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# BMJ Open

## The association of exercise and sedentary behaviors with incident end stage renal disease in the Southern Community Cohort Study

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3 **The association of exercise and sedentary behaviors with incident end stage renal disease in**  
4 **the Southern Community Cohort Study**  
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## ABSTRACT

**Objective:** Lifestyle factors, including sedentary time and physical activity, could independently contribute to risk of end stage renal disease (ESRD).

**Study Design:** Case-cohort study.

**Setting:** Southeastern US

**Participants:** The Southern Community Cohort Study recruited ~86,000 blacks and whites from 2002-2009. We assembled a case-cohort of 692 incident ESRD cases and a probability sample of 4113 participants.

**Predictors:** Sedentary time was calculated as hours/day from daily sitting activities. Physical activity was calculated as metabolic equivalent (MET)-hours/day from engagement in light, moderate, and vigorous activities.

**Outcomes:** Incident ESRD.

**Results:** At baseline, among the subcohort, mean (SD) age was 52 (8.6) years, and median (25<sup>th</sup>, 75<sup>th</sup>percentile) estimated glomerular filtration rate (eGFR) was 102.8 (85.9, 117.9) mL/min/1.73m<sup>2</sup>. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) for sedentary time and physical activity were 8.0 (5.5, 12.0) hours/day and 17.2 (8.7, 31.9) MET-hours/day, respectively. Median follow-up was 9.4 years. We observed significant interactions between eGFR and both physical activity and sedentary behavior (P<0.001). The partial effect plot of the association between physical activity and log relative hazard of ESRD suggests that ESRD risk decreases as physical activity increases when eGFR is 90 mL/min/1.73m<sup>2</sup>. The inverse association is most pronounced at physical activity levels >27 MET-hours/day. High levels of sitting time were associated with increased

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3 ESRD risk only among those with reduced kidney function (eGFR  $\leq 30$  mL/min/1.73m<sup>2</sup>); this  
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5 association was attenuated after excluding the first two years of follow-up.  
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8 **Conclusions:** In this high-risk population, physical activity appears to be associated with  
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10 reduced risk of ESRD among those with preserved kidney function. A positive association  
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12 between sitting time and ESRD observed among those with advanced kidney disease is likely  
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14 due to reverse causation.  
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16 **Abbreviations:** CHC=community health center; CI=confidence interval; CKD=chronic kidney  
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18 disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HR=hazard  
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20 ratio; MET=metabolic equivalent; SCCS=Southern Community Cohort Study; USRDS=United  
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22 States Renal Data System  
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### 28 **Strengths and limitations of this study**

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31 • The SCCS is a large, unique cohort of black and white participants with low  
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33 socioeconomic status and a high burden of risk factors for end-stage renal disease.  
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36 • The case-cohort design selected participants for measurement of serum creatinine,  
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38 therefore, baseline kidney function could be evaluated.  
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41 • Physical activity and sedentary behaviors were self-reported rather than objectively  
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43 measured; however, a validated questionnaire developed for the SCCS was used for  
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45 ascertainment of these measures.  
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48 • Only baseline data on physical activity and sedentary behaviors were included and  
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50 behaviors may have changed after enrollment.  
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## INTRODUCTION

In 2015, the age-adjusted incidence of end-stage renal disease (ESRD) in the United States was 357 per million [1]. With the growing burden of ESRD, there has been increasing focus on modifiable risk factors. Recent studies have shown that higher physical activity levels are associated with lower risk of chronic kidney disease (CKD) and slower decline in estimated glomerular filtration rate (eGFR) [2-8]. Studies that examined sedentary behaviors are limited but suggest that higher sedentary time is associated with reduced kidney function and increased CKD risk [4 9]. The association between physical activity, sedentary time, and ESRD is not well established though, with few studies suggesting an association between physical activity and ESRD and none with the ability to disentangle exercise behaviors from socioeconomic status (SES) [10 11].

To investigate whether sedentary time and physical activity were independently associated with risk of incident ESRD, we used a case-cohort design within the Southern Community Cohort Study (SCCS), a unique population of individuals with lower SES, a high burden of kidney disease risk factors, and robust measures of physical activity and sedentary time.

## METHODS

### Study population

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3 The SCCS is a prospective cohort study that recruited ~86,000 low-income black and white  
4 adults, aged 40-79 years, in the southeastern US (2002-2009) [12]. The majority (86%) were  
5 recruited at participating community health centers (CHC), which provide primary healthcare for  
6 under-insured populations. A detailed description of SCCS methods has been published  
7 (<http://www.southerncommunitystudy.org>) [13]. All participants provided written informed  
8 consent, and the study was approved by the Institutional Review Boards of Vanderbilt University  
9 Medical Center and Meharry Medical College. We used the STROBE cohort checklist when  
10 writing our report [14].

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21 Incident ESRD was identified by linking the SCCS cohort, using date of birth, Social  
22 Security number, and first and last name, with the nationwide US Renal Data System (USRDS)  
23 through March 31, 2015, the latest date for which data were available. Participants with an  
24 ESRD diagnosis prior to SCCS enrollment (prevalent cases) were excluded from the analysis.

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31 Approximately 46% of the cohort donated baseline blood samples during CHC  
32 recruitment, which have been frozen at -80°C. Participants were selected for measurement of  
33 creatinine using a case-cohort design, including all those with stored blood who had an incident  
34 ESRD diagnosis (n=737), and a probability sample of the entire cohort who donated blood  
35 (n=4,238). This sample constitutes 13% of SCCS participants who donated blood, and is  
36 comparable with respect to baseline sociodemographic characteristics and high prevalence of  
37 CKD risk factors [15].

### 38 39 40 41 42 43 44 45 46 **Patient and Public Involvement**

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49 There was no patient or public involvement in study design and conduct, dissemination of  
50 results, and evaluation in this study.

### 51 52 53 54 **Data collection**



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3 Standardized computer-assisted personal interviews were administered at enrollment to obtain  
4 data on demographic, medical, and lifestyle variables [13]. Body mass index (BMI) was  
5 calculated from self-reported height and weight. History of hypertension, diabetes, and  
6 hypercholesterolemia were self-reported by asking whether a doctor had ever diagnosed the  
7 participant with the condition.  
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14 Usual sedentary and active behaviors were assessed using a validated physical activity  
15 questionnaire (PAQ) developed specifically for the SCCS [16]. For sedentary behaviors,  
16 participants were asked questions about the amount of time per day typically spent sitting in a car  
17 or bus, at work, viewing television or movies, and other activities that involve sitting. For  
18 physical activity, participants were asked about time typically spent performing light, moderate,  
19 and strenuous activities at home and at work, as well as time spent doing moderate and vigorous  
20 exercise/sports. For all questions, participants provided open-ended duration responses (hours  
21 and minutes).  
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### 33 **Statistical Analysis**

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35 The study population was restricted to blacks and whites enrolled at CHCs, to ensure that  
36 participants had similar SES and equal access to healthcare regardless of race and had the  
37 opportunity to donate a blood specimen. Participants with missing data for any exercise metric  
38 (n=161) or demographic characteristic (n=212), and those with baseline eGFR>150  
39 ml/min/1.73m<sup>2</sup> (n=22), were excluded; thus, a total of 692 ESRD cases and 4,113 subcohort  
40 members were included in the analyses. Sedentary time was calculated as hours/day based on the  
41 sum of all individual sedentary behaviors. Total physical activity was calculated as the sum of  
42 light, moderate and strenuous household/occupational work as well as moderate and vigorous  
43 sports; values were transformed from hours/day into summary measures of energy expenditure,  
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3 defined as metabolic equivalent (MET)-hours/day. MET values for specific activities and  
4 intensities were based on the Compendium of Physical Activities [17]. Two MET-hours/day is  
5 roughly equivalent to participating in 1 hour of a light activity, 0.5 hours of a moderate activity  
6 such as walking, or 0.25 hours of a vigorous activity such as jogging [16].  
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13 Using sampling weight techniques, we described baseline characteristics of subcohort  
14 participants using means and standard deviations (SD) or medians and 25<sup>th</sup> and 75<sup>th</sup> percentiles.  
15 For descriptive purposes, sedentary time (hours/day) and physical activity (MET-hours/day)  
16 were also categorized into quartiles based on the subcohort distribution. Incidence rates (IR)  
17 were calculated from bootstrap probability resamples; the reported IRs were the means of the  
18 bootstrap replicates with confidence intervals (CI) at the 2.5 and 97.5 percentiles of the  
19 bootstrap distribution.  
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29 We calculated hazard ratios (HRs) and 95% CIs for the association of sedentary time and  
30 physical activity with ESRD from Cox regression models that accounted for the case-cohort  
31 design and the weighted sample [18]. Participants were considered at risk from the date of SCCS  
32 enrollment until the first occurrence of incident ESRD, death, or March 31, 2015. Total  
33 sedentary time and physical activity were modeled as restricted cubic splines with four knots and  
34 mutually adjusted in a single model. Additional covariates included age at enrollment (years),  
35 sex, race, education (< or ≥high school), income (< or ≥\$15,000), BMI (kg/m<sup>2</sup>), smoking (never  
36 or former/current), baseline eGFR (mL/min/1.73m<sup>2</sup>), and history of diagnosis of diabetes,  
37 hypertension and hypercholesterolemia (yes/no). Baseline serum levels of creatinine were used  
38 for estimation of eGFR using the CKD-EPI equation [19]. Continuous predictors (age, eGFR,  
39 and BMI) were added to the model as restricted cubic splines with four knots. To examine  
40 interactions between sedentary time or physical activity and baseline kidney function on ESRD  
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3 risk, multiplicative interaction terms between sedentary time/physical activity and eGFR were  
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5 added to the model.  
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8 We constructed partial effect plots of eGFR and physical activity or sedentary time on the  
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10 log relative hazard scale, which display the predicted outcome as a function of a single covariate  
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12 while holding all other covariates constant for different levels of baseline kidney function. We  
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14 also plotted the HRs of ESRD as a function of continuous MET-hours/day or sitting hours/day,  
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16 again holding all other covariates constant for different levels of baseline kidney function. The  
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18 CIs in the HR plots were generated using bootstrap resampling methods. Finally, in sensitivity  
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20 analyses to examine the potential for reverse causation among those with advanced kidney  
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22 disease, we calculated HRs and 95% CIs and constructed partial effect plots as above, excluding  
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24 the first two years of follow up. All analyses were conducted using R. For main effects and  
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26 interaction terms, P-values  $\leq 0.05$  were considered statistically significant.  
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### 33 **RESULTS**

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35 At baseline, mean (SD) age of subcohort participants was 52 (8.6) years (Table 1). Most  
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37 participants were women (60%), black (71%), reached high school (68%), and had income  
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39  $< \$15,000$  (62%). Approximately 75% were overweight or obese, and 55%, 23% and 35%  
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41 reported a diagnosis of hypertension, diabetes and hypercholesterolemia, respectively. Median  
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43 (25<sup>th</sup>, 75<sup>th</sup> percentile) baseline eGFR was 102.8 (85.9, 117.9) mL/min/1.73m<sup>2</sup> in the subcohort  
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45 and 62.9 (36.0, 98.1) among ESRD cases. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) for total sedentary time  
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47 and physical activity in the subcohort were 8.0 (5.5, 12.0) hours/day and 17.2 (8.7, 31.9) MET-  
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49 hours/day, respectively. The most common sedentary activity was watching TV or movies; for  
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51 physical activity, most energy expenditure came from moderate activities and sports.  
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3 Demographic characteristics by quartiles of physical activity and sedentary time are  
4 presented in Table 2. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) total physical activity in the highest activity  
5 quartile for the subcohort was 41.3 (33.2, 55.5) MET-hours/day, compared to 4.2 (2.0, 6.2) in the  
6 lowest quartile (Table 2a). Compared to individuals in the lower quartiles, subcohort members in  
7 the highest quartile of physical activity were younger, had higher education and income, and had  
8 lower prevalence of obesity, hypertension, hypercholesterolemia and diabetes. Median baseline  
9 eGFR was highest among those in the highest quartile of physical activity.  
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19 Median (25<sup>th</sup>, 75<sup>th</sup> percentile) total sitting hours in the subcohort was 15.5 (13.8, 18.0)  
20 hours/day in the highest sedentary time quartile and 4.0 (3.0, 5.0) hours/day for participants in  
21 the lowest quartile (Table 2b). Total physical activity was higher among participants in the third  
22 and fourth quartile of sedentary time compared to the lower two quartiles. Subcohort participants  
23 in the fourth quartile of sedentary time were more likely than those in lower quartiles to be black  
24 and obese, and to have  $\geq$ high school education or annual income  $\geq$ \$15,000. Prevalence of  
25 hypertension, hypercholesterolemia and diabetes did not vary consistently across quartiles of  
26 sitting time, nor did median baseline eGFR.  
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38 Participants were followed for a median (range) of 9.4 (0.1-12.8) years. Age-adjusted IRs  
39 for ESRD were 2.61, 2.38, 2.24, and 1.68/1000 person-years in quartiles 1-4 of physical activity,  
40 respectively; corresponding IRs in quartiles of sitting time were 2.13, 2.06, 2.07, and 2.64/1000  
41 person-years (Table 2). In unadjusted Cox models, the HRs for an interquartile range increase in  
42 physical activity or sedentary time were 0.65 (95% CI 0.58-0.73) and 1.09 (95% CI 1.00-1.20),  
43 respectively. In the multivariable model including both physical activity and sedentary time, and  
44 the interactions between physical activity\*eGFR and sedentary behavior\*eGFR, both  
45 interactions were statistically significant (chunk test P-value <0.001). Therefore, we present  
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3 partial effect plots based on the multivariable model to further tease out the shape of the  
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5 association between eGFR, physical activity, and sitting.  
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8 The partial effect plots show the association between physical activity (Figure 1a) or  
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10 sedentary time (Figure 1b) and log relative hazard of ESRD, by levels of baseline eGFR. When  
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12 eGFR is 30, the shape of the association suggests that risk of ESRD increases as activity  
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14 increases. In contrast, when eGFR is 90, log relative hazard of ESRD decreases as activity  
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16 increases, and the inverse association is most pronounced at levels of physical activity above 27  
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18 MET-hours/day. The predicted log relative hazard of ESRD is uniformly higher when eGFR is  
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20 30 compared to when eGFR is 60, and log relative hazard is lowest when eGFR is 90.  
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24 In the second plot, when eGFR is 30, the shape of the association shows increasing  
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26 ESRD risk as sedentary time increases. In contrast, when eGFR is 60 or 90, the shape of the  
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28 association is slightly decreasing or flat with increasing sedentary time. As for physical activity,  
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30 the predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to  
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32 when eGFR is 60 or 90.  
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35 The continuous HR plots present the associations between physical activity (Figure 2a) or  
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37 sedentary time (Figure 2b) and risk of incident ESRD. The HR plots are separated into three  
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39 levels of eGFR (30, 60, 90 mL/min/1.73m<sup>2</sup>). Each panel has its own reference level, which is  
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41 seen at the pinch in the confidence intervals where HR=1.0. The relative shape of the  
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43 associations at each level of eGFR corresponds to what is shown in the partial effect plots; in  
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45 particular, an inverse association between physical activity and risk of ESRD is apparent only  
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47 among those with preserved kidney function, while an increased risk of ESRD with increasing  
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49 sedentary time is observed among those with low eGFR.  
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3 In sensitivity analyses excluding the first two years of follow up, the interactions between  
4 sedentary time\*eGFR and physical activity\*eGFR remained statistically significant (P-  
5 value<0.001 for both); however, the positive association between sitting time and ESRD among  
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7 those with advanced kidney disease was no longer apparent.  
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## 14 **DISCUSSION**

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16 Among blacks and whites at high risk for ESRD, we observed a significant interaction  
17 between physical activity and baseline kidney function, suggesting that among individuals with  
18 preserved kidney function, higher physical activity is associated with a lower risk of developing  
19 ESRD. Similarly, we observed heterogeneity of the association of sitting time on ESRD risk, as  
20 demonstrated by the higher risk of ESRD associated with longer sitting time among those with  
21 eGFR  $\leq 30$  mL/min/1.73m<sup>2</sup>, which appears to be explained by reverse causation.  
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31 While physical activity is widely accepted as an important modifiable risk factor for  
32 cardiovascular disease, the association is not well established in kidney disease. A number of  
33 observational and interventional studies have examined the risks and benefits of physical activity  
34 among patients undergoing maintenance dialysis [20-23]. However, previous studies of incident  
35 kidney disease are limited and have reported inconsistent results. In a cross-sectional study of  
36 10,463 patients with diabetes and hypertension, lack of exercise was a significant risk factor for  
37 CKD [8]. In another cohort study of 6,972 patients with diabetes, participants who had more  
38 regular physical activity had a reduced risk of early diabetic CKD [3]. Among 4,011 participants  
39 from the Cardiovascular Health Study, those with the highest amount of physical activity had a  
40 lower risk of rapid kidney function decline [7]. In contrast, in a study of 3,653 black participants  
41 from the Jackson Heart Study, physical activity was not associated with rapid decline in eGFR  
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3 [24]. The inconsistency of results may be due in part to the fact that physical activity for these  
4 studies was defined in different ways, ranging from number of times per week the participant  
5 exercised [3 8] to categorization based on the American Heart Association's Life Simple 7 and  
6 the Minnesota Heart Survey [7 24].  
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12 We found that a high level of physical activity was associated with lower risk of ESRD  
13 among those with preserved kidney function. Two prior studies reported an association between  
14 physical activity and lower risk of ESRD. Among 59,552 participants from the Singapore  
15 Chinese Health Study, those engaged in any physical activity had a lower risk of ESRD, and a  
16 dose-response relationship with intensity of physical activity was noted [10]. Among individuals  
17 with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC), physical activity was  
18 inversely associated with risk of CKD progression (defined as 50% decrease in eGFR or incident  
19 ESRD). The CRIC results are somewhat inconsistent with our observation of no beneficial effect  
20 of physical activity among those with already reduced kidney function. It is possible that  
21 secondary factors such as hyperphosphatemia, acidosis, proteinuria, and glomerular hypertension  
22 and hypertrophy drive progression of CKD once established and, therefore, physical activity may  
23 have less of an impact on ESRD risk in this group [25 26]. Also, earlier and longer established  
24 control of primary CKD risk factors, such as blood pressure and blood sugar, through physical  
25 activity may have more of an impact earlier rather than later in the kidney disease course.  
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44 Diabetes, obesity, hypertension, and kidney dysfunction can lead to oxidative stress,  
45 insulin resistance, endothelial dysfunction, and increased circulating cytokines [27]. Physical  
46 activity has a beneficial effect on these metabolic disturbances, all common in patients with  
47 CKD, and these mechanisms may underlie our finding of reduced risk of ESRD with greater  
48 levels of physical activity. One important metabolic disturbance and risk factor for CKD is  
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3 inflammation, which has an inverse correlation with eGFR [28]. Patients with CKD/ESRD have  
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5 higher levels of pro-inflammatory adipokines or cytokines, such as leptin, tumor necrosis factor  
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7 alpha and interleukin 1 and 6 [28-30]. Exercise and physical activity have been shown to reduce  
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9 inflammatory molecules and create an anti-inflammatory environment in the general population  
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11 and in patients with CKD [30 31], a potential mechanisms for a beneficial effect of physical  
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13 activity on kidney function. Increased physical exercise and subsequent weight loss may also  
14  
15 help decrease the oxidative stress burden in patients with CKD [28 29 32]. Finally, excess  
16  
17 adiposity and lack of physical activity are the most common causes of insulin resistance [33] and  
18  
19 hyperglycemia. This metabolic dysregulation is a risk factor for reduced kidney function.  
20  
21 Exercise and physical activity decrease insulin resistance and improve endothelial responses to  
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23 insulin [33].  
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29 Sedentary behavior is hypothesized to be an independent risk factor for CKD and ESRD,  
30  
31 but few studies have examined this association. We observed a significant interaction between  
32  
33 sedentary time and eGFR, demonstrating that a higher amount of sitting time increased risk of  
34  
35 ESRD in participants with lower eGFR. We speculated that this may be a result of reverse  
36  
37 causation, whereby the presence of advanced kidney disease, uremia or other comorbidities and  
38  
39 subsequent fatigue in those with low eGFR, already at high risk for ESRD, may lead to increased  
40  
41 sedentary time and also prompt earlier initiation of dialysis. In fact, attenuation of the association  
42  
43 between sedentary time and ESRD after exclusion of the first two years of follow-up lends  
44  
45 support to this explanation.  
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50  
51 Sedentary behavior has, however, been shown to be associated with physiological risk  
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53 factors for CKD and ESRD including increased BMI, systolic blood pressure, triglycerides, and  
54  
55 decreased HDL cholesterol [34], and these pathways may mediate possible effects and should be  
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3 further explored. Two recent studies have reported associations between higher sedentary time  
4 and lower eGFR and higher odds of urinary albumin excretion time [4 9].  
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8 To our knowledge, this is one of few studies to investigate the association between  
9  
10 physical activity and ESRD and one of the first to examine sedentary behaviors. Strengths of our  
11 study include the prospective design and the unique cohort of participants with low SES and a  
12 high burden of risk factors for ESRD. An important strength is the ascertainment of a broad  
13 range of physical activity and sedentary behaviors from a validated questionnaire developed  
14 specifically for the SCCS [16]. Other strengths include the complete ascertainment of ESRD  
15 cases and the inclusion of baseline eGFR. A limitation of the study is that physical activity and  
16 sedentary behaviors were ascertained only at baseline and may have changed after enrollment.  
17  
18 Moreover, the physical activity and sedentary behaviors were self-reported by participants rather  
19 than objectively measured. Finally, baseline data on proteinuria was not available.  
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31 In conclusion, this study found that in a population at high risk for ESRD, higher levels  
32 of physical activity were associated with reduced risk of ESRD in those with preserved kidney  
33 function, and sedentary time was not associated with increased ESRD risk except in participants  
34 with low baseline eGFR. Physical activity and sedentary behaviors are modifiable risk factors  
35 that may be targets for possible interventions, especially in those with preserved kidney function.  
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#### 44 **Acknowledgements**

45  
46 None  
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#### 48 **Conflict of Interest Statement**

49  
50 None declared. The results presented in this paper have not been published previously in whole  
51 or part, except in abstract form.  
52  
53

#### 54 **Author Contributions**

1  
2  
3 Research idea and study design: MMP, JMT, EKK, EAA, TAI, TGS, LL; data acquisition: LL,  
4 WJB; data analysis/interpretation: MMP, JMT, EKK, TGS, JLM, CRC, EAA, KAK, EDS, WJB,  
5 TAI, LL; statistical analysis: MMP, TGS, JLM, EAA; supervision or mentorship: TGS, CRC,  
6 WJB, TAI, LL. Each author contributed important intellectual content during manuscript drafting  
7 or revision and accepts accountability for the overall work by ensuring that questions pertaining  
8 to the accuracy or integrity of any portion of the work are appropriately investigated and  
9 resolved.

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### 12 **Data Sharing Statement**

13  
14 The SCCS is committed to open sharing of its resources to provide for optimal utilization of  
15  
16 SCCS data and biologic specimens for research purposes. The proposed research will generate  
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18 biomarker data (serum trace metals, serum creatinine) which will be added to the SCCS  
19  
20 database. Consistent with current SCCS study operations, qualified researchers who wish to  
21  
22 collaborate with investigators from our study will have access to SCCS data upon approval of a  
23  
24 research proposal by the 12-member SCCS Data and Biospecimen Use Committee  
25  
26 (<https://ors.southerncommunitystudy.org/>). The SCCS has an open access policy for legitimate  
27  
28 scientific purposes, but because of privacy concerns, requires Committee review of all data  
29  
30 requests. All investigators are required to sign a data use agreement prior to receipt of SCCS  
31  
32 study data that provides for: (1) Sharing of the data only with investigators signing the data use  
33  
34 agreement; (2) Use of the data only for purposes approved by the DBU Committee; (3)  
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36 Agreement for review of manuscripts and statistical programs prior to submission of the results  
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38 for publication; (4) A 12-month time frame for completion of the analysis.  
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44 Prior to sharing of SCCS data for proposals approved by the Committee, datasets are de-  
45  
46 identified according to the HIPAA Safe-Harbor Method  
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48 ([http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/Deidentification/](http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/Deidentification/guidance.html)  
49  
50 [guidance.html](http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/Deidentification/guidance.html))  
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54 The following data elements are removed from datasets prior to release to investigators:  
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3 a. Name

4 b. All geographic identifiers for subdivisions smaller than a state, including street address, city,  
5 county, precinct, ZIP code, and the equivalent geocodes

6 a. De-identified geographic subdivisions will not be released when the total number of persons  
7 within that subdivision is known to be less than 300, to prevent potential disclosure of the  
8 identifier due to unique characteristics

9 c. All elements of dates (except year), including, but not limited to, date of birth, date of SCCS  
10 enrollment, date of diagnosis, date of death, and all ages over 89 or elements of date indicative of  
11 an age over 89

12 d. Telephone Numbers

13 e. Fax Numbers

14 f. Email Addresses

15 g. Social Security Numbers

16 h. Medical Record Numbers

17 i. Health Plan Beneficiary Numbers

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20 Transmission of potentially identifiable data is kept to a minimum and performed only as needed  
21 for study operations in accordance with HIPAA regulations.  
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**Table 1. Baseline characteristics of the probability sample (subcohort) of SCCS participants and ESRD cases**

	<b>Subcohort participants (n=4,113)</b>	<b>ESRD cases (n=692)</b>
Age at enrollment, years	52.2 ± 8.6	53.8 ± 8.0
Women	59.8	51.5
Race		
White	29.3	12.4
Black	70.7	87.6
Education		
<High school	32.3	40.3
≥High school	67.7	59.7
Household income		
<\$15,000/year	61.6	65.8
≥\$15,000/year	38.4	34.2
Cigarette smoking		
Current/former smoker	67.3	58.3
Never smoker	32.7	41.7
BMI, kg/m	30.3 ± 7.3	32.8 ± 8.8
Overweight or obese	74.8	82.5
Hypertension	55.5	86.0
Hypercholesterolemia	34.5	49.3
Diabetes	22.6	68.5
eGFR, ml/min/1.73m <sup>2</sup>	102.8 (85.9, 117.9)	62.9 (36.0, 98.1)
<b>Sedentary and physical activity measures</b>		
Sitting, h/d	8.0 (5.5,12.0)	8.2 (6.0,12.0)
Car or bus, h/d	1.5 ± 1.8	1.5 ± 2.0
At work, h/d	1.2 ± 2.3	0.9 ± 2.3
TV or movies, h/d	3.8 ± 2.9	4.3 ± 3.1
Home computer, h/d	0.5 ± 1.1	0.3 ± 0.9
Other, h/d <sup>a</sup>	2.3 ± 1.9	2.4 ± 2.0
Physical Activity, h/d	5.4 (2.9,9.4)	4.3 (2.3,7.4)
Household/occupational activity, MET-h/d		
Light	7.3 ± 6.2	5.9 ± 5.4
Moderate	9.7 ± 8.7	8.6 ± 7.9
Strenuous	5.0 ± 11.7	3.1 ± 9.4
Sports, MET-h/d		
Moderate	10.0 ± 8.8	8.9 ± 8.1
Vigorous	5.6 ± 12.0	3.5 ± 9.6
Total physical activity, MET-h/d <sup>b</sup>	17.2 (8.7,31.9)	13.9 (6.9,24.6)

*Note:* Values are listed as mean ± SD or % or median (25<sup>th</sup>,75<sup>th</sup> percentile)

<sup>a</sup>Includes sitting at meals, talking on the phone, reading, playing cards, or sewing.

<sup>b</sup>Includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study



**Table 2. Baseline characteristics of the subcohort of SCCS participants by quartiles of: a) physical activity, and b) sedentary time**

	<b>Q1: Subcohort (n=934)</b>	<b>Q2: Subcohort (n=994)</b>	<b>Q3: Subcohort (n=1045)</b>	<b>Q4: Subcohort (n=1140)</b>
<b>a)</b>				
ESRD Incidence Rate per 1000 person-year	2.61 (1.54, 3.87)	2.38 (1.36, 3.50)	2.24 (1.25, 3.30)	1.68 (0.93, 2.55)
Physical activity (MET-h/day) <sup>a</sup>	4.2 [2.0, 6.2]	10.6 [8.8, 12.6]	20.2 [17.2, 23.5]	41.3 [33.2, 55.5]
Sitting (h/day)	7.5 [5.0, 11.0]	8.0 [6.0, 12.0]	9.0 [6.0, 12.0]	8.5 [5.8, 12.0]
Age, years	54.6 (9.3)	53.1 (8.9)	52.4 (8.8)	49.7 (7.1)
Women	49.9	67.0	70.7	51.5
Black race	67.5	69.2	71.3	73.2
Less than high school	37.7	35.0	32.1	27.0
Less than \$15K/year	73.1	66.9	59.4	52.2
Current/former smoker	70.4	64.4	65.7	69.0
BMI, kg/m <sup>2</sup>	30.9 (7.9)	30.7 (7.4)	30.9 (7.2)	29.1 (6.8)
Overweight or obese	75.1	77.2	77.3	70.5
Hypertension	63.5	56.7	58.7	47.1
High cholesterol	38.7	38.1	38.7	25.7
Diabetes	27.6	24.4	23.8	17.0
eGFR, mL/min/1.73m <sup>2</sup>	99.2 [80.6, 114.8]	102.9 [84.8, 116.8]	102.1 [86.6, 117.6]	106.9 [89.9, 120.3]
<b>b)</b>				
ESRD Incidence Rate per 1000 person-year	2.13 (1.20, 3.20)	2.06 (1.18, 3.03)	2.07 (1.18, 3.12)	2.64 (1.46, 3.88)
Sitting (h/day)	4.0 [3.0, 5.0]	7.0 [6.3, 7.5]	10.0 [9.0, 11.0]	15.5 [13.8, 18.0]
Physical Activity (MET-h/day) <sup>a</sup>	15.8 [7.5, 32.4]	15.3 [8.6, 29.6]	18.4 [9.7, 32.7]	18.6 [9.8, 32.3]
Age, years	52.5 (8.9)	53.2 (8.5)	52.1 (8.9)	50.6 (7.8)
Women	58.2	57.3	63.1	60.6
Black race	71.0	66.0	67.7	79.6
Less than high school	39.8	29.5	29.0	31.0
Less than \$15K/year	69.4	60.6	58.9	57.2

Current/former smoker	65.8	65.2	68.2	70.4
BMI, kg/m <sup>2</sup>	29.5 (7.1)	29.7 (7.3)	30.7 (7.3)	31.5 (7.5)
Overweight or obese	71.6	72.0	77.1	78.7
Hypertension	53.5	58.1	55.8	54.6
High cholesterol	31.3	34.4	36.7	35.6
Diabetes	21.9	23.1	21.8	23.6
eGFR, mL/min/1.73m <sup>2</sup>	104.3 [88.9, 118.6]	102.1 [84.4, 115.2]	102.1 [85.4, 118.2]	103.4 [85.3, 120.1]

*Note:* Values are listed as mean ± SD or % or median (25<sup>th</sup>,75<sup>th</sup> percentile)

<sup>a</sup>Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

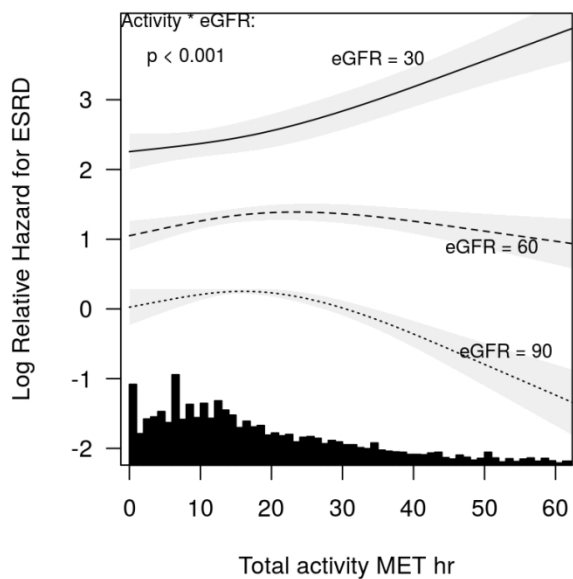
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study

**FIGURE LEGEND**

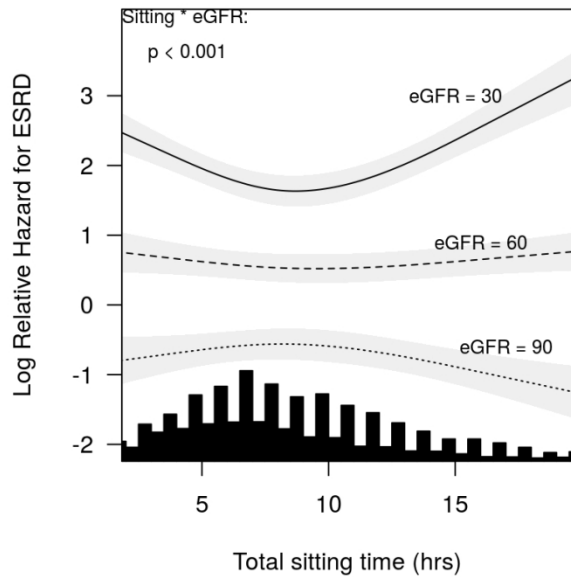
**Figure 1.** Partial effect plots of **a)** physical activity (MET-hours/day) and **b)** total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR

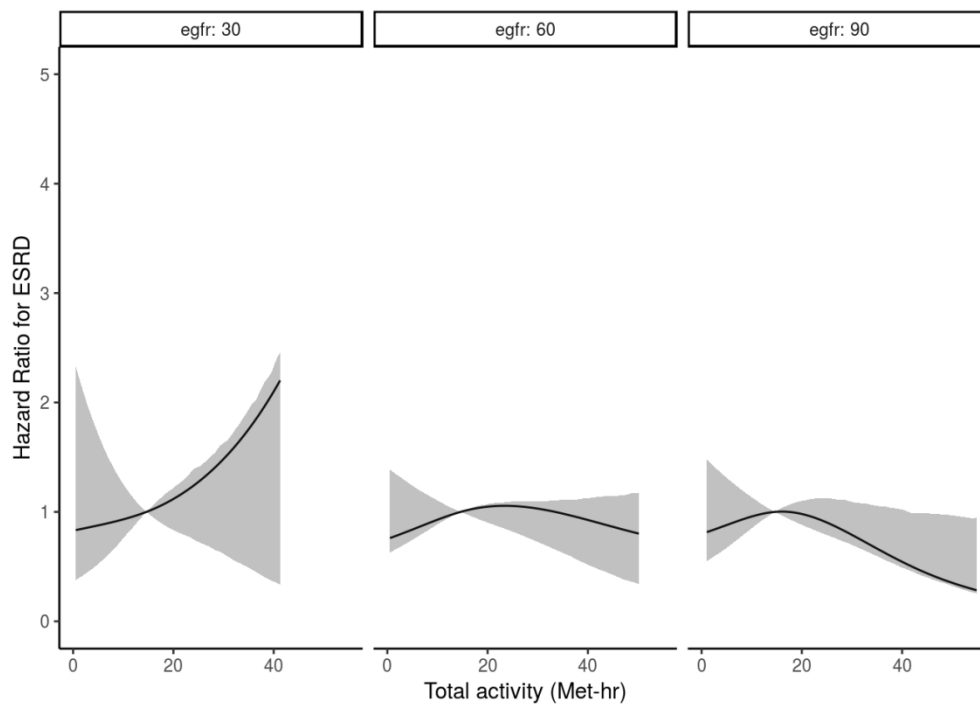
**Figure 2.** Plots of continuous hazard ratios of **a)** physical activity (MET-hours/day) and **b)** total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR. The confidence intervals in the HR plot were generated using bootstrap resampling methods

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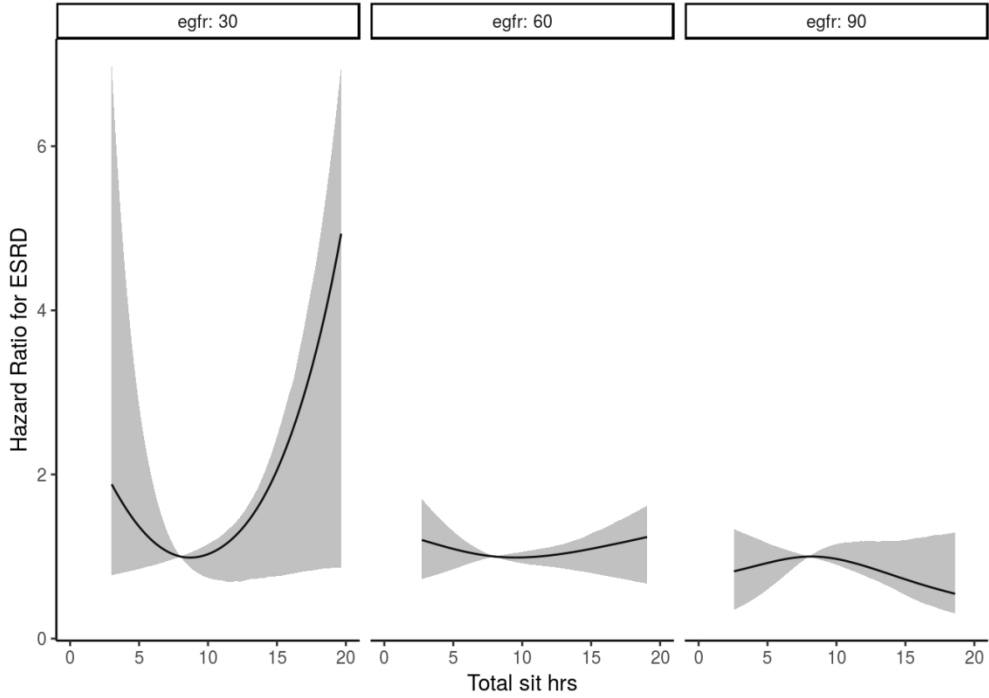


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# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
	#6b	For matched studies, give matching criteria and number of exposed and	NA



1		unexposed	
2	Variables	#7	Clearly define all outcomes, exposures, predictors, potential
3			5
4			Clearly define all outcomes, exposures, predictors, potential
5			5
6	Data sources /	#8	For each variable of interest give sources of data and details of methods
7	measurement		5
8			of assessment (measurement). Describe comparability of assessment
9			methods if there is more than one group. Give information separately
10			for for exposed and unexposed groups if applicable.
11			
12	Bias	#9	Describe any efforts to address potential sources of bias
13			6
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15	Study size	#10	Explain how the study size was arrived at
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18	Quantitative	#11	Explain how quantitative variables were handled in the analyses. If
19	variables		6
20			applicable, describe which groupings were chosen, and why
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22	Statistical	#12a	Describe all statistical methods, including those used to control for
23	methods		6-7
24			confounding
25			
26		#12b	Describe any methods used to examine subgroups and interactions
27			6-7
28		#12c	Explain how missing data were addressed
29			6
30		#12d	If applicable, explain how loss to follow-up was addressed
31			6
32		#12e	Describe any sensitivity analyses
33			7
34			
35	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers
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37			potentially eligible, examined for eligibility, confirmed eligible,
38			included in the study, completing follow-up, and analysed. Give
39			information separately for for exposed and unexposed groups if
40			applicable.
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43		#13b	Give reasons for non-participation at each stage
44			6
45		#13c	Consider use of a flow diagram
46			NA
47			
48	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical,
49			8
50			social) and information on exposures and potential confounders. Give
51			information separately for exposed and unexposed groups if applicable.
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53		#14b	Indicate number of participants with missing data for each variable of
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55			interest
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57		#14c	Summarise follow-up time (eg, average and total amount)
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1	Outcome data	#15	Report numbers of outcome events or summary measures over time.	9
2			Give information separately for exposed and unexposed groups if	
3			applicable.	
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6	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted	9
7			estimates and their precision (eg, 95% confidence interval). Make clear	
8			which confounders were adjusted for and why they were included	
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12		#16b	Report category boundaries when continuous variables were categorized	9
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14		#16c	If relevant, consider translating estimates of relative risk into absolute	NA
15			risk for a meaningful time period	
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18	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	10
19			interactions, and sensitivity analyses	
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21	Key results	#18	Summarise key results with reference to study objectives	10
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24	Limitations	#19	Discuss limitations of the study, taking into account sources of potential	13
25			bias or imprecision. Discuss both direction and magnitude of any	
26			potential bias.	
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29	Interpretation	#20	Give a cautious overall interpretation considering objectives,	11-12
30			limitations, multiplicity of analyses, results from similar studies, and	
31			other relevant evidence.	
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34	Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
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37	Funding	#22	Give the source of funding and the role of the funders for the present	14
38			study and, if applicable, for the original study on which the present	
39			article is based	
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42 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY.  
 43 This checklist was completed on 14. March 2019 using <https://www.goodreports.org/>, a tool made by the  
 44 [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## The association of exercise and sedentary behaviors with incident end stage renal disease in the Southern Community Cohort Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030661.R1
Article Type:	Research
Date Submitted by the Author:	16-Jul-2019
Complete List of Authors:	<p>Pike, Mindy; Vanderbilt University Medical Center, Division of Epidemiology, Department of Medicine  Taylor, Jacob; Vanderbilt University Medical Center, Division of Nephrology, Department of Medicine; Vanderbilt University Medical Center, Vanderbilt O'Brien Center for Kidney Disease  Kabagambe, Edmond; Vanderbilt University Medical Center, Division of Epidemiology, Department of Medicine  Stewart, Thomas; Vanderbilt University Medical Center, Department of Biostatistics  Robinson-Cohen, Cassianne; Vanderbilt University Division of Nephrology and Hypertension, Medicine; Vanderbilt-O'Brien Center for Kidney Disease, Vanderbilt University Medical Center  Morse, Jennifer; Vanderbilt University Medical Center, Department of Biostatistics  Akwo, Elvis; Vanderbilt University Division of Nephrology and Hypertension, Medicine; Vanderbilt-O'Brien Center for Kidney Disease, Vanderbilt University Medical Center  Abdel-Kader, Khaled; Vanderbilt University Division of Nephrology and Hypertension, Medicine; Vanderbilt-O'Brien Center for Kidney Disease, Vanderbilt University Medical Center  Siew, Edward; Vanderbilt University Division of Nephrology and Hypertension, Medicine; Vanderbilt-O'Brien Center for Kidney Disease, Vanderbilt University Medical Center  Blot, William; Vanderbilt University Medical Center, Division of Epidemiology, Department of Medicine  Ikizler, T. Alp; Vanderbilt University Division of Nephrology and Hypertension, Medicine; Vanderbilt-O'Brien Center for Kidney Disease, Vanderbilt University Medical Center,  Lipworth, Loren; Vanderbilt University Medical Center, Division of Epidemiology, Department of Medicine</p>
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Renal medicine
Keywords:	End stage renal failure < NEPHROLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

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Manuscripts

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3 **The association of exercise and sedentary behaviors with incident end stage renal disease in**  
4 **the Southern Community Cohort Study**  
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6 Mindy M Pike, MPH<sup>a</sup>; Jacob M Taylor, PhD<sup>b,c</sup>; Edmond K Kabagambe, PhD<sup>a</sup>; Thomas G  
7 Stewart, PhD<sup>d</sup>; Cassianne Robinson-Cohen, PhD<sup>b,c</sup>; Jennifer L Morse, MS<sup>d</sup>; Elvis A Akwo,  
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42 **Running Head:** Physical Activity and ESRD  
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45 **Key Words:** end stage renal disease, sedentary time, physical activity  
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48 **Word Count Abstract:** 283      **Text:** 3,610  
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## ABSTRACT

**Objective:** Lifestyle factors, including sedentary time and physical activity, could independently contribute to risk of end stage renal disease (ESRD).

**Study Design:** Case-cohort study.

**Setting:** Southeastern US

**Participants:** The Southern Community Cohort Study recruited ~86,000 blacks and whites from 2002-2009. We assembled a case-cohort of 692 incident ESRD cases and a probability sample of 4113 participants.

**Predictors:** Sedentary time was calculated as hours/day from daily sitting activities. Physical activity was calculated as metabolic equivalent (MET)-hours/day from engagement in light, moderate, and vigorous activities.

**Outcomes:** Incident ESRD.

**Results:** At baseline, among the subcohort, mean (SD) age was 52 (8.6) years, and median (25<sup>th</sup>, 75<sup>th</sup>percentile) estimated glomerular filtration rate (eGFR) was 102.8 (85.9, 117.9) mL/min/1.73m<sup>2</sup>. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) for sedentary time and physical activity were 8.0 (5.5, 12.0) hours/day and 17.2 (8.7, 31.9) MET-hours/day, respectively. Median follow-up was 9.4 years. We observed significant interactions between eGFR and both physical activity and sedentary behavior (P<0.001). The partial effect plot of the association between physical activity and log relative hazard of ESRD suggests that ESRD risk decreases as physical activity increases when eGFR is 90 mL/min/1.73m<sup>2</sup>. The inverse association is most pronounced at physical activity levels >27 MET-hours/day. High levels of sitting time were associated with increased ESRD risk only among those with reduced kidney function (eGFR ≤30 mL/min/1.73m<sup>2</sup>); this association was attenuated after excluding the first two years of follow-up.

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3 **Conclusions:** In a population with a high prevalence of CKD risk factors such as hypertension  
4 and diabetes, physical activity appears to be associated with reduced risk of ESRD among those  
5 with preserved kidney function. A positive association between sitting time and ESRD observed  
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7 among those with advanced kidney disease is likely due to reverse causation.  
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11 **Abbreviations:** CHC=community health center; CI=confidence interval; CKD=chronic kidney  
12 disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HR=hazard  
13 ratio; MET=metabolic equivalent; SCCS=Southern Community Cohort Study; USRDS=United  
14 States Renal Data System  
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#### 24 **Strengths and limitations of this study**

- 25  
26 • The SCCS is a large, unique cohort of black and white participants with low  
27 socioeconomic status and a high burden of risk factors for end-stage renal disease.  
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30 • The case-cohort design selected participants for measurement of serum creatinine,  
31 therefore, baseline kidney function could be evaluated.  
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34 • Physical activity and sedentary behaviors were self-reported rather than objectively  
35 measured; however, a validated questionnaire developed for the SCCS was used for  
36 ascertainment of these measures.  
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39 • Only baseline data on physical activity and sedentary behaviors were included and  
40 behaviors may have changed after enrollment.  
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## INTRODUCTION

In 2015, the age-adjusted incidence of end-stage renal disease (ESRD) in the United States was 357 per million [1]. With the growing burden of ESRD, there has been increasing focus on modifiable risk factors. Recent studies have shown that higher physical activity levels are associated with lower risk of chronic kidney disease (CKD) and slower decline in estimated glomerular filtration rate (eGFR) [2-8]. Studies that examined sedentary behaviors are limited but suggest that higher sedentary time is associated with reduced kidney function and increased CKD risk [4 9]. The association between physical activity, sedentary time, and ESRD is not well established though, with few studies suggesting an association between physical activity and ESRD and none with the ability to disentangle exercise behaviors from socioeconomic status (SES) [10 11].

To investigate whether sedentary time and physical activity were independently associated with risk of incident ESRD, we used a case-cohort design within the Southern Community Cohort Study (SCCS), a unique population of individuals with lower SES, a high burden of kidney disease risk factors, and robust measures of physical activity and sedentary time.

## METHODS

### Study population

The SCCS is a prospective cohort study that recruited ~86,000 primarily low-income black and white adults, aged 40-79 years, in the southeastern US (2002-2009) [12]. Participants eligible for enrollment spoke English and had not been treated for cancer in the 12 months before enrollment. The majority (86%) were recruited at participating community health centers (CHC),



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3 which provide primary healthcare for under-insured populations. A detailed description of SCCS  
4 methods has been published (<http://www.southerncommunitystudy.org>) [13]. All participants  
5 provided written informed consent, and the study was approved by the Institutional Review  
6 Boards of Vanderbilt University Medical Center and Meharry Medical College. We used the  
7 STROBE cohort checklist when writing our report [14].  
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14 Incident ESRD was identified by linking the SCCS cohort, using date of birth, Social  
15 Security number, and first and last name, with the nationwide US Renal Data System (USRDS)  
16 through March 31, 2015, the latest date for which data were available. ESRD cases in this  
17 registry are certified by a physician diagnosis and filed using a medical evidence report form (to  
18 the Medicare ESRD program), or when chronic dialysis or kidney transplant occurs, irrespective  
19 of the glomerular filtration rate. The USRDS is a national registry and therefore, ascertainment  
20 of ESRD cases is virtually complete [1]. Participants with an ESRD diagnosis prior to SCCS  
21 enrollment (prevalent cases) were excluded from the analysis.  
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33 Approximately 46% of the cohort donated baseline blood samples during CHC  
34 recruitment, which have been frozen at -80°C. Participants were selected for measurement of  
35 creatinine using a case-cohort design, including all those with stored blood who had an incident  
36 ESRD diagnosis (n=737), and a probability sample of the entire cohort who donated blood  
37 (n=4,238) [15 16]. Baseline serum levels of creatinine were measured using the Jaffe (Rate)  
38 method on a Beckman Coulter DXC 600 clinical chemistry analyzer. The creatinine assays were  
39 calibrated, and daily quality checks performed at three levels before sample testing. This sample  
40 constitutes 13% of SCCS participants who donated blood, and is comparable with respect to  
41 baseline sociodemographic characteristics including racial distribution, low income, and high  
42 prevalence of CKD risk factors [17]. The weighted subcohort included 70.8% blacks and 29.2%  
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3 whites, and the SCCS population included 67.3% blacks and 28.6% whites. In the subcohort and  
4  
5 overall SCCS population, about 32% had an education level below 12<sup>th</sup> grade, the majority had  
6  
7 an annual income of <\$15,000, and the prevalence of hypertension and diabetes was similar at  
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9 56% and 22%, respectively.

### 12 **Patient and Public Involvement**

14 There was no patient or public involvement in study design and conduct, dissemination of  
15  
16 results, and evaluation in this study.

### 19 **Data collection**

21 Standardized computer-assisted personal interviews were administered at enrollment to obtain  
22  
23 data on demographic, medical, and lifestyle variables [13]. Sections included demographic  
24  
25 characteristics (education, income, residence), tobacco use, personal and family medical history,  
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27 medication use, emotional well-being, occupation, physical activity, and diet. Body mass index  
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29 (BMI) was calculated from self-reported height and weight. History of hypertension, diabetes,  
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31 and hypercholesterolemia as well as stroke and cardiovascular disease were self-reported by  
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33 asking whether a doctor had ever diagnosed the participant with the condition. Self-reported  
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35 height and weight were compared with clinic recorded measurements for over 20% of  
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37 participants. In a series of validation studies, biomarkers, repeat interviews, or medical records  
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39 were used to assess the reliability of variables such as smoking status and self-reported diseases  
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41 including diabetes [13].

46 Usual sedentary and active behaviors were assessed using a validated physical activity  
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48 questionnaire (PAQ) developed specifically for the SCCS [18]. For sedentary behaviors,  
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50 participants were asked questions about the amount of time per day typically spent sitting in a car  
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52 or bus, at work, viewing television or movies, and other activities that involve sitting such as  
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3 sitting at meals, talking on the phone, reading, playing games, or sewing. For physical activity,  
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5 participants were asked about time typically spent performing light, moderate, and strenuous  
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7 activities at home and at work, as well as time spent doing moderate and vigorous  
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9 exercise/sports. Time spent doing work and home activities was assessed separately for week and  
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11 weekend days, and exercise and sports participation was assessed for a typical week. Examples  
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13 of light work were given to participants and included standing at work, shopping, cooking, and  
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15 child or elderly care. Moderate work examples included shop work, cleaning house, gardening,  
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17 mowing lawn, and home repair. Examples of strenuous work included loading or unloading  
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19 trucks, construction, farming, or other hard labor. Moderate sports included activities such as  
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21 bowling, dancing, and golfing, while vigorous sports included jogging, aerobics, tennis,  
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23 swimming, and weight lifting. For all questions, participants provided open-ended duration  
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25 responses (hours and minutes). The reliability and validity of the SCCS physical activity  
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27 questionnaire was evaluated in 118 randomly selected SCCS participants via use of  
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29 accelerometers [18].  
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### 35 **Statistical Analysis**

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37 The study population was restricted to blacks and whites enrolled at CHCs, to ensure that  
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39 participants had similar SES and equal access to healthcare regardless of race and had the  
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41 opportunity to donate a blood specimen. Participants with missing data for any exercise metric  
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43 (n=161) or demographic characteristic (n=212), and those with baseline eGFR>150  
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45 ml/min/1.73m<sup>2</sup> (n=22), were excluded; thus, a total of 692 ESRD cases and 4,113 subcohort  
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47 members were included in the analyses (Figure 1).  
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52 Sedentary time was calculated as hours/day based on the sum of all individual sedentary  
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54 behaviors. Total physical activity was calculated as the sum of light, moderate and strenuous  
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3 household/occupational work as well as moderate and vigorous sports; values were transformed  
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5 from hours/day into summary measures of energy expenditure, defined as metabolic equivalent  
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7 (MET)-hours/day. MET values for specific activities and intensities were based on the  
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9 Compendium of Physical Activities [19]. MET-hours reflect the weighted average of the  
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11 intensity (MET) and duration (hours) of activity behaviors. Two MET-hours/day is roughly  
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13 equivalent to participating in 1 hour of a light activity, 0.5 hours of a moderate activity such as  
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15 walking, or 0.25 hours of a vigorous activity such as jogging [18]. For example, one MET-hour  
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17 is roughly equivalent to the energy expenditure associated with walking very briskly (4 METS)  
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19 for 15 minutes (0.25 hours).  
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25 Using sampling weight techniques, we described baseline characteristics of subcohort  
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27 participants using means and standard deviations (SD) or medians and 25<sup>th</sup> and 75<sup>th</sup> percentiles.  
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29 For descriptive purposes, sedentary time (hours/day) and physical activity (MET-hours/day)  
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31 were also categorized into quartiles based on the subcohort distribution. Incidence rates (IR)  
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33 were calculated from bootstrap probability resamples; the reported IRs were the means of the  
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35 bootstrap replicates with confidence intervals (CI) at the 2.5 and 97.5 percentiles of the  
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37 bootstrap distribution.  
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41 We calculated hazard ratios (HRs) and 95% CIs for the association of sedentary time and  
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43 physical activity with ESRD from Cox regression models that accounted for the case-cohort  
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45 design and the weighted sample [15]. Participants were considered at risk from the date of SCCS  
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47 enrollment until the first occurrence of incident ESRD, death, or March 31, 2015. Total  
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49 sedentary time and physical activity were modeled as restricted cubic splines with four knots and  
50  
51 mutually adjusted in a single model. Additional covariates included age at enrollment (years),  
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53 sex, race, education (< or ≥high school), income (< or ≥\$15,000), BMI (kg/m<sup>2</sup>), smoking (never  
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3 or former/current), baseline eGFR (mL/min/1.73m<sup>2</sup>), and history of diagnosis of diabetes,  
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5 hypertension and hypercholesterolemia (yes/no). Baseline serum levels of creatinine were used  
6  
7 for estimation of eGFR using the CKD-EPI equation [20]. Continuous predictors (age, eGFR,  
8  
9 and BMI) were added to the model as restricted cubic splines with four knots. To examine  
10  
11 interactions between sedentary time or physical activity and baseline kidney function on ESRD  
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13 risk, multiplicative interaction terms between the nonlinear, continuous predictors of sedentary  
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15 time/physical activity and nonlinear, continuous eGFR were added to the model.  
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19 We constructed partial effect plots of eGFR and physical activity or sedentary time on the  
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21 log relative hazard scale, which display the predicted outcome as a function of a single covariate  
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23 while holding all other covariates constant for different levels of baseline kidney function. We  
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25 also plotted the HRs of ESRD as a function of continuous MET-hours/day or sitting hours/day,  
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27 again holding all other covariates constant for different levels of baseline kidney function. The  
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29 CIs in the HR plots were generated using bootstrap resampling methods.  
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33 To examine if the relationship with ESRD differed for different types of sitting, we also  
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35 modeled the individual sedentary behaviors, sitting in the car/bus, sitting at work, watching  
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37 TV/movies, and other sitting. The multivariable Cox model included sitting hours for each  
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39 category modeled as restricted cubic splines and mutually adjusted. Non-nested likelihood ratio  
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41 tests were used to compare this model to the Cox model including total sitting hours.  
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45 Finally, in sensitivity analyses to examine the potential for reverse causation among those  
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47 with advanced kidney disease, we calculated HRs and 95% CIs and constructed partial effect  
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49 plots as above, excluding the first two years of follow up. All analyses were conducted using R.  
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51 For main effects and interaction terms, P-values  $\leq 0.05$  were considered statistically significant.  
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## RESULTS

At baseline, mean (SD) age of subcohort participants was 52 (8.6) years (Table 1). Most participants were women (60%), black (71%), reached high school (68%), and had income <\$15,000 (62%). Approximately 75% were overweight or obese ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ), and 55%, 23% and 35% reported a diagnosis of hypertension, diabetes and hypercholesterolemia, respectively. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) baseline eGFR was 102.8 (85.9, 117.9) mL/min/1.73m<sup>2</sup> in the subcohort and 62.9 (36.0, 98.1) among ESRD cases. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) for total sedentary time and physical activity in the subcohort were 8.0 (5.5, 12.0) hours/day and 17.2 (8.7, 31.9) MET-hours/day, respectively. The most common sedentary activity was watching TV or movies; for physical activity, most energy expenditure came from moderate activities and sports.

Demographic characteristics by quartiles of physical activity and sedentary time are presented in Table 2. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) total physical activity in the highest activity quartile for the subcohort was 41.3 (33.2, 55.5) MET-hours/day, compared to 4.2 (2.0, 6.2) in the lowest quartile (Table 2a). Compared to individuals in the lower quartiles, subcohort members in the highest quartile of physical activity were younger, had higher education and income, and had lower prevalence of obesity, hypertension, hypercholesterolemia and diabetes. Median baseline eGFR was highest among those in the highest quartile of physical activity.

Median (25<sup>th</sup>, 75<sup>th</sup> percentile) total sitting hours in the subcohort was 15.5 (13.8, 18.0) hours/day in the highest sedentary time quartile and 4.0 (3.0, 5.0) hours/day for participants in the lowest quartile (Table 2b). Total physical activity was higher among participants in the third and fourth quartile of sedentary time compared to the lower two quartiles. Subcohort participants in the fourth quartile of sedentary time were more likely than those in lower quartiles to be black

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3 and obese, and to have  $\geq$ high school education or annual income  $\geq$ \$15,000. Prevalence of  
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5 hypertension, hypercholesterolemia and diabetes did not vary consistently across quartiles of  
6  
7 sitting time, nor did median baseline eGFR.  
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10 Participants were followed for a median (range) of 9.4 (0.1-12.8) years. Age-adjusted IRs  
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12 for ESRD were 2.61, 2.38, 2.24, and 1.68/1000 person-years in quartiles 1-4 of physical activity,  
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14 respectively; corresponding IRs in quartiles of sitting time were 2.13, 2.06, 2.07, and 2.64/1000  
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16 person-years (Table 2). In unadjusted Cox models, the HRs for an interquartile range increase in  
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18 physical activity or sedentary time were 0.65 (95% CI 0.58-0.73) and 1.09 (95% CI 1.00-1.20),  
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20 respectively. In the multivariable model including both physical activity and sedentary time, and  
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22 the interactions between physical activity\*eGFR and sedentary behavior\*eGFR, both  
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24 interactions were statistically significant (chunk test P-value <0.001). Therefore, we present  
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26 partial effect plots based on the multivariable model to further tease out the shape of the  
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28 association between eGFR, physical activity, and sitting.  
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33 The partial effect plots show the association between physical activity (Figure 2a) or  
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35 sedentary time (Figure 2b) and log relative hazard of ESRD, by levels of baseline eGFR. When  
36  
37 eGFR is 30, the shape of the association suggests that risk of ESRD increases as activity  
38  
39 increases. In contrast, when eGFR is 90, log relative hazard of ESRD decreases as activity  
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41 increases, and the inverse association is most pronounced at levels of physical activity above 27  
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43 MET-hours/day. The predicted log relative hazard of ESRD is uniformly higher when eGFR is  
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45 30 compared to when eGFR is 60, and log relative hazard is lowest when eGFR is 90.  
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49 In the second plot, when eGFR is 30, the shape of the association shows increasing  
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51 ESRD risk as sedentary time increases. In contrast, when eGFR is 60 or 90, the shape of the  
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53 association is slightly decreasing or flat with increasing sedentary time. As for physical activity,  
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3 the predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to  
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5 when eGFR is 60 or 90.  
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8 The continuous HR plots present the associations between physical activity (Figure 3a) or  
9  
10 sedentary time (Figure 3b) and risk of incident ESRD. The HR plots are separated into three  
11  
12 levels of eGFR (30, 60, 90 mL/min/1.73m<sup>2</sup>). Each panel has its own reference level, which is  
13  
14 seen at the pinch in the confidence intervals where HR=1.0. The relative shape of the  
15  
16 associations at each level of eGFR corresponds to what is shown in the partial effect plots; in  
17  
18 particular, an inverse association between physical activity and risk of ESRD is apparent only  
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20 among those with preserved kidney function, while an increased risk of ESRD with increasing  
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22 sedentary time is observed among those with low eGFR.  
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26 In analyses examining the individual types of sitting, the non-nested likelihood ratio test  
27  
28 indicated that the model with sitting hours by type did not significantly differ from the model  
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30 with total sitting hours (p=0.98). In sensitivity analyses excluding the first two years of follow  
31  
32 up, the interactions between sedentary time\*eGFR and physical activity\*eGFR remained  
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34 statistically significant (P-value<0.001 for both); however, the positive association between  
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36 sitting time and ESRD among those with advanced kidney disease was no longer apparent.  
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## 42 **DISCUSSION**

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44 Among blacks and whites at high risk for ESRD, we observed a significant interaction  
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46 between physical activity and baseline kidney function, suggesting that among individuals with  
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48 preserved kidney function, higher physical activity is associated with a lower risk of developing  
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50 ESRD. Similarly, we observed heterogeneity of the association of sitting time on ESRD risk, as  
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3 demonstrated by the higher risk of ESRD associated with longer sitting time among those with  
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5 eGFR  $\leq 30$  mL/min/1.73m<sup>2</sup>, which appears to be explained by reverse causation.  
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8 While physical activity is widely accepted as an important modifiable risk factor for  
9  
10 cardiovascular disease, the association is not well established in kidney disease. A number of  
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12 observational and interventional studies have examined the risks and benefits of physical activity  
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14 among patients undergoing maintenance dialysis [21-24]. However, previous studies of incident  
15  
16 kidney disease are limited and have reported inconsistent results. In a cross-sectional study of  
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18 10,463 patients with diabetes and hypertension, lack of exercise was a significant risk factor for  
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20 CKD [8]. In another cohort study of 6,972 patients with diabetes, participants who had more  
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22 regular physical activity had a reduced risk of early diabetic CKD [3]. Among 4,011 participants  
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24 from the Cardiovascular Health Study, those with the highest amount of physical activity had a  
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26 lower risk of rapid kidney function decline [7]. In contrast, in a study of 3,653 black participants  
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28 from the Jackson Heart Study, physical activity was not associated with rapid decline in eGFR  
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30 [25]. The inconsistency of results may be due in part to the fact that physical activity for these  
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32 studies was defined in different ways, ranging from number of times per week the participant  
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34 exercised [3 8] to categorization based on the American Heart Association's Life Simple 7 and  
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36 the Minnesota Heart Survey [7 25].  
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42 We found that a high level of physical activity was associated with lower risk of ESRD  
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44 among those with preserved kidney function. Two prior studies reported an association between  
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46 physical activity and lower risk of ESRD. Among 59,552 participants from the Singapore  
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48 Chinese Health Study, those engaged in any physical activity had a lower risk of ESRD, and a  
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50 dose-response relationship with intensity of physical activity was noted [10]. Among individuals  
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52 with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC), physical activity was  
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3 inversely associated with risk of CKD progression (defined as 50% decrease in eGFR or incident  
4 ESRD). The CRIC results are somewhat inconsistent with our observation of no beneficial effect  
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6 of physical activity among those with already reduced kidney function. It is possible that  
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8 secondary factors such as hyperphosphatemia, acidosis, proteinuria, and glomerular hypertension  
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10 and hypertrophy drive progression of CKD once established and, therefore, physical activity may  
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12 have less of an impact on ESRD risk in this group [26 27]. Also, earlier and longer established  
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14 control of primary CKD risk factors, such as blood pressure and blood sugar, through physical  
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16 activity may have more of an impact earlier rather than later in the kidney disease course.  
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22 Diabetes, obesity, hypertension, and kidney dysfunction can lead to oxidative stress,  
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24 insulin resistance, endothelial dysfunction, and increased circulating cytokines [28]. Physical  
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26 activity has a beneficial effect on these metabolic disturbances, all common in patients with  
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28 CKD, and these mechanisms may underlie our finding of reduced risk of ESRD with greater  
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30 levels of physical activity. One important metabolic disturbance and risk factor for CKD is  
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32 inflammation, which has an inverse correlation with eGFR [29]. Patients with CKD/ESRD have  
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34 higher levels of pro-inflammatory adipokines or cytokines, such as leptin, tumor necrosis factor  
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36 alpha and interleukin 1 and 6 [29-31]. Exercise and physical activity have been shown to reduce  
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38 inflammatory molecules and create an anti-inflammatory environment in the general population  
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40 and in patients with CKD [31 32], a potential mechanisms for a beneficial effect of physical  
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42 activity on kidney function. Increased physical exercise and subsequent weight loss may also  
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44 help decrease the oxidative stress burden in patients with CKD [29 30 33]. Finally, excess  
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46 adiposity and lack of physical activity are the most common causes of insulin resistance [34] and  
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48 hyperglycemia. This metabolic dysregulation is a risk factor for reduced kidney function.  
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3 Exercise and physical activity decrease insulin resistance and improve endothelial responses to  
4 insulin [34].  
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8 Sedentary behavior is hypothesized to be an independent risk factor for CKD and ESRD,  
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10 but few studies have examined this association. We observed a significant interaction between  
11 sedentary time and eGFR, demonstrating that a higher amount of sitting time increased risk of  
12 ESRD in participants with lower eGFR. We speculated that this may be a result of reverse  
13 causation, whereby the presence of advanced kidney disease, uremia or other comorbidities and  
14 subsequent fatigue in those with low eGFR, already at high risk for ESRD, may lead to increased  
15 sedentary time and also prompt earlier initiation of dialysis. In fact, attenuation of the association  
16 between sedentary time and ESRD after exclusion of the first two years of follow-up lends  
17 support to this explanation. Additionally, we observed that the model separating sitting time by  
18 type did not fit better than the model with total sitting time.  
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31 Sedentary behavior has, however, been shown to be associated with physiological risk  
32 factors for CKD and ESRD including increased BMI, systolic blood pressure, triglycerides, and  
33 decreased HDL cholesterol [35], and these pathways may mediate possible effects and should be  
34 further explored. Two recent studies have reported associations between higher sedentary time  
35 and lower eGFR and higher odds of urinary albumin excretion time [4 9].  
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43 To our knowledge, this is one of few studies to investigate the association between  
44 physical activity and ESRD and one of the first to examine sedentary behaviors. Strengths of our  
45 study include the prospective design and the unique cohort of participants with low SES and a  
46 high burden of risk factors for ESRD. An important strength is the ascertainment of a broad  
47 range of physical activity and sedentary behaviors from a validated questionnaire developed  
48 specifically for the SCCS [18]. Other strengths include the complete ascertainment of ESRD  
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3 cases and the inclusion of baseline eGFR. A limitation of the study is that physical activity and  
4 sedentary behaviors were ascertained only at baseline and may have changed after enrollment.  
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6 Moreover, the physical activity, sedentary behaviors, and covariates were self-reported by  
7  
8 participants rather than objectively measured. Although the probability sample is comparable to  
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10 the whole cohort, the findings might not be generalizable to all SCCS participants. Finally,  
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12 baseline data on proteinuria were not available.  
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17 In conclusion, this study found that in a population at high risk for ESRD, higher levels  
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19 of physical activity were associated with reduced risk of ESRD in those with preserved kidney  
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21 function, and sedentary time was not associated with increased ESRD risk except in participants  
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23 with low baseline eGFR. Physical activity and sedentary behaviors are modifiable risk factors  
24  
25 that may be targets for possible interventions, especially in those with preserved kidney function.  
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31 None  
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### 34 **Conflict of Interest Statement**

35 None declared. The results presented in this paper have not been published previously in whole  
36  
37 or part, except in abstract form.  
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### 41 **Author Contributions**

42 Research idea and study design: MMP, JMT, EKK, EAA, TAI, TGS, LL; data acquisition: LL,  
43  
44 WJB; data analysis/interpretation: MMP, JMT, EKK, TGS, JLM, CRC, EAA, KAK, EDS, WJB,  
45  
46 TAI, LL; statistical analysis: MMP, TGS, JLM, EAA; supervision or mentorship: TGS, CRC,  
47  
48 WJB, TAI, LL. Each author contributed important intellectual content during manuscript drafting  
49  
50 or revision and accepts accountability for the overall work by ensuring that questions pertaining  
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3 to the accuracy or integrity of any portion of the work are appropriately investigated and  
4  
5 resolved.  
6

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### 53 **Data Sharing Statement**

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3 The SCCS is committed to open sharing of its resources to provide for optimal utilization of  
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The SCCS is committed to open sharing of its resources to provide for optimal utilization of SCCS data and biologic specimens for research purposes. The proposed research will generate biomarker data (serum trace metals, serum creatinine) which will be added to the SCCS database. Consistent with current SCCS study operations, qualified researchers who wish to collaborate with investigators from our study will have access to SCCS data upon approval of a research proposal by the 12-member SCCS Data and Biospecimen Use Committee (<https://ors.southerncommunitystudy.org/>). The SCCS has an open access policy for legitimate scientific purposes, but because of privacy concerns, requires Committee review of all data requests. All investigators are required to sign a data use agreement prior to receipt of SCCS study data that provides for: (1) Sharing of the data only with investigators signing the data use agreement; (2) Use of the data only for purposes approved by the DBU Committee; (3) Agreement for review of manuscripts and statistical programs prior to submission of the results for publication; (4) A 12-month time frame for completion of the analysis.

Prior to sharing of SCCS data for proposals approved by the Committee, datasets are de-identified according to the HIPAA Safe-Harbor Method (<http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveridentities/Deidentification/guidance.html>)

The following data elements are removed from datasets prior to release to investigators:

- a. Name
- b. All geographic identifiers for subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and the equivalent geocodes
  - a. De-identified geographic subdivisions will not be released when the total number of persons within that subdivision is known to be less than 300, to prevent potential disclosure of the identifier due to unique characteristics
- c. All elements of dates (except year), including, but not limited to, date of birth, date of SCCS enrollment, date of diagnosis, date of death, and all ages over 89 or elements of date indicative of an age over 89
- d. Telephone Numbers

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3 e. Fax Numbers

4 f. Email Addresses

5 g. Social Security Numbers

6 h. Medical Record Numbers

7 i. Health Plan Beneficiary Numbers

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9 Transmission of potentially identifiable data is kept to a minimum and performed only as needed  
10 for study operations in accordance with HIPAA regulations.  
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**Table 1. Baseline characteristics of the probability sample (subcohort) of SCCS participants and ESRD cases**

	<b>Subcohort participants (n=4,113)</b>	<b>ESRD cases (n=692)</b>
Age at enrollment, years	52.2 ± 8.6	53.8 ± 8.0
Women	59.8	51.5
Race		
White	29.3	12.4
Black	70.7	87.6
Education		
<High school	32.3	40.3
≥High school	67.7	59.7
Household income		
<\$15,000/year	61.6	65.8
≥\$15,000/year	38.4	34.2
Cigarette smoking		
Current/former smoker	67.3	58.3
Never smoker	32.7	41.7
BMI, kg/m <sup>2</sup>	30.3 ± 7.3	32.8 ± 8.8
Overweight or obese (BMI≥25 kg/m <sup>2</sup> )	74.8	82.5
Hypertension	55.5	86.0
Hypercholesterolemia	34.5	49.3
Diabetes	22.6	68.5
eGFR, ml/min/1.73m <sup>2</sup>	102.8 (85.9, 117.9)	62.9 (36.0, 98.1)
<b>Sedentary and physical activity measures</b>		
Sitting, h/d	8.0 (5.5,12.0)	8.2 (6.0,12.0)
Car or bus, h/d	1.5 ± 1.8	1.5 ± 2.0
At work, h/d	1.2 ± 2.3	0.9 ± 2.3
TV or movies, h/d	3.8 ± 2.9	4.3 ± 3.1
Home computer, h/d	0.5 ± 1.1	0.3 ± 0.9
Other, h/d <sup>a</sup>	2.3 ± 1.9	2.4 ± 2.0
Physical Activity, h/d	5.4 (2.9,9.4)	4.3 (2.3,7.4)
Household/occupational activity, MET-h/d		
Light	7.3 ± 6.2	5.9 ± 5.4
Moderate	9.7 ± 8.7	8.6 ± 7.9
Strenuous	5.0 ± 11.7	3.1 ± 9.4
Sports, MET-h/d		
Moderate	10.0 ± 8.8	8.9 ± 8.1
Vigorous	5.6 ± 12.0	3.5 ± 9.6
Total physical activity, MET-h/d <sup>b</sup>	17.2 (8.7,31.9)	13.9 (6.9,24.6)

*Note:* Values are listed as mean ± SD or % or median (25<sup>th</sup>,75<sup>th</sup> percentile)

<sup>a</sup>Includes sitting at meals, talking on the phone, reading, playing cards, or sewing.

<sup>b</sup>Includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study

**Table 2. Baseline characteristics of the subcohort of SCCS participants by quartiles of: a) physical activity, and b) sedentary time**

	<b>Q1: Subcohort (n=934)</b>	<b>Q2: Subcohort (n=994)</b>	<b>Q3: Subcohort (n=1045)</b>	<b>Q4: Subcohort (n=1140)</b>
<b>a)</b>				
ESRD Incidence Rate per 1000 person-year	2.61 (1.54, 3.87)	2.38 (1.36, 3.50)	2.24 (1.25, 3.30)	1.68 (0.93, 2.55)
Physical activity (MET-h/day) <sup>a</sup>	4.2 [2.0, 6.2]	10.6 [8.8, 12.6]	20.2 [17.2, 23.5]	41.3 [33.2, 55.5]
Sitting (h/day)	7.5 [5.0, 11.0]	8.0 [6.0, 12.0]	9.0 [6.0, 12.0]	8.5 [5.8, 12.0]
Age, years	54.6 (9.3)	53.1 (8.9)	52.4 (8.8)	49.7 (7.1)
Women	49.9	67.0	70.7	51.5
Black race	67.5	69.2	71.3	73.2
Less than high school	37.7	35.0	32.1	27.0
Less than \$15K/year	73.1	66.9	59.4	52.2
Current/former smoker	70.4	64.4	65.7	69.0
BMI, kg/m <sup>2</sup>	30.9 (7.9)	30.7 (7.4)	30.9 (7.2)	29.1 (6.8)
Overweight or obese (BMI≥25 kg/m <sup>2</sup> )	75.1	77.2	77.3	70.5
Hypertension	63.5	56.7	58.7	47.1
High cholesterol	38.7	38.1	38.7	25.7
Diabetes	27.6	24.4	23.8	17.0
eGFR, mL/min/1.73m <sup>2</sup>	99.2	102.9	102.1	106.9
	[80.6, 114.8]	[84.8, 116.8]	[86.6, 117.6]	[89.9, 120.3]
<b>b)</b>				
ESRD Incidence Rate per 1000 person-year	2.13 (1.20, 3.20)	2.06 (1.18, 3.03)	2.07 (1.18, 3.12)	2.64 (1.46, 3.88)
Sitting (h/day)	4.0 [3.0, 5.0]	7.0 [6.3, 7.5]	10.0 [9.0, 11.0]	15.5 [13.8, 18.0]
Physical Activity (MET-h/day) <sup>a</sup>	15.8 [7.5, 32.4]	15.3 [8.6, 29.6]	18.4 [9.7, 32.7]	18.6 [9.8, 32.3]
Age, years	52.5 (8.9)	53.2 (8.5)	52.1 (8.9)	50.6 (7.8)
Women	58.2	57.3	63.1	60.6
Black race	71.0	66.0	67.7	79.6
Less than high school	39.8	29.5	29.0	31.0
Less than \$15K/year	69.4	60.6	58.9	57.2

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2					
3	Current/former smoker	65.8	65.2	68.2	70.4
4	BMI, kg/m <sup>2</sup>	29.5 (7.1)	29.7 (7.3)	30.7 (7.3)	31.5 (7.5)
5	Overweight or obese (BMI $\geq$ 25 kg/m <sup>2</sup> )	71.6	72.0	77.1	78.7
6	Hypertension	53.5	58.1	55.8	54.6
7	High cholesterol	31.3	34.4	36.7	35.6
8	Diabetes	21.9	23.1	21.8	23.6
9	eGFR, mL/min/1.73m <sup>2</sup>	104.3 [88.9,	102.1 [84.4, 115.2]	102.1 [85.4, 118.2]	103.4 [85.3, 120.1]
10		118.6]			
11					
12	<i>Note:</i> Values are listed as mean $\pm$ SD or % or median (25 <sup>th</sup> ,75 <sup>th</sup> percentile)				
13	<sup>a</sup> Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and				
14	vigorous sports.				
15	Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS,				
16	Southern Community Cohort Study				
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*Note:* Values are listed as mean  $\pm$  SD or % or median (25<sup>th</sup>,75<sup>th</sup> percentile)

<sup>a</sup>Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study

## FIGURE LEGEND

**Figure 1.** Study selection of the SCCS case-cohort.

**Figure 2.** Partial effect plots of **a)** physical activity (MET-hours/day) and **b)** total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR

**Figure 3.** Plots of continuous hazard ratios of **a)** physical activity (MET-hours/day) and **b)** total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR. The confidence intervals in the HR plot were generated using bootstrap resampling methods

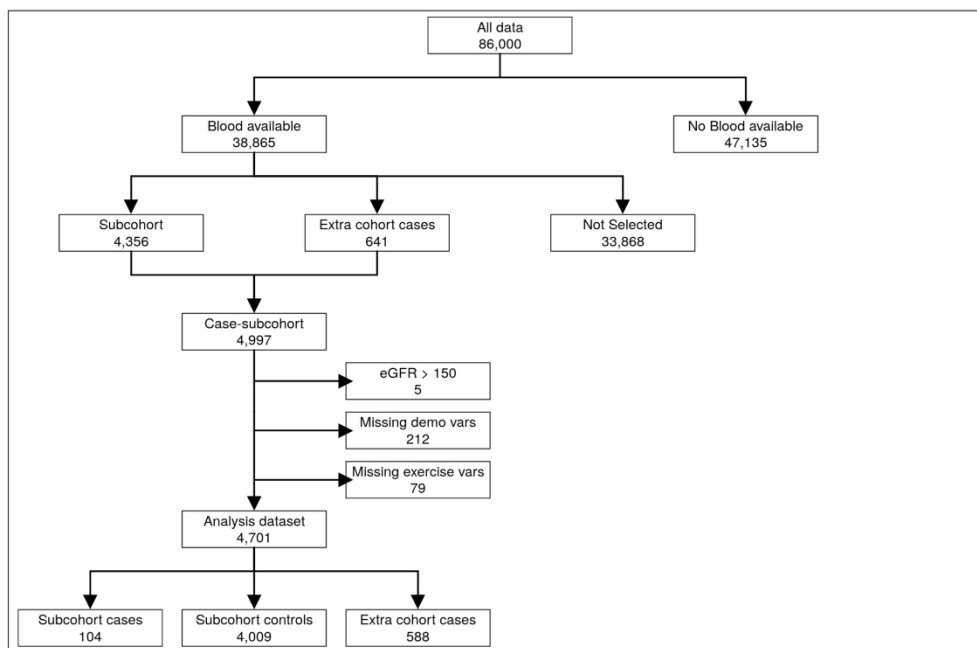


Figure 1. Study selection of the SCCS case-cohort.

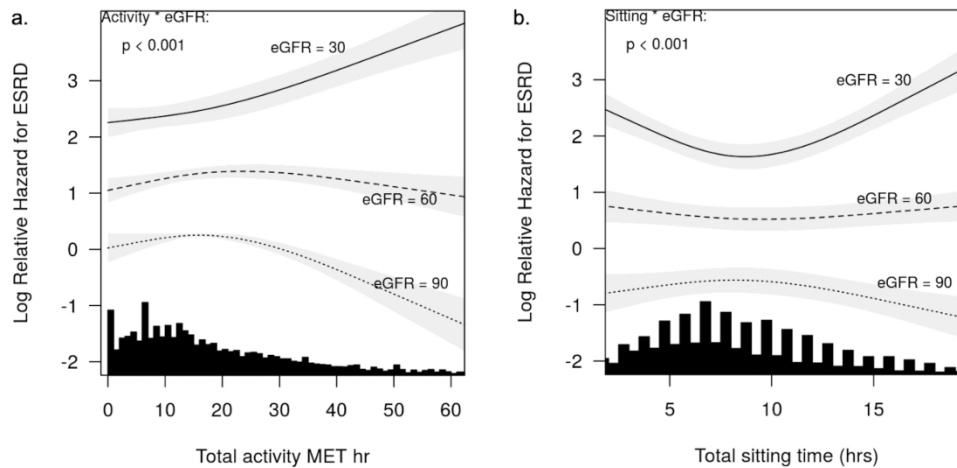


Figure 2. Partial effect plots of a) physical activity (MET-hours/day) and b) total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR



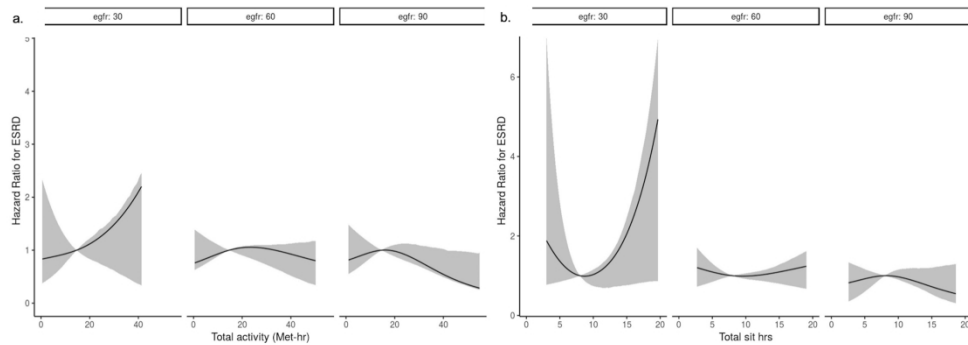


Figure 3. Plots of continuous hazard ratios of a) physical activity (MET-hours/day) and b) total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR. The confidence intervals in the HR plot were generated using bootstrap resampling methods

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
	#6b	For matched studies, give matching criteria and number of exposed and	NA

		unexposed	
1			
2	Variables	#7	Clearly define all outcomes, exposures, predictors, potential
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4			confounders, and effect modifiers. Give diagnostic criteria, if applicable
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6	Data sources /	#8	For each variable of interest give sources of data and details of methods
7	measurement		5
8			of assessment (measurement). Describe comparability of assessment
9			methods if there is more than one group. Give information separately
10			for for exposed and unexposed groups if applicable.
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12	Bias	#9	Describe any efforts to address potential sources of bias
13			6
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15	Study size	#10	Explain how the study size was arrived at
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18	Quantitative	#11	Explain how quantitative variables were handled in the analyses. If
19	variables		6
20			applicable, describe which groupings were chosen, and why
21			
22	Statistical	#12a	Describe all statistical methods, including those used to control for
23	methods		6-7
24			confounding
25		#12b	Describe any methods used to examine subgroups and interactions
26			6-7
27		#12c	Explain how missing data were addressed
28			6
29		#12d	If applicable, explain how loss to follow-up was addressed
30			6
31		#12e	Describe any sensitivity analyses
32			7
33			
34	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers
35			6
36			potentially eligible, examined for eligibility, confirmed eligible,
37			included in the study, completing follow-up, and analysed. Give
38			information separately for for exposed and unexposed groups if
39			applicable.
40		#13b	Give reasons for non-participation at each stage
41			6
42		#13c	Consider use of a flow diagram
43			NA
44			
45	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical,
46			8
47			social) and information on exposures and potential confounders. Give
48			information separately for exposed and unexposed groups if applicable.
49		#14b	Indicate number of participants with missing data for each variable of
50			6
51			interest
52		#14c	Summarise follow-up time (eg, average and total amount)
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1	Outcome data	#15	Report numbers of outcome events or summary measures over time.	9
2			Give information separately for exposed and unexposed groups if	
3			applicable.	
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6	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted	9
7			estimates and their precision (eg, 95% confidence interval). Make clear	
8			which confounders were adjusted for and why they were included	
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12		#16b	Report category boundaries when continuous variables were categorized	9
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14		#16c	If relevant, consider translating estimates of relative risk into absolute	NA
15			risk for a meaningful time period	
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18	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	10
19			interactions, and sensitivity analyses	
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22	Key results	#18	Summarise key results with reference to study objectives	10
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24	Limitations	#19	Discuss limitations of the study, taking into account sources of potential	13
25			bias or imprecision. Discuss both direction and magnitude of any	
26			potential bias.	
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29	Interpretation	#20	Give a cautious overall interpretation considering objectives,	11-12
30			limitations, multiplicity of analyses, results from similar studies, and	
31			other relevant evidence.	
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34	Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
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37	Funding	#22	Give the source of funding and the role of the funders for the present	14
38			study and, if applicable, for the original study on which the present	
39			article is based	
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 43 This checklist was completed on 14. March 2019 using <https://www.goodreports.org/>, a tool made by the  
 44 [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## The association of exercise and sedentary behaviors with incident end stage renal disease in the Southern Community Cohort Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030661.R2
Article Type:	Research
Date Submitted by the Author:	05-Aug-2019
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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Renal medicine
Keywords:	End stage renal failure < NEPHROLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

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Manuscripts

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3 **The association of exercise and sedentary behaviors with incident end stage renal disease in**  
4 **the Southern Community Cohort Study**  
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42 **Running Head:** Physical Activity and ESRD  
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45 **Key Words:** end stage renal disease, sedentary time, physical activity  
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48 **Word Count Abstract:** 287      **Text:** 3,678  
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## ABSTRACT

**Objective:** To examine whether lifestyle factors, including sedentary time and physical activity, could independently contribute to risk of end stage renal disease (ESRD).

**Study Design:** Case-cohort study.

**Setting:** Southeastern US

**Participants:** The Southern Community Cohort Study recruited ~86,000 black and white participants from 2002-2009. We assembled a case-cohort of 692 incident ESRD cases and a probability sample of 4113 participants.

**Predictors:** Sedentary time was calculated as hours/day from daily sitting activities. Physical activity was calculated as metabolic equivalent (MET)-hours/day from engagement in light, moderate, and vigorous activities.

**Outcomes:** Incident ESRD.

**Results:** At baseline, among the subcohort, mean (SD) age was 52 (8.6) years, and median (25<sup>th</sup>, 75<sup>th</sup>percentile) estimated glomerular filtration rate (eGFR) was 102.8 (85.9, 117.9) mL/min/1.73m<sup>2</sup>. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) for sedentary time and physical activity were 8.0 (5.5, 12.0) hours/day and 17.2 (8.7, 31.9) MET-hours/day, respectively. Median follow-up was 9.4 years. We observed significant interactions between eGFR and both physical activity and sedentary behavior (P<0.001). The partial effect plot of the association between physical activity and log relative hazard of ESRD suggests that ESRD risk decreases as physical activity increases when eGFR is 90 mL/min/1.73m<sup>2</sup>. The inverse association is most pronounced at physical activity levels >27 MET-hours/day. High levels of sitting time were associated with increased ESRD risk only among those with reduced kidney function (eGFR ≤30 mL/min/1.73m<sup>2</sup>); this association was attenuated after excluding the first two years of follow-up.



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3 **Conclusions:** In a population with a high prevalence of CKD risk factors such as hypertension  
4 and diabetes, physical activity appears to be associated with reduced risk of ESRD among those  
5 with preserved kidney function. A positive association between sitting time and ESRD observed  
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7 among those with advanced kidney disease is likely due to reverse causation.  
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11 **Abbreviations:** CHC=community health center; CI=confidence interval; CKD=chronic kidney  
12 disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HR=hazard  
13 ratio; MET=metabolic equivalent; SCCS=Southern Community Cohort Study; USRDS=United  
14 States Renal Data System  
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#### 24 **Strengths and limitations of this study**

- 25  
26 • The SCCS is a large, unique cohort of black and white participants with low  
27 socioeconomic status and a high burden of risk factors for end-stage renal disease.  
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- 29  
30 • The case-cohort design selected participants for measurement of serum creatinine,  
31 therefore, baseline kidney function could be evaluated.  
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- 33  
34 • Physical activity and sedentary behaviors were self-reported rather than objectively  
35 measured; however, a validated questionnaire developed for the SCCS was used for  
36 ascertainment of these measures.  
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39 • Only baseline data on physical activity and sedentary behaviors were included and  
40 behaviors may have changed after enrollment.  
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## INTRODUCTION

In 2015, the age-adjusted incidence of end-stage renal disease (ESRD) in the United States was 357 per million [1]. With the growing burden of ESRD, there has been increasing focus on modifiable risk factors, such as physical activity and sedentary behaviors. Through physical activity, control of primary risk factors for ESRD, such as diabetes, obesity, and hypertension, may lead to diverse benefits on the metabolic environment of kidney dysfunction. Recent studies have shown that higher physical activity levels are associated with better physical functioning, lower risk of chronic kidney disease (CKD), and slower decline in estimated glomerular filtration rate (eGFR) [2-8]. Studies that examined sedentary behaviors are limited but suggest that higher sedentary time is associated with reduced kidney function and increased CKD risk [4 9]. The association between physical activity, sedentary time, and ESRD is not well established though, with few studies suggesting an association between physical activity and ESRD and none with the ability to disentangle exercise behaviors from socioeconomic status (SES) [10 11].

We investigated whether sedentary time and physical activity were independently associated with risk of incident ESRD. We hypothesized that higher physical activity and shorter sedentary time would be associated with decreased risk of ESRD. To examine this association, we used a case-cohort design within the Southern Community Cohort Study (SCCS), a unique population of individuals with lower SES, a high burden of kidney disease risk factors, and robust measures of physical activity and sedentary time.

## METHODS

### Study population

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3 The SCCS is a prospective cohort study that recruited ~86,000 primarily low-income black and  
4 white adults, aged 40-79 years, in the southeastern US (2002-2009) [12]. Participants eligible for  
5 enrollment spoke English and had not been treated for cancer in the 12 months before  
6 enrollment. The majority (86%) were recruited at participating community health centers (CHC),  
7 which provide primary healthcare for under-insured populations. A detailed description of SCCS  
8 methods has been published (<http://www.southerncommunitystudy.org>) [13]. All participants  
9 provided written informed consent, and the study was approved by the Institutional Review  
10 Boards of Vanderbilt University Medical Center and Meharry Medical College. We used the  
11 STROBE cohort checklist when writing our report [14].  
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24 Incident ESRD was identified by linking the SCCS cohort, using date of birth, Social  
25 Security number, and first and last name, with the nationwide US Renal Data System (USRDS)  
26 through March 31, 2015, the latest date for which data were available. ESRD cases in this  
27 registry are certified by a physician diagnosis and filed using a medical evidence report form (to  
28 the Medicare ESRD program), or when chronic dialysis or kidney transplant occurs, irrespective  
29 of the glomerular filtration rate. The USRDS is a national registry and therefore, ascertainment  
30 of ESRD cases is virtually complete [1]. Participants with an ESRD diagnosis prior to SCCS  
31 enrollment (prevalent cases) were excluded from the analysis.  
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42 Approximately 46% of the cohort donated baseline blood samples during CHC  
43 recruitment, which have been frozen at -80°C. Participants were selected for measurement of  
44 creatinine using a case-cohort design, including all those with stored blood who had an incident  
45 ESRD diagnosis (n=737), and a probability sample of the entire cohort who donated blood  
46 (n=4,238) [15 16]. Baseline serum levels of creatinine were measured using the Jaffe (Rate)  
47 method on a Beckman Coulter DXC 600 clinical chemistry analyzer. The creatinine assays were  
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3 calibrated, and daily quality checks performed at three levels before sample testing. This sample  
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5 constitutes 13% of SCCS participants who donated blood, and is comparable with respect to  
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7 baseline sociodemographic characteristics including racial distribution, low income, and high  
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9 prevalence of CKD risk factors [17]. The weighted subcohort included 70.8% black participants  
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11 and 29.2% white participants, and the SCCS population included 67.3% black participants and  
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13 28.6% white participants. In the subcohort and overall SCCS population, about 32% had an  
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15 education level below 12<sup>th</sup> grade, the majority had an annual income of <\$15,000, and the  
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17 prevalence of hypertension and diabetes was similar at 56% and 22%, respectively.  
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### 20 21 **Patient and Public Involvement**

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23 There was no patient or public involvement in study design and conduct, dissemination of  
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25 results, and evaluation in this study.  
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### 28 29 **Data collection**

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31 Standardized computer-assisted personal interviews were administered at enrollment to obtain  
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33 data on demographic, medical, and lifestyle variables [13]. Sections included demographic  
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35 characteristics (education, income, residence), tobacco use, personal and family medical history,  
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37 medication use, emotional well-being, occupation, physical activity, and diet. Body mass index  
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39 (BMI) was calculated from self-reported height and weight. History of hypertension, diabetes,  
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41 and hypercholesterolemia as well as stroke and cardiovascular disease were self-reported by  
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43 asking whether a doctor had ever diagnosed the participant with the condition. Self-reported  
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45 height and weight were compared with clinic recorded measurements for over 20% of  
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47 participants. In a series of validation studies, biomarkers, repeat interviews, or medical records  
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49 were used to assess the reliability of variables such as smoking status and self-reported diseases  
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51 including diabetes [13].  
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3 Usual sedentary and active behaviors were assessed using a validated physical activity  
4 questionnaire (PAQ) developed specifically for the SCCS [18]. For sedentary behaviors,  
5 participants were asked questions about the amount of time per day typically spent sitting in a car  
6 or bus, at work, viewing television or movies, and other activities that involve sitting such as  
7 sitting at meals, talking on the phone, reading, playing games, or sewing. For physical activity,  
8 participants were asked about time typically spent performing light, moderate, and strenuous  
9 activities at home and at work, as well as time spent doing moderate and vigorous  
10 exercise/sports. Time spent doing work and home activities was assessed separately for week and  
11 weekend days, and exercise and sports participation was assessed for a typical week. Examples  
12 of light work were given to participants and included standing at work, shopping, cooking, and  
13 child or elderly care. Moderate work examples included shop work, cleaning house, gardening,  
14 mowing lawn, and home repair. Examples of strenuous work included loading or unloading  
15 trucks, construction, farming, or other hard labor. Moderate sports included activities such as  
16 bowling, dancing, and golfing, while vigorous sports included jogging, aerobics, tennis,  
17 swimming, and weight lifting. For all questions, participants provided open-ended duration  
18 responses (hours and minutes). The reliability and validity of the SCCS physical activity  
19 questionnaire was evaluated in 118 randomly selected SCCS participants via use of  
20 accelerometers [18].  
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#### 44 **Statistical Analysis**

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46 The study population was restricted to black and white participants enrolled at CHCs, to ensure  
47 that participants had similar SES and equal access to healthcare regardless of race and had the  
48 opportunity to donate a blood specimen. Participants with missing data for any exercise metric  
49 (n=161) or demographic characteristic (n=212), and those with baseline eGFR>150  
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3 ml/min/1.73m<sup>2</sup> (n=22), were excluded; thus, a total of 692 ESRD cases and 4,113 subcohort  
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5 members were included in the analyses (Figure 1).  
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9 Sedentary time was calculated as hours/day based on the sum of all individual sedentary  
10 behaviors. Total physical activity was calculated as the sum of light, moderate and strenuous  
11 household/occupational work as well as moderate and vigorous sports; values were transformed  
12 from hours/day into summary measures of energy expenditure, defined as metabolic equivalent  
13 (MET)-hours/day. MET values for specific activities and intensities were based on the  
14 Compendium of Physical Activities [19]. MET-hours reflect the weighted average of the  
15 intensity (MET) and duration (hours) of activity behaviors. Two MET-hours/day is roughly  
16 equivalent to participating in 1 hour of a light activity, 0.5 hours of a moderate activity such as  
17 walking, or 0.25 hours of a vigorous activity such as jogging [18]. For example, one MET-hour  
18 is roughly equivalent to the energy expenditure associated with walking very briskly (4 METS)  
19 for 15 minutes (0.25 hours).  
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34 Using sampling weight techniques, we described baseline characteristics of subcohort  
35 participants using means and standard deviations (SD) or medians and 25<sup>th</sup> and 75<sup>th</sup> percentiles.  
36 For descriptive purposes, sedentary time (hours/day) and physical activity (MET-hours/day)  
37 were also categorized into quartiles based on the subcohort distribution. Incidence rates (IR)  
38 were calculated from bootstrap probability resamples; the reported IRs were the means of the  
39 bootstrap replicates with confidence intervals (CI) at the 2.5 and 97.5 percentiles of the  
40 bootstrap distribution.  
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50 We calculated hazard ratios (HRs) and 95% CIs for the association of sedentary time and  
51 physical activity with ESRD from Cox regression models that accounted for the case-cohort  
52 design and the weighted sample [15]. Participants were considered at risk from the date of SCCS  
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3 enrollment until the first occurrence of incident ESRD, death, or March 31, 2015. Total  
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5 sedentary time and physical activity were modeled as restricted cubic splines with four knots and  
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7 mutually adjusted in a single model. Additional covariates included age at enrollment (years),  
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9 sex, race, education (< or  $\geq$ high school), income (< or  $\geq$ \$15,000), BMI ( $\text{kg}/\text{m}^2$ ), smoking (never  
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11 or former/current), baseline eGFR ( $\text{mL}/\text{min}/1.73\text{m}^2$ ), and history of diagnosis of diabetes,  
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13 hypertension and hypercholesterolemia (yes/no). Baseline serum levels of creatinine were used  
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15 for estimation of eGFR using the CKD-EPI equation [20]. Continuous predictors (age, eGFR,  
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17 and BMI) were added to the model as restricted cubic splines with four knots. To examine  
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19 interactions between sedentary time or physical activity and baseline kidney function on ESRD  
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21 risk, multiplicative interaction terms between the nonlinear, continuous predictors of sedentary  
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23 time/physical activity and nonlinear, continuous eGFR were added to the model.  
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29 We constructed partial effect plots of eGFR and physical activity or sedentary time on the  
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31 log relative hazard scale, which display the predicted outcome as a function of a single covariate  
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33 while holding all other covariates constant for different levels of baseline kidney function. We  
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35 also plotted the HRs of ESRD as a function of continuous MET-hours/day or sitting hours/day,  
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37 again holding all other covariates constant for different levels of baseline kidney function. The  
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39 CIs in the HR plots were generated using bootstrap resampling methods.  
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43 To examine if the relationship with ESRD differed for different types of sitting, we also  
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45 modeled the individual sedentary behaviors, sitting in the car/bus, sitting at work, watching  
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47 TV/movies, and other sitting. The multivariable Cox model included sitting hours for each  
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49 category modeled as restricted cubic splines and mutually adjusted. Non-nested likelihood ratio  
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51 tests were used to compare this model to the Cox model including total sitting hours.  
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3 Finally, in sensitivity analyses to examine the potential for reverse causation among those  
4 with advanced kidney disease, we calculated HRs and 95% CIs and constructed partial effect  
5 plots as above, excluding the first two years of follow up. All analyses were conducted using R.  
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8 For main effects and interaction terms, P-values  $\leq 0.05$  were considered statistically significant.  
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## 14 RESULTS

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16 At baseline, mean (SD) age of subcohort participants was 52 (8.6) years (Table 1). Most  
17 participants were women (60%), black (71%), reached high school (68%), and had income  
18  $< \$15,000$  (62%). Approximately 75% were overweight or obese ( $BMI \geq 25$  kg/m<sup>2</sup>), and 55%,  
19 23% and 35% reported a diagnosis of hypertension, diabetes and hypercholesterolemia,  
20 respectively. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) baseline eGFR was 102.8 (85.9, 117.9)  
21 mL/min/1.73m<sup>2</sup> in the subcohort and 62.9 (36.0, 98.1) among ESRD cases. Median (25<sup>th</sup>, 75<sup>th</sup>  
22 percentile) for total sedentary time and physical activity in the subcohort were 8.0 (5.5, 12.0)  
23 hours/day and 17.2 (8.7, 31.9) MET-hours/day, respectively. The most common sedentary  
24 activity was watching TV or movies; for physical activity, most energy expenditure came from  
25 moderate activities and sports.  
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40 Demographic characteristics by quartiles of physical activity and sedentary time are  
41 presented in Table 2. Median (25<sup>th</sup>, 75<sup>th</sup> percentile) total physical activity in the highest activity  
42 quartile for the subcohort was 41.3 (33.2, 55.5) MET-hours/day, compared to 4.2 (2.0, 6.2) in the  
43 lowest quartile (Table 2a). Compared to individuals in the lower quartiles, subcohort members in  
44 the highest quartile of physical activity were younger, had higher education and income, and had  
45 lower prevalence of obesity, hypertension, hypercholesterolemia and diabetes. Median baseline  
46 eGFR was highest among those in the highest quartile of physical activity.  
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3 Median (25<sup>th</sup>, 75<sup>th</sup> percentile) total sitting hours in the subcohort was 15.5 (13.8, 18.0)  
4 hours/day in the highest sedentary time quartile and 4.0 (3.0, 5.0) hours/day for participants in  
5 the lowest quartile (Table 2b). Total physical activity was higher among participants in the third  
6 and fourth quartile of sedentary time compared to the lower two quartiles. Subcohort participants  
7 in the fourth quartile of sedentary time were more likely than those in lower quartiles to be black  
8 and obese, and to have  $\geq$ high school education or annual income  $\geq$ \$15,000. Prevalence of  
9 hypertension, hypercholesterolemia and diabetes did not vary consistently across quartiles of  
10 sitting time, nor did median baseline eGFR.  
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21 Participants were followed for a median (range) of 9.4 (0.1-12.8) years. Age-adjusted IRs  
22 for ESRD were 2.61, 2.38, 2.24, and 1.68/1000 person-years in quartiles 1-4 of physical activity,  
23 respectively; corresponding IRs in quartiles of sitting time were 2.13, 2.06, 2.07, and 2.64/1000  
24 person-years (Table 2). In unadjusted Cox models, the HRs for an interquartile range increase in  
25 physical activity or sedentary time were 0.65 (95% CI 0.58-0.73) and 1.09 (95% CI 1.00-1.20),  
26 respectively. In the multivariable model including both physical activity and sedentary time, and  
27 the interactions between physical activity\*eGFR and sedentary behavior\*eGFR, both  
28 interactions were statistically significant (chunk test P-value <0.001). Therefore, we present  
29 partial effect plots based on the multivariable model to further tease out the shape of the  
30 association between eGFR, physical activity, and sitting.  
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44 The partial effect plots show the association between physical activity (Figure 2a) or  
45 sedentary time (Figure 2b) and log relative hazard of ESRD, by levels of baseline eGFR. When  
46 eGFR is 30, the shape of the association suggests that risk of ESRD increases as activity  
47 increases. In contrast, when eGFR is 90, log relative hazard of ESRD decreases as activity  
48 increases, and the inverse association is most pronounced at levels of physical activity above 27  
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3 MET-hours/day. The predicted log relative hazard of ESRD is uniformly higher when eGFR is  
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5 30 compared to when eGFR is 60, and log relative hazard is lowest when eGFR is 90.  
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8 In the second plot, when eGFR is 30, the shape of the association shows increasing  
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10 ESRD risk as sedentary time increases. In contrast, when eGFR is 60 or 90, the shape of the  
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12 association is slightly decreasing or flat with increasing sedentary time. As for physical activity,  
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14 the predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to  
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16 when eGFR is 60 or 90.  
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20 The continuous HR plots present the associations between physical activity (Figure 3a) or  
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22 sedentary time (Figure 3b) and risk of incident ESRD. The HR plots are separated into three  
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24 levels of eGFR (30, 60, 90 mL/min/1.73m<sup>2</sup>). Each panel has its own reference level, which is  
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26 seen at the pinch in the confidence intervals where HR=1.0. The relative shape of the  
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28 associations at each level of eGFR corresponds to what is shown in the partial effect plots; in  
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30 particular, an inverse association between physical activity and risk of ESRD is apparent only  
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32 among those with preserved kidney function, while an increased risk of ESRD with increasing  
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34 sedentary time is observed among those with low eGFR.  
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38 In analyses examining the individual types of sitting, the non-nested likelihood ratio test  
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40 indicated that the model with sitting hours by type did not significantly differ from the model  
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42 with total sitting hours (p=0.98). In sensitivity analyses excluding the first two years of follow  
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44 up, the interactions between sedentary time\*eGFR and physical activity\*eGFR remained  
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46 statistically significant (P-value<0.001 for both); however, the positive association between  
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48 sitting time and ESRD among those with advanced kidney disease was no longer apparent.  
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## 53 **DISCUSSION**

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3 Among black and white participants at high risk for ESRD, we observed a significant  
4 interaction between physical activity and baseline kidney function, suggesting that among  
5 individuals with preserved kidney function, higher physical activity is associated with a lower  
6 risk of developing ESRD. Similarly, we observed heterogeneity of the association of sitting time  
7 on ESRD risk, as demonstrated by the higher risk of ESRD associated with longer sitting time  
8 among those with  $eGFR \leq 30$  mL/min/1.73m<sup>2</sup>, which appears to be explained by reverse  
9 causation.  
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19 While physical activity is widely accepted as an important modifiable risk factor for  
20 cardiovascular disease, the association is not well established in kidney disease. A number of  
21 observational and interventional studies have examined the risks and benefits of physical activity  
22 among patients undergoing maintenance dialysis [21-24]. However, previous studies of incident  
23 kidney disease are limited and have reported inconsistent results. In a cross-sectional study of  
24 10,463 patients with diabetes and hypertension, lack of exercise was a significant risk factor for  
25 CKD [8]. In another cohort study of 6,972 patients with diabetes, participants who had more  
26 regular physical activity had a reduced risk of early diabetic CKD [3]. Among 4,011 participants  
27 from the Cardiovascular Health Study, those with the highest amount of physical activity had a  
28 lower risk of rapid kidney function decline [7]. In contrast, in a study of 3,653 black participants  
29 from the Jackson Heart Study, physical activity was not associated with rapid decline in eGFR  
30 [25]. The inconsistency of results may be due in part to the fact that physical activity for these  
31 studies was defined in different ways, ranging from number of times per week the participant  
32 exercised [3 8] to categorization based on the American Heart Association's Life Simple 7 and  
33 the Minnesota Heart Survey [7 25].  
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3 We found that a high level of physical activity was associated with lower risk of ESRD  
4 among those with preserved kidney function. Two prior studies reported an association between  
5 physical activity and lower risk of ESRD. Among 59,552 participants from the Singapore  
6 Chinese Health Study, those engaged in any physical activity had a lower risk of ESRD, and a  
7 dose-response relationship with intensity of physical activity was noted [10]. Among individuals  
8 with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC), physical activity was  
9 inversely associated with risk of CKD progression (defined as 50% decrease in eGFR or incident  
10 ESRD). The CRIC results are somewhat inconsistent with our observation of no beneficial effect  
11 of physical activity among those with already reduced kidney function. It is possible that  
12 secondary factors such as hyperphosphatemia, acidosis, proteinuria, and glomerular hypertension  
13 and hypertrophy drive progression of CKD once established and, therefore, physical activity may  
14 have less of an impact on ESRD risk in this group [26 27]. Also, earlier and longer established  
15 control of primary CKD risk factors, such as blood pressure and blood sugar, through physical  
16 activity may have more of an impact earlier rather than later in the kidney disease course.  
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35 Diabetes, obesity, hypertension, and kidney dysfunction can lead to oxidative stress,  
36 insulin resistance, endothelial dysfunction, and increased circulating cytokines [28]. Physical  
37 activity has a beneficial effect on these metabolic disturbances, all common in patients with  
38 CKD, and these mechanisms may underlie our finding of reduced risk of ESRD with greater  
39 levels of physical activity. One important metabolic disturbance and risk factor for CKD is  
40 inflammation, which has an inverse correlation with eGFR [29]. Patients with CKD/ESRD have  
41 higher levels of pro-inflammatory adipokines or cytokines, such as leptin, tumor necrosis factor  
42 alpha and interleukin 1 and 6 [29-31]. Exercise and physical activity have been shown to reduce  
43 inflammatory molecules and create an anti-inflammatory environment in the general population  
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3 and in patients with CKD [31 32], a potential mechanisms for a beneficial effect of physical  
4 activity on kidney function. Increased physical exercise and subsequent weight loss may also  
5 help decrease the oxidative stress burden in patients with CKD [29 30 33]. Finally, excess  
6 adiposity and lack of physical activity are the most common causes of insulin resistance [34] and  
7 hyperglycemia. This metabolic dysregulation is a risk factor for reduced kidney function.  
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Exercise and physical activity decrease insulin resistance and improve endothelial responses to insulin [34].

Sedentary behavior is hypothesized to be an independent risk factor for CKD and ESRD, but few studies have examined this association. We observed a significant interaction between sedentary time and eGFR, demonstrating that a higher amount of sitting time increased risk of ESRD in participants with lower eGFR. We speculated that this may be a result of reverse causation, whereby the presence of advanced kidney disease, uremia or other comorbidities and subsequent fatigue in those with low eGFR, already at high risk for ESRD, may lead to increased sedentary time and also prompt earlier initiation of dialysis. In fact, attenuation of the association between sedentary time and ESRD after exclusion of the first two years of follow-up lends support to this explanation. Additionally, we observed that the model separating sitting time by type did not fit better than the model with total sitting time.

Sedentary behavior has, however, been shown to be associated with physiological risk factors for CKD and ESRD including increased BMI, systolic blood pressure, triglycerides, and decreased HDL cholesterol [35], and these pathways may mediate possible effects and should be further explored. Two recent studies have reported associations between higher sedentary time and lower eGFR and higher odds of urinary albumin excretion time [4 9].

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3 To our knowledge, this is one of few studies to investigate the association between  
4 physical activity and ESRD and one of the first to examine sedentary behaviors. Strengths of our  
5 study include the prospective design and the unique cohort of participants with low SES and a  
6 high burden of risk factors for ESRD. An important strength is the ascertainment of a broad  
7 range of physical activity and sedentary behaviors from a validated questionnaire developed  
8 specifically for the SCCS [18]. Other strengths include the complete ascertainment of ESRD  
9 cases and the inclusion of baseline eGFR. A limitation of the study is that physical activity and  
10 sedentary behaviors were ascertained only at baseline and may have changed after enrollment.  
11 Moreover, the physical activity, sedentary behaviors, and covariates were self-reported by  
12 participants rather than objectively measured. Although the probability sample is comparable to  
13 the whole cohort, the findings might not be generalizable to all SCCS participants. Finally,  
14 baseline data on proteinuria were not available.

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17 In conclusion, this study found that in a population at high risk for ESRD, higher levels  
18 of physical activity were associated with reduced risk of ESRD in those with preserved kidney  
19 function, and sedentary time was not associated with increased ESRD risk except in participants  
20 with low baseline eGFR. Physical activity and sedentary behaviors are modifiable risk factors  
21 that may be targets for possible interventions, especially in those with preserved kidney function.

#### 22 **Acknowledgements**

23 None

#### 24 **Conflict of Interest Statement**

25 None declared. The results presented in this paper have not been published previously in whole  
26 or part, except in abstract form.

#### 27 **Author Contributions**

1  
2  
3 Research idea and study design: MMP, JMT, EKK, EAA, TAI, TGS, LL; data acquisition: LL,  
4 WJB; data analysis/interpretation: MMP, JMT, EKK, TGS, JLM, CRC, EAA, KAK, EDS, WJB,  
5 TAI, LL; statistical analysis: MMP, TGS, JLM, EAA; supervision or mentorship: TGS, CRC,  
6 WJB, TAI, LL. Each author contributed important intellectual content during manuscript drafting  
7 or revision and accepts accountability for the overall work by ensuring that questions pertaining  
8 to the accuracy or integrity of any portion of the work are appropriately investigated and  
9 resolved.

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### 12 **Data Sharing Statement**

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14 The SCCS is committed to open sharing of its resources to provide for optimal utilization of  
15  
16 SCCS data and biologic specimens for research purposes. The proposed research will generate  
17  
18 biomarker data (serum trace metals, serum creatinine) which will be added to the SCCS  
19  
20 database. Consistent with current SCCS study operations, qualified researchers who wish to  
21  
22 collaborate with investigators from our study will have access to SCCS data upon approval of a  
23  
24 research proposal by the 12-member SCCS Data and Biospecimen Use Committee  
25  
26 (<https://ors.southerncommunitystudy.org/>). The SCCS has an open access policy for legitimate  
27  
28 scientific purposes, but because of privacy concerns, requires Committee review of all data  
29  
30 requests. All investigators are required to sign a data use agreement prior to receipt of SCCS  
31  
32 study data that provides for: (1) Sharing of the data only with investigators signing the data use  
33  
34 agreement; (2) Use of the data only for purposes approved by the DBU Committee; (3)  
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36 Agreement for review of manuscripts and statistical programs prior to submission of the results  
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38 for publication; (4) A 12-month time frame for completion of the analysis.  
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44 Prior to sharing of SCCS data for proposals approved by the Committee, datasets are de-  
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46 identified according to the HIPAA Safe-Harbor Method  
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48 ([http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/Deidentification/](http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/Deidentification/guidance.html)  
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50 guidance.html)  
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53 The following data elements are removed from datasets prior to release to investigators:  
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3 a. Name

4 b. All geographic identifiers for subdivisions smaller than a state, including street address, city,  
5 county, precinct, ZIP code, and the equivalent geocodes

6 a. De-identified geographic subdivisions will not be released when the total number of persons  
7 within that subdivision is known to be less than 300, to prevent potential disclosure of the  
8 identifier due to unique characteristics

9 c. All elements of dates (except year), including, but not limited to, date of birth, date of SCCS  
10 enrollment, date of diagnosis, date of death, and all ages over 89 or elements of date indicative of  
11 an age over 89

12 d. Telephone Numbers

13 e. Fax Numbers

14 f. Email Addresses

15 g. Social Security Numbers

16 h. Medical Record Numbers

17 i. Health Plan Beneficiary Numbers

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20 Transmission of potentially identifiable data is kept to a minimum and performed only as needed  
21 for study operations in accordance with HIPAA regulations.  
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**Table 1. Baseline characteristics of the probability sample (subcohort) of SCCS participants and ESRD cases**

	<b>Subcohort participants (n=4,113)</b>	<b>ESRD cases (n=692)</b>
Age at enrollment, years	52.2 ± 8.6	53.8 ± 8.0
Women	59.8	51.5
Race		
White	29.3	12.4
Black	70.7	87.6
Education		
<High school	32.3	40.3
≥High school	67.7	59.7
Household income		
<\$15,000/year	61.6	65.8
≥\$15,000/year	38.4	34.2
Cigarette smoking		
Current/former smoker	67.3	58.3
Never smoker	32.7	41.7
BMI, kg/m <sup>2</sup>	30.3 ± 7.3	32.8 ± 8.8
Overweight or obese (BMI ≥ 25 kg/m <sup>2</sup> )	74.8	82.5
Hypertension	55.5	86.0
Hypercholesterolemia	34.5	49.3
Diabetes	22.6	68.5
eGFR, ml/min/1.73m <sup>2</sup>	102.8 (85.9, 117.9)	62.9 (36.0, 98.1)
<b>Sedentary and physical activity measures</b>		
Sitting, h/d	8.0 (5.5,12.0)	8.2 (6.0,12.0)
Car or bus, h/d	1.5 ± 1.8	1.5 ± 2.0
At work, h/d	1.2 ± 2.3	0.9 ± 2.3
TV or movies, h/d	3.8 ± 2.9	4.3 ± 3.1
Home computer, h/d	0.5 ± 1.1	0.3 ± 0.9
Other, h/d <sup>a</sup>	2.3 ± 1.9	2.4 ± 2.0
Physical Activity, h/d	5.4 (2.9,9.4)	4.3 (2.3,7.4)
Household/occupational activity, MET-h/d		
Light	7.3 ± 6.2	5.9 ± 5.4
Moderate	9.7 ± 8.7	8.6 ± 7.9
Strenuous	5.0 ± 11.7	3.1 ± 9.4
Sports, MET-h/d		
Moderate	10.0 ± 8.8	8.9 ± 8.1
Vigorous	5.6 ± 12.0	3.5 ± 9.6
Total physical activity, MET-h/d <sup>b</sup>	17.2 (8.7,31.9)	13.9 (6.9,24.6)

*Note:* Values are listed as mean ± SD or % or median (25<sup>th</sup>,75<sup>th</sup> percentile)

<sup>a</sup>Includes sitting at meals, talking on the phone, reading, playing cards, or sewing.

<sup>b</sup>Includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study

**Table 2. Baseline characteristics of the subcohort of SCCS participants by quartiles of: a) physical activity, and b) sedentary time**

	<b>Q1: Subcohort (n=934)</b>	<b>Q2: Subcohort (n=994)</b>	<b>Q3: Subcohort (n=1045)</b>	<b>Q4: Subcohort (n=1140)</b>
<b>a)</b>				
ESRD Incidence Rate per 1000 person-year	2.61 (1.54, 3.87)	2.38 (1.36, 3.50)	2.24 (1.25, 3.30)	1.68 (0.93, 2.55)
Physical activity (MET-h/day) <sup>a</sup>	4.2 [2.0, 6.2]	10.6 [8.8, 12.6]	20.2 [17.2, 23.5]	41.3 [33.2, 55.5]
Sitting (h/day)	7.5 [5.0, 11.0]	8.0 [6.0, 12.0]	9.0 [6.0, 12.0]	8.5 [5.8, 12.0]
Age, years	54.6 (9.3)	53.1 (8.9)	52.4 (8.8)	49.7 (7.1)
Women	49.9	67.0	70.7	51.5
Black race	67.5	69.2	71.3	73.2
Less than high school	37.7	35.0	32.1	27.0
Less than \$15K/year	73.1	66.9	59.4	52.2
Current/former smoker	70.4	64.4	65.7	69.0
BMI, kg/m <sup>2</sup>	30.9 (7.9)	30.7 (7.4)	30.9 (7.2)	29.1 (6.8)
Overweight or obese (BMI≥25 kg/m <sup>2</sup> )	75.1	77.2	77.3	70.5
Hypertension	63.5	56.7	58.7	47.1
High cholesterol	38.7	38.1	38.7	25.7
Diabetes	27.6	24.4	23.8	17.0
eGFR, mL/min/1.73m <sup>2</sup>	99.2	102.9	102.1	106.9
	[80.6, 114.8]	[84.8, 116.8]	[86.6, 117.6]	[89.9, 120.3]
<b>b)</b>				
ESRD Incidence Rate per 1000 person-year	2.13 (1.20, 3.20)	2.06 (1.18, 3.03)	2.07 (1.18, 3.12)	2.64 (1.46, 3.88)
Sitting (h/day)	4.0 [3.0, 5.0]	7.0 [6.3, 7.5]	10.0 [9.0, 11.0]	15.5 [13.8, 18.0]
Physical Activity (MET-h/day) <sup>a</sup>	15.8 [7.5, 32.4]	15.3 [8.6, 29.6]	18.4 [9.7, 32.7]	18.6 [9.8, 32.3]
Age, years	52.5 (8.9)	53.2 (8.5)	52.1 (8.9)	50.6 (7.8)
Women	58.2	57.3	63.1	60.6
Black race	71.0	66.0	67.7	79.6
Less than high school	39.8	29.5	29.0	31.0
Less than \$15K/year	69.4	60.6	58.9	57.2

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3	Current/former smoker	65.8	65.2	68.2	70.4
4	BMI, kg/m <sup>2</sup>	29.5 (7.1)	29.7 (7.3)	30.7 (7.3)	31.5 (7.5)
5	Overweight or obese (BMI $\geq$ 25 kg/m <sup>2</sup> )	71.6	72.0	77.1	78.7
6	Hypertension	53.5	58.1	55.8	54.6
7	High cholesterol	31.3	34.4	36.7	35.6
8	Diabetes	21.9	23.1	21.8	23.6
9	eGFR, mL/min/1.73m <sup>2</sup>	104.3 [88.9,	102.1 [84.4, 115.2]	102.1 [85.4, 118.2]	103.4 [85.3, 120.1]
10		118.6]			
11					
12	<i>Note:</i> Values are listed as mean $\pm$ SD or % or median (25 <sup>th</sup> ,75 <sup>th</sup> percentile)				
13	<sup>a</sup> Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and				
14	vigorous sports.				
15	Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS,				
16	Southern Community Cohort Study				
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*Note:* Values are listed as mean  $\pm$  SD or % or median (25<sup>th</sup>,75<sup>th</sup> percentile)

<sup>a</sup>Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study



## FIGURE LEGEND

**Figure 1.** Study selection of the SCCS case-cohort.

**Figure 2.** Partial effect plots of **a)** physical activity (MET-hours/day) and **b)** total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR

**Figure 3.** Plots of continuous hazard ratios of **a)** physical activity (MET-hours/day) and **b)** total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR. The confidence intervals in the HR plot were generated using bootstrap resampling methods



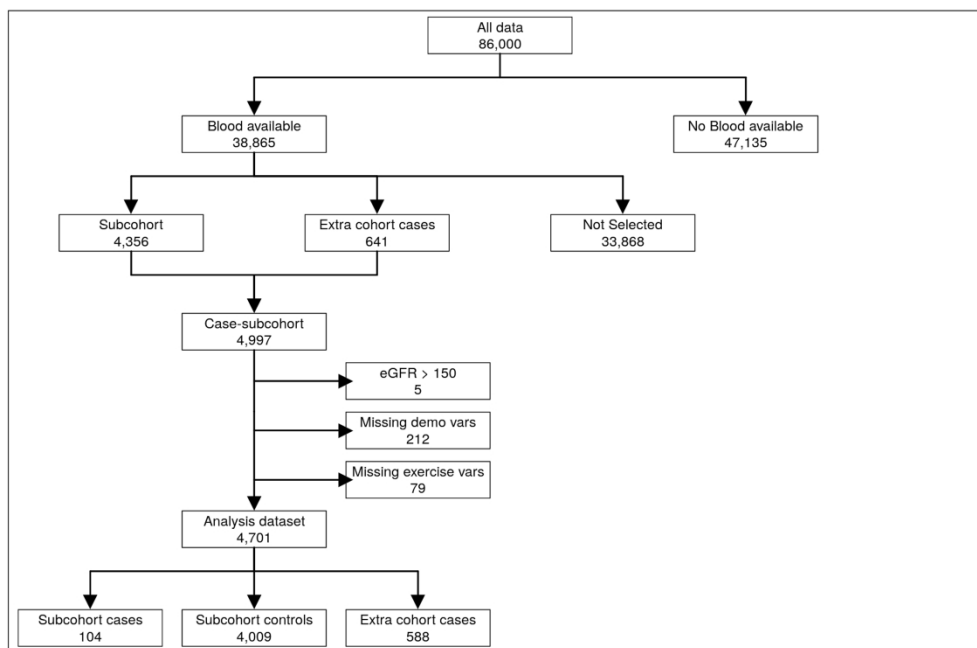


Figure 1. Study selection of the SCCS case-cohort.

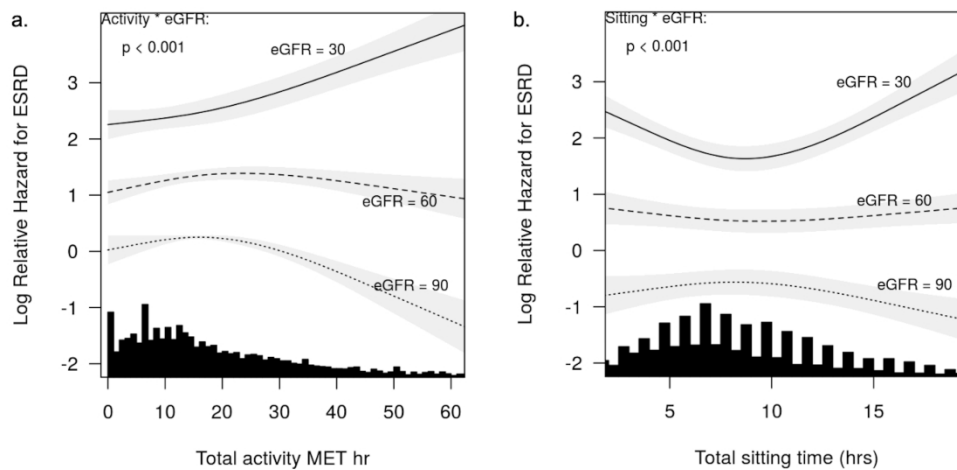


Figure 2. Partial effect plots of a) physical activity (MET-hours/day) and b) total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR

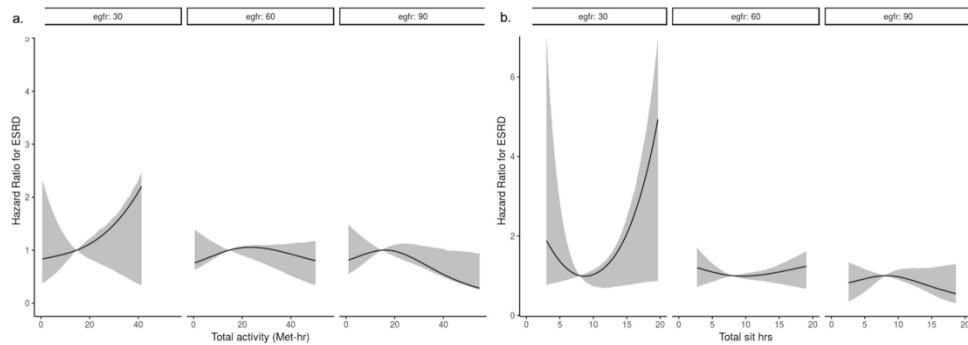


Figure 3. Plots of continuous hazard ratios of a) physical activity (MET-hours/day) and b) total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR. The confidence intervals in the HR plot were generated using bootstrap resampling methods

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
	#6b	For matched studies, give matching criteria and number of exposed and	NA

		unexposed	
1			
2	Variables	#7	Clearly define all outcomes, exposures, predictors, potential
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4			confounders, and effect modifiers. Give diagnostic criteria, if applicable
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6	Data sources /	#8	For each variable of interest give sources of data and details of methods
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8			of assessment (measurement). Describe comparability of assessment
9			methods if there is more than one group. Give information separately
10			for for exposed and unexposed groups if applicable.
11			
12	Bias	#9	Describe any efforts to address potential sources of bias
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15	Study size	#10	Explain how the study size was arrived at
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18	Quantitative	#11	Explain how quantitative variables were handled in the analyses. If
19	variables		6
20			applicable, describe which groupings were chosen, and why
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22	Statistical	#12a	Describe all statistical methods, including those used to control for
23	methods		6-7
24			confounding
25		#12b	Describe any methods used to examine subgroups and interactions
26			6-7
27		#12c	Explain how missing data were addressed
28			6
29		#12d	If applicable, explain how loss to follow-up was addressed
30			6
31		#12e	Describe any sensitivity analyses
32			7
33			
34	Participants	#13a	Report numbers of individuals at each stage of study—eg numbers
35			6
36			potentially eligible, examined for eligibility, confirmed eligible,
37			included in the study, completing follow-up, and analysed. Give
38			information separately for for exposed and unexposed groups if
39			applicable.
40		#13b	Give reasons for non-participation at each stage
41			6
42		#13c	Consider use of a flow diagram
43			NA
44			
45	Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical,
46			8
47			social) and information on exposures and potential confounders. Give
48			information separately for exposed and unexposed groups if applicable.
49		#14b	Indicate number of participants with missing data for each variable of
50			6
51			interest
52		#14c	Summarise follow-up time (eg, average and total amount)
53			9
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1	Outcome data	#15	Report numbers of outcome events or summary measures over time.	9
2			Give information separately for exposed and unexposed groups if	
3			applicable.	
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6	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted	9
7			estimates and their precision (eg, 95% confidence interval). Make clear	
8			which confounders were adjusted for and why they were included	
9				
10				
11				
12		#16b	Report category boundaries when continuous variables were categorized	9
13				
14		#16c	If relevant, consider translating estimates of relative risk into absolute	NA
15			risk for a meaningful time period	
16				
17				
18	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and	10
19			interactions, and sensitivity analyses	
20				
21	Key results	#18	Summarise key results with reference to study objectives	10
22				
23				
24	Limitations	#19	Discuss limitations of the study, taking into account sources of potential	13
25			bias or imprecision. Discuss both direction and magnitude of any	
26			potential bias.	
27				
28				
29	Interpretation	#20	Give a cautious overall interpretation considering objectives,	11-12
30			limitations, multiplicity of analyses, results from similar studies, and	
31			other relevant evidence.	
32				
33				
34	Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
35				
36				
37	Funding	#22	Give the source of funding and the role of the funders for the present	14
38			study and, if applicable, for the original study on which the present	
39			article is based	
40				
41				

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 43 This checklist was completed on 14. March 2019 using <https://www.goodreports.org/>, a tool made by the  
 44 [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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