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Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes

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Abstract

Background. Levels of physical exercise among haemodialysis patients are low. Increased physical activity in this population has been associated with improved health-related quality of life (HRQoL) and survival. However, results of previous studies may not be applicable to the haemodialysis population as a whole. The present study provides the first description of international patterns of exercise frequency and its association with exercise programmes and clinical outcomes among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

Methods. Data from a cross section of 20 920 DOPPS participants in 12 countries between 1996 and 2004 were analysed. Regular exercise was defined as exercise frequency equal to or more than once/week based on patient self-report. Linear mixed models and logistic regression assessed associations of exercise frequency with HRQoL and other psychosocial variables. Mortality risk was calculated in Cox proportional hazard models using patient-level (patient self-reported exercise frequency) and facility-level (the dialysis facility percentage of regular exercisers) predictors.

Results. Regular exercise frequency varied widely across countries and across dialysis facilities within a country. Overall, 47.4% of participants were categorized as regular exercisers. The odds of regular exercise was 38% higher for patients from facilities offering exercise programmes (adjusted odds ratio = 1.38 [95% confidence interval: 1.03–1.84]; P = 0.03). Regular exercisers had higher HRQoL, physical functioning and sleep quality scores; reported fewer limitations in physical activities; and were less bothered by bodily pain or lack of appetite ($P \leq 0.0001$ for all). Regular exercise was also correlated with more positive patient affect and fewer depressive symptoms ($P \leq 0.0001$). In models extensively adjusted for demographics, comorbidities and socio-economic indicators, mortality risk was lower among regular exercisers (hazard ratio = 0.73 [0.69–0.78]; $P < 0.0001$) and at facilities with more regular exercisers (0.92 [0.89–0.94]; $P < 0.0001$ per 10% more regular exercisers).

Conclusions. Results from an international study of haemodialysis patients indicate that regular exercise is associated with better outcomes in this population and that patients at facilities offering exercise programmes have higher odds of exercising. Dialysis facility efforts to increase patient physical activity may be beneficial.

Keywords: DOPPS; exercise; haemodialysis; mortality; quality of life

Introduction

In the general population, lifestyle changes that increase physical exercise result in lower mortality [1]. Current guidelines recommend that healthy individuals should perform a moderate amount of physical activity on most days [2].

Patients with end-stage renal disease (ESRD) on maintenance haemodialysis have very high mortality [3], and yet higher mortality risk has been reported for sedentary haemodialysis patients [4]. The positive effects of physical exercise reported in the general population may be highly relevant for ESRD patients. In addition to potentially reducing cardiovascular risk, exercise may improve physical functioning, which in turn can lead to improvement in health-related quality of life (HRQoL) [5]. Several pioneer studies of exercise training in haemodialysis have suggested that increasing patient physical activity may improve physiologic performance and possibly clinical outcomes. Aerobic training led to improved peak oxygen consumption, indicating that ESRD patients are able to respond physiologically to exercise [6–9]. Resistance training resulted in increased muscle mass, strength and physical functioning [10], while vigorous aerobic training has also been associated with decreased depression and improved HRQoL [11–14]. Additionally, a reduction in antihypertensive medications has been demonstrated [15], though the impact of physical exercise on anaemia and lipid profile remains unclear [6,16,17].

Despite the potential benefits of exercise, haemodialysis patients are less active than sedentary healthy people, with <50% of haemodialysis patients in the USA exercising at least once a week [18–21]. While clinical conditions limit the ability of some haemodialysis patients to exercise, it is likely that modifiable factors also contribute to the sedentary habits of many haemodialysis patients. For example, exercise assessment and counselling are not part of routine care in many haemodialysis units [21]. The present study describes international patterns of exercise and its associations with clinical characteristics, facility exercise programmes and outcomes among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

Methods

Study design and data sources

The DOPPS study design has been described previously [22,23]. The present study analysed data collected during DOPPS I (1996–2001) and DOPPS II (2002–04). In DOPPS I, 17 034 patients were randomly sampled from 308 dialysis facilities in France, Germany, Italy, Japan, Spain, the UK and the USA. DOPPS II included 12 839 patients from 322 facilities in the original seven countries plus Australia, Belgium, Canada, Sweden and New Zealand. Local institutional review boards approved the study and informed consent was obtained as required. Participants were observed until the earliest of death, transplantation, switch to peritoneal dialysis, withdrawal from dialysis, transfer to another facility or study end.

Patient demographics and clinical characteristics were obtained by medical record abstraction at study entry. DOPPS participants were asked to complete a self-administered questionnaire that included the same question on physical exercise frequency that was asked in the Dialysis Morbidity and Mortality Study (DMMS) Wave 2 [4] (How often do you exercise [do physical activity] during your leisure time?). Six answer options were given: 'Daily or almost daily', '4–5 times/week', '2–3 times/week', 'About once/week', 'Less than once/week' and 'Almost never or never' (labelled here as 'Never'). The DOPPS patient questionnaire also included the Kidney Disease Quality of Life Short Form (KDQoL-SF™) [24–27] and the short version of the Center for Epidemiological Studies Depression Screening Index (CES-D) [28].

The present study analysed patients for whom data on self-reported exercise frequency were available (*n* = 20 920 patients overall; 10 778 from 306 facilities in DOPPS I and 10 142 from 320 facilities in DOPPS

II). Data on physical functioning, sleep quality and affect were only collected in DOPPS I, while the CES-D was only administered in DOPPS II. Analyses of facility-level exercise were restricted to patients who had been at the facility for at least 30 days (n = 19 758). Separate analyses on availability of exercise programmes were conducted in 214 facilities participating in DOPPS III (2005–08).

Statistical methods

Standard descriptive statistics were used to present patient characteristics. Adjusted mean quality of life scores were calculated by mixed linear regression. Logistic regression was used to identify the association of patient characteristics, psychosocial variables and availability of facility exercise programmes with regular exercise. Mortality and hospitalization risks were assessed in Cox proportional hazards models.

When assessing the association with outcomes, four exercise frequency categories were used (once/week, 2–3 times/week, 4–5 times/week and 6–7 times/week) and never or less than once/week served as the reference group. In some analyses, exercise was also dichotomized as ‘regular exercise’ (equal to or more than once/week) versus ‘non-regular exercise’ (less than once/week or never) and treated as an ordered variable.

To partially address bias introduced by unmeasured patient-level confounders [29], the association between regular exercise and mortality was also assessed using a modified instrumental variable approach [30,31] where the predictor was the adjusted facility percentage of regular exercisers. This percentage was estimated by fitting a linear mixed-effects model where exercise frequency was the dependent variable; case-mix factors were varying variables and the facility was treated as a random effect. The intercept for the random effect was the expected level of regular exercise and was adjusted for the facility case mix. The adjusted facility percentage of regular exercisers (treated both as a continuous and as a categorical variable) was applied to all patients in a facility and was used to predict patient mortality risk in the Cox model.

To assess the impact of selected covariates on the association between regular exercise and mortality, models were adjusted in phases for demographic characteristics, 14 summary comorbid conditions, laboratory values, catheter use, socio-economic indicators and ability to walk. A missing indicator was used for all covariates except for race, which was not reported in only eight patients. To address bias introduced by facilities that provide overall higher quality care, facility-level models were also adjusted for indicators of achievement of clinical guidelines. Since adjustment for additional covariates did not impact the association between exercise and psychosocial outcomes, only results of fully adjusted models are shown. All models were stratified by country and account for facility clustering using generalized estimating equations (logistic models) and robust standard error estimation techniques (Cox models).

Sensitivity analyses assessed the associations between regular exercise and mortality among participants able to walk and not able to walk; with and without college education, private insurance, peripheral vascular disease and congestive heart failure; employed and not employed; living alone and not living alone; and body mass index (BMI) <18 and ≥18 kg/m^2. Additional analyses were restricted to prevalent patients only (on haemodialysis >120 days at study enrolment) and to patients treated at facilities not based in a hospital.

All analyses were performed with SAS, version 9.1 (SAS Institute; Cary, NC, USA). The authors have followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement guidelines for reporting observational studies [32].

Results

Study sample

Overall, 22 526 participants (75%) completed the patient questionnaire; of these, 20 920 (93%) answered the exercise question (‘responders’) and 1606 did not (‘non-responders’). The response rate to the patient questionnaire was higher in DOPPS countries outside of the USA (ranging from 78% in Japan to 92% in Italy vs 63% in the USA). Among participants who completed the patient questionnaire, the response rate to the exercise question was 89% in the USA and ≥95% in all other countries.

Median follow-up was 1.75 years. A total of 4143 deaths occurred with a crude death rate of 0.12 per year. For the rest of the patients, end of follow-up occurred for the following reasons: end of study period (12 963 participants = 61.7%), transfer out of the DOPPS facility (2108 participants = 10.1%), switch to peritoneal dialysis (336 participants = 1.6%), kidney transplant (1266 participants = 6.1%), recovery of renal function (88 participants = 0.42%), withdrawal from dialysis (11 participants = 0.05%) and refusal to continue study participation (five participants = 0.02%).

International patterns of physical exercise

Among responders, 43.9% (n = 9176) reported to never exercise, 8.5% (n = 1823) reported to exercise less than once/week, 10.5% (n = 2205) once/week, 17.0% (n = 3558) two to three times/week, 5.7% (n = 1201) four to five times/week and 14.1% (n = 2957) daily. Overall, 47.4% of participants (n = 9921) reported to exercise at least once a week and were categorized as regular exercisers. Exercise frequency was similar in DOPPS I and DOPPS II (data not shown) but varied widely across DOPPS countries (Figure 1) and across dialysis facilities within each country (Figure 2).

Availability of exercise programmes

In 2005–06, exercise programmes were relatively uncommon in most DOPPS countries and were not offered at all in France (Figure 3). Germany and Sweden were the exceptions; 57% of centres in Germany offered exercise programmes while on dialysis and 7% while not on dialysis; and 64% of centres in Sweden offered exercise programmes while on dialysis and 75% while not on dialysis.

Patient characteristics associated with regular exercise

Table 1 shows the demographic and clinical characteristics of non-responders vs responders and regular vs non-regular exercisers. Non-responders tended to be older, unemployed, had a lower level of education, had more comorbidities and, overall, were similar to the DOPPS participants who did not complete the patient questionnaire at all (data not shown). Patient characteristics positively associated with regular exercise were male sex, lower BMI, erythropoiesis-stimulating agent (ESA) use, having a college education and ability to walk. Patient characteristics inversely associated with regular exercise were older age, coronary artery disease, congestive heart failure (CHF), cerebrovascular disease, lung disease and smoking.

Distribution of patient characteristics in facilities with different levels of regular exercisers. Due to differences in patient case mix across the world, the distribution of patient characteristics across facility quartiles of regular exercisers was assessed separately within each DOPPS region (North America; Europe + Australia/New Zealand and Japan); results for North America are shown in Table 2. Overall, patient characteristics were generally similar across facility quartiles of regular exercisers. Patients at facilities with a higher percentage of regular exercisers were younger, more likely to have some college education and to be employed, and were less likely to be black and to use a catheter as vas-

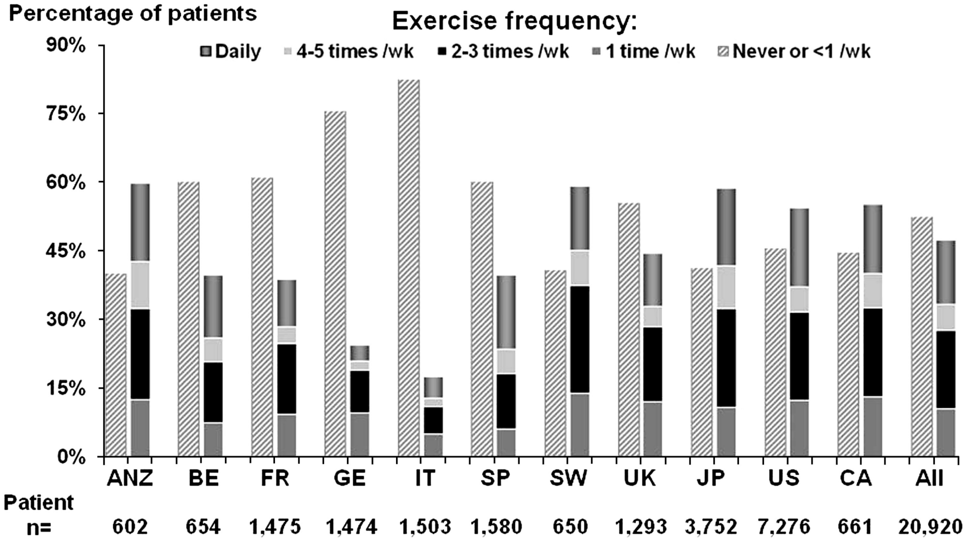

Fig. 1. Distribution of exercise frequency across DOPPS countries. As reported by DOPPS participants who answered the exercise frequency question in the patient questionnaire (n = 20 920). ANZ, Australia and New Zealand; BE, Belgium; FR, France; GE, Germany; IT, Italy; SP, Spain; SW, Sweden; UK, United Kingdom; JP, Japan; US, United States; CA, Canada. For each country, the left and right bars add to 100%.

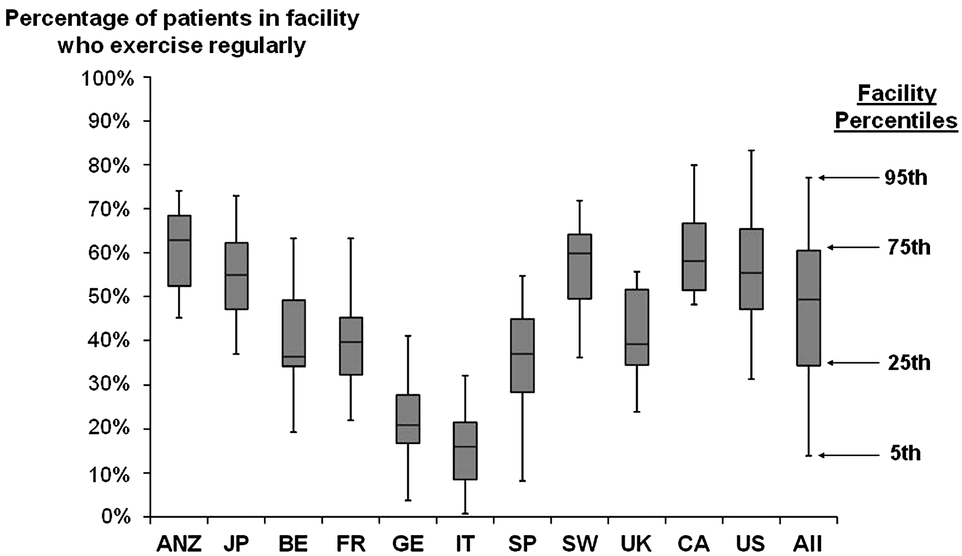

Fig. 2. Facility percentage of regular exercisers across DOPPS countries. Regular exercise is defined as exercising once or more than once/week. Restricted to patients treated at the facility for >30 days since study entry; median number of patients per facility: 44. ANZ, Australia and New Zealand; JP, Japan; BE, Belgium; FR, France; GE, Germany; IT, Italy; SP, Spain; SW, Sweden; UK, United Kingdom; CA, Canada; US, United States.

cular access. With the exception of congestive heart failure, peripheral vascular disease and cerebrovascular disease, the prevalence of comorbidities was similar in facilities with different levels of regular exercisers. Mean levels of albumin, an important predictor of mortality, did not differ by facility exercise category. Findings were generally comparable in other regions (data not shown).

Associations between regular exercise and patient outcomes

Patient self-reported psychosocial outcomes. Higher exercise frequency was associated with significantly better mental component, physical component, physical functioning and sleep quality scores of the KDQoL-SF™ (Table 3).

Exercise was inversely associated with reporting limitations in physical activities, severe bodily pain, lack of appetite, negative affect and CES-D score >10 (Table 4). The odds of CES-D score >10 was also lower for regular exercisers in analyses of patients with (odds ratio, OR = 0.50 [95% confidence interval: 0.38–0.66]) or without (0.61 [0.55–0.68]) a physician diagnosis of depression.

Hospitalizations. No significant association was found between regular exercise and hospitalizations (all cause: HR = 1.00 [0.96–1.04], P = 0.92; due to cardiac events: 0.97 [0.91–1.03], P = 0.29; due to amputations: 0.98 [0.83–1.17], P = 0.82) except those due to fractures (0.76 [0.61–0.94], P = 0.01).

Table 1. Characteristics of DOPPS participants who did not answer the exercise question ('non-responders') and of those who did ('responders'), and of regular versus non-regular exercisers

Mean (standard deviation) or % [ref. for AOR]	Non-responders[a] (*n* = 1606)	Responders, study sample (*n* = 20 920)	Regular exercisers[b] (*n* = 9921)	Non-regular exercisers (*n* = 10 999)	AOR[c] regular vs non-regular exercisers
Demographics					
Age (years) [per 1 year older]	63.5 (14.7)	60.7 (14.8)	59.5 (14.9)	61.9 (14.6)	0.99 (0.99–1.00)*
Male [vs female]	54.8	58.2	63.1	53.8	1.48 (1.39–1.58)*
Black [vs other races]	22.9	12.6	14	11.3	0.95 (0.85–1.06)
Duration of ESRD (SD) (years) [per 1 year]	2.9 (4.6)	3.6 (5.2)	3.7 (5.3)	3.5 (5.2)	0.99 (0.98–1.00)*
BMI (kg/m^2)					
Mean (SD)	24.7 (5.8)	24.5 (5.5)	24.2 (5.4)	24.8 (5.6)	0.98 (0.97–0.98)*
<20.1 kg/m^2	34	28.6	29.9	27.4	1.29 (1.17–1.42)*
20.1–22.8	19.4	21.1	22.7	19.7	1.36 (1.24–1.48)*
22.8–26.2	20.8	22.8	22.4	23.1	1.22 (1.12–1.33)*
>26.2 [ref]	25.8	27.5	25	29.8	
Catheter use	31.1	23.3	22.3	24.3	0.96 (0.88–1.04)
ESAs prescription [yes vs no]	75.8	78.1	79.7	76.6	1.13 (1.05–1.22)*
Comorbidities					
Diabetes [vs no]	41.0	34.5	33.4	35.6	0.94 (0.87–1.00)
Hypertension [vs no]	79.2	78.2	78.6	77.9	1.06 (0.98–1.15)
Coronary artery disease [vs no]	45.1	39.7	37.7	41.6	0.95 (0.89–1.02)
Congestive heart failure [vs no]	37.4	29.4	27.4	31.2	0.86 (0.80–0.93)*
Other cardiovascular diseases [vs no]	35.9	32	29.9	33.9	0.99 (0.92–1.06)
Peripheral vascular disease [vs no]	24.3	22.4	19.3	25.2	0.88 (0.81–0.95)*
Cerebrovascular disease [vs no]	18.1	14.6	12.9	16.2	0.87 (0.80–0.95)*
Recurrent cellulitis [vs no]	8.0	6.4	5.3	7.4	0.84 (0.73–0.96)*
GI bleed [vs no]	6.8	6	5.8	6.3	0.99 (0.87–1.11)
Lung disease [vs no]	11.6	10	8.7	11.2	0.87 (0.79–0.96)*
Neurologic disorder [vs no]	9.5	7.7	6.8	8.5	0.89 (0.80–0.99)*
Physician-diagnosed depression [vs no]	16.9	14.3	12.5	15.9	0.85 (0.78–0.93)*
Other psychiatric disorder [vs no]	4.0	4.3	4.3	4.4	1.01 (0.87–1.17)
Cancer (excluding skin) [vs no]	11.4	10.6	10.1	11	0.94 (0.86–1.04)
HIV [vs no]	1.1	0.8	0.8	0.8	0.61 (0.43–0.87)*
Laboratory values					
Haemoglobin (g/dL)					
Mean (SD)	10.5 (1.6)	10.6 (1.7)	10.7 (1.7)	10.6 (1.7)	1.05 (1.02–1.08)*
<10	32.6	31.6	31.6	31.7	0.87 (0.79–0.95)*
10–11	24.3	23.4	22.6	24.1	0.82 (0.75–0.91)*
11–12	17.5	18.9	19.3	18.5	0.95 (0.86–1.05)
>12 [ref]	13.8	17.8	18.6	17	
spKt/V					
Mean (SD)	1.3 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.00 (0.84–1.18)
≥1.2 [vs <1.2]	68.6	70	70.2	69.8	1.01 (0.92–1.10)
Creatinine (mg/dL)					
Mean (SD)	8.8 (3.4)	9.1 (3.2)	9.5 (3.3)	8.8 (3.1)	1.03 (1.02–1.05)*
<7.2	30.8	26.8	23.4	29.8	0.78 (0.70–0.87)*
7.2–9.1	20.1	21.5	20.4	22.5	0.86 (0.78–0.95)*
9.1–11.2	19.4	21	21.5	20.5	0.94 (0.85–1.03)
>11.2 [ref]	19.7	22.7	26.9	18.9	
Albumin (g/dL)					
Mean (SD)	3.6 (0.5)	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)	1.11 (1.01–1.22)*
<3.6	30.4	27.9	27.5	28.3	0.92 (0.84–1.02)
3.6–3.8 [ref]	20.5	18.4	19.8	17.1	
3.8–4.1	21.3	24	25.8	22.5	0.96 (0.87–1.05)
>4.1	11.1	14.8	15.5	14.2	1.02 (0.91–1.15)
Calcium (mg/dL)					
Mean (SD)	9.1 (1.0)	9.2 (1.0)	9.2 (1.0)	9.2 (1.0)	0.98 (0.94–1.03)
<9.5	56.8	55.6	56	55.3	0.97 (0.89–1.06)
9.5–10.5	20.9	23.8	23.6	24	0.92 (0.84–1.01)
>10.5 [ref]	6.5	8.3	8.8	7.8	
Phosphorus (mg/dL)					
Mean (SD)	5.7 (1.8)	5.6 (1.8)	5.7 (1.8)	5.6 (1.9)	0.99 (0.96–1.01)
<3.5	6.9	8.1	7.3	8.8	0.97 (0.87–1.08)
3.5–5.5	33.2	36.6	37	36.3	1.05 (0.98–1.12)
>5.5 [ref]	42.8	42.8	43.6	42.1	
PTH (pg/mL)					
Mean (SD)	301.8 (444.2)	284 (400.2)	282.1 (412.3)	285.7 (388.9)	1.00 (1.00–1.00)*
<300	80.9	79.7	79.8	79.6	1.10 (1.02–1.19)*
≥300 [ref]	19.1	20.3	20.2	20.4	

Continued

Table 1. *Continued*

Mean (standard deviation) or % [ref. for AOR]	Non-responders[a] (n = 1606)	Responders, study sample (n = 20 920)	Regular exercisers[b] (n = 9921)	Non-regular exercisers (n = 10 999)	AOR[c] regular vs non-regular exercisers
Socio-economic indicators					
Smoker [vs no]	16.7	18.6	18.7	18.6	0.82 (0.76–0.89)*
Some college education [vs no]	17.2	19.1	23.1	15.6	1.22 (1.12–1.33)*
Employed [vs no]	13.7	17.7	20.3	15.5	0.85 (0.77–0.93)*
Private insurance [vs other insurance]	17.0	18	18.5	17.4	0.97 (0.84–1.12)
Lives alone [vs no]	18.3	15.6	16	15.3	1.05 (0.96–1.14)
Able to walk [vs no]	68.8	77.6	81.6	74.1	1.32 (1.22–1.43)*

[a]Study participants who completed the DOPPS patient questionnaire but did not answer the question on physical exercise.
[b]Regular exercise defined as exercising once or more than once/week.
[c]OR, odds ratio; adjusted for all factors listed, DOPPS country and accounted for facility clustering.
SD, standard deviation; BMI, body mass index; ESA, erythropoiesis-stimulating agent; GI, gastro-intestinal; PTH, parathyroid hormone.
*P < 0.05.

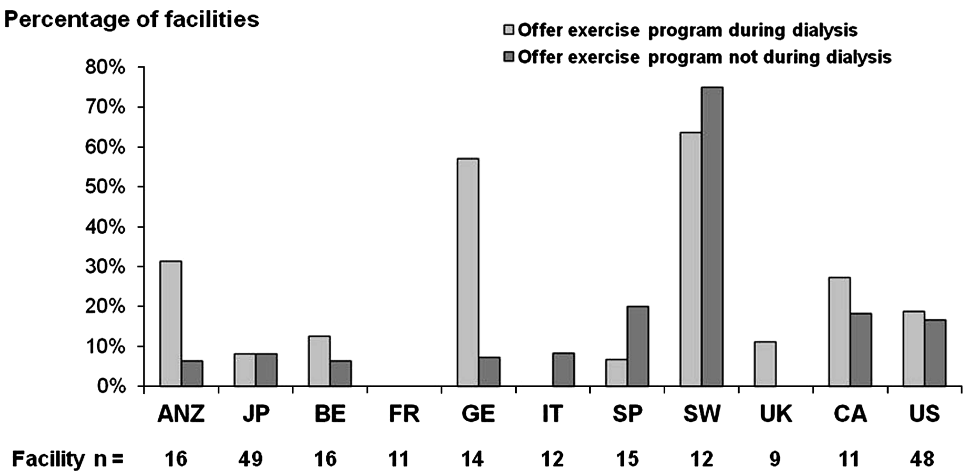

Fig. 3. Percentage of dialysis facilities offering exercise programmes, by DOPPS country. As reported in the unit practice survey in DOPPS III (2005–06); facility n = 204. ANZ, Australia and New Zealand; JP, Japan; BE, Belgium; FR, France; GE, Germany; IT, Italy; SP, Spain; SW, Sweden; UK, United Kingdom; CA, Canada; US, United States.

Mortality

Patient level. The associations between exercise frequency categories and mortality in models with different levels of adjustment are shown in Table 5. Mortality risk was lower for regular (equal to or more than once/week) versus non-regular (less than once/week) exercisers (adjusted HR = 0.73 [0.69–0.78], $P < 0.0001$). Mortality risk tended to decrease as exercise frequency increased (HR for participants who exercised once/week = 0.82 [0.73–0.91], P = 0.0002; HR for those who exercised 6–7 times/week = 0.69 [0.63–0.76], $P < 0.0001$) and patients who exercised daily had lower mortality risk (HR = 0.84 [0.74–0.96], P = 0.01) than patients exercising once/week. Additionally, greater exercise frequency was associated with longer survival when treated as an ordered variable (HR = 0.90 [0.88–0.92], $P < 0.0001$ for a five-level variable from never or less than once/week to 6–7 times/week; HR = 0.95 [0.91–1.00], P = 0.033 for a four–level variable excluding never or less than once/week).

Adjustment for demographics and comorbidities attenuated the HR somewhat, but the inverse association between exercise and mortality remained significant at all levels of adjustment. Analyses further adjusted for psychological factors (positive and negative affect, DOPPS I only) yielded similar results (data not shown). Other covariates associated with mortality in the fully adjusted model (at a significance level of $P < 0.05$) included age, duration of ESRD and most comorbidities (positive association), haemoglobin, serum albumin, creatinine, employment status and ability to walk (inverse association). No interactions were found between physical exercise and heart failure (P = 0.89), peripheral vascular disease (P = 0.08), BMI (P = 0.06), serum albumin (P = 0.18), haemoglobin (P = 0.52), positive (P = 0.99) and negative (P = 0.72) affect, and physician diagnosis of depression (P = 0.98).

The association of regular exercise with mortality was similar among participants with different socio-economic indicators, ability to walk and comorbidities (Figure 4). Similar results were found in analyses that used cardiovascular mortality as the outcome and in analyses restricted to prevalent patients and to patients treated at non-hospital-based facilities.

Facility level (instrumental variable analyses). Patients in facilities with more regular exercisers had lower mortality risk than patients in facilities with fewer regular exercisers

Table 2. Patient characteristics in facilities with different levels of regular exercisers: North America

	Facility % of patients exercising ≥1/week ('regular exercisers')				
Facility	<46.9[a]	46.9–55[a]	55–63.5[a]	>63.5[a]	
Facility	*n* = 61	*n* = 55	*n* = 55	*n* = 67	
Patient	*n* = 1426	*n* = 1436	*n* = 1401	*n* = 1464	
Mean (standard deviation) or %					P for trend
Demographics					
Age (years)	61.1 (14.8)	59.4 (15.5)	59.6 (15.3)	59.5 (15.3)	0.02
Male	51.5	54.1	54.7	54.1	0.16
Black	36.3	38.0	33.7	30.6	0.0001
Duration of ESRD (years)	3.0 (3.4)	3.4 (3.7)	3.5 (4.0)	3.5 (3.9)	0.001
BMI (SD) (kg/m^2)	26.3 (6.3)	26.0 (6.3)	25.9 (6.2)	26.0 (6.2)	0.19
Comorbidities					
Diabetes	48.9	45.6	45.6	46.6	0.25
Hypertension	86.2	86.4	86.4	83.1	0.03
Coronary artery disease	52.5	49.8	53.5	51.7	0.80
Congestive heart failure	45.4	43.1	41.7	40.5	0.01
Other cardiovascular disease	32.5	35.3	34.5	33.5	0.71
Peripheral vascular disease	26.9	27.5	25.9	24.8	0.13
Cerebrovascular disease	18.9	18.4	16.6	15.2	0.003
Recurrent cellulitis	10.3	8.7	10.3	10.9	0.36
GI bleed	9.0	7.7	8.0	7.0	0.08
Lung disease	11.3	14.0	12.0	11.8	0.90
Neurologic disorder	11.7	10.9	11.6	9.3	0.07
Physician-diagnosed depression	22.3	18.7	18.6	19.2	0.05
Other psychiatric disorders	4.2	5.3	3.9	4.5	0.80
Cancer other than skin	11.4	10.9	11.6	10.3	0.46
HIV	1.5	1.7	1.0	0.8	0.04
Laboratory values					
Haemoglobin (SD) (g/dL)	11.1 (1.5)	11.1 (1.4)	11.1 (1.5)	11.2 (1.6)	0.18
spKt/V (SD)	1.4 (0.3)	1.5 (0.3)	1.4 (0.3)	1.5 (0.3)	0.04
Creatinine (SD) (mg/dL)	9.1 (3.3)	9.8 (3.5)	9.3 (3.4)	9.4 (3.5)	0.19
Albumin (SD) (g/dL)	3.7 (0.4)	3.7 (0.5)	3.7 (0.5)	3.7 (0.5)	0.08
Calcium (SD) (mg/dL)	9.2 (0.9)	9.4 (1.0)	9.2 (0.9)	9.3 (0.9)	0.01
Phosphorous (SD) (mg/dL)	5.8 (1.8)	5.9 (1.9)	5.7 (1.8)	5.7 (1.8)	0.01
PTH	313.0	305.7	315.8	306.7	0.88
Socio-economic indicators					
Smoker	18.6	18.5	17.6	17.8	0.44
Some college education	22.4	27.1	27.0	26.1	0.06
Employed	7.5	11.6	10.6	12.5	0.0002
Private insurance	13.4	12.6	13.0	14.7	0.42
Lives alone	17.1	17.4	19.3	16.8	0.85
Able to walk	69.0	71.7	72.4	71.5	0.14
Facility indicators of clinical guidelines achievement					
% patients using a catheter	26.1	22.0	19.9	21.7	<0.0001
% patients prescribed an ESA	88.6	90.9	87.7	87.4	<0.0001
% patients with haemoglobin <11.0 g/dL	43.4	44.4	43.4	38.2	<0.0001
% patients with Kt/V <1.2	20.9	19.8	22.0	16.3	<0.0001
% patients with serum albumin <4.0 g/dL	69.1	66.0	70.4	70.7	<0.0001
% patients with serum phosphorus >5.5 mg/dL	50.0	52.0	48.0	47.8	<0.0001

Restricted to patients treated at the facility for >30 days since study entry (*n* = 5727) in 238 facilities in North America (US + Canada).
[a]Quartiles of facility % of patients exercising ≥1/week ('regular exercisers').
SD, standard deviation; BMI, body mass index; ESA, erythropoiesis-stimulating agents; GI, gastro-intestinal; PTH, parathyroid hormone.

(Figure 5). Every 10% increase in facility regular exercisers was associated with a 9% lower mortality risk (0.91 [0.89–0.94], P < 0.0001). Results of models that were further adjusted for facility achievement of clinical guidelines were virtually identical (0.92 [0.89–0.94], P < 0.0001).

Testing the instrumental variable assumptions

To evaluate the validity of the dialysis facility as an instrument [33,34], the following assumptions were tested:

Variations in the instrument (here, the dialysis facility) are associated with variation in the treatment, i.e. patients from different facilities have different levels of physical exercise. As shown in Figures 1 and 2, great variability in frequency of self-reported exercise was observed across countries as well as across facilities within the same country.

Allocation of patients to treatment is driven more by the instrument than by specific patient characteristics, i.e. facilities (rather than the patients alone) influence patient exercise status. Several findings support the role of the facility. First, the odds of regular exercise was higher for patients in DOPPS III facilities that offered exercise programmes than in those that did not (odds ra-

Table 3. Mean Kidney Disease Quality of Life (KDQoL) summary scores [95% confidence interval] by exercise frequency

KDQoL-SF™ score	Exercise frequency (times/week) <1 time or never	1 time	2–3 times	4–5 times	6–7 times	Per increase in each exercise frequency category	≥1 time
Mental component[a,c]	43.53 [43.26–43.80]	44.59 [44.07–45.11]	46.11 [45.69–46.52]	47.00 [46.32–47.69]	47.99 [47.54–48.45]	1.14 [1.03–1.26]	46.44 [46.16–46.71]*
Physical component[a,c]	34.38 [34.17–34.59]	36.46 [36.05–36.87]	37.17 [36.84–37.50]	38.82 [38.28–39.36]	39.13 [38.77–39.49]	1.24 [1.15–1.33]	37.79 [37.57–38.01]*
Physical functioning[a,d]	42.19 [41.44–42.93]	50.02 [48.56–51.49]	52.63 [51.45–53.80]	56.91 [54.83–58.99]	55.71 [54.47–56.94]	3.68 [3.28–4.09]	53.48 [52.70–54.26]*
Sleep quality[b,d]	5.41 [5.34–5.49]	5.75 [5.60–5.91]	5.79 [5.66–5.91]	6.19 [5.97–6.41]	6.24 [6.11–6.37]	0.21 [0.17–0.25]	5.97 [5.89–6.05]*

[a]On a scale of 0 (poor) to 100 (good).
[b]On a scale of 1 (poor) to 10 (good).
[c]Data on mental component and physical component summary scores were collected in DOPPS I and II; N = 17 224.
[d]Data on physical functioning and sleep quality were only collected in DOPPS I: N = 10 488.
Scores were adjusted for all factors listed in Table 1 (except Kt/V, PTH and ESA use), DOPPS country and accounted for facility clustering.
*P < 0.0001 for exercise frequency equal to or more than once a week vs less than once a week and per each increase in exercise frequency.

tio adjusted for age, sex, race, time on dialysis, BMI, 14 comorbidity classes, haemoglobin, creatinine, serum albumin, smoking status and country = 1.38 [1.03–1.84], P = 0.03). Second, among DOPPS I and II facilities in our primary analyses, we found that the fraction of variance associated with regular exercise was smaller in the model adjusted only for patient characteristics (R^2 = 0.07) than in the model with a facility term, i.e. adjusted for differences across facilities (R^2 = 0.17). Third, patient characteristics, including socio-economic indicators, were generally similar when categorized across facility percentages of regular exercisers (Table 2), achieving greater balance than distributions of patient characteristics categorized according to patient level of exercise (shown in Table 1).

The instrument is not otherwise related to the outcome of interest (mortality), i.e. the observed association between facility exercise and mortality is due to patient exercise status rather than other (e.g. contextual) effects. As evidence in support of this assumption, results of models adjusted and not adjusted for indicators of facility achievement of clinical guidelines—including use of a catheter as vascular access, low haemoglobin and serum albumin, and high serum phosphorus—were virtually identical (Figure 5). These findings suggest that the association between higher percentage of facility regular exercisers and mortality is independent of these facility practices.

Discussion

The present study provides the first international description of patterns of physical exercise and associated outcomes among haemodialysis patients. Exercise levels varied widely across the 12 DOPPS countries (Figure 1) and across dialysis facilities within countries (Figure 2). Overall, 47.4% of participants were classified as regular exercisers, defined here as exercise equal to or more than once/week. Exercise performed once or less than once/week was reported by 54% in the USA. This relatively low prevalence of regular exercise is in agreement with the DMMS study, which reported that 56% of patients starting dialysis in the USA in 1996–97 performed physical activity once or less than once/week [19]. Even lower exercise rates were recently reported in the United States Renal Data System Comprehensive Dialysis Study: 38% of men and 22% of women aged <65 years reported walking frequently for exercise [3]. These results suggest that physical exercise may be less common among haemodialysis patients than in the general US population, where the estimated prevalence of physical inactivity ranges from 14.3 to 38.2%[35]. However, differences in the definition of physical activity limit direct comparison. Despite the overall low levels of physical activity, the odds of regular exercise were significantly higher for patients from facilities that offered exercise programmes, providing some evidence that dialysis unit practices may be able to influence exercise habits among their patients.

As expected, regular exercise was positively associated with ability to walk and lower BMI, and inversely associated with older age and several comorbidities. Regular exercise was also associated with having some college education. Similar trends were reported among sedentary versus non-sedentary participants in the DMMS study [4]. As also reported in other populations [36–38], regular exercisers had higher mental component scores, physical component scores and physical functioning scores, and were more likely to report a ‘positive affect’. These findings are also consistent with results of the DMMS study [4,39] and of interventional studies of exercise programmes in haemodialysis patients [10,12,14,40]. In our study, the difference in KDQoL-SF™ scores between regular vs non-regular exercisers exceeded three points (Table 3), which has been considered the threshold indicating a clinically relevant finding [41]. Regular exercise was also associated with better sleep quality, less severe bodily pain and better appetite (Table 4). Due to the cross-sectional nature

Table 4. Association (odds ratio [95% confidence interval]) between exercise frequency and patient self-reported psychosocial variables

		Exercise frequency (times/week)					
	%	1 time	2–3 times	4–5 times	6–7 times	Per increase in each exercise frequency category	≥1 time/week
Limitations in physical activities[a]							
Severe with moderate activities	38	0.46 [0.38–0.54]	0.46 [0.40–0.53]	0.34 [0.27–0.44]	0.43 [0.37–0.50]	0.78 [0.76–0.81]	0.44 [0.40–0.49]
Severe with vigorous activities	69	0.58 [0.50–0.68]	0.51 [0.44–0.58]	0.41 [0.34–0.50]	0.46 [0.40–0.53]	0.81 [0.78–0.83]	0.50 [0.45–0.55]
Very severe to moderate bodily pain	45	0.82 [0.71–0.95]*	0.70 [0.63–0.79]	0.54 [0.44–0.67]	0.62 [0.55–0.69]	0.87 [0.85–0.90]	0.68 [0.63–0.74]
Very much to extremely bothered by lack of appetite	11	0.64 [0.54–0.76]	0.57 [0.49–0.65]	0.50 [0.39–0.64]	0.52 [0.44–0.62]	0.82 [0.79–0.86]	0.56 [0.51–0.62]
Positive affect	62	1.38 [1.19–1.59]	1.84 [1.62–2.09]	2.15 [1.76–2.62]	2.52 [2.22–2.86]	1.28 [1.24–1.32]	1.93 [1.76–2.11]
Negative affect	26	0.69 [0.58–0.82]	0.56 [0.48–0.65]	0.44 [0.33–0.58]	0.50 [0.43–0.58]	0.82 [0.79–0.85]	0.55 [0.50–0.61]
CES-D score ≥10[a]	44	0.81 [0.70–0.94]*	0.63 [0.56–0.72]	0.56 [0.46–0.68]	0.43 [0.37–0.49]	0.81 [0.78–0.84]	0.6 [0.55–0.66]

Reference group: exercise never or less than once/week.
[a]Data on limitations in physical activities (N = 10 344), bodily pain (N = 10 628), and positive (N = 10 431) and negative affect (N = 10 425) were only collected in DOPPS I; CES-D scores were only collected in DOPPS II (N = 8797).
Limitations in physical activities: reference—none or minimal.Severity of body pain: reference—mild to none.Lack of appetite: reference—moderately to not at all bothered (reference) (DOPPS I and II: N = 20 316).'Positive affect' = answered 'a good bit' or 'most' or 'all of the time' to the questions 'did you feel full of pep?', 'did you have a lot of energy?' and 'have you been a happy person?' [39]. Reference category answered 'some of the time', 'a little bit of the time' or 'none of the time'.'Negative affect' = answered 'a good bit' or 'most' or 'all of the time' to the questions 'have you felt so down in the dumps so that nothing could cheer you up?' and 'have you felt downhearted and blue?' [39]. Reference category answered 'some of the time', 'a little bit of the time' or 'none of the time'.CES-D score ≥10 (indication of probable depression) vs <10 (reference) [28,56].Odds ratios were adjusted for all factors listed in Table 1 (except Kt/V, PTH and ESA use), DOPPS country and accounted for facility clustering.
*P < 0.01; P-values for all other comparisons: <0.0001.

of our data, these results cannot establish a causal relationship; however, our findings are generally consistent with prior clinical trials in haemodialysis indicating that exercise training may lower physical pain [14] and increase caloric and protein intake [42].

Mortality risk was lower for participants who reported to exercise only once a week, compared to patients exercising less than once weekly or never. Whether such low exercise frequency can affect mortality risk is not clear, and this finding may be biased by patient health status. However, similar results were found in another cohort of haemodialysis patients [4] and among patients with coronary artery disease [43]. Despite the possible benefits of exercising just once weekly, we also found that mortality risk decreased as exercise frequency increased, i.e. that the association of exercise frequency with longer survival was dose dependent. Specifically, (i) patients who exercised daily had lower mortality risk than those exercising once/week, and (2) greater exercise frequency, treated as an ordered variable, was associated with longer survival. In sum, these findings suggest that while any (at least once weekly) exercise is better than none, the more exercise the better. However, these findings require additional study.

Despite extensive adjustment in these models, findings of analyses of patient-level exercise may be biased by the fact that patients who are able to exercise regularly may be overall healthier, have higher socio-economic status or otherwise be expected to survive longer (for reasons not due to exercise). This situation, which can be termed 'healthy patient bias', is partially addressed using instrumental variable analysis [29,33,44] that has recently been applied to several fields of medical research [30,31,44–49]. In the present study, the dialysis facility was used as the instrument and the adjusted facility percentage of regular exercisers was the instrumental variable. By this approach, we found that mortality risk was significantly lower for patients treated at facilities with higher percentages of regular exercisers. While the distribution of patient characteristics was similar in facilities with different levels of physical exercise (Table 2), we acknowledge that other contextual factors, including socio-economic disparities, may still contribute to the observed associations.

While there may be no perfect instrument in the observational setting, testing of the instrumental variable assumptions (detailed in the Results) provides support for the validity of the instrument. Wide variability was observed in the percentage of facility regular exercisers across facilities (Figure 2). Patient characteristics were generally similar across facility quartiles of regular exercisers (Table 2), i.e. patient health status does not 'in and of itself' determine differences in the facility percentage of exercisers. Further, facilities contributed to explaining variance in exercise frequency, with R^2 twice as large in a model adjusted for facility (R^2 = 0.17) vs a model adjusted only for patient characteristics (R^2 = 0.07). Finally, the association between facility exercise and mortality were virtually identical in a model further adjusted for facility indicators of achievement of clinical guidelines, indicating that the association be-

Table 5. Association (hazard ratio [95% confidence interval]) between exercise frequency and mortality

	Exercise frequency (times/week)					
Model adjustment[a]	1 time	2–3 times	4–5 times	6–7 times	Per increase in each exercise frequency category	≥1 time
Unadjusted	0.64 [0.58–0.71]	0.62 [0.56–0.68]	0.59 [0.50–0.69]	0.65 [0.59–0.71]	0.87 [0.85–0.89]	0.63 [0.59–0.67]
Age	0.72 [0.65–0.79]	0.67 [0.61–0.73]	0.64 [0.54–0.75]	0.66 [0.60–0.73]	0.88 [0.86–0.91]	0.67 [0.63–0.72]
Age, sex, race, duration of ESRD, BMI	0.70 [0.63–0.78]	0.65 [0.59–0.71]	0.61 [0.52–0.71]	0.63 [0.57–0.70]	0.87 [0.85–0.89]	0.65 [0.61–0.69]
Age, sex, race, duration of ESRD, BMI, 14 summary comorbid conditions[b]	0.8 [0.72–0.88]	0.71 [0.65–0.78]	0.68 [0.57–0.80]	0.69 [0.62–0.76]	0.9 [0.88–0.92]	0.72 [0.67–0.76]
Age, sex, race, duration of ESRD, BMI, 14 summary comorbid conditions, laboratory values[c], catheter use	0.81 [0.73–0.90]	0.72 [0.65–0.79]	0.7 [0.59–0.83]	0.69 [0.63–0.76]	0.9 [0.88–0.92]	0.73 [0.68–0.77]
Age, sex, race, duration of ESRD, BMI, 14 summary comorbid conditions[b], laboratory values, catheter use, socio-economic conditions[d]	0.8 [0.72–0.89]	0.71 [0.65–0.78]	0.71 [0.60–0.83]	0.69 [0.63–0.76]	0.9 [0.88–0.92]	0.72 [0.68–0.77]
Age, sex, race, duration of ESRD, BMI, 14 summary comorbid conditions[b], laboratory values, catheter use, socio-economic indicators, ability to walk	0.82 [0.73–0.91]*	0.72 [0.66–0.79]	0.73 [0.62–0.86]*	0.69 [0.63–0.76]	0.9 [0.88–0.92]	0.73 [0.69–0.78]

Reference group: Exercise never or less than once/week.Total patient N = 20 912.
[a]All models were stratified by country and accounted for facility clustering.
[b]14 summary comorbid conditions are listed in Table 1.
[c]Laboratory values: serum albumin, phosphorus, calcium, creatinine and Hgb.
[d]Socio-economic indicators: smoking, employment, education, insurance and living status.
*P ≤ 0.0002; P-values for all other comparisons: <0.0001.

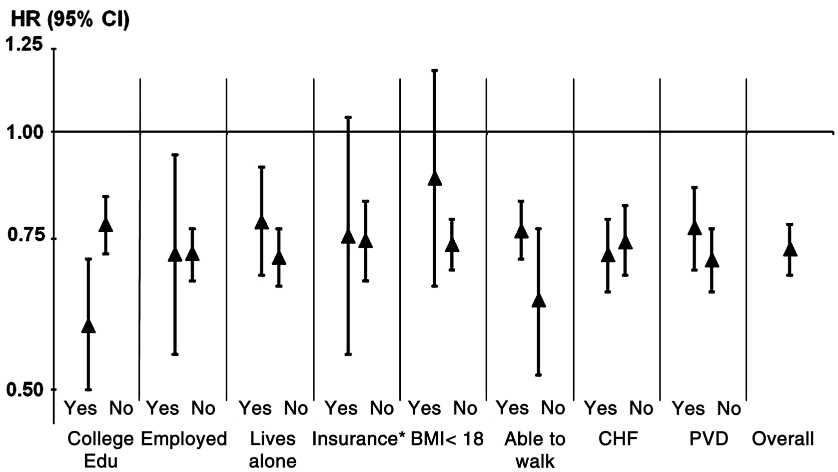

Fig. 4. Association between regular exercise and mortality among participants with different socio-economic indicator and comorbidity status. Regular exercise is defined as exercising once or more than once/week; reference = exercise less than once a week or never. Study participants: n = 20 912 [college education—yes: n = 3090, no: n = 13 053; employed—yes: n = 3403, no: n = 15 821; lives alone—yes: n = 3204, no: n = 17 271; private insurance (restricted to the USA only)—yes: n = 1027, no: n = 4679; BMI—<18: n = 1316, ≥18: n = 17 388; able to walk—n = 16 092; not able to walk —n = 1597; CHF—yes: n = 6100, no: n = 14 650; PVD—yes: n = 4653, no: n = 16 101]. Models were adjusted for all factors listed in Table 1 (except PTH and ESA use), stratified by country and account for facility clustering. Triangles represent estimates of the hazard ratios; vertical bars indicate the 95% confidence interval.

tween higher percentage of facility regular exercisers and mortality is independent of these facility practices.

In agreement with results of the DMMS study [19], 69% of DOPPS participants reported severe limitations in performing vigorous physical activities and 38% in performing moderate physical activities. High comorbidity burden leading to poor physical functioning, low exercise capacity [8,9] and muscle wasting [50,51] is certainly a major determinant of the sedentary lifestyle of many haemodialysis patients. While in some dialysis patients there may be no potential for improvement in physical functioning, in many others it is likely that poor physical performance is due in part to deconditioning and could be modified. In the present study, while the prevalence of comorbid conditions

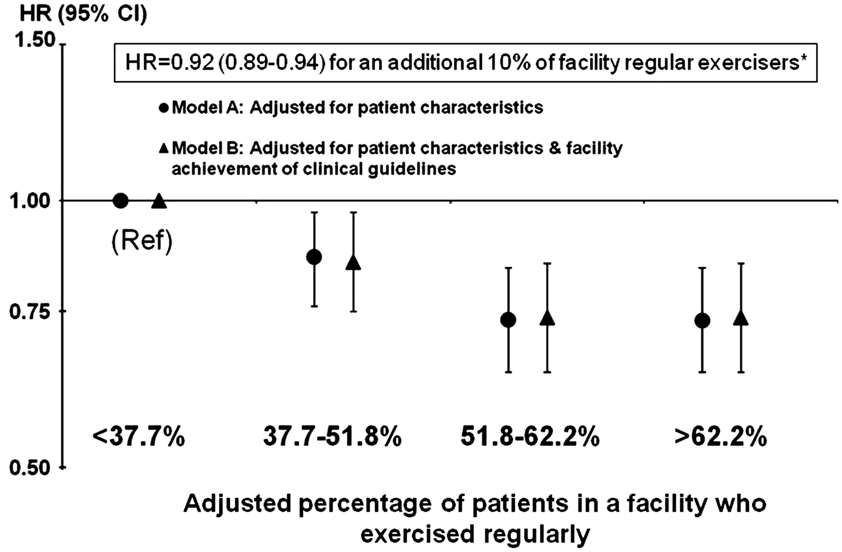

Fig. 5. Association between facility percentage of regular exercisers and patient mortality. Regular exercise is defined as exercising once or more than once/week. Restricted to patients treated at the facility for >30 days since study entry (facility: $n = 622$; participants: $n = 16\ 181$). Reference category: facilities in the lowest quartile of regular exercisers (i.e. facilities with <37.7% of patients who exercised once or more than once/week). Facility quartiles of regular exercisers (<37.7%, 37.7–51.8%, 51.8–62.2% and >62.2%) are different than those shown in Table 2 because: (i) participants from all DOPPS countries (vs North America only) were included; (ii) the percentage of facility regular exercisers was adjusted for demographics and comorbidities (vs crude percentage). Model A was adjusted for all patient characteristics listed in Table 2 (except Kt/V, PTH and ESA use); Model B was additionally adjusted for the facility indicators of clinical guidelines listed in Table 2; all models were stratified by country and account for facility clustering. Circles and triangles represent estimates of the hazard ratios; vertical bars indicate the 95% confidence interval.

was high for the entire study population, great variability was observed in the percentage of regular exercisers across facilities. Furthermore, beneficial effects of regular exercise were observed for participants able to walk as well as for those not able to walk, and no interaction was found between ability to walk and exercise frequency ($P = 0.76$). Overall, these results indicate that factors other than patient case mix are likely to contribute to levels of physical activity and suggest the possibility that facility practices can affect exercise frequency.

Lack of motivation [52,53] and increased perceived risk [54] by health care professionals have been identified as contributing factors to physical inactivity among haemodialysis patients. For example, levels of physical activity are not routinely assessed and patients are not counselled to exercise more [21,40,53]. In one report from the USA, only 45% of staff members surveyed believed that more than half of their patients would benefit from an exercise programme [52]. While specific information is not available, it is likely that similar thoughts were shared by many DOPPS investigators as indicated by the low percentage of centres offering exercise programmes. Cultural differences or educational efforts focused on physical exercise may have contributed to the very different practices observed in Germany and Sweden where exercise programmes were offered at most participating facilities. The higher prevalence of regular exercisers at facilities offering exercise programmes indicates that these interventions may be beneficial, with lessons to be learned by providers worldwide.

The established infrastructure and the collaborative support of the DOPPS investigators across 12 countries represent major strengths of the present study. The broad spectrum of data collected allowed us to adjust models for many potentially confounding covariates, including detailed comorbidities [22]. At the same time, several study limitations merit discussion. First, the definition of 'physical exercise' may not be completely accurate. To reduce the burden of data collection, information on exercise frequency was collected using a single question as previously done in the DMMS study [4,19] and the Comprehensive Dialysis Study [3] rather than a validated questionnaire [55]. Therefore, patient exercise status may be misclassified. However, self-reported frequency of exercise reported in the DOPPS was very similar to that found in the DMMS study [4], indicating that haemodialysis patients interpreted the term 'physical exercise' similarly. Furthermore, information on the duration or type of exercise was not available. For example, it is not clear what type of physical activity was performed by participants who were not able to walk but reported participating in physical exercise. It is plausible that these participants referred to upper body activities, such as those commonly undertaken by the elderly. Differences in the interpretation of the term 'exercise programmes' in different dialysis units or among different types of patients may have also affected the reported frequencies of exercise. Second, patients responding to the exercise question were younger and had fewer comorbidities and higher education and employment levels than those who did not, indicating a possible selection bias. However, the response rate in the current study (78%) was higher than in other studies, such as the DMMS study [4] (64%). Third, data on exercise frequency and psychosocial variables were collected at study entry in a cross section of DOPPS participants; therefore, our results only indicate an association of regular exercise with positive psychosocial outcomes and cannot exclude reverse causation. Since exercise levels and psychosocial outcomes were self-reported, we also acknowledge that the reported association may be inflated. However, these findings are consistent with relatively small clinical trials in which exercise resulted in better quality of life scores among dialysis patients [10,12,14,40]. Finally, we acknowledge that, despite the extensive adjustment and the use of an instrumental variable approach, the potential for residual bias due to unmeasured confounding remains.

In sum, the present study provides the first description of international patterns of physical exercise among haemodialysis patients and reports a strong association of regular exercise with higher HRQoL and longer survival. Our results also provide support for the possibility that dialysis unit practices that promote physical exercise may improve patients' sedentary lifestyles. It is, therefore, plausible that educational efforts aimed at increasing staff and patient awareness, and strategies to promote physical exercise, may lead to both increased physical activity and improved clinical outcomes among haemodialysis patients. Further studies are needed to assess the effectiveness, safety and feasibility of exercise programmes in this high-risk population.

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Mineral and bone disease pattern in elderly haemodialysis patients

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Abstract

Background. Although many studies have recently addressed the mineral and bone disorder of chronic kidney disease (CKD-MBD), only limited information is available for elderly dialysis patients.