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Effects of supervised exercise on depressive symptoms in hemodialysis patients: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: The reported prevalence rate of depressive symptoms in hemodialysis patients is 40%. Although appropriate management of these symptoms is important, they remain under-recognized and under-treated in hemodialysis patients. Here, we systematically reviewed relevant randomized controlled trials (RCTs) investigating the effects of supervised exercise training on depressive symptoms in hemodialysis patients.

Methods: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, CINAHL, Web of Science, PsycINFO, and PEDro databases were searched from the start until June 2016 for RCTs published in English evaluating the effects of supervised exercise training in hemodialysis patients. The main outcome measures were depressive symptoms.

Results: From a total of 10,923 screened references, five trials were included in the analysis. Exercise training was shown to significantly improve depressive symptoms in comparison with controls (standardized mean difference, SMD = − 1.19; $P < 0.001$) under a random effects model. Subgroup analyses indicated that aerobic exercise and interventions lasting ≥ 6 months significantly reduced depressive symptoms in hemodialysis patients ($P = 0.016$, $P < 0.001$, respectively).

Conclusions: The meta-analysis found that supervised exercise training tends to alleviate depressive symptoms in hemodialysis patients. As our database search identified only a small number of studies on the association between exercise and depressive symptoms, we would surmise that additional high-quality studies are required to explore further this association.

Trial registration: PROSPERO, CRD42015020701.

Keywords: Chronic kidney disease, Hemodialysis, Depressive symptoms, Exercise, Meta-analysis

Background

With the increasing prevalence of lifestyle-related diseases, such as diabetes, hypertension, and arteriosclerosis, there are more than 2 million patients undergoing hemodialysis worldwide [1]. Depressive symptoms are common among hemodialysis patients, with a prevalence rate of 40% according to the Dialysis Outcomes and Practice Patterns Study (DOPPS) [2]. Depression is one of the most serious comorbidities among hemodialysis patients [2–4] and is associated with elevated mortality risk [2, 5, 6] and reduced quality of life (QOL) [7, 8]. Although the appropriate management of depressive symptoms as a patient-reported outcome (PRO) is known to be clinically important, these symptoms remain under-recognized and under-treated in dialysis patients [9–11]. Exercise training is an effective non-pharmacological means of reducing depressive symptoms among people dwelling in the community [12, 13], cancer survivors [14, 15], multiple

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sclerosis patients [16], stroke patients [17], and patients with chronic illness [18].

Although supervised exercise training has been suggested to improve exercise capacity, muscular strength, and QOL in hemodialysis patients [19–22], it remains unclear whether such exercise regimes can ameliorate depressive symptoms in these patients. Systematic reviews with meta-analyses are generally considered good means of determining the efficacy and effectiveness of treatments on selected outcomes.

This study was performed to systematically review relevant randomized controlled trials (RCTs) investigating the effects of supervised exercise training on depressive symptoms in hemodialysis patients. In addition, we performed subgroup analyses to examine the differences in efficacy related to the training program.

Methods

This review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Additional file 1) and is one of a series of systematic reviews regarding the effects of exercise on depressive symptoms in hemodialysis patients. The protocol used for the systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: PROSPERO 2015: CRD4201502 0701), and our protocol has already been published (http://bmjopen.bmj.com/content/6/5/e010990.long) [23]. No ethical approval was required because this study did not include confidential personal data and did not involve patient intervention.

Study selection and data management

An electronic database search was performed in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, CINAHL, Web of Science, PsycINFO, and PEDro using the following terms: "dialysis," "renal replacement therapy," "exercise," "physical fitness," "cycling," "walking," and "physical therapy." The full strategy is described in Additional file 2. To identify any articles missed by the initial search, the reference lists of previously reported systematic reviews were also evaluated in addition to our electronic database search. EndNote X7 for Windows (Thompson Reuters, Philadelphia, PA) was used to manage literature records and data. Reviewers screened all titles, abstracts, and the full texts of the selected publications. In cases where required data were not available, the study authors were contacted by email.

Inclusion and exclusion criteria

Only RCTs published in English that evaluated the effects of supervised exercise training on at least depressive symptoms were included. Supervised exercise included resistance training, aerobic exercise, or combined exercise. Only RCTs treating patients at least 18 years of age and on hemodialysis were included in this meta-analysis. Patients affected by acute kidney failure were also excluded. The main outcome of the study was depressive symptoms.

Risk of bias

The methodological quality of trials included in the review was assessed independently using the Cochrane Collaboration tool [24] by three reviewers to determine the risk of bias. Studies were graded as having a "low risk," "high risk," or "unclear risk" of bias across the seven specified domains: random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other sources of bias. Furthermore, the risk of bias of references was assessed using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX) [25], which consists of 15 different items and shows reliable performance for comprehensive review of exercise 1 training trials.

Data analysis and statistical methods

The effect sizes obtained from the RCTs are reported as mean change scores (Cohen's *d*). Although some of the included studies reported change scores and the standard deviations (SDs), we calculated change scores for those that did not by subtracting the mean baseline score from the mean follow-up score and calculated the change score SD. A random effects model was used to compute the overall or mean effect size (ES), as this model assumes that the samples are from populations with different ESs and that the true effect differs between studies. We used fixed effect models in cases in which the degree of statistical heterogeneity was low, while random effect models were used in all other cases. The 95% confidence interval (CI) around the mean ES was further calculated. To test for homogeneity of variance among ESs, we calculated the overall I^2 values, which represent the magnitude of heterogeneity where a larger number indicates greater heterogeneity; I^2 values of 25, 50, and 75% are related to low, moderate, and high degrees of heterogeneity, respectively.

Subgroup analyses were performed based on the categorical variables of exercise mode (i.e., Aerobic vs. Other), exercise duration (≥6 months vs. < 6 months), and type of exercise intervention (intradialytic exercise vs. non-intradialytic exercise). These were identified based on clinical relevance and experience with the characteristics of exercise training interventions. The analyses were performed using R version 3.3.0 (R Foundation for Statistical

Computing, Vienna, Austria). In all analyses, $P < 0.05$ was taken to indicate statistical significance [26].

Results

A total of 10,923 references were initially screened, of which 7640 had no duplicates and 7307 were rejected at the title and abstract stage. We then identified 333 studies for potential inclusion and full-text review, and five trials were finally entered into the analysis [27–31] (Fig. 1).

Participants and interventions

The trials included in the analysis are summarized in Table 1. The studies assessed depressive symptoms using the Center for Epidemiologic Studies Depression Questionnaire [27], Self-rating Depression Scale [28, 29], or the Beck Depression Inventory [30, 31]. Three of the studies used an intradialytic exercise program with interventions ranging in duration from 10 weeks to 6 months. Four studies used aerobic training, and one study used a combined exercise program that included calisthenics, steps, flexibility, and low weight resistance training. The interventions were performed two to four times per week in five studies.

Depressive symptoms

Comparison of exercise intervention groups and control groups indicated a small but significant overall standardized mean difference (SMD) = – 0.67 (CI, – 0.97 to – 0.36; $P < 0.001$) under a fixed effects model (Fig. 2). The mean ES was slightly smaller, but still statistically significant, under a random effects model (SMD = – 1.19; CI, – 2.17 to – 0.22; $P < 0.017$).

Subgroup analyses indicated significant reductions in depressive symptoms among hemodialysis patients associated with aerobic exercise and interventions lasting ≥ 6 months ($P = 0.016$, $P < 0.001$, respectively). However, no significant difference was seen in the remedial effects on depressive symptom between intradialytic and pre- or post-dialysis exercise programs (Figs. 3, 4, 5).

Assessment of bias risks

In the studies included in the analysis, the risks of bias were frequently high or unclear (Table 2). The methods used for random sequence generation, patient allocation, and assessor blinding to patient allocation were unclear in all studies. All trials clearly documented no blinding of participants and personnel. The outcome data were incomplete in one study and were reported only selectively in another study. The total TESTEX score, study quality score, and study reporting score of 5 studies were 7.40 ± 0.89, 1.80 ± 0.48, and 5.60 ± 1.14, respectively.

Discussion

The present meta-analysis was performed to determine the efficacy of supervised exercise training for reducing depressive symptoms in hemodialysis patients. The overall analysis tends to that exercise contributed to a reduction in depressive symptoms, and subgroup analyses showed that aerobic exercise and interventions lasting ≥

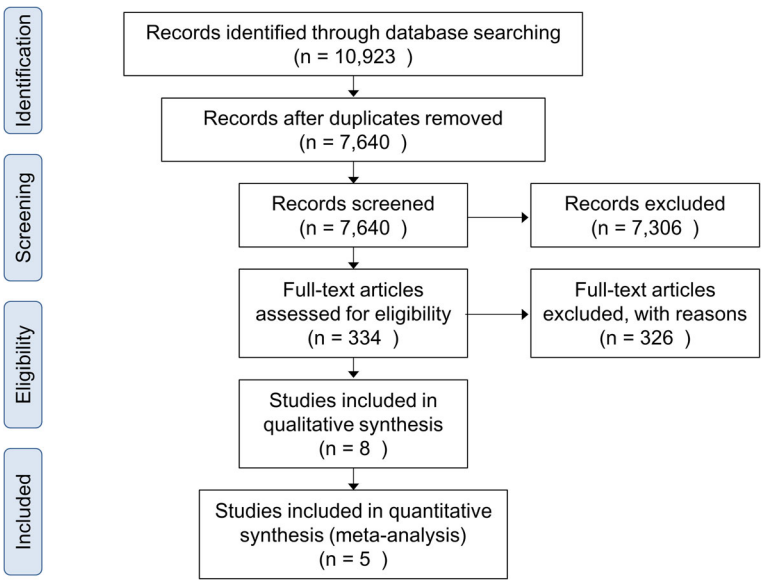

Fig. 1 PRISMA flow diagram showing selection of randomized controlled trials

Table 1 Characteristics of included studies

Studies	Year	Location	Mean age (SD)	Mean duration of dialysis therapy (SD), years	No. in groups (control, training)	Duration of intervention (weeks or months)	Type of intervention in control group	Type of intervention in exercise group	Training program	Intensity of program	Measure
Carmack et al. [26]	1995	USA	All 44.1	No data	Ex 23 Con 25	10 weeks	Usual care	Intradialytic	Aerobic exercise for 20 – 30 min using cycle ergometer 3 times per week	No data	CES-D
Giannaki et al. [27]	2013	Greece	Ex 56.4 (12.5) Con 55.7 (10.4) Total: no data	Ex 3.9 (1.3) Con 4.0 (1.7) Total: no data	Ex 15 Con 7	6 months	Placebo	Intradialytic	Progressive aerobic exercise training using a recumbent cycle ergometer 3 times a week	60–65% of the patient's maximal exercise capacity (in Watts)	SDS
van Vilsteren et al. [28]	2005	The Netherlands	Ex 52 (15) Con 58 (16)	Ex 3.22 (4.08) years Con 3.90 (4.41) years	Ex 53 Con 43	12 weeks	Usual care	Pre-dialysis strength training Intradialytic Exercise counseling	A 5–10-min warm up and cool down A 20-min exercise program including calisthenics, steps, flexibility, and low weight resistance training Cycling 20–30 min 2–3 times per week Techniques based on the transtheoretical model, motivational interviews, and health counseling	Borg scale 12–16 (< 60% maximal capacity)	SDS
Kouidi et al. [29]	1997	Greece	Ex 49.6 (12.1) Con 52.8 (10.2)	Ex 5.9 (4.9) Con 6.2 (5.4)	Ex 20 Con 11	6 months	Usual care	Non-dialysis days	Supervised exercise (stationary cycling, walking or jogging, calisthenics, aerobics, swimming, and/or game sports) 90 min 3–4 times weekly	50–60% of their VO_2max or 60–70% of their HRmax	BDI
Ouzouni et al. [30]	2009	Greece	Ex 47.4 (15.7) Con 50.5 (11.7)	Ex 7.7 (7.0) Con 8.6 (6.0)	Ex 19 Con 14	10 months	Usual care	Intradialytic	60–90 min 3 times weekly (cycling: 30 min; strength training: 30 min; flexibility exercise: 30 min)	Borg scale 13–14 ("somewhat hard")	BDI

SD standard deviation, *Ex* exercise, *Con* control, *CES-D* Center for Epidemiologic Studies Depression Scale, *SDS* Self-rating Depression Scale, *BDI* Beck Depression Inventory

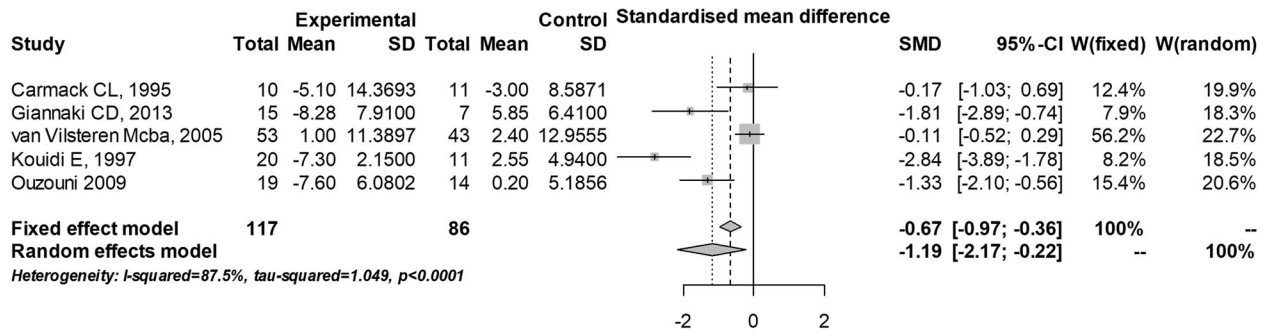

Fig. 2 Forest plot showing the effects of supervised exercise training compared with usual care on changes in depressive symptoms

6 months had greater probabilities of reducing the depressive symptoms in these patients. However, the results of the present study and other high-quality studies are required in order to clarify how exercise affects depressive symptoms in hemodialysis patients. To our knowledge, this is the first systematic review and meta-analysis regarding the efficacy of supervised exercise training for depression in hemodialysis patients taking the forms of exercise used and intervention durations into consideration.

The results presented here were consistent with previous meta-analyses regarding the effects of exercise on depression and depressive symptoms in other populations [32, 33]. A previous meta-analysis of 90 RCTs indicated that exercise reduces depressive symptoms among patients with various chronic illnesses, including chronic obstructive pulmonary disease, cardiovascular, fibromyalgia, multiple sclerosis, cancer, and chronic pain disorder [18]. However, it was unclear whether supervised exercise training could reduce depressive symptoms in hemodialysis patients due to major differences from those in populations including cancer survivors, stroke survivors, those with multiple sclerosis, those with other chronic illnesses, and the population in general. There are obvious differences with respect to age, prevalence of comorbidities, the presence of dialysis-related symptoms, and the overlap between symptoms of advanced kidney disease and those of depression. Therefore, the present study was performed using data from trials conducted only in hemodialysis patients, and our results indicated that, consistent with those in other populations, supervised exercise has a positive effect on depressive symptoms in these patients.

Observations regarding the release of monoamine neurotransmitters (i.e., serotonin, dopamine, and norepinephrine) and endorphins during aerobic exercise provided preliminary mechanistic support for the use of aerobic exercise to reduce and manage depressive symptoms [34, 35], and thus avoiding the common side effects associated with antidepressant medications [36]. Physical activity is associated with improved neurological function, with increased levels of neurotropic factors in the brain and improvements in mood [37]. However,

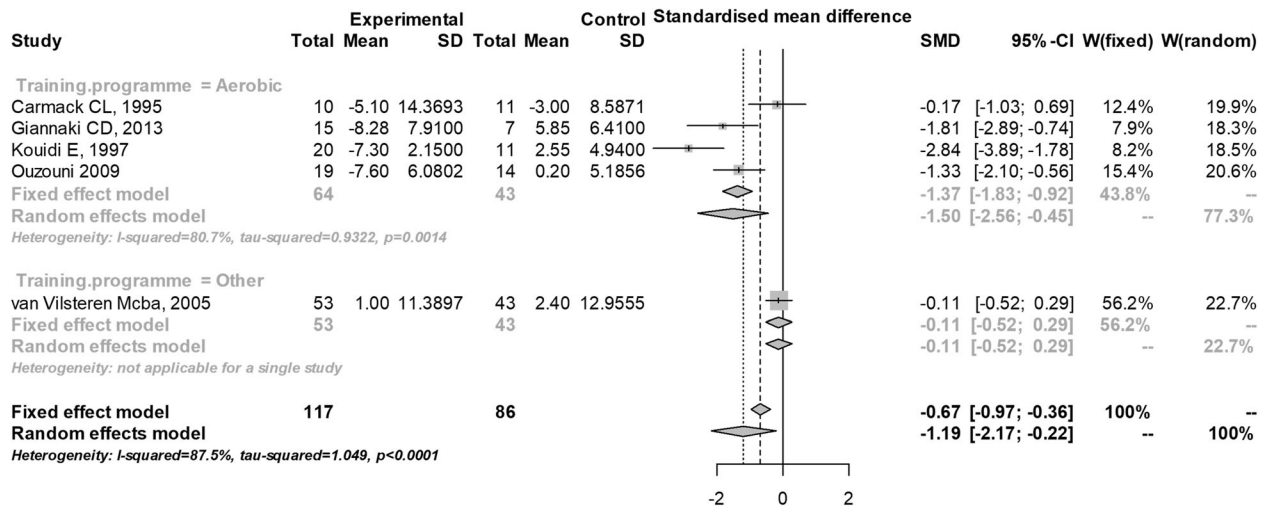

Fig. 3 Subgroup analysis of training program

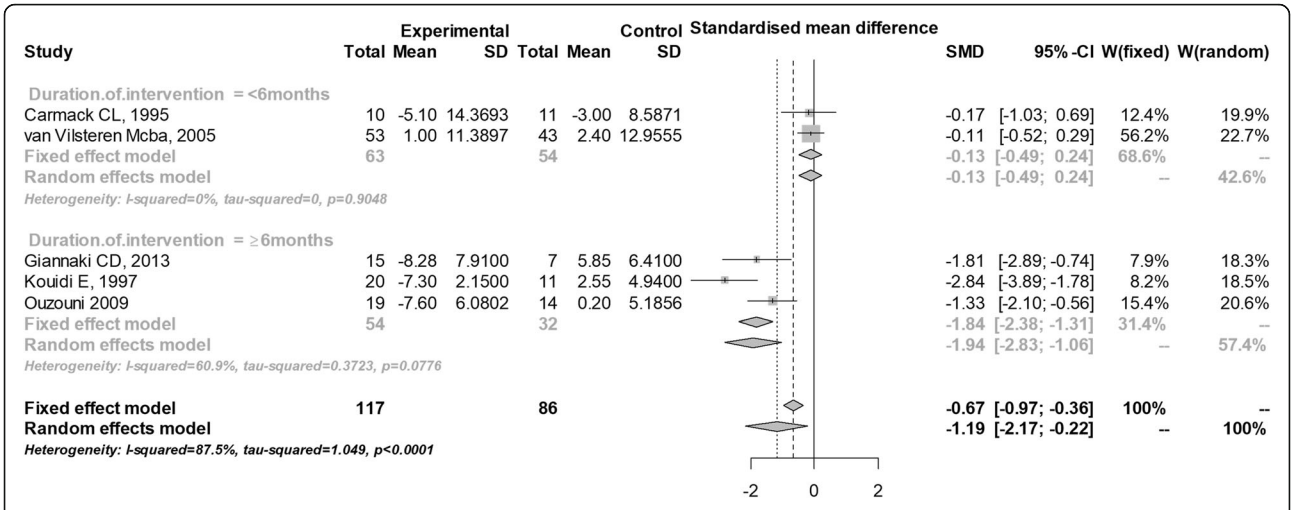

Fig. 4 Subgroup analysis of intervention duration

these hypotheses cannot fully explain the complex physiological and psychosocial etiologies of depressive symptoms, because the studies included in our meta-analysis rarely reported physiological measures. Further studies are therefore needed to examine the mechanisms underlying the exercise-induced reduction of depressive symptoms.

Based on the results of this study, we may be possible to recommend a structured, supervised aerobic exercise program for at least 6 months to manage or reduce depressive symptoms in hemodialysis patients. Exercise programs of 10–16 weeks produced greater effects in the general population than those lasting < 9 weeks [38]. In addition, Craft and Landers reported that interventions of longer duration resulted in greater decreases in depressive scores [39]. Therefore, further studies are required to examine not only the various effects of exercise on outcomes, but also how best to improve adherence to participation in exercise programs and which types of intervention have the greatest efficacy in hemodialysis patients with depressive symptoms.

Many Cochrane reviews have included cases that analyzed low-quality studies. The analysis of the present study ultimately included five studies with high inconsistency, imprecision, and high risk for bias. Implication for practice, we rated the quality of the body of evidence concerning the effects of exercise on depressive symptoms as low. However, this study helped to confirm that further investigation is necessary, as it clarified that the evidence is poor. It will be important for future studies to calculate sample size according to optimal information size and to report the risk of bias with regard to random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other sources of bias. Finally, we would suggest that many additional studies are required to examine different variables such as exercise mode, exercise duration, and type of exercise intervention.

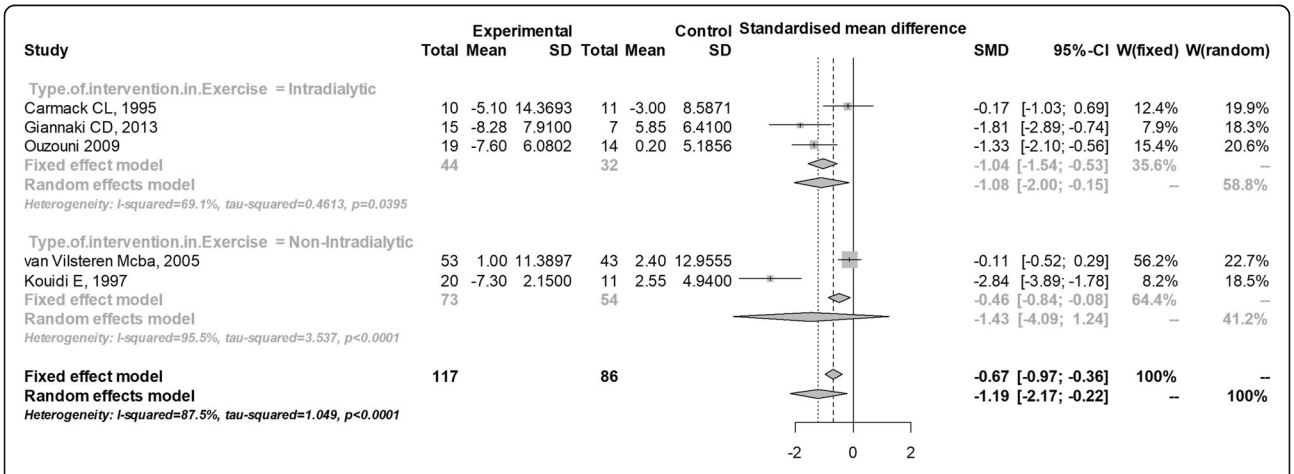

Fig. 5 Subgroup analysis of type of exercise intervention

Table 2 Summary of risk of bias assessment

Studies	Cochrane Collaboration tool							TESTEX		
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Total score (15 points)	Study quality score (5 points)	Study reporting score (10 points)
Carmack et al. [26]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	6	2	4
Giannaki et al. [27]	Unclear	Unclear	High bias	Unclear	Low bias	Low bias	Unclear	7	2	5
van Vilsteren et al. [28]	Unclear	Unclear	Unclear	Unclear	High bias	Unclear	Low bias	8	1	7
Kouidi et al. [29]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	8	2	6
Ouzouni et al. [30]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	8	2	6

This study had a number of limitations due to the original studies and the paucity of data. First, the number of eligible studies investigating the associations between exercise and depressive symptoms was small. And we could not assess publish bias. Second, the studies included in the analyses used a number of different methods to evaluate depressive symptoms. Third, the included studies had high degrees of heterogeneity with regard to the exercise interventions (i.e., differences in modality, duration, volume, and intensity). Therefore, additional RCTs are required to establish adequate evidence. Fourth, the studies eligible for the meta-analysis examined the effects only of exercise therapy. Further randomized control trials and meta-analyses are required to evaluate the effects of exercise in hemodialysis patients with high depressive scores in comparison to other treatment modalities, including cognitive-behavioral therapy and antidepressant medication. Bridle et al. suggested that new RCTs should stratify randomization by severity of depression, receipt of antidepressant medications, and/or level of regular exercise [40]. In fact, appropriate antidepressant treatment may be necessary in chronic hemodialysis patients [41, 42].

Conclusions

The meta-analysis found that supervised exercise training tends to alleviate depressive symptoms in hemodialysis patients. As our database search identified only a small number of studies on the association between exercise and depressive symptoms, we would surmise that additional high-quality studies are required to explore further this association.

Additional files

Additional file 1: PRISMA 2009 Checklist. (DOC 69 kb)

Additional file 2: Search strategy. (DOCX 24.3 kb)

Abbreviations

CI: Confidence interval; DOPPS: Dialysis Outcomes and Practice Patterns Study; ES: Effect size; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; PRO: Patient-reported outcome; QOL: Quality of life; RCTs: Randomized controlled trials; SDs: Standard deviations; SMD: Standardized mean difference; TESTEX: Tool for the assEssment of Study qualiTy and reporting in EXercise

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Availability of data and materials

We decided not to share the data in our study because all data are thoroughly described and reflected in the accompanying tables and figures (all relevant data are within the paper).

Authors' contributions

TS, RM, KH, and AM contributed to the research idea and study design; TS, RM, KY, MH, and TW contributed to the data acquisition; RM, MH, and TW contributed to the quality assessment of a risk of bias; TS, RM, KH, and AM contributed to the data analysis/interpretation; TS, RM, and KH contributed to the statistical analysis; AM contributed to the supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision. All authors read an approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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