and women respectively [150].

#### **2.4.8 Nutrition**

Dietary factors such as reducing the intake of salt, alcohol, and animal proteins may be important for preserving renal health. Salt intake may be directly and indirectly linked to renal function. Indirectly, salt intake has been shown to be related to hypertension [151]. The DASH Sodium trial showed that reducing sodium intake decreased blood pressure in individuals with and without hypertension. A few studies have also highlighted direct links between salt intake and renal health [152, 153]. In animal models, high salt diets lead to increased renal fibrosis in normotensive and hypertensive rats [154].

Alcohol intake may be another important dietary factor for preserving renal health. While moderate alcohol consumption may have beneficial effects, such as increased HDL cholesterol, excessive alcohol intake may lead to renal damage. The AusDiab study reported an increase risk for albuminuria in individuals who self reported heavy alcohol consumption during the five years of study follow-up [155]. In addition, alcohol intake is a potent risk factor for hypertension.

In individuals with pre-dialysis CKD, reducing animal protein intake may slow the progression of CKD. The MDRD study examined the effects of a two-three year protein restricted diet and the risk of developing renal failure or all cause mortality. After six years of follow-up there was no benefit of protein restriction. A significant limitation of the study was the lack of dietary information during follow-up. A meta-analysis by Pedrini et al examined the relationship between dietary protein intake and renal function in diabetic and non-diabetic CKD

[156]. In individuals with non-diabetic CKD, a low protein diet was associated with a reduced risk for renal failure and death compared to individuals with a normal protein diet. In individuals with diabetic CKD, a low protein diet was associated with a reduced risk for renal function declines.

#### **2.4.9 Other**

Other causes of kidney disease include inflammation, genetic disorders, auto-immune disease, kidney obstructions, and birth defects. Glomerulonephritis is a group of disease that cause inflammation and is the third most common cause of CKD. Chronic inflammation can also be caused by repeated urinary tract infections. Genetic diseases such as polycystic kidney disease also cause damage to the kidney by the formation of large cysts. These cysts cause an increase in renal volume eventually leading to renal failure.

### 3.0 CHAPTER 3

#### 3.1 PHYSICAL ACTIVITY IN EPIDEMIOLOGICAL STUDIES

Physical activity is any bodily movement that results in energy expenditure, which encompasses structured planned movements such as exercise as well as unstructured movements [157]. Physical activity occurs in four major domains: leisure, occupational, household, and transportation. The various domains and types of physical activity add to the complexity of activity assessment, especially in the free living environment [158].

There are also many dimensions of physical activity including frequency, duration and intensity which further complicates activity assessment. *Frequency* is a measure of how often physical activities are performed over specific time frames (e.g. how many times per month?). *Duration* of physical activity refers to the amount of time spent in a bout of an activity each time it is performed (minutes, hours, days, etc.). *Intensity* of physical activity refers to the level of effort or physiological demand that an activity requires [159]. In many epidemiological studies, metabolic equivalents (METs) are used to express activities as intensity weighted values (1 MET = resting metabolic rate). Light activities, such as sitting or standing, have a MET level of less than three. Activities of moderate intensity, such as brisk walking, are said to have a MET value between three and six. Vigorous physical activities, such as running, have a MET of six or

greater. Physical activity can occur along a spectrum of intensities which have important implications for which assessment tool is most appropriate (Figure 1).

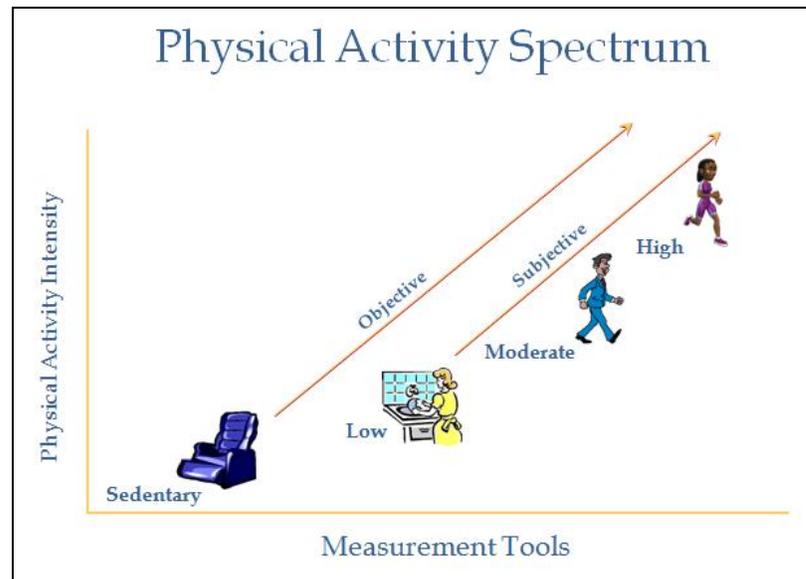


Figure 3-1 Physical activity spectrum

### 3.1.1 Subjective Assessment

Subjective measures are the most frequently used method of assessing physical activity in free-living individuals. Subjective methods can include physical activity records or logs, which require individuals to record every activity done over a predetermined period of observation. However, these methods are utilized less frequently in large populations and community-based studies due to the high associated staff and participant burden with completing and calculating summary estimates. As such, physical activity questionnaires will likely continue to be the primary method used to estimate physical activity levels in research studies due to their low cost and relative ease of administration.

Physical activity questionnaires vary in their complexity, physical activity domain (e.g., leisure, occupational, transportation, activities of daily living), recall time frame (e.g., past 24-hours, week, month, year), mode of administration (i.e., interviewer- vs. self-administered), and characteristics of the targeted population (i.e., older adults, women, children). Physical activity questionnaires may also vary by study design, with some developed to use for surveillance while others are sensitive to behavior change for use in intervention studies. Understanding the intended use and psychometric properties (i.e., test-retest reliability, validity, and sensitivity) of a physical activity questionnaire will help researchers identify which questionnaire is most appropriate for the study population being investigated. Further use of an appropriate measure will improve the overall precision of the physical activity estimate and enhance the ability to establish significant relationships between physical activity and the health-related outcomes of interest. It is important to note that failure to account for the psychometric properties of a physical activity questionnaire may increase the risk of non-differential misclassification which can weaken or eliminate association between physical activity and health outcomes.

Questionnaires vary in their complexity from a single global question about general physical activity level (i.e., low, moderate, and high activity) to activity-specific questionnaires that inquire about physical activity done over an individual's lifetime. A simple questionnaire such as the Lipid Research Clinics physical activity questionnaire is one example of a global measure. With global questionnaires, participants are asked questions such as, "Thinking about the things you do at work, how would you rate yourself as to the amount of physical activity you get compared with others of your age and sex?" Global queries such as these can be used to crudely group individuals by their activity or inactivity status. On the other end of the complexity spectrum, activity-specific questionnaires or historical questionnaires such as the

Historical version of the Modifiable Activity Questionnaire (MAQ) ask about participation (i.e., frequency and duration) in leisure activities over specific periods during an individual's lifetime.

In general, physical activity can be classified into one of four domains (i.e., leisure, occupation, transportation, and household activities). Thus, physical activity questionnaires may differ in the types of activities they try to capture. Since it is imperative to capture accurate information on the types of activities that elicit the greatest energy expenditure in the targeted population, you need to find a physical activity questionnaire that measures all key domains.

One study which highlights the importance of assessing all of the key domains of physical activity was a study by Kriska et al. which examined the association between physical activity, assessed with the modifiable activity questionnaire (MAQ), and serum insulin levels in two different populations (Pima Indians in Arizona and individuals from the island nation of Mauritius). The MAQ assesses activities during leisure and occupation. For Arizona Pima Indians, the majority of their physical activity was accumulated during leisure while individuals in Mauritius accumulated over 90% of their activity from occupational activities [160]. If the MAQ had not assessed leisure time physical activity, it's likely the results of study would not have impacted in Pima Indian data. However, failure to assess occupation activity in individuals from Mauritius would have missed most of the activity performed in this population.

While questionnaires accurately measure activities of moderate- to vigorous- intensity, they are less accurate with light intensity activities, such as light cleaning. Many researchers only measure physical activity during leisure because there tends to be little between person variation in occupation, transportation, and household activities. However, the assumption of homogeneity of activity outside of leisure (occupation, transportation, and household) may not be valid in all populations, with Mauritius as a good example of this.

Questionnaires also vary in the time frame of interest ranging from past day to participation in physical activity across the lifespan. Short term questionnaires which ask about activity performed in the past week or day provide a good estimate of an individual's current activity level; however, they may also be subject to issues of seasonality and changes in health status. Physical activity questionnaires that utilize a shorter recall time frame may also be repeated a number of times throughout the year to provide an estimate of physical activity done over a longer period of time (i.e., four measures spaced three months apart would provide an estimate of physical activity done over the past year). Physical activity questionnaires may also ask questions about participation in activity in the past year or lifetime to provide a more general estimate of one's physical activity level. The estimates generated from these physical activity questionnaires may relate better with chronic conditions (i.e., obesity, cardiovascular disease, type 2 diabetes mellitus) which may take many years to develop.

As stated previously, physical activities can occur along a spectrum of intensity. Questionnaires may ask participants about the activities they perform and then compare those activities to a standardized intensity scoring compendium. Compendiums of physical activity intensity have been published which code various activities by their respective intensity level [161]. Light activities, such as sitting or standing, have a MET level of less than three. Activities of moderate intensity, such as brisk walking, are said to have a MET value between three and six. Vigorous physical activities, such as running, have a MET of six or greater. Since questionnaires are more accurate at assessing activities at the higher end of the physical activity intensity spectrum, many avoid querying activities at the lower end of the intensity spectrum. There are a few questionnaires however, which do attempt to assess activities of low intensity

[162, 163]. It is unlikely that the inclusion of low intensity activities improves physical activity assessment in questionnaires [164].

Questionnaires may be either self- or interviewer-administered. Interview-administered questionnaires such as the MAQ require an interviewer to go through the questionnaires with the participant. It is important to train interviewers on the proper method of administering interviewer-administered questionnaires to improve the precision of the physical activity estimate. Self-administered questionnaires are completed by the participant and can either be done in-person (i.e., Women's Health Initiative Physical Activity Questionnaire) or administered via the mail (i.e., Nurses' Health Study Physical Activity Questionnaire) [165]. If using a self-administered questionnaire it is important for the study staff to review the physical activity questionnaire (PAQ) thoroughly to make sure all items are completed properly.

The population of interest may also be an important question when deciding which questionnaire to use. Questionnaires may be designed for specific ages, gender, ethnicities, and disease. There are specific questionnaires designed for elderly populations, such as the Yale Physical Activity Survey, which ask questions about the physical activities that are most commonly performed by older adults (e.g., walking, gardening) [166, 167]. It is important to take these population characteristics into account in order to select the most appropriate assessment tool that has been shown to be valid and reliable in that particular population. A questionnaire that was developed for use in one population or setting (i.e., surveillance vs. intervention) may not be appropriate to use in another.

### 3.1.2 Objective Assessment

Physical activity assessed objectively addresses some of the short-comings of subjective assessment. One of the main advantages of objective assessment is that it doesn't rely on recall which may be a source of bias in subjective assessment [159]. Some objective measures of physical activity also perform better at assessing components of physical activity which are not accurately assessed by questionnaires such as activities which occur at the lower end of the intensity spectrum or activities which are spontaneous/unstructured [168]. There are a variety of objective assessment tools available including pedometers and accelerometers which are described in more detail elsewhere [159]. Accelerometers are objective measures of physical activity which are frequently used to assess free living physical activity [169]. Physical activity was assessed via accelerometer in both manuscript 1 and manuscript 2 and will be described below in more detail.

Accelerometers are movement monitors that have the ability to not only capture movement, but also the intensity of that movement in one or more planes [170]. They are typically attached to a person's waist with a belt clip; however, some monitors can also be worn on the back, wrist, ankle, or even a shoe [171]. Although there is no one true "gold standard", accelerometers are considered to be one of the best available methods for assessing free living physical activity levels and are often used to validate the much simpler, less expensive pedometer and physical activity questionnaires [172].

Accelerometers operate by measuring acceleration along a given axis, using a number of technologies including piezo-electric, micro-mechanical springs, and changes in capacitance [173]. Multiple axis measurements can also be bundled into a single monitor, allowing movement in multiple planes to be captured. The major function of accelerometers is that the

sensor converts movements into electrical signals (counts) that are proportional to the muscular force producing motion [174]. These counts are summed over a specified period of time (epoch) and stored.

Intensity of physical activity has most often been determined by comparing the counts accumulated during various activities to measured oxygen consumption. Regression equations are then used to develop prediction equations to calculate intensity specific count cut points. These cut points represent a range of accelerometer counts which correspond to light, moderate, and vigorous physical activity. Figure 2 provides an example of the metabolic cost of various activities and the counts associated with that metabolic cost from a calibration study by Freedson et al [174]. Using the Freedson established cut points, activities of light (1-3 METs), moderate (3-6 METs), and vigorous intensity (>6 METs) are associated with cut points of 100-1951, 1952-5723, and greater than 5724 respectively.



**Figure 3-2 Accelerometer Cut Points**

Although accelerometers have shown promise for assessing physical activity in free living conditions, they are not without their limitations. Accelerometers were design to assess simple ambulatory activities such as walking and running. One of the major limitations of accelerometers, when worn on the hip, is their limited ability to accurately assess more complex lifestyle oriented movement such as those using the upper extremities [168]. The narrow ability to assess more complex movements limit the accelerometers ability to measure activities that may be common in many individuals' daily lives. As result, there are a variety of intensity cut points derived from various calibration studies which differ on the range of activity intensity (light, moderate, and vigorous) as well as the types of physical activities (lifestyle oriented activity, walking, running, etc.) used to develop prediction equations [174-178]. Results from

these various calibration studies reveal the need to develop regression equations from a full spectrum of physical activity intensity from a variety of activities [168]. Accelerometers are also unable to measure activities such as swimming, and underestimate energy expenditure in activities such as weight lifting and cycling. One remedy may be to have participants complete an activity log during times the monitor is not worn, such as swimming, or when performing activities such as cycling or weight lifting. Correction equations may then be used to adjust the accelerometer data [168].

## **4.0 CHAPTER 4**

### **4.1 PHYSICAL ACTIVITY AND CHRONIC KIDNEY DISEASE**

Physical activity has been shown to prevent and/or delay the onset of many chronic conditions such as diabetes and cardiovascular disease. The vast amount of evidence for the benefits of a healthy lifestyle was discussed in the 1996 Surgeon General's Report on Physical Activity and Health which recommended that all adults should achieve at least 150 minutes of physical activity per week [179]. Since this report, increasing levels of physical activity and reducing levels of inactivity continue to be health goals for our nation, as documented by Healthy People 2010 [36].

Despite these national goals and recommendations, physical activity levels are still low for many Americans, placing them at risk for developing chronic disease such as CKD and subsequent complications for the disease. A survey of nephrologists at the 2003 World Congress of Nephrology indicated that 95% of the nephrologists surveyed believe that a sedentary lifestyle was an important risk factor in individuals with CKD [35]. Individuals with ESRD especially, are at greater risk for diminished functional capacity and quality of life when leading a sedentary lifestyle [43, 180]. In the Wave 2 of the Dialysis Morbidity and Mortality Study, less than half of the study participants on dialysis engaged in physical activities more than once per week and 75% reported limitations in their ability to engage in vigorous physical activity [41]. These

reported limitations in their exercise capacity were associated with an increase risk for mortality in this population [42, 43]. Even though exercise capacity is diminished in individuals with ESRD, it's important to note that exercise training has been shown to improve aerobic capacity, physical function, and health related quality of life in these individuals [45-49, 181].

The benefits of physical activity go beyond improving physical function in individuals with ESRD. There is also some evidence to suggest that physical activity can also be effective at preventing the development of CKD [153]. The benefits of physical activity in preserving renal health may be related to physical activity's affect on important risk factors for CKD. Physical activity, along with dietary changes and weight loss, has been shown to prevent and or delay the onset of many chronic conditions such as diabetes, the leading cause of CKD [50]. In addition to preventing the development of diabetes in high risk individuals, physical activity may help individuals with diabetes better manage their diabetes through improved glucose control which is important for preventing diabetic complications such as CKD [51]. Blood pressure control is also key, especially among individuals with diabetes, in preventing CKD development and progression [52]. Physical activity has been shown to reduce blood pressure, especially in individuals with hypertension [53, 182, 183]. Improving lipid profiles and reducing levels of inflammation are also potentially important factors in preventing CKD progression, and may be beneficially impacted upon by physical activity [54, 55, 184].

#### **4.1.1 Physical Activity and Diabetes**

Diabetes is the leading cause of CKD and ESRD. The increased risk for CKD and other macrovascular and microvascular complications that diabetes imposes has prompted many health care professionals to investigate ways to prevent diabetes development. In addition to preventing

the development of diabetes in individuals at high risk, proper diabetes management is crucial for preventing complications of the disease. Lifestyle approaches which include increasing physical activity levels have been used in both the prevention of diabetes development as well as proper management of the disease.

There have been numerous studies which documented the benefits of lifestyle modifications, which includes physical activity, for preventing and/or delaying the onset of diabetes in high risk individuals. One of the first studies to show the benefits of lifestyle on reducing diabetes risk was the Malmo feasibility study which examined the effects of physical activity and diet on the risk of type 2 diabetes development in nearly 7000 males aged 47-49 from Malmo, Sweden. After six years of follow-up, the accumulated diabetes incidence was 10.6% and 28.6% in the intervention and control group respectively [185]. Although the major limitation of the study is that individuals were not randomly assigned to their intervention groups, it did support a beneficial role of lifestyle on diabetes prevention.

Since the Malmo trial, numerous other studies have shown the effectiveness of lifestyle in preventing diabetes development. One of the most successful trials, the US Diabetes Prevention Program (DPP), also examined the association between lifestyle (diet, exercise, and weight loss) and diabetes development in individuals at high risk for diabetes. Compared to the control group, the lifestyle arm of the intervention resulted in a 58% reduction in diabetes incidence [186]. The study also showed that achieving the lifestyle goals reduced diabetes risk across all gender, age, and racial groups regardless of BMI. While the study wasn't powered to test the association between physical activity and diabetes risk independently, it is important to note that among individuals who didn't meet their weight loss goal, those who did meet their physical activity goal had a 44% lower risk of diabetes development [187].

In individuals who have already converted to diabetes, lifestyle modifications may be no less important because of their potential to reduce the risk for subsequent complications [188]. The importance of metabolic control (glycemic control and insulin sensitivity) for reducing the risk for diabetes complications has been demonstrated in numerous studies of both type 1 and type 2 diabetes patients [189-192]. Participating in regular physical activity may be one strategy for improving metabolic control [193]. A meta-analysis of clinical controlled trials by Boule et al examined the association between exercise and glycemic control in type 2 diabetes patients. The analysis included 14 trials with interventions ranging between eight and fifty two weeks. The exercise interventions ranged from 3-6 days per week with an average duration of 52 minutes. The analysis indicated a 0.66% reduction in HbA<sub>1c</sub> levels from baseline in the intervention group versus the controls ( $p < 0.01$ ) [194]. A more recent meta-analysis examining the association between exercise and glycemic control in type 2 diabetes patients by Thomas et al produced similar results showing a reduction of 0.6% in HbA<sub>1c</sub> from baseline in the intervention versus the control group [195]. Both of these meta-analysis showed that the results were independent of weight loss.

#### **4.1.2 Physical Activity and Blood Pressure**

Hypertension is the second leading cause of CKD and is often a comorbid condition in patients with diabetes. The prevalence of hypertension in individuals with diabetes is as high as 60% and the co-occurrence of these two conditions are associated with faster progression of CKD [182, 196]. In addition to metabolic control, reducing hypertension is critical for reducing the risk of CKD development and progression among individuals with diabetes [197]. Even among individuals without hypertension, high normal blood pressures (systolic 130-139 mm Hg or

diastolic 85-89 mm Hg) are associated with an increased risk for cardiovascular events in individuals with or without CKD [198, 199]. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends an aggressive goal for blood pressure control (systolic <130 mm Hg and diastolic <85 mm Hg) in individuals with diabetes and other high risk groups [200].

Effective treatment of hypertension, most often pharmacologically, is associated with slowing the progression of CKD [95, 98]. In addition to pharmacological treatments, physical activity is recognized as an effective treatment of hypertension by the American College of Sports Medicine and the American Heart Association [200-203]. A meta-analysis of 53 randomized controlled trials showed that increasing physical activity levels was associated with an approximate decrease in systolic blood pressure of 4 mm Hg [204]. The blood pressure lowering effects of physical activity was highest among individuals with hypertension and in African Americans (5 mm Hg and 11 mm Hg respectively). A more recent meta-analysis confirmed these results indicating that physical activity can lead to reductions in systolic blood pressure of 3 mm Hg, with a greater effect in hypertensive individuals (-6.9 mm Hg) [205]. Few studies however have examined the effects of physical activity on lowering blood pressure in individuals with diabetes [182]. One study of patients with type 2 diabetes by Schneider et al. did show that one year of moderately intense exercise, three to four days per week, had a blood pressure lowering effect [206].

The results of these studies demonstrate the benefits of exercise in reducing blood pressure, especially in individuals with hypertension. Regular participation in physical activities, along with appropriate pharmaceutical treatments, should be a part of a strategy to slow the progression and occurrence of CKD.

### 4.1.3 Physical Activity and Lipids

Individuals with CKD have abnormal lipid profiles which may be cause and consequence of the disease [207]. The most common manifestations of lipid abnormalities are elevated triglycerides and lipoprotein (a), and reduced HDL cholesterol levels. Results from both animal and human studies have shown that elevated triglycerides and reduced HDL cholesterol levels are associated with faster progression of CKD [208, 209]. Although most of the studies in humans have been small, meta-analysis has documented the benefits of reducing lipid levels on renal outcomes. Reducing lipid levels slows the decline in GFR and decreases proteinuria, as document by a meta-analysis by Fried et al [210]. A nother meta-analysis by Sandhu similarly showed that reducing lipids slowed the progression of CKD and reduced proteinuria, however, the results were not significant in individuals with diabetic or hypertensive nephropathy [211].

While statin therapy has been shown to be effective in reducing lipid levels, lifestyle modification may also have therapeutic benefits. Numerous studies have indicated that exercise can improve both triglyceride and HDL levels. Improvement in triglycerides and HDL are more pronounced in individuals with elevated baseline lines but also documented in individuals with low levels [212, 213]. While exercise can affect triglyceride and HDL levels acutely, chronic exercise, lasting at least 12 weeks, is what is most often required to induce improvements in these factors [214-216]. A study by Goldberg et al showed that twelve months of endurance training led to a 23% reduction in triglycerides and a 21% increase in HDL cholesterol levels in hemodialysis patients [217]. A study of non-dialysis CKD patients showed that cardiac rehabilitation programming, which included exercise, led to reductions in triglycerides, total and LDL cholesterol levels [45]. Overall, the literature supports the idea that chronic physical

activity can cause reductions in triglyceride levels between 4-37% and increases in HDL can between 4-18% [184].

The relationship between kidney function with total cholesterol and LDL cholesterol is more complex. In both hemodialysis and non-dialysis CKD, LDL levels may be within the normal the range [218]. However, when protein is present in the urine, LDL and total cholesterol levels may be elevated [218]. The relationship between total cholesterol, LDL, and physical activity is also less clear. Some studies have shown that no relationship exist between physical activity and total cholesterol, however, a few studies have shown an inverse relationship [219-221]. The relationship between physical activity and total cholesterol may be mediated by weight loss [222]. There have also been conflicting reports on the effects of physical activity on LDL, which also may be mediated by weight loss [184, 223, 224].

#### **4.1.4 Physical Activity and Inflammation**

Cytokines may be classified as either pro- or anti-inflammatory, both of which having important roles in vascular health [225]. Under conditions of chronic disease such as CKD, there is often an imbalance in the circulating levels of cytokines, with pro-inflammatory cytokines levels being greater. This imbalance that is seen in individuals with CKD leads to faster progression of the disease, increased cardiovascular risk, and early mortality [226, 227]. Reducing the levels of inflammation has been shown to preserve renal function [226, 228, 229].

Physical activity may affect inflammation by both increasing the levels anti-inflammatory cytokines and reducing the levels of pro-inflammatory cytokines. A study of 28 patients with coronary heart disease by Goldhammer et al, showed that 12 weeks of high intensity aerobic training reduced levels of pro-inflammatory cytokines and increased levels of anti-inflammatory

cytokines [230]. A study by Smith et al showed similar results in patients at high risk for developing heart disease. In this study, individuals received a six month tailored exercise program. Overall, pro-inflammatory cytokines (CRP, TNF- $\alpha$ , IL-6, and interferon gamma) decreased by 58% and anti-inflammatory cytokines (IL-10, IL-4, and TGF- $\beta$ 1) increased by 35% [231]. The Finnish Diabetes Prevention Program examined the effects of the individual components of the lifestyle modification (diet, weight loss, physical activity) on CRP and IL-6. Leisure time physical activity of moderate intensity was related to reductions in both CRP and IL-6 independent of BMI [232]. While few studies examined the association between physical activity and inflammation in patients with CKD, the Progressive Exercise for Anabolism in Kidney Disease documented a decrease in CRP levels after 12 weeks of resistance training in patients on hemodialysis [233].

#### **4.1.5 Physical Activity and Albuminuria**

In addition to being related to risk factors for CKD, physical activity is also related to markers of renal damage such as albuminuria. Acutely, physical activity can cause an increase in albumin in the urine and is associated with the intensity of the activity [234]. This increase in albuminuria after intense physical activity is believed to have no long term consequences and albuminuria levels should return to normal with 24 to 48 hours [235]. While physical activity increases albuminuria acutely, long-term engagement in aerobic physical activities of moderate intensity may decrease levels of albuminuria through reduction in endothelial dysfunction [225, 236, 237]. A study of 372 individuals with type 2 diabetes by Calle-Pascual et al showed that albuminuria was prevalent in approximately 60% in individuals whose physical activity energy expenditure was less than 500 kcal/wk compared to only 33% in individuals who accumulated

over 1000 kcal/wk. This negative association between albuminuria and physical activity was independent of blood pressure (systolic and diastolic) and glucose control [238]. The Finnish Diabetic Nephropathy (FinnDiane) study which examined the association between leisure time physical activity and albuminuria similarly found that compared to individuals who were active, inactive individuals had nearly twice the odds of having albuminuria [239].

The association between physical activity and albuminuria is also documented in “healthy” individuals without diabetes. Robinson et al. examined the association between self-reported physical activity and albuminuria in women without diabetes using data from the Nurse’s Health Study I (NHS I) and the Nurse’s Health Study II (NHS II). Even at low levels of albuminuria (<5 mg/d), individuals with the highest level of physical activity had lower levels of albuminuria compared to individuals who self-reported no physical activity [240].

Few studies have examined the effects of physical activity on albuminuria prospectively. Studies in animal models suggest that engaging in moderate intensity physical activity can reduce albuminuria [241]. In human studies however, the results are a little more mixed. The DPP compared the prevalence of albuminuria in three groups (control, metformin, intense lifestyle-diet, physical activity, and weight loss) at baseline and at the study’s end. Prevalence of albuminuria remained unchanged in both the metformin and intense lifestyle intervention groups. Individuals in the control group however, were more likely to have increased albuminuria compared to the two intervention arms which bordered on significance ( $p=0.07$ ) [242]. Another prospective study to examine the association between albuminuria, GFR and physical activity was the Australian Diabetes Study (AusDiab). Individuals who self reported at least 150 minutes of leisure time physical activity were deemed sufficiently active. Compared to the sufficiently active group, individuals who were inactive had a 1.3 odds of having albuminuria at baseline.

Baseline physical activity was not however, associated with incident albuminuria during the five year study follow-up [59]. A study by Lazarevic et al. examined the effects of six months of moderate physical activity on the prevalence of albuminuria in thirty males with diabetes. The intervention consisted of supervised brisk walking on three to five days per week. The intervention successful reduced the prevalence of albuminuria from 20% to 3.3% [243]. The study was limited however by the small sample and lack of control group.

#### **4.1.6 Physical Activity and Renal Function**

The association between physical activity and eGFR has also been assessed in a few epidemiological studies. Data from NHANES was analyzed by Stengel et al. which examined the cross-sectional relationship between subjectively assessed physical activity and the odds having CKD. Individuals were classified as being inactive, moderately active, and very active. The results from the study indicated a graded relationship between level of physical activity and odds of having CKD. Compared to the very active group, individuals who were moderately active or inactive had a 1.2 and 2.2 odds of having CKD [39]. Another analysis of NHANES data by Finkelstein et al. examined the association between physical activity and eGFR (estimated using the Cockcroft Gault equation) in individuals with and without metabolic syndrome [38]. Physical activity was assessed with a PAQ and was analyzed with three separate activity variables: 1) total number of activities performed 2) the number of different types of activities 3) total METs. In individuals without metabolic syndrome, the number of activities performed and total METs were positively associated with eGFR. In individuals with metabolic syndrome, only the number of activities performed was positively associated with eGFR.

Other population based studies have also shown a relationship between physical activity and CKD. The second Health Survey of Nord-Trondelag County (HUNT II) study is a population based study of adults (>20 years of age) in Norway [40]. CKD was defined by having an eGFR <45 mL/min/1.73 m<sup>2</sup> (estimated using the MDRD study equation). Participants self-reported the amount of time spent in light or intensity activities during leisure. Individuals who self-reported no leisure physical activity had more the twice the odds of having CKD compared to individuals who self-reported at least some activity.

#### **4.1.7 Conclusions**

There is a paucity of research which examines the association between physical activity and CKD or renal function in humans. While some of the existing literature does support a relationship between physical activity and renal function, there are still some unanswered questions. The fact that physical activity can occur along a range of intensity levels raises an important question; what levels of intensity of physical activity are related to health outcomes such as renal function? While our national recommendations for physical activity advocate moderate to vigorous intensity activities, do activities of lower intensity benefit renal health? These are questions that current technology allows us to address with the use of an objective measure of physical activity, namely accelerometers. Addressing these questions in future examinations will help guide our future intervention efforts in the CKD populations.

The literature also does not adequately address the relationship between physical activity and renal health in minority populations. Few studies have examined the association between physical activity and CKD in minority groups such as American Indians. Considering the fact that American Indians are twice as likely to development CKD as whites, it is important to

explore the potential benefits of modifiable lifestyle factors such as physical activity in this population. Existing data sets from the Strong Heart Study may allow us to investigate this area further and begin to determine what the potential renal health benefits of physical activity are in diverse populations.

## **5.0 CHAPTER 5**

### **5.1 STUDY OBJECTIVES**

The aim of this dissertation is to examine the relationship between subjectively and objectively assessed physical activity with CKD/renal function in both a nationally representative sample of the US and a high risk minority population. Specific methodology for each manuscript will be described in further detail later. In brief, manuscript 1 will describe physical activity objectively by race/ethnicity and gender in a nationally representative sample. This will provide insight into how active minority populations are in the US and describe how much light, moderate to vigorous and total activity is performed in these groups. This will lead to examination of the association between various intensities of physical activity and renal function in the same nationally representative sample as the focus of manuscript #2. We will then determine the longitudinal effects of physical activity on this condition in a minority population which is at high risk (manuscript #3).

The Strong Heart Study will be used to determine the association between physical activity and CKD/renal function in Native American communities from three geographical locations in the US. Specifically, using data from the Strong Heart Study, we will assess the association between baseline levels of self-reported physical activity and incident CKD during subsequent clinic visits (1989-1991 and 1993-1995). Few studies have examined the association

between physical activity and CKD/renal function prospectively. Even fewer have examined this association in minority populations such as from Native Americans where the risk of CKD development is high.

## **5.2 METHODS**

To examine the objectives which were previously described for this dissertation, two data sets will be used, the National Health and Nutrition Examination Survey (NHANES) and the Strong Heart Study (SHS). Analysis for manuscripts 1 and 2 will both utilize the NHANES data sets from different cycles (manuscript 1:2003-2004, manuscript 2: 2003-2006). NHANES is cross-sectional study on a nationally representative sample of non-institutionalized citizens in the US. Manuscript 3 will be analyzed using the SHS data set. The SHS is a longitudinal study of 13 American Indians tribes from three locations (Phoenix, Oklahoma, North and South Dakota) which was designed to examine cardiovascular morbidity, mortality and CVD risk factors. Specific information about each study population, data collection methods will be described in further detail below.

## **5.3 BRIEF OVERVIEW OF NHANES**

In order to describe physical activity levels in nationally representative population by race/ethnicity and gender (Manuscript 1) and then examine the relationship between these activity levels and renal function (Manuscript 2), the NHANES data set will be used. NHANES

is a cross-sectional observational study conducted by the National Center for Health Statistics of the Centers for Disease Control which began in the early 1960s and was conducted as a series of surveys focusing on different population groups and health topics. In 1999, the survey became a continuous program that had a changing focus on a variety of health outcomes. The continuous NHANES survey over-samples adolescents (12-19 years of age), persons greater than or equal to 60 years of age, African Americans, Mexican Americans, and individuals with low income so that nationally representative estimates of the civilian non-institutionalized population can be generated [244]. Previous NHANES cycles also over-sampled from specific subgroups depending on the public health trends at the time.

The NHANES continuous survey utilizes a complex random survey design which occurs in four stages (Figure 2). During the first stage, primary sampling units (PSUs) are selected which are, in most cases, counties. The second stage consists of dividing these PSUs into segments (city blocks). From these segments, households are then randomly selected. In the final stage, individuals are randomly selected from each household for inclusion in the survey. Each selected individual is assigned a sample weight which is an estimate of how many people they represent in the general population. That sample weight reflects the unequal probability of being selected as well as adjustments for non-response and other factors. It's important to take into consideration the complex survey design as well as the sampling weights into all analysis of NHANES data. Failure to take the complex design factors into consideration may lead to bias estimates and overstating significance [245].

Data for NHANES is collected by trained clinicians in Mobile Examination Centers which travel to each location across the country. Personal interviews are conducted, in the participant's home, in which demographic, socioeconomic, dietary, and health-related questions

on behaviors such as physical activity are collected. In addition to detailed survey data, trained medical staff collects information on medical, dental, and physiological measurements, as well as laboratory tests (e.g. creatinine, fasting lipids).

### **5.3.1 Measures**

#### **5.3.1.1 Demographics**

Demographic information such as age, race/ethnicity, health status, and education was assessed by questionnaire during the in home interview. Participants were categorized as non-Hispanic white, non-Hispanic black, and Hispanic (including Mexican American and other Hispanic) based on self-report. Age in years was calculated from self-report. Participants over the age of 85 were assigned the age of 85 to protect confidentiality. General health status was self-reported as excellent, very good, good, fair, or poor. Education was determined by questionnaire: “What is the highest grade or level of school you have completed or the highest degree you have received?” Participants were categorized as: “Some college or beyond” or “High school or less”.

#### **5.3.1.2 Physical Activity**

Since the annual NHANES survey started in 1999, a self reported (questionnaire) measure of physical activity has been included in each cycle. The physical activity questionnaire used in NHANES assesses activities of moderate and vigorous intensity performed during the last 30 days from three domains: household, transportation, and leisure. Activities performed for *transportation* was assessed by asking participants if they walked or biked to school, work, or to do errands. To assess *household* activities, participants were asked if they performed any activities of moderate intensity or greater around the home or yard for ten minutes. To assess

activities performed during *leisure*, more detailed information about 47 specific activities of moderate or vigorous intensity was queried (e.g. walking, running, swimming, yoga, tennis, etc). Participants were also asked if they engaged in any muscle strengthening activities such as push-ups or calisthenics. The NHANES physical activity questionnaire also asks participants to report the amount of time spent during sedentary activities (TV watching and computer use).

In the 2003-2004 study cycle, NHANES began to assess physical activity objectively with an accelerometer. Physical activity was assessed with the Actigraph AM-7164 accelerometer (formerly the CSA/MTI AM-7164, manufactured by ActiGraph of Ft. Walton Beach, FL), which is a pager size device powered by a small lithium battery. The accelerometers were attached to an elasticized belt and worn on the right hip. The accelerometer measures the duration and intensity of physical activity by capturing the magnitude of acceleration (intensity) and summing up the magnitudes (intensity counts) within a specified time interval (epoch). We used a one-minute epoch.

Participants were asked to wear the device for seven days while they were awake, and to take it off for swimming or bathing. Monitors were returned by express mail to NHANES, where data were downloaded from the device, and the device was checked to determine whether it was still within the manufacturer's calibration specifications using an Actigraph calibrator.

NHANES used standardized data quality procedures to maximize the accuracy of the accelerometry data, which are described in more detail elsewhere [246]. In brief, participants with at least four days in which the accelerometer was worn for at least 600 minutes are included in analysis. Any block of time greater than or equal to 60 minutes where the activity count was equal to zero was considered time when the monitor was not worn. Based on a previous calibration study by Freedson and colleagues, a minute of accelerometer data was coded as

sedentary if it contained less than 260 activity counts. A minute was coded as light physical activity if it recorded an accelerometer count between 260-1951. A minute was coded as moderate-vigorous intensity if activity counts were greater than or equal to 1952 [174]. Counts derived during minutes of light and moderate-vigorous activity respectively, were individually summed and divided by the number of days worn to calculate daily averages for those specific intensities. Total physical activity was the sum of the counts derived during minutes of light and moderate-vigorous activity.

### **5.3.1.3 Laboratory Data**

Serum creatinine was assessed by the Jaffe rate reaction method. Serum creatinine levels were used to estimate glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) study formula:  $eGFR = 1.86.3 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age}^{-0.203}$  (X 0.742 for women) (X 1.21 for Non-Hispanic Black). Urinary albumin was assessed using a solid-phase fluorescent immunoassay described by Chavers et al [247]. Urinary creatinine was assessed using the Jaffe rate reaction method with a CX3 analyzer. The albumin to creatinine (A/C) ratio was defined with the following equation: urinary albumin/urinary creatinine. Microalbuminuria was defined as having an A/C ratio > 30 mg/g. Renal function was classified into five stages based on the National Kidney Foundation KDOQI guidelines for defining CKD[248]:

- 1) Normal = eGFR between 90 - 130 mL/min/1.73 m<sup>2</sup> with no evidence of renal damage (A/C ratio <30 mg/g);
- 2) Stage 1 = eGFR between 90 - 130 mL/min/1.73 m<sup>2</sup> plus evidence of renal damage (A/C ratio >30 mg/g);

- 3) Stage 2 = eGFR between 60 - 89 mL/min/1.73 m<sup>2</sup> plus evidence of renal damage
- 4) Stage 3 was divided into early (3a) and late (3b) sub-categories [81]
  - a. Stage 3a = eGFR between 46 - 59 mL/min/1.73 m<sup>2</sup>
  - b. Stage 3b = eGFR between 30 - 45 mL/min/1.73 m<sup>2</sup>

Individuals with eGFR <30 mL/min/1.73 m<sup>2</sup> were dropped from the analysis since the disease had progressed into late stages and the objective of the study was to examine the association between physical activity and renal function at early stages of the disease. Remaining individuals were then dichotomized into two groups based on renal function: 1) normal and 2) mild to moderate renal function (CKD stages 1-3b).

To assess serum lipid levels as part of NHANES, blood samples were drawn from individuals over the age of six by trained clinicians in the MEC's. Fasting was not required for all blood draws, however, approximately 1/3 of the participants (those who attended the morning session) were asked to provide a fasting sample. Both total cholesterol and HDL cholesterol was assessed on all participants regardless of fasting status. Total cholesterol was assessed enzymatically and HDL cholesterol was measured using the Roche/Boehringer-Mannheim direct HDL method. Triglycerides were assessed using a timed-end point method only from participants who provided a fasting blood sample. LDL cholesterol was estimated with the following equation: total cholesterol – HDL cholesterol – triglycerides/5, where triglycerides/5 is an estimate of VLDL cholesterol [246].

Fasting glucose was assessed only on those participants who provided a fasting sample. Glucose concentrations was assessed by measuring the concentrations of nicotinamide adenine dinucleotide (NADH) spectrophotometrically at 340 nm. NADH concentrations are directly proportional to glucose concentrations [246]. Fasting glucose levels were used to assess diabetes

status. Individuals with a fasting glucose level above 125 mg/dL , self reported as having diabetes, or self-reported use of insulin were classified as having diabetes [249].

Other laboratory measures included serum cotinine and C-reactive protein (CRP). Serum cotinine was used to assess currently smoking status. Current smoking status was determined as having a serum cotinine greater than 3 ng/mL. CRP was measured to assess systemic inflammation using latex-enhanced nephelometry during the examination visit [246].

#### **5.3.1.4 Anthropometrics**

Weight was measured in pounds on a Toledo digital scale. Weight was then converted into kilograms using standard procedures. Height was measured in centimeters with a vertical ruler. The participants were asked to stand completely straight with their feet flat on the ground. The back of the head was against the vertical board aligned in the Frankfort horizontal plane. Body Mass Index (BMI) was calculated by dividing weight in kilograms by height in meters squared ( $\text{kg}/\text{m}^2$ ). Waist circumference was also used as a measure adiposity. Waist circumference in centimeters was measured across the midaxillary line of the body with the participant asked to breathe quietly [250]. Measured where across the midaxillary line of the body (the midaxillary line is an imaginary line through the axilla parallel to the long axis of the body and midway between its ventral and dorsal surfaces)

#### **5.3.1.5 Blood Pressure**

Systolic and diastolic blood pressures were measured by trained clinicians using standard procedures on the participant's right arm with a mercury sphygmomanometer. A more detailed description of the procedures for measuring blood pressure are available elsewhere [250]. In brief each participant was instructed to sit quietly for five minutes before MEC clinicians

attempted three blood pressures measures. Pulse pressure was determined by taking the difference between systolic and diastolic pressure. Mean arterial pressure (MAP) was calculated with the following formula:  $MAP = \text{diastolic} + \text{pulse pressure}/3$ .

### **5.3.2 Statistical Analysis**

The primary objective and hypothesis for manuscript 1 and manuscript 2 are briefly described below. More detailed analysis plans are described within the context of each paper.

#### **5.3.2.1 Paper #1: Objectively measured physical activity of U.S. adults by sex, age, and racial/ethnic groups: a cross-sectional study**

The purpose of paper #1 was to examine differences in physical activity by sex, age and racial/ethnic groups in a national sample of adults. Specific detailed information about the analysis plan and results can be found in the context of the manuscript, which was published in the International Journal of Behavior Nutrition and Physical Activity in 2009 and is attached in the appendix. The abstract for paper 1 is provided below:

**Background:** Accelerometers were incorporated in the 2003-2004 National Health and Nutritional Examination Survey (NHANES) study cycle for objective assessment of physical activity. This is the first time that objective physical activity data are available on a nationally representative sample of U.S. residents. The use of accelerometers allows researchers to measure total physical activity, including light intensity and unstructured activities, which may be a better predictor health outcomes than structured activity alone. The aim of this study was to examine objectively determined physical activity levels by sex, age and racial/ethnic groups in a national sample of U.S. adults.

**Methods:** Data were obtained from the 2003-2004 NHANES, a cross-sectional study of a complex, multistage probability sample of the U.S. population. Physical activity was assessed with the Actigraph AM-7164 accelerometer for seven days following an examination. 2,688 U.S. adults with valid accelerometer data (i.e. at least four days with at least 10 hours of wear-time) were included in the analysis. Mean daily total physical activity counts, as well as counts accumulated in minutes of light, and moderate-vigorous intensity physical activity are presented by sex across age and racial/ethnic groups. Generalized linear modeling using the log link function was performed to compare physical activity in sex and racial/ethnic groups adjusting for age.

**Results:** Physical activity decreases with age for both men and women across all racial/ethnic groups with men being more active than women, with the exception of Hispanic women. Hispanic women are more active at middle age (40-59 years) compared to younger or older age and not significantly less active than men in middle or older age (i.e. age 40-59 or age 60 and older). Hispanic men accumulate more total and light intensity physical activity counts than their white and black counterparts for all age groups.

**Conclusion:** Physical activity levels measured objectively by accelerometer demonstrated that Hispanic men are, in general, more active than their white and black counterparts. This appears to be in contrast to self-reported physical activity previously reported in the literature and identifies the need to use objective measures in situations where the contribution of light intensity and/or unstructured physical activity cannot be assumed homogenous across the populations of interest.

### **5.3.2.2 Paper #2: The association between physical activity and renal function: NHANES**

The purpose of this study is to determine the association between time spent at all levels of physical activity intensity (light, moderate to vigorous, total, and sedentary) and renal function in a nationally representative population. Specific detailed information about the analysis plan and results can be found in the context of the manuscript, which was submitted to Medicine and Science and Sport and Exercise in August 2010, and is also attached in the appendix. The abstract for manuscript 2 is provided below:

**Background:** Chronic kidney disease (CKD) is a condition characterized by the deterioration of renal function which can lead to end stage renal disease (ESRD). Previous studies have shown that physical activity may have renal benefits. One question that remains is what intensity of physical activity is related to these beneficial effects. The purpose of this study is to determine the association between time spent at all levels of physical activity (light, moderate to vigorous, total, and sedentary) and renal function in a nationally representative population.

**Methods:** Data were obtained from the 2003-2004 and 2005-2006 NHANES, a cross-sectional study of a complex, multistage probability sample of the U.S. population. Physical activity was assessed with the Actigraph AM-7164 accelerometer for seven days following an examination. A minute of accelerometer data was coded as either sedentary (counts <100), light (counts between 100-1952), or moderate to vigorous (counts >1952). Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) study formula. To assess linear associations between levels of physical activity and sedentary activity with log transformed eGFR, linear regression was used.

**Results:** In general, physical activity (light and total) was related to log eGFR in females and males. For females, the association between light and total physical activity with log eGFR was consistent regardless of diabetes status. For males, the association between light and total physical activity and log eGFR was only significant in males without diabetes.

**Conclusions:** To the author's knowledge, this was the first study to examine the association between physical activity, measured objectively with an accelerometer, and eGFR. The results of our analysis indicate that total and light physical activities are positively associated with log eGFR.

### **5.3.2.3 Paper #3: The Association between Physical Activity and Chronic Kidney Disease in Native Americans: Strong Heart Study**

The purpose of this paper is to determine the association between subjectively assessed physical activity and the development of CKD in American Indians. Using data from the Strong Heart Study, we will assess the association between baseline levels of subjectively assessed physical activity and the 10 year incidences of CKD. We will also examine the association between baseline (subjectively assessed) physical activity with change in renal function over the same time frame. The background and proposed analysis for this effort is presented in more detail in Chapter 6.

## 6.0 CHAPTER 6

### 6.1 BRIEF OVERVIEW OF THE STRONG HEART STUDY

The SHS was the largest epidemiologic study of cardiovascular disease and its risk factors among American Indian men and women. The SHS was designed to estimate cardiovascular disease mortality and morbidity and the prevalence of known and suspected cardiovascular disease risk factors in American Indians and to assess the significance of these risk factors in a longitudinal analysis. The study included thirteen American Indian tribes and communities in three geographic areas: 1) an area near Phoenix, Arizona (*Gila River and Salt River Pima/Maricopa, and Akchin Pima/Papago*), 2) the southwestern area of Oklahoma (*Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa and Wichita*), and 3) western and central North and South Dakota (*Oglala Sioux, Cheyenne River Sioux, and Spirit Lake Communities*). The SHS assessed physical activity subjectively with the Modifiable Activity Questionnaire at baseline and collected measures of renal function during all three examination visits.

In its initial stages, the SHS included three components. The first was a survey to determine cardiovascular disease mortality rates from 1984 to 1994. Individuals were eligible for the study if they lived in one of the tribal areas for at least six months and were between the ages of 45-74 during the two year examination cycle. Participants were recruited through a local tribal population list and community advertisements. SHS was able to collect clinical

examinations of 4,549 tribal members between the ages of 45-74 (62% of the total population in age group).

A follow-up of the original cohort was performed between 1993 and 1995 to gather more information about cardiovascular disease risk factors in American Indians. The SHS re-examined 89% of the surviving members of the original cohort. A second follow-up was performed between 1998 and 1999 where 88% of the surviving cohort was re-examined. The purpose of this manuscript is to examine the association between baseline physical activity and the development of CKD during these two follow-up visits using these clinical examination data. More detailed information about the measures used to assess physical activity and CKD are explained below.

### **6.1.1 Measures**

Clinical examinations were collected for all participants at local Indian Health Services (IHS) hospitals and clinics by trained staff. During the examinations, personal interviews and physical examinations were performed at which time demographic, medical history, self reported physical activity, diet, anthropometric, and laboratory information was collected.

#### **6.1.1.1 Physical Activity**

Physical activity was assessed with the Modifiable Activity Questionnaire (MAQ) [251]. The MAQ is an interview administered questionnaire which asks participants to recall moderate and high intensity leisure and occupational activities performed during the past year. The leisure activity portion of the questionnaire is composed of activities which are most commonly performed by the target population and was developed during pilot testing of the questionnaire.

As the interviewer reads from the list of activities, the participant indicates which of those activities they have performed. Participants are then asked to estimate the average frequency and duration they performed those activities.

The MAQ also assess inactivity by asking participants about the average number of hours per day they usually spend watching television. Also, included was a question that attempted to estimate the extent to which their activity was limited by asking whether the individuals has spent one or more weeks confined to a bed or chair because of injury, illness, or surgery.

To assess occupational activities, participants were asked about each job held over the past year for at least a month. Each job “entry” is assigned a job code which best categorizes the job. Occupations such as homemaker, retired, unemployed, or disable, are listed if no other job is identified. Participants are then asked about their usual transportation to that job as well as typical job schedule (days/week and hours/day). If the participant walks or bikes for transportation, the average duration is recorded. Based on the average hours per day the individual spent on the job, the participant is asked to estimate the number of hours spent sitting out of the total hours per day at that job. Finally, they are asked about the types of activities performed on the job when they are not sitting. The interviewer then assigns a letter code which best categorizes these activities. The categories are listed as follows (See Table 6.1):

**Table 6.1 Modifiable Activity Questionnaire Categories for Occupational Activities**

Category A (Includes all sitting activities)	Category B (includes most indoor activities)	Category C (heavy industrial work, outdoor construction, farming)
<ul style="list-style-type: none"> <li>• Sitting</li> <li>• Standing still w/o heavy lifting</li> <li>• Light cleaning</li> <li>• Driving a bus, taxi, tractor</li> <li>• Jewelry making/weaving</li> <li>• General office work</li> <li>• Occasional/short distance walking</li> </ul>	<ul style="list-style-type: none"> <li>• Carrying light loads</li> <li>• Continuous walking</li> <li>• Heavy cleaning</li> <li>• Gardening, planting, weeding</li> <li>• Painting/plastering</li> <li>• Plumbing/welding</li> <li>• Electrical work</li> <li>• Sheep herding</li> </ul>	<ul style="list-style-type: none"> <li>• Carrying moderate to heavy loads</li> <li>• Heavy construction</li> <li>• Farming, hoeing, digging, mowing, raking</li> <li>• Digging ditches, shoveling</li> <li>• Chopping (ax), sawing wood</li> <li>• Tree/pole climbing</li> <li>• Water/coal/wood hauling</li> </ul>

Leisure activities are calculated by summing the hours for all activities listed. Activity can also be expressed by their weighted metabolic cost (MET) by multiplying the hours spent for each specific activity by that activity's estimated MET value. Hours of occupation activities are calculated with the following equation if category B is selected:

$$(12 \text{ months/year}) \times (4 \text{ week/month}) \times (\text{days/week}) \times (\text{h/day of moderate activity}) / 52$$

*weeks/year*

*[where h/day = (average hours/ day at the job-sitting hours) + (min/day walking or bicycling to work / 60) ]*

If category C is selected, and the number of minutes walked or biked to/from work equals zero, the following equation is used:

$$(12 \text{ month/year}) \times (4 \text{ week/month}) \times (\text{days/week}) \times (\text{hours/day} - \text{hours sitting}) / 52 \text{ weeks/year}$$

If category A or category C is selected, and the number of minutes walked or biked to/from work does not equals zero, the following equation is used

$$[(12 \text{ month/year}) \times (4 \text{ week/month}) \times (\text{days/week}) \times (\text{min/day walked or biked to/from work} / 60)] / 52 \text{ weeks/year}$$

To express by their weighted metabolic cost, the hours per week are multiplied by 4 and 7 for categories B and C respectively. Note that no activity credit is given for category A.

The weekly total physical activity is assessed by averaging the sum of past year leisure and occupational activities.

The MAQ was only administered at baseline. To assess activity status at exam 2, participants were asked if their activity levels changed from exam 1. If they asked yes, they were asked if their activity levels had increased or decreased.

#### **6.1.1.2 Anthropometrics**

Height was measured in centimeters with a vertical rule. The participant was asked to stand completely straight with their back against the wall. Each measurement was rounded to the nearest centimeter. Weight was measured with the participant standing in the middle of a balance scale. Each measurement was rounded to the nearest kilogram. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. Waist circumference in centimeters was measured at the level of the umbilicus (navel) with the patient supine and the participant is instructed to "breathe quietly".

#### **6.1.1.3 Fasting Blood Samples**

Fasting blood samples were used to measure lipids, glucose, insulin, creatinine, fibrinogen, and HbA1c on all individuals including those on renal dialysis or renal replacement therapy when possible. Lipid measures included HDL, LDL, VLDL triglycerides, total cholesterol, and ApoA-I and ApoB lipoproteins. All lipids were analyzed using the Hitachi Hitach 705 clinical chemistry analyzer. Serum creatinine, at Exams 1 and II were assessed using the automated alkaline picrate methodology on a rapid flow analyzer. Serum creatinine was assessed using a

different assay at Exam III so all analysis for of creatinine data was only performed using Exam I and II data.

Fasting glucose was assessed on a Hitachi analyzer using a glucose oxidase technique. Fasting glucose concentrations will be used to define normal fasting glucose, impaired fasting glucose, and diabetes according to criteria developed by the ADA. Insulin was assessed with an overnight radioimmunoassay using the Morgan and Lazarow method [252]. If individuals are being treated with insulin, their data will be analyzed separately. Insulin resistance will be estimated using the homeostasis model which is calculated with the following formula:  $HOMA-IR = \text{fasting serum insulin (uU/ml)} \times \text{fasting plasma glucose (mmol/l)} / 22.5$  [253].

#### **6.1.1.4 Urinary Analysis**

Urinary analysis was performed at the NIDDK lab for exams 1 and 2. Exam 3 urinary analysis was performed at the PML using the same methodology. After fasting blood samples were collected, participants were asked to provide a urine specimen. Urinary albumin was assessed using an automated nephelometric immunochemical procedure with a Behring Nephelometer. Urinary creatinine was assessed using automated alkaline picrate methodology on a rapid flow analyzer.

#### **6.1.1.5 Physical Examination**

Blood pressure was measured after participants were rested for 5 minutes, using 3 measurements with a Baum mercury sphygmomanometer. Hypertension will be defined as having a blood pressure  $\geq 140$  or  $\geq 90$  mmHg, self reported physician diagnosed hypertension, or taking blood pressure medications.

#### **6.1.1.6 Personal Interview**

A personal interview was conducted by study clinicians where demographic information, medical history, physical activity and dietary information were collected. Current smoking status will be determined through self report. Participants will be asked if they currently or ever smoked cigarettes or other tobacco products such as pipes or cigars. Alcohol intake will be collected through self report as the number of alcoholic beverages consumed per week. During the examination, participants will be asked about their current and medical history including current medications taken (blood pressure, lipid lowering) and history of cardiovascular disease (heart failure, stroke, etc.).

#### **6.1.2 Statistical Analysis**

The proposed analytical procedures for paper # 3, *The Association between Physical Activity and Chronic Kidney Disease in Native Americans: Strong Heart Study*, are briefly described below.

The primary aim of paper #3 is to determine the association between baseline physical activity and change in kidney function during follow-up visits. We also plan to look at baseline physical activity and the incidence of CKD and/or albuminuria during follow-up. To test these aims the following statistical procedures will be performed:

Physical activity will be coded into three groups. Among those individuals who reported any leisure or occupational activity, their activity levels will be divided into two groups (above and below the median). Individuals who reported no leisure or occupational activity will be the reference group.

**AIM 1: To determine the relationship between physical activity at baseline and change in eGFR during follow-up**

**HO1: Individuals who are less physically active at baseline will have a greater decrease in renal function compared to individuals who are more active at baseline.**

To test this hypothesis, generalized linear modeling using a repeated measures design will be used. Individuals with and without CKD at baseline will be included in the analysis. Follow-up will include Exam I and II because they used the same assay to assess serum creatinine. Exam III will be omitted from this analysis because a different assay was used to assess serum creatinine. We also excluded individuals who were on dialysis during exams 1 or 2. Estimated GFR will be the dependent variable and modeled as a function of baseline physical activity as the primary predictor. Physical activity will be coded into three groups. Among those individuals who reported any leisure, their activity levels will be divided into a high and low activity group (above and below the median), with the high activity group being the reference. Individuals who reported did not report any leisure activity will be the “no LTPA” group. A variety of models will be fit that adjust for covariates (age, gender, baseline eGFR, baseline ACR, clinic site, hypertension status, smoking status, lipid levels, history of heart failure, and BMI.)

**AIM 2a: To determine the relationship between baseline physical activity and the incidence of albuminuria.**

**HO2a: Individuals who are less physical active at baseline will have a higher incidence of albuminuria during follow-up.**

To test this hypothesis logistic regression will be performed. In this analysis individuals free from albuminuria at baseline will be identified and their subsequent disease status will be determined at the Examination II and III clinic visits. Anyone who develops albuminuria will be considered a case. Physical activity will be coded into three groups. Among those individuals who reported any leisure, their activity levels will be divided into a high and low activity group (above and below the median), with the high activity group being the reference. Individuals who reported did not report any leisure activity will be the “no LTPA” group. Multivariate analyses using logistic regression modeling will be used to determine if there is an association between physical activity and the odds of developing albuminuria during study follow-up. A variety of models will be fit that adjust for covariates (age, gender, baseline eGFR, clinic site, hypertension status, smoking status, lipid levels, baseline ACR, and BMI.)

**AIM 2b: To determine the relationship between baseline physical activity and the incidence of CKD.**

**HO2b: Individuals who are less physical active at baseline will have a higher incidence of CKD during follow-up.**

To test this hypothesis, logistic regression will be performed. In this analysis individuals free from CKD at baseline will be identified and eGFR will also be determined at the Examination II clinic visit. Exam III will be omitted from this analysis because a different assay was used to assess serum creatinine. Our outcome measure will be the presence or absence of CKD (eGFR <60 mL/min/1.73 m<sup>2</sup>). Anyone who develops CKD during the follow-up time period will be considered a case. Physical activity will be coded three groups. Among those individuals who reported any leisure, their activity levels will be divided into a high and low activity group (above and below the median), with the high activity group being the reference. Individuals who reported did not report any leisure activity will be the “no LTPA” group. Multivariate analyses using logistic regression modeling will be used to determine if there is an association between physical activity and the odds of developing CKD during study follow-up. A variety of models will be fit that adjust for covariates (age, gender, baseline eGFR, clinic site, hypertension status, smoking status, lipid levels, history of heart failure, albuminuria, and BMI.)

### **6.1.3 Statistical Power Calculations**

To calculate statistical power for these analyses, G Power 3.1.2 software was used [255]. The primary aim of this dissertation is to determine the association between physical activity (none, low, high) at baseline and change in eGFR during follow-up. There were 4549 individuals in SHS at baseline out of which, 2,993 individuals had available data on baseline physical activity and eGFR at exams 1 and 2. Assuming that the correlation between eGFR at exams 1 and 2 will be 0.30, we will have 95% power to detect a small effect size of 0.05 between the three activity groups. If we assume that the correlation between eGFR at the two exam visits will be 0.50, we would also have 95 % power to detect that same effect size (See table 6.2).

**Table 6.2 Statistical power analysis for repeated measures ANOVA**

Effect Sizes	Sample Size	Correlation*	Statistical Power	Correlation8	Statistical Power
0.05	2993	0.30	95	0.50	95
0.10	2993	0.30	95	0.50	95
0.25	2993	0.30	95.2	0.50	95.1
0.35	2993	0.30	95.5	0.50	95.3
*Correlation between repeated measures (eGFR) at examination visits 1 and 2					

The second aim of the dissertation was to determine the association between baseline physical activity and the incidence of albuminuria. There were 2405 individuals with available data on baseline physical activity albuminuria at all three exams, of which 1876 were free from albuminuria at baseline. At baseline, 30% of the individuals who self-reported no leisure physical activity had albuminuria compared to 19% of the individuals who self-reported high physical activity levels. Assuming a similar percentage of individuals will develop albuminuria during follow-up in these respective activity groups, we would 96.4% power to detect a difference in the incidence of albuminuria in these groups. If the proportion of individuals who develop albuminuria in the self-reported no activity group is 28% compared to 19% in individuals in the high activity group, we would have 88.6% power to detect a difference in the incidence of albuminuria in these groups (See table 6.3).

**Table 6.3 Statistical power analysis between proportions of two independent groups**

Sample Size Group1 <sup>†</sup>	Sample Size Group 2 <sup>#</sup>	Proportion Difference (proportion 1– proportion 2)*	Statistical Power
710	1614	11	96.4
710	1614	9	99.6
710	1614	7	72.3
*The difference between the proportion of individuals who develop albuminuria in no activity compared to the high activity group <sup>†</sup> the number of participants who reported no leisure physical activity <sup>#</sup> the number of participants who reported high levels of leisure physical activity			

### 6.1.4 Baseline Characteristics

At baseline, the SHS included 4549 individuals, 4060 of which had available data on GFR, physical activity, and relevant covariates (See Figure 3). Individuals who were not included in this analysis were similar in age, BMI, HDL and LDL cholesterol, and percentage who reported they currently smoked compared to the individuals who were included. Individuals who were excluded were however, more likely to have hypertension, diabetes, and albuminuria ( $p<0.05$ ). A slightly higher percentage of the individuals who were not included in this analysis also had CKD compared to the individuals who were included although it failed to reach significance ( $p=0.08$ ).

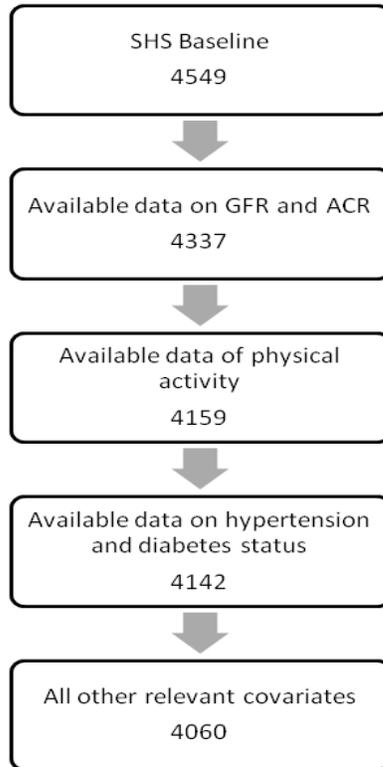


Figure 6-1 Participant flow chart

The individuals included in this analysis were between the ages of 45 and 74 (mean age 56). Approximately 60% of the participants were women. Table 6.4 describes the baseline characteristics of the populations stratified by gender. CKD and albuminuria were highly prevalent at baseline with women carrying a higher burden of these conditions compared to men ( $p < 0.01$ ). Albuminuria was prevalent in approximately 27% of men and 30% of women. The prevalence of CKD was approximately 5% in men and women had more than double the prevalence (13.34%) of CKD compared to men. Risk factors for CKD and albuminuria were also high in this population. Approximately 40% of men and 46% of women had diabetes at baseline. Hypertension was prevalent in approximately 40% of men and 38% of women. Men and women in this cohort also had a high prevalence of obesity. Men and women had an average BMI of 30 and 31.6 respectively. Physical inactivity was also prevalent in this population with approximately 16% of men and 19% of women reporting no participation in any physical activities during leisure.

**Table 6.4 Characteristics of Strong Heart Study participants at baseline stratified by gender**

	Men N=1642	Women N=2418	P-value
Age ( $\pm$ SD)	55.8	56.6	<0.01
BMI ( $\pm$ SD)	30.0	31.6	<0.01
Smoking status % yes	40.7	29.4	<0.01
Hypertension % yes	40.2	37.6	0.10
Diabetes Status	40.5	46.0	<0.01
HDL ( $\pm$ SD)	43.3	48.1	<0.01
LDL ( $\pm$ SD)	118.7	115.8	0.01
Total Cholesterol ( $\pm$ SD)	188.3	191.1	0.02
Triglycerides ( $\pm$ SD)	131.2	136.2	<0.01
CKD %	5.28	13.34	<0.01
Albuminuria %	26.71	30.18	0.02
No LTPA	16.0	19.4	0.01

Characteristics of the population at baseline by study center are presented in Tables 6.5 and 6.6 for men and women respectively. Of the 3,967 individuals included in the analysis, there were approximately an equal number of individuals from each study center (AZ=1312, OK=1339, SD=1316). Individuals from Arizona had higher BMI's, a higher burden of diabetes and albuminuria, and were less physically active than the Dakota and Oklahoma centers. The prevalence of CKD however, was highest in women from Oklahoma compared to women from the other centers. The mean age between the centers were fairly similar though men from Arizona were slightly younger than individuals from the other centers (women: AZ=56, OK=57.3, SK=56.4 yrs; men: AZ=54.8, OK=56.2, SD=56.3 yrs).

**Table 6.5 Descriptive Characteristics at Baseline for Women by Study Center**

	AZ (N=861)	OK(N=786)	SD (N=771)	Total (N=2418)
Age ( $\pm$ SD)	56.0	57.3	56.4	<0.01
BMI ( $\pm$ SD)	33.3	31.1	30.2	<0.01
Smoking status % yes	12.8	31.2	46.1	<0.01
Hypertension % yes	41.9	42.3	28.0	<0.01
Diabetes Status %	65.7	35.6	34.5	<0.01
HDL ( $\pm$ SD)	46.7	49.9	49.0	<0.01
LDL ( $\pm$ SD)	105.9	117.7	124.8	<0.01
Total Cholesterol ( $\pm$ SD)	179.7	194.6	200.3	<0.01
Triglycerides ( $\pm$ SD)	140.7	134.8	132.7	0.02
CKD %	12.5	15.2	12.4	0.18
Albuminuria %	48.8	20.3	19.3	<0.01
GFR mL/kg/min	81.8	76.0	87.1	<0.01
No LTPA	26.8	14.8	15.7	<0.01

**Table 6.6 Descriptive Characteristics at Baseline for Men by Study Center**

	AZ (N=479)	OK(N=583)	SD (N=658)	Total (N=1642)
Age ( $\pm$ SD)	54.8	56.2	56.3	<0.01
BMI ( $\pm$ SD)	31.4	30.3	28.5	<0.01
Smoking status % yes	31.4	36.3	52.8	<0.01
Hypertension % yes	44.8	47.0	29.3	<0.01
Diabetes Status %	58.9	37.4	28.6	<0.01
HDL ( $\pm$ SD)	44.3	41.7	44.2	<0.01
LDL ( $\pm$ SD)	102.9	123.3	127.1	<0.01
Total Cholesterol ( $\pm$ SD)	173.3	192.7	196.1	<0.01
Triglycerides ( $\pm$ SD)	130.6	138.5	124.5	<0.01
CKD %	6.3	6.0	3.8	0.13
Albuminuria %	43.3	21.1	18.8	<0.01
GFR mL/kg/min	92.7	82.4	85.5	<0.01
No LTPA	22.5	10.0	16.6	<0.01

Table 6.7 provides descriptive characteristics at baseline of men and women by age group (45-54yrs, 55-64yrs, >65yrs). In general, as individuals aged, the prevalence of diabetes, hypertension, CKD, and albuminuria increased and ( $p < 0.01$ ). Physical individual also increased with age. In addition, smoking status and BMI were lower in older individuals ( $p < 0.01$ ). In men, LDL and total cholesterol was also lower in older individuals.

**Table 6.7 Descriptive characteristics at baseline of men and women stratified by age groups**

	MEN N=1591				WOMEN N=2376			
	45-54 n=839	55-64 N=504	>65 N=265	p-value	45-54 N=1123	55-64 N=798	>65 N=447	p-value
BMI ( $\pm$ SD)	30.7	29.5	28.4	<0.01	31.9	31.8	30.5	<0.01
Smoking status % yes	43.1	41.5	32.3	0.01	35.1	26.5	20.2	<0.01
Hypertension % yes	35.6	41.5	52.5	<0.01	26.8	41.4	58.5	<0.01
Diabetes status % yes	39.5	41.9	41.8	0.62	39.9	51.5	52.3	<0.01
HDL ( $\pm$ SD)	43.4	43.7	42.1	0.31	47.4	48.7	48.9	0.03
LDL ( $\pm$ SD)	120.6	117.8	113.6	0.01	115.2	117.6	114.9	0.24
Total Cholesterol ( $\pm$ SD)	190.9	186.5	181.5	<0.01	189.6	194.2	191.0	0.04
Triglycerides ( $\pm$ SD)	135.1	124.6	128.7	0.06	134.9	139.1	136.0	0.16
CKD %	2.6	6.3	12.2	<0.01	5.7	15.2	30.6	<0.01
Albuminuria %	25.3	25.0	33.1	0.03	26.4	31.1	38.6	<0.01
GFR mL/kg/min	90.4	84.1	78.4	<0.01	83.4	77.3	69.8	<0.01
No LTPA %	10.6	18.6	28.1	<0.01	14.4	21.7	27.9	<0.01

Presented in Table 6.8 are descriptive characteristics of the population at baseline by CKD status for men and women. As expected, individuals with CKD had a higher prevalence of diabetes and hypertension ( $p < 0.01$ ). In addition, women with CKD had higher triglycerides, LDL and total cholesterol compared to women without CKD ( $p < 0.01$ ). Men with CKD had lower levels of HDL cholesterol compared to men without CKD ( $p = 0.01$ ). Of interest, even individuals without CKD at baseline had a high prevalence of risk factors for CKD. In those individuals without CKD, diabetes was prevalent in approximately 40% of men and 44% of women. Hypertension was prevalent in approximately 39% of men and 34% of women without CKD at baseline.

**Table 6.8 Descriptive characteristics of Strong Heart Study participants at baseline stratified by CKD and gender**

	Men			Women		
	No CKD N=1548	W/ CKD N=94	P-value	No CKD N=2087	W/ CKD N=331	P-value
Age ( $\pm$ SD)	55.5 (7.9)	61.4 (8.6)	<0.01	55.6 (7.8)	62.4 (7.7)	<0.01
BMI ( $\pm$ SD)	30.0 (5.9)	29.9 (7.9)	0.92	31.8	30.6	<0.01
Smoking status % yes	41.5	25.0	<0.01	30.1	24.6	0.05
Hypertension % yes	38.8	65.4	>0.01	33.7	63.1	<0.01
Diabetes Status	39.7	56.0	<0.01	44.4	56.5	<0.01
HDL ( $\pm$ SD)	43.5 (13.5)	39.5 (15.1)	0.01	47.9 (21.8)	49.3 (14.4)	0.08
LDL ( $\pm$ SD)	119.0 (32.7)	113.5 (34.9)	0.15	115.0 (32.3)	120.8 (41.7)	<0.01
Total Cholesterol ( $\pm$ SD)	188.6 (36.7)	181.4 (38.5)	0.08	189.7 (37.0)	200.3 (48.6)	<0.01
Triglycerides ( $\pm$ SD)	130.6 (71.5)	142.1 (72.7)	0.07	133.9 (68.5)	151.2 (75.4)	<0.01
Albuminuria %	24.8	61.9	<0.01	26.4	54.6	<0.01
No LTPA	15.4	26.2	0.01	17.8	29.7	<0.01

Individuals with CKD self-reported higher levels of inactivity compared to individuals without CKD ( $p < 0.01$ ). CKD was prevalent in approximately 9% of men who reported no LTPA compared to 5 and 4% of men who reported low or high amounts of LTPA. The prevalence of CKD was also higher in women with approximately 21% of women who reported no LTPA having CKD at baseline compared to nearly 12% of women who reported low or high levels of LTPA.

Table 6.9 shows the odds of having CKD by categories of physical activity and gender. In women, there was a 1.52 (95% confidence interval: 1.05, 2.21) odds of having CKD at baseline in individuals who reported no LTPA compared to individuals who reported high levels of LTPA after adjusting for age. However, after adjusting for diabetes status, hypertension, HDL cholesterol, and triglyceride levels, this relationship was attenuated and no longer significant (OR=1.41; 95% confidence interval: 0.96, 2.08). In men, there was also a higher

odds of having CKD at baseline in individuals who reported no LTPA compared to individuals who reported high levels of LTPA, but the relationship failed to reach significance (OR=1.70;95% confidence interval: 0.77, 3.72).

**Table 6.9 The cross-sectional relationship between CKD and physical activity by gender**

	Physical Activity Levels	Model 1	Model 2	Model 3
Men	High	--	--	--
	Low	1.27 (0.66, 2.43)	1.16 (0.60, 2.26)	1.09 (0.55, 2.15)
	None	1.70 (0.77, 3.72)	1.61 (0.70, 3.66)	1.48 (0.64, 3.41)
Women	High	--	--	--
	Low	0.98 (0.70, 1.36)	0.99 (0.71, 1.38)	0.89 (0.63, 1.26)
	None	1.52 (1.05, 2.21)	1.52 (1.04, 2.24)	1.41 (0.96, 2.08)
Odds ratios (95% Confidence Intervals)				
Model 1: Age adjusted				
Model 2: Model 1 + study site, smoking status, history of heart failure				
Model 3: Model 2 + diabetes status, hypertension, HDL cholesterol, triglycerides				

The prevalence of albuminuria was also higher at baseline among individuals who were inactive. At baseline, albuminuria was prevalent in 35% of men who self-reported no leisure time physical activity (LTPA) compared to approximately 28 and 22% of men who self reported low and high levels of physical activity. The prevalence of albuminuria was higher in women who self reported no LTPA (40%) compared to women who self reported low and high levels of LTPA (30% and 28% respectively).

Table 6.10 shows the odds of having albuminuria at baseline by categories of physical activity and gender. Compared to individuals who self reported high levels of LTPA, men and women who self reported no LTPA have 1.78 (95% confidence interval: 1.29, 2.46) and 1.94 (95% confidence interval: 1.52, 2.46) odds of having albuminuria at baseline adjusting for age. After adjusting for diabetes status, the relationship between LTPA and albuminuria was no

longer significant in men (OR=1.34; 95% confidence interval: 0.93, 1.95). In women however, individuals who self reported no LTPA still had a 1.35 (95% confidence interval: 1.04, 1.78) odds of having albuminuria compared to women who reported high levels of LTPA.

**Table 6.10 The cross-sectional relationship between albuminuria and physical activity by gender**

	Physical Activity Levels	Model 1	Model 2	Model 3
Men	High	--	--	--
	Low	1.37 (1.06, 1.75)	1.27 (0.98, 1.64)	1.16 (0.87, 1.54)
	None	1.78 (1.29, 2.46)	1.46 (1.04, 2.05)	1.34 (0.93, 1.95)
Women	High	--	--	--
	Low	1.32 (1.08, 1.62)	1.20 (0.97, 1.48)	1.03 (0.81, 1.30)
	None	1.94 (1.52, 2.47)	1.50 (1.16, 1.93)	1.34 (1.01, 1.77)
Odds ratios (95% Confidence Intervals)				
Model 1: Age adjusted				
Model 2: Model 1 + study site, smoking status				
Model 3: Model 2 + diabetes status, hypertension, HDL cholesterol, triglycerides				

### 6.1.5 Physical activity and kidney function: Prospective Analysis

**AIM 1a: To determine the relationship between physical activity at baseline and change in eGFR during follow-up**

**HO1a: Individuals who are less physically active at baseline will have a greater decrease in renal function compared to individuals who are more active at baseline.**

At baseline, mean eGFR was similar between men who reported no, low, and high levels of LTPA (86, 87 and 86 mL/min, p=0.40). From exam 1 to exam 2, men who reported no LTPA

experienced a greater decrease in mean eGFR compared to men who reported low or high amounts of LTPA independent of baseline eGFR, albuminuria, age, smoking status, diabetes, hypertension, HDL cholesterol, triglycerides, or history of heart failure ( $p=0.04$ ) (see figure 4). The average yearly change in mean eGFR was -1.85, -0.74, and -0.34 mL/min from exam 1 to exam 2 in men who reported no, low, and high levels of LTPA respectively. A rapid decline in eGFR was defined as a reduction in eGFR  $>3$  mL/min per year. A higher percentage of individuals who reported no LTPA experienced rapid declines in eGFR ( $>3$  mL/min) compared to individuals who reported low and high levels of LTPA (37, 28, and 23% respectively,  $p<0.01$ ). This increased odds of experiencing accelerated declines in eGFR in the no LTPA group was independent of age, smoking status, diabetes, hypertension, HDL cholesterol, triglycerides, history of heart failure, baseline eGFR and baseline albuminuria ( $p=0.01$ )

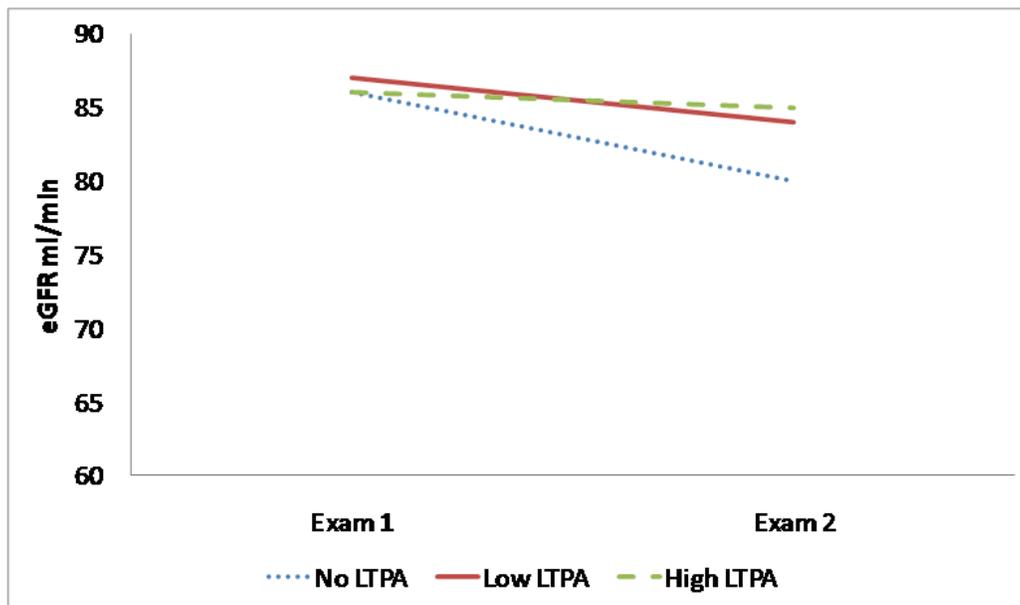


Figure 6-2 Mean eGFR by categories of physical activity from exam1 to exam 2 in men

In women, mean eGFR at baseline was the same in all three activity groups (78 mL/min). The average yearly change in eGFR from exam 1 to exam 2 was -1.76, -1.13, and -0.96 in women who reported no, low, and high levels of LTPA respectively. This change in eGFR was not statistically different between the three activity groups (p=0.64) (see figure 5). However, when examining individuals who reported no change in their activity status at exam 2, women who reported no LTPA have a faster decrease in eGFR compared to women who reported low and high levels of LTPA which bordered on significance (p=0.07). Women who reported no LTPA at baseline had higher odds of experiencing rapid declines in kidney controlling for age and baseline eGFR (OR=1.37; 95%CI: 1.01, 1.88). This relationship was attenuated and no longer significant after further adjusting for diabetes status, hypertension, and baseline albuminuria (OR=1.21; 95%CI: 0.88, 1.68).

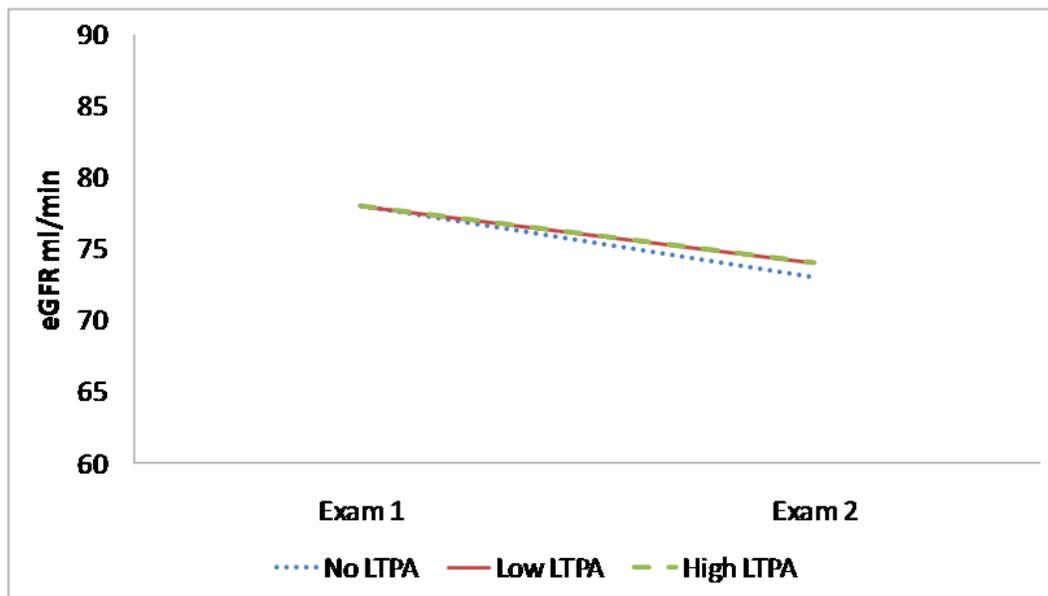


Figure 6-3 Mean eGFR by categories of physical activity from exam1 to exam 2 in women

**AIM 1b: To determine the relationship between physical activity at baseline and change in albumin to creatinine ratio during follow-up**

**HO1b: Individuals who are less physically active at baseline will have a greater increase in albumin to creatinine ratio compared to individuals who are more active at baseline.**

At baseline, mean urinary albumin to creatinine ratio (ACR) was higher in men who reported no LTPA compared to men who reported low or high amounts of LTPA (men: 98 vs. 61 and 47 mg/g;  $p < 0.01$ ). Mean ACR increased from exam 1 to exam 2 in all three activity groups with men who reported no LTPA had an experiencing a greater increase compared to men who reported low or high amounts of LTPA which bordered on significance ( $p = 0.06$ ). There was a further increase in mean ACR from exam 2 to exam 3. The mean change in ACR from all three exam visits were not statistically different from each activity group ( $p = 0.52$ ) (see figure 6). When examining individuals who reported no change in their activity levels, individuals who reported no LTPA at baseline had a slightly higher increase in ACR from exam 1 to exam 3 compared to individuals who reported low or high LTPA which bordered on significance ( $p = 0.08$ ).

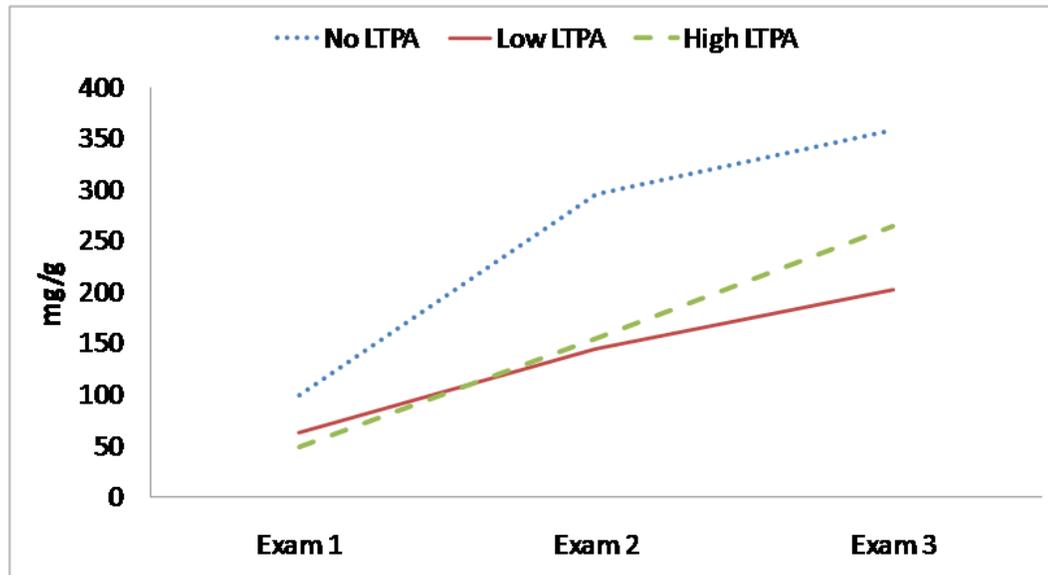


Figure 6-4 Mean urinary albumin to creatinine ratio by categories of physical activity from exam 1 to exam 3 in men

In women, mean ACR at baseline was higher in individuals who reported no LTPA compared to individuals who reported low and high LTPA (121 vs. 93 and 49 mg/g,  $p < 0.01$ ). Mean ACR increased in both exam 2 and exam 3 in all three activity group. The change in mean ACR between the three activity groups was not statistical different ( $p = 0.42$ ) (see figure 7). Only examining individuals who reported no change in their activity levels at exam 2 did not change the results ( $p = 0.38$ ).

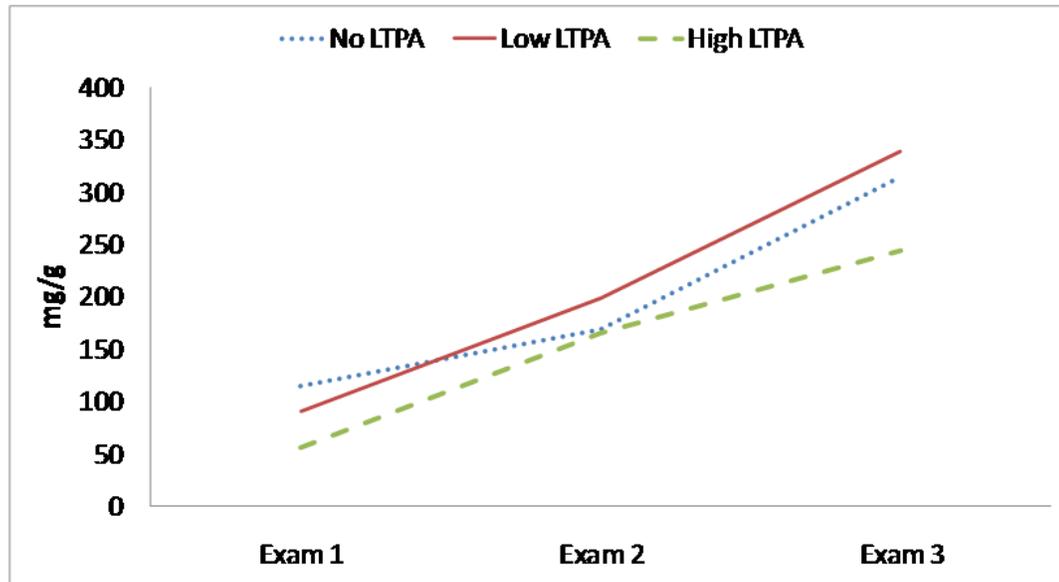


Figure 6-5 Mean urinary albumin to creatinine ratio by categories of physical activity from exam 1 to exam 3 in women

**AIM 2a: To determine the relationship between baseline physical activity and the incidence of albuminuria.**

**HO2a: Individuals who are less physical active at baseline will have a higher incidence of albuminuria during follow-up.**

Table 6.11 shows the five year incidence (Exam 1 to Exam 2) of albuminuria in men and women by categories of physical activity. Women who reported no LTPA had a 1.82 (95% CI; 1.23, 2.70) odds of developing albuminuria compared to women who reported high levels of LTPA after adjusting for age. After adjusting for baseline albumin to creatinine ratio, this relationship was attenuated and no longer significant (OR=1.39; 95% CI: 0.91, 2.14). However, when examining women who reported an increase in their activity levels at exam 2, individuals

who reported no LTPA have baseline had a higher odds of developing albuminuria compared to women who reported high levels of LTPA (OR= 3.0; 95% confidence interval: 1.17, 7.66).

In men, individuals who reported no LTPA had a 1.34 odds of developing albuminuria adjusting for age, however, the relationship failed to reach significance (95% CI; 0.77, 2.30). Change in activity levels at exam 2 did not affect the results.

**Table 6.11 The five year incidence of albuminuria by levels of physical activity and gender**

	Physical Activity Levels	Model 1	Model 2	Model 3
Men	High	--	--	--
	Low	0.98 (0.65, 1.46)	0.87 (0.56, 1.33)	0.86 (0.47, 1.60)
	None	1.34 (0.77, 2.30)	0.89 (0.49, 1.63)	0.87 (0.56, 1.35)
Women				
	High	--	--	--
	Low	1.28 (0.94, 1.76)	1.16 (0.83, 1.62)	1.12 (0.79, 1.58)
	None	1.82 (1.23, 2.70)	1.39 (0.91, 2.14)	1.44 (0.93, 2.23)
Odds ratios (95% Confidence Intervals)				
Model 1: Age adjusted				
Model 2: Model 1 + study site, smoking status, baseline ACR				
Model 3: Model 2 + diabetes status, hypertension, HDL cholesterol, triglycerides				

The ten year incidence (Exam 1 to Exam 3) of albuminuria by physical activity categories for men and women are shown in Table 6.12. For men and women, individuals who reported no LTPA had a 2.07 (95% CI; 1.23, 3.48) and 1.54 (95% CI; 1.05, 2.26) odds of developing albuminuria compared to individuals who reported high levels of LTPA adjusted for age. After further controlling for current smoking status, study center, and baseline albumin to creatinine ratio, this relationship was attenuated and no longer significant. In men, change in activity levels at exam 2 did not affect the results. However, in women who reported an increase in their activity levels at exam 2, individuals who reported no LTPA at baseline had a 3.52 odds (95%

confidence interval; 1.50, 8.23) of developing albuminuria compared to individuals who reported high levels of LTPA.

**Table 6.12 The ten year incidence of albuminuria by levels of physical activity and gender**

	Physical Activity Level	Model 1	Model 2	Model 3
Men	High	--	--	--
	Low	1.12 (0.76, 1.64)	1.06 (0.71, 1.59)	1.16 (0.76, 1.78)
	None	2.07 (1.23, 3.48)	1.61 (0.92, 2.81)	1.64 (0.91, 2.97)
Women	High	--	--	--
	Low	1.13 (0.85, 1.49)	1.04 (0.78, 1.40)	1.01 (0.74, 1.38)
	None	1.54 (1.05, 2.26)	1.23 (0.82, 1.86)	1.40 (0.91, 2.15)
Odds ratios (95% Confidence Intervals)				
Model 1: Age adjusted				
Model 2: Model 1 + study site, smoking status, baseline ACR				
Model 3: Model 2 + diabetes status, hypertension, HDL cholesterol, triglycerides				

**AIM 2b: To determine the relationship between baseline physical activity and the incidence of CKD.**

**HO2b: Individuals who are less physical active at baseline will have a higher incidence of CKD during follow-up.**

Table 6.13 shows the 5 year incidence of CKD by categories of LTPA for men and women. In women, individuals who reported no LTPA had a greater odds of developing CKD compared to women who reported high amounts of LTPA after adjusting for age which bordered on significance (OR=1.46; 95% CI: 0.99 to 2.15). When examining individuals who reported a decrease in their activity status at exam 2, individuals who reported no LTPA at baseline had a higher odds of developing CKD compared to women who reported low or high levels of LTPA (OR=2.73; 95% CI: 1.32, 5.65).

In men, those who reported no LTPA also had a higher odds of developing CKD compared to men who reported high amounts of LTPA, but the relationship failed to reach significance after age adjustment (OR=1.34; 95% CI: 0.62 to 2.65). Change in activity levels at exam 2 did not affect the results.

**Table 6.13 The five year incidence of CKD by levels of physical activity and gender**

	Physical Activity Levels	Model 1	Model 2	Model 3
Men	High	--	--	--
	Low	1.33 (0.68, 2.60)	1.25 (0.74, 2.11)	1.25 (0.73, 2.12)
	None	1.34 (0.81, 2.21)	1.28 (0.62, 2.65)	1.34 (0.64, 2.79)
Women	High	--	--	--
	Low	1.20 (0.87, 1.64)	1.12 (0.81, 1.57)	1.08 (0.77, 1.50)
	None	1.46 (0.99, 2.15)	1.31 (0.88, 1.97)	1.28 (0.85, 1.91)
Odds ratios (95% Confidence Intervals)				
Model 1: Age adjusted				
Model 2: Model 1 + study site, smoking status, history of heart failure, albuminuria				
Model 3: Model 2 + diabetes status, hypertension, HDL cholesterol, triglycerides				

### 6.1.6 Discussion

This was the first study to examine the relationship between physical activity and renal function/CKD in American Indians, a high risk population. The results of our analysis indicated that physical activity at baseline was related to rapid declines in kidney function over a five year period, independent of age and baseline eGFR. These results were similar to published reports for the Cardiovascular Health Study (CHS) by Cohen et al [60]. CHS is a community based prospective cohort study of men and women of at least 65 years of age. A rapid decline in renal function was defined as having a yearly decrease in eGFR of > 3 mL/min, assessed using

cystatin C. The study indicated that individuals who self reported high levels of physical activity had lower odds of having rapid declines in renal function compared to individuals who reported low amounts of physical activity. It's important to note that CHS was a population of older adults who were primarily white and African American which may not be generalizable to younger populations. Our results from the SHS show a similar relationship between physical activity and renal function in a younger population of American Indians. These findings provide additional evidence that physical activity may aid in slowing the progression of CKD in high risk populations.

In addition to being related to rapid changes in renal function, physical activity was also related to albuminuria, which may indicate endothelial dysfunction or kidney damage. At baseline, individuals who reported no LTPA had higher odds of having albuminuria independent of age. Even among individuals without albuminuria at baseline, those who reported no LTPA had higher albumin to creatinine ratios in the normal range. Those individuals with high normal levels were more likely to develop albuminuria over the 10 year study follow-up. This may be of great importance for American Indian populations considering the high prevalence of albuminuria. Albuminuria was prevalent in approximately 30% of the SHS population compared to 13% of the US population based on results from NHANES [256].

Few studies have looked at the relationship between of physical activity and albuminuria prospectively, but the Diabetes Prevention Program (DPP) did compared the prevalence of albuminuria in three groups (control, metformin, intense lifestyle: diet, physical activity, and weight loss) at baseline and at the study's end. While the prevalence of albuminuria (ACR >30 mg/g) remained unchanged in the metformin and intense lifestyle intervention groups, a higher percentage of individuals in the intensive lifestyle group experienced improvements in

albuminuria over the average three and a half years of study follow-up which bordered on significance ( $p=0.07$ ). Unfortunately, the independent effects of physical activity on albuminuria were not examined in the DPP so future studies will have to investigate this relationship more thoroughly.

Physical activity was not however, shown to be related to the development of CKD from exam 1 to exam 2. We were able to document that a higher percentage of individuals who reported no LTPA at baseline developed CKD at exam 2. Approximately 17% of the individuals who reported no LTPA at baseline developed CKD compared to 10% of individuals who reported high levels of LTPA at baseline. However, we lacked sufficient power to detect a difference statistically. One limitation of this study is that exam 3 used a different assay to measure serum creatinine from what was used during the previous 2 exam cycles. This prevented us from being able to compare kidney function over all three exam cycles. It's possible that we may have been able to detect difference in CKD development by physical activity with longer follow-up data.

There were some other important limitations to our analysis. The Modifiable Activity Questionnaire (MAQ) was used only at baseline to assess physical activity which limits our ability to look at the effects of change in activity status on kidney function or CKD development. During follow-up exams, individuals were asked if their activity levels had changed from the previous exam. This allowed us to make some crude assessment of change in activity status; however, it is not clear if that question is a valid estimate of physical activity stability or change over time. The MAQ also does not provide information on activities of lower intensity. Given the results from paper 2 of this dissertation, light intensity physical activities may contribute to

better kidney health. Future analysis using accelerometry may help elucidate the benefit of light intensity activity on CKD.

Another limitation of this analysis is the lack of control for ACE-inhibitor use at exams 2 and 3. ACE-inhibitors are used to treat hypertension and they also have the added benefit of reducing urinary albumin excretion. It is important to establish if the benefits of physical activity are independent or in addition to the benefits of pharmacological treatments. We were also limited by not having the data on mortality, which was collected by the SHS. Individuals who were experiencing rapid declines in the renal function are also more likely to suffer pre-mature mortality. Including mortality for cardiovascular disease or renal complications would likely strengthen our study findings.

Despite the limitations, this study highlights the potential benefits of physical activity for kidney function. This is one of the few studies which examine the relationship between physical activity and kidney function prospectively and the only study to do so in American Indians. Given the high risk for CKD in this population, the results of this analysis provide useful information for individuals in this population. Future interventions will have to examine the affects of change in physical activity over time and kidney function.

## **7.0 CHAPTER 7**

### **7.1 CONCLUSIONS**

Chronic kidney disease is a serious public health concern because of the large physical and economic burden on society [65]. Because of the large burden of the disease, it is important to determine what factors are associated with the development and progression of the disease, especially in early stages. The benefits of physical activity to kidney health have been demonstrated in a few studies but there are still many questions which remain unanswered.

Many studies, which sought to examine the relationship between physical activity and chronic disease, used questionnaires to assess physical activity levels. Questionnaires are reasonably accurate for assessing activities of moderate to vigorous intensity. However, it is important to note that a large proportion of activity in a typical day occurs in light activity or in unplanned movement across various levels of intensity. Therefore, results of studies that have used questionnaires can more accurately investigate the benefits of engaging in moderate to vigorous intensity activity for the prevention of various chronic conditions relative to that of light intensity or unstructured activity.

In paper 1, we described physical activity by intensity in a nationally representative population using accelerometers. We confirmed the fact that lower intensity activities comprise the largest proportion of total movement. The importance of examining activities of lower

intensity is not just that they are being performed in high volume, but that they may make an important contribution to our overall health. This point has yet to be proven in regard to kidney function, which is what paper 2 was able to accomplish.

In paper 2, we were able to follow up on the results from paper 1 and show that lower intensity physical activity has important benefits for kidney function. Using accelerometers, we showed that light intensity physical activity was positively associated with kidney function, independent of moderate to vigorous intensity activity. I think it's worth re-stating that previous research, and thus current public health recommendations, has focused on moderate intensity activity as being important for achieving health benefits. *This was a new and exciting finding which lends credence to the notion that every step counts.*

Understanding the relationship between various intensities of physical activity and kidney function was an important finding, but it is only part of the story. Cross-sectional relationships can only tell us but so much. We also need to understand the prospective relationship between physical activity and kidney function, which is lacking in the field. Paper 3 was the first study to examine the relationship between physical activity and kidney function/CKD in American Indians. The results of this paper provided evidence that physical activity can potentially preserve kidney function even in a population with a high prevalence of kidney damage and CKD risk factors. Not only have we documented the benefit of physical activity on kidney function cross-sectionally, but we now see this relationship prospectively as well. Unfortunately, accelerometers were not used to assess activity during the early stages of the Strong Heart Study (SHS), so we were unable to examine the relationship between varying intensities of activity and kidney function in paper 3. If the SHS incorporates accelerometers, in addition to

questionnaires, during future examinations, we can explore the relationship between varying intensities of activity and kidney function prospectively.

## **7.2 PUBLIC HEALTH SIGNIFICANCE**

The results of these three papers provided valuable information on how varying intensities of activity are related to CKD cross-sectionally and for understanding the benefits of moderate intensity physical activity prospectively. With the use of accelerometers we were able to document, for the first time, the benefits of lower intensity activity in regard to kidney function. More attention should be paid to the idea that total movement counts in addition to our planned activities of moderate intensity. The Canadian physical activity recommendations, for example, now include recommendations for accumulating activities of lower intensity in addition to moderate intensity activities. Our findings support these recommendations and there needs to be increased awareness about the benefits of physical activity for preserving kidney function. According to a survey at the World Congress of Nephrology in 2003, 95% of nephrologists surveyed agreed that a sedentary lifestyle contributed to CKD risk. Despite this, neither the Surgeon General's Report on Physical Activity and Health nor the National Kidney Foundation talk about the benefits of physical activity for renal health. With the growing evidence from this effort and the work of others, we may be able to increase awareness.

In addition to increasing public awareness, this research begins to answer important questions about how varying intensities of activities are related to kidney function. There have been previous studies using accelerometers which have focused on moderate and vigorous intensity activity, despite having the ability to incorporate lower intensity activities. Many

researchers have operated under the assumption that the higher intensity activities is where the “action” is. Our public health recommendations over the years have certainly reflected that message. We now understand that it’s not all about moderate intensity activity but that light activity and total volume of movement are also important in relationship to some diseases and conditions. This fact needs to be taken into consideration in future studies. Now that we understand the importance of exploring how varying intensities of activity are related to kidney function, we can look to understand the mechanisms of that relationship.

### **7.3 FUTURE DIRECTIONS**

The results of this dissertation have produced some new and exciting findings which have enhanced our understanding of physical activity and how it relates to kidney function. However, there are some interesting questions which have been raised from these investigations which future studies will need to address.

In paper 1, we found that Hispanics were more active (light, moderate to vigorous, and total activity) than both whites and blacks. This result was surprising because previous analysis of all surveillance system physical activity data, including NHANES, reported Hispanics to be less active than whites or blacks. This raises some important questions about physical activity assessment in surveillance systems. The NHANES physical activity questionnaires (PAQ) assess activities performed in the household, for transportation, and during leisure time. One possible explanation for the contrasting findings between objective and subjective measures of activity is that the PAQ used in NHANES is not a valid assessment tool for Hispanics. Hispanics may be performing activities during leisure which are not capture by the PAQ because the wording of

the questions, their activities are spontaneous in nature, or they are performing lower intensity activities which the questionnaire are either unable or inaccurate at assessing. The difficulties in assessing activity in diverse populations with a single questionnaire may highlight the importance of using objective assessment in those populations.

Another more likely source of conflict between the two measures may be issues with content validity. The PAQ may perform equally well in all races at assessing activities in the household, during transportation, and leisure, it just may fail to include all appropriate domains for all the racial/ethnicity groups in the population. The NHANES PAQ does not include occupational activities as part of their assessment. Potentially, occupational activities may comprise a large proportion of activity in Hispanics which is being missed by the PAQ currently used in NHANES as well as other surveillance systems. Future studies should try to figure out if content validity is the sources of error which can be corrected by including all appropriate domains of activity.

The results of this dissertation also raise questions about an important debate over the value of subjective assessment and what roles questionnaires should play in research. Some feel that objective measures, such as accelerometers, provide the best method for assessing activities therefore eliminating the need for questionnaires. Others feel that subjective assessment has an important role when used appropriately. Now the question is, when is it appropriate to use questionnaires? Some feel the answer to this question is all about intensity. The thought is that when moderate to vigorous activity is most important, than either tool may show the same things. However, when light activity is the critical intensity component, objective assessment would likely be the method of choice.

In paper 2 we showed that objectively assessed light intensity activity was related to kidney function while moderate to vigorous activity (MVPA) assessed objectively or subjectively were not. It would appear that both objective and subjective assessment tools agree with each other and gives support to the idea that intensity is an important factor for determining when to use subjective or objective assessment.

With the results of paper 2 showing that light activity was related to kidney function, indicating the need of objective assessment, how do we explain the results from paper 3 which showed that subjectively assessed physical activity was related to kidney function? Are the findings from these two papers in conflict with each other? On the surface it may appear that they are. There are several important factors which must be considered when attempting to address these questions. The first possibility we must consider is that while neither subjectively nor objectively assessed moderate to vigorous activity was related to kidney function in paper 2, they may have been unrelated for different reasons.

The lack of a relationship between objectively assessed MVPA via accelerometry and kidney function may be due to the lack of variation in activity. A large proportion of the NHANES population accumulated few minutes of MVPA. We may have missed a true relationship simply because people are not engaging in significant amounts of MVPA as it was defined in our study. We defined MVPA as a minute of activity of 1952 counts using the Freedson cutpoint. Some may argue that that cutpoint is too high for assessing MVPA in the general population, especially in older adults. If this is true, there are some activities that may truly be moderate intensity that we classified as light intensity because of the cutpoints we used. Using a lower cutpoint for MVPA may have revealed a significant relationship. There are however concerns with using some of the lower cutpoints which have been proposed by Swartz,

Matthews, and others. The lower cutpoints tend to overestimate resting energy expenditure. We could then classify activities which are light intensity, inaccurately as moderate intensity activities. This is truly a difficult issue to solve. Future studies which use a wide range of activities over the complete range of intensity levels may produce more accurate cutpoints. We can then have a better idea if MVPA is truly related to kidney function.

In regards to the questionnaire, the lack of a relationship between subjectively assessed physical activity and kidney function in paper may be related to the validity of the NHANES PAQ. Surveillance systems PAQ's rely on face validity for their development and are often not evaluate against a criterion measure. In paper 3, subjectively assessed physical activity was shown to be related to kidney function. The MAQ however has been developed, pilot tested, and validated for use in American Indian populations. Caspersen and others have shown the importance of using a valid measure of physical activity when assessing its relationship with cardiovascular disease. It's likely that there is a relationship between physical activity and kidney function we just need to ensure we are using a valid tool to assess physical activity.

Another possible explanation for the contrasting findings from papers 2 and 3 is related to the characteristics of the NHANES and SHS populations. The SHS is an older population with a higher burden of chronic disease compared to the NHANES population. Given the high risk of disease in the SHS population, individuals who perform activity at any intensity are probably less likely to develop CKD than individuals who perform no activity. The results of the questionnaire, which we used to crudely group individuals in no activity and high/low activity, was not precise enough to separate out the benefits of the various activity intensities and may just be reflecting the fact that individuals who reported high levels of moderate activity probably engaged in high amounts of all intensities of activity. In order to explore this hypothesis further,

we could use a validated PAQ and accelerometer in a generally healthy population with a large variation of activity levels to see if the results from paper 2 are the same.

Understanding the situations in which subjectively and objective assessment is most appropriate is very important. It's likely that intensity of activity does play an important role for determining what assessment tool to use. This was beyond the scope of our current project but it does give us some ideas moving forward. First, we need to make sure we are using a valid and appropriate questionnaire which shows good agreement with a criterion measure. We can then examine the relationship between objectively and subjectively assessed physical activity and various health outcomes and determine if questionnaire has good construct validity.

Lastly, we know that physical activity is related to kidney function. There are still important questions as to how varying intensities of activity is related. Future studies will need to determine if lower intensity activity provides any benefits to preserving kidney function over time. It would also be interesting to know what through what mechanisms varying intensities of activity have their affect. Some have suggested that sedentary behavior is unique associated with CKD through lipid metabolism. Moderate to vigorous intensity activity may affect kidney function risk through inflammation, oxidative stress, blood pressure control, or other vascular mechanism which have yet to be explored. Light intensity activities may be related to kidney function through similar mechanism as those related to moderate activity, as well as other physiological pathways. There may be statistical procedures, as well as study designs, which can help to examine this further. In the current analysis of the SHS, we used the MAQ to assess physical activity. This allowed us to crudely group individuals into categories of activity. In future analysis of the SHS, we can also incorporate accelerometers to examine the relationship

between varying intensities of activities prospectively, but begin to understand their mechanisms as well.

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