Physical Activity and Clinical Outcomes in the Setting of Chronic Kidney Disease

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Abstract

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Background: Physical activity promotes diverse metabolic benefits that may counteract the toxic biochemical environment of chronic kidney disease (CKD). We tested the hypotheses that greater physical activity levels are associated with lower kidney disease progression, cardiovascular outcomes, and death in a prospective cohort study of stage III-IV CKD patients.

Design and setting: We studied 304 participants from the Seattle Kidney Study, a Nephrology clinic-based study of CKD, who had an estimated glomerular filtration rate (eGFR) of 15 to 59 mL/min/1.73 m^2. Participants completed questionnaires regarding the frequency and duration of physical activity, and we converted these responses to minutes/week. We used generalized estimating equations and proportional hazards models to quantify associations of physical activity with relative annual decline in eGFR, defined using longitudinal serum cystatin C, and time to clinical outcomes, respectively.

Results: Mean eGFR at baseline was 38 mL/min/1.73 m^2, mean age was 62 years and mean relative annual change in eGFR was -7%. After adjustment for potential confounders, greater physical activity levels were associated with statistically slower

rates of kidney function decline. Each one-category increase in physical activity group was associated with a 1.9% per year slower decline in kidney function (p=0.031). During a median 3.3 years of follow-up, 54 participants died, 48 participants were hospitalized for heart failure and 28 participants developed a component of the composite cardiovascular outcome (incidence rates: 60, 52 and 13 per 1000 person-years, respectively). Our investigation found no association between either the presence or the duration of physical activity with all-cause mortality. On the other hand, we found associations of any physical activity with hospitalized heart failure and with a composite cardiovascular outcome after adjustment for established cardiovascular risk factors.

Conclusions: Even moderate levels of physical activity may be sufficient to confer health benefits among CKD patients. Physical activity is emerging as one of few modifiable risk factors for major adverse health outcomes in this high-risk patient population.

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Chapter 1 Physical Activity and Kidney Function Decline in Persons with Chronic Kidney Disease

1.1 Background

Chronic kidney disease (CKD) is a common condition, generally defined by the loss of more than half of the normal kidney function of a healthy young adult.[1] Kidney dysfunction leads to the retention of metabolic waste products, which promote metabolic disturbances that amplify the risks of cardiovascular diseases, disability, and continued progression of kidney failure.[2-6] While the initial causes of CKD are diverse, the metabolic consequences appear to be similar across a wide range of kidney diseases.

Physical activity confers diverse metabolic benefits that may counteract the adverse metabolic environment of kidney dysfunction. Moreover, a sedentary lifestyle may also contribute to the *development* of kidney disease, particularly through diabetes and hypertension, which are the two most common causes of CKD in Western society.[7-19] For example, adiposity directly promotes hypertension - the key determinant of renal disease progression – which subsequently increases the activity of the renin-angiotensin system, results in interstitial fibrosis and hypoxia, and may contribute to the development and progression of kidney injury.[20-23]

We previously demonstrated an association of greater leisure-time physical activity with lower rates of kidney function decline in a community-based study of ambulatory older adults.[24] However, no prospective human studies have reported associations of physical activity with kidney disease outcomes among individuals who have established CKD. Similar to hypertension and diabetes, CKD progresses insidiously with non-existent or subtle symptoms, precisely at the time when physical activity interventions might be most effective.

We hypothesized that greater physical activity levels would be associated with lower rates of kidney function decline among individuals who have established CKD. To test this hypothesis, we evaluated self-reported leisure-time activity in a clinic-based study of 214 CKD patients not undergoing dialysis and delineated associations with longitudinal changes in kidney function using serial measurements of plasma cystatin C concentration.

1.2 Materials and Methods

1.2.1 Study Population

The Seattle Kidney Study (SKS) is a clinic-based, prospective cohort study of subjects with CKD based in Seattle, Washington. The SKS began recruiting participants in 2004 from outpatient nephrology clinics at Harborview Medical Center and the Veterans' Affairs Medical Center, affiliated hospitals of the University of Washington. Eligibility criteria are age greater than 18 years and CKD of any stage not requiring dialysis. Exclusion criteria are current or prior kidney transplantation, dementia, institutionalization, expected to start renal replacement therapy or leave the area within 3 months, participation in a clinical trial, non-English speaking, or inability to undergo the informed consent process. For the current analyses, we restricted our study population to those with moderate-to-severe CKD (stage III-IV; estimated GFR 15-59 ml/min/1.73m^2) by excluding 114 participants who had an eGFR $\geq$ 60ml/min/m^2 and 12 who had an eGFR <15ml/min/m^2 at baseline. We further excluded 26 participants with completely missing physical activity data. To focus on participants who had the capacity to exercise, we further excluded 46 patients who were unable to ambulate and required the use of a wheelchair. Finally, we excluded 100 subjects who had either no follow-up information (n=10) or fewer than the two eGFR measurements necessary to calculate a slope, for a total of 214 participants for analysis (Figure 1).

The 90 subjects who were excluded due to lack of follow-up eGFR measurements were of similar age, had a similar baseline eGFR, and had similar amounts of physical activity compared to included participants. Among them, 22 (24%) died prior to scheduled follow-up. Institutional review boards have repetitively approved the SKS since its inception.

1.2.2 Measurement of physical activity

The Four Week Physical Activity History Questionnaire (FWH) was administered at baseline to estimate each participant's self-reported leisure-time physical activity level. The FWH queries participants regarding the frequency and duration in which they engaged in each of the following activities during the prior month: walking for exercise, jogging, biking, aerobics, golf, tennis, swimming, weight training, treadmill or aerobic machine.[25] To calculate minutes per week of total leisure-time activity, for each activity performed, we multiplied the frequency by the duration in the prior month, divided by 4 weeks, and summed across all activities.

The FWH questionnaire has been validated in the general population against doubly labeled water, heart rate monitoring, changes in maximal oxygen uptake, and accelerometry.[26-30] In a subset of 48 SKS participants, the mean estimated metabolic equivalent of task (MET) hours per week from the questionnaire was significantly associated with objectively measured energy expenditure using accelerometry (intraclass correlation coefficient (ICC): 0.28, p=0.037) and with percent time spent in moderate to vigorous activities (ICC=0.38, p=0.018).[31]

The minutes per week of physical activity were categorized as none, 1 to 60 minutes per week, 60 to 150 minutes per week and more than 150 minutes per week. The uppermost physical activity category was defined so as to correspond to an adherence to the American Heart Association Physical Activity Guidelines of 150 minutes per week of moderate physical activity.[32]

1.2.3 Measurement of kidney function outcomes

Serum creatinine and cystatin C measurements are performed annually in SKS. We decided *a priori* to evaluate cystatin C-based estimates of GFR because serum creatinine levels depend on muscle mass, which declines with older age and may be influenced by exercise.[33] In secondary analyses, we also assessed GFR using the serum-creatinine-based CKD-EPI equation.[34] Cystatin C and creatinine-based estimates of GFR provide similar precision and validity compared to gold-standard radionucleotide measurement of GFR. Serum cystatin C levels were measured from frozen serum samples stored at −70°C using a particle-enhanced immunonephelometric assay with a nephelometer (BNII, Siemens Healthcare Diagnostics Inc., Deerfield, Illinois). The assay is stable through several freeze-thaw cycles.[35] We calculated estimated GFR at each SKS study exam using the equation:[36]

$$\text{Estimated GFR}_{\text{cystatin C}} = 127.7 \cdot \text{cystatin C}^{-1.17} \cdot \text{age}^{-0.13} \cdot (0.91 \text{ if female; } 1.06 \text{ if black})$$

The primary study outcome was the relative annualized change in kidney function, defined by the exponentiated slope of log-transformed eGFR. The secondary outcome was incident end stage renal disease (ESRD), defined as the first occurrence of initiation of chronic dialysis or kidney transplantation. Incident ESRD events were identified during twice yearly surveillance calls in which participants were asked to report any hospitalizations, procedures, or surgeries since their previous study visit. Study coordinators also specifically inquired about initiation of dialysis and fistula placement since the previous encounter. All self-reported initiations of dialysis or kidney transplantations were subsequently verified through medical record review.

1.2.4 Measurement of covariates

1.2.4.a Physical and medication information

Weight was measured using calibrated scales, height with a wall-mounted tape measure, and waist circumference using a constant-tension tape. Medications were assessed by inventory assessment and missing medication data were completed by chart review when participants did not bring their medication containers to the study visit.[37] Smoking status (current, former, or never) and alcohol use (current use *versus* none) were determined via baseline lifestyle questionnaires. Three seated blood pressure measurements were recorded using an automated sphygmomanometer; the average of the last two readings was retained for analyses.

1.2.4.b Blood samples and analytical procedures

Blood samples were collected after an overnight fast and urine was collected as timed overnight voids. Except for hemoglobin A1c, which was measured on fresh blood, serum, plasma, and urine were stored at -80 °C until analysis. Concentrations of albumin, low-density lipoprotein (LDL) cholesterol, C-reactive protein (CRP) were measured in serum. Urine albumin and creatinine were measured in spot morning or overnight urine collections.

1.2.4.c Prevalent conditions

Prevalent conditions were determined based on participant responses to questionnaires and hospitalizations that occurred after initial SKS enrollment but prior to the initial assessment for this study. Prevalent coronary artery disease was defined as self-reported previous myocardial infarction, cardiac arrest, coronary artery bypass graft or percutaneous coronary intervention. Prevalent peripheral vascular disease was defined as self-reported claudication, peripheral vascular surgery, or lower extremity amputation. Prevalent cerebrovascular disease was defined as self-reported stroke or carotid endarterectomy. We defined diabetes by any of the following: use of an oral hypoglycemic medication or insulin, fasting blood sugar ≥126mg/dL, non-fasting blood sugar ≥200, or hemoglobin A1c ≥6.5%.

Hypertension was defined by the use of any antihypertensive medication, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg.[38]

1.2.4.d Physical performance measures

The get up and go test of lower extremity function was assessed by taking the faster of two attempts per participant at getting up from a fully seated position, walking around a cone placed four meters away, and returning back to a seated position. For the six-minute walk test, coordinators asked participants to walk as fast as they could along a marked indoor corridor and recorded the total distance travelled after 6 minutes. If the participant could not complete the full 6-minute walk, the total distance achieved was used. The Short Physical Performance Battery (SPPB), a lower extremity physical performance test comprised of a test of three timed tasks (i.e., gait speed, chair rise, and three standing positions to assess balance) was performed and the score was calculated as recommended.[39] A summary score of 0 to 12 (higher score indicating better function) is based on performance on the three tasks and a score below 8 is associated with disability in lower extremity functioning.

1.2.5 Statistical analyses

We tabulated baseline participant characteristics according to physical activity category. We used generalized estimating equations (GEE), accounting for within-participant clustering across time, to determine if the annualized relative change in eGFR differed across physical activity categories, after adjusting for potential confounding variables.[40] Using graphical methods and residual analyses, we determined that a relative change (log eGFR) model best fit the observed slope eGFR data; therefore we used this model in longitudinal analyses.

We chose covariates as potential confounding factors *a priori* based on plausibility that they could confound the association of physical activity level with kidney function change. We investigated groups

of potential confounding factors by constructing nested multivariable models. We conducted subgroup analyses to evaluate whether associations of both the presence and the duration of physical activity with change in kidney function differed after excluding participants who had prevalent coronary artery disease, those with prevalent diabetes and those who scored below 8 on the SPPB.

For the analysis of incident treated ESRD as the outcome, participants were considered at risk from the date of their baseline SKS study visit until the first occurrence of dialysis initiation, kidney transplantation, censoring due to death, loss to follow-up or end of study data collection period (January 1, 2012), whichever came first. We used Cox proportional hazards regression to estimate the relative hazard of ESRD after adjustment for factors selected *a priori* based on evidence that they might confound the association between physical activity and ESRD. The exposure definition and regression models were similar to those constructed to evaluate kidney function change, with additional adjustment for baseline kidney function, using cystatin C, in the final model. To assess the importance of competing risks, we performed sensitivity analyses using end-stage renal disease or death as the failure variable.

Because the physical activity questionnaire was designed as a checklist for each of 12 activities (*i.e.,* only a check box for "yes"), we were unable to distinguish between activities that were missing on the questionnaire and activities that were not performed. Along with the checklist of the 12 activities, participants were asked to answer the question: "In the past month, how often did you exercise", with the answer choices being "never", "<1/week", "1/week", "2-3/week", ">3/week". Participants who did not check any boxes on the checklist and answered "never" to the secondary question were considered to have performed no physical activity (0 minutes/week, n=56). For participants who did not check any boxes on the checklist but answered anything but "never" to the secondary question (n=26), we used a multiple imputation procedure to replace missing values. Multiple imputation is an efficient and practical

method to deal with missing data, in which each missing value is replaced by a list of *m* (in our case, m=10) simulated values.[41] We performed multivariate imputation by the chained equations (MICE) method of multiple imputation to create 10 plausible alternative versions of the complete data set; each of these 10 data sets was analyzed by a complete-data method.[41] Point estimates and variances across the datasets were combined using Rubin's rule to produce a single result for all 10 estimates.[42] We assumed that the data were missing at random (MAR) and the imputation model contained all covariates from the fullest regression model, in addition to auxiliary variables, which included all questions from the physical activity questionnaire, and baseline eGFR. Validity of the inferences obtained from the imputation procedure relies on the MAR assumption that differences in the likelihood of missingness in the questionnaire can be explained by differences in the observed auxiliary variables.[43]

We fit a linear relationship of physical activity duration and relative change in kidney function among participants who reported performing any physical activity (referred to hereafter as "active"), based on a visual assessment that the associations were generally linear across the densest spectrum of data and that fractional polynomial assessment indicated that nonlinear models did not fit the data statistically better than the linear form.[44]

Walking is a physical activity that is highly accessible, readily adopted and rarely associated with injury. In an attempt to characterize the association of walking time and kidney function decline, we secondarily examined the association of minutes of walking per week with annualized relative change in eGFR. For these analyses, we additionally adjusted for time spent in other leisure-time activities.

We also evaluated whether associations of physical activity and kidney function change differed according to stage of CKD, sex and race. A 3-way multiplicative interaction term (e.g. race*time*physical activity) and the corresponding 2-way interaction terms were entered in the second regression model

and the Wald test was used to assess statistical significance of the three-way interaction term. All p-values were two-tailed (α=0.05). All analyses were performed using STATA release 11.2 (College Station, TX).

1.3 Results

1.3.1 Description of participant characteristics

Demographics, co-morbid diseases, and laboratory characteristics differed between participants in the highest versus lowest physical activity groups (Table 1.1). The highest physical activity group was characterized by a greater proportion of Caucasian participants, greater education, lower body mass indices, faster get up and go speeds, and a lower prevalence of coronary artery disease, peripheral vascular disease, and diabetes. Baseline estimated GFR did not materially differ by physical activity group. Among the participants who reported engaging in *any* physical activity, 71 (45%) reported engaging in walking only and 55 (35%) reported engaging in a combination of walking and other leisure-time activities. Among the 214 study participants, 94 had two eGFR measurements, 96 had three eGFR measurements, and 24 had four eGFR measurements, resulting in a median follow-up time of 3 years.

1.3.2 Association of physical activity with kidney function decline

The mean relative annual change in $eGFR_{cystatin\ C}$ was -7.1% per year (interquartile range -16.8%, +4.9% per year). Participants who self-reported engaging in the greatest physical activity levels had the lowest annualized rate of kidney function decline -5.0% per year among participants in the highest physical activity group *versus* -10.6% per year among inactive participants. After adjustment, greater physical activity levels were associated with statistically slower rates of kidney function decline. Each

one-category increase in physical activity group was associated with a 1.9% per year slower decline in kidney function (p=0.031). (Table 1.2)

To evaluate whether observed associations of physical activity with kidney function decline might reflect poor health status among individuals with the lowest physical activity scores, we repeated our analyses after removing subjects with prevalent coronary artery disease and diabetes (separately), and those with an SPPB score below 8. The magnitude of the association between physical activity and kidney function decline was similar in the restricted subgroups of 115 participants without prevalent coronary artery disease, 98 participants free of diabetes, and 158 with an SPPB score greater than or equal to 8 at baseline (Table 1.3). Associations of physical activity category with kidney function decline were also similar comparing subsets of the participants with a baseline eGFR of 15-30, 30-45, or 45-60 mL/min per 1.73 m^2 (p-for-interaction=0.65). No statistical interaction of physical activity and kidney function decline was observed for sex (p=0.27), race (p=0.54) or BMI (p=0.73).

Analyses defining walking minutes per week as the exposure of interest produced similar effect estimates to those from our primary analyses, but the linearity of the duration-risk association was less clear (Supplement Table 1.1). Participants who had longer durations of walking time had slower annualized rates of kidney function decline – 5.3% per year among participants who self-reported walking ≥ 150 minutes per week *versus* – 8.6% per year among participants who reported zero minutes of walking for exercise per week (p-for-trend: 0.13). Lastly, estimation of GFR using creatinine and the CKD-EPI equation did not materially alter the observed associations (Supplement Table 1.2).

1.3.3 Association of physical activity with incident end-stage renal disease

The incidence rate of ESRD was higher in participants reporting no physical activity in the previous month than in those reporting any. However, in fully adjusted models, physical activity was not

associated with initiation of dialysis or renal transplantation in participants who reported any physical activity, relative to those who reported none (Table 1.4), (HR for any vs. no physical activity: 1.15, 95%CI: 0.50-2.66).

1.4 Discussion

In this prospective study of stage III-IV CKD patients, greater self-reported physical activity was associated with slower rates of kidney function decline. Associations were quantitatively similar for total leisure-time physical activity and walking alone, persisted after adjustment for potential confounding factors, and were robust to the exclusion of the most disabled subjects. These findings are consistent with our previous work in a community-based cohort of healthy older adults, in which greater physical activity levels were associated with a lower risk of rapid kidney function decline, defined as a loss of more than 3.0 ml/min per 1.73 m^2 per year in estimated GFR.[24] Our results extend these observations from the general population to individuals who significant kidney function impairment at baseline.

In our study, there was no suggestion that greater physical activity levels were associated with a lower risk of incident end-stage renal disease. Our findings were based on only 33 ESRD treatment initiations and require replication because the association between physical activity levels and progression to ESRD among CKD patients has not been previously reported in the published literature. Nonetheless, associations of greater physical activity levels with lower ESRD rates would be consistent with our primary findings for kidney disease progression.

Several small interventional studies have investigated the effects of prescribed exercise regimens on kidney function among patients who have established CKD, with conflicting results. The largest of these studies randomly assigned 30 non-diabetic CKD patients to either daily bicycling or maintenance of

usual lifestyle.[45] After 20 months median intervention time and follow-up, despite a significant increase in the VO_{2peak} in the exercise arm, there was no change in the rate of loss of GFR (monthly change, -0.27 (95% CI: -1.31, 0.57) ml/min/1.73m^2 in the exercise group vs. -0.28 (95% CI: -0.93, 0.18) ml/min1.73m^2 in the control group). Similarly, a pilot study that assigned seven obese, diabetic CKD subjects to 18 months of aerobic exercise training and four similar subjects to no intervention, found no subsequent changes in eGFR after the interventional period. A recent study in 21 individuals with stage II-IV CKD (eGFR 15 – 90 ml/min/1.73m^2) randomized participants to either 48 weeks of aerobic exercise training (three times per week, 55 minutes per session) and dietary counseling or standard of care. While the intervention led to a significant improvement in maximal oxygen consumption, heart rate and lipid profile, the linear slope of eGFR was not different between treatment groups.[46] However, two studies did report significant effects of exercise interventions on kidney function. The first assigned 17 adults with CKD to low-intensity aerobic exercise and matched them to 9 control participants who remained sedentary.[47] Participants in the exercise group had cystatin-C levels (in mg/l) that diminished significantly whereas no such change was noted in the control group. The second assigned ten participants with both CKD and cardiovascular disease to a combination of in-hospital aerobic exercise and at-home daily walking for 12 weeks and compared the change in eGFR levels to that in nine control participants.[48] The exercise intervention significantly improved serum creatinine-based eGFR levels, in ml/min/1.73m^2, (from 47.0 ± 13.7 at baseline to 55.2 ± 16.9 at 12 weeks) but no such difference was detected in the control group (from 47.9 ± 9.5 at baseline to 44.6 ± 8.2 at 12 weeks). While intriguing, previous interventional studies lack sufficient power to determine effects on kidney function. Observational studies in this area, though limited by potential bias and confounding, have demonstrated fairly consistent protective associations of physical activity on kidney function decline, using larger sample sizes, longer duration of follow-up, and study populations that are more representative of general outpatient CKD patients.

Diabetes, obesity, hypertension and kidney dysfunction lead to activation of the renin-angiotensin system, oxidative stress, insulin resistance, endothelial dysfunction, elevated low-grade inflammation, and increased circulating cytokines.[49] These metabolic disturbances are highly prevalent both in CKD patients and physically inactive individuals, and augment the risks of micro and macro-vascular disease.[50-56] Aerobic exercise may attenuate or reverse these adverse metabolic processes, which can impact the kidney, in terms of inflammation, fibrosis, and progression, regardless of the primary initiating cause of CKD.

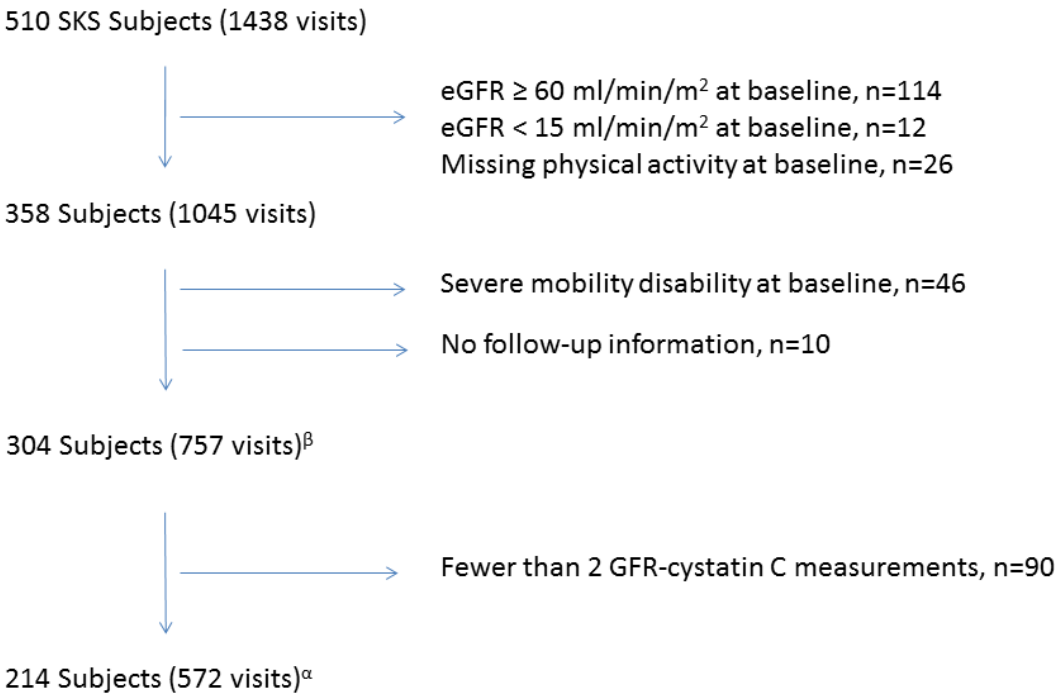
The most important limitation of our study is the potential for confounding, because other healthy characteristics are linked with a greater desire and capacity to exercise. In order to address this concern, we first excluded individuals who were unable to ambulate and used a wheelchair, to limit our study population to persons who had the capacity to exercise. We then adjusted for a group of characteristics that are linked with kidney function decline. Finally, we found similar associations of exercise with kidney function decline among subgroups of participants who were free of coronary artery disease, diabetes and scored well on the SPPB at baseline. Complete separation of physical activity from related characteristics that may influence kidney function decline requires randomized clinical trials, which are an appropriate next scientific step. Furthermore, the preponderance of male participants in our study, stemming from the inclusion of a Veterans' Administration study site, may limit the applicability of our findings to a more typical CKD patient population. Based on this study and other published work, we believe future clinical trials should be broadly inclusive, target basic physical activities, such as regular walking, and include ample follow-up time to ascertain relevant changes in kidney function.

A second limitation is the use of self-report to measure physical activity, potentially leading to misclassification. Some subjects may have underreported activity while others may have over-reported

their level of activity. However, the FWH instrument used in our study has been shown to be a reliable and valid measure of physical activity in CKD patients.[31] Moreover, participants were not aware of their future kidney function decline status at the time they completed their baseline physical activity assessment, suggesting that potential misclassification was likely independent of the outcome. Therefore, misclassification of physical activity in this study is likely to have biased our results toward the null.

In conclusion, our prospective data demonstrate an association of greater physical activity with slower rates of kidney function decline among patients who have established CKD. Associations were independent of measured confounders, persisted across different types of physical activity, strengthened with greater physical activity levels, and are supported by biologic evidence demonstrating effects of exercise on metabolic pathways that directly impact kidney function. Physical activity is emerging as one of the few modifiable risk factors for important sequelae of CKD, and a potentially viable interventional strategy toward reducing the morbidity, mortality and health costs for one of the most expensive chronic diseases in the Western World. Targeted clinical trials remain a necessary next step forward for testing this promising intervention.

Figure 1.1. Participant Flow



αParticipants included in the analyses presented in Chapter 1
βParticipants included in the analyses presented in Chapter 2

Table 1.1. Baseline characteristics of Seattle Kidney Study participants, according to physical activity category (n=214)

	Physical Activity Category			
	None	Low	Moderate	High
	0 min/week	1 - 60 min/week	60-150 min/week	> 150 min/week
N	56	54	46	58
Age at baseline (years)	63.8 (±11.4)	60.4 (±13.2)	60.6 (±11.9)	64.3 (±12.3)
Male gender	48 (85.7%)	40 (74.1%)	39 (84.8%)	52 (89.7%)
White Race	35 (62.5%)	40 (74.1%)	34 (73.9%)	40 (69%)
Study site: Harborview Medical Center	19 (33.9%)	26 (48.2%)	20 (43.5%)	28 (48.3%)
Study site: Veterans' Affairs Medical Center	37 (66.1%)	28 (51.9%)	26 (56.5%)	30 (51.7%)
Current smoking	10 (17.9%)	6 (11.1%)	9 (19.6%)	6 (10.3%)
Any alcohol use	23 (41.1%)	14 (26.4%)	11 (23.9%)	21 (36.2%)
College education or higher	6 (10.7%)	14 (25.9%)	8 (17.4%)	17 (29.3%)
Body mass index (kg/m^2)	32.9 (±7.1)	34.0 (±8.8)	30.2 (±7.2)	29.9 (±6.3)
Systolic blood pressure (mmHg)	140.2 (±22.6)	127.4 (±21.3)	128.7 (±20.6)	134.3 (±20.2)
Physical function				
6 Minute-Walk (m)	354.3 (±106.2)	389.2 (±78.6)	399.2 (±84.2)	385.3 (±97.6)
Get Up and Go (s)	13.0 (±3.7)	11.4 (±5)	11.2 (±4.1)	10.7 (±3.8)
Short Physical Performance Battery	7.6 (±3.6)	8.7 (±3.0)	9.8 (±2.4)	9.6 (±3.7)
Number of IADL[†] tasks requiring assistance	1.07 (±1.4)	0.7 (±1.4)	0.3 (±0.8)	0.4 (±0.9)
Assistive device use				
Cane	33 (19.3%)	23 (19.3%)	15 (13.4%)	15 (9.9%)

	Physical Activity Category			
	None	Low	Moderate	High
Walker	15 (8.8%)	6 (5.0%)	5 (4.5%)	8 (5.3%)
Other (e.g. crutches, etc.)	20 (11.7%)	10 (8.4%)	6 (5.4%)	12 (7.9%)
Laboratory Measurements				
C-reactive protein (mg/L)	7.1 (±8.9)	6.6 (±9)	4.7 (±8.4)	5.1 (±7.4)
Glucose (mg/dL)	114.0 (±44.5)	113.1 (±30.9)	124.9 (±57.8)	116.8 (±47)
High-density lipoprotein (mg/dL)	37.5 (±12.5)	40.9 (±19.8)	37.2 (±11.7)	39.6 (±12.8)
Low-density lipoprotein (mg/dL)	97.8 (±29.7)	95.9 (±38.2)	102.9 (±55.2)	99.3 (±36.6)
Triglycerides (mg/dL)	173.5 (±108.3)	174.9 (±113.8)	186.4 (±141.4)	166.9 (±167.8)
Kidney Function				
eGFR- Cystatin C (ml/min per 1.73 m^2)	35.7 (±12.1)	40.5 (±13.2)	39.7 (±12)	41.3 (±10.5)
eGFR- CKD EPI (ml/min per 1.73 m^2)	33.8 (±16.3)	38.5 (±16.1)	38.3 (±20)	36.6 (±12.8)
Albumin to creatinine ratio (mg/g)	808.4 (±1291.7)	636.5 (±1444.1)	925.4 (±1452.4)	627.0 (±1049.5)
Medications				
Ace Inhibitor	27 (48.2%)	27 (50%)	23 (50%)	34 (58.6%)
ARBS	22 (39.3%)	23 (42.6%)	16 (34.8%)	23 (39.7%)
Statin	35 (62.5%)	35 (64.8%)	30 (65.2%)	32 (55.2%)
Prevalent Disease				
Coronary artery disease$^{\alpha}$	32 (57.1%)	27 (50%)	20 (43.5%)	20 (34.5%)
Peripheral vascular disease$^{\beta}$	6 (10.7%)	4 (7.4%)	3 (6.5%)	4 (6.9%)
Cerebrovascular disease$^{\gamma}$	10 (17.9%)	10 (18.5%)	8 (17.4%)	12 (20.7%)

	Physical Activity Category			
	None	Low	Moderate	High
Diabetes[δ]	33 (58.9%)	33 (61.1%)	25 (54.3%)	25 (43.1%)
Hypertension[ε]	54 (96.4%)	54 (100%)	46 (100%)	54 (93.1%)

Data are crude means (±SD) for continuous variables and number (proportion) for categorical variables

[α]Prevalent coronary artery disease was defined as self-reported previous myocardial infarction, cardiac arrest, coronary artery bypass graft or percutaneous coronary intervention.

[β]Prevalent peripheral vascular disease was defined as self-reported claudication, peripheral vascular surgery, or lower extremity amputation.

[γ]Prevalent cerebrovascular disease was defined as self-reported stroke or carotid endarterectomy.

[δ] Diabetes was defined by any of the following: use of an oral hypoglycemic medication or insulin, fasting blood sugar ≥126mg/dL, non-fasting blood sugar ≥200mg/dL, or hemoglobin A1c ≥6.5%

[ε]Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medications

[†]Instrumental activities of daily living, include the ability to use the telephone, to go grocery shopping, to prepare one's own meals, to perform light housekeeping tasks, to do laundry, to travel independently on public transportation, by car or by taxi, to manage medications, and to handle finances.

Table 1.2 Association of Physical Activity and Annualized Relative Change in eGFR-cystatin C

Leisure-time Physical Activity Level	Percent Annual Decline in eGFR-cystatin C (95% CI)			
	Unadjusted	Model 1	Model 2	Model 3
None	10.7 (7.7, 13.7)	10.9 (7.8, 14.0)	10.4 (7.3, 13.4)	8.9 (5.5,12.1)
1-60 minutes per week	6.4 (2.2, 10.4)	6.6 (2.2, 10.7)	6.8 (2.7, 10.8)	7.0 (2.7,11.1)
60-150 minutes per week	5.7 (1.3, 10.0)	5.9 (1.3, 10.3)	5.0 (0.6, 9.2)	4.9 (0.4,9.2)
≥150 minutes per week	4.9 (1.1, 8.5)	5.1 (1.2, 8.8)	4.4 (0.7,7.9)	3.7 (-0.2,7.5)
p-for-trend	0.014	0.014	0.007	0.031

Abbreviations: CI, confidence interval, eGFR, estimated glomerular filtration rate
Model 1: age, race, gender, study site
Model 2: Model 1 + education, body mass index, diabetes, smoking status, alcohol, prevalent coronary artery disease
Model 3: Model 2 + hemoglobin a1c, systolic blood pressure, ACE-inhibitor use, ARB use, statin use, C-reactive protein
Note: Declines in relative kidney function are presented as a positive number, and increases are presented as negative numbers.

Table 1.3 Association of physical activity with decline in kidney function in subgroups of participants

Leisure-time Physical Activity Level	Adjusted* Percent Annual Decline in eGFR-cystatin C								
	Participants with no prevalent coronary artery disease[α] at baseline (n=115)			Participants with no prevalent diabetes at baseline[β] (n=98)			Participants with SPPB≥ 8[γ] at baseline (n=185)		
	n	% change per year	95 % CI[α]	n	% change per year	95 % CI	n	% change per year	95 % CI
None	22	-5.8	(-8.7, -2.8)	22	-13.0	(-18.4, -7.2)	41	-7.6	(-11.8, -3.3)
1-60 minutes per week	29	-1.9	(-5.3, +1.5)	21	-3.3	(-11.1, +5.2)	49	-7.5	(-12.2, -2.6)
60-150 minutes per week	26	-2.8	(-6.3, +0.7)	22	-5.3	(-12.3, +2.3)	43	-5.3	(-10.0, -0.4)
≥150 minutes per week	38	-2.7	(+5.3, 0.0)	33	-3.0	(-8.7, +3.2)	52	-3.8	(-8.0, +0.6)
p-for-trend		0.147			0.022			0.167	

Abbreviations: CI, confidence interval, SPPB, Short Physical Performance Battery, eGFR, estimated glomerular filtration rate

*Adjusted for age, race, gender, site, smoking status, alcohol use, ACE-inhibitor use, ARB use, statin use

[α] Prevalent coronary artery disease was defined as self-reported previous myocardial infarction, cardiac arrest, coronary artery bypass graft or percutaneous coronary intervention.

[β] Prevalent diabetes was defined by any of the following: use of an oral hypoglycemic medication or insulin, fasting blood sugar ≥126mg/dL, non-fasting blood sugar ≥200mg/dL, or hemoglobin A1c ≥6.5%.

[γ] A score below 8 is associated with disability in lower extremity functioning.[39]

Table 1.4 Association of physical activity duration with incident end-stage renal disease

Physical Activity Level	n (# events)	Incidence rate (per 100 p-y)	Model 1	Model 2	Model 3
			HR (95% CI)	HR (95% CI)	HR (95% CI)
None	54 (5)	6.76	1.0 (ref)	1.0 (ref)	1.0 (ref)
Any	160 (28)	4.53	0.63 (0.29, 1.28)	0.63 (0.27, 1.47)	1.15 (0.50, 2.66)
Among those who reported any physical activity, per additional 30 min/week			0.94 (0.86, 1.03)	0.94 (0.87, 1.02)	0.99 (0.84, 1.16)
p-value for continuous association			0.18	0.14	0.87

Model 1: age, race, gender, site
Model 2: Model 1 + education, body mass index, diabetes, smoking status, alcohol, prevalent coronary artery disease
Model 3: Model 2 + hemoglobin a1c, systolic blood pressure, ACE-inhibitor use, ARB use, statin use, C-reactive protein, baseline GFR-cystatin C

Chapter 2 Physical Activity, Cardiovascular Outcomes and All-Cause Mortality in Persons with Chronic Kidney Disease

2.1 Background

Chronic kidney disease (CKD) is associated with increased risks of developing cardiovascular events and a considerably shortened lifespan, independent of major chronic diseases including diabetes and hypertension, and other traditional cardiovascular risk factors either alone or in combination.[57-60] Even mild kidney dysfunction has been associated with cardiovascular disease (CVD) and mortality in community-based, prospective studies.[61-64] The majority of individuals with CKD die of CVD before they fully progress to end-stage renal disease (ESRD), which requires dialysis or transplantation for survival.[65] Although the prevention and delay of ESRD remains an important goal in CKD patients, it is also crucial to focus on reducing the disproportionate CVD burden in this population.

Observational studies from the general population consistently report associations between physical activity and lower risks of myocardial infarction, stroke, and ultimately death from CVD.[9,66,67] In randomized controlled trials among individuals without known kidney disease, moderate physical activity levels lead to improvements in fasting and postprandial glucose-insulin homeostasis, weight loss and/or maintenance, increased in HDL cholesterol, reductions in LDL cholesterol and triglycerides, blood pressure, and possibly serum inflammatory markers, and improvements in endothelial function.[68-71] Not surprisingly, a physically inactive lifestyle contributes to obesity, diabetes, hypertension, and dynapenia (the age-related loss of muscle strength), each of which are independently associated with CVD risk. The substantial overlap of metabolic abnormalities common to physically inactive and kidney disease states

suggests that promoting physical activity might be particularly important in the setting of CKD; however, this hypothesis had not been adequately explored.

The primary aim of this study was to evaluate the prospective associations of leisure-time physical activity with cardiovascular events and mortality in a clinic-based study of 304 CKD patients not undergoing dialysis. We hypothesized that greater physical activity levelswould be associated with lower rates of major cardiovascular events and death among individuals who have established CKD.

2.2 Methods

2.2.1 Study population

We studied 314 participants from the Seattle Kidney Study (see section 1.2.1), restricting our study population to those with moderate-to-severe (stage III-IV) CKD and who had the capacity to exercise. We excluded 10 participants who were missing follow-up information, leaving a total analytic sample of 304 subjects (Figure 1.1).

2.2.2 Measurement of physical activity

Physical activity was measured using the Four Week Physical Activity History Questionnaire (FWH), administered at baseline to estimate each participant's self-reported leisure-time physical activity level (see section 1.2.2). Both the estimation of minutes per week of leisure-time activity and the imputation method used to characterize the primary exposure were performed in the same way as described in Chapter 1. In order to evaluate both the presence and duration of physical activity as unique exposures of interest, we examined whether the risk of events differed (1) between participants participating in any

versus no physical activity and, (2) among participants reporting any activity, for each additional 30 minutes of self-reported physical activity duration per week.

2.2.3 Outcome Ascertainment

Study coordinators screened for major events including hospitalizations, cardiovascular procedures, and dialysis during annual study examinations and/or interim (at 6 month intervals) telephone interviews. Deaths were identified from proxies during interim surveillance calls, during scheduling calls for annual visits, by screening medical records when available, and by linkage with the social security death index. Self-reported hospitalizations and procedures were investigated in detail by study coordinators by accessing medical records to verify mention of the event on discharge summaries or outpatient procedure reports. For hospitalizations and procedures, coordinators transcribed the hospital discharge or procedure summary and accessed related laboratory reports, imaging studies, and consultation reports. Major study end points, including symptomatic heart failure (HF), myocardial infarction (MI), resuscitated cardiac arrest, coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), and stroke and carotid endarterectomy, were determined by two independent physicians who reviewed the medical records (interrater agreement kappa =0.68). Confirmation of symptomatic HF required a heart failure diagnosis by a treating physician and either HF symptoms (shortness of breath, fatigue, orthopnea, and paroxysmal nocturnal dyspnea) and signs (edema, rales, tachycardia, gallop rhythm, and displaced apical impulse) or supportive clinical findings on echocardiography, contrast ventriculography, or chest radiography.

Study outcomes included (1) all -cause mortality, (2) symptomatic, hospitalized heart failure, and (3) a combined cardiovascular endpoint that included acute MI, cardiac arrest, coronary revascularization procedure (CABG or PCI), acute stroke, and carotid endarterectomy. This composite outcome was chosen to reflect endpoints that are clinically relevant to CKD patients, to reduce the potential for

competing risks in outcome ascertainment, and to maintain consistency with endpoints from large-scale cardiovascular epidemiologic studies.[72]

2.2.4 Measurement of covariates

The measurement of clinical, physical functioning, and lifestyle and anthropometric characteristics was previously described in Section 1.2.4. Prevalent medical conditions were ascertained based on participant responses to questionnaires, and were also inferred from medication use, laboratory findings, and hospitalizations that occurred after initial SKS enrollment but prior to baseline. We defined a combined prevalent cardiovascular disease status as any pre-baseline evidence of myocardial infarction, cardiac arrest, CABG, PCI, acute stroke or coronary endarterectomy. Prevalent heart failure was defined as either a positive response to the question, "has a doctor ever told you that you had heart failure?", the use of digoxin, or at least two out of the following three heart failure symptoms: dyspnea after walking less than one block, paroxysmal nocturnal dyspnea or orthopnea. Prevalent stroke, myocardial infarction, and cardiac arrest were based on a self-reported physician diagnosis. To ensure the veracity of our self-reported measure of prevalent medical conditions, we compared participant responses for the prevalent conditions to a criterion standard of diagnosis and procedure codes in electronic medical records among a subsample of 164 Veterans' Affairs Medical Center (VAMC) study participants who had at least two primary care visits and a minimum of 7 years of medical contact with the VAMC. Sensitivity and specificity for MI were 83% and 80%, for stroke were 77% and 94%, and for heart failure were 61% and 93%, respectively (Supplementary Table 4), comparable measurement properties to those from large general population cohort studies.[73]

2.2.5 Statistical Analyses

We tabulated participant characteristics for all 304 participants with respect to categories of baseline physical activity, as done previously in Chapter 1. For each outcome, participants were considered at risk from the date of their baseline exam until the first post-baseline occurrence of the outcome, death, date their data were censored due to loss to follow-up (n=18), or end of data collection, January 1st, 2012.

We calculated unadjusted incidence rates as the number of events divided by person-years at risk and used Cox proportional hazards regression to estimate the relative hazard of each of the events after adjustment for covariates selected *a priori* based on suspicion that they may confound the association between physical activity and our outcomes of interest. In order to evaluate groups of potential confounding factors, we constructing nested multivariable models. The first, basic model included age, sex, study site and race/ethnicity, and the baseline hazard was allowed to vary by prevalent cardiovascular disease status. The second model added current smoking status, current alcohol use, education, BMI, diabetes status and baseline eGFR. The third model added systolic blood pressure and medications, including use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and/or statins.

Additionally, prevalent cases at baseline were specifically excluded for each outcome. Specifically, we excluded 81 participants with prevalent heart failure at baseline for the heart failure analyses and 115 participants with a history of any of the conditions making up the composite cardiovascular events for the combined cardiovascular outcome analyses.

We investigated potential nonlinear physical activity-cardiovascular risk relationships by modeling physical activity minutes per week with each study outcome, including all active and non-active participants, using adjusted penalized spline models with minutes per week of physical activity as the flexibly modeled exposure variable and graphically displayed the spline at the mean value of adjustment covariates.[74] The penalized spline was computed using the default algorithm of the survival package in R

2.12.1 (R Foundation for Statistical Computing, Vienna, Austria), which uses evenly spaced knots, cubic polynomials and a roughness penalty to restrict the overall flexibility of the fitted curve.

In order to evaluate the influence of subclinical disease on the observed results, analyses were repeated after early events (i.e., events within the first year of follow-up) were excluded. Because walking was the most commonly reported activity (Figure 2.1), that it is accessible to individuals with a wide range of physical abilities and disabilities, and requires no specialized equipment, or space, we also examined the associations of walking time alone with incident events. For those analyses, regression models were additionally adjusted for time spent in other leisure-time activities.

Secondarily, in order to explore potential differences in the associations of physical activity with events across subgroups of interest, we stratified event rates and hazard ratios by event type, by stage of CKD, by prevalent diabetes status and among those who scored above or below 8 on the SPPB, a cut-point below which disability in lower extremity functioning is most pronounced.[39]

We used the likelihood ratio test to evaluate the statistical significance of interactions. All p-values were two-tailed (α=0.05). Analyses were performed using Stata release 11.2 (College Station, TX) unless otherwise stated earlier.

2.3 Results

2.3.1 Baseline characteristics

The study population was characterized by being 82% male, with a mean age of 62 years, and a mean $eGFR_{cystatin\ C}$ of 37.6 ml/min/1.73 m^2 (interquartile range: 28.8 – 49.2 ml/min/1.73 m^2). Participants with higher self-reported physical activity levels were more likely to be Caucasian, less likely

to be current smokers, less likely to have comorbid cardiovascular conditions, and were characterized by lower BMI, better physical functioning and less frequent use of a cane, and higher eGFR (Table 2.1).

2.3.2 Event rates

During a median follow-up of 3 years (interquartile range 2 – 3.75 years), there were 54 deaths, 48 instances of hospitalized symptomatic heart failure, and 28 occurrences of the composite cardiovascular endpoint outcome, providing incidence rates of 60.2, 58.3, and 32.7 events per 1000 person-years, respectively (Table 2.2). For all examined events, unadjusted incidence rates were highest in participants reporting zero minutes of physical activity per week. Event rates were highest in participants with the lowest eGFR and in those with prevalent coronary artery disease at baseline (Table 2.3).

2.3.3 Adjusted association of physical activity with mortality

There was no association of physical activity with all-cause mortality when physical activity was analyzed as none *versus* any or continuously as an amount (Table 2.4a). After full adjustment, the hazard ratio for all-cause mortality with every additional 30 minutes of self-reported physical activity, among participants who reported any activity, was 0.99 (95% CI: 0.92, 1.06; p=0.73). The spline models show graphically that the association between physical activity minutes per week and all-cause mortality is flat below approximately 120 minutes per week, after which additional physical activity duration appears to be associated with a lower hazard of death (p-for-nonlinearity = 0.75) (Figure 2.2.a).

2.3.4 Adjusted association of physical activity with heart failure

After full adjustment, both the presence and duration of physical activity were associated with a decreased risk of heart failure. Participants who self-reported any physical activity in the previous month had an estimated 57% lower risk of heart failure (95% CI: 19% to 78% lower, p=0.009), compared to those who reported being inactive. When examined continuously, among self-reportedly active

participants, every additional 30 minutes of physical activity per week was associated with an estimated 20% lower risk of incident heart failure (95% CI: 6% to 31% lower, p=0.007) (Table 2.4b). The reduced risk of heart failure associated with physical activity was present even among patients with no reported history of heart failure at baseline (HR=0.46), though this estimate was statistically imprecise (95% CI: 0.16 – 1.36) (Table 2.5). In the regression spline model, the test for non-linearity in the relationship between minutes per week of physical activity and risk of incident heart failure was negative (p=0.62). Upon visual inspection, the risk of CHF appeared to drop steadily with increasing physical activity duration until approximately 120 minutes per week, at which point the risk of heart failure rose with increasing duration of physical activity, albeit with wide confidence intervals indicating a lack of precision for these estimates (Figure 2.2.b).

2.3.5 Adjusted association of physical activity with the composite cardiovascular outcome

Participants who reported any physical activity were substantially less likely to develop the composite end-point than those who reported no physical activity (HR: 0.16, 95%CI: 0.07, 0.38, p<0.001). However, among participants reporting any physical activity, additional time spent in these activities was not associated with differing risks of the composite endpoint (HR: 1.02 per additional 30 min/week, 95% CI: 0.92, 1.16) (Table 2.4c). After exclusion of participants with prevalent cardiovascular conditions at baseline, the association between the presence of physical activity and the risk of the combined cardiovascular event remained strong (HR: 0.12, 95%CI: 0.02, 0.64) (Table 2.5). Further exploration of the association of physical activity duration with the risk of the combined outcome revealed a S-shaped curve with a nadir near 60 minutes per week and a subsequent decline in risk beyond 120 minutes per week (Figure 2.2.c)

2.3.6 Associations among subgroups

Though limited in statistical power due to the relatively low number of events, stratified analyses suggested that the magnitude of the adjusted associations of any versus no physical activity and all-cause mortality was stronger in participants with the highest physical functioning at baseline (p-for interaction = 0.04). Overall, no differences in associations of physical activity and outcomes, between individuals with and without prevalent disease at baseline were noted (Supplement Table 5).

2.3.7 Secondary analyses

Because the inability to engage in physical activity may reflect subclinical cardiovascular disease, analyses were conducted after exclusion of 35 events that occurred within the first year of follow-up. After this exclusion, all examined associations between physical activity duration and events remained materially unchanged (Supplement Table 6).

Risk reductions for both the presence and duration of walking time, after adjustment for time spent in other leisure-time activities, were similar to those overall physical activity time (Supplement Table 7).

2.4 Discussion

We examined the relation between physical activity levels and all-cause mortality and cardiovascular events in a cohort of ambulatory adults with CKD not requiring dialysis. Our investigation found no association between either the presence or the duration of physical activity with all-cause mortality, over a median of 3 years of follow-up. On the other hand, we found associations of any physical activity with hospitalized heart failure and with a composite cardiovascular outcome after adjustment for established cardiovascular risk factors. Taken together, these findings suggest a possible role for even small amounts of physical activity for prevention of major cardiovascular events in the setting of mild-moderate kidney disease.

Our results are consistent with a study conducted in 811 predominantly non-diabetic stage III-IV CKD patients enrolled in the Modification of Diet in Renal Disease trial, which found no association of physical activity with all-cause mortality.[75] Conversely, a prospective study of 907 adult participants with CKD of any stage (including dialysis-requiring stage V) in the National Health and Nutrition Examination Survey III (NHANES) followed for death over 7 years, found that persons who reported having met the AHA physical activity guidelines had a 56% lower risk of all-cause mortality.[76] Our results are similar in direction and magnitude to those from a large prospective cohort of over 50,000 Finnish adults without kidney disease; multivariable-adjusted hazard ratios of heart failure with moderate and high leisure-time activity of 0.83, and 0.65 ($p < 0.001$, for trend) for men and 0.84, and 0.75 ($p < 0.001$, for trend) for women, respectively, relative to those who reported low or no physical activity.[77]

Although the association of physical activity with HF was robust, the association between physical activity and the composite cardiovascular end-point was inconsistent, depending on how physical activity was modeled. Longer durations of physical activity, examined continuously, were not associated with the risk of a combined end-point, yet when physical activity was examined as any versus none, an inverse association was noted. These results could potentially be explained by a threshold effect noted in the S-shaped relationship between exposure and outcome, such that physical activity offers some protection against the composite endpoint, but that this protection wanes as the amount of physical activity exceeds a given threshold. However, these analyses were plagued by a lack of statistical power, with resultant wide confidence intervals. Further exploration of this duration-response relationship between physical activity and a composite CVD endpoint with a larger sample is warranted.

Diabetes, obesity, hypertension, and the presence of kidney dysfunction *per se* lead to activation of the renin-angiotensin system, oxidative stress, endothelial dysfunction, elevated asymmetric dimethyl arginine, low-grade inflammation with increased circulating cytokines, and dyslipidemia.[49] These

metabolic disturbances are highly prevalent both in CKD patients[51-54,78] and in physically inactive individuals[55,56] and augment the risks of micro and macro-vascular disease. In particular, oxidative stress is highly prevalent in CKD patients, perhaps due to both the high prevalence of diabetes mellitus in the CKD population and to the retention of solutes that are excreted with normal kidney function.[79-82]

The effects of physical activity on oxidation pathways in the setting of renal dysfunction have been investigated in animal models, in which 5/6 nephrectomized rats (experimental model of CKD) were randomized to either regular cages or cages equipped with running wheels. Sedentary rats exhibited oxidative stress and upregulation of the reactive oxygen species-generating enzyme, NAD(P)H oxidase in the left ventricle, while voluntary exercise lowered NAD(P)H oxidase.[83]

The most important limitation of our study is the potential for residual confounding, because a wide array of lifestyle and health characteristics are linked with a greater desire and capacity to exercise and poorer health may lead to a reduction in physical activity. This reduction in activity due to subclinical or clinical illness may lead to a non-conservative bias. The influence of measured confounders on the inverse relation between physical activity and HF was modest in this study, suggesting that this association is not likely to be explained by underlying illness among the least physically active subjects. Among individuals with CKD, measurement of physical activity is probably also a measure of disability or reduced function.[31] Since reduced function is associated with increased risk of mortality and CVD in the general population and in the CKD setting,[84,85] the elevated risk of heart failure among the physically inactive may be interpreted as the effect of reduced ability rather than of a physically inactive lifestyle. However, we observed no notable change in risk estimates after exclusion of subjects with prevalent chronic diseases. Furthermore, additional elimination of undiagnosed disabling disease by exclusion of early endpoints had only a negligible effect on risk estimates in our study.

Kidney dysfunction itself and the nearly ubiquitous nature of subclinical or clinical cardiovascular disease in this study population at baseline, in combination with measuring physical activity at a single time-point, impede us from fully elucidating the interplay through time of the progression of CKD, changes in physical activity and progression toward subclinical and clinical outcomes. CKD is a silent and often unrecognized disease, such that identifying patients early in the pathogenesis of disease, when we would expect therapeutic interventions to be most successful, is difficult. While we attempted to alleviate this concern by adjusting for measured subclinical disease and baseline kidney function, and stratified analyses by prevalent cardiovascular status, a fully comprehensive view of the time course of kidney and CVD progression and changes in physical activity over time would be ideal.

Although our data require confirmation through additional investigations, they suggest that physical activity may help to prevent or postpone consequences of left ventricular hypertrophy and ischemic heart disease in this high-risk population.

Our results add to a growing body of evidence suggesting that lifestyle approaches can yield substantial benefits for patients with CKD.[75,76,83] Nonetheless, given the limitations of nonrandomized studies in addressing these questions, randomized trials will be needed to better quantify the safety, feasibility and effectiveness of physical activity in patients with CKD.

Table 2.1 Baseline characteristics of Seattle Kidney Study participants, according to leisure-time physical activity category (n=304)

	Physical Activity Category			
	None	Low	Moderate	High
	0 min/week	1 - 60 min/week	60-150 min/week	> 150 min/week
N	84	84	62	84
Age at baseline (years)	63.4 (±12.4)	59.8 (±13.5)	60.9 (±11.7)	63.9 (±13.4)
Male gender	71 (84.5%)	60 (71.4%)	51 (82.3%)	77 (91.7%)
White race	54 (64.3%)	59 (70.2%)	45 (72.6%)	62 (73.8%)
Current smoking	19 (22.6%)	15 (17.9%)	14 (22.6%)	12 (14.3%)
Any alcohol use	32 (38.1%)	25 (30.5%)	15 (24.2%)	29 (34.5%)
College education or higher	10 (17.4%)	19 (33.3%)	8 (14.0%)	20 (35.1%)
Body mass index (kg/m^2)	32.6 (±7)	32.7 (±8.7)	30.2 (±6.9)	29.8 (±6.3)
Systolic blood pressure (mmHg)	138.3 (±22.7)	130.2 (±24.4)	129.1 (±20.1)	133.9 (±20.8)
Physical function				
6 Minute-Walk (m)	361.4 (±94.9)	384.5 (±93.1)	389.5 (±86.7)	401.3 (±96.1)
Get Up and Go (s)	12.3 (±3.6)	11.6 (±5)	11.7 (±4.3)	10.7 (±3.7)
Assistive device use				
Cane	20 (25.3%)	12 (14.5%)	8 (12.7%)	11 (13.9%)
Walker	5 (6.3%)	7 (8.4%)	3 (4.8%)	3 (3.8%)
Other (e.g. crutches, etc.)	6 (7.6%)	5 (6.0%)	5 (6.0%)	7 (8.9%)
Laboratory measurements				
Creatinine (mg/dL)	2.4 (±1.3)	2.3 (±1.5)	2.3 (±1.1)	2.1 (±0.8)
C-reactive protein (mg/L),	3.8 (1.6, 8.3)	2.9 (0.9, 6.4)	1.9 (0.9, 5.7)	2.5 (0.8, 6.3)

	Physical Activity Category			
	None	Low	Moderate	High
median (interquartile range)				
Cystatin C (mg/L)	2.0 (±0.7)	2.0 (±0.7)	2.0 (±0.7)	1.8 (±0.5)
Glucose (mg/dL)	120.4 (±50.1)	119.9 (±49.3)	118.9 (±54.4)	119.2 (±51.5)
High-density lipoprotein (mg/dL)	39.0 (±15.6)	40.1 (±18.1)	37.6 (±12.6)	39.4 (±14.9)
Low-density lipoprotein (mg/dL)	100.9 (±37.9)	102.3 (±42.9)	104.7 (±52.2)	98.3 (±36.7)
Triglycerides (mg/dL)	170.0 (±113.7)	166.3 (±106.8)	191.5 (±144.5)	165.3 (±149.2)
Kidney Function				
eGFRcystatin C (ml/min per 1.73 m^2)	36.9 (±12.6)	38.7 (±14.1)	38.7 (±12.8)	41.5 (±11)
eGFR- CKD EPI (ml/min per 1.73 m^2)	34.8 (±16.3)	37.0 (±17.5)	37.8 (±21.2)	37.8 (±13.5)
Albumin to creatinine ratio (mg/g), median (interquartile range)	273.2 (30.2, 1230.9)	175.7 (9.1, 575.0)	106.1 (9.8, 973.0)	198.2 (15.1, 688.8)
Medications				
ACE inhibitor	44 (52.4%)	39 (46.4%)	36 (58.1%)	49 (58.3%)
ARBS	36 (42.9%)	31 (36.9%)	19 (30.6%)	31 (36.9%)
Statin	54 (64.3%)	49 (58.3%)	42 (67.7%)	47 (56.0%)
Prevalent disease				
Coronary artery disease$^{\alpha}$	49 (58.3%)	43 (51.2%)	27 (43.5%)	31 (36.9%)
Peripheral vascular disease$^{\beta}$	23 (27.4%)	20 (23.8%)	16 (25.8%)	19 (22.6%)
Cerebrovascular disease$^{\gamma}$	18 (21.4%)	14 (16.7%)	10 (16.1%)	16 (19.0%)
Symptomatic heart failure$^{\mu}$	29 (36.7%)	24 (28.9%)	17 (26.9%)	11 (13.9%)
Diabetes$^{\delta}$	52 (61.9%)	51 (60.7%)	34 (54.8%)	38 (45.2%)

	Physical Activity Category			
	None	Low	Moderate	High
Hypertension[ε]	81 (96.4%)	83 (98.8%)	61 (98.4%)	80 (95.2%)

Data are crude means (±SD) for continuous variables and number (proportion) for categorical variables, unless otherwise stated

[α]Prevalent coronary artery disease was defined as self-reported previous myocardial infarction, cardiac arrest, coronary artery bypass graft or percutaneous coronary intervention.

[β]Prevalent peripheral vascular disease was defined as self-reported claudication, peripheral vascular surgery, or lower extremity amputation.

[γ]Prevalent cerebrovascular disease was defined as self-reported stroke or carotid endarterectomy.

[μ]Prevalent heart failure was defined as either a self-reported history of heart failure, use of digoxin, or at least two out of the following three heart failure symptoms: dyspnea after walking less than one block, paroxysmal nocturnal dyspnea or orthopnea.

[δ] Diabetes was defined by any of the following: use of an oral hypoglycemic medication or insulin, fasting blood sugar ≥126mg/dL, non-fasting blood sugar ≥200, or hemoglobin A1c ≥6.5%.

[ε]Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medications.

Figure 2.1 Frequency of types of leisure-time physical activities

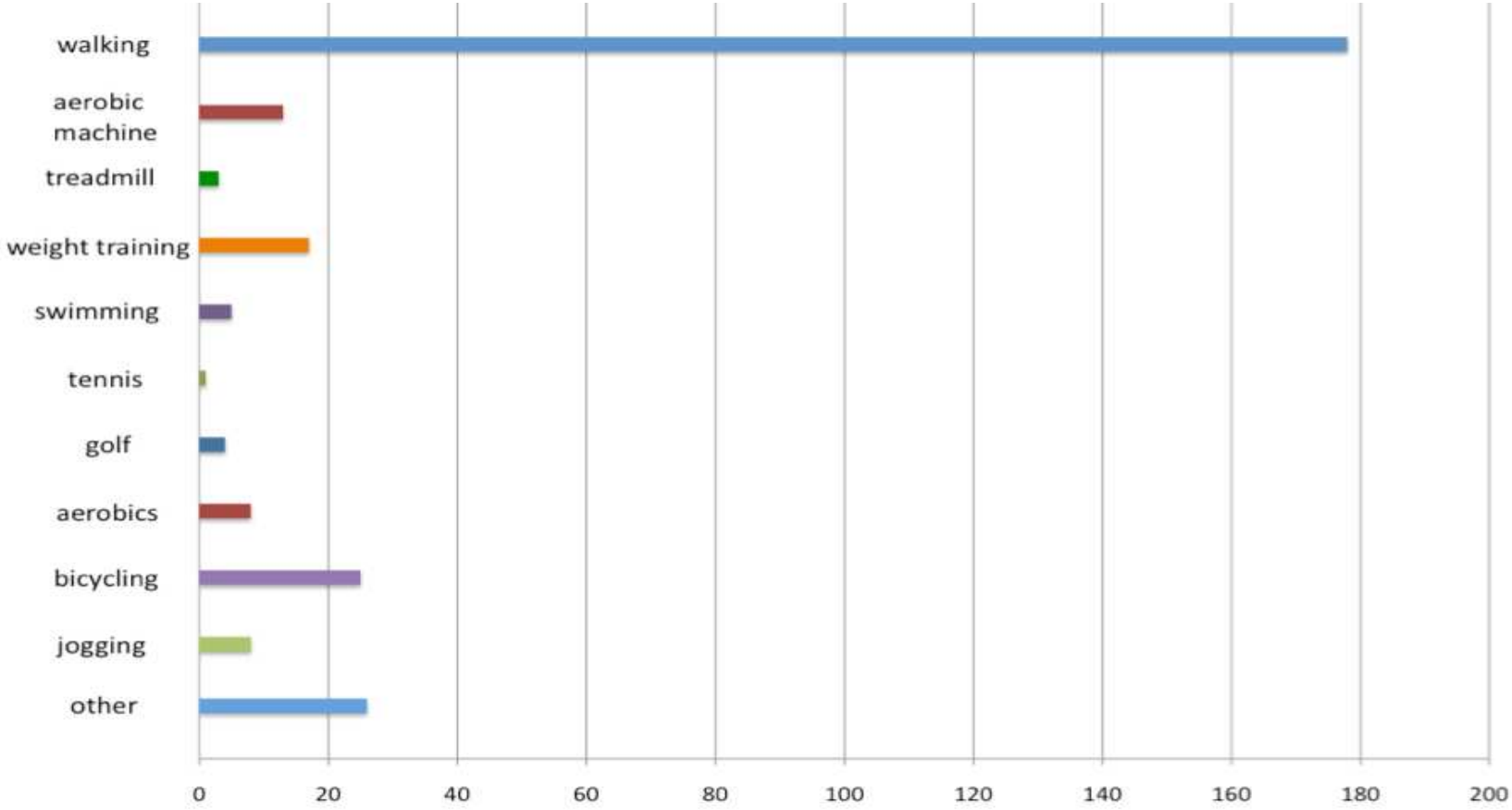


Table 2.2 Crude event incidence rates (per 1000 person-years), overall and by physical activity group

Exposure		All-Cause Mortality		Hospitalized Heart Failure		Composite Cardiovascular Endpoint*		Myocardial Infarction, CABG or PCI		Stroke or Carotid Endarterectomy	
	N	# events	IR[†]	# events	IR	# events	IR	# events	IR	# events	IR
Overall	304	54	60.2	48	58.3	28	32.7	19	21.8	11	12.5
Physical Activity Category											
None	78	16	71.7	20	105.3	17	84.1	9	42.0	9	42.8
Low (1-60 min/week)	84	12	47.7	16	72.1	4	16.1	4	16.0	1	4.0
Moderate (60-150 min/week)	63	11	59.6	6	33.2	3	17.0	2	11.2	1	5.5
High (≥150 min/week)	79	15	62.9	6	25.9	4	17.4	4	17.4	0	0.0

Abbreviations: IR, incidence rate, per 1000 person-years, CABG, coronary artery bypass graft surgery, PCI, percutaneous coronary intervention
*Composite cardiovascular endpoint is the first post-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke, or carotid endarterectomy.

Table 2.3 Crude event rates by CKD stage and by prevalent cardiovascular disease

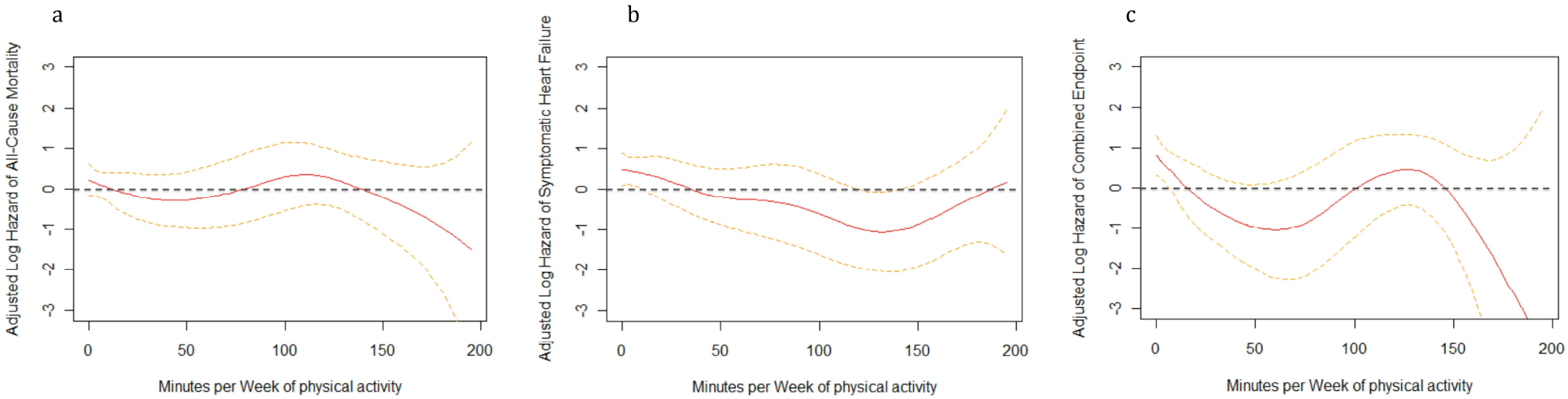
Exposure		All-Cause Mortality		Symptomatic Heart Failure		Composite Cardiovascular Endpoint*		Myocardial Infarction, CABG[§] or PCI[ß]		Stroke or Carotid Endarterectomy	
	N	# events	IR[†]	# events	IR	# events	IR	# events	IR	# events	IR
Baseline Stage of CKD[α]											
Stage IV	97	23	77.4	19	70.7	12	42.8	7	24.3	6	20.8
Stage IIIa	100	15	50.9	13	46.4	8	28.2	6	20.7	2	6.9
Stage IIIb	107	16	52.3	16	58.2	8	27.3	6	20.4	3	9.8
Prevalent Component of Composite Cardiovascular Disease Outcome											
Yes	115	33	105.6	23	82.5	18	61.3	12	40.1	8	26.1
No	189	21	35.9	25	45.9	10	17.8	7	12.2	3	5.2
Prevalent Heart Failure											
Yes	81	18	79.3	31	159.6	10	45.4	7	31.6	3	13.3
No	223	36	53.7	17	27.0	18	28.3	12	18.5	8	12.2

Abbreviations: CKD, chronic kidney disease IR, incidence rate, per 1000 person-years, CABG, coronary artery bypass graft surgery, PCI, percutaneous coronary intervention

[α]Chronic Kidney Disease Stage IV: eGFR 15-30 ml/min/1.73m^2; Stage IIIa : eGFR 30-45 ml/min/1.73m^2; Stage IIIb: eGFR 45-60 ml/min/1.73m^2

*Composite cardiovascular endpoint is the first post-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke or carotid endarterectomy.

Figure 2.2 Adjusted[†] continuous associations of physical activity (minutes per week) with (a) incident all-cause mortality, (b) heart failure and (c) combined cardiovascular endpoint*



*Composite cardiovascular endpoint is the first post-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke, or carotid endarterectomy.

[†]Splines adjusted for age, gender, race, site, cystatin-c estimated glomerular filtration rate and the baseline hazards were stratified by prevalent cardiovascular disease at baseline. Yellow dotted lines represent the 'twice standard-error curve' of the pointwise standard errors of the adjusted log hazards and the zero-level black dotted line represents the null hypothesis of no association between physical activity and each of the outcomes.

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Table 2.4 Association of physical activity with all-cause mortality (a), heart failure (b) and a composite cardiovascular endpoint (c)

Leisure-time Physical Activity	Hazard Ratio (95% CI)			
	Unadjusted	Model 1	Model 2	Model 3
a. All-Cause Mortality				
Any *versus* none	0.76 (0.42, 1.37)	0.83 (0.46, 1.51)	0.84 (0.45, 1.56)	0.85 (0.46, 1.59)
Among any[†], per additional 30 min/week	0.99 (0.93, 1.05)	0.98 (0.92, 1.04)	0.99 (0.92, 1.05)	0.99 (0.92, 1.06)
p-value[α]	0.78	0.51	0.66	0.73
b. Symptomatic Heart Failure				
Any *versus* none	0.42 (0.24, 0.75)	0.43 (0.24, 0.78)	0.46 (0.25, 0.86)	0.43 (0.22, 0.81)
Among any, per additional 30 min/week	0.84 (0.74, 0.97)	0.80 (0.69, 0.94)	0.80 (0.68, 0.94)	0.80 (0.69, 0.94)
p-value	0.015	0.005	0.006	0.007
c. Combined Cardiovascular Endpoint*				
Any *versus* none	0.21 (0.10, 0.44)	0.18 (0.08, 0.40)	0.15 (0.06, 0.37)	0.16 (0.07, 0.38)
Among any, per additional 30 min/week	1.02 (0.92, 1.13)	1.01 (0.90, 1.12)	1.03 (0.92, 1.16)	1.02 (0.91, 1.16)
p-value	0.73	0.93	0.63	0.63

In adjusted models, baseline hazard functions are stratified by prevalent cardiovascular disease status.
Model 1 includes age, sex, study site and race/ethnicity.
Model 2 adds current smoking status, current alcohol use, education, body mass index, diabetes status and baseline eGFR.
Model 3 adds systolic blood pressure and medications: use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and/or statins.
*Combined cardiovascular endpoint is the first post-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke or carotid endarterectomy
[†]Participants reporting *any* physical activity in the previous month.
[α]Wald test statistic for continuous physical activity among participants reporting *any* physical activity in the previous month

Table 2.5 Association of Physical Activity with Heart Failure and Composite Endpoint, by prevalent disease status at baseline.

Physical Activity Level	Outcome	Adjusted* Hazard Ratio (95% CI)			
		Prevalent cardiovascular disease at baseline		Prevalent heart failure at baseline	
		Yes (n=115)	No (n=189)	Yes (n=81)	No (n=223)
Any *versus* None	All-Cause Mortality	0.82 (0.36,1.85)	0.49 (0.13,1.83)	0.72 (0.25,2.11)	0.85 (0.38,1.92)
		p-for interaction= 0.83		p-for interaction= 0.80	
	Heart Failure	0.28 (0.10,0.73)	0.63 (0.20,1.97)	0.55 (0.24,1.27)	0.46 (0.16,1.36)
		p-for interaction= 0.23		p-for interaction= 0.20	
	Combined Cardiovascular Endpoint	0.14 (0.04,0.45	0.12 (0.02,0.64)	0.03 (0.01,0.69)	0.21 (0.07,0.60)
		p-for interaction= 0.98		p-for interaction= 0.98	
Among participants reporting any physical activity, per additional 30 minutes per week	All-Cause Mortality	1.00 (0.90,1.10)	0.90 (0.77,1.05)	1.04 (0.86,1.25)	0.96 (0.89,1.05)
		p-for interaction= 0.31		p-for interaction= 0.43	
	Heart Failure	0.84 (0.63,1.14)	0.74 (0.59, 0.93)	0.84 (0.68,1.04)	0.77 (0.57,1.05)
		p-for interaction= 0.63		p-for interaction= 0.55	
	Combined Cardiovascular Endpoint	0.95 (0.67,1.35)	0.88 (0.67,1.14)	-	1.03 (0.92,1.15)
		p-for interaction= 0.79		-	

*Adjusted for age, sex, study site and race/ethnicity, current smoking status, current alcohol use, education, body mass index, diabetes status (for analyses not stratified by diabetes status), baseline eGFR, systolic blood pressure.

Composite prevalent cardiovascular disease includes a pre-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke, or carotid endarterectomy.

Blank cells (-) indicate instances where parameter estimates and standard errors were inestimable robustly, due to restricted numbers of events in subgroup.

Appendix

Supplementary Table 1. Association of Walking Time and Annualized Relative Change in eGFR-cystatin C

Walking duration per week	N	Percent Annual Change in eGFR-cystatin C (95% CI)							
		Unadjusted		Model 1		Model 2		Model 3	
None	88	-10.9	(-13.5,-8.1)	-11.2	(-14.0,-8.1)	-10.8	(-12.7,-7.3)	-8.6	(-11.6,-5.5)
1-60 minutes per week	50	-4.7	(-9.1,+0.1)	-4.7	(-9.4,+0.3)	-4.2	(-11.2,+0.4)	-3.6	(-8.4,+1.3)
60-150 minutes per week	43	-3.5	(-7.7,+0.9)	-3.8	(-8.4,+0.1)	-4.5	(-8.7,-0.2)	-4.7	(-9.2,0.0)
≥150 minutes per week	33	-7.1	(-11.7,-2.4)	-7.5	(-12.4,-2.4)	-6.1	(-10.6,-1.4)	-5.3	(-10.6,+3.5)
p-for-trend in categories[α]		0.016		0.027		0.030		0.130	

Model 1: age, race, gender, site, time spent in other leisure-time activities
Model 2: Model 1 + education, body mass index, diabetes, smoking status, alcohol, prevalent coronary artery disease
Model 3: Model 2 + hemoglobin a1c, systolic blood pressure, ACE-inhibitor use, ARB use, statin use, C-reactive protein
[α]Wald test statistic for ordinal categories of physical activity among all participants

Supplementary Table 2. Association of Physical Activity and Annualized Relative Change in eGFR-CKDEPI

Leisure-time Physical Activity Level	Percent Annual Change in eGFR-CKD-EPI					
	Model 1		Model 2		Model 3	
	% change per year	95 % CI	% change per year	95 % CI	% change per year	95 % CI
None	-13.6	(-17.6, -9.3)	-13.4	(-17.7,-9.0)	-12.1	(-16.3,-7.7)
0-60 minutes per week	-5.0	(-9.6, -0.2)	-4.5	(-9.1,+0.4)	-4.4	(-8.9,+0.3)
60-150 minutes per week	-5.3	(-10.5, 0.0)	-5.5	(-10.7,-0.1)	-5.3	(-10.2,-0.1)
>150 minutes per week	-7.5	(-12.7, -3.2)	-7.7	(-11.9,-3.3)	-7.4	(-11.4,-3.1)
p-for-trend[α]	0.073		0.115		0.188	

Model 1: age, race, gender, site
Model 2: Model 1 + education, body mass index, diabetes, smoking status, alcohol, prevalent coronary artery disease
Model 3: Model 2 + hemoglobin a1c, systolic blood pressure, ACE-inhibitor use, ARB use, statin use, C-reactive protein, baseline GFR-cystatin C
[α]Wald test statistic for ordinal categories of physical activity among all participants

Supplementary Table 3. Association of Physical Activity with Incident Death or End-Stage Renal Disease

Physical Activity Level	N (# events)	IR	Model 1		Model 2		Model 3	
			HR	95% CI	HR	95% CI	HR	95% CI
None	54 (18)	12.16	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Any	160 (40)	7.85	0.68	(0.37, 1.24)	0.65	(0.35, 1.22)	1.06	(0.54, 2.06)
Among those who reported any physical activity, each additional 30 min/week			0.97	(0.91, 1.04)	0.97	(0.91, 1.03)	0.99	(0.90, 1.08)

Abbreviations: IR, incidence rate, per 1000 person-years, HR, hazard ratio, CI, confidence interval
Model 1: age, race, gender, site
Model 2: Model 1 + education, body mass index, diabetes, smoking status, alcohol, prevalent coronary artery disease
Model 3: Model 2 + hemoglobin A1c, systolic blood pressure, ACE-inhibitor use, ARB use, statin use, C-reactive protein

Supplementary Table 4. Sensitivity, specificity, positive and negative predictive values of self-reported prevalent disease status at baseline.

Prevalent Disease	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Myocardial Infarction	83%	80%	42%	97%
Stroke	77%	94%	68%	96%
Heart Failure	61%	93%	81%	83%

Note: Questionnaire responses to “has a doctor ever told you that you had” each given condition were compared to the criterion standard of medical record review.

Supplementary Table 5. Association of Physical Activity with Events, According to Baseline Prevalent Disease Status

Physical Activity Exposure	Outcome	Adjusted* Hazard Ratio (95% CI)			
		Prevalent diabetes at baseline		Moderate-High Functioning[†]	
		Yes (n=171)	No (n=133)	Yes (n=218)	No (n=86)
Any *versus* None	All-Cause Mortality	0.75 (0.36,1.57)	0.97 (0.24,3.84)	0.40 (0.16,0.99)	2.07 (0.73,5.85)
		p-for interaction= 0.55		p-for interaction= 0.04	
	Heart Failure	0.40 (0.19,0.78)	1.42 (0.19, 10.7)	0.50 (0.19,1.26)	0.29 (0.11,0.81)
		p-for interaction= 0.81		p-for interaction= 0.84	
	Combined Cardiovascular Endpoint	0.22 (0.09,0.59)	0.09 (0.01,0.63)	0.14 (0.05,0.44)	0.21 (0.04,1.07)
		p-for interaction= 0.42		p-for interaction= 0.98	
Among participants reporting any physical activity, per additional 30 minutes per week	All-Cause Mortality	1.00 (0.90,1.10)	0.94 (0.82,1.07)	0.89 (0.78,1.02)	1.01 (0.92,1.11)
		p-for interaction= 0.68		p-for interaction= 0.18	
	Heart Failure	0.76 (0.62,0.93)	-	0.79 (0.64,0.98)	0.86 (0.68,1.10)
		-		p-for interaction= 0.70	
	Combined Cardiovascular Endpoint	1.05 (0.91,1.21)	0.79 (0.48,1.31)	1.06 (0.91,1.22)	-
		p-for interaction= 0.54		-	

*Adjusted for age, sex, study site and race/ethnicity, current smoking status, current alcohol use, education, body mass index, diabetes status (for analyses not stratified by diabetes status), baseline eGFR, systolic blood pressure.
Composite prevalent cardiovascular disease includes a pre-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke, or carotid endarterectomy.
Blank cells (-) indicate instances where parameter estimates and standard errors were inestimable robustly, due to restricted numbers of events in subgroup.
[†]Physical function was assessed using the Short Physical Performance Battery. A score greater than 7 was considered moderate-high functioning.[39]

Supplementary Table 6. Association of Physical Activity with Events, after exclusion of the 35 occurrences of either all-cause mortality, hospitalized heart failure or the combined cardiovascular event), within the first year of follow-up

Leisure-time Physical Activity Level	Adjusted Hazard Ratio (95% CI)		
	All-Cause Mortality	Symptomatic Heart Failure	Combined Cardiovascular Event*
Any *versus* None	0.97 (0.45, 2.11)	0.30 (0.13, 0.71)	0.23 (0.09, 0.55)
Among participants reporting any physical activity, per additional 30 min/week	0.99 (0.93, 1.05)	0.84 (0.72, 0.99)	0.80 (0.60, 1.02)
p-value	0.68	0.03	0.07

Baseline hazard function stratified by prevalent cardiovascular disease status.
Adjustment model includes age, sex, study site and race/ethnicity, current smoking status, current alcohol use, education, body mass index, diabetes status and baseline eGFR, and systolic blood pressure
*Composite cardiovascular endpoint is the first post-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke or carotid endarterectomy

Supplementary Table 7 Association of Walking time with All-Cause Mortality, Heart Failure, and Composite Endpoint

Walking duration	Adjusted Hazard Ratio (95% CI)		
	All-Cause Mortality	Symptomatic Heart Failure	Combined Cardiovascular Event*
Any *versus* None	0.72 (0.32, 1.58)	0.44 (0.21, 0.93)	0.18 (0.07, 0.47)
Among participants reporting any physical activity, per additional 30 min/week	0.93 (0.84, 1.04)	0.76 (0.63, 0.93)	0.98 (0.83, 1.15)
p-value for continuous	0.17	0.007	0.76

Baseline hazard function stratified by prevalent cardiovascular disease status.
Adjustment model includes age, sex, study site and race/ethnicity, current smoking status, current alcohol use, education, body mass index, diabetes status and baseline eGFR, and systolic blood pressure
*Composite cardiovascular endpoint is the first post-baseline occurrence of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, stroke or carotid endarterectomy

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Research Experience

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2002 – 2004	Research Assistant, Institut Armand Frappier Institut National de la Recherche Scientifique, Laval, Quebec.

Teaching Experience

2010 – 2012	Teaching Assistant, HUBIO 530: Epidemiology University of Washington Presented 2 lectures: “Misclassification” and “Screening” Led weekly journal club
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First-Authored Publications

Robinson-Cohen C, Littman AJ, Duncan GE, Roshanravan B, Ikizler TA, Himmelfarb J, Kestenbaum BR. Assessment of Physical Activity in Chronic Kidney Disease. J Ren Nutr. 2012 Jun 26.

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