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Self-Reported Physical Activity and Survival in Adults Treated With Hemodialysis: A DIET-HD Cohort Study

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Introduction: Regular physical activity is associated with longevity in adults receiving hemodialysis, but it is uncertain whether this association varies by causal pathways (cardiovascular and noncardiovascular).

Methods: DIET-HD was a prospective, multinational study of adults undergoing hemodialysis across Europe and Argentina. We classified participants as physically inactive, occasionally active (irregularly to once a week), or frequently active (twice a week or more), using a self-reported questionnaire. Potential confounders were balanced across exposure groups using propensity scores. Weighted Cox proportional hazards models with double robust estimators evaluated the association between physical activity and all-cause, cardiovascular, and noncardiovascular mortality.

Results: Of 8043 participants in DIET-HD, 6147 (76%) had information on physical activity. A total of 2940 (48%) were physically inactive, 1981 (32%) occasionally active, and 1226 (20%) frequently active. In a median follow-up of 3.8 years (19,677 person-years), 2337 (38%) deaths occurred, including 1050 (45%) from cardiovascular causes. After propensity score weighting, occasional physical activity was associated with lower all-cause (adjusted hazard ratio [aHR] = 0.80, 95% CI = 0.72–0.89), cardiovascular (aHR = 0.82, 95% CI = 0.70–0.96), and noncardiovascular (aHR = 0.81, 95% CI = 0.69–0.94) mortality compared with inactivity. Frequent physical activity was associated with lower all-cause (aHR = 0.82, 95% CI = 0.71–0.95) and cardiovascular (aHR = 0.77, 95% CI = 0.62–0.94) mortality, but not noncardiovascular mortality (aHR = 0.88, 95% CI = 0.72–1.08). A dose-dependent association of physical activity with cardiovascular death was observed (*P* trend = 0.01).

Conclusion: Compared with self-reported physical inactivity, occasional and frequent physical activities were associated, dose dependently, with lower cardiovascular mortality in adults receiving hemodialysis.

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Life expectancy at the initiation of hemodialysis treatment is markedly lower than that of the general population, with fewer than half of individuals between 65 and 74 years surviving beyond 5 years. Cardiovascular disease is the leading cause of mortality accounting for 48% of deaths.[1] In the general population, physical inactivity is a leading risk factor for death and is responsible for 6% of cardiovascular disease, 10% of type 2 diabetes, and 10% of some cancers worldwide.[2]

The 2005 Kidney Disease Outcome Quality Improvement Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients recommend 30 minutes of moderate exercise on most days for adults receiving dialysis treatments, but this recommendation

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was based mostly on evidence from the general population and nondialysis groups at high risk of cardiovascular disease.[3] The combined evidence from randomized controlled trials has revealed exercise training to reduce cardiovascular mortality, but not all-cause mortality, in adults with coronary heart disease.[4] Nonetheless, given the different epidemiology and causal pathways for cardiovascular disease, strategies proven to reduce cardiovascular events in the general population have not been generalizable to people on hemodialysis.[5,6]

Multiple trials have evaluated the effects of exercise training for adults undergoing hemodialysis.[7] Although they have revealed positive impacts on physical fitness, physical functioning, and health-related quality of life, they were of insufficient duration and lacked the necessary power to evaluate patient important outcomes, including mortality and cardiovascular events.[7] Few cohort studies have evaluated the association between physical activity and all-cause mortality among adults receiving hemodialysis treatments and have not evaluated cause-specific deaths.[8–11] We evaluated the association between physical activity and all-cause and cause-specific mortality in a large cohort of well-characterized adults undergoing hemodialysis.

METHODS

Study Design

This is a substudy evaluating self-reported physical activity within the DIET-HD cohort.[12,13] DIET-HD is a prospective, multinational study primarily designed to evaluate dietary intake in adults undergoing maintenance hemodialysis.[12]

Study Population

Adults aged ≥18 years undergoing maintenance hemodialysis in a dialysis provider network in Europe (France, Germany, Italy, Hungary, Poland, Portugal, Romania, Spain, Sweden, and Turkey) and South America (Argentina) were eligible for enrolment. Participants unable to complete a food frequency questionnaire with short life expectancy or expected to undergo kidney transplantation within 6 months were excluded.

Baseline Characteristics

We extracted information regarding sociodemographic characteristics, education, living arrangements, smoking status, comorbidities, medication, blood pressure, dialysis prescription, vascular access, and status on the transplantation waiting list from the database of the dialysis provider using data linkage. Blood samples were collected routinely before the midweek dialysis treatment in line with the local protocols. The diets of the participants were evaluated once at baseline through the Global Allergy and Asthma European Network food frequency questionnaire, which evaluates the intake of 32 food groups in the past 12 months across countries.[14,15]

Physical Activity Assessment

Physical activity was evaluated using a single question asked verbally by physicians within 1 month of enrolment in the study requesting the patient to self-rate their level of physical activity as either none, irregularly, once a week, more than once a week, or daily. Physical activity was defined as any bodily movement resulting in energy expenditure, including activities related to occupation, transportation, sports, or household maintenance. In this analysis, physical activity was categorized as frequent activity (more than once a week to daily), occasional activity (irregularly to once a week), or inactivity (no physical activity). The thresholds were decided as to distribute the participants evenly across groups to enable balancing of the covariates. There was no structured exercise program in place at the participating dialysis units.

Outcomes

All-cause mortality, cardiovascular mortality, and noncardiovascular mortality were recorded on or before March 23, 2019. Causes of death were obtained from the death certificates of the participants and recorded according to the United States coding for the hemodialysis population.[16] We classified sudden death, acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, and congestive cardiac failure as cardiovascular deaths.

The study was in accordance with the Declaration of Helsinki and was approved by all relevant institutional ethics committees. All participants provided written informed consent to participate in the study.

Statistical Analysis

Mean and SDs were used to describe continuous, normally distributed variables. Median and interquartile range were used to describe continuous, nonnormally distributed variables. The period of observation ranged from the time of inclusion to the time of death or censoring (departure from the dialysis network, kidney transplantation, transfer to another kidney replacement modality, ceased dialysis treatment, recovered kidney function, went on vacation, lost to follow-up, or survival until the end of follow-up).

Table 1. Characteristics of participants

	Level of physical activity			
Participants characteristics	Inactive	Occasional	Frequent	Missing, %
N	2940	1981	1226	
Age ≥ 65 yr	1787 (60.8)	872 (44.0)	511 (41.7)	0
Sex (number of men, %)	1597 (54.3)	1212 (61.2)	775 (63.2)	0
Ethnicity				5.9
White/Hispanic	2610 (95.5)	1815 (96.3)	1136 (97.2)	
Black	82 (3.0)	43 (2.3)	19 (1.6)	
Others	40 (1.5)	27 (1.4)	14 (1.2)	
Body mass index				2.2
$<$18.5 kg/m^2	137 (4.8)	83 (4.3)	52 (4.3)	
18.5–24.9 kg/m^2	1146 (40.0)	832 (43.0)	548 (45.2)	
25–29.9 kg/m^2	959 (33.5)	645 (33.4)	424 (35.0)	
$\geq$30 kg/m^2	624 (21.8)	373 (19.3)	188 (15.5)	
Occupation status				3
Working	208 (7.3)	273 (14.2)	188 (15.6)	
Retired	2219 (78.4)	1357 (70.4)	875 (72.7)	
Unemployed	403 (14.2)	298 (15.5)	141 (11.7)	
Having a life partner	1723 (66.2)	1239 (70.6)	753 (67.8)	11
Secondary level education	1003 (36.2)	935 (49.0)	659 (55.1)	4.5
Country				0
Argentina	366 (12.4)	180 (9.1)	35 (2.9)	
France	64 (2.2)	19 (1.0)	19 (1.5)	
Germany	41 (1.4)	59 (3.0)	36 (2.9)	
Hungary	100 (3.4)	156 (7.9)	244 (19.9)	
Italy	378 (12.9)	122 (6.2)	34 (2.8)	
Poland	135 (4.6)	193 (9.7)	61 (5.0)	
Portugal	881 (30.0)	399 (20.1)	157 (12.8)	
Romania	341 (11.6)	336 (17.0)	291 (23.7)	
Spain	480 (16.3)	303 (15.3)	224 (18.3)	
Sweden	6 (0.2)	13 (0.7)	19 (1.5)	
Turkey	148 (5.0)	201 (10.1)	106 (8.6)	
Former or current smoker	900 (31.2)	664 (34.3)	439 (36.4)	1.9
Etiology of kidney disease				0
Diabetes	795 (27.0)	393 (19.8)	196 (16.0)	
Hypertension	561 (19.1)	352 (17.8)	214 (17.5)	
Glomerular disease	868 (29.5)	762 (38.5)	562 (45.8)	
Others	716 (24.4)	474 (23.9)	254 (20.7)	
$>$5 yr on HD	1172 (39.9)	764 (38.6)	534 (43.6)	0
$>$12 h of HD/wk	426 (14.8)	372 (19.2)	241 (19.9)	2.1
$>$4 kg loss per HD	3.1 (1.3)	3.1 (1.3)	3.0 (1.4)	3.5
Kt/V ≥ 1.4	2537 (89.4)	1717 (89.3)	1068 (88.5)	2.9
Dialyzed through AVF	2256 (76.9)	1627 (82.3)	1059 (86.6)	0.2
Listed for transplant	369 (12.6)	455 (23.0)	283 (23.1)	0.2
Comorbidities				
Comorbidity index $>$ 5	2110 (71.8)	1060 (53.5)	592 (48.3)	0
Coronary heart disease	712 (25.6)	468 (25.5)	245 (21.6)	6.4
Congestive heart failure	607 (20.9)	364 (18.7)	197 (16.3)	1.5
Arrhythmia	633 (22.7)	338 (18.4)	226 (19.9)	6.3
Cerebrovascular disease	477 (17.1)	258 (14.1)	116 (10.2)	6.3
Hypertension	2466 (84.3)	1702 (87.1)	1073 (89.6)	1.1
Diabetes	1111 (38.0)	546 (28.1)	264 (22.1)	1.4
Cancer	445 (15.1)	262 (13.2)	199 (16.2)	0
Gastrointestinal disease	719 (24.5)	508 (25.6)	326 (26.6)	0
Pulmonary disease	462 (15.7)	233 (11.8)	123 (10.0)	0
Neurologic disorder	284 (10.2)	152 (8.3)	97 (8.6)	6.5
Psychiatric disorder	456 (16.4)	235 (12.8)	118 (10.4)	6.4
Predialysis SBP $>$ 140 mm Hg	130.0 (22.6)	132.2 (21.6)	133.6 (19.5)	9.3
Under ACEI or ARB	1071 (37.5)	734 (39.2)	523 (43.7)	3.6
$>$4 Different drug class	825 (40.7)	631 (46.7)	420 (45.8)	30.1

(Continued on following page)

Table 1. (Continued) Characteristics of participants

Participants characteristics	Level of physical activity			Missing, %
	Inactive	Occasional	Frequent	
Potassium, mEq/l	5.0 (0.7)	5.0 (0.7)	5.1 (0.7)	67.5
Calcium, mg/dl	8.9 (0.7)	9.0 (0.8)	9.0 (0.7)	2.2
Phosphate, mg/dl	4.5 (1.4)	4.8 (1.4)	4.9 (1.5)	2.3
PTH, pg/ml	424.4 (394.4)	448.4 (374.4)	424.3 (372.4)	50.3
Albumin, g/dl	39.1 (3.6)	40.1 (3.6)	40.1 (3.4)	28.2
Hemoglobin, g/dl	11.1 (1.3)	11.0 (1.3)	11.1 (1.2)	2.3

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AVF, arteriovenous fistula; HD, hemodialysis; Kt/V, dialysis adequacy; mEq, milliequivalent; PTH, parathyroid hormone; SBP, systolic blood pressure.

To evaluate the association between physical activity and clinical outcomes, we calculated the average treatment effect (ATE) in the entire cohort and the ATE for the control group (ATC). In causal inference, these 2 quantities have slightly different interpretations. The ATE represents the average effect of physical activity if everyone in the population were to be exposed to the different levels of physical activity, whereas the ATC represents the average effect of physical activity if the population associated with the control group were to be exposed to the different levels of physical activity.

There were scattered missing data across the cases (Table 1). We imputed 5 data sets using chained equations. For each imputed data set, propensity scores for the 3 levels of physical activity were computed using generalized boosted regressions. We then reweighted the observations across the exposure groups using inverse probability treatment weighting, to create 3 groups that were similar for all measured baseline characteristics, except for their physical activity level. The variables included in the propensity score model were age, sex, ethnicity, country of living, sociodemographic characteristics, coexisting diseases, dialysis prescription, clinical and biochemical parameters, and dietary intake of food groups (the complete list is available online in the Supplementary Materials). Balance of the covariates across the groups was evaluated using the standardized mean difference.

We then conducted Cox proportional hazards models within each imputed data set to evaluate the association between physical activity and mortality, estimating the linearized standard errors. Because the performance of inverse probability treatment weighting in the context of high treatment selection depends on the correct specification of both the exposure and propensity score models,[17] we regressed the outcomes on physical activity and on all the covariates included in the propensity score model, thereby obtaining double robust estimators of the exposure effects.[18] We also conducted a sensitivity analysis for the ATC using optimal full matching (Supplementary Statistical Methods). We modeled all the nonlinear effects of continuous covariates using cubic b-splines. We tested for interaction with age (below versus greater than 65 years), sex, presence of coronary heart disease, and presence of diabetes. We conducted a competing risk analysis for the competing event of transplantation on all-cause mortality and for the competing event of noncardiovascular on cardiovascular mortality and vice versa. We combined the estimates obtained from each imputed data set using the Rubin's rules.[19] We tested the assumption of proportional hazards using plots of the Schoenfeld residuals.

We calculated the e-value, which is the magnitude of the association between an unmeasured confounder and the exposure of interest, and of the association between the unmeasured confounder and the outcome, needed to bias the results as to observe an association when there is none. It appraises the vulnerability of the findings to an unmeasured confounder.[20]

The level of significance was set as 0.05 (2-tailed). We used R version 3.5.1 and the TWANG package to build the propensity score models,[21] the cobalt package to evaluate the balance of the covariates across the 3 exposure groups,[22] and the survey and survival packages for the outcome models.[23,24]

RESULTS

Baseline Characteristics

A total of 9690 participants completed the food frequency questionnaire (Figure 1). Of the 6147 participants (76.4%) who completed the physical activity question (Supplementary Table S1), 2940 (47.8%) reported no physical activity, 1981 (32.2%) reported occasional activity, and 1226 (19.9%) reported frequent activity. Before propensity score weighting, the inactive group was older, included a higher proportion of women, had lower educational attainment, smoked less frequently, had a significantly higher prevalence of diabetes mellitus, and had a slightly lower prevalence of hypertension. The Charlson comorbidity index was highest among the physically inactive individuals who were also less likely to have a functioning arteriovenous fistula or be waitlisted for kidney transplantation (Table 1 and Supplementary Table S2). After

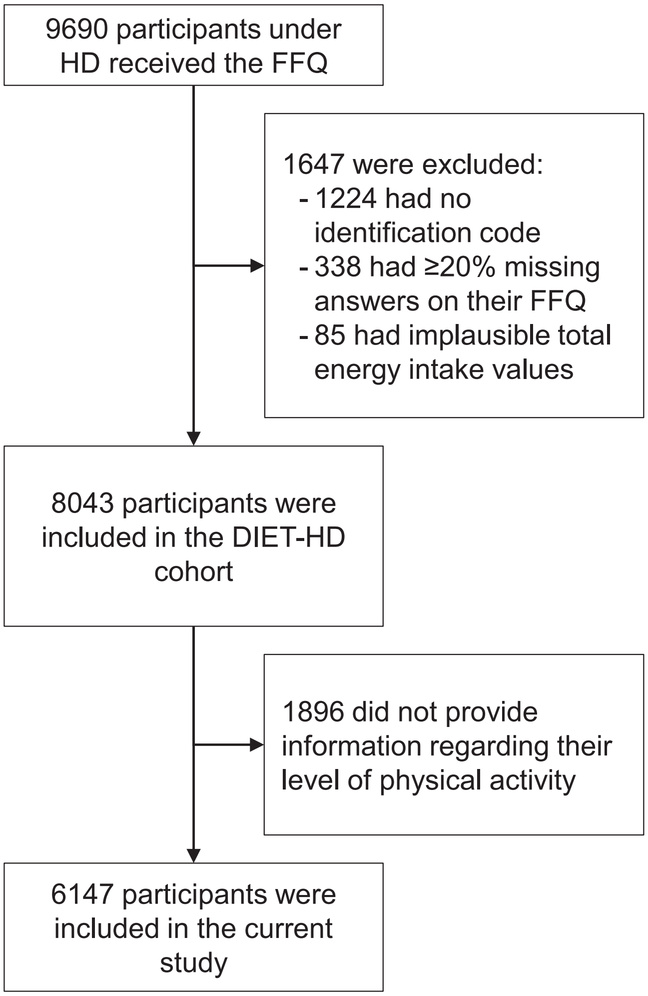


Figure 1. Flow diagram of the study participants. FFQ, food frequency questionnaire; HD, hemodialysis.

propensity score weighting, the exposure groups were suitably balanced across all baseline characteristics, as illustrated by the maximum standardized mean difference across the groups of 0.17 (Figure 2 and Supplementary Table S3). The minimum and maximum weights were 1.03 and 31.6 for the ATE and 0.2 and 27.5 for the ATC, respectively.

Unweighted and Unadjusted Association of Physical Activity and All-Cause and Cause-Specific Mortality

In a median follow-up of 3.82 years (19,677 person-years), 2337 (38%) deaths occurred, of which 1050 (45%) were from cardiovascular causes (Figure 3a–c). A total of 379 (30.9%) deaths were recorded among frequently active participants compared with 621 (31.3%) among occasionally active participants and 1337 (45.4%) among the inactive participants. In the unadjusted analysis, frequent and occasional physical activities were associated with lower risks of death compared with physical inactivity (HR = 0.64, 95% CI = 0.58–0.70 and 0.62, 95% CI = 0.55–0.69, respectively; *P* for trend < 0.001). Frequent and occasional physical activities were also associated with lower risks of cardiovascular death and noncardiovascular death (Supplementary Table S4).

Propensity Score-Weighted and Regression-Adjusted Association of Physical Activity and All-Cause Mortality

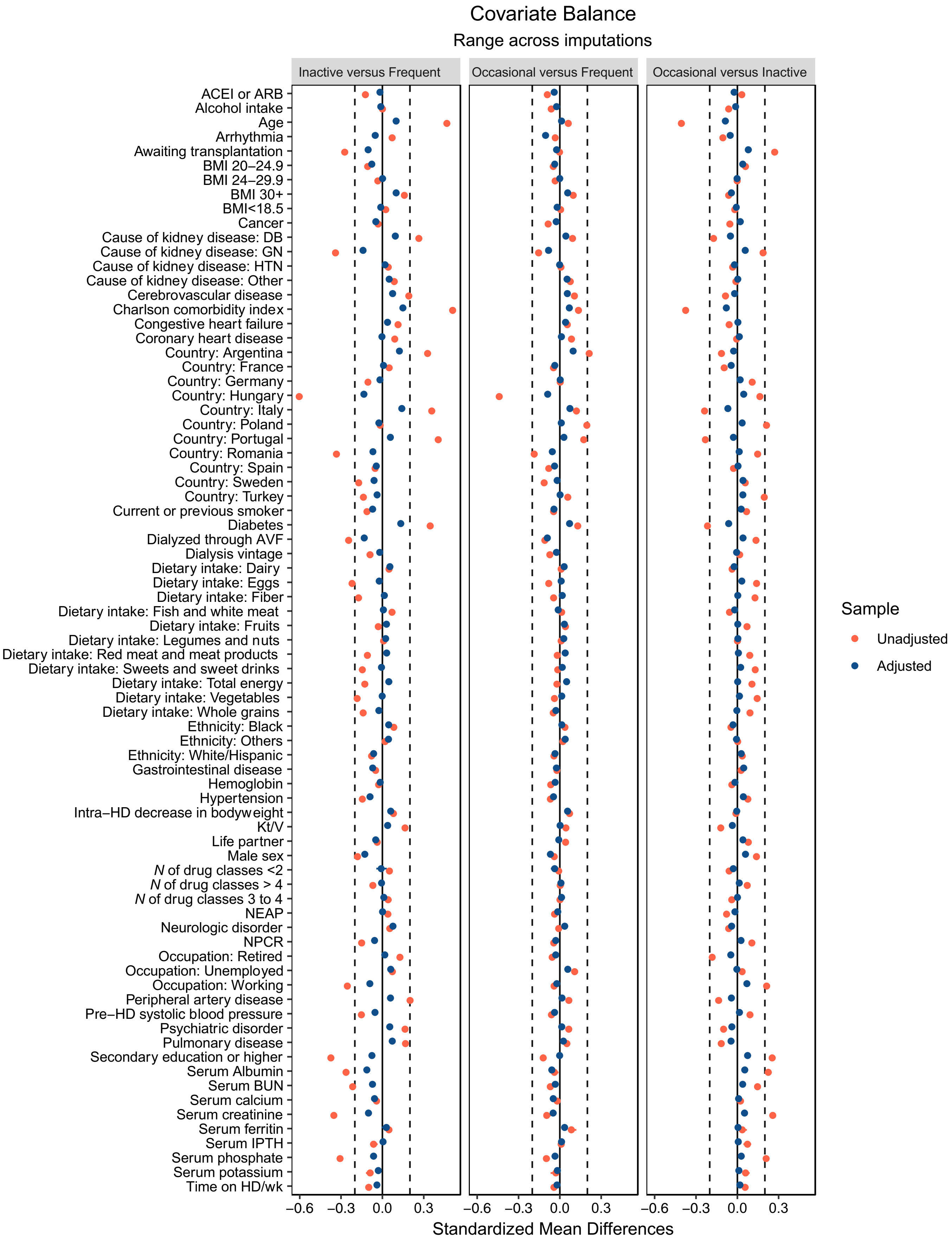
After weighing the participants, such that the baseline characteristics were balanced across the exposure groups (ATE) (Figure 2), and adjusting for the baseline characteristics through regression, frequent and occasional physical activities were associated with similarly lower risks of mortality compared with physical inactivity (aHR = 0.80, 95% CI = 0.72–0.89 and 0.82, 95% CI = 0.71–0.95, respectively; *P* for trend 0.002). After weighing the participants such that all groups resembled the control group (ATC), occasional physical activity was associated with an aHR for all-cause mortality of 0.81 (95% CI = 0.72–0.92) and frequent physical activity with an aHR of 0.77 (95% CI = 0.65–0.91; *P* for trend < 0.001) (Table 2 and Figure 4).

Propensity Score-Weighted and Regression-Adjusted Association of Physical Activity and Cardiovascular Mortality

After weighing the participants such that the baseline characteristics were balanced across the exposure groups (ATE) (Figure 2), and adjusting for the baseline characteristics through regression, physical activity had a dose-response relationship with cardiovascular mortality, such that those with occasional physical activity had an intermediate risk of mortality (HR = 0.82, 95% CI = 0.70–0.96) and those with frequent physical activity had the lowest risk of mortality (HR = 0.77, 95% CI = 0.62–0.94; *P* for trend 0.007) compared with the physically inactive participants. After weighing the participants such that, for all measured baseline characteristics, all 3 groups resembled the physically inactive group (ATC), occasional physical activity was associated with a HR for cardiovascular mortality of 0.79 (95% CI = 0.66–0.95) and frequent physical activity with a HR of 0.68 (95% CI = 0.53–0.87; *P* for trend < 0.001) (Table 2 and Figure 4).

Propensity Score-Weighted and Regression-Adjusted Association of Physical Activity and Noncardiovascular Mortality

After weighing the participants such that the baseline characteristics were balanced across the exposure groups (ATE) (Figure 2), and adjusting for the baseline characteristics through regression, occasional physical activity (HR = 0.81, 95% CI = 0.69–0.94; *P* = 0.005), but not frequent physical activity (HR = 0.88, 95%


Covariate Balance
Range across imputations
Inactive versus Frequent
Occasional versus Frequent
Occasional versus Inactive
ACEI or ARB
Alcohol intake
Age
Arrhythmia
Awaiting transplantation
BMI 20–24.9
BMI 24–29.9
BMI 30+
BMI<18.5
Cancer
Cause of kidney disease: DB
Cause of kidney disease: GN
Cause of kidney disease: HTN
Cause of kidney disease: Other
Cerebrovascular disease
Charlson comorbidity index
Congestive heart failure
Coronary heart disease
Country: Argentina
Country: France
Country: Germany
Country: Hungary
Country: Italy
Country: Poland
Country: Portugal
Country: Romania
Country: Spain
Country: Sweden
Country: Turkey
Current or previous smoker
Diabetes
Dialyzed through AVF
Dialysis vintage
Dietary intake: Dairy
Dietary intake: Eggs
Dietary intake: Fiber
Dietary intake: Fish and white meat
Dietary intake: Fruits
Dietary intake: Legumes and nuts
Dietary intake: Red meat and meat products
Dietary intake: Sweets and sweet drinks
Dietary intake: Total energy
Dietary intake: Vegetables
Dietary intake: Whole grains
Ethnicity: Black
Ethnicity: Others
Ethnicity: White/Hispanic
Gastrointestinal disease
Hemoglobin
Hypertension
Intra–HD decrease in bodyweight
Kt/V
Life partner
Male sex
N of drug classes <2
N of drug classes > 4
N of drug classes 3 to 4
NEAP
Neurologic disorder
NPCR
Occupation: Retired
Occupation: Unemployed
Occupation: Working
Peripheral artery disease
Pre–HD systolic blood pressure
Psychiatric disorder
Pulmonary disease
Secondary education or higher
Serum Albumin
Serum BUN
Serum calcium
Serum creatinine
Serum ferritin
Serum IPTH
Serum phosphate
Serum potassium
Time on HD/wk
–0.6
–0.3
0.0
0.3
Standardized Mean Differences
Sample
Unadjusted
Adjusted

CI = 0.72–1.08; $P = 0.22$), was associated with a lower risk of noncardiovascular mortality compared with physical inactivity (pooled P 0.02; P for trend 0.13). After weighing the participants such that all groups resembled the control group (ATC), occasional physical activity (HR = 0.85, 95% CI = 0.72–1.00) and frequent physical activity (HR = 0.85, 95% CI = 0.67–1.06) were not associated with a lower risk of noncardiovascular death (pooled $P = 0.09$) (Table 2 and Figure 4).

Sensitivity Analyses

Tests for interaction terms with age, sex, presence of coronary heart disease, and presence of diabetes were all nonsignificant for all-cause mortality ($P =$ 0.96, 0.22, 0.86, and 0.50), cardiovascular mortality ($P =$ 0.69, 0.12, 0.87, and 0.53), and noncardiovascular mortality ($P =$ 0.81, 0.34, 0.85, and 0.11). The estimates of the association between physical activity and all-cause mortality remained relatively unchanged after accounting for the competing risk of transplantation over the outcome of all-cause mortality. Similarly, accounting for the competing risk of noncardiovascular death for cardiovascular death, and vice versa for noncardiovascular death, yielded similar HRs (Supplementary Table S4). Other potential competing events such as change of dialysis modality were rare. Optimal full matching resulted in similar findings for all-cause and cause-specific mortality compared with inverse probability treatment weighting (Supplementary Table S6).

Assessment of the Vulnerability to Unmeasured Confounders

Table 3 illustrates the e-values for each estimated effect. The e-value for the strongest estimate of the ATE, that is, the association of frequent physical activity with cardiovascular mortality, to be biased from 1.00 to the observed 0.77 was 1.69. The e-value for the CI of the same estimate to be biased as to exclude 1.00 was 1.26. The prevalence ratio of an unmeasured confounder among frequently active versus inactive individuals (and its HR for cardiovascular mortality) as low as 1.26 could lead to the spurious conclusion that frequent physical activity was associated with lower cardiovascular mortality. We thus cannot exclude the possibility that residual confounding explained the association we observed.

DISCUSSION

In adults on hemodialysis, occasional and frequent physical activities were associated with lower risks of all-cause mortality and cardiovascular mortality. The magnitude of the associations with both cardiovascular and noncardiovascular deaths was clinically important, and a dose-dependent association was observed with cardiovascular mortality, such that occasional activity was associated with an 18% reduction and frequent activity with a 23% reduction in cardiovascular mortality.

In this cohort, nearly half of the participants reported no physical activity, which is slightly more than the 35%[8] and 44%[10] prevalence reported in similar studies. The findings in relation to all-cause mortality concur with those of previously published cohort studies, which have reported adjusted HR for all-cause mortality among physically active individuals between 0.29 and 0.73.[8–11] This analysis extends knowledge through evaluation of cause-specific deaths, use of advanced statistical methods, and significantly longer follow-up time (median 3.8 years versus <1,[8] 1.6,[9] 1.8,[10] and 2.6[11] years). Furthermore, we have adjusted for diet which is likely to be linked to the level of physical activity and was associated with survival in this population.[25]

We have identified a dose-dependent association of physical activity frequency with cardiovascular mortality, but not for noncardiovascular mortality. In the general population, physical inactivity has been independently associated with several noncommunicable diseases other than cardiovascular diseases, including diabetes and certain cancers.[2] It is possible that the association between cardiovascular mortality and physical activity is stronger than that of noncardiovascular mortality. Indeed, trial-based evidence in adults with coronary heart disease not on hemodialysis has suggested that exercise training is protective against cardiovascular mortality but not all-cause mortality.[4] Nevertheless, in our study, the lack of dose-dependent association with noncardiovascular death may be due to the capacity of the single-question assessment to discriminate across

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Figure 2. Balance of the covariates across levels of physical activity before (orange) and after (blue) weighting the participants by their propensity score. Created using the Cobalt package version 4.1.0 (Greifer N: cobalt: Covariate Balance Tables and Plots. R package version 4.1.0., 2020). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AVF, arteriovenous fistula; BMI, body mass index; BUN, blood urea nitrogen; DB, diabetes; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; IPTH, intact parathyroid hormone; Kt/V, dialysis adequacy; N, number; NEAP, net endogenous acid production[33] (estimated using the Remer and Manz's equation); NPCR, normalized protein catabolic rate (calculated using the urea extraction rate).

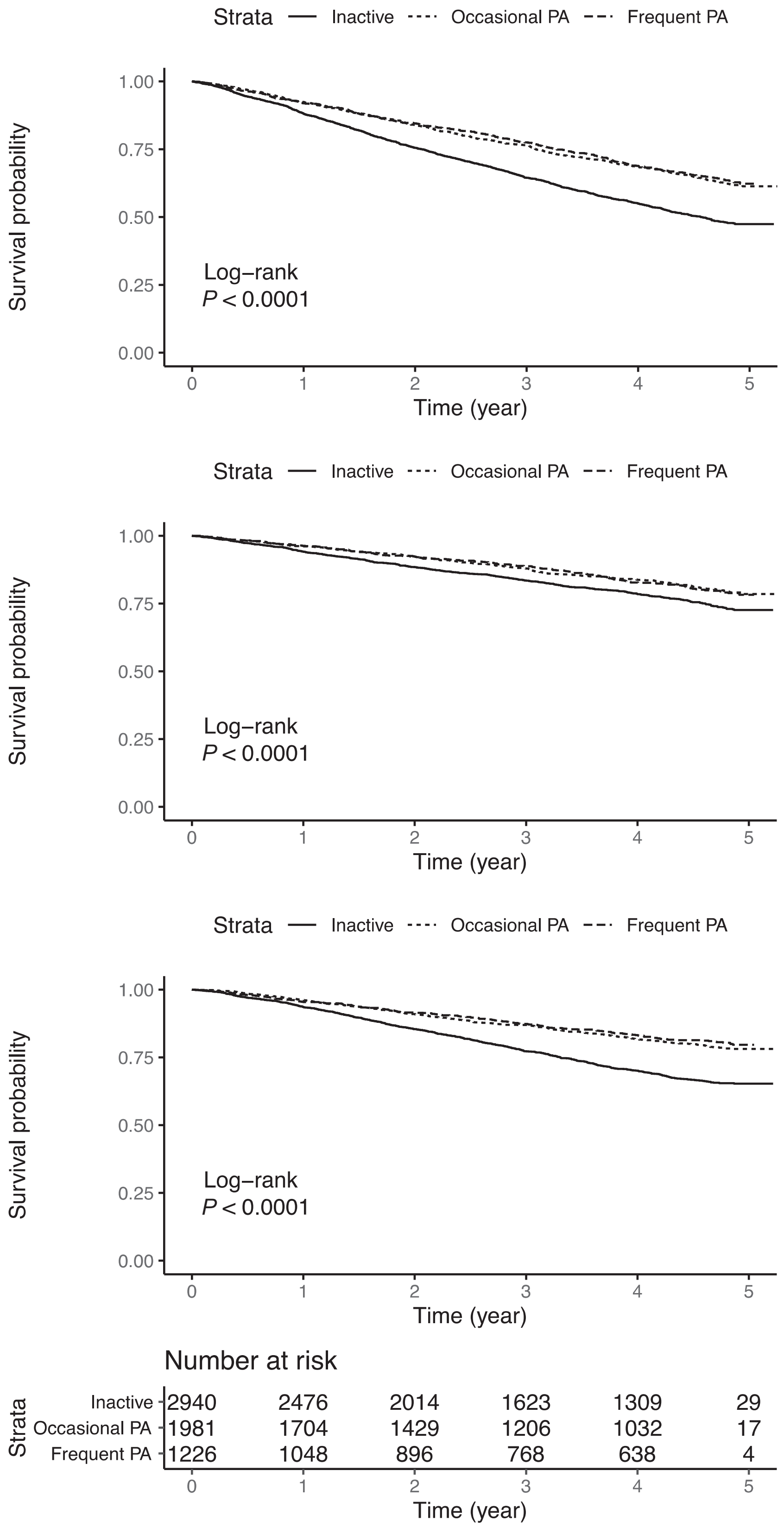

Figure 3. (a) All-cause and (b,c) cause-specific mortality Kaplan-Meier estimates per level of physical activity. PA, physical activity.

levels of intensity of physical activity. It may be that the single self-reported question was effective at differentiating between sedentary and active individuals but not as effective at differentiating low levels of physical activity from higher levels. Furthermore, the number of noncardiovascular mortality events was relatively low among the frequently active individuals.

Table 2. Propensity score-weighted and regression-adjusted hazard ratios for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality

	ATE				ATC			
Physical activity level	**Hazard ratio**	***P***	**Pooled *P***	***P* trend**	**Hazard ratio**	***P***	**Pooled *P***	***P* trend**
All-cause mortality								
Inactive	1.00		<0.001	0.002	1.00		<0.001	<0.001
Occasional	0.80 (0.72–0.89)	<0.001			0.81 (0.72–0.92)	<0.001		
Frequent	0.82 (0.71–0.95)	0.01			0.77 (0.65–0.91)	0.002		
Cardiovascular mortality								
Inactive	1.00		0.009	0.007	1.00		0.001	<0.001
Occasional	0.82 (0.70–0.96)	0.01			0.79 (0.66–0.95)	0.01		
Frequent	0.77 (0.62–0.94)	0.01			0.68 (0.53–0.87)	0.002		
Noncardiovascular mortality								
Inactive	1.00		0.02	0.13	1.00		0.09	0.084
Occasional	0.81 (0.69–0.94)	0.005			0.85 (0.72–1.00)	0.05		
Frequent	0.88 (0.72–1.08)	0.22			0.85 (0.67–1.06)	0.15		

ATC, average treatment effect for the control; ATE, average treatment effect; Kt/V, dialysis adequacy.
Adjusted for age; sex; ethnicity; country of living; education level; presence of a life partner; working status; body mass index; underlying kidney disease etiology; Kt/V; number of minutes of dialysis per week; intradialytic body weight reduction; predialysis systolic blood pressure; smoking status; Charlson comorbidity index; whether they are listed for kidney transplantation; type of vascular access; presence of hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, arrhythmias, atherosclerotic cerebrovascular disease, peripheral artery disease, cancer, gastrointestinal diseases, pulmonary diseases, neurologic disorders, and psychiatric disorders; number of prescription drugs from different classes; whether they are receiving angiotensin-converting enzyme inhibitors; whether they are receiving angiotensin II receptor blockers; hemoglobin level; number of years on dialysis; serum chemistry (calcium, phosphate, potassium); serum albumin; serum creatinine; blood urea nitrogen; ferritin; intact parathyroid hormone level; normalized protein catabolic rate; alcohol intake; dietary intake of fiber, whole grains, fruits, vegetables, legumes and nuts, dairy, fish and white meat, red meat and meat products, eggs, and sweets and sweet drinks; and daily total energy intake.

Similarly to other cohorts, we found that even low levels of physical activity that were below the recommended daily amount were associated with lower mortality.[10,11] Furthermore, most of the apparent mortality benefit was observed when comparing the occasionally active with the physically inactive, with only a small apparent benefit from comparing the frequently active with the occasionally active, a phenomenon that has also been observed in the general population.[26] Although this finding may highlight the risks of sedentarism, it may also result from the lack of information collected on the intensity of involvement of the participants in physical activity. The estimates of the ATC were of greater magnitude than those of the ATE, suggesting inactive individuals may gain the most from engaging in physical activity. Such findings are encouraging for people undergoing hemodialysis who often face physical limitations and reduced exercise capacity.[27–30] They may also inform future randomized controlled trials by suggesting that even low doses of physical activity may provide benefits.

Despite extensive adjustment for baseline characteristics and the use of novel statistical methods, we could not exclude residual confounding. Indeed, our

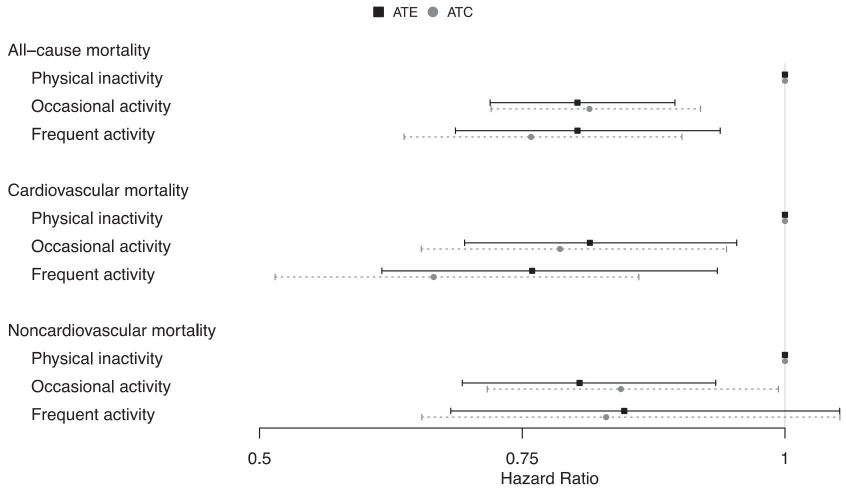

Figure 4. Propensity score-weighted and regression-adjusted hazard ratios for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality. Physical activity was evaluated using a single question at baseline requesting the patient to self-rate their level of physical activity as either none, irregularly, once a week, more than once a week, or daily. Physical activity was categorized as frequent activity (more than once a week to daily), occasional activity (irregularly to once a week), or inactivity (no physical activity). ATC, average treatment effect for the control; ATE, average treatment effect.

Table 3. E-values for the propensity score-weighted and regression-adjusted estimates of the association between physical activity and all-cause, cardiovascular, and noncardiovascular mortality

	To bias the point estimate from 1.0 to the observed point estimate		To bias the upper limit of the 95% CI from 1.0 to the observed upper limit of the 95% CI	
Estimated effect	**ATE**	**ATC**	**ATE**	**ATC**
All-cause				
Physically inactive	—	—	—	—
Occasional physical activity	1.48	1.46	1.31	1.25
Frequent physical activity	1.44	1.54	1.19	1.27
Cardiovascular mortality				
Physically inactive	—	—	—	—
Occasional physical activity	1.56	1.63	1.2	1.23
Frequent physical activity	1.69	1.94	1.26	1.44
Noncardiovascular mortality				
Physically inactive	—	—	—	—
Occasional physical activity	1.58	1.48	1.26	1
Frequent physical activity	1.53	1.63	1	1

ATC, average treatment effect in the control group; ATE, average treatment effect.

evaluation of the e-value indicates that unmeasured confounders of the effect of physical activity on mortality may have biased our results to reveal a false protective association. This limitation is shared with other observational studies of the association between physical activity and mortality. To our knowledge, a single randomized controlled trial has evaluated the impact of exercise training on mortality for adults undergoing hemodialysis and found similar death rates among individuals randomized to 6 months of home-based walking sessions (24 of 151) compared with usual care (22 of 145).[31] Nevertheless, the intervention was of short duration and the trial was not powered to evaluate differences in mortality.

Our findings are consistent with the ample evidence that physical activity is beneficial in the general population.[32] Although they suggest that increased physical activity would also lead to benefits in people receiving hemodialysis, the potential harms have not yet been evaluated in this population. On balance, recommending some level of physical activity could be justified before definitive trials are conducted. Our results indeed suggest that even low levels of physical activities that are likely to be safe may yield significant improvement in mortality.

This study has several potential limitations. Confounding from unmeasured determinants of better health could explain our findings. We excluded the participants who did not answer the question regarding physical activity which could introduce a selection bias toward more active participants. Yet, approximately half of the participants reported being inactive. Physical activity was self-reported and measured at a single time point using a single question, which could lead to misclassification of the exposure, and no information was available on the type, intensity, and duration of physical activity. Furthermore, differing interpretations of the definition of physical activity by the participants cannot be excluded. For example, some participants may have only considered sport-related activities whereas others may have considered activities related to transportation or house maintenance. Dietary intake was evaluated solely at baseline; hence, we could not account for changes in the diet over time. Moreover, social desirability may have biased our measurement of the exposure toward higher levels of physical activity.

Our study has significant strengths. The DIET-HD is a large multinational prospective cohort of adults undergoing maintenance hemodialysis with long-term follow-up. We successfully used propensity score weighting to balance the covariates across each exposure group and provided double robust estimates of the effects. We adjusted for characteristics of the diets of the participants which have been linked to mortality in hemodialysis[25] and are common confounders for physical activity. We also evaluated the vulnerability of our findings to unmeasured confounders, thereby providing more informed inferences of the effect of physical activity on mortality.

In conclusion, occasional and frequent physical activities were associated with better survival in adults undergoing hemodialysis. Future research should focus on pragmatic randomized controlled trials of low-intensity physical activity for sedentary adults receiving hemodialysis treatments.

DISCLOSURE

DWJ reports receiving consultancy fees, research grants, speaker's honoraria, and travel sponsorships from Baxter Healthcare and Fresenius Medical Care; consultancy fees from AstraZeneca and AWAK; speaker's honoraria and travel sponsorships from Ono; and travel sponsorships from Amgen. He is also a current recipient of an Australian National Health and Medical Research Council Practitioner Fellowship. Daiichi Sankyo awarded a grant to the institution of MT in lieu of a personal honorarium for a lecture at a scientific meeting in 2017. The lecture topic was not related to the topic of this article. MT also reports receiving a lecture fee from B. Braun in 2019; the fee was donated to charity. The lecture topic was not related to the topic of this article. All the other authors declared no competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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AUTHOR CONTRIBUTIONS

Conception and design: ABJ, GW, VS, JCC, and GFMS. Data acquisition: MR and PN. Data analysis: ABJ, GW, VS, ATP, and GFMS. Data interpretation: ABJ, GW, VS, MR, SCP, PN, VGL, DWJ, MT, JH, JCC, ATP, and GFMS. Study supervision and mentorship: GFMS, JCC, ATP, and GW. Each author contributed important intellectual content during manuscript drafting or revision and gave final approval of the version to be submitted.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Statistical Methods.

Complete list of variables included in the propensity score model.

Optimal full matching analysis.

Supplementary Results. Results from the optimal full matching analysis.

Table S1. Characteristics of the participants included compared to those excluded.

Table S2. Characteristics of participants' dietary intake.

Table S3. Mean and maximum standardised mean difference for all baseline characteristics included in the propensity score model across imputed datasets.

Table S4. Unadjusted and unweighted hazard ratios for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality.

Table S5. Results of the competing risk analysis: propensity score-weighted and regression-adjusted[1] hazard ratios for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality.

Table S6. Estimates of the average treatment effect in the control obtained through optimal full matching.

STROBE Statement.

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