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Renal Replacement Therapy

REVIEW

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Duration-stratified effects of exercise therapy on health-related quality of life in hemodialysis patients: a systematic review and meta-analysis

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Abstract

Background Patients on maintenance hemodialysis (HD) have reduced health-related quality of life (HRQoL). Structured exercise therapy is recommended, but domain-specific effects and the influence of intervention duration remain uncertain. This study evaluated the impact of structured exercise therapy on multiple HRQoL domains, including fatigue and depression, stratified by intervention duration.

Methods We conducted a systematic review and meta-analysis, searching MEDLINE (PubMed) through November 2024. The protocol was registered in PROSPERO (CRD42025642273). We included trials comparing structured exercise with non-exercise controls in adult HD patients. Primary outcomes were Short Form (SF)-36 Physical and Mental Component Summaries (PCS, MCS), fatigue, pain, general health, and depression (Beck Depression Inventory). Data were synthesized using random-effects models, stratified by intervention duration (≤ 3 versus > 3 months). Risk of bias was assessed using the Cochrane RoB 2 tool.

Results We identified 94 randomized controlled trials (5228 participants); 22 reported HRQoL outcomes and were meta-analyzed. Exercise significantly improved fatigue (mean difference [MD] + 7.27, 95% confidence interval [CI] 4.75–9.80) and reduced depressive symptoms in > 3-month trials (MD −7.62, 95% CI −8.34 to −6.90); no ≤ 3-month depression data were available. In overall analyses, general health (MD + 11.59, 95% CI 6.98–16.21) and PCS (MD + 5.83, 95% CI 0.71–10.94) improved, whereas MCS (MD + 7.60, 95% CI −3.75 to 18.94) and pain (MD + 2.19, 95% CI −4.41 to 8.79) showed no clear benefit. Short-term interventions (≤ 3 months) yielded significant improvements in pain and general health. In longer-term interventions (> 3 months), general health estimates were similar in magnitude but statistically nonsignificant, and pain effects were also nonsignificant with substantial heterogeneity. Fatigue improved in both duration strata.

Conclusions Structured exercise therapy appears to improve fatigue in patients on maintenance HD and may provide additional gains in PCS and general health with interventions longer than 3 months. Improvements in depressive symptoms were observed from limited evidence, and duration-specific effects remain uncertain because no trials

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assessed depression at ≤ 3 months. Effects on pain and MCS remain uncertain owing to substantial heterogeneity. Larger long-term trials are needed to clarify the sustainability of HRQoL benefits beyond 3 months.

Keywords Hemodialysis, Exercise therapy, Intradialytic exercise, Health-related quality of life, Fatigue, Depression, Randomized controlled trials, Meta-analysis

Background

Maintenance hemodialysis (HD) is a life-sustaining treatment for patients with end-stage renal disease, but these patients often experience a significant decline in their health-related quality of life (HRQoL) [1, 2]. Beyond medical comorbidities such as cardiovascular disease, they frequently endure chronic fatigue, depressive mood, and sarcopenia-related physical frailty [3]. Large international cohort studies have confirmed that reduced HRQoL independently predicts poor clinical outcomes, including increased risks of mortality and hospitalization [1, 2]. As the global HD population becomes older and medically more complex, improving HRQoL is a central priority for patient-centered care.

Although exercise training is expected to improve HRQoL in patients on maintenance HD, several gaps remain. Several systematic reviews have pooled HD and peritoneal dialysis patients, limiting the applicability of their findings to HD alone [4]. Many studies have focused on Short Form (SF)-36 summary scores, such as the Physical Component Summary (PCS) and Mental Component Summary (MCS), while individual patient-reported outcomes (fatigue, depression, pain, general health) have received less attention [5]. Recent network meta-analyses comparing exercise modalities suggest potential advantages of combined aerobic and resistance training showing promise, but the optimal modality and intensity for specific HRQoL domains are still uncertain [6, 7].

Moreover, while trials have explored various intervention durations, systematic stratification by follow-up period (≤ 3 months versus > 3 months) to assess the sustainability and duration-dependence of HRQoL improvements has not been performed [4, 6, 7]. Studies focusing on fatigue improvement via intradialytic exercise report promising effects, yet synthesis across modalities and follow-up periods is still limited [8, 9]. Therefore, an updated synthesis that addresses these limitations, particularly the impact of intervention duration on multiple HRQoL domains, is needed to inform clinical practice.

Historically, Japan was among the first countries to issue a dedicated guideline to recommend exercise in dialysis patients in 2018, led by the Japanese Society of Renal Rehabilitation [10]. Following this initiative, intradialytic exercise delivered by medical professionals became reimbursable under the Japanese national health insurance system, although coverage is currently limited to the first 90 days of a program. Internationally, the UK Renal Association HD guideline also recommends that exercise during dialysis should be available as a treatment option across HD units to enhance physical function [11]. In this context, it is particularly important to clarify whether the benefits of exercise differ between short-term programs (≤ 3 months, roughly corresponding to the current reimbursement window in Japan) and longer-term interventions, because such information is directly relevant for clinical practice and health policy.

To address these questions, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) of exercise training in adults undergoing maintenance HD. This work updates and extends the 2018 Japanese renal rehabilitation guideline [10] by incorporating trials published thereafter and by explicitly examining duration-dependent effects across multiple HRQoL domains. Our aim is to provide evidence that can inform exercise prescriptions and future guideline refinement in Japan and internationally.

Methods

Protocol and registration

A detailed protocol was developed in advance in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines [12] and prospectively registered in PROSPERO (CRD42025642273). This registration covers both physical function and HRQoL outcomes of exercise interventions in HD patients. The present manuscript explicitly reports the HRQoL-focused component of the registered protocol; other prespecified outcome domains (e.g., physical function and clinical outcomes) will be reported separately. The present review follows this prespecified protocol and is reported in accordance with the PRISMA 2020 statement [13]. The PRISMA flow diagram is shown in Fig. 1.

Eligibility criteria

We established the following eligibility criteria in advance for this systematic review and meta-analysis.

Study design

We included all RCTs and cross-over RCTs.

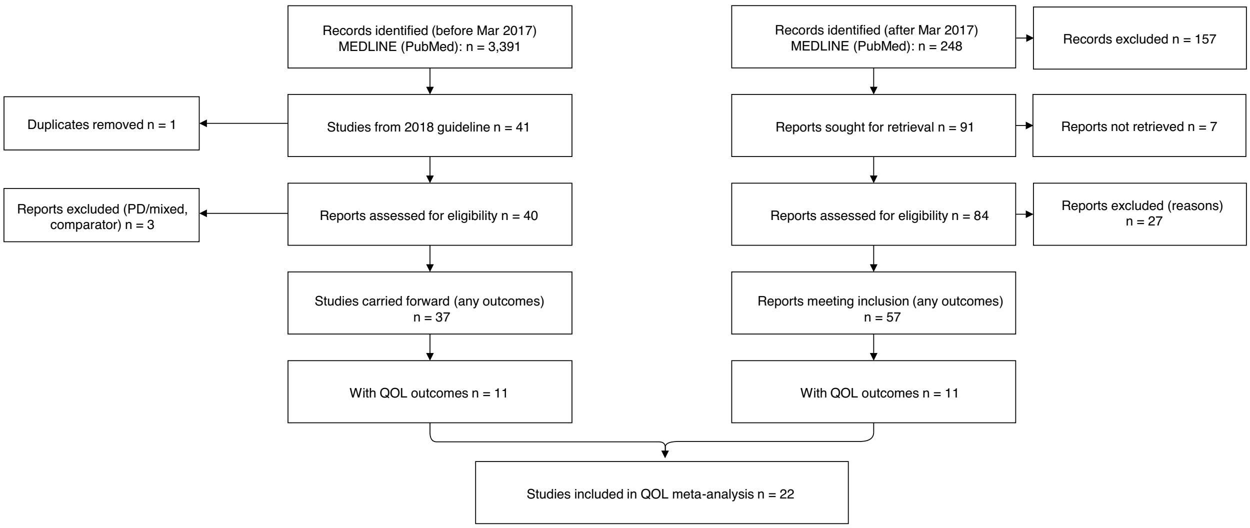


Fig. 1 PRISMA flow diagram for the HRQoL review in maintenance hemodialysis

Participants

We included adult patients undergoing maintenance HD. We excluded studies involving children and adults receiving peritoneal dialysis. Because previous guideline-related systematic reviews analyzed HD and peritoneal dialysis patients together, we restricted this review to HD patients only.

-Interventions: we included interventions consisting of a structured program of regular physical exercise targeting improvement in general fitness. We excluded studies evaluating the effects of single or couple of exercise bouts during HD sessions, respiratory muscle training, training of limited body parts such as hand exercises, and electrical muscle stimulation.

Comparators

Eligible studies had to include a control group that did not participate in any exercise training except for light stretching. When two or more arms from a multiple-arm RCT were relevant to a meta-analysis, we chose the intervention that seemed more likely to be implemented in the clinical setting. Care was taken not to include the same participants twice in either the treatment or the control group for all meta-analyses. Co-interventions with exercise training were allowed if the co-interventions were also administered to the control group.

Outcomes

We included studies that evaluated any of the following HRQoL domains as primary or secondary outcomes: SF-36 PCS, SF-36 MCS, fatigue, pain, general health, and depression.

Language and publication status

We included studies indexed in MEDLINE (PubMed) published in English without restriction on publication status.

Information sources

A systematic search was conducted using MEDLINE (via PubMed) in March 2017 and November 2024. Results of the search in March 2017 were utilized for the previous Renal Rehabilitation Guideline 2018 published by the Japanese Society of Renal Rehabilitation [10]. For the systematic review of studies published after the previous guideline, we conducted an updated search in November 2024. The selected studies from both periods were integrated for meta-analysis. Only MEDLINE (PubMed) was used as an information source; no additional databases, manual reference checks, or trial registry searches were performed.

Search strategy

The search strategy was structured using combinations of MeSH terms and free-text terms on the basis of the predefined PICO framework. Key terms covered HD (e.g., "renal dialysis", "hemodialysis") and exercise/physical activity concepts (e.g., "exercise", "exercise therapy"). Additional rehabilitation-related terms (e.g., frailty/skeletal muscle) were included within the same concept block as part of the guideline-related search framework (Supplementary Table S1). For the search period before March 2017, we did not limit to RCTs and excluded non-RCTs during screening. For the updated search (November 2024), we applied the "randomized controlled trial" filter and limited it to English. The complete search strategy with execution dates is detailed in Supplementary Table S1.

Study selection / Selection process

All literature information identified through the search was imported into Rayyan [14], a free web and mobile app for systematic review management, and duplicate articles were removed using automated duplicate detection followed by manual verification. Five pairs of blinded reviewers were assigned to screen all publications first through titles and abstracts (first screening) and then reviewed full-text articles (second screening). When a mismatch for decisions to include or exclude studies was found, another round of screening or a third reviewer was assigned to discuss decisions. Any disagreements between reviewers at each screening stage were resolved through discussion between the reviewers, and if consensus could not be reached, by consulting a third reviewer. The entire study selection process is shown in a PRISMA flow diagram.

Data collection process

Data from each trial were extracted using a prespecified, pilot-tested standardized form. Two reviewers independently performed data extraction, and discrepancies were resolved through discussion or, when needed, consultation with a third reviewer. When information was missing or only presented graphically, we contacted corresponding authors; if no response was obtained, data were treated as missing. In multi-arm trials, we selected the intervention arm judged most relevant to clinical practice and avoided double-counting participants. For the main analyses. we used the longest available follow-up, whereas the subgroup analyses used time points matching the predefined duration windows (≤ 3 months or >3 months). If multiple reports from the same study registry ID were found, one report per overlapping outcome was selected to avoid duplicate inclusion of participants.

Data items/variables

We extracted study characteristics (first author, year, country, design, and setting), participant demographics (numbers randomized and analyzed, age, sex, dialysis vintage, and key comorbidities), and details of the intervention and comparator (exercise modality, intensity, frequency, session and total duration, setting, supervision, and co-interventions). For HRQoL outcomes, we recorded the instruments used (SF-36 or Kidney Disease Quality of Life (KDQOL)-based subscales and the Beck Depression Inventory), their scoring range, and the direction in which higher or lower scores indicate better status. For each arm and time point, we abstracted baseline and final means (standard deviations) or change scores when available, and used the longest follow-up for the main analyses and the time point corresponding to the predefined duration strata for subgroup analyses. All HRQoL outcomes were treated as continuous variables.

Risk of bias assessment

The risk of bias for each included RCT was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool [15]. The following five bias domains were assessed as low risk, several concerns, or high risk: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The overall risk was finally assessed. The risk of bias assessment was performed independently by the aforementioned pairs of reviewers. Any disagreements between reviewers were resolved by discussion between the reviewers, and if consensus could not be reached, by consulting a third reviewer. The risk-of-bias results informed the qualitative interpretation of findings.

Effect measures

For continuous HRQoL outcomes (SF-36 PCS, SF-36 MCS, fatigue, pain, general health, and depression), we used the mean difference (MD) between groups at the end of follow-up as the primary effect measure and calculated 95% confidence intervals (CIs). Meta-analyses included only trials reporting outcomes on compatible scales, defined a priori as SF-36 or KDQOL-based subscales for fatigue, pain, and general health, and the Beck Depression Inventory (BDI) for depression. For SF-36 and KDQOL domains, higher scores indicate better status; therefore, a positive MD favors exercise. For depression, lower BDI scores indicate fewer symptoms; therefore, a negative MD favors exercise.

Synthesis methods/statistical analysis

For outcomes that were clinically homogeneous and suitable for quantitative synthesis, we performed random-effects meta-analyses of the MD between intervention and control groups with 95% CIs. Statistical analyses were conducted in Review Manager (RevMan) Web (Cochrane; release 1.2x, accessed November 2024). Random-effects models used the Hartung–Knapp–Sidik–Jonkman adjustment, and between-study variance (τ^2) was estimated by restricted maximum likelihood (REML) [16]. Heterogeneity was examined by visual inspection of forest plots, quantified using τ^2 and I^2 [17–19].

We conducted preplanned subgroup analyses by follow-up duration (≤ 3 months versus > 3 months) for all HRQoL outcomes to assess the impact of intervention duration on treatment effects. Additionally, we performed exploratory subgroup analyses by exercise modality (aerobic versus resistance/combined) for selected outcomes (SF-36 PCS, SF-36 MCS, and fatigue) to examine potential differences in effectiveness between exercise types.

Role of artificial intelligence in manuscript preparation

Generative artificial intelligence (AI) tools (ChatGPT, OpenAI) were used only to support English editing and drafting of manuscript text. They were not used for data generation or analysis, and all content was reviewed and approved by the authors, who take full responsibility for the work.

Results

Study selection

The search initially identified 3391 articles published before March 2017 and 248 articles published after March 2017 (searched in November 2024), totaling 3639 records. After removing duplicates and initial screening, 124 articles (40 from the pre-2017 search and 84 from the post-2017 search) were selected for full-text assessment. After detailed review of the full texts based on prespecified eligibility criteria, 30 articles were excluded, and 94 RCTs (37 from the pre-2017 search and 57 from the post-2017 search) met the inclusion criteria for the systematic review. Of these, 22 trials reporting HRQoL outcomes were included in the quantitative synthesis (meta-analysis). The details of the study selection process are shown in the PRISMA flow diagram (Fig. 1). Excluded full-text articles with reasons for exclusion are listed in Supplementary Table S3.

Characteristics of included studies

These 22 HRQoL trials involved a total of 1387 registered participants (1168 analyzed) and were predominantly single-center, small-scale studies (17/22 single-center; median 45 participants, range 18–335), with no HRQoL-eligible trials conducted in Japan. Detailed characteristics of the 22 HRQoL trials are summarized in Table 1.

Risk of bias in included studies

The judgments for individual study–outcome pairs are displayed within the right-hand bands of each forest plot, and a summary of risk-of-bias judgments across outcomes is provided in Supplementary Table S2.

Effects on HRQoL outcomes by intervention duration

Outcomes showing statistically significant improvements in overall and long-term analyses

Fatigue improved in both ≤ 3-month and > 3-month programs. In total, 15 RCTs (439 participants in the exercise group, 441 in the control group, 880 total) reported fatigue outcomes (Fig. 2). Exercise significantly improved fatigue scores compared with control (MD + 7.27 points, 95% CI 4.75–9.80; $P < 0.0001$; 15 studies), with moderate heterogeneity ($I^2 = 43\%$; $\tau^2 = 5.62$). In duration-stratified analyses (random-effects, HKSJ method), statistically significant improvements were observed for both shorter (≤ 3 months) and longer (> 3 months) programs. For interventions of 3 months or less (nine studies), the MD was + 7.78 (95% CI 3.72–11.84; $P = 0.002$; $I^2 = 39\%$). For interventions longer than 3 months (six studies), the MD was + 6.37 (95% CI 1.94–10.79; $P = 0.01$; $I^2 = 47\%$). The test for subgroup differences was not statistically significant ($P = 0.57$), with no evidence of subgroup differences ($P = 0.57$).

In total, three RCTs (108 participants in total) evaluated depressive symptoms using BDI (Fig. 3). All three interventions extended beyond 3 months. Exercise therapy significantly reduced symptom scores compared with control (MD −7.62 points, 95% CI −8.34 to −6.90; $P = 0.0005$; $I^2 = 0\%$; $\tau^2 = 0.00$). No trials reported depression outcomes at ≤ 3 months; therefore, duration-stratified estimates for depression could not be calculated.

Outcomes with significant benefits only in overall or short-term analyses

SF-36 PCS, general health, and pain domains showed significant improvements in the overall analyses, or in short-term trials, but not consistently in the > 3-month subgroup.

A total of eight RCTs (130 participants in the exercise group, 112 in the control group, 242 total) reported PCS (Fig. 4). Exercise therapy significantly improved PCS compared with control in the overall analysis (MD + 5.83 points, 95% CI 0.71–10.94; $P = 0.03$; 8 studies), with low heterogeneity ($I^2 = 18\%$; $\tau^2 = 3.73$). In subgroup analyses by follow-up duration, the MD was + 5.91 (95% CI −8.85 to 20.66; $P = 0.23$; $I^2 = 38\%$; three studies) for interventions of 3 months or less and + 7.03 (95% CI −7.33 to 21.40; $P = 0.25$; $I^2 = 81\%$; five studies) for interventions longer than 3 months. Although neither subgroup reached statistical significance, both point estimates favored exercise with similar magnitude. The test for subgroup differences was not significant ($P = 0.86$).

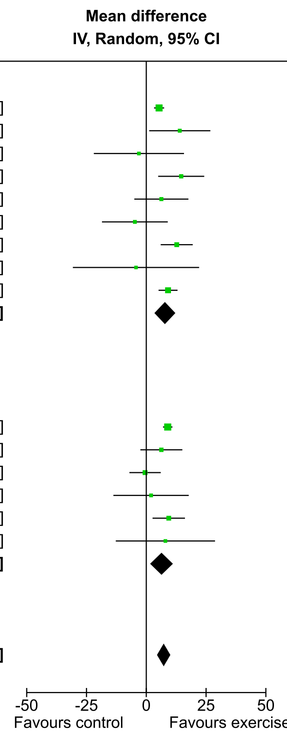
General health was reported in 14 RCTs (644 participants total) (Fig. 5). Exercise significantly improved general health scores compared with control in the

Table 1 Abstract table/characteristics of included studies

Study	Year	Country	Setting	Sample size (analyzed)	Male (%)		Mean age (years)		Hemodialysis period (month)		Intervention period (week)
					Exercise	Control	Exercise	Control	Exercise	Control	
Abdelbasset et al. [20]	2022	Saudi Arabia	Single	50 (43)	33.3	27.3	53.6 ± 17.8	48.7 ± 18.5	28.6 ± 7.3	26.9 ± 7.8	12
Abreu et al. [21]	2017	Brazil	Single	61 (44)	45.5	38.5	45.7 ± 15.2	42.5 ± 13.5	71.2 ± 45.5	70.1 ± 49.9	12
Deus et al. [22]	2021	Brazil	NR	202 (157)	56.8	52.6	67.27 ± 3.24	66.33 ± 3.88	54.09 ± 11.05	55.47 ± 8.171	24
Dobsak et al. [23]	2012	Czech	Single	21 (21)	36.4	40	58.2 ± 7.2	60.1 ± 8.2	49.2 ± 25.2	49.2 ± 27.6	20
Giannaki et al. [24]	2013	Greece	Single	24 (22)	73.3	71.4	56.4 ± 12.5	56.8 ± 16.5	46.8 ± 15.6	43.2 ± 18.0	24
Greenwood et al. [25]	2021	UK	Multi	335 (280)	58.5	62.1	60.5 ± 15.0	59.8 ± 14.1	NR	NR	24
Hristea et al. [26]	2016	France	multi	21 (16)	NI	NI	68.5 ± 13.97	70.8 ± 15.18	139 ± 255.5	96 ± 86	24
Jamshidpour et al. [27]	2020	Iran	Single	30 (28)	80	61	64.93 ± 7.79	58.46 ± 11.85	37.8 ± 32.4	40.6 ± 33.4	8
Koh et al. [28]	2010	Australia	Multi	49 (31)	66.7	50	52.3 ± 10.9	51.3 ± 14.4	32.1 ± 26.7	25.8 ± 22.2	24
Kouidi et al. [29]	2010	Greece	Single	50 (44)	58.3	60	46.3 ± 11.2	45.8 ± 10.9	73.2 ± 55.2	75.6 ± 58.8	48
Kouidi et al. [30]	1997	Greece	Single	36 (31)	55	36.4	49.6 ± 12.1	52.8 ± 10.2	64.8 ± 54.0	74.4 ± 64.8	24
Lin et al. [31]	2021	Taiwan	Single	64 (64)	68.8	59.4	62.0 ± 9.5	62.1 ± 12.3	80.4 ± 68.4	74.4 ± 61.2	12
Liu et al. [32]	2023	China	Single	84 (84)	35.7	61.9	56.3 ± 11.10	59.2 ± 10.41	126.2 ± 74.08	113.1 ± 45.27	24
Lopes et al. [33]	2019	Brazil	NR	53 (36)	42.6	65	56.2 ± 12.5	56.9 ± 12.4	72.1 ± 50.3	53.2 ± 44.1	12
Malagoni et al. [34]	2008	Italy	Single	31 (20)	76.9	57.1	62 ± 10	66 ± 14	78 ± 50	90 ± 73	24
Martin-Alemañy et al. [35]	2020	Mexico	Single	30 (22)	33.3	60	30.3 ± 10.8	27.1 ± 8.1	19(8–36)	28(8–48)	12
Marzougui et al. [36]	2023	Tunisia	Single	25 (22)	63.6	36.4	49.00 ± 12.51	48.63 ± 9.53	115.79 ± 28.48	111.31 ± 23.53	12
Ouzouni et al. [37]	2009	Greece	Single	35 (33)	73.7	92.9	47.4 ± 15.7	50.5 ± 11.7	92.4 ± 84.0	103.2 ± 72.0	10
Parsons et al. [38]	2004	Canada	Single	18 (13)	50	57.1	60 ± 17	49 ± 25	35 ± 25	49 ± 26	8
Rosa et al. [39]	2018	Brazil	Single	59 (52)	71.4	62.5	54.49 ± 11.97	57.10 ± 16.20	18.48 ± 15.12	28.2 ± 19.92	12
Song et al. [40]	2012	Korea	Single	40 (40)	40	60	52.1 ± 12.4	54.6 ± 10.1	38.9 ± 26.1	45.9 ± 56.2	12
Wu et al. [41]	2014	China	Single	69 (65)	84.4	84.8	45 ± 8.2	44 ± 6.7	55.5 ± 37.3	39.8 ± 29.7	12

NR not reported in the original article, *NI* not investigated/not assessed in the original article

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95% CI	A	B	C	D	E	F
1.1.1 ≤ 3 mo														
Abdelbasset 2022	6.72	4.35	21	1.36	2.34	22	19.7%	5.36 [3.26 , 7.46]	?	+	+	?	?	?
Abreu 2017	8	22	25	-6	21	19	2.8%	14.00 [1.21 , 26.79]	?	?	?	?	+	?
Jamshidpour 2020	-5	26.2	15	-1.92	24.66	13	1.4%	-3.08 [-21.93 , 15.77]	+	+	+	+	+	+
Lin 2021	15	21.1	32	0.4	18.1	32	4.5%	14.60 [4.97 , 24.23]	?	?	−	−	+	−
Lopes 2019	3.1	14.6	16	-3.2	20	20	3.4%	6.30 [-5.01 , 17.61]	+	?	+	−	+	−
Martin-Alemañy 2020	-1.43	9.5	9	3.34	22.6	13	2.4%	-4.77 [-18.53 , 8.99]	?	?	+	?	+	?
Marzougui 2023	13.18	7.59	11	0.45	8.43	11	7.7%	12.73 [6.03 , 19.43]	+	+	+	+	−	−
Parsons 2004	-3.5	30.3	6	0.8	14.1	7	0.7%	-4.30 [-30.70 , 22.10]	−	−	?	−	−	−
Wu 2014	10.2	8.5	32	1.1	7.8	33	13.7%	9.10 [5.13 , 13.07]	?	−	?	−	−	−
Subtotal (HKSJ[a])			**167**			**170**	**56.2%**	**7.78 [3.72 , 11.84]**						
Test for overall effect: T = 4.42, df = 8 (P = 0.002)														
Heterogeneity: Tau² (REML[b]) = 7.14; Chi² = 14.28, df = 8 (P = 0.07); I² = 39%														
1.1.2 > 3 mo														
Deus 2021	7.52	6.288	81	-1.44	6.313	76	20.1%	8.96 [6.99 , 10.93]	?	−	−	−	−	−
Dobsak 2012	6.9	5.1	11	0.6	13.3	10	5.2%	6.30 [-2.48 , 15.08]	+	?	−	−	+	−
Greenwood 2021	1.1	26.4	114	1.6	24.9	122	7.9%	-0.50 [-7.06 , 6.06]	+	−	?	−	+	−
Koh 2010	-2	21	15	-4	23	15	1.9%	2.00 [-13.76 , 17.76]	+	?	−	−	+	−
Liu 2023	7.9	13.47	42	-1.5	17.9	42	7.6%	9.40 [2.62 , 16.18]	?	+	+	−	?	−
Malagoni 2008	1	25	9	-7	16	6	1.1%	8.00 [-12.75 , 28.75]	?	−	?	−	+	−
Subtotal (HKSJ[a])			**272**			**271**	**43.8%**	**6.37 [1.94 , 10.79]**						
Test for overall effect: T = 3.69, df = 5 (P = 0.01)														
Heterogeneity: Tau² (REML[b]) = 10.25; Chi² = 8.22, df = 5 (P = 0.14); I² = 47%														
Total (HKSJ[a])			**439**			**441**	**100.0%**	**7.27 [4.75 , 9.80]**						



Test for overall effect: T = 6.19, df = 14 (P < 0.0001)
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%
Heterogeneity: Tau² (REML[b]) = 5.62; Chi² = 23.73, df = 14 (P = 0.05); I² = 43%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Fig. 2 Fatigue scores: exercise versus usual care, stratified by follow-up duration

overall analysis (MD + 11.59 points, 95% CI 6.98–16.21; $P = 0.0001$; 14 studies), with substantial heterogeneity ($I^2 = 71\%$; $\tau^2 = 29.61$). In duration-stratified analyses, a statistically significant improvement was observed for interventions of 3 months or less (nine studies; MD + 12.57, 95% CI 6.12–19.02; $P = 0.002$; $I^2 = 66\%$). For interventions longer than 3 months (five studies), the MD was + 10.00 (95% CI −0.14 to 20.14; $P = 0.05$; $I^2 = 63\%$), indicating a similar point estimate but loss of statistical significance and persistent heterogeneity. The test for subgroup differences was not statistically significant ($P = 0.58$).

Pain was evaluated in 14 RCTs (325 participants in the exercise group, 319 in the control group, 644 total) (Fig. 6). In the overall analysis, the effect of exercise on the SF-36 pain domain was not statistically significant (MD + 2.19 points, 95% CI −4.41 to 8.79; $P = 0.49$; 14 studies), and heterogeneity was very high ($I^2 = 89\%$; $\tau^2 = 103.47$). However, in duration-stratified analyses, short-term interventions (≤ 3 months; nine studies) showed a statistically significant improvement in pain (MD + 4.06, 95% CI 0.54–7.57; $P = 0.03$; $I^2 = 0\%$), whereas longer-term interventions (> 3 months; five studies) did not (MD −0.56, 95% CI −20.68 to 19.55; $P = 0.94$; $I^2 = 92\%$). The test for subgroup differences was not statistically significant ($P = 0.53$).

Outcomes without statistical benefit

SF-36 MCS did not show a statistically significant benefit of exercise in either the overall or duration-stratified analyses. A total of eight RCTs (130 participants in the exercise group, 112 in the control group, 242 total) reported MCS (Fig. 7). The overall pooled estimate favored exercise but was not statistically significant (MD + 7.60 points, 95% CI −3.75 to 18.94; $P = 0.16$; eight studies).

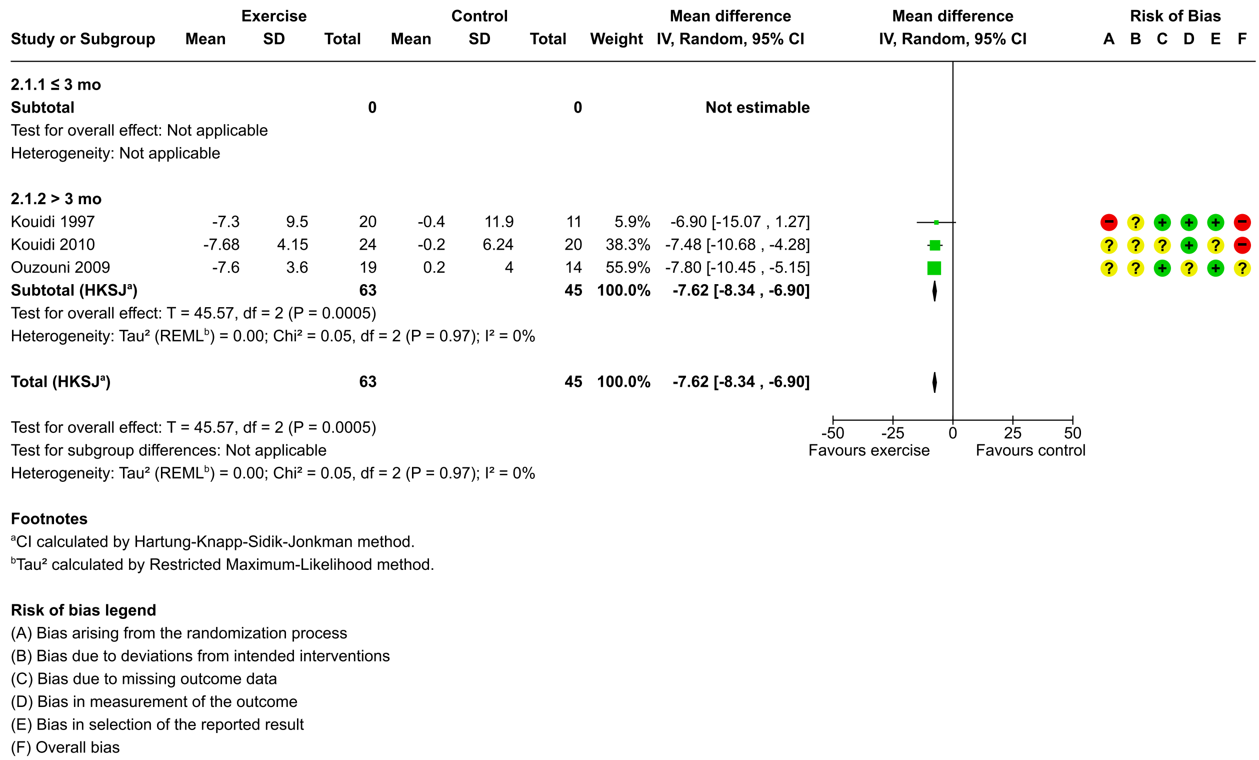


Fig. 3 Depression scores: exercise versus usual care, stratified by follow-up duration

In subgroup analyses, the MD was + 3.36 (95% CI −11.16 to 17.88; $P=0.42$; $I^2=33\%$; three studies) for interventions of 3 months or less and + 10.89 (95% CI −9.90 to 31.67; $P=0.22$; $I^2=92\%$; five studies) for interventions longer than 3 months. Neither subgroup reached statistical significance, and the test for subgroup differences was not significant ($P=0.36$).

Exploratory analyses by exercise modality

In prespecified exploratory analyses, we compared aerobic versus resistance/combined modalities for PCS, MCS, and fatigue (Supplementary Figs. S1–S3). PCS and MCS showed similar estimates between modalities with wide confidence intervals. For fatigue, both aerobic and resistance/combined programs demonstrated statistically significant improvements relative to control, although the estimates carry considerable uncertainty.

Discussion

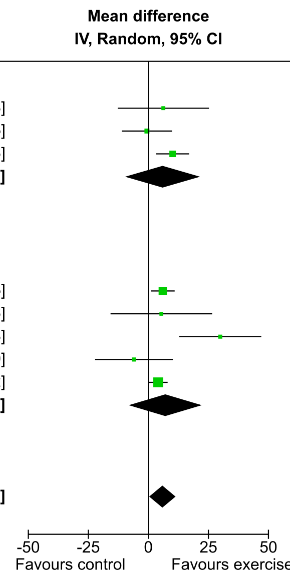
This synthesis identified 94 RCTs of structured exercise therapy in maintenance HD, of which 22 reported HRQoL outcomes and were included in the meta-analysis. Stratifying these trials by intervention duration (≤ 3 months versus > 3 months) highlights three main patterns. Fatigue and depressive symptoms, which are among the most troublesome complaints in this population, showed consistent improvements of a magnitude likely to be clinically meaningful. By contrast, SF-36 PCS and general health improved in the overall analyses, but confidence intervals for the > 3-month subgroup were wide and crossed the null, reflecting small numbers of long-term trials and substantial heterogeneity. For SF-36 MCS and pain, pooled estimates tended to favor structured exercise therapy but did not reach statistical significance, and wide prediction intervals suggest that true effects may vary considerably across settings.

Interpretation of fatigue and depression outcomes

The consistent improvements in fatigue across both shorter (≤ 3 months) and longer (> 3 months) programs are biologically plausible, as cumulative training over several months may be necessary to induce neuromuscular and behavioral adaptations that reduce subjective fatigue, particularly in HD patients who exhibit intramuscular energy metabolism deficits, reduced oxidative potential, and central activation failure [42, 43].

Depressive symptoms also showed a large and consistent reduction in longer-term (> 3 months) programs. No short-term trials (≤ 3 months) in our analysis assessed depression using validated scales, restricting the discussion of effectiveness compared to long-term interventions. These findings extend previous systematic reviews

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95% CI	A	B	C	D	E	F
3.1.1 ≤ 3 mo														
Jamshidpour 2020	2.72	23.74	15	-3.51	27.09	13	2.8%	6.23 [-12.77 , 25.23]	+	+	+	+	+	+
Rosa 2018	6.5	20.36	28	7.1	18.07	24	8.5%	-0.60 [-11.05 , 9.85]	+	+	+	?	?	?
Song 2012	8	9.8	20	-2.1	12.2	20	17.1%	10.10 [3.24 , 16.96]	+	?	−	+	+	−
Subtotal (HKSJ[a])			**63**			**57**	**28.3%**	**5.91 [-8.85 , 20.66]**						
Test for overall effect: T = 1.72, df = 2 (P = 0.23)														
Heterogeneity: Tau² (REML[b]) = 18.91; Chi² = 2.82, df = 2 (P = 0.24); I² = 38%														
3.1.2 > 3 mo														
Dobsak 2012	5.2	4.4	11	-0.8	6.8	10	26.9%	6.00 [1.05 , 10.95]	+	?	−	−	+	−
Giannaki 2013	11.5	15.6	15	6.1	26.5	7	2.3%	5.40 [-15.76 , 26.56]	+	?	+	−	+	−
Hristea 2016	24.18	13.32	7	-5.75	21.37	9	3.4%	29.93 [12.83 , 47.03]	+	?	−	?	+	−
Koh 2010	-6	20	15	0	25	15	3.8%	-6.00 [-22.20 , 10.20]	+	?	−	−	+	−
Ouzouni 2009	4	5.5	19	-0.1	5.8	14	35.3%	4.10 [0.18 , 8.02]	?	?	+	?	+	?
Subtotal (HKSJ[a])			**67**			**55**	**71.7%**	**7.03 [-7.33 , 21.40]**						
Test for overall effect: T = 1.36, df = 4 (P = 0.25)														
Heterogeneity: Tau² (REML[b]) = 68.18; Chi² = 10.28, df = 4 (P = 0.04); I² = 81%														
Total (HKSJ[a])			**130**			**112**	**100.0%**	**5.83 [0.71 , 10.94]**						



Test for overall effect: T = 2.69, df = 7 (P = 0.03)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%
Heterogeneity: Tau² (REML[b]) = 3.73; Chi² = 13.35, df = 7 (P = 0.06); I² = 18%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Fig. 4 SF-36 Physical Component Summary: exercise versus usual care, stratified by follow-up duration

that identified structured exercise therapy as beneficial for psychological well-being in dialysis populations but did not examine duration-specific effects [4, 5]. Potential neurobiological mechanisms have been reviewed elsewhere, including changes in neurotransmission and neurotrophic signaling [44–46], but a detailed discussion is beyond the scope of this review. Given the small number of trials, conclusions about the optimal program duration for depressive symptoms should remain cautious.

These results are consistent with guideline recommendations from the Japanese Renal Rehabilitation Society and the UK Renal Association, which advocate structured exercise programs in HD settings [10, 11].

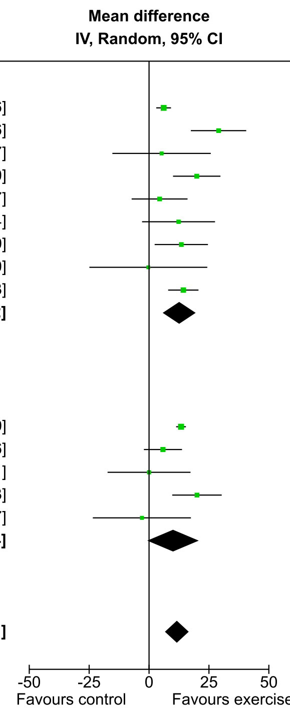
Interpretation of outcomes with limited long-term evidence

SF-36 PCS and general health showed significant overall improvements, but in the > 3-month subgroup, CIs widened and crossed the null. This pattern suggests that the absence of statistical significance may partly reflect the small number of long-term trials and substantial heterogeneity rather than a true attenuation of effect. The overall PCS improvement of + 5.83 points approaches the minimal clinically important difference of 5.7 points previously estimated for stage 5 chronic kidney disease [47], indicating that the pooled effect may be clinically relevant even though the durability of benefit beyond 3 months remains uncertain.

As low HRQoL scores, particularly SF-36 PCS, are strong independent predictors of hospitalization and mortality in HD cohorts [1, 2], even modest improvements in PCS and general health may have broader implications beyond symptomatic relief and should be explored further in larger, more homogeneous long-term trials.

For SF-36 MCS and pain, pooled estimates favored exercise but did not reach statistical significance, and both heterogeneity and prediction intervals were very wide, indicating that true effects in future settings could range from meaningful benefit to no effect or harm [16–19]. Previous meta-analyses have likewise reported inconsistent effects for mental health and pain outcomes [4, 5]. A recent meta-analysis suggested that exercise interventions lasting > 12 weeks may improve MCS among patients receiving dialysis, although it was not specific to HD [48]. The Cochrane review also reported

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95% CI	RoB A	RoB B	RoB C	RoB D	RoB E	RoB F
4.1.1 ≤ 3 mo														
Abdelbasset 2022	7.98	5.7	21	1.9	4.5	22	13.4%	6.08 [3.00 , 9.16]	?	+	+	?	?	?
Abreu 2017	25	17	25	-4	21	19	6.7%	29.00 [17.44 , 40.56]	?	?	?	?	+	?
Jamshidpour 2020	7.93	26.76	15	2.7	28.4	13	3.1%	5.23 [-15.31 , 25.77]	+	+	+	+	+	+
Lin 2021	14.5	20.6	32	-5.4	19.8	32	7.8%	19.90 [10.00 , 29.80]	?	?	-	-	+	-
Lopes 2019	4.4	17.7	16	0	17.8	20	6.6%	4.40 [-7.27 , 16.07]	+	?	+	-	+	-
Martin-Alemañy 2020	12.86	18.2	9	0.55	17.5	13	4.8%	12.31 [-2.92 , 27.54]	?	?	+	?	+	?
Marzougui 2023	15	7.04	11	1.54	17.46	11	6.9%	13.46 [2.33 , 24.59]	+	+	+	+	-	-
Parsons 2004	-8.1	22.7	6	-7.8	22.4	7	2.3%	-0.30 [-24.90 , 24.30]	-	-	?	-	-	-
Wu 2014	14.7	15.8	32	0.4	9.3	33	10.7%	14.30 [7.97 , 20.63]	?	-	?	-	-	-
Subtotal (HKSJ[a])			**167**			**170**	**62.2%**	**12.57 [6.12 , 19.02]**						
Test for overall effect: T = 4.49, df = 8 (P = 0.002)														
Heterogeneity: Tau² (REML[b]) = 39.24; Chi² = 24.25, df = 8 (P = 0.002); I² = 66%														
4.1.2 > 3 mo														
Deus 2021	11.97	6.818	81	-1.37	6.275	76	14.0%	13.34 [11.29 , 15.39]	?	-	-	-	-	-
Dobsak 2012	4.6	8.7	11	-1.2	9.8	10	9.3%	5.80 [-2.16 , 13.76]	+	?	-	-	+	-
Koh 2010	-3	21	15	-3	27	15	4.0%	0.00 [-17.31 , 17.31]	+	?	-	-	+	-
Liu 2023	20	22.22	42	0	25.93	42	7.5%	20.00 [9.67 , 30.33]	?	+	+	-	?	-
Malagoni 2008	-7	16	9	-4	22	6	3.1%	-3.00 [-23.47 , 17.47]	?	-	?	-	+	-
Subtotal (HKSJ[a])			**158**			**149**	**37.8%**	**10.00 [-0.14 , 20.14]**						
Test for overall effect: T = 2.74, df = 4 (P = 0.05)														
Heterogeneity: Tau² (REML[b]) = 31.61; Chi² = 9.49, df = 4 (P = 0.05); I² = 63%														
Total (HKSJ[a])			**325**			**319**	**100.0%**	**11.59 [6.98 , 16.21]**						



Test for overall effect: T = 5.43, df = 13 (P = 0.0001)
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%
Heterogeneity: Tau² (REML[b]) = 29.61; Chi² = 38.32, df = 13 (P = 0.0003); I² = 71%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Fig. 5 General health scores: exercise versus usual care, stratified by follow-up duration

nonsignificant effects and substantial heterogeneity in MCS,consistent with our results, warranting cautious interpretation [4].

The substantial heterogeneity observed for pain and MCS may reflect clinical and methodological diversity across trials. In the included RCTs, exercise interventions differed in modality (e.g., aerobic/endurance-based programs, resistance training, and combined programs). HRQoL was assessed using SF-36 domains/component summaries (including studies administering the SF-36 within KDQOL-based instruments that include an SF-36 generic core), and differences in instrument version/language adaptation and scoring procedures may add further variability. Importantly, pain and MCS are patient-reported outcomes, and blinding is often not feasible in exercise trials; consistent with this, our RoB 2 assessments judged high risk of bias for a substantial proportion of pain and MCS results (pain: 10/14 trials; MCS: 5/8 trials). Pain is a complex, multidimensional experience influenced by biological, psychological, and social factors. Heterogeneity in pain outcomes may also reflect between-study differences in pain etiology, chronicity, management, cultural context, and how pain was assessed (e.g., instrument choice, scoring, and timing) [49, 50]. A more specific and detailed assessment may be warranted for pain in this population. For similar reasons, MCS may also be prone to substantial heterogeneity; variations in exercise modality and other program characteristics could contribute, as suggested in a recent meta-analysis of dialysis populations [48].

Therefore, pooled estimates for pain and MCS should be interpreted cautiously as average effects and true effects may vary across contexts. Given the substantial heterogeneity and imprecision, these pooled estimates should not be interpreted as definitive evidence of no effect.

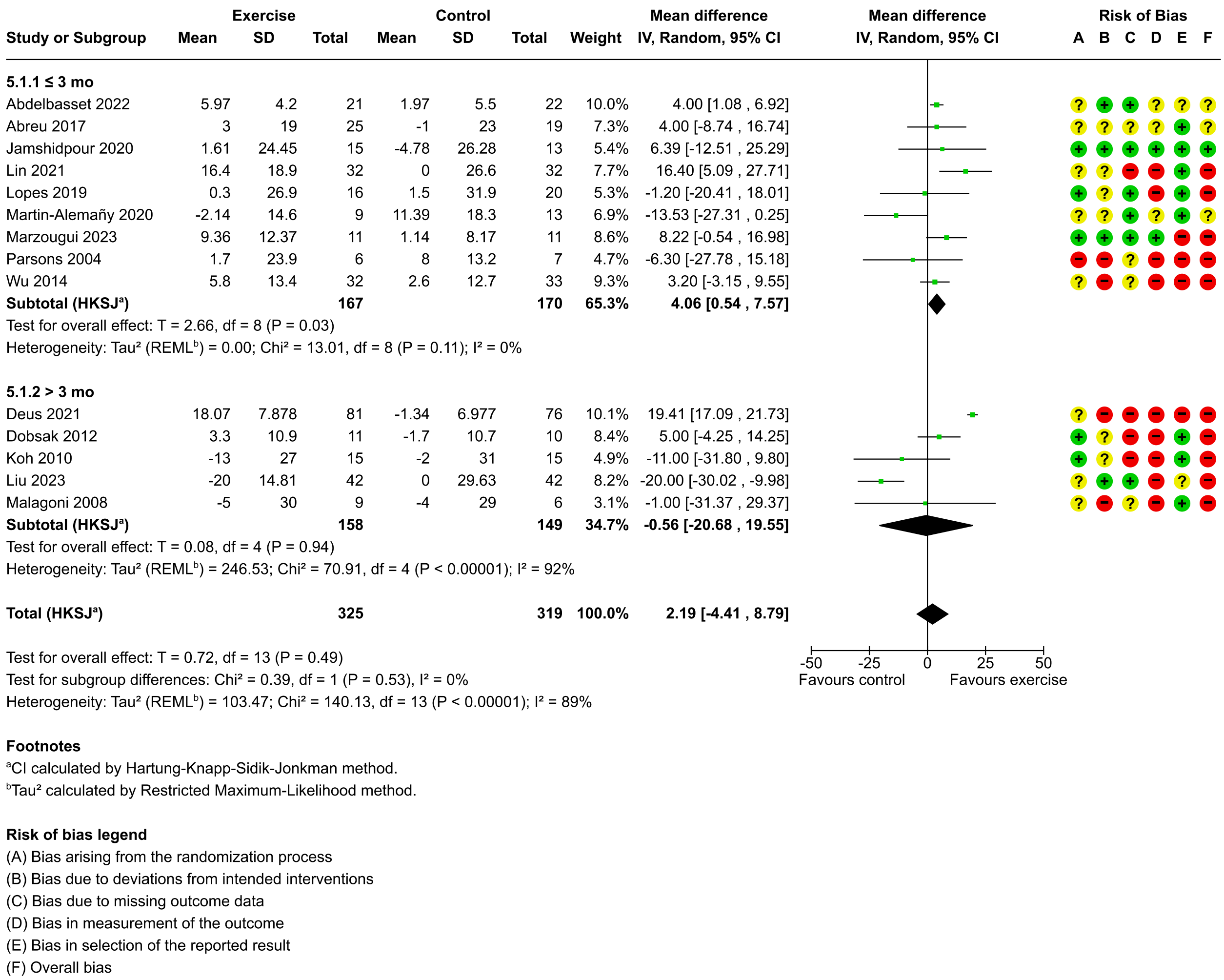


Fig. 6 Pain scores: exercise versus usual care, stratified by follow-up duration

Clinical implications

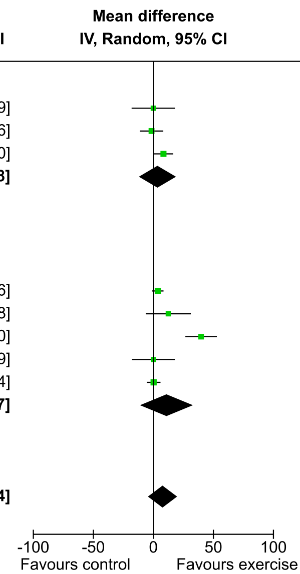
The duration-stratified presentation has practical implications for program design. Fatigue appears to be a consistent target across both ≤ 3-month and > 3-month programs. Improvements in depressive symptoms were observed in trials longer than 3 months; however, evidence is limited and no ≤ 3-month depression data were available. Therefore, clinicians may consider sustained exercise support on an individualized basis, while acknowledging uncertainty regarding duration-specific effects for depression. Given the interindividual variability and the substantial heterogeneity for certain outcomes, monitoring and flexible program adjustments remain prudent [51].

Exploratory modality analyses (Supplementary Figs. S1–S3) and previous network meta-analyses suggest broadly comparable effects of aerobic and resistance/combined regimens for PCS, MCS, and fatigue, allowing clinicians to tailor prescriptions to patient preferences, dialysis schedules, and facility resources without clear evidence that one modality is superior for HRQoL [6, 7]. Understanding and addressing barriers to exercise participation, including physical limitations, psychological factors, and organizational constraints, is essential for successful implementation [51, 52]. The findings align with existing guideline recommendations advocating structured exercise in dialysis populations [10, 11], and our analysis provides a descriptive summary of patterns across HRQoL domains, while acknowledging uncertainty in domain- and duration-specific effects.

In health systems such as Japan, where intradialytic exercise delivered by medical professionals is currently reimbursed only for the first 90 days of a program, our duration-stratified findings (including fatigue improvements observed across both ≤ 3-month and > 3-month programs) may inform discussion about how best to sustain access to structured exercise beyond the initial coverage window. These considerations should be

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95% CI	A	B	C	D	E	F
6.1.1 ≤ 3 mo														
Jamshidpour 2020	-3.05	23.39	15	-2.98	25.1	13	10.0%	-0.07 [-18.13 , 17.99]	+	+	+	+	+	+
Rosa 2018	2.69	16.44	28	4.22	19.15	24	13.6%	-1.53 [-11.32 , 8.26]	+	+	+	?	?	?
Song 2012	6.5	13.7	20	-1.9	12.4	20	14.2%	8.40 [0.30 , 16.50]	+	?	−	+	+	−
Subtotal (HKSJ[a])			**63**			**57**	**37.8%**	**3.36 [-11.16 , 17.88]**						
Test for overall effect: T = 1.00, df = 2 (P = 0.42)														
Heterogeneity: Tau² (REML[b]) = 15.22; Chi² = 2.55, df = 2 (P = 0.28); I² = 33%														
6.1.2 > 3 mo														
Dobsak 2012	4.7	5.5	11	1	5.6	10	15.3%	3.70 [-1.06 , 8.46]	+	?	−	−	+	−
Giannaki 2013	9.3	18.7	15	-3.1	21.9	7	9.7%	12.40 [-6.38 , 31.18]	+	?	+	−	+	−
Hristea 2016	30.89	10.61	7	-8.87	16.11	9	12.1%	39.76 [26.62 , 52.90]	+	?	−	?	+	−
Koh 2010	-2	25	15	-2	25	15	10.0%	0.00 [-17.89 , 17.89]	+	?	−	−	+	−
Ouzouni 2009	0	10	19	-0.2	6.8	14	15.0%	0.20 [-5.54 , 5.94]	?	?	+	?	+	?
Subtotal (HKSJ[a])			**67**			**55**	**62.2%**	**10.89 [-9.90 , 31.67]**						
Test for overall effect: T = 1.45, df = 4 (P = 0.22)														
Heterogeneity: Tau² (REML[b]) = 240.35; Chi² = 30.77, df = 4 (P < 0.00001); I² = 92%														
Total (HKSJ[a])			**130**			**112**	**100.0%**	**7.60 [-3.75 , 18.94]**						

Test for overall effect: T = 1.58, df = 7 (P = 0.16)
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%
Heterogeneity: Tau² (REML[b]) = 141.85; Chi² = 33.43, df = 7 (P < 0.0001); I² = 87%



Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
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(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Fig. 7 SF-36 Mental Component Summary: exercise versus usual care, stratified by follow-up duration

integrated with evidence on physical function from the Cochrane review and subsequent network meta-analyses [4, 6, 7]. Given limited long-term evidence and substantial heterogeneity for pain and MCS, any implications for sustaining program availability beyond time-limited coverage should be regarded as preliminary and hypothesis-generating.

Limitations and future directions

Several limitations warrant consideration. Most included trials were small (median $n=52$) and single-center, limiting generalizability and increasing susceptibility to study-level biases. Risk of bias was frequently judged as high across outcomes, including pain and MCS (Supplementary Table S2). Our search was restricted to MEDLINE (PubMed) and English-language publications, and no additional databases, trial registries, or manual reference checks were performed; therefore, eligible studies indexed elsewhere or published after the last search (November 2024) may have been missed. Exclusion of smaller studies indexed outside MEDLINE may have led to an overestimation of the treatment effect or an underestimation of the true variance between studies. In addition, because evidence published after November 2024 was not captured, these findings should be interpreted cautiously.

A critical limitation is the scarcity of trials exceeding 3 months (PCS: five trials; general health: five trials; fatigue: six trials; depression: three trials), which precludes definitive conclusions regarding long-term effects. Future research should prioritize adequately powered, multicenter RCTs evaluating programs of at least 3–6 months' duration, with preregistered duration-based subgroup analyses. Additionally, many outcome reports lacked standardized minimal clinically important difference thresholds, and adverse events were inconsistently reported. Addressing these gaps through large-scale trials with extended follow-up and harmonized outcome definitions represents a priority for advancing renal rehabilitation.

Conclusions

Structured exercise therapy appears to improve fatigue in patients on maintenance HD and may provide additional gains in PCS and general health. Improvements in depressive symptoms were observed in trials longer than 3 months; however, duration-specific effects remain uncertain because short-term depression data were unavailable and longer-term evidence was limited. Effects on MCS and pain remain uncertain owing to heterogeneity. Larger long-term trials are needed to clarify the sustainability of HRQoL benefits beyond 3 months.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-026-00710-6.

Additional file1 (PDF 333 kb)

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Not applicable

Author contributions
YH, DU, SK, HM, MN, AH, ST, HK, and TSa undertook this review. The titles and abstracts were screened independently by HK and TSa in the primary search for RCTs and by all nine review authors (YH, DU, SK, HM, MN, AH, ST, HK, and TSa) in the secondary screening and full-text assessment. Data extraction was performed by YH, DU, SK, HM, MN, AH, ST, HK, and TSa. TSo, NF, MS, IN, KY, and JH provided supervision. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Ichiei Narita is a member of the Editorial Board of Renal Replacement Therapy. The other authors declare that they have no competing interests.

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