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The association of exercise and sedentary behaviours with incident end-stage renal disease: 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 South-eastern USA.
Participants The Southern Community Cohort Study recruited ~86 000 black and white participants from 2002 to 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 (25th, 75th centile) estimated glomerular filtration rate (eGFR) was 102.8 (85.9–117.9) mL/min/1.73 m^2. Medians (25th–75th centile) 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 behaviour (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/1.73 m^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/1.73 m^2); this association was attenuated after excluding the first 2 years of follow-up.
Conclusions In a population with a high prevalence of chronic kidney disease 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.

Strengths and limitations of this study

- ► The Southern Community Cohort Study (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 creatine, therefore, baseline kidney function could be evaluated.
- ► Physical activity and sedentary behaviours 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 behaviours were included and behaviours may have changed after enrolment.

INTRODUCTION

In 2015, the age-adjusted incidence of end-stage renal disease (ESRD) in USA 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 behaviours. 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 behaviours 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 behaviours from socioeconomic status (SES).[10 11]

We investigated whether sedentary time and physical activity were independently associated with risk of incident ESRD. We hypothesised 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 south-eastern USA (2002–2009).[12] Participants eligible for enrolment spoke English and had not been treated for cancer in the 12 months before enrolment. The majority (86%) were recruited at participating community health centres (CHCs), which provide primary healthcare for underinsured populations. A detailed description of SCCS methods has been published (http://www.southerncommunitystudy.org).[13] All participants provided written informed consent. We used the Strengthening the Reporting of Observational studies in Epidemiology (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 names, with the nationwide US Renal Data System (USRDS) through 31 March 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 programme), 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 enrolment (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 creatine 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=4238).[15 16] Baseline serum levels of creatine were measured using the Jaffe (rate) method on a Beckman Coulter DXC 600 clinical chemistry analyser. The creatine 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 the twelfth 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

Standardised computer-assisted personal interviews were administered at enrolment 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 hypercholesterolaemia 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 behaviours were assessed using a validated Physical Activity Questionnaire (PAQ) developed specifically for the SCCS.[18] For sedentary behaviours, 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 labour. Moderate sports included activities such as bowling, dancing and golfing, while vigorous sports included jogging, aerobics,

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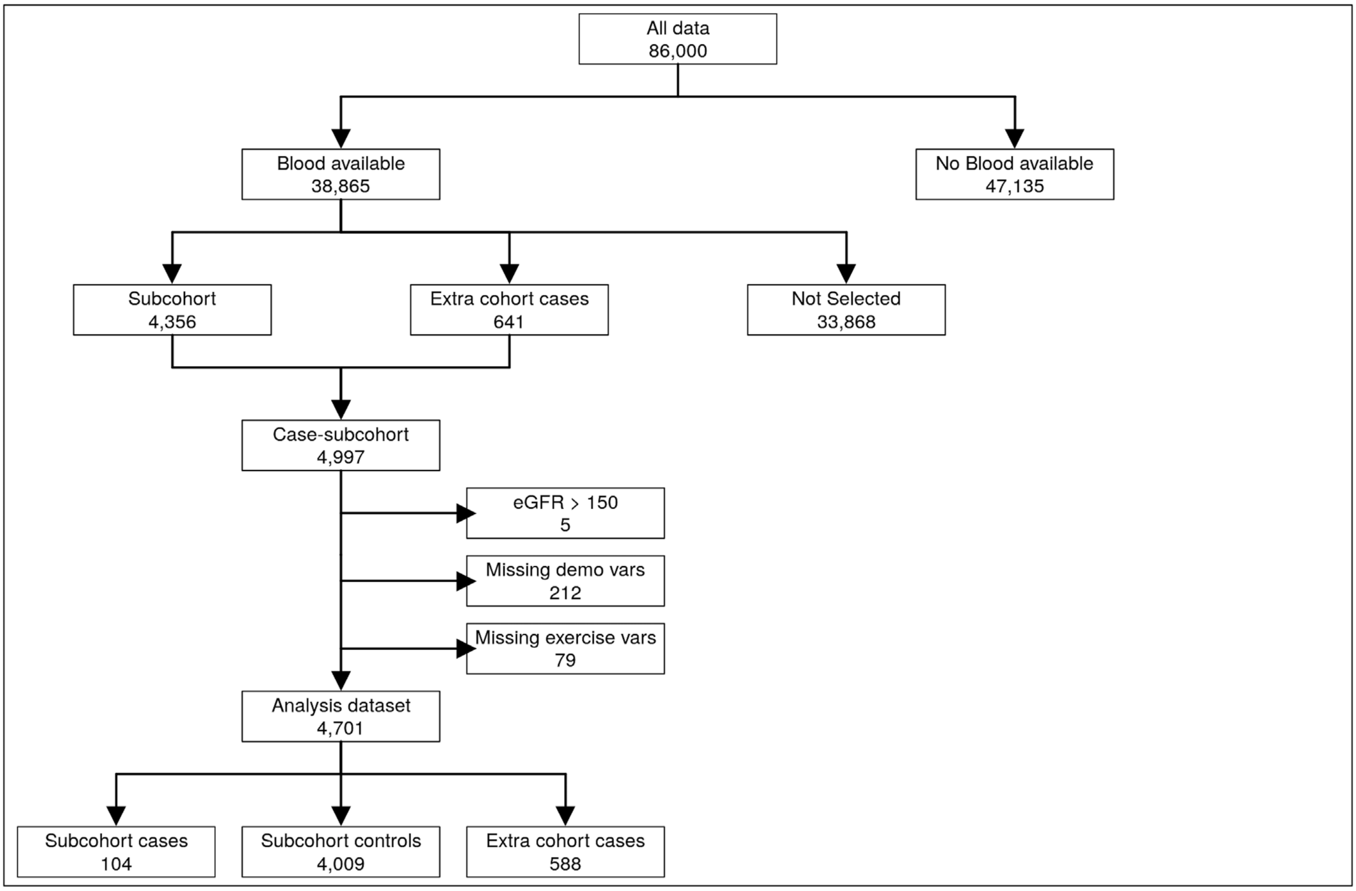

Figure 1 Study selection of the SCCS case-cohort. eGFR, estimated glomerular filtration rate; SCCS, Southern Community Cohort Study.

tennis, swimming and weightlifting. For all questions, participants provided open-ended duration responses (hours and minutes). The reliability and validity of the SCCS PAQ 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=79) or demographic characteristic (n=212), and those with baseline eGFR >150 mL/min/1.73 m^2 (n=5), were excluded; thus, a total of 692 ESRD cases and 4113 subcohort members were included in the analyses (figure 1).

Sedentary time was calculated as hours/day based on the sum of all individual sedentary behaviours. 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 behaviours. 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, 1 MET-hour is roughly equivalent to the energy expenditure associated with walking very briskly (4 METs) for 15 min (0.25 hours).

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

We calculated 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 enrolment until the first occurrence of incident ESRD, death or 31 March 2015. Total sedentary time and physical activity were modelled as restricted cubic splines with four knots and mutually adjusted in a single model. Additional covariates included age at enrolment (years), sex, race, education (< or ≥high school), income (< or ≥$15,000), BMI (kg/m^2), smoking (never or former/current), baseline eGFR (mL/min/1.73 m^2) and history of diagnosis of diabetes, hypertension and hypercholesterolaemia (yes/no). Baseline serum levels of creatine were used for estimation of eGFR using the Chronic Kidney Disease Epidemiology Collaboration (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 non-linear, continuous predictors of sedentary time/physical activity and non-linear, 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 modelled the individual sedentary behaviours, sitting in the car/bus, sitting at work, watching TV/movies and other sitting. The multivariable Cox model included sitting hours for each category modelled 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 2 years of follow-up. All analyses were conducted using R. For main effects and interaction terms, p≤0.05 was 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 hypercholesterolaemia, respectively. Median (25th–75th centile) baseline eGFR was 102.8 (85.9–117.9) mL/min/1.73 m^2 in the subcohort and 62.9 (36.0–98.1) among ESRD cases. Median (25th–75th centile) 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 centile) total physical activity in the highest activity quartile for the subcohort was 41.3 (33.2–55.5) MET-hours/day, compared with 4.2 (2.0–6.2) in the lowest quartile (table 2A). Compared with 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, hypercholesterolaemia and diabetes. Median baseline eGFR was highest among those in the highest quartile of physical activity.

Median (25th–75th centile) 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 quartiles of sedentary time compared with 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 at least high school education or annual income ≥$15 000. Prevalence of hypertension, hypercholesterolaemia 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 2.61/1000, 2.38/1000, 2.24/1000 and 1.68/1000 person-years in the first to fourth quartiles of physical activity, respectively; corresponding IRs in quartiles of sitting time were 2.13/1000, 2.06/1000, 2.07/1000 and 2.64/1000 person-years (table 2). In unadjusted Cox models, the HRs for an IQR increase in physical activity or sedentary time were 0.65 (95% CI 0.58 to 0.73) and 1.09 (95% CI 1.00 to 1.20), respectively. In the multivariable model including both physical activity and sedentary time, and the interactions between physical activity*eGFR and sedentary behaviour*eGFR, both interactions were statistically significant (chunk test p<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 with 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

Table 1 Baseline characteristics of the probability sample (subcohort) of SCCS participants and ESRD cases

	Subcohort participants (n=4113)	ESRD cases (n=692)
Age at enrolment, 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
Hypercholesterolaemia	34.5	49.3
Diabetes	22.6	68.5
eGFR, ml/min/1.73 m^2	102.8 (85.9–117.9)	62.9 (36.0–98.1)
Sedentary and physical activity measures		
Sitting, hours/day	8.0 (5.5–12.0)	8.2 (6.0–12.0)
Car or bus, hours/day	1.5±1.8	1.5±2.0
At work, hours/day	1.2±2.3	0.9±2.3
TV or movies, hours/day	3.8±2.9	4.3±3.1
Home computer, hours/day	0.5±1.1	0.3±0.9
Other, hours/day*	2.3±1.9	2.4±2.0
Physical activity, hours/day	5.4 (2.9–9.4)	4.3 (2.3–7.4)
Household/occupational activity, MET-hours/day		
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-hours/day		
Moderate	10.0±8.8	8.9±8.1
Vigorous	5.6±12.0	3.5±9.6
Total physical activity, MET-hours/day†	17.2 (8.7–31.9)	13.9 (6.9–24.6)

Values are listed as mean±SD or % or median (25th–75th centile).
*Includes sitting at meals, talking on the phone, reading, playing cards or sewing.
†Includes light, moderate and strenuous household/occupational activity as well as moderate and vigorous sports.
BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MET, metabolic equivalent; SCCS, Southern Community Cohort Study.

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 with 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/1.73 m^2). Each panel has its own reference level, which is seen at the pinch

Table 2 Baseline characteristics of the subcohort of SCCS participants by quartiles of: (A) physical activity (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-hours/day)*	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 (hours/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 $15 000/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/1.73 m^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-years	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 (hours/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-hours/day)*	15.8 (7.5–32.4)	15.3 (8.6–29.6)	18.4 (9.7–32.7)	18.6 (9.8–32.3)
Age, years	52.5 (8.9)	53.2 (8.5)	52.1 (8.9)	50.6 (7.8)
Women	58.2	57.3	63.1	60.6
Black race	71.0	66.0	67.7	79.6
Less than high school	39.8	29.5	29.0	31.0
Less than $15 000/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/1.73 m^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)

Values are listed as mean±SD or % or median (25th–75th centile).
*Total physical activity includes light, moderate and strenuous household/occupational activity as well as moderate and vigorous sports.
BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MET, metabolic equivalent; SCCS, Southern Community Cohort Study.

in the CIs 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 2 years of follow-up, the interactions between sedentary time*eGFR and physical activity*eGFR remained statistically significant (p<0.001 for

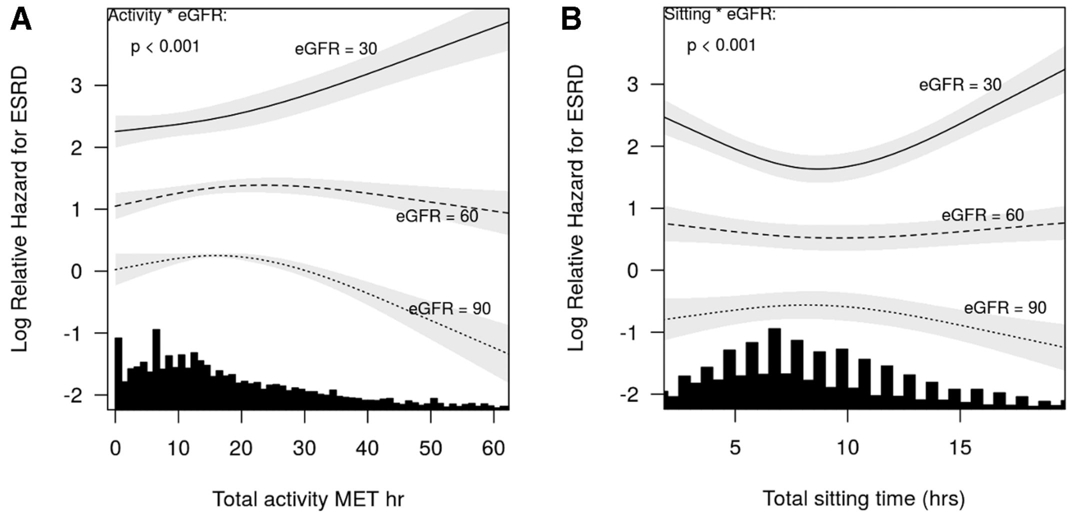

Figure 2 Partial effect plots of (A) Physical activity (MET-hours/day) (B) Total sitting time (hours/day) and log relative hazard of ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR. BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MET, metabolic equivalent.

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 ≤30 mL/min/1.73 m^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 6972 patients with diabetes, participants who had more regular physical activity had a reduced risk of early diabetic CKD.[3] Among 4011 participants from the Cardiovascular Health Study, those with the highest amount of physical activity had a lower risk of rapid kidney function

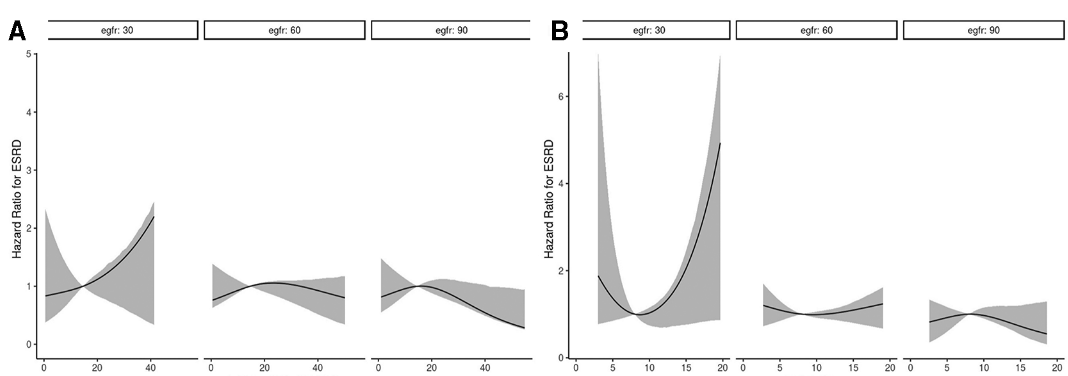

Figure 3 Plots of continuous HRs of (A) Physical activity (MET-hours/day) (B) Total sitting time (hours/day) and ESRD by baseline levels of eGFR. The plot is based on the multivariable Cox model that includes terms for physical activity, sedentary time, BMI, smoking status, age, sex, race, education, income, diabetes, hypertension, high cholesterol, eGFR, and the interactions between physical activity and eGFR and sedentary time and eGFR. The CIs in the HR plot were generated using bootstrap resampling methods. BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MET, metabolic equivalent.

decline.[7] In contrast, in a study of 3653 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 categorisation based on the American Heart Association Life's 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 59552 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 hyperphosphataemia, 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 proinflammatory adipokines or cytokines, such as leptin, tumour necrosis factor α and interleukin (IL) 1 and IL-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] 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 hyperglycaemia. 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 behaviour is hypothesised 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, uraemia 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 2 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 behaviour has, however, been shown to be associated with physiological risk factors for CKD and ESRD including increased BMI, systolic blood pressure, triglycerides and decreased high-density lipoprotein (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 behaviours. 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 behaviours 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 behaviours were ascertained only at baseline and may have changed after enrolment. Moreover, the physical activity, sedentary behaviours 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 generalisable 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 behaviours are modifiable risk factors that may be targets for possible interventions, especially in those with preserved kidney function.

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