

Physical Activity and Mortality in Chronic Kidney Disease (NHANES III)

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Background and objectives: Chronic kidney disease (CKD) is associated with impaired physical activity. However, it is unclear whether the associations of physical activity with mortality are modified by the presence of CKD. Therefore, we examined the effects of CKD on the associations of physical activity with mortality.

Design, setting, participants, & measurements: This was an observational study of 15,368 adult participants in the National Health and Nutrition Examination Survey III; 5.9% had CKD (eGFR < 60 ml/min per 1.73 m²). Based on the frequency and intensity of leisure time physical activity obtained by a questionnaire, participants were divided into inactive, insufficiently active, and active groups. Time to mortality was examined in Cox models, taking into account the complex survey design.

Results: Inactivity was present in 13.5% of the non-CKD and 28.0% of the CKD groups ($P < 0.001$). In two separate multivariable Cox models, compared with the physically inactive group, hazard ratios (95% confidence intervals) of mortality for insufficiently active and active groups were 0.60 (0.45 to 0.81) and 0.59 (0.45 to 0.77) in the non-CKD subpopulation and 0.58 (0.42 to 0.79) and 0.44 (0.33 to 0.58) in the CKD subpopulation. These hazard ratios did not differ significantly between the CKD and non-CKD subpopulations ($P > 0.3$).

Conclusions: Physical inactivity is associated with increased mortality in CKD and non-CKD populations. As in the non-CKD population, increased physical activity might have a survival benefit in the CKD population.

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There are >16 million U.S. adults with stage III and IV chronic kidney disease (CKD) (1), yet there are only ~400,000 in stage V CKD. A vast majority of those with moderate CKD die before they reach ESRD (2). However, the current focus of the providers taking care of the stage III and IV CKD population is on measures to slow the progression of kidney disease rather than on measures that could reduce the mortality in this population.

Increased physical activity is associated with better survival in the general population. A previous analysis of the Modification of Diet in Renal Disease (MDRD) Study suggested that higher levels of physical activity were not significantly associated with reduced mortality in the CKD population (3). To our knowledge, there are no other data on exercise and survival in the CKD population. Therefore, we examined whether the presence of CKD modifies the association of exercise with mortality in the National Health and Nutrition Examination Survey (NHANES) III.

Materials and Methods

Study Population and Baseline Data

From 1988 to 1994, the National Center for Health Statistics conducted NHANES III, a cross-sectional survey of the U.S. population. A complex, multistage sampling design was used to allow results to be extrapolated to the entire noninstitutionalized civilian U.S. population as of the early 1990s (4). There were 15,378 NHANES III adult subjects ≥ 20 yr of age with nonmissing data on physical activity and estimated GFR (eGFR) <150 ml/min per 1.73 m². Of these, follow-up data were missing in 10 participants, and the final subpopulation sample included for this analysis consisted of 15,368 participants.

Details on data collection in NHANES have been published elsewhere (5). In brief, a home interview by trained personnel was followed by an examination by a physician at a mobile examination center (5). A physical activity questionnaire was administered at a home interview for all participants. They were asked about the frequency of leisure time activity in the past month. This included the frequency of walking a mile without stopping, running or jogging, riding a bicycle or exercise bike, swimming, aerobics, dancing, calisthenics, garden or yard work, lifting weights, or other activities.

Based on the Compendium of Physical Activities, the level of physical activity was assessed using metabolic equivalent (MET) intensity levels (6). One MET is defined as the energy expenditure at resting metabolic rate (as occurs with sitting quietly or watching television). Riding a stationary bike with very light effort or walking the dog is considered 3 METs of physical activity. A jog/walk combination with jogging for <10 min is considered 6 METs, whereas running at 6 mph is considered 10 METs of physical activity.

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In this study, we defined the inactive group as those with no reported leisure time physical activity. Active group was defined as those who had recommended levels of physical activity (7) *i.e.*, self-reported leisure time moderate activity (METs ranging from 3 to 6) of five or more times per week or leisure time vigorous activity (MET > 6) three or more times per week. Insufficiently active group was defined as those who were not inactive and did not meet the criteria for recommended levels of physical activity.

Serum creatinine was measured using a kinetic rate Jaffe method in NHANES III. These serum creatinine measurements were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH) as standard creatinine = $-0.184 + 0.960 \times \text{NHANES III-measured serum creatinine}$ (1). eGFR was estimated as $175 \times (\text{standardized serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if the individual is woman) $\times 1.212$ (if the individual is African American) (8).

The National Cholesterol Education Program Adult Treatment Panel III definition (9) was used to determine the presence of metabolic syndrome. A consensus statement of the Centers for Disease Control (CDC) and the American Heart Association categorized C-reactive protein (CRP) level >3 mg/L as high risk (10). Therefore, elevated CRP was defined as CRP level >3 mg/L.

Follow-Up Data

The National Center for Health Statistics created an NHANES III-Linked Mortality File that contains mortality follow-up data from the date of NHANES III survey participation (1988–1994) through December 31, 2000. This information was based on the results from a probabilistic match between NHANES III and National Death Index death certificate records, the details of which are provided elsewhere (11).

Statistical Analyses

NHANES III is based on a complex multistage probability sample design. Several aspects of the NHANES design must be taken into account in data analysis, including the sampling weights and the complex survey design. We used the svy suite of commands in Stata 10 (Stata 10, College Station, TX) and followed the analytical guidelines for NHANES data proposed by the CDC (4). It should be noted that the svy suite of commands in Stata use the complex survey design of NHANES to calculate the expected means and proportions of the entire U.S. noninstitutionalized civilian CKD population, and hence, means and proportions are presented with the estimated value and 95% confidence intervals (CIs).

In a multivariate logistic regression model, compared with the non-CKD subpopulation, whether CKD was associated with higher prevalence of physical inactivity was examined adjusted for demographics, myocardial infarction, stroke, history of congestive heart failure, claudication, cancer, lung disease, diabetes, BP, and smoking.

Survival Analyses. Using the inactive group as the reference, the associations of insufficiently active and active groups with mortality were examined in Cox proportional models adjusted for age, gender, race, smoking, diabetes, history of claudication, myocardial infarction, stroke, congestive heart failure, cancer, lung disease, systolic and diastolic BP, eGFR, body mass index, serum albumin, and albuminuria. This Cox regression model was first applied in the entire cohort and then separately in the non-CKD and CKD subgroups.

The assumption of proportional hazards was examined by comparing the logarithm of the hazard ratio for each predictor variable in the first year of follow-up to the logarithm of the hazard ratio of the predictor variables after year 1. No models showed proportional hazards assumption violations with respect to exercise level.

The factors age, diastolic BP, diabetes, and smoking exhibited a significant deviation from proportional hazards ($P < 0.05$) in at least one of the models. Hence, each of the Cox regressions was stratified by each of these factors (using tertiles for the continuous variables age and diastolic BP) to allow separate baseline hazard functions within each strata. Furthermore, within each age stratum, age was adjusted as a continuous variable.

Sensitivity Analyses. It could be argued that most classified to have CKD based on an eGFR cut-off of 60 ml/min per 1.73 m² might actually have only age-related decline in GFR. Therefore, we refit the Cox regression model relating mortality to physical activity in the CKD group in those with more advanced CKD (eGFR < 50 ml/min per 1.73 m²).

The definition of recommended levels of physical activity (at least five times of moderate activity or at least three times of vigorous activity per week) is based on the frequency of these activities. It is possible that the individual frequency of moderate or vigorous activities by itself might not meet the above criteria, but a combination of these two might (*e.g.*, moderate activity four times per week with vigorous activity once a week). Therefore, a sensitivity analyses of the linear combination was used where physical inactivity was defined as no reported activity, insufficient activity was defined where the sum of (weekly frequency of moderate activity/5) + (weekly frequency of vigorous activity/3) is <1, and recommended activity was defined where the sum of (weekly frequency of moderate activity/5) + (weekly frequency of vigorous activity/3) is ≥ 1 . With this definition, 243 participants were reclassified to have recommended levels of activity.

Results

The mean age was 44.6 ± 0.45 yr. Forty-eight percent were men, 85% were white, 11% were African Americans, and 5.9% had CKD. Fifteen percent were physically inactive, 43% were insufficiently active, and 42% had recommended levels of physical activity.

The baseline clinical characteristics by physical activity groups in non-CKD and CKD are described in Table 1. In general, the inactive group was older and had higher comorbidity. Male gender and non-African-American race were associated with greater physical activity. Physical inactivity was associated with greater prevalence of metabolic syndrome and elevated CRP in non-CKD and CKD populations (Table 1).

In a multivariate logistic regression model, compared with the non-CKD subpopulation, CKD was associated with higher prevalence of physical inactivity (odds ratio, 1.30; 95% CI, 1.03 to 1.64) adjusted for demographics, myocardial infarction, stroke, history of congestive heart failure, claudication, cancer, lung disease, diabetes, BP, and smoking.

Associations of Physical Activity with Mortality in Non-CKD

Over a mean of 8.8 yr of follow-up, there were 1073 deaths in the non-CKD subpopulation. In this population, compared with the physically inactive group, hazard ratios (95% CIs) of mortality for insufficiently active and active groups were 0.60 (0.45 to 0.81) and 0.59 (0.45 to 0.77), respectively, in a multivariate Cox model adjusted for gender, race, myocardial infarction, stroke, congestive heart failure, cancer, claudication, lung disease, systolic BP, body mass index, serum albumin, albuminuria, and eGFR and stratified by diabetes, smoking, and tertiles

Table 1. Baseline characteristics by levels of physical activity in non-CKD and CKD populations

	eGFR = 60 to 150 ml/min per 1.73 m ²			eGFR < 60 ml/min per 1.73 m ²		
	Inactive (14.0%)	Insufficient Activity (43.6%)	Recommended Activity (42.4%)	Inactive (29.0%)	Insufficient Activity (30.8%)	Recommended Activity (40.2%)
Demographics						
Age (yr) ^{a,b}	48 ± 0.5	42 ± 0.4	43 ± 0.6	73 ± 0.9	66 ± 1.1	68 ± 1.1
Male gender (%) ^{a,b}	37 (34–40)	47 (46–49)	54 (53–56)	27 (22–33)	40 (33–48)	43 (35–51)
African-American race (%) ^a	17 (14–19)	10 (9–11)	10 (9–12)	12 (9–16)	7 (5–11)	5 (4–7)
Clinical parameters						
Metabolic syndrome (%) ^{a,b}	26.6 (23.8–29.7)	20.9 (19.1–22.7)	17.4 (15.9–18.9)	62.1 (55.7–68.1)	51.8 (43.2–60.3)	48.3 (42.5–54.2)
Diabetes (%) ^a	10.2 (8.5–12.1)	6.5 (5.5–7.6)	4.8 (4.1–5.5)	25.4 (20.5–31.1)	17.8 (13.1–23.9)	19.6 (18.5–23.2)
Myocardial infarction (%) ^a	5.3 (4.2–6.7)	1.9 (1.5–2.4)	2.8 (2.3–3.4)	13.9 (10.5–18.2)	10.7 (7.6–14.9)	18.6 (12.5–26.7)
Congestive heart failure (%) ^a	4.1 (3.2–5.2)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	16.9 (12.7–22.1)	9.6 (6.7–13.5)	11.8 (7.8–17.5)
Stroke (%) ^a	4.5 (3.5–5.7)	1.1 (0.8–1.5)	1.1 (0.7–1.6)	12.3 (9.3–16.1)	8.0 (5.4–11.5)	8.1 (4.8–13.2)
Current smoker (%) ^a	34.6 (31.5–37.9)	31.1 (28.8–33.4)	25.8 (23.7–28.1)	17.2 (12.1–24.0)	18.1 (12.0–26.4)	9.5 (6.6–13.5)
Waist circumference (cm) ^a	94 ± 0.7	92 ± 0.4	90 ± 0.3	100 ± 1.5	99 ± 0.9	97 ± 0.8
Systolic BP (mmHg) ^{a,b}	124 ± 0.5	120 ± 0.4	121 ± 0.5	142 ± 1.3	140 ± 1.4	140 ± 1.9
Diastolic BP (mmHg) ^b	74 ± 0.4	74 ± 0.2	74 ± 0.2	73 ± 0.6	77 ± 1.0	75 ± 0.8
span lang=IT eGFR (ml/min per 1.73 m ²) ^a	95.6 ± 0.7	94.9 ± 0.5	92.9 ± 0.5	46.9 ± 0.8	50.8 ± 0.4	49.8 ± 0.5
Elevated CRP (%) ^{a,b}	33.7 (30.7–37.7)	25.8 (23.1–28.7)	19.8 (18.0–21.6)	51.8 (44.6–58.9)	42.5 (35.4–50.1)	41.7 (34.9–48.9)
Serum albumin (g/dl) ^{a,b}	4.1 ± 0.02	4.2 ± 0.02	4.2 ± 0.02	4.0 ± 0.03	4.0 ± 0.03	4.1 ± 0.02

Percentages shown as percent (95% CI); continuous measures shown as mean ± SE.

^a*p* < 0.05 within non-CKD group.^b*p* < 0.05 within CKD group.

of age and diastolic BP. Within each stratum, age was adjusted as a continuous variable in the above model.

Associations of Physical Activity with Mortality in CKD

Over a mean follow-up of 7 yr, there were 364 deaths in the CKD subpopulation. In the CKD subpopulation, in a similar model as described above, compared with the physically inactive group, hazard ratios (95% CIs) of mortality for insufficiently active and active groups were 0.58 (0.42 to 0.79) and 0.44 (0.33 to 0.58) in a multivariate Cox model (Figure 1).

The hazard ratios relating mortality to insufficiently active and active groups (compared with inactive patients) did not differ significantly between the CKD and non-CKD subpopulations ($P > 0.3$ for both insufficiently active and active groups), indicating that the associations of physical activity with mortality did not differ by the presence or absence of CKD.

Sensitivity Analyses Results

When the alternative definition of physical activity groups was used, the results were similar.

There were 2.3% with more advanced CKD defined as eGFR <50 ml/min per 1.73 m^2 . The mean eGFR in this subgroup was 40 ml/min per 1.73 m^2 , and 359 (61%) died during the follow-up. Within this subgroup of more advanced CKD patients, compared with the physically inactive group, hazard ratios (95% CIs) of mortality for insufficiently active and active groups were 0.64 (0.46 to 0.88) and 0.50 (0.33 to 0.74) in a multivariate Cox model as described above.

Discussion

The results of this study indicated that the presence of CKD is associated with decreased physical activity. Furthermore, leisure time physical activity is associated with decreased mortality in the CKD population (Figure 1).

Lower GFR is associated with physical inactivity (12). In patients with CKD (mean eGFR, 29.9 ± 17.0 ml/min per 1.73 m^2) not requiring renal replacement therapy, peak oxygen uptake on the symptom-limited treadmill test and physical performance measures (gait speed, sit-to-stand, and 6-min walk)

were reduced compared with sedentary age-predicted norms (13). In a cross-sectional study, CKD was associated with lower self-reported physical function (14). In elderly persons, those in the highest (≥ 1.13 mg/L) quartile of cystatin C had a significantly higher risk of developing functional limitation than those in the lowest quartile (<0.86 mg/L) (15). Patients with dialysis-treated CKD 5 exhibited more functionally significant muscle wasting than patients with CKD 4 (16).

Nonetheless, the functional limitations that are commonly seen in the CKD and dialysis population could be improved with increased physical activity. In a cardiac rehabilitation program, those with CKD compared with the non-CKD population had worse functional status, but cardiac rehabilitation achieved significant improvements in 6-min walk distances and physical activity levels in both groups (17). In a multidisciplinary program of obese CKD patients, a regimen that included diet and exercise resulted in significant weight loss and improved physical functioning (18). Both aerobic and resistance training in CKD and dialysis patients can improve physical functioning (19–23). Resistance exercise training also seems to increase muscle strength and size in the CKD population (19–21).

Thus, there is a considerable body of evidence that CKD is associated with poor functional status, and aerobic or resistance training can improve functional status in this population. However, there is a dearth of studies on the effects of physical activity on survival in the CKD population.

Chen *et al.* (3) found that three derived physical activity variables (indoor activity, exercise, and outdoor activity) were not associated with mortality in predominantly nondiabetic CKD stage III to IV patients enrolled in the MDRD Study. In contrast, the results of this study indicate that leisure time physical activity is associated with lower mortality.

The mean GFR was 34 ml/min per 1.73 m^2 in the MDRD cohort, which is comparable to the mean eGFR of 40 ml/min per 1.73 m^2 of those in the <50 ml/min per 1.73 m^2 subgroup in this study. Therefore, the differences in the level of kidney function are an unlikely explanation for the discrepant results of these studies. However, the methods of assessment of physical activity differ substantially between the two studies. Moreover, over a comparable follow-up period, there were only 24.6% deaths in the MDRD cohort, whereas 61% in this study with eGFR <50 ml/min per 1.73 m^2 died. These differences reflect the different study design of these studies: NHANES III was designed as a representative sample of the noninstitutionalized U.S. adult population, whereas the MDRD Study was designed as a clinical trial of reduction in protein intake and BP on progression of CKD.

In this study, physical inactivity was associated with greater prevalence of metabolic syndrome and elevated CRP in both the non-CKD and CKD populations. The results of these cross-sectional analyses are supported by previously published data. An aerobic/resistance-training program in conjunction with dietary intervention promoted weight loss and improved components of metabolic syndrome in overweight and obese women (24). In another study of obese premenopausal women, sustained weight loss after 1 yr of a multidisciplinary program of weight reduction (diet, exercise, behavioral counseling) was

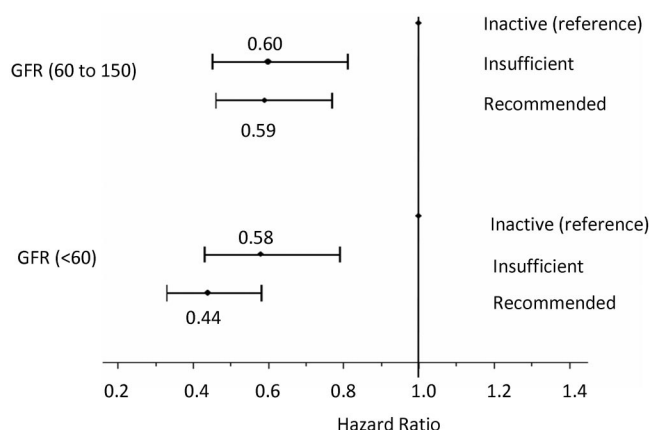


Figure 1. Associations of physical activity with mortality in non-CKD and CKD subpopulations in NHANES III.

associated with reduction of cytokine concentrations (25). In a randomized controlled trial, 24 hemodialysis patients were randomized to progressive resistance training + usual care and 25 patients to usual care control only. There were statistically significant improvements in not only muscle strength and muscle mass but also in CRP in the intervention group (20).

Although physical inactivity was associated with increased mortality, the observed mortality of those with insufficient physical activity and recommended levels of physical activity were similar in this study. These data are consistent with previous reports of similar associations of moderate and vigorous activities with mortality (26). However, information on only the frequency of physical activity and not the duration was collected in NHANES III.

The strengths of this study include very careful data collection in NHANES III. The major limitations of this study include that of all observational studies that use existing data. The observational nature of the study limits inference beyond associations. Like any observational study, unmeasured residual confounding needs to be considered while interpreting the results. There were no longitudinal data available on the associations of physical activity with CRP or metabolic syndrome in this dataset. Finally, the physical activities were self-reported. Despite this limitation, there is a strong association of physical inactivity with mortality in the moderate and advanced CKD populations.

In summary, physical inactivity is associated with increased mortality in CKD and non-CKD populations. These data suggest that increased physical activity might have a survival benefit in the CKD population. This is particularly important as most patients with stage III CKD die before they develop ESRD.

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Disclosures

None.

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