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Racial Differences in Associations of Physical Activity with Chronic Kidney Disease and End-Stage Renal Disease in American Adults: the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

By

Xiaoran Ye
Master of Public Health

Epidemiology

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William McClellan
Committee Chair

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Xiaoran Ye

Bachelor of Medicine
Anhui Medical University
2012

Thesis Committee Chair: William McClellan, M.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2015

Abstract

Racial Differences in Associations of Physical Activity with Chronic Kidney Disease and End-Stage Renal Disease in American Adults: the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

By Xiaoran Ye

Background Physical inactivity is a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD). We investigated whether there were racial disparities in the associations of physical activity with CKD and ESRD.

Methods We analyzed data from 30,239 participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study who had estimated GFR (eGFR) and urinary albumin-to-creatinine ratio (ACR) measured and physical activity level (poor, intermediate, or ideal) reported at baseline. We identified incident ESRD using linked data from the United States Renal Data System. We fitted multivariable logistic models and Cox proportional hazard models to estimate ORs of CKD and HRs of ESRD for physical activity levels among African Americans and whites.

Results At baseline, African Americans were more likely to be physically inactive than whites (37.7% and 32.1%, respectively). The incidence rates of ESRD among African Americans and whites were 385 and 79 cases per 100,000 person-years, respectively. Among participants who were inactive relative to those with ideal physical activity, African Americans were less likely than whites to have reduced kidney function (eGFR < 60/ mL/ min/ 1.73 m^2) (ORs = 1.52 and 1.62, 95% CI: 1.30 – 1.77 and 1.42 – 1.84, respectively) and albuminuria (ACR ≥ 30 mg/g) (ORs = 1.26 and 1.31, 95% CI: 1.11 – 1.43 and 1.16 – 1.48, respectively), but more likely than whites to develop ESRD (HRs = 2.12 and 1.50, 95% CI = 1.52 – 2.95 and 0.88 – 2.57, respectively). The associations of physical activity with CKD and ESRD were not modified by race ($P_{interaction} > 0.05$).

Conclusion These results suggest that lower physical activity level may be associated with higher prevalence of CKD among African Americans and whites, and higher risk for ESRD among African Americans. The associations of physical activity with CKD and ESRD may not be modified by race.

Key words: physical activity, chronic kidney disease, albuminuria, end-stage renal disease, race.

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BACKGROUND/LITERATURE REVIEW

Chronic Kidney Disease and End-Stage Renal Disease

The definition and classification of chronic kidney disease (CKD) were introduced in the 2002 Kidney Disease Quality Outcome Initiative (K/DOQI) guidelines by National Kidney Foundation (NFK). CKD is defined as kidney damage or glomerular filtration rate (GFR) < 60/ mL/ min/ 1.73 m^2 for 3 months or more, irrespective of diagnosis. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies [1]. Albuminuria, defined as albumin-to-creatinine ratio (ACR) ≥ 30 mg/ g in two of three spot urine specimens, is a sensitive marker of kidney damage. GFR is difficult to measure, but can be estimated easily from calibrated serum creatinine and estimating equations [2].

The key outcomes of CKD include progression to end-stage renal disease (ESRD) and premature death due to cardiovascular disease. ESRD is an administrative term based on the occurrence of signs and symptoms of kidney failure necessitating initiation of treatment by replacement therapy including dialysis and transplantation [1].

Epidemiology of CKD

CKD is a global health problem for all race/ethnic groups. The prevalence of CKD is estimated to be 8-16% worldwide and more than 10% of adults, 20 million people, in the US in 2014 [3]. For adults 30 years or older, the projected future prevalence of CKD in the US increases to 14.4% in 2020 and 16.7% in 2030 [4]. Old age, diabetes, high blood pressure, cardiovascular disease, obesity, high cholesterol, lupus, a family history of CKD or ESRD, and history of acute kidney injury (AKI) were generally associated with CKD [3, 5, 6].

Risk Factors for CKD

Through 2007 to 2012, in National Health and Nutrition Examination Survey (NHANES) population, about one third of people 60 years or older had CKD during 2007 to 2012. The prevalence was much lower among those in age groups of 20-39 and 40-59, which were 5.7% and 8.9%, respectively. The difference of prevalence of estimated GFR (eGFR) < 60/ mL/ min/ 1.73 m^2 is more distinctive than that of ACR > 30 mg/g [6]. The frequency of albuminuria is not significantly influenced by aging but related to advanced age together with comorbid condition, especially among males [7].

Diabetes is generally known as a risk factor for CKD. Recent data indicate that 29.1 million people or 9.3% of the population in the US have diabetes, among which 27.8% are undiagnosed [8]. Among people with diabetes, 39.2% of them had CKD, including reduced eGFR (19.6%) and albuminuria (28.6%) from 2007 to 2012. For those who self-reported diabetes, 40.4% of them had CKD [6]. There are 30% of US adults considered to have pre-diabetes among which 17.7% have CKD [9-11].

Hypertension is another well-established cause of CKD. Recent data suggest 67 million US adults (31%) have high blood pressure. An additional one third of US population have prehypertension. Through 2007 to 2012, 31.0%, 17.1% and 19.8% of people with hypertension had CKD, reduced eGFR and albuminuria, respectively. The prevalence of CKD was slightly lower among those who self-reported hypertension than among all hypertension patients [6]. Among those with prehypertension and undiagnosed hypertension, 17.3% and 22.0% of them had CKD [12].

Cardiovascular disease (CVD) is a primary cause of morbidity and premature mortality in CKD. In the US, about 85.6 million people are living with some form of CVD or the after-effects of stroke. CVD is more prevalent among African Americans that nearly half of them have some form of CVD [13]. Traditional CVD risk factors, including older age, hypertension, smoking, physical inactivity, dyslipidemia and diabetes, are involved in cardiomyopathy, atherosclerosis and arteriosclerosis. These risk factors promote the development and progression of both CKD and CVD [14]. In NHANES population, 39.5%, 26.8% and 23.8% of those who self-reported CVD had CKD, reduced eGFR and albuminuria, respectively [6].

Obese individuals are at higher risk for CKD. Morbid obesity with body mass index (BMI) ≥ 35 kg/m^2 also contributes to the development of CKD in the general population (RR = 2.3, 95% CI: 1.1 - 4.9) [15]. Hallan S, et al. found the similar association in Norway that those obese people with BMI ≥ 30 km/m^2 were at 77 percent higher risk of CKD (RR = 1.77, 95% CI: 1.47 – 2.14) [16]. The national data suggest 16.6%, 7.3% and 11.5% of those with obesity (BMI ≥ 30) had CKD, reduced eGFR and albuminuria, respectively.

A 10-year follow-up study found hypercholesterolemia was positively associated with increased risk of CKD stage 1 or 2 (RR = 1.13, 95% CI: 1.02 – 1.25) [17]. Schaeffner ES, et al. found a trend of increasing risk for elevated creatinine levels (≥ 1.5 mg/dL) indicating renal dysfunction as total cholesterol increased in men. They also reported those with HDL < 40 mg/dL were at higher risk of both elevated creatinine level and reduced eGFR compared to those with HDL > 40 mg/dL [18].

Lupus is an autoimmune disease more prevalent among young women. In systemic lupus erythematous (SLE) patients, those with lupus nephritis are at increased risk of developing CKD and the increasing rate of CKD progression. The progressive loss of kidney function is related with sustained proteinuria and high cholesterol level [19].

Individuals reporting a family member with ESRD are more likely to have CKD in their lifetime compared to those without family history of ESRD. In a cross-sectional study, Reasons for Geographic and Racial Differences in Stroke (REGARDS), 9.5% of participants reported a family history of ESRD. Among those, African Americans were more likely to develop stage 3 and 4 CKD, which were more serious stages of CKD [20]. A cross-sectional study in England found the prevalence of microalbuminuria was 9.5% in those with a family history of CKD, significantly higher than 1.4% in those with no family history of CKD ($p = 0.001$) [21].

History of AKI is also associated with development of CKD. Nearly 30% of patients without claims for CKD in the year before an AKI hospitalization claimed for CKD in the one year following the AKI [6]. Lakhmir SC, et al. further found the severity of AKI was a robust prediction of progression to CKD [22].

Epidemiology of ESRD

A total of 114,136 and 114,813 patients began ESRD therapy in 2011 and 2012, respectively, in the US [3]. The prevalent cases increased to 636,905 at the end of 2012 with an increase of 3.7% since 2011. Meanwhile, the incidence rate of ESRD has declined since 2009. The adjusted incidence rate of ESRD decreased to 353 per million year in 2012 [6]. The distribution incident ESRD varied geographically. In general, there were more incident ESRD cases in middle and southern USA, including Mississippi River valleys and Texas [6]. For age 45 and over, there had been increasing incident ESRD cases for years until the past two to three years. In 2012, the adjusted incidence rates for African Americans were 3.3 times greater than for whites [6].

Independent risk factors for ESRD include male sex, older age, African American race, lower education level, lower socioeconomic status (SES), hypertension, diabetes, proteinuria, lower hemoglobin level, elevated serum uric acid level and family history of kidney disease [23].

Risk Factors for ESRD

Males had about 15 percent higher incidence and point prevalence of ESRD than females [6]. The difference may be associated with more rapid progression of CKD in males than females and probably due to sex hormones [24].

The adjusted incidence rates of ESRD increased consistently from 13 to 1,618 per million population with increasing age groups from 0-19 to 75+ [6]. Those who were older than 65 had the highest incidence rates which were greater than 1,000 per million population and highest point prevalence which were greater than 6,000 per million population [6]. This may reflect the increasing cumulative risk for ESRD across the time horizons for all age groups among both males and females [25].

By 2010, the African-American population represented 12.6% of the U.S. population, but they accounted for 31.5% of patients diagnosed with ESRD [6]. SES, which is commonly measured by income, education and occupation, is adversely associated with incidence and prevalence of ESRD. The complex interplay between race and SES also contributes to the variability of risk for ESRD [26].

More than one third and one fourth of incident and prevalent cases of ESRD reported diabetes and hypertension, respectively [6]. There is a threefold increased risk for ESRD in people with diabetes compared to those without diabetes [27]. Hypertension is an independent predictor of accelerated loss of renal function and careful blood pressure control helps reduce the incidence of ESRD [28].

Proteinuria is a strong and sensitive predictor of ESRD. Proteinuria (1+) was found to be associated with 93 percent and 142 percent higher odds of ESRD in men and women, respectively (95% CI: 1.53 – 2.41, 1.91 – 3.06, respectively) [29].

Family history of ESRD is common among older Americans and associated with the increased risk of ESRD after adjusted for demographics, comorbid conditions and SES (HR = 1.82, 95% CI: 1.00 – 3.28) [30].

Physical Activity

It is well acknowledged that regular physical activity can reduce the risk of many diseases including heart disease and type 2 diabetes, and produce long-term health benefits. The “2008 Physical Activity Guidelines for Americans” recommends adults do at least 150 minutes a week of moderate-intensity physical activity, such as brisk walking, or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of both [31].

Physical Activity and Kidney Disease

Lack of physical activity is a risk factor for cardiovascular disease [32, 33], CKD [15], and ESRD [34]. Exercise training improves many of the risk factors associated with the development and progression of CKD [35]. In persons with established CKD, higher physical activity levels are associated with slower rates of eGFR loss [36], slower progression of CKD [37], and decreased all-cause mortality.[38]

The mechanism for a possible benefit of physical activity on albuminuria is unclear but may be related to effects of physical activity on the vascular endothelium, possibly mediated by nitric oxide [39]. Renal vascular endothelium damage is associated with elevated urinary excretion of albumin and preceded occurrence of microalbuminuria [40]. Nitric oxide is a vasorelaxant, and impaired nitric oxide activity causes endothelial dysfunction. This pathogenic mechanism results in an increased permeability of the vascular wall and generates albuminuria [41]. In patients with chronic heart failure, regular physical exercise improves oxygen uptake and nitric oxide activity, and thus corrects endothelial dysfunction and improves endothelium-dependent vasodilation in skeletal muscle vasculature [42]. In patients with coronary artery disease, exercise training improves brachial flow-mediated dilation and endothelium-dependent vasodilation in coronary vessels [43]. Physical exercise may have similar effects on endothelium in the renal vasculature, decreasing urinary excretion of albumin.

Metabolic disturbances including activation of the renin-angiotensin system, insulin resistance, oxidative stress, endothelial dysfunction, increased circulation cytokines and increased inflammation, can be caused by hypertension, diabetes, obesity and kidney dysfunction [44]. These disturbances are more prevalent in physically inactive people and CKD patients, and increase the risks for micro- and macro-vascular diseases [45]. Physical activity may attenuate the metabolic processes and affect the kidney, by decreasing inflammation, fibrosis and slowing down the decline of eGFR and the progression from CKD to ESRD [36].

Racial Disparities in CKD and ESRD

Though the prevalence of CKD is comparable or higher among whites compared with African Americans [46, 47], albuminuria is more prevalent in African Americans [10]. The risk for ESRD among African Americans is three- to four times higher than for whites [48, 49]. Risk factors, including genetic basis [50], SES, hypertension, diabetes, access to diabetes care, preventive care, and primary physician visits [51, 52], have been studied in relation to the racial disparity. African Americans are less likely to be as physically active as whites [53, 54]. Whether the associations of physical activity with CKD and ESRD differ by race is rarely studied.

Objective

The objective of this study was to investigate whether there are racial differences in the associations of physical activity with the prevalence of CKD and risk for ESRD, using baseline and follow-up data previously collected in a population-based cohort in the US, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.

METHODS

Study Design

The REGARDS study is a population-based cohort study of individuals 45 years or older designed to investigate the causes for the excess stroke risk in the Southeastern United States (US) and among African Americans. The methods of the REGARDS study have been described in detail elsewhere [55]. Overall, 30,239 participants were enrolled between 2003 and 2007. Exclusion criteria were missing value on physical activity category, race/ethnicity other than non-Hispanic black or white. After these exclusions, data from 29,733 participants were available for analysis. Consent was obtained verbally and later in writing. The study was approved by the institutional review boards of the participating institutions.

Data Collection

Briefly, individuals were identified from commercially available lists of residents, and recruited using an initial mailing followed by telephone contact. Using a computer-assisted telephone interview, trained interviewers obtained demographic information and medical history. A brief physical exam including two sitting blood pressure measurements using a standard technique and collection of blood and urine samples was conducted in-person (usually in the home) 3-4 weeks after the telephone interview. Self-administered questionnaires were left with the participant to be completed after the in-person visit and returned by self- addressed prepaid envelopes. Follow-up interviews are attempted every 6 months, and there is a standard protocol for tracking missed contacts.

Low annual household income was defined as below $20,000, and low educational attainment was defined as not having completed high school. Hypertension was defined as either self-reported use of antihypertensive medications or a mean SBP ≥140 mmHg or mean DBP ≥90 mmHg. Diabetes was defined as (1) self-reported use of insulin or oral hypoglycemics, (2) a fasting blood glucose greater than or equal to 126 mg/dl, or (3) a nonfasting blood glucose greater than or equal to 200 mg/dl.

Assessment of physical activity Frequency is a widely used measure of physical activity [56, 57]. In this study, intense physical activity frequency was decided by each participant's answer to the question: How many times per week do you engage in intense physical activity, enough to work up a sweat? Participants' answers were categorized into three levels based on the American Heart Association (AHA) definitions for adults (> 20 y of age) [58]. No intense physical activity, 1 to 3 times intense physical activity per week and 4 or more times intense physical activity per week were categorized as poor, intermediate and ideal physical activity levels, respectively [59].

Reduced kidney function Serum creatinine was measured using colorimetric reflectance spectrophotometry of the Ortho Vitros Clinical Chemistry System 950IRC instrument (Johnson & Johnson Clinical Diagnostics, New Brunswick, NJ). eGFR was calculated from isotope dilution mass spectrometry- traceable serum creatinine values using the CKD-EPI equation.[60]. Reduced kidney function was defined as a baseline estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, corresponding to stage 3-5 (moderate-severe) CKD [61].

Albuminuria Urine albumin and creatinine were measured using a BN ProSpec Nephelometer (Dade Behring, Marburg, Germany; interassay coefficient of variation, 2.2-4.3%) and Modular-P chemistry analyzer (Roche Hitachi, Indianapolis, IN; interassay coefficient of variation, 2.6-8.6%), respectively [62]. Albuminuria was defined as a baseline urinary albumin:creatine ratio (ACR) ≥ 30 mg/g.

ESRD The incidence of ESRD was determined using linked data from the United States Renal Data System registry, which records > 90% of incident ESRD in the United States. Follow-up time included time from study enrollment to first ESRD treatment, death, or last date of follow-up (9/1/09; mean follow-up, 3.4 years). Participants who had ESRD prior to enrollment were excluded from relevant analyses, and included participants were censored at death or last date of follow-up.

Statistical analyses

Participant characteristics were compared across category of physical activity using χ^2 or ANOVA tests for categorical and continuous variables, respectively. We used log-transformed ACR and reported the geometric means. Crude prevalence of albuminuria and reduced kidney function and crude incidence of ESRD were calculated by physical activity category and race. Incident rate ratios for African Americans compared with whites were computed as the ratios of each group's incidence rates.

Race-stratified logistic regression was used to examine associations [prevalence odds ratios (PORs)] between physical activity frequency and prevalence of reduced eGFR and ACR at baseline. We examined the assumption of Cox proportional hazard model by plotting the natural logarithm of the cumulative hazard of ESRD by race and physical activity category. Then we fitted the race-stratified Cox proportional hazard model of time to ESRD to obtain hazard ratios (HRs) of incident ESRD by race and physical activity. Groups of covariates were chosen and entered sequentially to the models to assess confounding: demographics (age, sex), then socioeconomic status (income, education), and finally clinical (diabetes, hypertension). The potential for effect modification between physical activity and race was assessed by the two-way interaction terms in each model. The statistical significance of interaction terms was assessed with Wald χ^2 tests. For this study, participants were limited to those with physical activity information (N = 29,733); of these pariticipatns, those with complete information for assessment of reduced kidney function (N = 28,445) and prevalent albuminuria (N = 28,270) and free of ESRD at the start of the study (N = 29,563) were included in the respective analyses. All analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC).

RESULTS

Participant characteristics

The mean age of 29,733 participants was 64.8 years, 55.1% were female, and 41.5% were African American. A total of 12.4% and 18.1% of participants reported less than less than high school education and being in low-income households (< $20,000 per year), respectively. Hypertension (59.3%), diabetes (22.0%), obesity (38.4%) and smoking (14.6%) were prevalent among participants. In general, females, African Americans, current smokers and those with less than a high school education, a low income, hypertension, diabetes and obesity were more likely to be less physical active. Participant characteristics by physical activity level and race are shown in Table 1. African American participants were more likely to be younger, female, current smoking, and to have less than a high school education, and to have a low income, hypertension, diabetes and obesity at baseline compared to whites. African Americans were more likely to be physically inactive than whites (37.7% and 32.1%, respectively). On average, African American participants had higher eGFRs and albumin creatinine ratios (ACRs) than whites did.

Prevalence of reduced kidney function, by physical activity level

The crude prevalence of reduced kidney function (eGFR < 60 ml/min/1.73m^2) increased with decreasing of physical activity frequency in both African American and white participants at baseline (Table 2). The differences of prevalence of reduced kidney function across physical activity levels were statistically significant in both races. For all three categories of physical activity, the prevalence of having reduced kidney function among African Americans was slightly higher than among whites (Figure 1). For example, in the intermediate physically active category, the prevalence of reduced kidney function was 9.9% and 9.2% among African Americans and whites (Table 2). Individuals within poor level of physical activity had statistically significant 52 percent and 62 percent higher prevalence odds of having reduced kidney function, for African Americans and whites, compared with those with ideal physical activity after fully adjusted for demographics, SES and clinical characteristics (Table 3; 95% CI: 1.30 – 1.77 and 1.42 – 1.84, respectively). Tests for interactions of race with level of physical activity were not statistically significant after adjustment ($P_{interaction} = 0.521$).

Prevalence of albuminuria, by physical activity level

The crude prevalence of albuminuria among participants with ideal and intermediate physical activity was comparable and lower than among participants with poor physical activity, regardless of race, at baseline (Table 2). And the differences of prevalence of albuminuria across activity levels were statistically significant in both races. Additionally, albuminuria was more prevalent among American Africans than among whites overall (19.5% vs. 12.3%) and within each physical activity category (Figure 2). The prevalence odds of albuminuria among participants with intermediate physical activity level were not statistically significantly different compared to those with ideal activity level, regardless of race. However, those who were physically inactive did have 26 and 31 percent higher fully-adjusted prevalence odds of albuminuria, for African

Americans and whites, relative to those who were ideally physically active (Table 3; 95% CI: 1.11 – 1.43 and 1.16 – 1.48, respectively). The association of physical activity with albuminuria was not statistically significantly modified by race ($P_{interaction}$ = 0.457).

Incidence of ESRD, by physical activity level

During the follow-up from 2003 to 2014 with the median of 6.6 years, a total of 372 participants developed incident ESRD with an incidence rate of 199 persons per 100,000 person-years. There were 283 incident cases of ESRD among African Americans and 89 among white participants. The incidence rate of ESRD among African Americans was 306 persons per 100,000 person-years greater than that among whites (385 vs. 79, respectively). The incidence rate of ESRD of African Americans within each level of physical activity was higher than whites within corresponding level of activity (Figure 3). The crude incidence rate of incident ESRD and its difference between two races tended to increase with decreasing physical activity frequency, especially among African Americans (Table 2). The crude incidence of ESRD was statistically significantly different across levels of activity only among African Americans (Table 2). There appeared to be a tendency that less frequent physical activity was associated with increasing fully-adjusted risk for incident ESRD among African Americans (Table 3). For example, African American individuals who engaged in intermediate and poor levels of physical activities relative to those within ideal levels of activities were of 19 and 112 percent higher risk for incident ESRD (95% CI: 0.83 – 1.70 and 1.52 – 2.95, respectively). However, this tendency was not statistically significant among whites. The risk for ESRD among white participants who took intermediate and poor physical activities was not significantly different from those took ideal activities. The interaction of race with physical activity in the fully-adjusted model was not statistically significant ($P_{interaction}$ = 0.113).

DISCUSSION

Our results suggested that physical inactivity levels may be associated with higher prevalence of reduced kidney function and albuminuria in both African Americans and whites, and higher risk of ESRD in African Americans. Our results suggested that the effect of physical activity on CKD and ESRD might not be modified by race.

The mechanism for a possible benefit of physical activity on albuminuria is unclear but may be related to effects of physical activity on the vascular endothelium, possibly mediated by nitric oxide [39]. Renal vascular endothelium damage is associated with elevated urinary excretion of albumin and preceded occurrence of microalbuminuria [40]. Nitric oxide is a vasorelaxant, and impaired nitric oxide activity causes endothelial dysfunction. This pathogenic mechanism results in an increased permeability of the vascular wall and generates albuminuria [41]. In patients with chronic heart failure, regular physical exercise improves oxygen uptake and nitric oxide activity, and thus corrects endothelial dysfunction and improves endothelium-dependent vasodilation in skeletal muscle vasculature [42]. In patients with coronary artery disease, exercise training improves brachial flow-mediated dilation and endothelium-dependent vasodilation in coronary vessels [43]. Physical exercise may have similar effects on endothelium in the renal vasculature, decreasing urinary excretion of albumin.

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The results of our study were consistent with those of several previous studies. Two cohort studies in the US [15, 39], one cohort study in Australia [63], and one cross-sectional study in the UK [64] found similar results that higher activity level was associated with decreased eGFR and/or ACR. One population based cohort study in the US also found that higher physical activity level was associated with lower risk for ESRD [34]. However, one hospital-based cohort study in Seattle reached conflicting results [36]. This may have been due to the difference in study populations and the small sample size of the Seattle study. To the best of our knowledge, no previous study focused on racial differences in the associations of physical activity with CKD and ESRD.

Major limitations of our study include that measurement data on physical activity, eGFR, and albuminuria were collected only one time at baseline, which may have introduced some exposure and outcome misclassification; data on some potential confounders were not available in REGARDS study, such as genotype and primary physician visits; our follow-up time may have been too short to observe long-term incident ESRD. On the other hand, our geographically diverse sample of African Americans and whites was the major strength of our study. Future studies may follow-up participants and ascertain physical activity and CKD measurement data periodically to assess the potential temporal association between activity and CKD.

In conclusion, our findings, taken in context with those from previous studies, suggest that lower physical activity level may be associated with a higher prevalence of reduced kidney function and albuminuria among African Americans and whites, and higher risk for ESRD among African Americans. The associations of physical activity with CKD and ESRD may not be modified by race.

References

1. National Kidney Foundation, *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Am J Kidney Dis, 2002. **39**(2 Suppl 1): p. S1-266.
2. Levey, A.S., et al., *Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO).* Kidney Int, 2005. **67**(6): p. 2089-100.
3. U.S. CDC, *National Chronic Kidney Disease Fact Sheet: General Information and National Estimates on Chronic Kidney Disease in the United States, 2014*. 2014, Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention.
4. Hoerger, T.J., et al., *The Future Burden of CKD in the United States: A Simulation Model for the CDC CKD Initiative.* Am J Kidney Dis, 2015. **65**(3): p. 403-11.
5. Levey, A.S. and J. Coresh, *Chronic kidney disease.* Lancet, 2012. **379**(9811): p. 165-80.
6. U.S. Renal Data System, *2014 Annual data report: epidemiology of kidney disease in the United States*. 2014: Bethesda, MD.
7. Krol, E., et al., *Aging or comorbid conditions - what is the main cause of kidney damage?* J Nephrol, 2010. **23**(4): p. 444-52.
8. U.S. CDC., *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. 2014: Atlanta, GA.

9. Plantinga, L.C., et al., *Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes.* Clin J Am Soc Nephrol, 2010. **5**(4): p. 673-82.

10. Cowie, C.C., et al., *Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006.* Diabetes Care, 2009. **32**(2): p. 287-94.

11. U.S. CDC., *National diabetes fact sheet: General information and national estimates on diabetes in the United States, 2007*. 2008, US Department of Health and Human Services, Centers for Disease Control and Prevention: Atlanta, GA.

12. Crews, D.C., et al., *Prevalence of chronic kidney disease in persons with undiagnosed or prehypertension in the United States.* Hypertension, 2010. **55**(5): p. 1102-9.

13. Mozaffarian, D., et al., *Heart disease and stroke statistics--2015 update: a report from the American Heart Association.* Circulation, 2015. **131**(4): p. e29-322.

14. Menon, V., A. Gul, and M.J. Sarnak, *Cardiovascular risk factors in chronic kidney disease.* Kidney Int, 2005. **68**(4): p. 1413-8.

15. Stengel, B., et al., *Lifestyle factors, obesity and the risk of chronic kidney disease.* Epidemiology, 2003. **14**(4): p. 479-87.

16. Hallan, S., et al., *Obesity, smoking, and physical inactivity as risk factors for CKD: are men more vulnerable?* Am J Kidney Dis, 2006. **47**(3): p. 396-405.

17. Yamagata, K., et al., *Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study.* Kidney Int, 2007. **71**(2): p. 159-66.
18. Schaeffner, E.S., et al., *Cholesterol and the risk of renal dysfunction in apparently healthy men.* J Am Soc Nephrol, 2003. **14**(8): p. 2084-91.
19. Bradshaw, S.E., *Lupus nephritis: Sustained proteinuria and dyslipidemia are risk factors for progressive CKD in patients with lupus nephritis.* Nat Rev Nephrol, 2011. **7**(4): p. 184.
20. McClellan, W.M., et al., *Individuals with a family history of ESRD are a high-risk population for CKD: implications for targeted surveillance and intervention activities.* Am J Kidney Dis, 2009. **53**(3 Suppl 3): p. S100-6.
21. Bello, A.K., et al., *A population-based screening for microalbuminuria among relatives of CKD patients: the Kidney Evaluation and Awareness Program in Sheffield (KEAPS).* Am J Kidney Dis, 2008. **52**(3): p. 434-43.
22. Chawla, L.S., et al., *The severity of acute kidney injury predicts progression to chronic kidney disease.* Kidney Int, 2011. **79**(12): p. 1361-9.
23. Hsu, C.Y., et al., *Risk factors for end-stage renal disease: 25-year follow-up.* Arch Intern Med, 2009. **169**(4): p. 342-50.
24. Neugarten, J. and L. Golestaneh, *Gender and the prevalence and progression of renal disease.* Adv Chronic Kidney Dis, 2013. **20**(5): p. 390-5.
25. Turin, T.C., et al., *Lifetime risk of ESRD.* J Am Soc Nephrol, 2012. **23**(9): p. 1569-78.

26. Patzer, R.E. and W.M. McClellan, *Influence of race, ethnicity and socioeconomic status on kidney disease.* Nat Rev Nephrol, 2012. **8**(9): p. 533-41.

27. Jones, C.A., et al., *Epidemic of end-stage renal disease in people with diabetes in the United States population: do we know the cause?* Kidney Int, 2005. **67**(5): p. 1684-91.

28. Walker, W.G., *Hypertension-related renal injury: a major contributor to end-stage renal disease.* Am J Kidney Dis, 1993. **22**(1): p. 164-73.

29. Iseki, K., et al., *Proteinuria and the risk of developing end-stage renal disease.* Kidney Int, 2003. **63**(4): p. 1468-74.

30. McClellan, W.M., et al., *Association of family history of ESRD, prevalent albuminuria, and reduced GFR with incident ESRD.* Am J Kidney Dis, 2012. **59**(1): p. 25-31.

31. *2008 Physical Activity Guidelines for Americans.* Journal of Cardiovascular Nursing, 2009. **24**(1): p. 2-3.

32. Leon, A.S. and J. Connett, *Physical activity and 10.5 year mortality in the Multiple Risk Factor Intervention Trial (MRFIT).* Int J Epidemiol, 1991. **20**(3): p. 690-7.

33. Nocon, M., et al., *Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis.* Eur J Cardiovasc Prev Rehabil, 2008. **15**(3): p. 239-46.

34. Muntner, P., et al., *Cardiovascular risk factors in CKD associate with both ESRD and mortality.* J Am Soc Nephrol, 2013. **24**(7): p. 1159-65.

35. Stump, C.S., *Physical Activity in the Prevention of Chronic Kidney Disease.* Cardiorenal Med, 2011. **1**(3): p. 164-173.

36. Robinson-Cohen, C., et al., *Physical activity and change in estimated GFR among persons with CKD.* J Am Soc Nephrol, 2014. **25**(2): p. 399-406.

37. Teng, H.L., et al., *Effects of targeted interventions on lifestyle modifications of chronic kidney disease patients: randomized controlled trial.* West J Nurs Res, 2013. **35**(9): p. 1107-27.

38. Ricardo, A.C., et al., *Adherence to a healthy lifestyle and all-cause mortality in CKD.* Clin J Am Soc Nephrol, 2013. **8**(4): p. 602-9.

39. Robinson, E.S., et al., *Physical activity and albuminuria.* Am J Epidemiol, 2010. **171**(5): p. 515-21.

40. Ochodnicky, P., et al., *Microalbuminuria and endothelial dysfunction: emerging targets for primary prevention of end-organ damage.* J Cardiovasc Pharmacol, 2006. **47 Suppl 2**: p. S151-62; discussion S172-6.

41. Erdely, A., et al., *DOCA/NaCl-induced chronic kidney disease: a comparison of renal nitric oxide production in resistant and susceptible rat strains.* Am J Physiol Renal Physiol, 2007. **292**(1): p. F192-6.

42. Hambrecht, R., et al., *Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure.* Circulation, 1998. **98**(24): p. 2709-15.

43. Hambrecht, R., et al., *Effect of exercise on coronary endothelial function in patients with coronary artery disease.* N Engl J Med, 2000. **342**(7): p. 454-60.

44. Amann, K., C. Wanner, and E. Ritz, *Cross-talk between the kidney and the cardiovascular system.* J Am Soc Nephrol, 2006. **17**(8): p. 2112-9.

45. Himmelfarb, J., et al., *The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia.* Kidney Int, 2002. **62**(5): p. 1524-38.

46. McClellan, W., et al., *Racial differences in the prevalence of chronic kidney disease among participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study.* J Am Soc Nephrol, 2006. **17**(6): p. 1710-5.

47. Coresh, J., et al., *Prevalence of chronic kidney disease in the United States.* JAMA, 2007. **298**(17): p. 2038-47.

48. McClellan, W.M., et al., *Albuminuria and racial disparities in the risk for ESRD.* J Am Soc Nephrol, 2011. **22**(9): p. 1721-8.

49. Clase, C.M., A.X. Garg, and B.A. Kiberd, *Prevalence of low glomerular filtration rate in nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III).* J Am Soc Nephrol, 2002. **13**(5): p. 1338-49.

50. Quaggin, S.E. and A.L. George, Jr., *Apolipoprotein l1 and the genetic basis for racial disparity in chronic kidney disease.* J Am Soc Nephrol, 2011. **22**(11): p. 1955-8.

51. Li, S., et al., *Differences between blacks and whites in the incidence of end-stage renal disease and associated risk factors.* Adv Ren Replace Ther, 2004. **11**(1): p. 5-13.

52. Volkova, N., et al., *Neighborhood poverty and racial differences in ESRD incidence.* J Am Soc Nephrol, 2008. **19**(2): p. 356-64.

53. Short, V.L., A. Gamble, and V. Mendy, *Racial differences in ideal cardiovascular health metrics among Mississippi adults, 2009 Mississippi Behavioral Risk Factor Surveillance System.* Prev Chronic Dis, 2013. **10**: p. E194.

54. McDonnell, M.N., et al., *Physical activity frequency and risk of incident stroke in a national US study of blacks and whites.* Stroke, 2013. **44**(9): p. 2519-24.

55. Howard, V.J., et al., *The reasons for geographic and racial differences in stroke study: objectives and design.* Neuroepidemiology, 2005. **25**(3): p. 135-43.

56. Washburn, R.A., L.L. Adams, and G.T. Haile, *Physical activity assessment for epidemiologic research: the utility of two simplified approaches.* Prev Med, 1987. **16**(5): p. 636-46.

57. Washburn, R.A., et al., *The validity of self-reported exercise-induced sweating as a measure of physical activity.* Am J Epidemiol, 1990. **132**(1): p. 107-13.

58. Lloyd-Jones, D.M., et al., *Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond.* Circulation, 2010. **121**(4): p. 586-613.

59. Thacker, E.L., et al., *The American Heart Association Life's Simple 7 and incident cognitive impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) study.* J Am Heart Assoc, 2014. **3**(3): p. e000635.

60. Levey, A.S., et al., *A new equation to estimate glomerular filtration rate.* Ann Intern Med, 2009. **150**(9): p. 604-12.

61. Levey, A.S., et al., *National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Ann Intern Med, 2003. **139**(2): p. 137-47.

62. Warnock, D.G., et al., *Kidney function, albuminuria, and all-cause mortality in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study.* Am J Kidney Dis, 2010. **56**(5): p. 861-71.

63. White, S.L., et al., *Physical inactivity and chronic kidney disease in Australian adults: the AusDiab study.* Nutr Metab Cardiovasc Dis, 2011. **21**(2): p. 104-12.

64. Bharakhada, N., et al., *Association of sitting time and physical activity with CKD: a cross-sectional study in family practices.* Am J Kidney Dis, 2012. **60**(4): p. 583-90.

TABLES

Table 1 Baseline characteristics of cohort participants, by race and physical activity levels, REGARDS study (N = 29,733)

	PA levels[a]							
	African American				White			
	Total	Ideal	Intermediate	Poor	Total	Ideal	Intermediate	Poor
N	12,332	3,240 (26.3)	4,441 (36.0)	4,651 (37.7)	17,401	5,558 (31.9)	6,254 (35.9)	5,589 (32.1)
Female (%)	62.1	54.4	60.9	68.7	50.2	41.2	50.4	58.9
Age (y)[b]	64.0 (9.3)	63.6 (9.0)	63.2 (9.0)	65.1 (9.6)	65.4(9.5)	65.6 (9.2)	64.2 (9.4)	66.5 (9.7)
Low income (%)[c]	26.9	25.5	23.1	31.5	11.9	10.3	9.3	16.4
Education <HS (%)	19.8	19.2	16.2	23.6	7.2	7.2	5.4	9.3
Insured (%)	90.1	88.2	90.2	91.3	95.6	95.6	95.4	95.7
Usual medical care (%)	67.7	66.0	68.6	67.9	77.1	77.3	78.4	75.5
Current smoker (%)	17.5	18.1	15.5	18.9	12.5	10.3	11.7	15.5
Hypertension (%)	71.2	66.8	70.4	75.0	50.6	47.1	47.8	57.2
Diabetes (%)	29.5	25.3	29.0	33.0	15.3	13.0	13.4	19.8
Dyslipidemia (%)	52.7	50.2	53.3	53.9	60.2	58.7	59.7	62.3
BMI > 30kg/m^2 (%)	47.8	41.6	49.0	50.9	31.3	23.7	31.2	39.0
Family history of ESRD (%)	10.3	9.8	10.3	10.5	4.7	4.5	4.8	4.9
eGFR (ml/min/ 1.73 m^2)[b]	88.5 (23.7)	90.5 (22.0)	90.0 (22.4)	85.8 (25.8)	82.6(17.2)	83.3 (15.7)	83.7 (16.6)	80.6 (19.1)
Median ACR (mg/g)	8.0	7.5	7.5	8.9	7.1	6.8	6.7	8.2

Abbreviations: REGARDS, Reasons for Geographic and Racial Differences in Stroke; PA, physical activity; HS, high school; BMI, body mass index; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio; CKD, chronic kidney disease.

Missing data (whites and blacks): education < HS, n = 23; insurance, n = 27; usual medical care, n = 2,349; current smoker, n = 109; hypertension, n = 73; diabetes, n = 1,116; dyslipidemia, n = 1,120; BMI > 30kg/m^2, n = 215; family history of ESRD, n = 8,847; eGFR, n = 1,288; ACR, n = 1,463.

$P < 0.05$ in African Americans and whites across PA levels, by chi-square (categorical) and ANOVA (continuous) tests, for all characteristics shown, except insurance in whites, usual medical care in whites and family history of ESRD in African Americans and whites (all $p > 0.05$).

[a]Poor, intermediate and ideal PA levels are defined as no intense PA, 1 to 3 times intense PA per week, 4 or more intense PA per week, respectively.

[b]Values are mean with SD in parentheses.

[c]Household income less than $20,000 per year.

Table 2 Crude prevalence of reduced kidney function[a] and albuminuria[b] and crude incidence of ESRD, by race and physical activity levels, REGARDS study

Outcome	PA levels[c]							
	African American				White			
	Ideal	Intermediate	Poor	P[d]	Ideal	Intermediate	Poor	P[d]
Crude prevalence of reduced kidney function								
No. of events	286	419	695	< 0.0001	455	557	816	< 0.0001
No. of individuals	3085	4217	4338		5377	6051	5377	
Prevalence	9.3	9.9	16.0		8.5	9.2	15.2	
Crude prevalence albuminuria								
No. of events	524	757	974	< 0.0001	588	610	845	< 0.0001
No. of individuals	3091	4215	4286		5342	6022	5314	
Prevalence	17.0	18.0	22.7		11.0	10.1	15.9	
Crude incidence of ESRD								
No. of events	49	83	151	< 0.0001	23	30	36	0.104
No. of individuals	3226	4404	4576		5549	6243	5565	
Incidence (per million person-years)	2502.1	3031.3	5677.1		625.4	717.5	1044.1	

Abbreviations: REGARDS, Reasons for Geographic and Racial Differences in Stroke; PA, physical activity; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
[a]A baseline estimated glomerular filtration rate < 60 ml/min/1.73 m^2.
[b]A baseline urinary albumin:creatine ratio ≥ 30 mg/g.
[c]Poor, intermediate and ideal PA levels are defined as no intense PA, 1 to 3 times intense PA per week, 4 or more intense PA per week, respectively.
[d]By χ^2 (reduced kidney function, albuminuria) and log-rank (ESRD) tests of equality across PA levels.

Table 3 Crude and adjusted prevalence odds ratios for reduced kidney function[a] and albuminuria[b] and hazard ratios for incident ESRD, by race and physical activity levels, REGARDS study

Model	PA levels[c]						P[d]
	African American			White			
	Ideal	Intermediate	Poor	Ideal	Intermediate	Poor	
Prevalence odds ratios (95% CI) for reduced kidney function							
Unadjusted	1.00	1.08 (0.92, 1.26)	1.87 (1.61, 2.16)	1.00	1.10 (0.96, 1.25)	1.94 (1.71, 2.19)	0.918
Adjusted[e]							
+ demographics	1.00	1.12 (0.95, 1.31)	1.67 (1.43, 1.94)	1.00	1.25 (1.09, 1.44)	1.82 (1.60, 2.07)	0.374
+ SES	1.00	1.12 (0.95, 1.32)	1.65 (1.42, 1.92)	1.00	1.00 (0.89, 1.13)	1.53 (1.36, 1.72)	0.343
+ clinical	1.00	1.06 (0.89, 1.25)	1.52 (1.30, 1.77)	1.00	1.24 (1.08, 1.43)	1.62 (1.42, 1.84)	0.521
Prevalence odds ratios (95% CI) for albuminuria							
Unadjusted	1.00	1.07 (0.95, 1.21)	1.44 (1.28, 1.62)	1.00	0.91 (0.80, 1.03)	1.53 (1.37, 1.71)	0.410
Adjusted[e]							
+ demographics	1.00	1.10 (0.97, 1.25)	1.44 (1.28, 1.63)	1.00	0.99 (0.88, 1.12)	1.57 (1.40, 1.77)	0.248
+ SES	1.00	1.11 (0.98, 1.26)	1.42 (1.26, 1.60)	1.00	1.13 (0.99, 1.29)	1.43 (1.26, 1.63)	0.241
+ clinical	1.00	1.03 (0.91, 1.17)	1.26 (1.11, 1.43)	1.00	0.96 (0.84, 1.09)	1.31 (1.16, 1.48)	0.457
Hazard ratios (95% CI) for incident ESRD							
Unadjusted	1.00	1.21 (0.85, 1.72)	2.28 (1.65, 3.15)	1.00	1.15 (0.67, 1.98)	1.68 (1.00, 2.84)	0.235
Adjusted[e]							
+ demographics	1.00	1.25 (0.88, 1.78)	2.40 (1.74, 3.33)	1.00	1.28 (0.74, 2.20)	1.97 (1.16, 3.33)	0.263
+ SES	1.00	1.28 (0.90, 1.82)	2.37 (1.71, 3.28)	1.00	1.30 (0.75, 2.24)	1.92 (1.13, 3.26)	0.273
+ clinical	1.00	1.19 (0.83, 1.70)	2.12 (1.52, 2.95)	1.00	1.26 (0.73, 2.17)	1.50 (0.88, 2.57)	0.113

Abbreviations: REGARDS, Reasons for Geographic and Racial Differences in Stroke; PA, physical activity; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

[a]A baseline estimated glomerular filtration rate < 60 ml/min/1.73 m^2.

[b]A baseline urinary albumin:creatine ratio ≥ 30 mg/g.

[c]Poor, intermediate and ideal PA levels are defined as no intense PA, 1 to 3 times intense PA per week, 4 or more intense PA per week, respectively.

[d]P for interaction by Wald $\chi 2$ test between race and physical activity levels in an overall model.

[e]Demographics: age, gender, race (overall models only); SES: education, income; clinical: smoke, hypertension, diabetes.

FIGURES

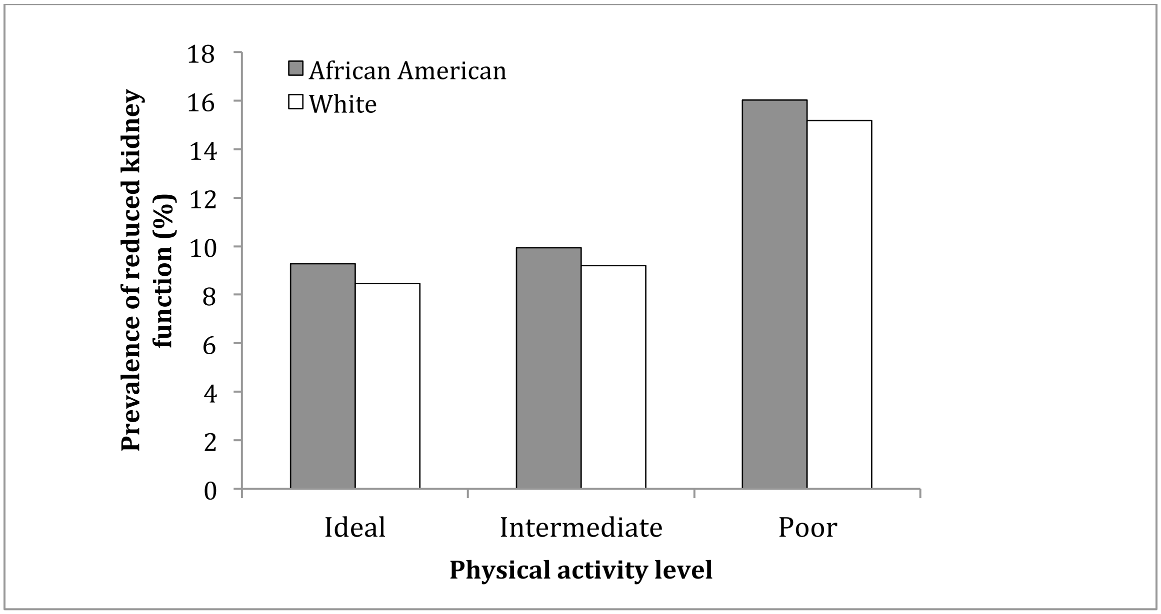

Figure 1. Prevalence of reduced kidney function, by race and physical activity level.

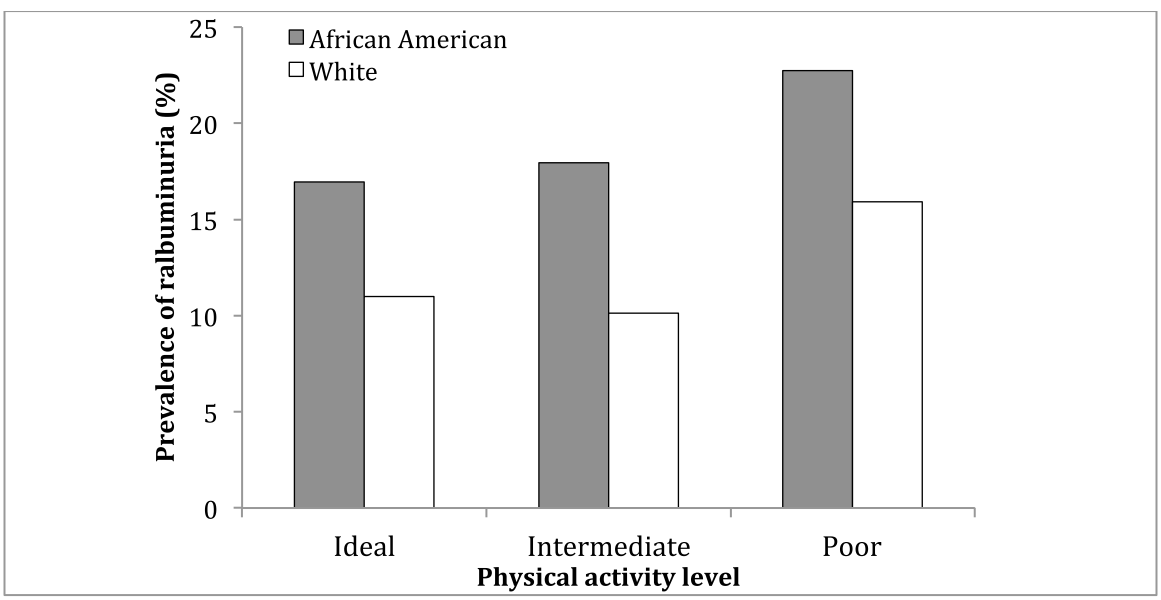

Figure 2. Prevalence of albuminuria, by race and physical activity level

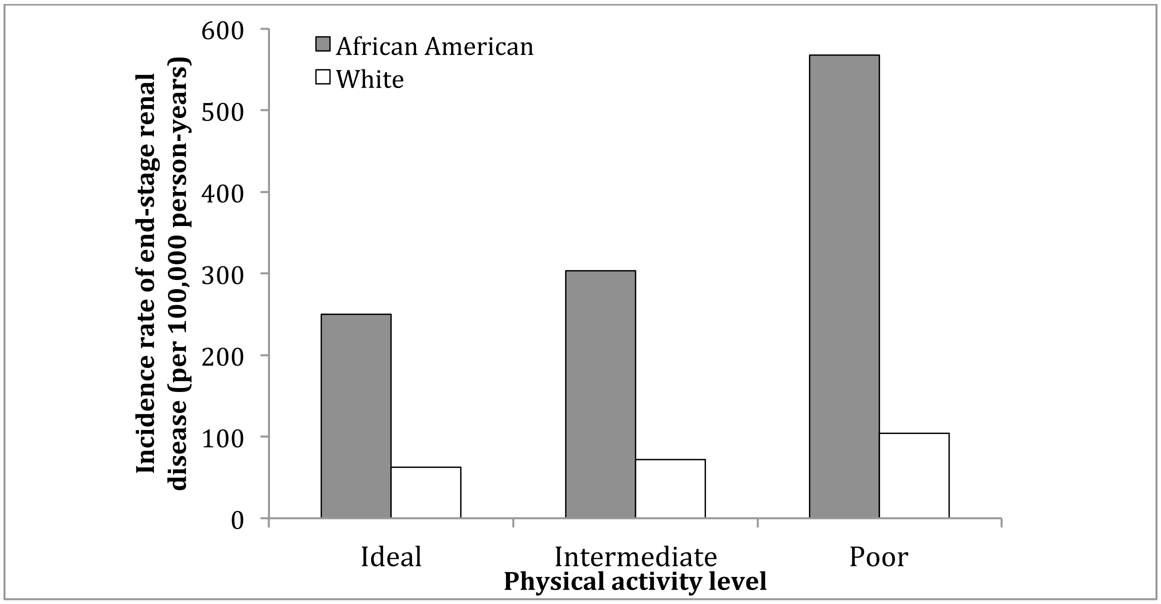

Figure 3. Incidence rate of end-stage renal disease, by race and physical activity level