Association of Physical Activity With Mortality in the US Dialysis Population

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• ***Background:*** **It is unclear whether the protective benefits of regular physical activity on mortality extend to patients with end-stage renal disease (ESRD). We tested this hypothesis in a national cohort of new patients with ESRD in the United States.** ***Methods:*** **Data for a subset of patients (n = 2,507; 62%) from the Dialysis Morbidity and Mortality Wave 2 study were used to explore the associations of exercise and limitations in physical activity with mortality.** ***Results:*** **Overall, 56% of patients exercised less than once a week, whereas the remainder reported more frequent physical activity; 2 to 3 times/wk in 18%, 4 to 5 times/wk in 6%, and daily exercise in 20%. Severe limitations in vigorous and moderate physical activities were reported by 75% and 42%, respectively. Mortality risks were greatest for those with severe limitations in either moderate (relative risk [RR], 1.72; 95% confidence interval [CI], 1.44 to 2.05) or vigorous physical activities (RR, 1.51; 95% CI, 1.20 to 1.90) compared with those reporting minimal or no limitations. Conversely, mortality risks were lower for patients who exercised 2 to 3 (RR, 0.74; 95% CI, 0.58 to 0.95) or 4 to 5 times/wk (RR, 0.70; 95% CI, 0.47 to 1.07), whereas no advantage was associated with daily exercise (RR, 1.06; 95% CI, 0.86 to 1.30).** ***Conclusion:*** **Although limitations in physical activity are common among new patients with ESRD in the United States and correlate highly with increased mortality risk, this study shows an association of frequent exercise of up to 4 to 5 times/wk with improved survival. The surprising lack of association of daily exercise with increased survival deserves additional study.** ***Am J Kidney Dis*** **45:690-701.**

INDEX WORDS: Exercise; limitations in physical activities; prevalence; mortality.

EPIDEMIOLOGICAL characteristics of physical activity in patients with end-stage renal disease (ESRD) are largely unexplored. Available data show that self-reported physical functioning is extremely low in long-term dialysis patients and similar to that of patients with congestive heart failure.[1,2] Despite this, recent interventional studies of hemodialysis (HD) patients have shown substantial improvements in test results for patient physical performance after prescribed exercise programs.[3] Although the benefits of increased physical activity on all-cause and cardiovascular mortality have been well established in the general population, studies of ESRD populations are lacking.[4-7] Moreover, potential benefits of exercise intervention programs in improving survival in this high-risk population have not been evaluated in randomized controlled clinical trials.

Evidence from observational studies of the general population suggests that increased physical activity is strongly and inversely associated with all-cause and cardiovascular mortality.[4-12] A graded inverse relationship is seen between measures of total physical activity and deaths from all causes. This protective effect of regular physical activity is consistent within different strata in the general population, healthy individuals, and those with known cardiovascular disease. Furthermore, evidence suggests that maintenance or improvement in physical activity or fitness levels over time is associated with lower risk for death.[7,10] An even stronger inverse association exists between physical activity level and

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mortality from cardiovascular causes.[5,6,8] These associations suggest a causal inverse relationship between physical fitness and cardiovascular mortality in that they are consistent, strong, graded, plausible, coherent, and temporally related.[5,6,8]

A largely unexplored question is whether physical inactivity is associated independently with increased mortality among patients with ESRD. Moreover, it also is unclear whether increased participation in moderate to vigorous activities by patients with ESRD reduces the risk for future mortality. The goals of this study were to: (1) describe the patterns of exercise and perceived limitations in physical activity among new patients with ESRD in the United States, and (2) evaluate their associations with all-cause and cardiovascular mortality.

METHODS

The Dialysis Morbidity and Mortality Study (DMMS) Wave 2, a special study of the US Renal Data System (USRDS), served as the primary source of data for these analyses. Several published reports describe the study design of this special study, and a copy of data collection instruments may be found in the Annual Data Report of the USRDS.[13] In brief, this study included a nationally representative sample of patients who started dialysis therapy in 1996 and 1997. Patient data on the presence of medical conditions and assignment to peritoneal dialysis (PD) or HD were obtained through a Medical Questionnaire completed by personnel at each dialysis facility. These included information on demographics, prior medical history, laboratory results, vascular access, and medication use, all obtained from review of patient medical records. Data for physical activity, pre-ESRD care, and quality-of-life measures were captured through a Patient Questionnaire using the Kidney Disease Quality of Life Short Form. The reliability and validity of all components of the Kidney Disease Quality of Life have been supported in multiple studies.[14-16]

Definitions of Physical Activity

Respondents to the patient questionnaire were asked to comment on the frequency of their participation in regular physical activity during their leisure time. Possible answers ranged from daily or almost daily, 4 to 5 times/wk, 2 to 3 times/wk, less than or equal to 1 time/wk, and never. Similarly, respondents also were asked to rate the degree of limitation in vigorous and moderate physical activities. Examples of vigorous activities included running and participating in strenuous sports, whereas examples of moderate physical activities included moving a table, pushing a vacuum cleaner, or playing golf. Possible answers ranged from no limitations, minimal limitations, to severe limitations for each physical activity group.

Ascertainment of Mortality Data

The DMMS Wave 2 data set was linked with the US Renal Database, a renal registry that captures data on all US patients undergoing dialysis. This allowed merging of data on dates and causes of death by USRDS identification number for each study participant. Causes of death were obtained from the Center for Medicare and Medicaid Services Death Notification Form, which list 59 categories for cause of death.[17] For purposes of this study, deaths from cardiovascular disease were classified as those that resulted directly or indirectly from a cardiac- or vascular-related event. Patients were systematically excluded from the original data set if the Medicare identification number prevented linking with existing USRDS mortality data or the number of days at risk could not be calculated (n = 180), patients were younger than 15 years (n = 35), and patients did not respond to the exercise- or physical activity–appropriate segments of the patient questionnaire (n = 1,424 and 1,360, respectively). After exclusion, there were 2,386 patients available who responded to the question on exercise frequency and 2,450 patients who responded to the question on physical activity limitations.

Data Analysis

Descriptive characteristics were performed for the entire population and for patient groups classified by both frequency of exercise and degree of limitation in physical activity.

Kaplan-Meier actuarial survival curves were calculated for the entire cohort by frequency of exercise and degree of limitation in moderate and vigorous physical activities. Survival probabilities were estimated for each group and compared using the log-rank method. Similar comparisons were made for patients with and without diabetes and those treated with either HD or PD.

Univariate and multivariate Cox regression modeling explored the association of exercise frequency and physical activity limitations with all-cause and cardiovascular mortality. Patients were followed up until the earliest of death, loss to follow-up, or end of study. Multivariate models of increasing complexity were built to see whether the association between exercise frequency and mortality risk could be explained by demographic factors, coexisting medical conditions, and laboratory measures of comorbidity. Demographic variables of interest included age at study start, sex, and race. Comorbid conditions were represented by dichotomized variables denoting the presence or absence of coronary artery disease, congestive heart failure, peripheral vascular disease, left ventricular hypertrophy, undernourished state (based on a subjective caregiver classification), serum albumin level, phosphorus level, and hematocrit. Additional models were constructed in which we also adjusted for measures of pre-ESRD care. For these analyses, variables were included to represent treatment with erythropoietin in the pre-ESRD period, frequency of visits to a nephrologist or dietitian in the pre-ESRD period, and late referral (first seen by a nephrologist within 4 months of ESRD start). These surrogate markers of pre-ESRD care have shown a strong correlation with survival in prior analyses.[18,19]

Several sensitivity analyses were performed to test the robustness of these associations. First, to reduce the possibility of confounding by early post-ESRD deaths on the exercise-mortality relationship, survival analyses were conditioned to begin 60 days after the first dialysis treatment. Second, acknowledging the strong correlation between limitation in physical activity and the likelihood of exercise, we evaluated the relationship of exercise frequency with mortality separately for patient groups reporting either minimal to no limitations in physical activity or severe limitations in physical activity. Third, additional models were constructed to determine whether these associations remained steadfast when patients were censored at renal transplantation.

A second series of models evaluated the associations of limitations in moderate and vigorous physical activities with mortality. In a manner similar to that described, multivariable models were developed to determine whether associations between limitations in physical activities with mortality could be explained by baseline differences between groups, especially measuring comorbidity burden and pre-ESRD care. Finally, these analyses were repeated to determine the associations of exercise frequency and self-reported limitations in physical activity with cardiovascular mortality risk. For each regression model, interactions were sought between physical activity and other listed covariates, with special consideration for age, race, and sex. The proportional hazards assumption was tested for each dependent variable of interest by evaluating for a time-covariate interaction. All statistical analyses were carried out using SAS software (version 8.0; SAS Institute, Cary NC).

RESULTS

Characteristics of Respondents

Of 4,025 patients enrolled in the DMMS Wave 2 during 1996 and 1997, a total of 64% responded to the questions on moderate and vigorous physical activity limitations and 63% responded to the question on frequency of exercise. Mean age of the study population was 57 ± 16 years. Of these, 53% were men, 64% were white, and 9% were of Hispanic ethnicity. HD was the initial modality for 52%, and PD, for 48% of patients. In general, nonresponders were slightly older (59 ± 16 versus 58 ± 16 years), had fewer men (52% versus 54%) and whites (59% versus 65%), and were characterized by a relatively greater cardiovascular risk profile (eg, heart failure, 39% versus 34%; cerebral vascular disease, 15% versus 11%) than those who responded.

Patterns of Exercise Among New Patients With ESRD at ESRD Start

Overall, 56% of patients reported exercising at a frequency of 1 time/wk or less, with the remaining 44% exercising at least 2 to 3 times/wk or more, as shown in Fig 1.

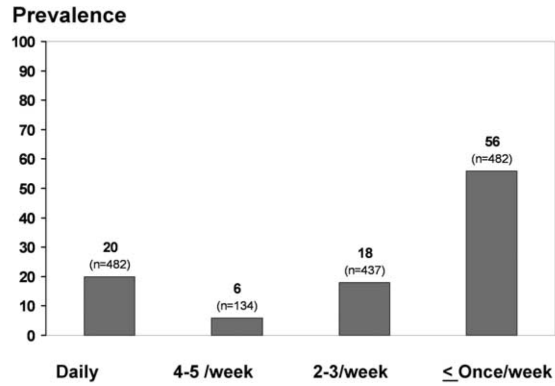

Fig 1. Frequency of exercise among new patients with ESRD in the United States.

Characteristics of patients in each of the 4 exercise categories are listed in Table 1. In general, patients who exercised 2 to 3 times/wk or 4 to 5 times/wk had a lower prevalence of coronary disease, congestive heart failure, and tobacco use compared with patients in the remaining categories, although it is noteworthy that most other comorbid conditions including such objective measures of comorbidity as body mass index or serum albumin level did not vary significantly among exercise categories. Patients who exercised 2 to 3 times/wk or 4 to 5 times/wk also were more likely to receive better pre-ESRD care and less likely to report severe limitations in moderate or vigorous physical activities compared with patients in the remaining groups.

Limitations in Moderate and Vigorous Physical Activities at ESRD Onset

Overall, 75% of respondents reported severe limitations in vigorous physical activities, whereas 42% reported severe limitations in moderate physical activities at ESRD initiation, as shown in Fig 2. In general, patients reporting severe limitations in physical activity were older; had a greater percentage of females, whites, and non-Hispanics; and had a greater prevalence of malnutrition and comorbid medical conditions compared with those reporting little or no limitations (Table 2). Conversely, patients who reported minimal or no limitations were more likely to select PD over HD, remain in full- or part-time employment, be referred early, and be seen more often by a nephrologist or dietitian during the pre-ESRD period.

Table 1. Frequency of Reported Exercise Among New Patients With ESRD in the United States

	≤1 Time/Wk (n = 1,333)	2-3 Times/Wk (n = 437)	4-5 Times/Wk (n = 134)	Daily/Almost Daily (n = 482)
Demographic factors				
Mean age at study start (y)	57.6 ± 16	56.0 ± 16	58.4 ± 15	58.8 ± 16*
Sex (%)				
Male (*v* female)	48.7	58.6	65.1	63.0†
Race (%)				
White	64.5	64.3	69.0	65.0
Black	27.5	24.5	20.2	26.6
Asian	1.7	3.3	4.7	3.1
Ethnicity (%)				
Hispanic (*v* non-Hispanic)	10.0	9.3	7.8	7.0‡
Cause of ESRD (%)				
Glomerulonephritis	8.6	10.7	12.4	8.7
Diabetes	39.4	36.2	45.7	40.7
Hypertension	28.8	27.1	24.0	25.7
Clinical factors (% yes)				
Diabetes (as comorbid condition)	45.7	41.2	50.4	46.6
Coronary artery disease§	37.4	35.7	31.0	38.3
Congestive heart failure	35.6	27.6	27.1	30.9‖
Peripheral vascular disease#	16.9	16.2	18.6	16.8
Left ventricular hypertrophy¶	20.4	20.2	17.8	19.8
Cardiomegaly**	24.8	26.0	20.2	24.0
Smoker††	42.8	41.2	39.5	46.2
Neoplasm	9.8	8.6	10.1	10.2
Undernourished state	17.4	16.2	18.6	17.2
Chronic lung disease	11.6	8.3	9.3	9.8
Body mass index (kg/m^2)	26.1 ± 6.3	25.5 ± 6.1	25.6 ± 5.4	26.1 ± 6.0
% Obese (body mass index > 30 kg/m^2)	20.5	20.6	16.2	21
Laboratory values				
Hematocrit (%)	30.3 ± 6.1	31.0 ± 5.7	29.0 ± 6.4	30.6 ± 6.0
Serum albumin (g/dL)	3.5 ± 0.6	3.5 ± 0.6	3.5 ± 0.6	3.5 ± 0.6
Serum phosphate (mg/dL)	5.6 ± 1.9	5.5 ± 1.7	5.6 ± 1.7	5.4 ± 1.8‡
Serum calcium (mg/dL)	8.7 ± 1.1	8.7 ± 1.0	8.8 ± 1.0	8.6 ± 3.8
Serum parathyroid hormone (ng/mL)	313 ± 313	337 ± 387	322 ± 354	363 ± 597
Serum creatinine (mg/dL)‡‡	8.6 ± 3.9	8.7 ± 3.6	8.2 ± 3.3	8.6 ± 3.8
Dialysis modality (%)				
PD	48.6	51.7	55.0	43.1‡
Pre-ESRD care factors				
Late referral (≤4 mo of ESRD start)	36.2	31.2	27.9	22.0‡
Visits to nephrologist (≥2 *v* >2)	62.7	66.4	71.3	60.4*
Visits to dietitian (≥2 *v* <2)	51.7	62.6	55.0	51.4†
Erythropoietin use pre-ESRD	25.0	27.6	32.6	24.4
Socioeconomic factors (%)				
Employment full-time (*v* other)	28	33.8	27.9	24.6‡
Education (%)				
College (*v* elementary)	29.5	34.5	40.3	32.2‡
Limitations in physical activity (%)				
Moderate activities				
No limitations	18.8	26.7	28.7	27.2†
Minimal limitations	33.8	40.5	39.5	32.2‡
Severe limitations	44.2	30.2	29.5	38.1†
Vigorous activities				
No limitations	7.8	6.4	7.8	8.7
Minimal limitations	13.5	20.7	27.9	21.1†

(Continued)

Table 1 (Cont'd). Frequency of Reported Exercise Among New Patients With ESRD in the United States

	≤1 Time/Wk (n = 1,333)	2-3 Times/Wk (n = 437)	4-5 Times/Wk (n = 134)	Daily/Almost Daily (n = 482)
Severe Limitations	75.0	70.7	62.0	66.7‖

NOTE. Data expressed as percent or mean ± SD. To convert albumin in g/dL to g/L, multiply by 10; phosphate in mg/dL to mmol/L, multiply by 0.3229; calcium in mg/dL to mmol/L, multiply by 0.2495; creatinine in mg/dL to μmol/L, multiply by 88.4.
*$P = 0.06$ for group comparisons.
†$P < 0.001$ for group comparisons.
‡$P < 0.05$ for group comparisons.
§Coronary artery disease was defined as present in patients who had a history of coronary artery disease or myocardial infarction, prior angiography for coronary artery disease, abnormal angiogram or angioplasty, or coronary artery bypass grafting.
‖$P < 0.01$ for group comparisons.
#Includes a history of peripheral vascular disease, amputation, intermittent claudication, or absent pulses.
¶Includes a history of left ventricular hypertrophy on echocardiogram or electrocardiogram.
**Cardiac enlargement on chest radiograph.
††Present or past smokers.
‡‡Recorded before the first dialysis treatment.

Patient Survival by Exercise Frequency

Overall, there were 1,366 deaths (57.3%) and 487 transplantations (20.4%) during a mean follow-up of 3.6 ± 1.9 years (median, 4.0 years; range, 1 month to 5.9 years) in the final study cohort (n = 2,386). Kaplan-Meier survival curves were estimated for all patients by exercise frequency (Fig 3). Survival was greatest for patients who exercised between 2 to 3 times/wk and 4 to 5 times/wk (47.6% ± 2.6% and 45.9% ± 4.6%, respectively) compared with patients who exercised daily (37.8% ± 2.4%) or at most 1 time/wk (40.0% ± 1.5%). In the unadjusted Cox model, patients who exercised either 2 to 3 times/wk or 4 to 5 times/wk experienced a significantly lower death risk by 29% and 33% compared with those who were more sedentary (≤1 time/wk; referent group) or those who exercised daily (Table 3), respectively. Multivariate modeling with adjustment for known mortality predictors confirmed the survival advantage of a 2- to 3-times/wk or 4- to 5-times/wk exercise pattern (relative risk [RR], 0.74; 95% confidence interval [CI], 0.58 to 0.95; RR, 0.70; 95% CI, 0.47 to 1.04, respectively), whereas no such benefit was seen for those reporting daily exercise (adjusted RR, 1.06; 95% CI, 0.86 to 1.30).

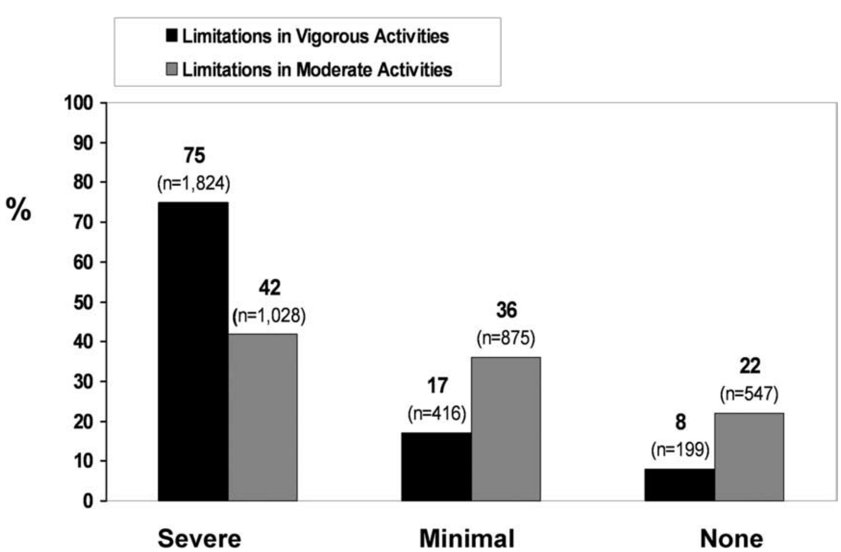

Fig 2. Limitations in moderate and vigorous physical activities among new patients with ESRD in the United States.

Table 2. Characteristics of Patients at ESRD Onset With Limitations in Physical Activities in the United States

	Moderate Activities		Vigorous Activities	
	Not Limited (n = 1,422)	Limited (n = 1,028)	Not Limited (n = 615)	Limited (n = 1,824)
Demographic factors				
Mean age at study start (y)	54.0 ± 16.0	63.0 ± 13.6*	53.2 ± 16	59.2 ± 15.0*
Sex (%)				
Male (*v* female)	56.5	47.5*	59.0	50.3*
Race (%)				
White (*v* nonwhite)	62.5	67.0†	52.6	68.1*
Black	28.2	25.8	35.1	24.6*
Asian	2.8	2.0	3.3	2.3
Ethnicity (%)				
Hispanic (*v* non-Hispanic)	10.1	7.8	13.0	7.9*
Cause of ESRD (%)				
Glomerulonephritis	11.2	6.7*	12.5	8.1‡
Diabetes	37.3	43.4‡	33.7	41.9*
Hypertension	27.9	27.4	31.3	26.6†
Clinical factors (% yes *v* no)				
Diabetes (as a comorbid condition)	41.7	51.2*	37.5	48.4*
Coronary artery disease§	29.4	48.5*	24.7	41.6*
Congestive heart failure	26.8	43.3*	26.0	36.4*
Peripheral vascular disease‖	11.6	24.3*	8.5	19.8*
Pericarditis	2.8	3.1	3.1	2.9
Left ventricular hypertrophy#	17.9	22.4‡	18.2	20.1
Cardiomegaly¶	21.6	30.2*	21.2	26.3†
Smoker**	41.4	42.7	39.2	42.9
Neoplasm	7.8	11.6‡	7.5	10.1
Undernourished	12.8	23.5*	10.9	19.2*
Body mass index (kg/m^2)	26.2 ± 6.0	25.5 ± 6.3†	26.4 ± 6.3	25.8 ± 6.1
Obese (body mass index > 30 kg/m^2)	21	18.8	22.1	19.8
Laboratory values				
Hematocrit (%)	30.7 ± 6.0	30.2 ± 6.0	30.4 ± 5.7	30.5 ± 6.1
Serum albumin (g/dL)	3.6 ± 0.55	3.4 ± 0.55*	3.6 ± 0.55	3.5 ± 0.56‡
Serum phosphate (mg/dL)	5.7 ± 1.8	5.4 ± 1.8*	5.7 ± 1.8	5.5 ± 1.8
Serum calcium (mg/dL)	8.7 ± 1.0	8.7 ± 1.1	8.6 ± 1.0	8.7 ± 1.1
Serum parathyroid hormone (ng/mL)	340 ± 384	288 ± 364‡	384 ± 381	298 ± 375*
Serum creatinine (mg/dL)††	9.0 ± 4.0	7.8 ± 3.2*	9.4 ± 4.1	8.2 ± 3.6*
Dialysis modality (%)				
PD	54.4	37.7*	47.6	47.5
Pre-ESRD care (%)				
Late referral (≤4 mo of ESRD start)	32.9	39.1‡	35.9	35.2
Visits to nephrologists (≥2 *v* >2)	65.6	57.8*	62.0	62.8
Visits to dietitian (≥2 *v* <2)	54.6	49.5†	56.8	51.5†
Erythropoietin use pre-ESRD (yes *v* no)	26.2	24.2	24.7	25.8

(Continued)

Table 2 (Cont'd). Characteristics of Patients at ESRD Onset With Limitations in Physical Activities in the United States

	Moderate Activities		Vigorous Activities	
	Not Limited (n = 1,422)	Limited (n = 1,028)	Not Limited (n = 615)	Limited (n = 1,824)
Socioeconomic factors (%)				
Employment (%)				
Full-time (*v* other)	36.4	16.0*	37.7	24.5*
Part-time (*v* other)	6.7	4.8	7.8	5.5†

NOTE. Data expressed as percent or mean ± SD. To convert albumin in g/dL to g/L, multiply by 10; phosphate in mg/dL to mmol/L, multiply by 0.3229; calcium in mg/dL to mmol/L, multiply by 0.2495; creatinine in mg/dL to μmol/L, multiply by 88.4.

*$P < 0.001$ for bivariate comparisons.

†$P < 0.05$ for bivariate comparisons.

‡$P < 0.01$ for bivariate comparisons.

§Coronary artery disease was defined as present in patients who had a history of coronary artery disease or myocardial infarction, prior angiography for coronary artery disease, abnormal angiogram or angioplasty, or coronary artery bypass grafting.

‖Includes a history of peripheral vascular disease, amputation, intermittent claudication, or absent pulses.

#Includes a history of left ventricular hypertrophy on echocardiogram or electrocardiogram.

¶Cardiac enlargement on chest radiograph.

**Present or past smokers.

††Recorded before the first dialysis treatment.

Results were virtually unchanged when transplantation was included as a censoring event, thereby removing its associated survival advantage. Furthermore, a similar pattern was observed when we excluded deaths within the first 6 months after dialysis therapy initiation (data not shown).

In subgroup analyses, associations of exercise 2 to 3 times/wk or 4 to 5 times/wk with mortality were similar for almost all groups examined. In particular, patients with and without diabetes and those treated with either HD or PD had a trend of lower mortality risk, although these did not always achieve the conventional level of statistical significance. Conversely, we found that the association of frequent exercise with mortality differed significantly between whites and nonwhites ($P = 0.006$ for interaction) and older and younger patients ($P = 0.005$ for interaction). Positive associations of frequent exercise with

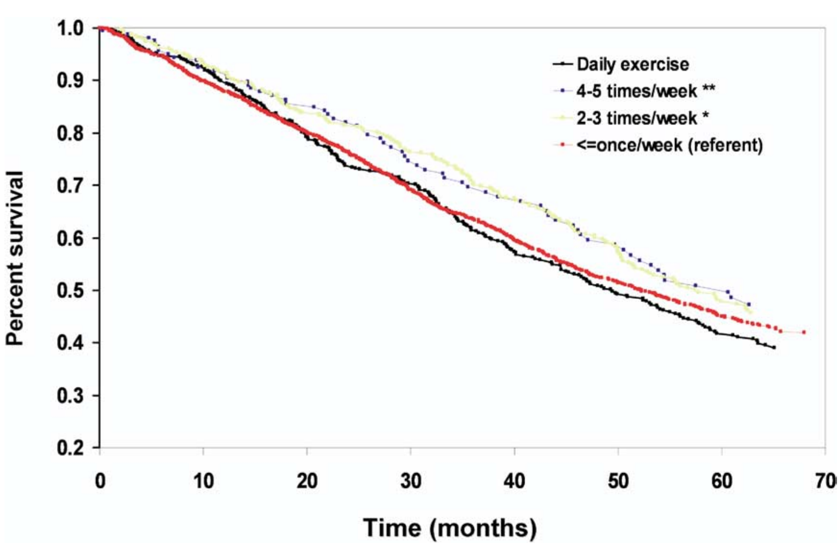

Fig 3. Adjusted Cox survival curves for new patients with ESRD in the United States by exercise frequency, adjusted for age at study start, sex, race, cause of ESRD, coronary artery disease, peripheral vascular and cerebrovascular disease, congestive heart failure, left ventricular hypertrophy, anemia, and phosphorous and serum albumin levels. *$P < 0.05$. **$P < 0.01$.

Table 3. Relative Mortality Risks by Exercise Frequency Among New Patients With ESRD in the United States

	Exercise Frequency	Unadjusted RR (95% CI)	Multivariable RR*† (95% CI)
All patients (n = 2,064)	≤1 time/wk	1.00	1.00
	2-3 times/wk	0.71 (0.57-0.89)‡	0.74 (0.58-0.95)§
	4-5 times/wk	0.67 (0.46-0.98)§	0.70 (0.47-1.04)‖
	Daily/almost daily	0.97 (0.80-1.17)	1.06 (0.86-1.30)
Age ≥ 65 y (n = 822)	≤ 1 time/wk	1.00	1.00
	2-3 times/wk	0.69 (0.51-0.95)§	0.66 (0.48-0.91)§
	4-5 times/wk	0.71 (0.44-1.14)	0.66 (0.41-1.05)
	Daily/almost daily	0.94 (0.73-1.23)	0.94 (0.72-1.23)
Age < 65 y (n = 1,242)	≤1 time/wk	1.00	1.00
	2-3 times/wk	0.70 (0.47-1.04)	0.82 (0.55-1.23)
	4-5 times/wk	0.63 (0.31-1.28)	0.76 (0.37-1.56)
	Daily/almost daily	1.17 (0.85-1.61)	1.24 (0.90-1.72)
White patients (n = 1,347)	≤1 time/wk	1.00	1.00
	2-3 times/wk	0.54 (0.39-0.73)#	0.59 (0.43-0.81)#
	4-5 times/wk	0.73 (0.47-1.13)	0.78 (0.50-1.21)
	Daily/almost daily	0.95 (0.75-1.21)	0.98 (0.77-1.10)
Nonwhite (n = 717)	≤1 time/wk	1.00	1.00
	2-3 times/wk	1.17 (0.78-1.77)	1.26 (0.83-1.90)
	4-5 times/wk	0.63 (0.26-1.56)	0.56 (0.23-1.39)
	Daily/almost daily	1.21 (0.89-1.91)	1.33 (0.90-1.96)
Moderate activities			
Minimal or no limitations (n = 1,227)	≤1 time/wk	1.00	1.00
	2-3 times/wk	0.75 (0.52-1.07)	0.77 (0.53-1.11)
	4-5 times/wk	0.59 (0.30-1.10)	0.55 (0.29-1.06)
	Daily/almost daily	1.15 (0.85-1.56)	1.16 (0.84-1.59)
Severe limitations (n = 837)	≤1 time/wk	1.00	1.00
	2-3 times/wk	0.81 (0.58-1.13)	0.81 (0.58-1.15)
	4-5 times/wk	1.14 (0.70-1.87)	0.96 (0.58-1.59)
	Daily/almost daily	1.06 (0.81-1.39)	1.03 (0.79-1.36)
Vigorous activities			
Minimal or no limitations (n = 561)	≤1 time/wk	1.00	1.00
	2-3 times/wk	0.44 (0.23-0.86)§	0.50 (0.25-0.98)§
	4-5 times/wk	0.52 (0.21-1.29)	0.54 (0.21-1.36)
	Daily/almost daily	0.99 (0.63-1.54)	1.14 (0.71-1.82)
Severe limitations (n = 1,503)	≤1 time/wk	1.00	1.00
	2-3 times/wk	0.77 (0.59-1.00)§	0.82 (0.63-1.07)
	4-5 times/wk	0.87 (0.56-1.34)	0.80 (0.52-1.24)
	Daily/almost daily	1.12 (0.89-1.41)	1.07 (0.85-1.36)

*Model adjusted for age at study start (60 days after the initiation of long-term regular dialysis therapy), sex, race, cause of ESRD, congestive heart failure, coronary artery disease, left ventricular hypertrophy, cerebral and peripheral vascular disease, hematocrit, and serum phosphorus and albumin levels.

†Relative risks and 95% confidence limits.

‡$P < 0.01$ on comparing all categories with the referent (≤1 time/wk; RR, 1.00).

§$P \leq 0.05$ on comparing all categories with the referent (≤1 time/wk; RR, 1.00).

‖$P = 0.07$ on comparing all categories with the referent (≤1 time/wk; RR, 1.00).

#$P < 0.001$ on comparing all categories with the referent (≤1 time/wk; RR, 1.00).

lower mortality seen in whites and older patients (>65 years) did not extend to nonwhites and younger patients.

Acknowledging that the relationship between exercise and mortality may vary for individuals with limitations in physical activities, these analyses were repeated stratified by type and degree of limitation in physical activity (Table 3). In each of these analyses, the adjusted model favored a trend of lower mortal-

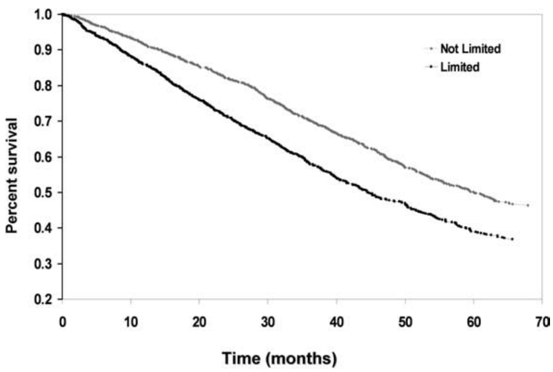

Fig 4. Adjusted Cox survival curves for new patients with ESRD in the United States with and without severe limitations in moderate physical activities, adjusted for age at study start, sex, race, cause of ESRD, coronary artery disease, peripheral vascular and cerebrovascular disease, congestive heart failure, left ventricular hypertrophy, anemia, and phosphorous and serum albumin levels. *$P < 0.0001$.

ity risk for patients who exercised 2 to 3 times/wk or 4 to 5 times/wk compared with the referent. However, risk estimates tended to be lower for patients who reported little or no limitations compared with those who reported severe limitations, especially for those in the vigorous activity stratum ($P = 0.2$ for interaction).

Patient Survival by Limitations in Moderate or Vigorous Physical Activities

Cumulative survival was significantly lower for patients reporting severe limitations in either moderate or vigorous physical activities compared with patients reporting little or no limitations during follow-up (37.9% ± 1.2% versus 53.6% ± 2.1% and 27.8% ± 1.4% versus 52.0% ± 1.4%, respectively; $P < 0.0001$; Figs 4 and 5). Table 4 lists mortality risk associations by limitations in moderate and vigorous physical activities. In the unadjusted model, patients with severe limitations in moderate physical activities experienced more than a 2-fold greater mortality risk on follow-up compared with patients with minimal or no limitations (RR, 2.60; CI, 2.23 to 3.04). With adjustment for case mix, the risk, although attenuated, remained significantly greater for patients with severe limitations (RR, 1.72; CI, 1.44 to 2.05).

Mortality risk associations of patients reporting limitations in vigorous physical activities were similar to those described, with the greatest risk for death occurring in those with severe limitations (adjusted RR, 1.51). Among patients with (RR, 1.41) and without diabetes (RR, 1.63) and PD (RR, 1.50) and HD patients (RR, 1.48), adjusted mortality risks were significantly greater in those with severe limitations.

Cardiovascular Mortality Associations

RR for cardiovascular death was significantly lower only for patients who exercised 2 to 3 times/wk (RR, 0.72; 95% CI, 0.53 to 0.98) compared with the referent. With adjustment for case mix, the magnitude of the association remained and followed a similar trend (RR, 0.80; 95% CI, 0.58 to 1.08). The relationship between exercise frequency and noncardiovascular causes of death followed a similar pattern (RR, 0.67; 95% CI, 0.45 to 1.06). Finally, patients who reported severe limitations in either moderate or vigorous physical activities experienced significantly increased cardiovascular mortality in multivariable analysis (RR, 1.59; 95% CI, 1.27 to 1.99; RR, 1.47; 95% CI, 1.10 to 1.97, respectively).

DISCUSSION

Despite the increased attention given to physical activity in the general population, few studies have explored its importance among long-term dialysis patients, a population characterized by considerable morbidity and mortality. In this study, the prevalence of severe limitations in physical activities was substantial, with 74% of

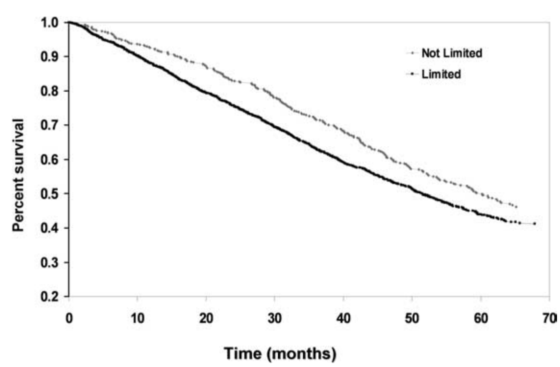

Fig 5. Adjusted Cox survival curves for new patients with ESRD in the United States with and without severe limitations in vigorous physical activities, adjusted for age at study start, sex, race, cause of ESRD, coronary artery disease, peripheral vascular and cerebrovascular disease, congestive heart failure, left ventricular hypertrophy, anemia, and phosphorous and serum albumin levels. *$P = 0.01$.

Table 4. Relative Mortality Risks by Degree of Limitation in Moderate and Vigorous Physical Activities

Moderate Activities		Unadjusted RR (95% CI)	Multivariable RR (95% CI)
All patients (n = 2,116)	Minimal or none	1.00	1.00
	Severe	2.60 (2.23-3.04)*	1.72 (1.44-2.05)*
With diabetes (n = 876)	Minimal or none	1.00	1.00
	Severe	2.10 (1.69-2.61)*	1.56 (1.22-1.99)*
Without diabetes (n = 1,240)	Minimal or none	1.00	1.00
	Severe	3.09 (2.47-3.86)*	1.95 (1.51-2.51)*
PD (n = 989)	Minimal or none	1.00	1.00
	Severe	3.04 (2.42-3.81)*	1.87 (1.44-2.43)*
HD (n = 1,128)	Minimal or none	1.00	1.00
	Severe	2.26 (1.83-2.81)*	1.59 (1.25-2.02)*
Vigorous Activities		**Unadjusted RR (95% CI)**	**Multivariable RR (95% CI)**
All patients (n = 2,107)	Minimal or none	1.00	1.00
	Severe	2.24 (1.80-2.77)*	1.51 (1.20-190)*
With diabetes (n = 871)	Minimal or none	1.00	1.00
	Severe	1.80 (1.34-2.43)*	1.41 (1.03-1.94)†
Without diabetes (n = 1,236)	Minimal or none	1.00	1.00
	Severe	2.60 (1.91-3.55)*	1.63 (1.16-2.28)‡
PD (n = 984)	Minimal or none	1.00	1.00
	Severe	2.33 (1.69-3.24)*	1.50 (1.04-2.15)†
HD (n = 1,123)	Minimal or none	1.00	1.00
	Severe	2.16 (1.62-2.88)*	1.48 (1.10-2.00)‡

NOTE. Model adjusted for age at study start, sex, race, cause of ESRD, congestive heart failure, coronary artery disease, left ventricular hypertrophy, cerebral and peripheral vascular disease, hematocrit, and serum phosphorus and albumin levels.

*$P < 0.001$ on comparing patients with severe limitations with those with minimal to no limitations in physical activities by means of Cox proportional hazards regression.

†$P < 0.05$ on comparing patients with severe limitations with those with minimal to no limitations in physical activities by means of Cox proportional hazards regression.

‡$P < 0.01$ on comparing patients with severe limitations with those with minimal to no limitations in physical activities by means of Cox proportional hazards regression.

patients describing severe limitations in vigorous physical activities and 42% describing severe limitations in moderate activities. Nevertheless, despite these perceived limitations in physical activity, 44% of new patients with ESRD reported exercising 2 to 3 times/wk or more, suggesting that a large percentage of new patients with ESRD participate in regular physical activities. We found that regular exercise (between 2 to 3 and 4 to 5 times/wk) was associated with lower all-cause and cardiovascular mortality, although this benefit did not extend to those who reported daily exercise. We also found that patients reporting severe limitations in both moderate and vigorous physical activities experienced significantly increased all-cause and cardiovascular mortality independent of known mortality predictors. These observations suggest that despite the significant comorbidity burden and perceived limitations in physical activities among new patients with ESRD in the United States, increased exercise may confer a survival advantage.

One of the principal findings of this study is the association of frequent exercise with lower risk for death. Patients who exercised 2 to 3 times/wk or 4 to 5 times/wk had significantly lower risk for death compared with those who were more sedentary. Moreover, patients who exercised 2 to 3 times/wk experienced a significantly lower risk for cardiovascular death. These findings were confirmed in sensitivity analyses. First, we adjusted for a large number of known mortality predictors because we hypothesized that these might explain, in part, the benefit of frequent exercise. Second, we showed that these results were consistent among most subgroups. Third, we showed that associations followed a similar trend among persons with limitations in moderate and vigorous physical activities. Finally, we found that the relationship of increased exercise with survival was present even when excluding deaths occurring within the first 60 days of dialysis therapy initiation, thereby limiting the possibility of a spurious association through confounding (ie, patients with greater prevalence of comorbidity exercise less frequently and therefore die sooner).[20]

A surprising finding in this study is the lack of association between daily exercise and improved survival. It is possible that the adverse cardiovascular risk profile, greater among those reporting daily exercise compared with those reporting less frequent exercise, contributed to this finding. It also might be argued that the lack of regular pre-ESRD care in this group, indicated by a relatively low use of erythropoietin and less frequent visits to a nephrologist or dietitian, also may have contributed to these findings.[18,19,21,22] However, when we adjusted sequentially for these differences (data not shown), the associations were virtually unchanged. Finally, the possibility of error in reporting of exercise frequency, perhaps from lack of recall, cannot be ignored. Such a finding may have resulted in misclassification of exercise groups.

We hypothesized that patients with the greatest limitations in physical activities (moderate or severe) would experience the greatest mortality risk compared with those with few or no limitations. In support of this, we found that patients reporting severe limitations in either moderate or physical activities had greater all-cause and cardiovascular mortality, and these relationships remained significant after several levels of adjustment. However, one could argue that degree of limitation in physical activity is a surrogate measure of either comorbidity burden or illness severity, rather than an index of physical activity. Consequently, the increased hazard of death associated with severe limitations in physical activity may simply reflect the severity of measured clinical conditions or unmeasured comorbidity, rather than physical activity. Conversely, the broad adjustment for several demographic, clinical, and laboratory measures in these analyses suggest that physical inactivity may in itself be independently associated with increased mortality.

Evidence from observational studies of the general population suggests that increased physical activity is strongly and inversely associated with all-cause and cardiovascular mortality.[4-12] However, whether this benefit extends to populations who, on average, have a greater prevalence of cardiovascular conditions, malnutrition, and anemia compared with similar aged persons in the general population is unclear. Recently published data from the British Regional Heart Study suggest that increased physical activity may offer a survival benefit in older patients with cardiovascular disease. In a longitudinal cohort of 772 men with coronary disease followed up for 5 years, participants in light and moderate activities compared with nonparticipants had 58% and 53% lower all-cause mortality.[9] Our observations are consistent with these and perhaps even more striking given the overall greater prevalence of comorbid conditions found in new patients with ESRD.[23-25]

Our analyses suggest that increased physical activity, measured by either degree of limitation in physical activities or frequency of participation in physical activities, may confer a survival advantage. However, there are inherent limitations in this study design that should be considered in the context of our findings. First, responders (62% to 64%) differed from nonresponders in that they had a lower prevalence of cardiovascular conditions (diabetes, 41% versus 46%; coronary disease, 38% versus 39%; and heart failure, 34% versus 39%), as well as lower overall mortality (57% versus 66%). Despite these differences, the prevalence of comorbidity and overall mortality were equally substantial in both groups and argue against a major selection bias. Second, the association of less frequent exercise with elevated mortality risk may reflect the number and/or severity of coexisting comorbid conditions recorded at ESRD initiation, rather than a true measure of physical activity.[16] We attempted to exclude this possibility by excluding deaths within the first 6 months after dialysis therapy initiation. Third, the possibility of transplantation bias also was considered because patients who reported few or no limitations would be more likely to get waitlisted and undergo transplantation. The inclusion of renal transplantation as a censoring event in the ancillary analyses eliminated this possibility. Finally, our definitions of physical activity were based on self-report questionnaires and therefore represent a subjective assessment of physical activity.[14] We did not objectively measure degrees or intensity of physical activity or changes in physical activity occurring over time, measures that may have strengthened the validity of our observations.

Nevertheless, the current study has several strengths. In its favor are the longitudinal design with ascertainment of outcome after the patients initiated dialysis therapy; inclusion of an incident ESRD population, limiting survival bias associated with the use of prevalent cohorts; extensive adjustment for potential confounders; and generalizability to the entire US ESRD population.

In conclusion, this study provides evidence that limitations in moderate and vigorous physical activities are common among new dialysis patients in the United States. Despite these, a large percentage of patients participate in regular physical activities. Moreover, it shows that new patients with ESRD with severe limitations in moderate or vigorous activities have substantially increased mortality risk beyond that of more physically active people, and patients who exercise 2 to 3 times/wk or 4 to 5 times/wk experience significantly improved survival. Future efforts should test the validity of these observations in randomized clinical trials, while at the same time promoting physically active lifestyles for all patients approaching ESRD.

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