Article

Associations of Self-Reported Physical Activity Types and Levels with Quality of Life, Depression Symptoms, and Mortality in Hemodialysis Patients: The DOPPS

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Abstract

Background and objectives Physical activity has been associated with better health status in diverse populations, but the association in patients on maintenance hemodialysis is less established. Patient-reported physical activities and associations with mortality, health-related quality of life, and depression symptoms in patients on maintenance hemodialysis in 12 countries were examined.

Design, setting, participants, & measurements In total, 5763 patients enrolled in phase 4 of the Dialysis Outcomes and Practice Patterns Study (2009–2011) were classified into five aerobic physical activity categories (never/rarely active to very active) and by muscle strength/flexibility activity using the Rapid Assessment of Physical Activity questionnaire. The Kidney Disease Quality of Life scale was used for health-related quality of life. The Center for Epidemiologic Studies Depression scale was used for depression symptoms. Linear regression was used for associations of physical activity with health-related quality of life and depression symptoms scores. Cox regression was used for association of physical activity with mortality.

Results The median (interquartile range) of follow-up was 1.6 (0.9–2.5) years; 29% of patients were classified as never/rarely active, 20% of patients were classified as very active, and 20.5% of patients reported strength/flexibility activities. Percentages of very active patients were greater in clinics offering exercise programs. Aerobic activity, but not strength/flexibility activity, was associated positively with health-related quality of life and inversely with depression symptoms and mortality (adjusted hazard ratio of death for very active versus never/rarely active, 0.60; 95% confidence interval, 0.47 to 0.77). Similar associations with aerobic activity were observed in strata of age, sex, time on dialysis, and diabetes status.

Conclusions The findings are consistent with the health benefits of aerobic physical activity for patients on maintenance hemodialysis. Greater physical activity was observed in facilities providing exercise programs, suggesting a possible opportunity for improving patient outcomes.

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Introduction

Physical activity positively affects health status in different types of populations (1–9). Previous studies in patients with CKD and patients on maintenance hemodialysis (MHD) have shown associations of physical activity with improved outcomes (10–18). However, it is uncertain whether the benefits of types and levels of physical activity apply for different outcomes, such as health-related quality of life (HRQOL), depression, and survival, in patients on MHD with diverse clinical characteristics.

Clinical trials have shown that interventions promoting physical activity at home or in-center are effective in improving outcomes, particularly HRQOL and physical functioning (11,12). To promote physical activity in patients with CKD and patients on dialysis, the Kidney Disease Outcomes Quality Initiative recommends physical activity programs and periodic evaluation of their results (19). However, the effectiveness of promoting physical activity as part of routine patient management in dialysis units needs to be investigated.

The objectives of this study using a large international sample of patients on MHD were to (*1*) describe types and levels of physical activity; (*2*) describe associations of patient characteristics with different levels and types of physical activity; (*3*) investigate associations of types of physical activity and levels of aerobic activity with mortality, HRQOL, and depression symptoms; and (*4*) examine whether associations between physical activity and outcomes vary by levels of demographic factors, vintage (length of time on dialysis), and diagnoses of heart failure, ischemic heart disease, and diabetes.

Materials and Methods

Data were from phase 4 (2009–2011) of the Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective cohort study in hemodialysis facilities of 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, the United Kingdom, and the United States). Additional details of the DOPPS design have been described previously (20,21). Briefly, the DOPPS is on the basis of nationally representative samples of randomly selected dialysis facilities and patients. Institutional review boards approved the study, and informed patient consent was obtained in accordance with local requirements. At study baseline, detailed patient data, including sociodemographic characteristics, laboratory values, patient self-reported physical activity, and 14 summary comorbid conditions, were collected. Changes in these variables across time were not assessed in this study. A description of the components of summary comorbid conditions may be found in a previous publication (21). A patient questionnaire was used at baseline for collecting patient self-reported data on HRQOL, depression symptoms, and physical activity. Follow-up outcome data were collected throughout the follow-up period until December 23, 2011.

From the initial sample of 11,733 patients, 2030 (17%) patients treated at facilities of large dialysis organizations in the United States were excluded, because data on comorbidity, physical activity, HRQOL, and depression symptoms were, in general, limited or not available. Additionally, 576 (5%) patients were excluded because of inability to walk. Among the remaining 9127 patients, 7603 (83%) patients responded to the patient questionnaire shortly after study enrollment. Among the 7603 patients who responded to the patient questionnaire, 1840 patients did not provide complete responses on physical activity. Consequently, the main analysis for physical activity was on the basis of data of 5763 patients who completed all seven questions of the aerobic portion of the physical activity survey and at least one of the strength and flexibility questions. Patients who did not respond to the question regarding strength or flexibility training were treated as not participating in strength/flexibility training.

Assessment of Physical Activity

Physical activity levels were measured at baseline using the Rapid Assessment of Physical Activity (RAPA), a self-administered questionnaire composed of nine binary (yes or no) questions with graphic and textual illustrations (22). Seven of the questions asked about light, moderate, or vigorous physical activity for specific frequencies and durations. Five categories of aerobic activity were defined: (*1*) never/rarely active (sedentary), (*2*) infrequently active, (*3*) sometimes active, (*4*) often active, and (*5*) very active. These categories correspond to the categories originally proposed in the work by Topolski *et al.* (22). In some analyses, these five categories were collapsed into two groups: active (sometimes to very active) and inactive (infrequently or never/rarely active). Patients were also classified by their responses to the two binary questions regarding muscle strength and flexibility activities: (*1*) neither muscle strength nor flexibility, (*2*) only strength, (*3*) only flexibility, or (*4*) both strength and flexibility activities. Comparisons with measures by accelerometer (23) and the long form of the Community Healthy Activities Model Program for Seniors (CHAMPS) (22) support the RAPA as a valid self-reported physical activity instrument. To investigate the association of hemodialysis facility exercise programs with patient self-reported physical activity, medical directors of dialysis units were asked whether their units provided an exercise program or access to an exercise program for their patients on hemodialysis.

Assessment of HRQOL and Depression Symptoms

Patient responses to the 36-item version of the Kidney Disease Quality of Life questionnaire were used to calculate scores of the kidney disease burden (KDB) and two HRQOL summaries (*i.e.*, the physical component summary [PCS] and the mental component summary [MCS]) (24,25). KDB scores may vary from 0–100, with higher scores indicating lower perceived burden. Because of the weighting used, PCS scores ranged from 4.8 to 66.7, and MCS scores ranged from 1.4 to 74.7. Higher PCS and MCS scores indicate better physical and mental quality of life, respectively. A difference in HRQOL score >3 points was considered clinically significant (26). The 10-item Center for Epidemiologic Studies Depression Scale (CES-D) was used to determine depression symptoms score, with possible scores ranging from 0–30 and a score$\geq$10 defining higher depression probability (27,28).

Statistical Analyses

For assessing associations between aerobic physical activity and outcomes (mortality, HRQOL, and depression symptoms), patients classified as infrequently active, sometimes active, often active, and very active were compared with those classified as never/rarely active (sedentary). For some analyses, aerobic physical activity was also treated as a binary variable, with infrequently or never/rarely active as the reference category. For associations with strength or flexibility activities, those who did not engage in either of these activities served as the reference group. Minimal and extensive adjustments were made for the covariates listed in Table 1. Additionally, models were either stratified by region (Europe/Australia/New Zealand, Japan, or North America) or adjusted for region.

Linear mixed models were used to analyze associations with continuous outcomes. Logistic regression was used to model binary outcomes, with generalized estimating equations accounting for clustering of patients within facilities assuming an exchangeable working correlation matrix. Cox regression was used to estimate associations between physical activity and all-cause mortality using the sandwich covariance estimators to account for facility clustering effects (29). Time at risk started from the date that the physical activity survey was completed and ended at the date of death, 7 days after departure from the facility, 7 days after changing dialysis modality, date of withdrawing from dialysis, date of transplantation, or latest data collection date for nondeparted study patients, whichever occurred first. The proportional hazards assumption was confirmed by testing log (time) interactions and examining log-log survival plots.

Missing covariate data were imputed using the IVEware Sequential Regression Multiple Imputation Method (30) and analyzed using the MIANALYZE procedure in SAS/STAT 9.2. Five samples of imputed data were generated.

Table 1. Distribution of patient characteristics by aerobic physical activity levels and adjusted odds ratios comparing sometimes or very active with less or never active

Characteristic	Physical Activity Levels					Odds Ratio[a] (95% CI) Comparing Sometimes to Very Active with Less Active or Never Active	
	Never/Rarely Active (*n*=1649)	Infrequently Active (*n*=599)	Sometimes Active (*n*=969)	Often Active (*n*=1733)	Very Active (*n*=1173)	Minimally Adjusted	Extensively Adjusted
Age, yr[b]	68.6 (12.8)	62.7 (14.7)	62.0 (14.5)	61.9 (14.5)	59.5 (14.9)	0.83 (0.79 to 0.87)	0.84 (0.80 to 0.89)
Men, %	55.7	63.1	56.0	63.7	71.0	1.24 (1.11 to 1.38)	1.17 (1.03 to 1.33)
Black, %	3.8	5.7	4.4	5.5	7.6	0.87 (0.65 to 1.15)	0.80 (0.59 to 1.09)
Smoker, %	15.2	17.7	16.5	17.5	16.4	0.82 (0.70 to 0.96)	0.82 (0.70 to 0.97)
At least some college	16.6	25.4	30.9	31.6	30.5	1.46 (1.26 to 1.69)	1.44 (1.24 to 1.68)
Employed (versus unemployed)	7.0	14.4	16.2	18.1	22.9	1.33 (1.09 to 1.62)	1.26 (1.03 to 1.53)
Lives alone (versus does not live alone)	17.0	16.2	19.7	20.0	19.9	1.18 (1.02 to 1.38)	1.19 (1.02 to 1.39)
Assistance with walking	33.1	15.7	18.7	13.7	8.8	0.48 (0.41 to 0.56)	0.56 (0.47 to 0.66)
Body mass index, kg/m^2	26.1 (6.2)	25.5 (6.4)	25.4 (6.3)	25.1 (6.1)	25.6 (5.6)	0.98 (0.97 to 0.99)	0.98 (0.97 to 0.99)
Median yr on dialysis [IQR]	2.4 [0.6–5.8]	2.6 [0.7–6.5]	2.2 [0.6–6.4]	2.8 [0.7–7.1]	2.5 [0.7–5.8]	1.01 (0.97 to 1.05)	1.00 (0.96 to 1.04)
Diabetes	41.2	41.6	38.9	35.9	34.3	0.84 (0.75 to 0.93)	0.95 (0.84 to 1.07)
Hypertension	84.1	84.1	83.5	84.9	87.4	0.96 (0.81 to 1.15)	0.98 (0.82 to 1.17)
Coronary disease	40.4	34.6	37.2	34.0	32.6	0.95 (0.84 to 1.07)	1.00 (0.88 to 1.14)
Heart failure	23.5	22.3	23.1	21.5	17.7	0.92 (0.79 to 1.06)	0.96 (0.82 to 1.12)
Other cardiovascular disease	33.4	26.5	29.9	29.9	25.0	1.02 (0.90 to 1.15)	1.05 (0.92 to 1.20)
Peripheral vascular disease	33.3	28.5	26.1	23.4	21.6	0.86 (0.76 to 0.97)	0.96 (0.84 to 1.11)
Cerebrovascular disease	18.1	14.1	16.3	13.7	11.4	0.99 (0.85 to 1.16)	1.04 (0.88 to 1.22)
Recurrent cellulitis	10.1	9.9	8.1	6.7	6.0	0.70 (0.57 to 0.86)	0.77 (0.61 to 0.96)
Gastrointestinal bleed	4.3	4.4	4.8	5.5	4.7	1.22 (0.94 to 1.60)	1.26 (0.97 to 1.64)
Lung disease	14.9	12.6	12.0	10.3	9.7	0.89 (0.75 to 1.06)	0.93 (0.78 to 1.10)
Neurologic disorder	13.1	8.7	9.0	6.9	4.8	0.72 (0.59 to 0.88)	0.71 (0.58 to 0.87)
Psychiatric disorders	17.7	14.6	19.5	15.0	14.3	0.92 (0.78 to 1.08)	0.98 (0.84 to 1.15)
Nonskin cancer	17.8	12.2	13.7	14.7	12.3	0.97 (0.84 to 1.13)	0.94 (0.80 to 1.09)
HIV	0.3	0.3	0.2	0.9	0.3	1.00 (0.38 to 2.62)	1.03 (0.39 to 2.73)
Access by catheter	27.5	17.9	24.9	17.8	19.7	0.86 (0.74 to 1.00)	0.89 (0.75 to 1.04)
Hemoglobin, g/dl	11.30 (1.39)	11.02 (1.45)	11.17 (1.40)	11.19 (1.37)	11.39 (1.32)	1.05 (1.01 to 1.09)	1.03 (0.99 to 1.08)
spKt/V[c]	1.50 (0.32)	1.44 (0.32)	1.49 (0.32)	1.44 (0.32)	1.45 (0.31)	1.01 (0.99 to 1.03)	0.99 (0.97 to 1.02)
Systolic BP$<$120 mmHg, %	25.6	20.9	22.6	23.7	19.7	0.98 (0.85 to 1.13)	0.96 (0.83 to 1.11)
Systolic BP$>$160 mmHg, %	17.7	23.0	21.5	17.8	19.4	0.91 (0.77 to 1.06)	0.92 (0.78 to 1.09)
Serum creatinine, mg/dl	8.03 (2.66)	9.11 (3.03)	8.78 (3.03)	9.29 (3.16)	9.47 (3.26)	1.04 (1.01 to 1.07)	1.03 (1.00 to 1.06)
Serum albumin, g/dl	3.69 (0.54)	3.74 (0.54)	3.75 (0.51)	3.76 (0.45)	3.82 (0.47)	1.27 (1.11 to 1.46)	1.18 (1.03 to 1.35)
Serum calcium, mg/dl	8.94 (0.88)	8.89 (0.83)	8.99 (0.88)	8.99 (0.88)	8.95 (0.84)	1.07 (1.01 to 1.14)	1.04 (0.98 to 1.10)
Serum phosphorus, mg/dl	4.93 (1.60)	5.27 (1.64)	5.29 (1.55)	5.35 (1.67)	5.42 (1.69)	1.03 (0.99 to 1.07)	1.02 (0.98 to 1.06)

Table 1. (Continued)

Characteristic	Physical Activity Levels					Odds Ratio[a] (95% CI) Comparing Sometimes to Very Active with Less Active or Never Active	
	Never/Rarely Active (*n*=1649)	Infrequently Active (*n*=599)	Sometimes Active (*n*=969)	Often Active (*n*=1733)	Very Active (*n*=1173)	Minimally Adjusted	Extensively Adjusted
Median PTH, pg/ml [IQR][d]	212 [110–367]	199 [107–337]	216 [115–354]	192 [104–341]	217 [118–379]	0.99 (0.97 to 1.01)	0.99 (0.96 to 1.01)
nPCR, g/kg per day[e]	0.99 (0.25)	0.99 (0.24)	0.99 (0.24)	0.99 (0.24)	0.99 (0.23)	1.02 (1.00 to 1.05)	1.01 (0.98 to 1.04)

For the five aerobic physical activity levels from never/rarely to very active, the percentages of patients in each category by region were, for Europe/Australia/New Zealand, 38%, 9%, 14%, 19%, and 20%, respectively; for Japan, 16%, 14%, 18%, 34%, and 18%, respectively; and for North America, 18%, 9%, 24%, 25%, and 23%, respectively. Results are described by mean (SD), percentage, or median [IQR]. The minimally adjusted models included geographic region, age, sex, race, smoking, employment status, education, living with family, number of years on dialysis, and assistance with walking. The extensively adjusted models included body mass index, comorbidities (diabetes, hypertension, coronary disease, heart failure, other cardiovascular disease, peripheral vascular disease, cerebrovascular disease, recurrent cellulitis, gastrointestinal bleed, lung disease, neurologic disorder, psychiatric disorders, nonskin cancer, and HIV), catheter use, hemoglobin, spKt/V, systolic BP: <120, 120–160 (reference), and >160 mmHg, serum creatinine, albumin, calcium, phosphorus, PTH, and nPCR plus variables in the minimally adjusted models. All models accounted for facility clustering effects. IQR, interquartile range; spKt/V, single pool Kt/V; PTH, parathyroid hormone; nPCR, normalized protein catabolic rate; 95% CI, 95% confidence interval.

[a]Unless otherwise indicated, odds ratio indicate likelihood of sometimes to very active versus infrequently active or never/rarely active per 1-unit increase for continuous variable or compared with the referent group for dichotomous variables.

[b]Age per 10 years older.

[c]spKt/V per 0.1 higher.

[d]PTH per 100 pg/ml higher.

[e]nPCR per 0.1 g/kg per day higher.

For each analysis, five estimates specific to each dataset were generated and pooled to obtain the final estimate, with variance estimated using Rubin's equation (30). The percentage missing for covariates was <10% for all imputed variables with four exceptions: 15% for parathyroid hormone and 20%–30% for reporting of HIV, single-pool Kt/V, and normalized protein catabolic rate. Sensitivity analyses examined the effect of including patients who had missing physical activity data but for whom scores of aerobic physical activity could still be calculated. All analyses were repeated on a subset of patients that excluded those requiring assistance with walking, living in a nursing home, or reporting great difficulty in climbing stairs. The SAS software, version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

Results

The 5763 patients who completed all sections of the physical activity questionnaire—on whom the main study analyses are based—were younger, had longer time on dialysis, and had a moderately lower prevalence of comorbid conditions than the 3364 patients who either did not complete a questionnaire or did not fully complete the physical activity questionnaire (Supplemental Table 1). Among 5763 patients in the main study analyses, the distribution by aerobic physical activity levels was 28.6% never or rarely active (sedentary), 10.4% infrequently active, 16.8% sometimes active, 23.8% often active, and 20.4% very active. For strength/flexibility, 9.3% reported flexibility activities, 4.3% reported strength activities, and 6.8% reported both flexibility and strength activities.

Associations of Patient Characteristics with Physical Activity (the Outcome)

Table 1 displays the distribution of patient characteristics by category of aerobic physical activity and the relationship of each patient characteristic with the adjusted odds of greater aerobic physical activity (sometimes to very active) versus less or no aerobic physical activity. Aerobic physical activity level was positively associated with men, college education, being employed, living alone, and higher concentration of serum albumin. Aerobic physical activity level was inversely associated with age, needing assistance with walking, body mass index, recurrent cellulitis, and neurologic disorder. There was a moderate difference in aerobic physical activity level by region, which was accounted for by adjusting the logistic models for the study region. In general, the associations of patient characteristics with strength and flexibility followed a pattern similar to that observed for aerobic physical activity (data not shown). Approximately 27% of the dialysis units reported exercise programs. The percentage of units offering exercise programs was 14% in Japan, 27% in Europe and Australia/New Zealand, and 37% in North America. The percentage of patients who reported being sometimes active, often active, or very active in aerobic physical activity was higher in the 27% of dialysis units that offered exercise programs than in units that did not offer exercise programs (70% versus 57%). The higher level of aerobic physical activity in units offering an exercise program remained after adjustment for age, sex, region, vintage, and assistance with walking (adjusted odds ratio, 1.79; 95% confidence interval [95% CI], 1.45 to 2.22; $P<0.001$).

Associations of Physical Activity (Predictor) with Measures of HRQOL and Depression Symptoms

There were (Table 2) monotonic associations of higher self-reported aerobic physical activity level with higher scores of PCS (*i.e.*, better physical HRQOL), MCS (*i.e.*, better mental HRQOL), and KDB (*i.e.*, less perceived disease burden). The extensively adjusted differences in HRQOL scores comparing very active with never/rarely active were 6.7 points (95% CI, 5.79 to 7.56) for PCS, 3.7 points (95% CI, 2.76 to 4.65) for MCS, and 9.9 points (95% CI, 7.75 to 11.99) for KDB. Higher aerobic activity level was associated with a lower mean depressive symptom (CES-D) score and lower odds of a CES-D score≥10 (extensively adjusted odds ratio, 0.43; 95% CI, 0.35 to 0.52). The associations of muscle strength and flexibility activity with HRQOL and depression symptoms were, in general, weak and inconsistent (Supplemental Table 2).

Association of Physical Activity with Mortality

Median (interquartile range) follow-up time was 1.6 (0.9–2.5) years, during which time 973 deaths occurred, yielding a crude death rate of 10.3 deaths per 100 patient-years (0.103/year). Cardiovascular disease was the main reported cause of death: 33.3% for patients infrequently or never/rarely active and 36.0% for patients sometimes to very active. An inverse association was seen between aerobic physical activity level and mortality (Table 3). Compared with never/rarely active patients, the extensively adjusted hazard ratio was 0.89 (95% CI, 0.72 to 1.10) for infrequently active, 0.84 (95% CI, 0.67 to 1.05) for sometimes active, 0.81 (95% CI, 0.68 to 0.96) for often active, and 0.60 (95% CI, 0.47 to 0.77) for very active (*P* for trend<0.001) patients. A sensitivity analysis of mortality in a sample of 6915 patients that included the data of 1152 patients who responded to at least one aerobic physical activity question showed results similar to results on the basis of the sample of 5763 patients (Supplemental Table 3). Similar results were observed in a Cox model that excluded patients who lived in nursing homes, needed assistance with walking, or had difficulty climbing stairs (Supplemental Table 4). As shown in Table 4, the associations of muscle strength and flexibility activities with mortality were weak and inconsistent.

Extensively Adjusted Associations of Physical Activity with Outcomes by Subgroups Defined by Age, Vintage, Sex, and Diagnoses of Diabetes, Heart Failure, and Ischemic/Coronary Heart Disease

The inverse association of aerobic physical activity (sometimes to very active compared with never/rarely active) with mortality did not differ appreciably by subgroups of age (≥60 versus <60 years), sex, time on dialysis (>6 versus ≤6 months), and diabetes status (*P* for interaction >0.45) (Figure 1). The inverse association between aerobic physical activity and mortality was stronger in patients without than patients with coronary/ischemic heart disease (*P* for interaction=0.11). A lower mortality in patients who reported higher aerobic physical activity (sometimes to very active)

Table 2. Differences in health-related quality of life and depression symptoms scores (both as continuous and dichotomous variables) by aerobic physical activity level

Outcome	Physical Activity Levels									
	Minimally Adjusted Mean Difference (95% CI)					Extensively Adjusted Mean Difference (95% CI)				
	Never/ Rarely	Infrequently	Sometimes	Often	Very	Never/ Rarely	Infrequently	Sometimes	Often	Very
PCS score	Ref=0	1.59 (0.64 to 2.55)	3.66 (2.73 to 4.60)	4.05 (3.17 to 4.94)	7.18 (6.25 to 8.11)	Ref=0	1.60 (0.69 to 2.52)	3.55 (2.62 to 4.48)	3.82 (2.96 to 4.68)	6.67 (5.79 to 7.56)
MCS score	Ref=0	2.25 (1.17 to 3.33)	3.58 (2.66 to 4.50)	3.09 (2.22 to 3.95)	4.06 (3.10 to 5.02)	Ref=0	2.15 (1.09 to 3.22)	3.60 (2.69 to 4.51)	2.92 (2.07 to 3.78)	3.70 (2.76 to 4.65)
KDB score	Ref=0	0.92 (−1.47 to 3.32)	7.13 (5.04 to 9.22)	5.84 (3.89 to 7.79)	10.28 (8.15 to 12.42)	Ref=0	1.00 (−1.38 to 3.37)	7.05 (4.98 to 9.11)	5.65 (3.72 to 7.59)	9.87 (7.75 to 11.99)
CES-D score	Ref=0	−1.04 (−1.59 to −0.49)	−2.27 (−2.76 to −1.79)	−2.00 (−2.45 to −1.55)	−2.68 (−3.23 to −2.13)	Ref=0	−0.97 (−1.51 to −0.44)	−2.24 (−2.72 to −1.76)	−1.90 (−2.34 to −1.46)	−2.45 (−3.00 to −1.91)
CES-D ≥10	Ref=1	0.77 (0.63 to 0.95)	0.53 (0.44 to 0.63)	0.52 (0.44 to 0.61)	0.41 (0.34 to 0.50)	Ref=1	0.79 (0.64 to 0.97)	0.52 (0.43 to 0.62)	0.53 (0.45 to 0.62)	0.43 (0.35 to 0.52)

Linear models were used for health-related quality of life and CES-D as continuous outcomes; logistic regression was used for comparing CES-D≥10 with <10. The minimally adjusted models included geographic region, age, sex, race, smoking, employment status, education, living with family, assistance with walking, number of years on dialysis, and muscle strength/flexibility. The extensively adjusted models included body mass index, comorbidities (diabetes, hypertension, coronary disease, heart failure, other cardiovascular disease, peripheral vascular disease, cerebrovascular disease, recurrent cellulitis, gastrointestinal bleed, lung disease, neurologic disorder, psychiatric disorders, nonskin cancer, and HIV), catheter use, blood hemoglobin, dialysis dose by Kt/V, systolic BP<120 mmHg, systolic BP>160 mmHg, serum creatinine, serum albumin, serum calcium, serum phosphorus, parathyroid hormone, and normalized protein catabolic rate. All models accounted for facility clustering effects. PCS, physical component summary; MCS, mental component summary; KDB, kidney disease burden; CES-D, Center for Epi-demoiologic Studies Depression Scale; Ref, reference; 95% CI, 95% confidence interval.

Table 3. Minimally and extensively adjusted hazard ratios for all-cause mortality by level of aerobic physical activity: Results of Cox regression analyses

Aerobic Activity Level	Number of Deaths/Total	Hazard Ratio (95% CI)	
		Minimally Adjusted	Extensively Adjusted
Never/rarely active	427/1649	1 (reference)	1 (reference)
Infrequently active	93/599	0.92 (0.76 to 1.13)	0.89 (0.72 to 1.10)
Sometimes active	143/969	0.87 (0.70 to 1.08)	0.84 (0.67 to 1.05)
Often active	191/1373	0.82 (0.69 to 0.98)	0.81 (0.68 to 0.96)
Very active	119/1173	0.61 (0.48 to 0.77)	0.60 (0.47 to 0.77)
Total	973/5763		
P for trend		<0.001	<0.001

The minimally adjusted models included geographic region, age, sex, race, smoking, employment status, education, living conditions, assistance with walking, number of years on dialysis, and muscle strength/flexibility. The extensively adjusted models included body mass index, comorbidities (diabetes, hypertension, coronary disease, heart failure, other cardiovascular disease, peripheral vascular disease, cerebrovascular disease, recurrent cellulitis, gastrointestinal bleed, lung disease, neurologic disorder, psychiatric disorders, nonskin cancer, and HIV), catheter use, blood hemoglobin, dialysis dose by Kt/V, systolic BP<120 mmHg, systolic BP>160 mmHg, serum creatinine, serum albumin, serum calcium, serum phosphorus, parathyroid hormone, and normalized protein catabolic rate. All models accounted for facility clustering effects. 95% CI, 95% confidence interval.

Table 4. Cox adjusted hazard ratios of associations between muscle strength or flexibility and death

Muscle Strength or Flexibility	No. of Deaths/No. of Patients	Minimally Adjusted HR (95% CI)	Extensively Adjusted HR (95% CI)
None	826/4584	1 (reference)	1 (reference)
Strength	25/250	0.74 (0.48 to 1.14)	0.78 (0.50 to 1.22)
Flexibility	52/535	0.80 (0.59 to 1.07)	0.76 (0.56 to 1.03)
Both	70/394	1.27 (0.95 to 1.69)	1.25 (0.90 to 1.72)
Total	973/5763		
P for trend		0.81	>0.99

The minimally adjusted models included geographic region, age, sex, number of years on dialysis, race, smoking, employment status, education, living conditions, assistance with walking, and aerobic physical activity levels. The extensively adjusted models included body mass index, comorbidities (diabetes, hypertension, coronary disease, heart failure, other cardiovascular disease, peripheral vascular disease, cerebrovascular disease, recurrent cellulitis, gastrointestinal bleed, lung disease, neurologic disorder, psychiatric disorders, nonskin cancer, and HIV), catheter use, hemoglobin, single-pool Kt/V, systolic BP<120 mmHg, systolic BP>160 mmHg, creatinine, albumin, calcium, phosphorus, parathyroid hormone, and normalized protein catabolic rate plus variables in the minimally adjusted models. All models accounted for facility clustering effects. HR, hazard ratio; 95% CI, 95% confidence interval.

was observed in patients without heart failure but not in patients with heart failure.

The association of higher aerobic physical activity with higher HRQOL scores and lower depression symptoms did not differ appreciably by age, sex, time on dialysis, diabetes status, heart failure, or coronary/ischemic heart disease (Table 5), with the exception of higher aerobic physical activity seeming to be more strongly associated with higher MCS score and lower depression symptom score for patients ≥60 years of age than younger patients. After extensive covariate adjustment, most of the score differences between aerobic physical activity categories were >3 points for HRQOL and >1.5 points for depression symptoms.

Discussion

The results of this study indicate better HRQOL, greater survival, and lower depression symptoms in patients on MHD engaged in higher levels of aerobic physical activity. The differences in depression symptoms, HRQOL, and mortality increased monotonically across the five categories of aerobic physical activity. The differences in HRQOL by physical activity levels were larger than the threshold value proposed as clinically significant (26). Our results suggest that the association of higher aerobic physical activity with greater HRQOL, lower depression symptoms, and lower mortality applies to diverse subgroups of patients on MHD. Regarding the absence of an association of aerobic physical activity with mortality in patients with congestive heart failure (CHF), additional analyses were carried out that suggest that the nature of the relationship is very much cutpoint-dependent, ranging from a possible survival benefit to no benefit depending on whether the middle aerobic physical activity level is assigned to the less active or the more active aerobic physical activity dichotomous group, respectively. Because of the variability in the mortality results for study

Subgroups	Number of Patients	Number of Deaths	Hazard Ratio (95% CI)	P-value for Interaction
Time on Dialysis (months)				
>6	4101	739	0.79 (0.67-0.94)	0.80
≤6	1662	234	0.83 (0.62-1.11)	
Age (years)				
≥60	3716	798	0.78 (0.66-0.92)	0.46
<60	2047	175	0.89 (0.65-1.22)	
Sex				
Female	2216	337	0.86 (0.67-1.09)	0.47
Male	3547	636	0.77 (0.65-0.92)	
Diabetes				
Yes	2201	435	0.84 (0.68-1.04)	0.47
No	3562	538	0.76 (0.62-0.93)	
Heart Failure				
Yes	1245	337	1.00 (0.79-1.28)	0.008
No	4518	636	0.71 (0.60-0.84)	
Coronary/Ischemic Heart Disease				
Yes	2083	520	0.88 (0.73-1.07)	0.11
No	3680	453	0.71 (0.58-0.88)	

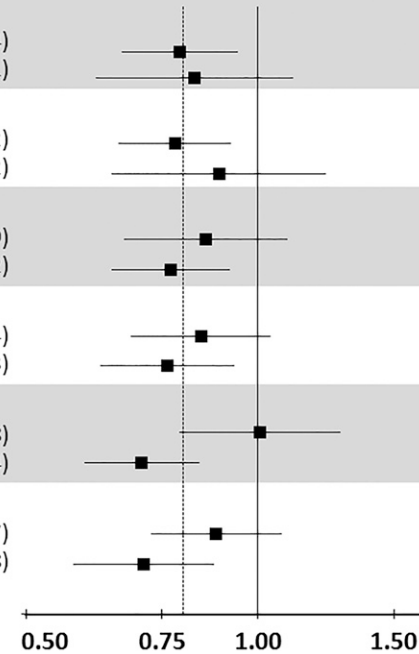

Figure 1. | Patient subgroup comparisons regarding the association of mortality with greater aerobic physical activity (sometimes to very active versus infrequently or never/rarely active) after extensive covariate adjustment. The hazard ratios (HRs) for mortality were adjusted for geographic region, age, sex, number of years on dialysis, race, smoking, employment status, education, living conditions, assistance with walking, muscle strength/flexibility, body mass index, diabetes, hypertension, coronary disease, heart failure, other cardiovascular disease, peripheral vascular disease, cerebrovascular disease, recurrent cellulitis, gastrointestinal bleed, lung disease, neurologic disorder, psychiatric disorders, nonskin cancer, HIV, catheter use, blood hemoglobin, dialysis dose by Kt/V, systolic BP<120 mmHg, systolic BP>160 mmHg, serum creatinine, serum albumin, serum calcium, serum phosphorus, parathyroid hormone, and normalized protein catabolic rate. All models accounted for facility clustering effects. The dashed vertical line indicates the overall HR (0.80), and the solid vertical line indicates no effect (HR, 1.00). 95% CI, 95% confidence interval.

patients with CHF in our dataset, we are hesitant to make any conclusion regarding the relationship of aerobic physical activity with survival in patients with CHF and feel that this relationship should continue to be evaluated in future studies. It should be noted that a recent randomized trial in heart failure patients without CKD showed modest reduction in mortality for those assigned to a rigorous exercise training program (6). Despite the inconsistent association between aerobic physical activity levels and mortality in patients with CHF, we consistently observed higher HRQOL and lower depression symptom scores in patients with CHF who reported greater aerobic physical activity levels.

Previous studies suggest that implementation of exercise programs in hemodialysis units improves HRQOL, reduces depression symptoms, and improves control of cardiovascular risk factors in patients on hemodialysis (12,31–34). Our findings provide additional support to the promotion of physical activity programs in hemodialysis units. Despite the evidence supporting a role of physical activity in improving outcomes, the nephrology community has apparently not emphasized counseling and exercise programs to improve physical activity for patients on MHD (35–37).

Some patient subgroups may deserve special attention to improve physical activity. Our results indicate a higher percentage of inactivity in women than men. This finding is consistent with observations in the general population and from a large sample of patients on dialysis treated in 297 clinics in the United States (14,38). The findings indicating higher likelihood of inactivity in patients who have less formal education or are unemployed are also consistent with previous observations (14,39).

This study is not the first large prospective cohort to show associations of higher physical activity with improved outcomes in patients on MHD. However, it expands on previous investigations by providing more detailed descriptions of types and levels of physical activities and their associations with HRQOL, depression symptoms, and mortality. In previous studies on the basis of data from DOPPS phases 1 and 2 (10) and the Dialysis Morbidity and Mortality Study (DMMS) wave 2 (17), physical activity was assessed by asking patients: "How often do you exercise [do physical activity] during your leisure time?" Patients who reported exercising one or more times per week had higher HRQOL, better sleep quality, and lower mortality. Similarly, in the DMMS, the hazard of death adjusted for several covariates was higher for sedentary patients. In the Comprehensive Dialysis Study (14), the Human Activity Profile (40) was administered to determine the most demanding activity that the patients were able to perform. Physical activity level was

Table 5. Extensively adjusted difference in the scores of each patient-reported outcome for sometimes to very active patients versus less active patients by categories of six binary covariates

Subgroups	Difference in Scores (95% CI)			
	Physical Component Summary	Mental Component Summary	Kidney Disease Burden	Depression Symptoms by CES-D
Time on dialysis (mo)				
>6	4.19 (3.45 to 4.93)	2.77 (1.82 to 3.73)	7.49 (5.78 to 9.20)	−1.82 (−1.42 to −2.23)
≤6	3.44 (2.38 to 4.50)	2.33 (0.74 to 3.91)	5.36 (2.75 to 7.98)	−1.86 (−1.13 to −2.59)
P for interaction	0.19	0.67	0.17	0.93
Age (yr)				
≥60	4.05 (3.25 to 4.85)	3.25 (2.45 to 4.05)	7.42 (5.69 to 9.15)	−2.02 (−1.60 to −2.44)
<60	3.82 (2.90 to 4.75)	1.38 (0.29 to 2.47)	5.75 (3.32 to 8.19)	−1.44 (−0.90 to −1.98)
P for interaction	0.68	0.005	0.26	0.08
Sex				
Women	4.10 (3.19 to 5.00)	2.07 (1.10 to 3.04)	7.04 (4.85 to 9.23)	−1.85 (−1.34 to −2.36)
Men	3.90 (3.14 to 4.67)	3.01 (2.16 to 3.87)	6.78 (4.99 to 8.57)	−1.83 (−1.42 to −2.23)
P for interaction	0.71	0.14	0.85	0.94
Diabetes				
Yes	3.92 (3.07 to 4.77)	3.09 (2.08 to 4.09)	6.99 (4.82 to 9.16)	−2.07 (−1.58 to −2.56)
No	4.01 (3.20 to 4.82)	2.36 (1.47 to 3.25)	6.81 (5.00 to 8.62)	−1.68 (−1.26 to −2.10)
P for interaction	0.86	0.29	0.90	0.20
Heart failure				
Yes	3.53 (2.30 to 4.76)	2.64 (1.23 to 4.05)	7.63 (4.76 to 10.51)	−1.93 (−1.25 to −2.60)
No	4.11 (3.41 to 4.81)	2.65 (1.92 to 3.38)	6.66 (5.03 to 8.29)	−1.81 (−1.43 to −2.19)
P for interaction	0.37	0.99	0.55	0.75
Coronary/ischemic heart disease				
Yes	3.83 (2.65 to 5.01)	3.00 (2.00 to 4.01)	7.93 (5.69 to 10.17)	−1.88 (−1.38 to −2.37)
No	4.07 (3.38 to 4.76)	2.43 (1.64 to 3.23)	6.26 (4.48 to 8.04)	−1.81 (−1.39 to −2.23)
P for interaction	0.69	0.35	0.23	0.83

All differences were adjusted for geographic region, age, sex, race, smoking, employment status, education, living conditions, assistance with walking, muscle strength/flexibility, body mass index, number of years on dialysis, diabetes, hypertension, coronary disease, heart failure, other cardiovascular disease, peripheral vascular disease, cerebrovascular disease, recurrent cellulitis, gastrointestinal bleed, lung disease, neurologic disorder, psychiatric disorders, nonskin cancer, HIV, catheter use, blood hemoglobin, dialysis dose by Kt/V, systolic BP<120 mmHg, systolic BP>160 mmHg, serum creatinine, serum albumin, serum calcium, serum phosphorus, parathyroid hormone, and normalized protein catabolic rate. All models accounted for facility clustering effects. 95% CI, 95% confidence interval.

found to be inversely associated with mortality across the range of Human Activity Profile scores. Despite differences in the way that physical activity has been assessed across studies, the results are in agreement by showing improved outcomes in patients on dialysis at higher levels of physical activity.

The associations between higher aerobic physical activity and improved outcomes described in this study are likely generalizable to the broad MHD population worldwide. However, because the study is observational, it is not possible to conclude if the associations are causal. Nonresponse to the physical activity questionnaire is another potential limitation. Nonresponse could have introduced bias in estimating physical activity if the participation of the patients was associated with level of physical activity, patient characteristics (such as comorbidities), or outcome status. Similar results in the association between aerobic physical activity and mortality were observed in the analyses that excluded and included the data of patients who partially completed physical activity questionnaires. Despite these findings, it is not possible to rule out an overestimation of the associations between aerobic physical activity and mortality caused by information bias.

The lack of information about the severity of comorbidities could have resulted in residual confounding, which may likely be greater in patients with disabling comorbidities. Because the analyses were cross-sectional, it is not possible to conclude on the direction of the associations of physical activity with depression symptoms and HRQOL. Results from randomized clinical trials, however, have shown that exercise training is associated with subsequent improvement in HRQOL and reduction in depression symptoms in patients on chronic dialysis (12,32).

In addition to residual confounding, it is important to consider that physical activity level was on the basis of self-report instead of objective measures of physical activity. However, the patient's responses to the RAPA questionnaire have shown fairly good correlations and diagnostic accuracy compared with direct measurement of physical activity through use of an accelerometer and the long form of the CHAMPS, which had been validated previously against an objective direct measure of physical activity and caloric expenditure levels (22,23). Another limitation is the lack of information about the types of exercise programs offered in dialysis units that were associated with a higher percentage of patients having greater aerobic physical activity levels. Data from a 16-week comparative clinical trial of 286 patients on MHD provided evidence that a program combining home exercise and in-center cycling during hemodialysis improves physical performance and HRQOL (12). A possible effect of physical activity in reducing mortality was not reported in this trial.

In conclusion, self-reported aerobic physical activity was strongly associated with better HRQOL, fewer depression symptoms, and lower mortality in patients on MHD from 12 countries. Similar associations of aerobic physical activity with patient-centered outcomes and mortality were observed in several subgroups of patients. Long-duration randomized clinical trials are needed to evaluate the effectiveness of interventions to increase physical activity and determine if improvement in physical activity is associated with improvement in HRQOL and survival in patients on MHD.

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