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The association of exercise and sedentary behaviors with incident end stage renal disease in 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^{th}, 75^{th}percentile) estimated glomerular filtration rate (eGFR) was 102.8 (85.9, 117.9) mL/min/1.73m^2. Median (25^{th}, 75^{th} 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^2. 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^2); this association was attenuated after excluding the first two years of follow-up.

Conclusions: In this high-risk population, physical activity appears to be associated with reduced risk of ESRD among those with preserved kidney function. A positive association between sitting time and ESRD observed among those with advanced kidney disease is likely due to reverse causation.

Abbreviations: CHC=community health center; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HR=hazard ratio; MET=metabolic equivalent; SCCS=Southern Community Cohort Study; USRDS=United States Renal Data System

Strengths and limitations of this study

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

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

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

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

Patient and Public Involvement

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

Data collection

Standardized computer-assisted personal interviews were administered at enrollment to obtain data on demographic, medical, and lifestyle variables [13]. Body mass index (BMI) was calculated from self-reported height and weight. History of hypertension, diabetes, and hypercholesterolemia were self-reported by asking whether a doctor had ever diagnosed the participant with the condition.

Usual sedentary and active behaviors were assessed using a validated physical activity questionnaire (PAQ) developed specifically for the SCCS [16]. For sedentary behaviors, participants were asked questions about the amount of time per day typically spent sitting in a car or bus, at work, viewing television or movies, and other activities that involve sitting. For physical activity, participants were asked about time typically spent performing light, moderate, and strenuous activities at home and at work, as well as time spent doing moderate and vigorous exercise/sports. For all questions, participants provided open-ended duration responses (hours and minutes).

Statistical Analysis

The study population was restricted to blacks and whites enrolled at CHCs, to ensure that participants had similar SES and equal access to healthcare regardless of race and had the opportunity to donate a blood specimen. Participants with missing data for any exercise metric (n=161) or demographic characteristic (n=212), and those with baseline eGFR>150 ml/min/1.73m^2 (n=22), were excluded; thus, a total of 692 ESRD cases and 4,113 subcohort members were included in the analyses. Sedentary time was calculated as hours/day based on the sum of all individual sedentary behaviors. Total physical activity was calculated as the sum of light, moderate and strenuous household/occupational work as well as moderate and vigorous sports; values were transformed from hours/day into summary measures of energy expenditure,

defined as metabolic equivalent (MET)-hours/day. MET values for specific activities and intensities were based on the Compendium of Physical Activities [17]. Two MET-hours/day is roughly equivalent to participating in 1 hour of a light activity, 0.5 hours of a moderate activity such as walking, or 0.25 hours of a vigorous activity such as jogging [16].

Using sampling weight techniques, we described baseline characteristics of subcohort participants using means and standard deviations (SD) or medians and 25th and 75th percentiles. For descriptive purposes, sedentary time (hours/day) and physical activity (MET-hours/day) were also categorized into quartiles based on the subcohort distribution. Incidence rates (IR) were calculated from bootstrap probability resamples; the reported IRs were the means of the bootstrap replicates with confidence intervals (CI) at the 2.5 and 97.5 percentiles of the bootstrap distribution.

We calculated hazard ratios (HRs) and 95% CIs for the association of sedentary time and physical activity with ESRD from Cox regression models that accounted for the case-cohort design and the weighted sample [18]. Participants were considered at risk from the date of SCCS enrollment until the first occurrence of incident ESRD, death, or March 31, 2015. Total sedentary time and physical activity were modeled as restricted cubic splines with four knots and mutually adjusted in a single model. Additional covariates included age at enrollment (years), sex, race, education (< or ≥high school), income (< or ≥$15,000), BMI (kg/m^2), smoking (never or former/current), baseline eGFR (mL/min/1.73m^2), and history of diagnosis of diabetes, hypertension and hypercholesterolemia (yes/no). Baseline serum levels of creatinine were used for estimation of eGFR using the CKD-EPI equation [19]. Continuous predictors (age, eGFR, and BMI) were added to the model as restricted cubic splines with four knots. To examine interactions between sedentary time or physical activity and baseline kidney function on ESRD

risk, multiplicative interaction terms between sedentary time/physical activity and eGFR were added to the model.

We constructed partial effect plots of eGFR and physical activity or sedentary time on the log relative hazard scale, which display the predicted outcome as a function of a single covariate while holding all other covariates constant for different levels of baseline kidney function. We also plotted the HRs of ESRD as a function of continuous MET-hours/day or sitting hours/day, again holding all other covariates constant for different levels of baseline kidney function. The CIs in the HR plots were generated using bootstrap resampling methods. Finally, in sensitivity analyses to examine the potential for reverse causation among those with advanced kidney disease, we calculated HRs and 95% CIs and constructed partial effect plots as above, excluding the first two years of follow up. All analyses were conducted using R. For main effects and interaction terms, P-values ≤0.05 were considered statistically significant.

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, and 55%, 23% and 35% reported a diagnosis of hypertension, diabetes and hypercholesterolemia, respectively. Median (25^{th}, 75^{th} percentile) baseline eGFR was 102.8 (85.9, 117.9) mL/min/1.73m^2 in the subcohort and 62.9 (36.0, 98.1) among ESRD cases. Median (25^{th}, 75^{th} 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 (25th, 75th 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 (25th, 75th 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 and obese, and to have ≥high school education or annual income ≥$15,000. Prevalence of hypertension, hypercholesterolemia and diabetes did not vary consistently across quartiles of sitting time, nor did median baseline eGFR.

Participants were followed for a median (range) of 9.4 (0.1-12.8) years. Age-adjusted IRs for ESRD were 2.61, 2.38, 2.24, and 1.68/1000 person-years in quartiles 1-4 of physical activity, respectively; corresponding IRs in quartiles of sitting time were 2.13, 2.06, 2.07, and 2.64/1000 person-years (Table 2). In unadjusted Cox models, the HRs for an interquartile range increase in physical activity or sedentary time were 0.65 (95% CI 0.58-0.73) and 1.09 (95% CI 1.00-1.20), respectively. In the multivariable model including both physical activity and sedentary time, and the interactions between physical activity*eGFR and sedentary behavior*eGFR, both interactions were statistically significant (chunk test P-value <0.001). Therefore, we present

partial effect plots based on the multivariable model to further tease out the shape of the association between eGFR, physical activity, and sitting.

The partial effect plots show the association between physical activity (Figure 1a) or sedentary time (Figure 1b) and log relative hazard of ESRD, by levels of baseline eGFR. When eGFR is 30, the shape of the association suggests that risk of ESRD increases as activity increases. In contrast, when eGFR is 90, log relative hazard of ESRD decreases as activity increases, and the inverse association is most pronounced at levels of physical activity above 27 MET-hours/day. The predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to when eGFR is 60, and log relative hazard is lowest when eGFR is 90.

In the second plot, when eGFR is 30, the shape of the association shows increasing ESRD risk as sedentary time increases. In contrast, when eGFR is 60 or 90, the shape of the association is slightly decreasing or flat with increasing sedentary time. As for physical activity, the predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to when eGFR is 60 or 90.

The continuous HR plots present the associations between physical activity (Figure 2a) or sedentary time (Figure 2b) and risk of incident ESRD. The HR plots are separated into three levels of eGFR (30, 60, 90 mL/min/1.73m^2). Each panel has its own reference level, which is seen at the pinch in the confidence intervals where HR=1.0. The relative shape of the associations at each level of eGFR corresponds to what is shown in the partial effect plots; in particular, an inverse association between physical activity and risk of ESRD is apparent only among those with preserved kidney function, while an increased risk of ESRD with increasing sedentary time is observed among those with low eGFR.

In sensitivity analyses excluding the first two years of follow up, the interactions between sedentary time*eGFR and physical activity*eGFR remained statistically significant (P-value<0.001 for both); however, the positive association between sitting time and ESRD among those with advanced kidney disease was no longer apparent.

DISCUSSION

Among blacks and whites at high risk for ESRD, we observed a significant interaction between physical activity and baseline kidney function, suggesting that among individuals with preserved kidney function, higher physical activity is associated with a lower risk of developing ESRD. Similarly, we observed heterogeneity of the association of sitting time on ESRD risk, as demonstrated by the higher risk of ESRD associated with longer sitting time among those with eGFR ≤30 mL/min/1.73m^2, which appears to be explained by reverse causation.

While physical activity is widely accepted as an important modifiable risk factor for cardiovascular disease, the association is not well established in kidney disease. A number of observational and interventional studies have examined the risks and benefits of physical activity among patients undergoing maintenance dialysis [20-23]. However, previous studies of incident kidney disease are limited and have reported inconsistent results. In a cross-sectional study of 10,463 patients with diabetes and hypertension, lack of exercise was a significant risk factor for CKD [8]. In another cohort study of 6,972 patients with diabetes, participants who had more regular physical activity had a reduced risk of early diabetic CKD [3]. Among 4,011 participants from the Cardiovascular Health Study, those with the highest amount of physical activity had a lower risk of rapid kidney function decline [7]. In contrast, in a study of 3,653 black participants from the Jackson Heart Study, physical activity was not associated with rapid decline in eGFR

[24]. The inconsistency of results may be due in part to the fact that physical activity for these studies was defined in different ways, ranging from number of times per week the participant exercised [3 8] to categorization based on the American Heart Association's Life Simple 7 and the Minnesota Heart Survey [7 24].

We found that a high level of physical activity was associated with lower risk of ESRD among those with preserved kidney function. Two prior studies reported an association between physical activity and lower risk of ESRD. Among 59,552 participants from the Singapore Chinese Health Study, those engaged in any physical activity had a lower risk of ESRD, and a dose-response relationship with intensity of physical activity was noted [10]. Among individuals with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC), physical activity was inversely associated with risk of CKD progression (defined as 50% decrease in eGFR or incident ESRD). The CRIC results are somewhat inconsistent with our observation of no beneficial effect of physical activity among those with already reduced kidney function. It is possible that secondary factors such as hyperphosphatemia, acidosis, proteinuria, and glomerular hypertension and hypertrophy drive progression of CKD once established and, therefore, physical activity may have less of an impact on ESRD risk in this group [25 26]. Also, earlier and longer established control of primary CKD risk factors, such as blood pressure and blood sugar, through physical activity may have more of an impact earlier rather than later in the kidney disease course.

Diabetes, obesity, hypertension, and kidney dysfunction can lead to oxidative stress, insulin resistance, endothelial dysfunction, and increased circulating cytokines [27]. Physical activity has a beneficial effect on these metabolic disturbances, all common in patients with CKD, and these mechanisms may underlie our finding of reduced risk of ESRD with greater levels of physical activity. One important metabolic disturbance and risk factor for CKD is

inflammation, which has an inverse correlation with eGFR [28]. Patients with CKD/ESRD have higher levels of pro-inflammatory adipokines or cytokines, such as leptin, tumor necrosis factor alpha and interleukin 1 and 6 [28-30]. Exercise and physical activity have been shown to reduce inflammatory molecules and create an anti-inflammatory environment in the general population and in patients with CKD [30 31], a potential mechanisms for a beneficial effect of physical activity on kidney function. Increased physical exercise and subsequent weight loss may also help decrease the oxidative stress burden in patients with CKD [28 29 32]. Finally, excess adiposity and lack of physical activity are the most common causes of insulin resistance [33] and hyperglycemia. This metabolic dysregulation is a risk factor for reduced kidney function. Exercise and physical activity decrease insulin resistance and improve endothelial responses to insulin [33].

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.

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 [34], 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].

To our knowledge, this is one of few studies to investigate the association between physical activity and ESRD and one of the first to examine sedentary behaviors. Strengths of our study include the prospective design and the unique cohort of participants with low SES and a high burden of risk factors for ESRD. An important strength is the ascertainment of a broad range of physical activity and sedentary behaviors from a validated questionnaire developed specifically for the SCCS [16]. Other strengths include the complete ascertainment of ESRD cases and the inclusion of baseline eGFR. A limitation of the study is that physical activity and sedentary behaviors were ascertained only at baseline and may have changed after enrollment. Moreover, the physical activity and sedentary behaviors were self-reported by participants rather than objectively measured. Finally, baseline data on proteinuria was not available.

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

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None

Conflict of Interest Statement

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

Author Contributions

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

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wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Data Sharing Statement

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/coveredentities/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
e. Fax Numbers
f. Email Addresses
g. Social Security Numbers
h. Medical Record Numbers
i. Health Plan Beneficiary Numbers
Transmission of potentially identifiable data is kept to a minimum and performed only as needed 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

	Subcohort participants (n=4,113)	ESRD cases (n=692)
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^2	102.8 (85.9, 117.9)	62.9 (36.0, 98.1)
Sedentary and physical activity measures		
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[a]	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[b]	17.2 (8.7,31.9)	13.9 (6.9,24.6)

Note: Values are listed as mean ± SD or % or median (25th,75th percentile)

[a]Includes sitting at meals, talking on the phone, reading, playing cards, or sewing.

[b]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

a)	Q1: Subcohort (n=934)	Q2: Subcohort (n=994)	Q3: Subcohort (n=1045)	Q4: Subcohort (n=1140)
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)[a]	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^2	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^2	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)	Q1: Subcohort (n=1054)	Q2: Subcohort (n=1084)	Q3: Subcohort (n=1119)	Q4: Subcohort (n=856)
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)[a]	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 schol	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^2	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^2	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 (25th,75th percentile)

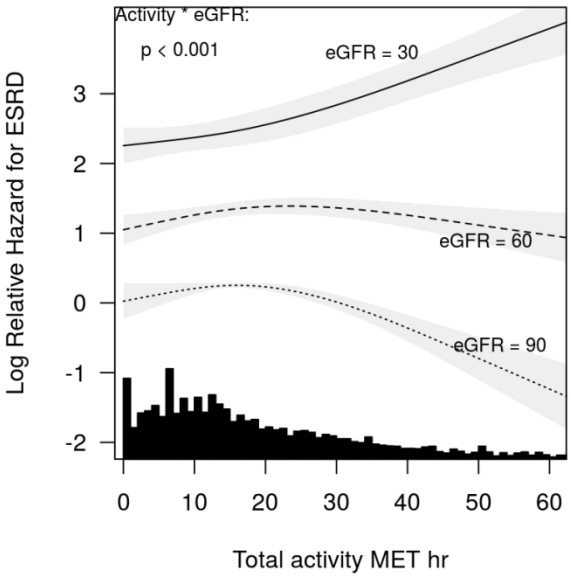
[a]Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

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


Activity * eGFR:
p < 0.001
eGFR = 30
eGFR = 60
eGFR = 90
Log Relative Hazard for ESRD
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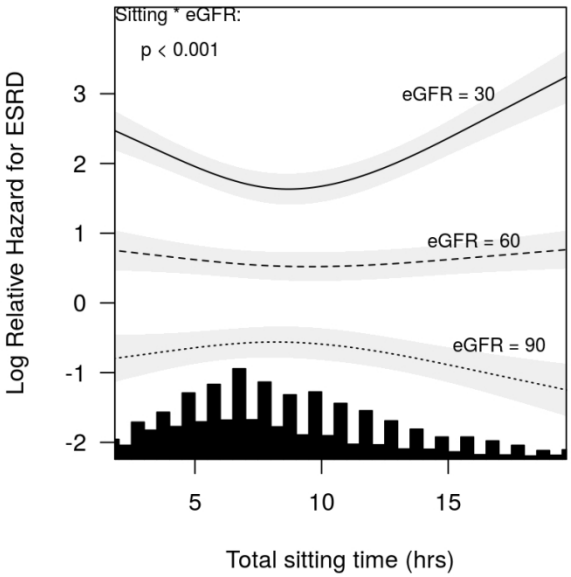
Total activity MET hr


Sitting * eGFR:
p < 0.001
eGFR = 30
eGFR = 60
eGFR = 90
Log Relative Hazard for ESRD
3
2
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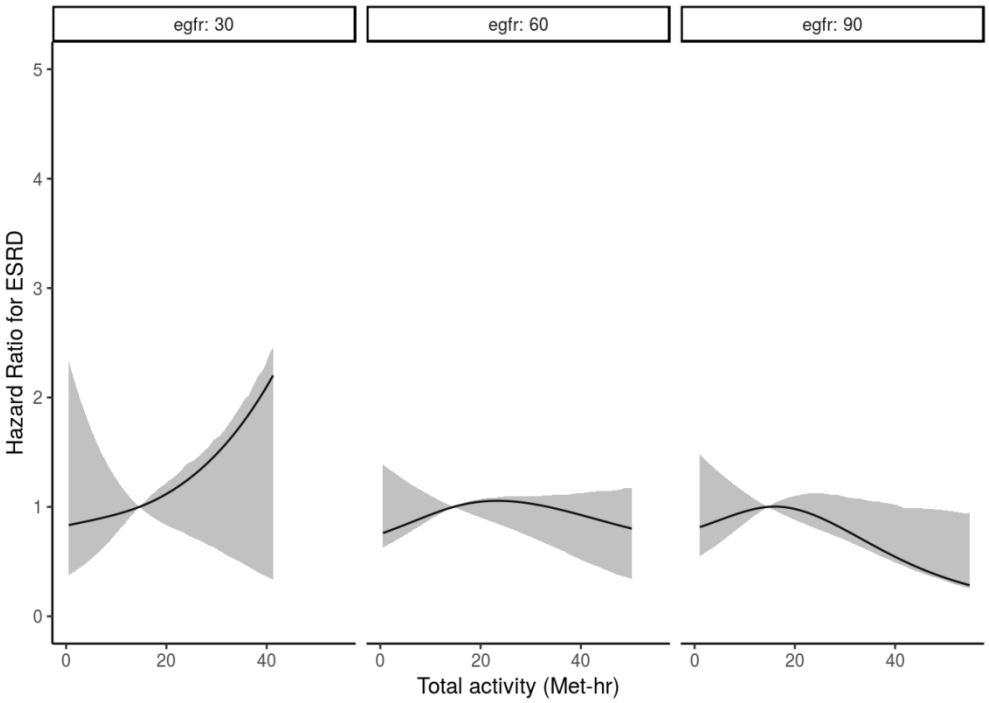
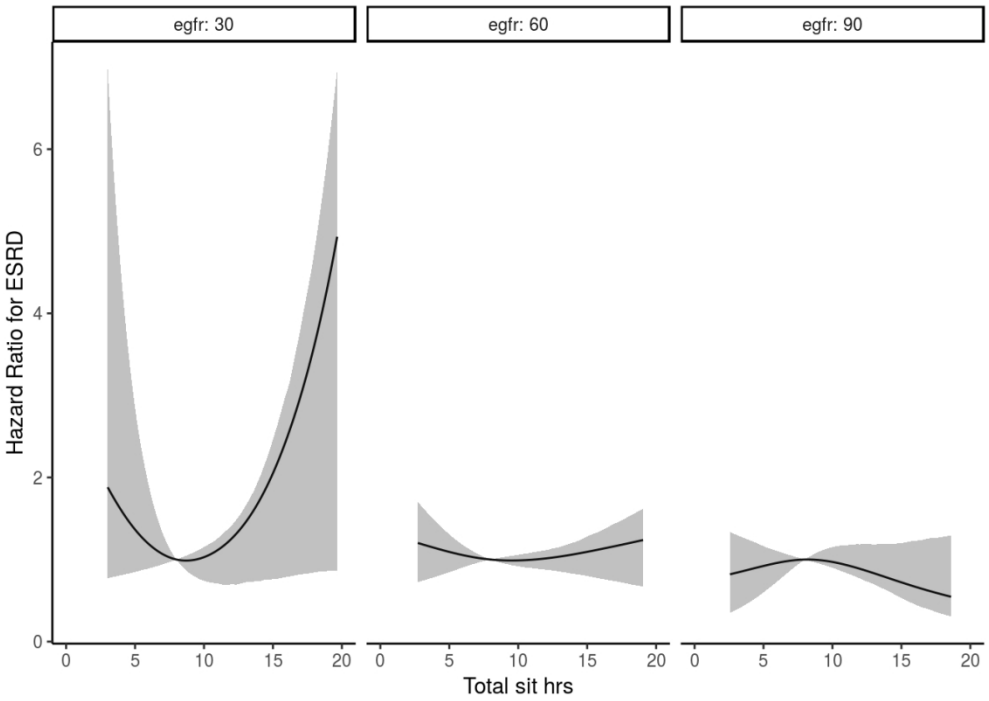
Total sitting time (hrs)


egfr: 30
egfr: 60
egfr: 90
Hazard Ratio for ESRD
0
1
2
3
4
5
0
20
40
Total activity (Met-hr)


egfr: 30
egfr: 60
egfr: 90
Hazard Ratio for ESRD
0
2
4
6
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10
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20
Total sit hrs

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, Gotzsche PC, Vandenbroucke JP. The Strengthening the 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	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
	#12b	Describe any methods used to examine subgroups and interactions	6-7
	#12c	Explain how missing data were addressed	6
	#12d	If applicable, explain how loss to follow-up was addressed	6
	#12e	Describe any sensitivity analyses	7
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
	#13b	Give reasons for non-participation at each stage	6
	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
	#14b	Indicate number of participants with missing data for each variable of interest	6
	#14c	Summarise follow-up time (eg, average and total amount)	9

Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
	#16b	Report category boundaries when continuous variables were categorized	9
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

This checklist was completed on 14. March 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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

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Running Head: Physical Activity and ESRD

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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^{th}, 75^{th}percentile) estimated glomerular filtration rate (eGFR) was 102.8 (85.9, 117.9) mL/min/1.73m^2. Median (25^{th}, 75^{th} 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^2. 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^2); this association was attenuated after excluding the first two years of follow-up.

Conclusions: In a population with a high prevalence of CKD risk factors such as hypertension and diabetes, physical activity appears to be associated with reduced risk of ESRD among those with preserved kidney function. A positive association between sitting time and ESRD observed among those with advanced kidney disease is likely due to reverse causation.

Abbreviations: CHC=community health center; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HR=hazard ratio; MET=metabolic equivalent; SCCS=Southern Community Cohort Study; USRDS=United States Renal Data System

Strengths and limitations of this study

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

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),

which provide primary healthcare for under-insured populations. A detailed description of SCCS methods has been published (http://www.southerncommunitystudy.org) [13]. All participants provided written informed consent, and the study was approved by the Institutional Review Boards of Vanderbilt University Medical Center and Meharry Medical College. We used the STROBE cohort checklist when writing our report [14].

Incident ESRD was identified by linking the SCCS cohort, using date of birth, Social Security number, and first and last name, with the nationwide US Renal Data System (USRDS) through March 31, 2015, the latest date for which data were available. ESRD cases in this registry are certified by a physician diagnosis and filed using a medical evidence report form (to the Medicare ESRD program), or when chronic dialysis or kidney transplant occurs, irrespective of the glomerular filtration rate. The USRDS is a national registry and therefore, ascertainment of ESRD cases is virtually complete [1]. Participants with an ESRD diagnosis prior to SCCS enrollment (prevalent cases) were excluded from the analysis.

Approximately 46% of the cohort donated baseline blood samples during CHC recruitment, which have been frozen at -80°C. Participants were selected for measurement of creatinine using a case-cohort design, including all those with stored blood who had an incident ESRD diagnosis (n=737), and a probability sample of the entire cohort who donated blood (n=4,238) [15 16]. Baseline serum levels of creatinine were measured using the Jaffe (Rate) method on a Beckman Coulter DXC 600 clinical chemistry analyzer. The creatinine assays were calibrated, and daily quality checks performed at three levels before sample testing. This sample constitutes 13% of SCCS participants who donated blood, and is comparable with respect to baseline sociodemographic characteristics including racial distribution, low income, and high prevalence of CKD risk factors [17]. The weighted subcohort included 70.8% blacks and 29.2%

whites, and the SCCS population included 67.3% blacks and 28.6% whites. In the subcohort and overall SCCS population, about 32% had an education level below 12th grade, the majority had an annual income of <$15,000, and the prevalence of hypertension and diabetes was similar at 56% and 22%, respectively.

Patient and Public Involvement

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

Data collection

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

Usual sedentary and active behaviors were assessed using a validated physical activity questionnaire (PAQ) developed specifically for the SCCS [18]. For sedentary behaviors, participants were asked questions about the amount of time per day typically spent sitting in a car or bus, at work, viewing television or movies, and other activities that involve sitting such as

sitting at meals, talking on the phone, reading, playing games, or sewing. For physical activity, participants were asked about time typically spent performing light, moderate, and strenuous activities at home and at work, as well as time spent doing moderate and vigorous exercise/sports. Time spent doing work and home activities was assessed separately for week and weekend days, and exercise and sports participation was assessed for a typical week. Examples of light work were given to participants and included standing at work, shopping, cooking, and child or elderly care. Moderate work examples included shop work, cleaning house, gardening, mowing lawn, and home repair. Examples of strenuous work included loading or unloading trucks, construction, farming, or other hard labor. Moderate sports included activities such as bowling, dancing, and golfing, while vigorous sports included jogging, aerobics, tennis, swimming, and weight lifting. For all questions, participants provided open-ended duration responses (hours and minutes). The reliability and validity of the SCCS physical activity questionnaire was evaluated in 118 randomly selected SCCS participants via use of accelerometers [18].

Statistical Analysis

The study population was restricted to blacks and whites enrolled at CHCs, to ensure that participants had similar SES and equal access to healthcare regardless of race and had the opportunity to donate a blood specimen. Participants with missing data for any exercise metric (n=161) or demographic characteristic (n=212), and those with baseline eGFR>150 ml/min/1.73m^2 (n=22), were excluded; thus, a total of 692 ESRD cases and 4,113 subcohort members were included in the analyses (Figure 1).

Sedentary time was calculated as hours/day based on the sum of all individual sedentary behaviors. Total physical activity was calculated as the sum of light, moderate and strenuous

household/occupational work as well as moderate and vigorous sports; values were transformed from hours/day into summary measures of energy expenditure, defined as metabolic equivalent (MET)-hours/day. MET values for specific activities and intensities were based on the Compendium of Physical Activities [19]. MET-hours reflect the weighted average of the intensity (MET) and duration (hours) of activity behaviors. Two MET-hours/day is roughly equivalent to participating in 1 hour of a light activity, 0.5 hours of a moderate activity such as walking, or 0.25 hours of a vigorous activity such as jogging [18]. For example, one MET-hour is roughly equivalent to the energy expenditure associated with walking very briskly (4 METS) for 15 minutes (0.25 hours).

Using sampling weight techniques, we described baseline characteristics of subcohort participants using means and standard deviations (SD) or medians and 25th and 75th percentiles. For descriptive purposes, sedentary time (hours/day) and physical activity (MET-hours/day) were also categorized into quartiles based on the subcohort distribution. Incidence rates (IR) were calculated from bootstrap probability resamples; the reported IRs were the means of the bootstrap replicates with confidence intervals (CI) at the 2.5 and 97.5 percentiles of the bootstrap distribution.

We calculated hazard ratios (HRs) and 95% CIs for the association of sedentary time and physical activity with ESRD from Cox regression models that accounted for the case-cohort design and the weighted sample [15]. Participants were considered at risk from the date of SCCS enrollment until the first occurrence of incident ESRD, death, or March 31, 2015. Total sedentary time and physical activity were modeled as restricted cubic splines with four knots and mutually adjusted in a single model. Additional covariates included age at enrollment (years), sex, race, education ($<$ or $\geq$high school), income ($<$ or $\geq$\$15,000), BMI (kg/m^2), smoking (never

or former/current), baseline eGFR (mL/min/1.73m^2), and history of diagnosis of diabetes, hypertension and hypercholesterolemia (yes/no). Baseline serum levels of creatinine were used for estimation of eGFR using the CKD-EPI equation [20]. Continuous predictors (age, eGFR, and BMI) were added to the model as restricted cubic splines with four knots. To examine interactions between sedentary time or physical activity and baseline kidney function on ESRD risk, multiplicative interaction terms between the nonlinear, continuous predictors of sedentary time/physical activity and nonlinear, continuous eGFR were added to the model.

We constructed partial effect plots of eGFR and physical activity or sedentary time on the log relative hazard scale, which display the predicted outcome as a function of a single covariate while holding all other covariates constant for different levels of baseline kidney function. We also plotted the HRs of ESRD as a function of continuous MET-hours/day or sitting hours/day, again holding all other covariates constant for different levels of baseline kidney function. The CIs in the HR plots were generated using bootstrap resampling methods.

To examine if the relationship with ESRD differed for different types of sitting, we also modeled the individual sedentary behaviors, sitting in the car/bus, sitting at work, watching TV/movies, and other sitting. The multivariable Cox model included sitting hours for each category modeled as restricted cubic splines and mutually adjusted. Non-nested likelihood ratio tests were used to compare this model to the Cox model including total sitting hours.

Finally, in sensitivity analyses to examine the potential for reverse causation among those with advanced kidney disease, we calculated HRs and 95% CIs and constructed partial effect plots as above, excluding the first two years of follow up. All analyses were conducted using R. For main effects and interaction terms, P-values ≤ 0.05 were considered statistically significant.

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 (BMI≥25 kg/m^2), and 55%, 23% and 35% reported a diagnosis of hypertension, diabetes and hypercholesterolemia, respectively. Median (25th, 75th percentile) baseline eGFR was 102.8 (85.9, 117.9) mL/min/1.73m^2 in the subcohort and 62.9 (36.0, 98.1) among ESRD cases. Median (25th, 75th 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 (25th, 75th 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 (25th, 75th 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

and obese, and to have ≥high school education or annual income ≥$15,000. Prevalence of hypertension, hypercholesterolemia and diabetes did not vary consistently across quartiles of sitting time, nor did median baseline eGFR.

Participants were followed for a median (range) of 9.4 (0.1-12.8) years. Age-adjusted IRs for ESRD were 2.61, 2.38, 2.24, and 1.68/1000 person-years in quartiles 1-4 of physical activity, respectively; corresponding IRs in quartiles of sitting time were 2.13, 2.06, 2.07, and 2.64/1000 person-years (Table 2). In unadjusted Cox models, the HRs for an interquartile range increase in physical activity or sedentary time were 0.65 (95% CI 0.58-0.73) and 1.09 (95% CI 1.00-1.20), respectively. In the multivariable model including both physical activity and sedentary time, and the interactions between physical activity*eGFR and sedentary behavior*eGFR, both interactions were statistically significant (chunk test P-value <0.001). Therefore, we present partial effect plots based on the multivariable model to further tease out the shape of the association between eGFR, physical activity, and sitting.

The partial effect plots show the association between physical activity (Figure 2a) or sedentary time (Figure 2b) and log relative hazard of ESRD, by levels of baseline eGFR. When eGFR is 30, the shape of the association suggests that risk of ESRD increases as activity increases. In contrast, when eGFR is 90, log relative hazard of ESRD decreases as activity increases, and the inverse association is most pronounced at levels of physical activity above 27 MET-hours/day. The predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to when eGFR is 60, and log relative hazard is lowest when eGFR is 90.

In the second plot, when eGFR is 30, the shape of the association shows increasing ESRD risk as sedentary time increases. In contrast, when eGFR is 60 or 90, the shape of the association is slightly decreasing or flat with increasing sedentary time. As for physical activity,

the predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to when eGFR is 60 or 90.

The continuous HR plots present the associations between physical activity (Figure 3a) or sedentary time (Figure 3b) and risk of incident ESRD. The HR plots are separated into three levels of eGFR (30, 60, 90 mL/min/1.73m^2). Each panel has its own reference level, which is seen at the pinch in the confidence intervals where HR=1.0. The relative shape of the associations at each level of eGFR corresponds to what is shown in the partial effect plots; in particular, an inverse association between physical activity and risk of ESRD is apparent only among those with preserved kidney function, while an increased risk of ESRD with increasing sedentary time is observed among those with low eGFR.

In analyses examining the individual types of sitting, the non-nested likelihood ratio test indicated that the model with sitting hours by type did not significantly differ from the model with total sitting hours (p=0.98). In sensitivity analyses excluding the first two years of follow up, the interactions between sedentary time*eGFR and physical activity*eGFR remained statistically significant (P-value<0.001 for both); however, the positive association between sitting time and ESRD among those with advanced kidney disease was no longer apparent.

DISCUSSION

Among blacks and whites at high risk for ESRD, we observed a significant interaction between physical activity and baseline kidney function, suggesting that among individuals with preserved kidney function, higher physical activity is associated with a lower risk of developing ESRD. Similarly, we observed heterogeneity of the association of sitting time on ESRD risk, as

demonstrated by the higher risk of ESRD associated with longer sitting time among those with eGFR ≤30 mL/min/1.73m^2, which appears to be explained by reverse causation.

While physical activity is widely accepted as an important modifiable risk factor for cardiovascular disease, the association is not well established in kidney disease. A number of observational and interventional studies have examined the risks and benefits of physical activity among patients undergoing maintenance dialysis [21-24]. However, previous studies of incident kidney disease are limited and have reported inconsistent results. In a cross-sectional study of 10,463 patients with diabetes and hypertension, lack of exercise was a significant risk factor for CKD [8]. In another cohort study of 6,972 patients with diabetes, participants who had more regular physical activity had a reduced risk of early diabetic CKD [3]. Among 4,011 participants from the Cardiovascular Health Study, those with the highest amount of physical activity had a lower risk of rapid kidney function decline [7]. In contrast, in a study of 3,653 black participants from the Jackson Heart Study, physical activity was not associated with rapid decline in eGFR [25]. The inconsistency of results may be due in part to the fact that physical activity for these studies was defined in different ways, ranging from number of times per week the participant exercised [3 8] to categorization based on the American Heart Association's Life Simple 7 and the Minnesota Heart Survey [7 25].

We found that a high level of physical activity was associated with lower risk of ESRD among those with preserved kidney function. Two prior studies reported an association between physical activity and lower risk of ESRD. Among 59,552 participants from the Singapore Chinese Health Study, those engaged in any physical activity had a lower risk of ESRD, and a dose-response relationship with intensity of physical activity was noted [10]. Among individuals with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC), physical activity was

inversely associated with risk of CKD progression (defined as 50% decrease in eGFR or incident ESRD). The CRIC results are somewhat inconsistent with our observation of no beneficial effect of physical activity among those with already reduced kidney function. It is possible that secondary factors such as hyperphosphatemia, acidosis, proteinuria, and glomerular hypertension and hypertrophy drive progression of CKD once established and, therefore, physical activity may have less of an impact on ESRD risk in this group [26 27]. Also, earlier and longer established control of primary CKD risk factors, such as blood pressure and blood sugar, through physical activity may have more of an impact earlier rather than later in the kidney disease course.

Diabetes, obesity, hypertension, and kidney dysfunction can lead to oxidative stress, insulin resistance, endothelial dysfunction, and increased circulating cytokines [28]. Physical activity has a beneficial effect on these metabolic disturbances, all common in patients with CKD, and these mechanisms may underlie our finding of reduced risk of ESRD with greater levels of physical activity. One important metabolic disturbance and risk factor for CKD is inflammation, which has an inverse correlation with eGFR [29]. Patients with CKD/ESRD have higher levels of pro-inflammatory adipokines or cytokines, such as leptin, tumor necrosis factor alpha and interleukin 1 and 6 [29-31]. Exercise and physical activity have been shown to reduce inflammatory molecules and create an anti-inflammatory environment in the general population and in patients with CKD [31 32], a potential mechanisms for a beneficial effect of physical activity on kidney function. Increased physical exercise and subsequent weight loss may also help decrease the oxidative stress burden in patients with CKD [29 30 33]. Finally, excess adiposity and lack of physical activity are the most common causes of insulin resistance [34] and hyperglycemia. This metabolic dysregulation is a risk factor for reduced kidney function.

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].

To our knowledge, this is one of few studies to investigate the association between physical activity and ESRD and one of the first to examine sedentary behaviors. Strengths of our study include the prospective design and the unique cohort of participants with low SES and a high burden of risk factors for ESRD. An important strength is the ascertainment of a broad range of physical activity and sedentary behaviors from a validated questionnaire developed specifically for the SCCS [18]. Other strengths include the complete ascertainment of ESRD

cases and the inclusion of baseline eGFR. A limitation of the study is that physical activity and sedentary behaviors were ascertained only at baseline and may have changed after enrollment. Moreover, the physical activity, sedentary behaviors, and covariates were self-reported by participants rather than objectively measured. Although the probability sample is comparable to the whole cohort, the findings might not be generalizable to all SCCS participants. Finally, baseline data on proteinuria were not available.

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

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None

Conflict of Interest Statement

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

Author Contributions

Research idea and study design: MMP, JMT, EKK, EAA, TAI, TGS, LL; data acquisition: LL, WJB; data analysis/interpretation: MMP, JMT, EKK, TGS, JLM, CRC, EAA, KAK, EDS, WJB, TAI, LL; statistical analysis: MMP, TGS, JLM, EAA; supervision or mentorship: TGS, CRC, WJB, TAI, LL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining

to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Data Sharing Statement

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/coveredentities/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

e. Fax Numbers
f. Email Addresses
g. Social Security Numbers
h. Medical Record Numbers
i. Health Plan Beneficiary Numbers
Transmission of potentially identifiable data is kept to a minimum and performed only as needed 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

	Subcohort participants (n=4,113)	ESRD cases (n=692)
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^2	30.3 ± 7.3	32.8 ± 8.8
Overweight or obese (BMI≥25 kg/m^2)	74.8	82.5
Hypertension	55.5	86.0
Hypercholesterolemia	34.5	49.3
Diabetes	22.6	68.5
eGFR, ml/min/1.73m^2	102.8 (85.9, 117.9)	62.9 (36.0, 98.1)
Sedentary and physical activity measures		
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[a]	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[b]	17.2 (8.7,31.9)	13.9 (6.9,24.6)

Note: Values are listed as mean ± SD or % or median (25th,75th percentile)

[a]Includes sitting at meals, talking on the phone, reading, playing cards, or sewing.

[b]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

a)	Q1: Subcohort (n=934)	Q2: Subcohort (n=994)	Q3: Subcohort (n=1045)	Q4: Subcohort (n=1140)
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)[a]	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^2	30.9 (7.9)	30.7 (7.4)	30.9 (7.2)	29.1 (6.8)
Overweight or obese (BMI≥25 kg/m^2)	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^2	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)	Q1: Subcohort (n=1054)	Q2: Subcohort (n=1084)	Q3: Subcohort (n=1119)	Q4: Subcohort (n=856)
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)[a]	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 schol	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^2	29.5 (7.1)	29.7 (7.3)	30.7 (7.3)	31.5 (7.5)
Overweight or obese (BMI≥25 kg/m^2)	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^2	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 (25th,75th percentile)

[a]Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

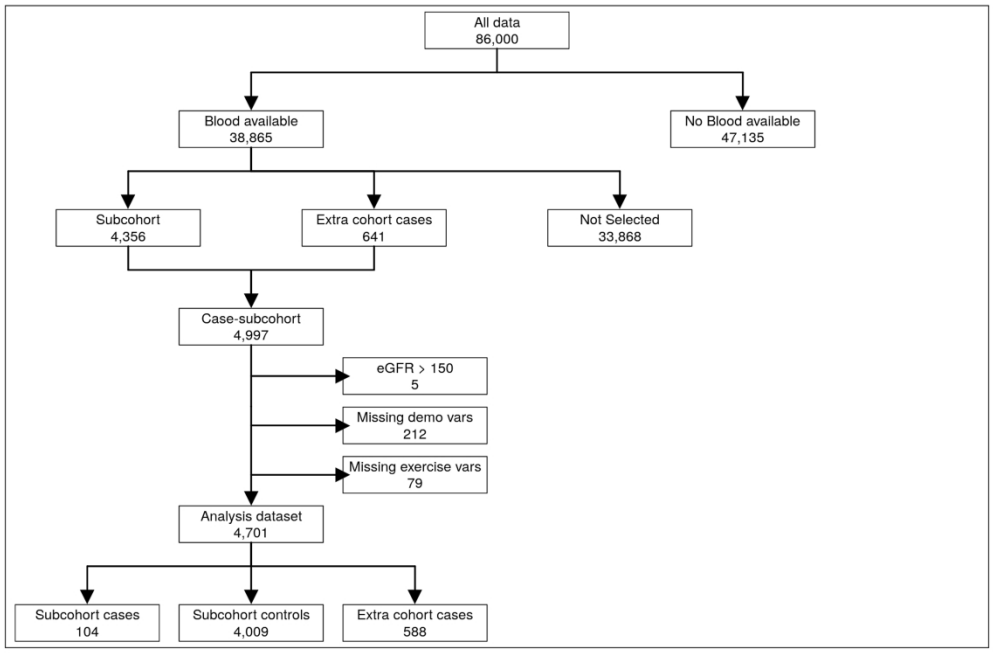
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study

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



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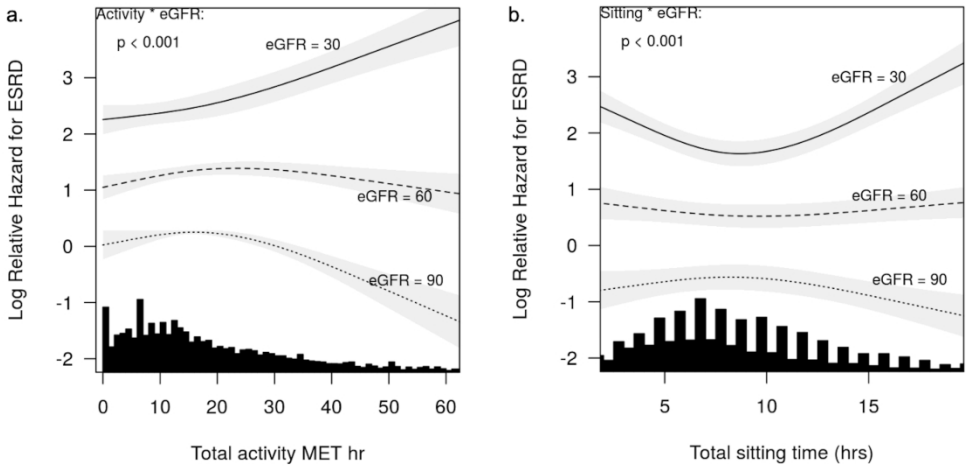

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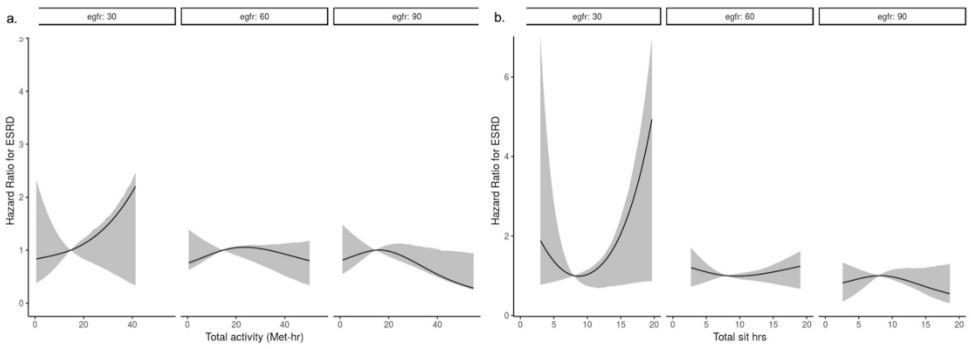

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Reporting checklist for cohort study.

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:

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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	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
	#12b	Describe any methods used to examine subgroups and interactions	6-7
	#12c	Explain how missing data were addressed	6
	#12d	If applicable, explain how loss to follow-up was addressed	6
	#12e	Describe any sensitivity analyses	7
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
	#13b	Give reasons for non-participation at each stage	6
	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
	#14b	Indicate number of participants with missing data for each variable of interest	6
	#14c	Summarise follow-up time (eg, average and total amount)	9

Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
	#16b	Report category boundaries when continuous variables were categorized	9
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

This checklist was completed on 14. March 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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

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

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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^{th}, 75^{th}percentile) estimated glomerular filtration rate (eGFR) was 102.8 (85.9, 117.9) mL/min/1.73m^2. Median (25^{th}, 75^{th} 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^2. 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^2); this association was attenuated after excluding the first two years of follow-up.

Conclusions: In a population with a high prevalence of CKD risk factors such as hypertension and diabetes, physical activity appears to be associated with reduced risk of ESRD among those with preserved kidney function. A positive association between sitting time and ESRD observed among those with advanced kidney disease is likely due to reverse causation.

Abbreviations: CHC=community health center; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HR=hazard ratio; MET=metabolic equivalent; SCCS=Southern Community Cohort Study; USRDS=United States Renal Data System

Strengths and limitations of this study

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

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

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), which provide primary healthcare for under-insured populations. A detailed description of SCCS methods has been published (http://www.southerncommunitystudy.org) [13]. All participants provided written informed consent, and the study was approved by the Institutional Review Boards of Vanderbilt University Medical Center and Meharry Medical College. We used the STROBE cohort checklist when writing our report [14].

Incident ESRD was identified by linking the SCCS cohort, using date of birth, Social Security number, and first and last name, with the nationwide US Renal Data System (USRDS) through March 31, 2015, the latest date for which data were available. ESRD cases in this registry are certified by a physician diagnosis and filed using a medical evidence report form (to the Medicare ESRD program), or when chronic dialysis or kidney transplant occurs, irrespective of the glomerular filtration rate. The USRDS is a national registry and therefore, ascertainment of ESRD cases is virtually complete [1]. Participants with an ESRD diagnosis prior to SCCS enrollment (prevalent cases) were excluded from the analysis.

Approximately 46% of the cohort donated baseline blood samples during CHC recruitment, which have been frozen at -80°C. Participants were selected for measurement of creatinine using a case-cohort design, including all those with stored blood who had an incident ESRD diagnosis (n=737), and a probability sample of the entire cohort who donated blood (n=4,238) [15 16]. Baseline serum levels of creatinine were measured using the Jaffe (Rate) method on a Beckman Coulter DXC 600 clinical chemistry analyzer. The creatinine assays were

calibrated, and daily quality checks performed at three levels before sample testing. This sample constitutes 13% of SCCS participants who donated blood, and is comparable with respect to baseline sociodemographic characteristics including racial distribution, low income, and high prevalence of CKD risk factors [17]. The weighted subcohort included 70.8% black participants and 29.2% white participants, and the SCCS population included 67.3% black participants and 28.6% white participants. In the subcohort and overall SCCS population, about 32% had an education level below 12th grade, the majority had an annual income of <$15,000, and the prevalence of hypertension and diabetes was similar at 56% and 22%, respectively.

Patient and Public Involvement

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

Data collection

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

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

Statistical Analysis

The study population was restricted to black and white participants enrolled at CHCs, to ensure that participants had similar SES and equal access to healthcare regardless of race and had the opportunity to donate a blood specimen. Participants with missing data for any exercise metric (n=161) or demographic characteristic (n=212), and those with baseline eGFR>150

ml/min/1.73m^2 (n=22), were excluded; thus, a total of 692 ESRD cases and 4,113 subcohort members were included in the analyses (Figure 1).

Sedentary time was calculated as hours/day based on the sum of all individual sedentary behaviors. Total physical activity was calculated as the sum of light, moderate and strenuous household/occupational work as well as moderate and vigorous sports; values were transformed from hours/day into summary measures of energy expenditure, defined as metabolic equivalent (MET)-hours/day. MET values for specific activities and intensities were based on the Compendium of Physical Activities [19]. MET-hours reflect the weighted average of the intensity (MET) and duration (hours) of activity behaviors. Two MET-hours/day is roughly equivalent to participating in 1 hour of a light activity, 0.5 hours of a moderate activity such as walking, or 0.25 hours of a vigorous activity such as jogging [18]. For example, one MET-hour is roughly equivalent to the energy expenditure associated with walking very briskly (4 METS) for 15 minutes (0.25 hours).

Using sampling weight techniques, we described baseline characteristics of subcohort participants using means and standard deviations (SD) or medians and 25th and 75th percentiles. For descriptive purposes, sedentary time (hours/day) and physical activity (MET-hours/day) were also categorized into quartiles based on the subcohort distribution. Incidence rates (IR) were calculated from bootstrap probability resamples; the reported IRs were the means of the bootstrap replicates with confidence intervals (CI) at the 2.5 and 97.5 percentiles of the bootstrap distribution.

We calculated hazard ratios (HRs) and 95% CIs for the association of sedentary time and physical activity with ESRD from Cox regression models that accounted for the case-cohort design and the weighted sample [15]. Participants were considered at risk from the date of SCCS

enrollment until the first occurrence of incident ESRD, death, or March 31, 2015. Total sedentary time and physical activity were modeled as restricted cubic splines with four knots and mutually adjusted in a single model. Additional covariates included age at enrollment (years), sex, race, education (< or ≥high school), income (< or ≥$15,000), BMI (kg/m^2), smoking (never or former/current), baseline eGFR (mL/min/1.73m^2), and history of diagnosis of diabetes, hypertension and hypercholesterolemia (yes/no). Baseline serum levels of creatinine were used for estimation of eGFR using the CKD-EPI equation [20]. Continuous predictors (age, eGFR, and BMI) were added to the model as restricted cubic splines with four knots. To examine interactions between sedentary time or physical activity and baseline kidney function on ESRD risk, multiplicative interaction terms between the nonlinear, continuous predictors of sedentary time/physical activity and nonlinear, continuous eGFR were added to the model.

We constructed partial effect plots of eGFR and physical activity or sedentary time on the log relative hazard scale, which display the predicted outcome as a function of a single covariate while holding all other covariates constant for different levels of baseline kidney function. We also plotted the HRs of ESRD as a function of continuous MET-hours/day or sitting hours/day, again holding all other covariates constant for different levels of baseline kidney function. The CIs in the HR plots were generated using bootstrap resampling methods.

To examine if the relationship with ESRD differed for different types of sitting, we also modeled the individual sedentary behaviors, sitting in the car/bus, sitting at work, watching TV/movies, and other sitting. The multivariable Cox model included sitting hours for each category modeled as restricted cubic splines and mutually adjusted. Non-nested likelihood ratio tests were used to compare this model to the Cox model including total sitting hours.

Finally, in sensitivity analyses to examine the potential for reverse causation among those with advanced kidney disease, we calculated HRs and 95% CIs and constructed partial effect plots as above, excluding the first two years of follow up. All analyses were conducted using R. For main effects and interaction terms, P-values ≤0.05 were considered statistically significant.

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 (BMI≥25 kg/m^2), and 55%, 23% and 35% reported a diagnosis of hypertension, diabetes and hypercholesterolemia, respectively. Median (25th, 75th percentile) baseline eGFR was 102.8 (85.9, 117.9) mL/min/1.73m^2 in the subcohort and 62.9 (36.0, 98.1) among ESRD cases. Median (25th, 75th 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 (25th, 75th 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 (25th, 75th 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 and obese, and to have ≥high school education or annual income ≥$15,000. Prevalence of hypertension, hypercholesterolemia and diabetes did not vary consistently across quartiles of sitting time, nor did median baseline eGFR.

Participants were followed for a median (range) of 9.4 (0.1-12.8) years. Age-adjusted IRs for ESRD were 2.61, 2.38, 2.24, and 1.68/1000 person-years in quartiles 1-4 of physical activity, respectively; corresponding IRs in quartiles of sitting time were 2.13, 2.06, 2.07, and 2.64/1000 person-years (Table 2). In unadjusted Cox models, the HRs for an interquartile range increase in physical activity or sedentary time were 0.65 (95% CI 0.58-0.73) and 1.09 (95% CI 1.00-1.20), respectively. In the multivariable model including both physical activity and sedentary time, and the interactions between physical activity*eGFR and sedentary behavior*eGFR, both interactions were statistically significant (chunk test P-value <0.001). Therefore, we present partial effect plots based on the multivariable model to further tease out the shape of the association between eGFR, physical activity, and sitting.

The partial effect plots show the association between physical activity (Figure 2a) or sedentary time (Figure 2b) and log relative hazard of ESRD, by levels of baseline eGFR. When eGFR is 30, the shape of the association suggests that risk of ESRD increases as activity increases. In contrast, when eGFR is 90, log relative hazard of ESRD decreases as activity increases, and the inverse association is most pronounced at levels of physical activity above 27

MET-hours/day. The predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to when eGFR is 60, and log relative hazard is lowest when eGFR is 90.

In the second plot, when eGFR is 30, the shape of the association shows increasing ESRD risk as sedentary time increases. In contrast, when eGFR is 60 or 90, the shape of the association is slightly decreasing or flat with increasing sedentary time. As for physical activity, the predicted log relative hazard of ESRD is uniformly higher when eGFR is 30 compared to when eGFR is 60 or 90.

The continuous HR plots present the associations between physical activity (Figure 3a) or sedentary time (Figure 3b) and risk of incident ESRD. The HR plots are separated into three levels of eGFR (30, 60, 90 mL/min/1.73m^2). Each panel has its own reference level, which is seen at the pinch in the confidence intervals where HR=1.0. The relative shape of the associations at each level of eGFR corresponds to what is shown in the partial effect plots; in particular, an inverse association between physical activity and risk of ESRD is apparent only among those with preserved kidney function, while an increased risk of ESRD with increasing sedentary time is observed among those with low eGFR.

In analyses examining the individual types of sitting, the non-nested likelihood ratio test indicated that the model with sitting hours by type did not significantly differ from the model with total sitting hours (p=0.98). In sensitivity analyses excluding the first two years of follow up, the interactions between sedentary time*eGFR and physical activity*eGFR remained statistically significant (P-value<0.001 for both); however, the positive association between sitting time and ESRD among those with advanced kidney disease was no longer apparent.

DISCUSSION

Among black and white participants at high risk for ESRD, we observed a significant interaction between physical activity and baseline kidney function, suggesting that among individuals with preserved kidney function, higher physical activity is associated with a lower risk of developing ESRD. Similarly, we observed heterogeneity of the association of sitting time on ESRD risk, as demonstrated by the higher risk of ESRD associated with longer sitting time among those with eGFR $\leq$30 mL/min/1.73m^2, which appears to be explained by reverse causation.

While physical activity is widely accepted as an important modifiable risk factor for cardiovascular disease, the association is not well established in kidney disease. A number of observational and interventional studies have examined the risks and benefits of physical activity among patients undergoing maintenance dialysis [21-24]. However, previous studies of incident kidney disease are limited and have reported inconsistent results. In a cross-sectional study of 10,463 patients with diabetes and hypertension, lack of exercise was a significant risk factor for CKD [8]. In another cohort study of 6,972 patients with diabetes, participants who had more regular physical activity had a reduced risk of early diabetic CKD [3]. Among 4,011 participants from the Cardiovascular Health Study, those with the highest amount of physical activity had a lower risk of rapid kidney function decline [7]. In contrast, in a study of 3,653 black participants from the Jackson Heart Study, physical activity was not associated with rapid decline in eGFR [25]. The inconsistency of results may be due in part to the fact that physical activity for these studies was defined in different ways, ranging from number of times per week the participant exercised [3 8] to categorization based on the American Heart Association's Life Simple 7 and the Minnesota Heart Survey [7 25].

We found that a high level of physical activity was associated with lower risk of ESRD among those with preserved kidney function. Two prior studies reported an association between physical activity and lower risk of ESRD. Among 59,552 participants from the Singapore Chinese Health Study, those engaged in any physical activity had a lower risk of ESRD, and a dose-response relationship with intensity of physical activity was noted [10]. Among individuals with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC), physical activity was inversely associated with risk of CKD progression (defined as 50% decrease in eGFR or incident ESRD). The CRIC results are somewhat inconsistent with our observation of no beneficial effect of physical activity among those with already reduced kidney function. It is possible that secondary factors such as hyperphosphatemia, acidosis, proteinuria, and glomerular hypertension and hypertrophy drive progression of CKD once established and, therefore, physical activity may have less of an impact on ESRD risk in this group [26 27]. Also, earlier and longer established control of primary CKD risk factors, such as blood pressure and blood sugar, through physical activity may have more of an impact earlier rather than later in the kidney disease course.

Diabetes, obesity, hypertension, and kidney dysfunction can lead to oxidative stress, insulin resistance, endothelial dysfunction, and increased circulating cytokines [28]. Physical activity has a beneficial effect on these metabolic disturbances, all common in patients with CKD, and these mechanisms may underlie our finding of reduced risk of ESRD with greater levels of physical activity. One important metabolic disturbance and risk factor for CKD is inflammation, which has an inverse correlation with eGFR [29]. Patients with CKD/ESRD have higher levels of pro-inflammatory adipokines or cytokines, such as leptin, tumor necrosis factor alpha and interleukin 1 and 6 [29-31]. Exercise and physical activity have been shown to reduce inflammatory molecules and create an anti-inflammatory environment in the general population

and in patients with CKD [31 32], a potential mechanisms for a beneficial effect of physical activity on kidney function. Increased physical exercise and subsequent weight loss may also help decrease the oxidative stress burden in patients with CKD [29 30 33]. Finally, excess adiposity and lack of physical activity are the most common causes of insulin resistance [34] and hyperglycemia. This metabolic dysregulation is a risk factor for reduced kidney function. 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].

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

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

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None

Conflict of Interest Statement

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

Author Contributions

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

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Data Sharing Statement

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/coveredentities/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
e. Fax Numbers
f. Email Addresses
g. Social Security Numbers
h. Medical Record Numbers
i. Health Plan Beneficiary Numbers
Transmission of potentially identifiable data is kept to a minimum and performed only as needed 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

	Subcohort participants (n=4,113)	ESRD cases (n=692)
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^2	30.3 ± 7.3	32.8 ± 8.8
Overweight or obese (BMI≥25 kg/m^2)	74.8	82.5
Hypertension	55.5	86.0
Hypercholesterolemia	34.5	49.3
Diabetes	22.6	68.5
eGFR, ml/min/1.73m^2	102.8 (85.9, 117.9)	62.9 (36.0, 98.1)
Sedentary and physical activity measures		
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[a]	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[b]	17.2 (8.7,31.9)	13.9 (6.9,24.6)

Note: Values are listed as mean ± SD or % or median (25th,75th percentile)

[a]Includes sitting at meals, talking on the phone, reading, playing cards, or sewing.

[b]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

a)	Q1: Subcohort (n=934)	Q2: Subcohort (n=994)	Q3: Subcohort (n=1045)	Q4: Subcohort (n=1140)
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)[a]	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^2	30.9 (7.9)	30.7 (7.4)	30.9 (7.2)	29.1 (6.8)
Overweight or obese (BMI≥25 kg/m^2)	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^2	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)	Q1: Subcohort (n=1054)	Q2: Subcohort (n=1084)	Q3: Subcohort (n=1119)	Q4: Subcohort (n=856)
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)[a]	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 schol	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^2	29.5 (7.1)	29.7 (7.3)	30.7 (7.3)	31.5 (7.5)
Overweight or obese (BMI≥25 kg/m^2)	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^2	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 (25th,75th percentile)

[a]Total physical activity includes light, moderate, and strenuous household/occupational activity as well as moderate and vigorous sports.

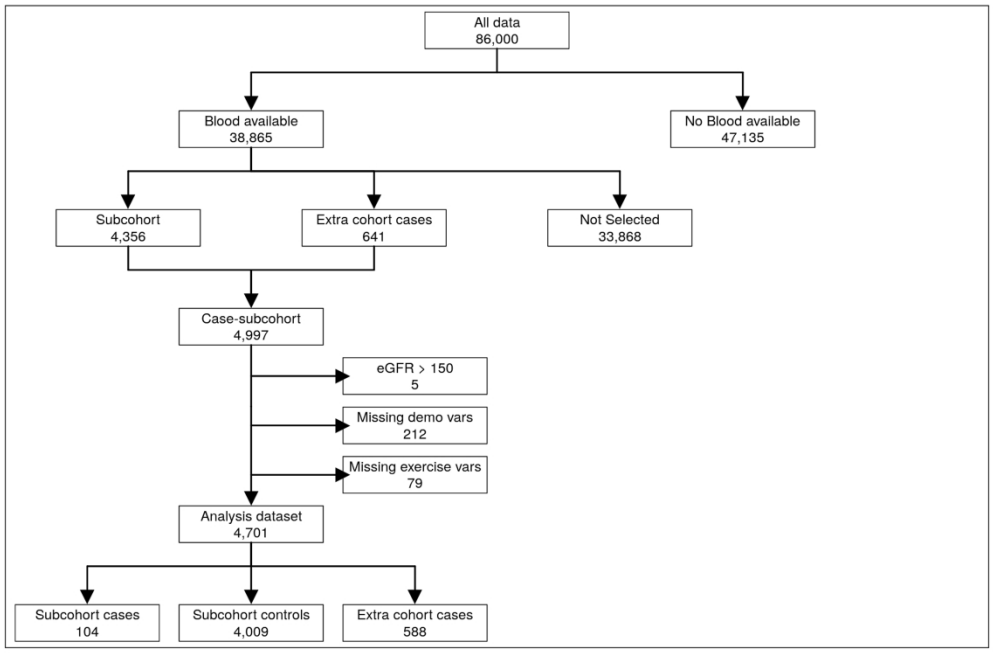
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SCCS, Southern Community Cohort Study

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



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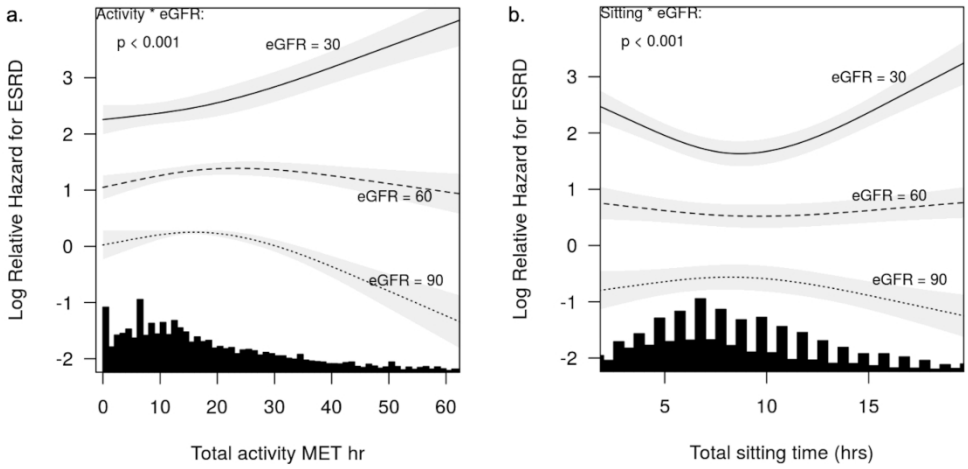
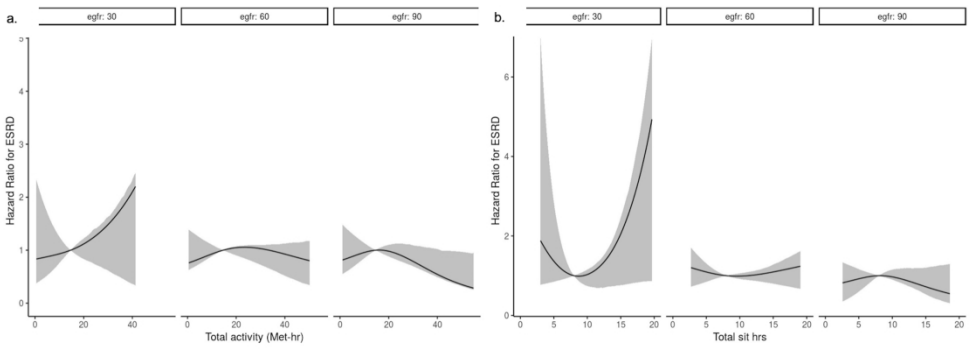


Figure 2. Partial effect plots of a) physical activity (MET-hours/day) and b) total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age,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



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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, Gotzsche PC, Vandenbroucke JP. The Strengthening the 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	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
	#12b	Describe any methods used to examine subgroups and interactions	6-7
	#12c	Explain how missing data were addressed	6
	#12d	If applicable, explain how loss to follow-up was addressed	6
	#12e	Describe any sensitivity analyses	7
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
	#13b	Give reasons for non-participation at each stage	6
	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
	#14b	Indicate number of participants with missing data for each variable of interest	6
	#14c	Summarise follow-up time (eg, average and total amount)	9

Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
	#16b	Report category boundaries when continuous variables were categorized	9
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10
Key results	#18	Summarise key results with reference to study objectives	10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

This checklist was completed on 14. March 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai