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

Amelie Bernier-Jean1, Germaine Wong1, Valeria Saglimbene1,2, Marinella Ruospo2, Suetonia C. Palmer3, Patrizia Natale1,2, Vanessa Garcia-Larsen4, David W. Johnson5,6, Marcello Tonelli7, Jörgen Hegbrant8, Jonathan C. Craig9, Armando Teixeira-Pinto1 and Giovanni F.M. Strippoli1,2

1School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia; 2Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy; 3Department of Medicine, University of Otago, Christchurch, New Zealand; 4Program in Human Nutrition, Department of International Health, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; 5Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; 6Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia; 7Cumming School of Medicine, University of Calgary, Calgary, Canada; 8Department of Nephrology, Lund University, Lund, Sweden; and 9College of Medicine and Public Health, Flinders University, Bedford Park, Australia

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.

Kidney Int Rep (2021) 6, 3014–3025; https://doi.org/10.1016/j.ekir.2021.09.002
KEYWORDS: hemodialysis; mortality; physical activity
© 2021 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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...
was based mostly on evidence from the general population and nondialysis groups at high risk of cardiovascular disease. 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. 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.

Multiple trials have evaluated the effects of exercise training for adults undergoing hemodialysis. 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. 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.

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. DIET-HD is a prospective, multinational study primarily designed to evaluate dietary intake in adults undergoing maintenance hemodialysis.

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.

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. 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

| Participants characteristics | Inactive | Occasional | Frequent | Missing, % |
|------------------------------|----------|------------|----------|------------|
| N                            | 2940     | 1981       | 1226     | 0          |
| Age $\geqslant$ 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                    | 2610 (95.5) | 1815 (96.3) | 1136 (97.2) | 5.9        |
| Black/Hispanic               | 82 (3.0)   | 43 (2.3)   | 19 (1.6)  |            |
| Others                       | 40 (1.5)   | 27 (1.4)   | 14 (1.2)  |            |
| Body mass index              | 137 (4.8)  | 83 (4.3)   | 52 (4.3)  |            |
| $<18.5$ kg/m²                | 1146 (40.0) | 832 (43.0) | 548 (45.2) |            |
| $18.5$–$24.9$ kg/m²          | 959 (33.5) | 645 (33.4) | 424 (35.0) |            |
| $\geqslant30$ kg/m²          | 624 (21.8) | 379 (19.3) | 188 (15.5) |            |
| Occupation status            | 208 (7.3)  | 273 (14.2) | 188 (15.6) |            |
| Working                      | 2219 (78.4) | 1357 (70.4) | 875 (72.7) |            |
| Retired                      | 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                      | 366 (12.4) | 180 (9.1)  | 35 (2.9)  |            |
| 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          | 31 (1.3)   | 31 (1.3)   | 3.0 (1.4)  | 3.5        |
| Kt/V $\geqslant$ 1.4         | 2537 (89.4) | 1717 (89.3) | 1068 (88.5) | 2.9        |
| Diastolized through AVF      | 2256 (76.9) | 1627 (82.3) | 1059 (86.6) | 0.2        |
| Listed for transplant        | 369 (12.6) | 456 (23.0) | 283 (23.1) | 0.2        |
| Comorbidities                | 2110 (71.8) | 1060 (53.5) | 592 (48.3) |            |
| Coronary heart disease       | 712 (25.6) | 468 (25.5) | 245 (21.6) | 6.4        |
| Congestive heart failure     | 607 (20.9) | 364 (18.7) | 197 (18.3) | 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                 | 2486 (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)
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, 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. 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. 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.

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, the cobalt package to evaluate the balance of the covariates across the 3 exposure groups, and the survey and survival packages for the outcome models.

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).
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%
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%\(^6\) 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 \(<1,\)\(^8\) \(1.6,\)\(^6\) \(1.8,\)\(^10\) 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...
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.
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. 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. 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. They may also inform future randomized controlled trials by suggesting that even low doses of physical activity may provide benefits.

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.

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

| Physical activity level | ATE Hazard ratio (95% CI) | P pooled | P trend | ATC Hazard ratio (95% CI) | P pooled | 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   | 0.002   | 0.81 (0.72–0.92)         | <0.001   | <0.001  |
| Frequent               | 0.82 (0.71–0.95)         | 0.01     |         | 0.77 (0.65–0.91)         | 0.002    |         |
| Cardiovascular mortality|                         |          |         |                          |          |         |
| Inactive               | 1.00                     | <0.001   | 0.007   | 1.00                     | <0.001   | <0.001  |
| Occasional             | 0.82 (0.70–0.96)         | 0.01     |         | 0.79 (0.66–0.93)         | 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.

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.
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). 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. 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.

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.
This work was supported by the provider of renal services Diaverum, which funded overhead costs for study coordinators in each contributing country and material printing. ABJ was supported by a scholarship from the National Health and Medical Research Council (GNT1151246) for the completion of this study. The contents of the published material are solely the responsibility of the individual authors and do not reflect the views of the National Health and Medical Research Council.

CONFLICTS OF INTEREST
None declared.

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, ATP, PN, VGL, 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 non-cardiovascular mortality.
Table S5. Results of the competing risk analysis: propensity score-weighted and regression-adjusted 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.
Supplementary References.

REFERENCES
1. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2019;73(suppl 1):A7–A8. https://doi.org/10.1053/j.ajkd.2019.01.001.
2. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380:219–229. https://doi.org/10.1016/S0140-6736(12)60319-5.
3. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;46(suppl 3):S1–S153.
4. Anderson L, Thompson DR, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2016;2016:CD001800. https://doi.org/10.1002/14651858.CD001800.pub3.
5. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;157:263–275. https://doi.org/10.7326/0003-4819-157-4-201208210-00007.
6. Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;156:445–459. https://doi.org/10.7326/0003-4819-156-6-201203200-00007.
7. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev. 2011:10:CD003236. https://doi.org/10.1002/14651858.CD003236.pub2.
8. O’Hare AM, Tawney K, Baczetti P, Johansen KL. Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. Am J Kidney Dis. 2003;41:447–454. https://doi.org/10.1053/ajkd.2003.50055.
9. Lopes AA, Lantz B, Morgenstern H, et al. Associations of self-reported physical activity types and levels with quality of life, depression symptoms, and mortality in hemodialysis patients: the DOPPS. Clin J Am Soc Nephrol. 2014;9:1702–1712. https://doi.org/10.2215/CJN.12371213.
10. Tentori F, Elder SJ, Thumma J, et al. Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. Nephrol Dial Transplant. 2010;25:3050–3062. https://doi.org/10.1093/ndt/gfq138.
11. Johansen KL, Kayesen GA, Dalrymple LS, et al. Association of physical activity with survival among ambulatory patients on dialysis: the comprehensive dialysis study. Clin J Am Soc Nephrol. 2013;8:248–253. https://doi.org/10.2215/CJN.08560812.
12. Palmer SC, Ruospo M, Campbell KL, et al. Nutrition and dietary intake and their association with mortality and hospitalisation in adults with chronic kidney disease treated with haemodialysis: protocol for DIET-HD, a prospective multinational cohort study. BMJ Open. 2015;5. https://doi.org/10.1136/bmjopen-2014-006897. e006897-e006897.
13. Saglimbene VM, Wong G, Ruospo M, et al. Dietary n-3 polyunsaturated fatty acid intake and all-cause and cardiovascular mortality in adults on haemodialysis: the DIET-HD multinational cohort study. Clin Nutr. 2018;38:429–437. https://doi.org/10.1016/j.clnu.2017.11.020.
14. Garcia-Larson V, Lucynska M, Kowalski ML, et al. Use of a common food frequency questionnaire (FFQ) to assess dietary patterns and their relation to allergy and asthma in Europe: pilot study of the GA2LEN FFQ. Eur J Clin Nutr. 2011;65:750–756. https://doi.org/10.1038/ejcn.2011.15.
