Exercise interventions for improving objective physical function in patients with end-stage kidney disease on dialysis: a systematic review and meta-analysis

Exercise Interventions for Improving Objective Physical Function in End-Stage Kidney Disease Patients on Dialysis: A Systematic Review and Meta-Analysis

Abbreviated Title/Running Head: Exercise and Physical Function in Dialysis Patients

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Abstract

Background: Patients with end stage kidney disease on dialysis have increased mortality and reduced physical activity contributing to impaired physical function. While exercise programmes have demonstrated a positive effect on physiological outcomes such as cardiovascular function and strength, there is a reduced focus on physical function. The aim of this review was to determine whether exercise programmes improve objective measures of physical function indicative of activities of daily living for end stage kidney disease patients on dialysis.

Methods: A systematic search of Medline, Embase, the Cochrane Central Register of Controlled Trials, and CINAHL, identified 27 randomised control trials. Only randomised control trials utilising an exercise intervention or significant muscular activation in the intervention, a usual care, non-exercising control group, and at least one objective measure of physical function was included. Participants were ≥18 years of age, with end stage kidney disease, undergoing haemo- or peritoneal dialysis. Systematic review of the literature and quality assessment of the included studies used the Cochrane Collaboration's tool for assessing risk bias. A meta-analysis was completed for the six-minute walk test.

Results: Data from 27 studies with 1156 participants showed exercise, regardless of modality, generally increased six-minute walk test distance, sit-to-stand time or repetitions, grip strength, as well as step and stair climb times or repetitions, dynamic mobility, and short physical performance battery scores.

Conclusion: From the evidence available, exercise, regardless of modality, improved objective measures of physical function for end stage kidney disease patients undergoing dialysis. It is acknowledged that further well-designed RCTs are required.

Keywords: Dialysis, End-stage Kidney Disease, Intradialytic Exercise, Physical Function, Systematic Review

1. Introduction

End-stage kidney disease (ESKD) is near or complete and permanent kidney failure requiring renal replacement therapy (RRT) via dialysis or transplantation to account for kidney function that is inadequate to sustain life (71). The prevalence of ESKD is proportional to the escalating worldwide epidemic of lifestyle-related diseases such as type 2 diabetes and hypertension (28). Combined with an ageing population in many countries and approximately 1 in 8 people developing chronic kidney disease (CKD), of which 10% progress to ESKD, the result is almost double the already large number of patients requiring RRT over the last decade, with approximately 53% of these receiving haemodialysis (HD) (1, 44, 83).

Among HD patients there is a strong link between the increase in mortality and the low levels of both objective and self-reported physical function (65). This is exacerbated by HD patients being significantly more sedentary than otherwise healthy inactive populations (38). In fact, HD patients classified as sedentary are more than 60% more likely to die each year compared with HD patients who are regularly physically active (63). While survival rates are slowly improving among HD patients, this is resulting in greater numbers of frail older adults on HD, and so frailty is also a well-established predictor of both disability and mortality among HD patients (56).

It is commonly suggested that aerobic exercise among HD patients improves exercise capacity measured by peak oxygen consumption ($\dot{V}O_2$ peak) (79). However, it has been previously highlighted that many of the studies that have measured $\dot{V}O_2$ peak have done so on more physically active patients with higher levels of physical function (65). By contrast, muscular strength may also be improved when progressive resistance training is incorporated into an exercise program for HD patients (11). Patient reported physical function as measured by the SF-36 quality of life questionnaire may also improve following exercise training for HD patients (79), although there is have been mixed outcomes regarding the SF-36, with a recent review with a primary focus on intradialytic exercise suggested that improvements on the SF-36 may not be as noteworthy as previously reported (91). However, given the strong relationship between physical function and outcomes for HD patients such as mortality, it is surprising that objective measures of physical function are used infrequently. The six-minute walk test

(6MWT) is the most common measure of physical function used by studies of exercise within HD patients, and while the 6MWT is a predictor of all-cause mortality and is also associated with cardiorespiratory fitness and endurance, it does not incorporate other domains of physical function such as strength, balance, or functional joint mobility (3, 70, 72). Additionally, the efficacy of exercise for dialysis patients may also vary between delivery of intradialytic compared with interdialytic exercise (46).

Recent reviews on exercise for physical function among CKD patients have lacked a focus on objectively measured physical function among HD patients. The majority of reviews over the last 10 years where physical function was an outcome have either not followed a systematic review process (2, 8, 25, 26, 34, 36, 37, 40, 47, 59, 61, 67, 68, 82, 86, 87), have included the full spectrum of CKD where level of physical function varies significantly (2, 4, 24, 25, 29, 30, 33, 34, 40, 47-49, 61, 64, 67, 75, 86), have only included a specific modality of exercise such as aerobic or resistance exercise (7, 11, 75, 91), have specifically focussed on solely intradialytic exercise (91), or have included studies that are not randomised controlled trials or controlled trials using matched controls (5, 10, 11, 39, 49, 51, 64). Of the reviews that did meet these criteria, many are now dated, reviewing studies from before 2000, and thus do not include a number of contemporary training studies exploring exercise among patients on dialysis. Therefore, the purpose of this review was to systematically explore high quality examples of research using different modalities of exercise performed both intradialytically and interdialytically to determine if exercise improves objective measures of physical function among HD patients (ESKD; stage 5 CKD), with a focus on contemporary training studies.

2. Methods

2.1 Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.2 Search Strategy

The electronic database search included MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and CINAHL. Search strategy utilised the following search strings in separate fields: [(kidney disease) OR (renal failure)] AND [(dialysis) OR (haemodialysis) OR (hemodialysis)] AND [(exercise) OR (training)] AND [(function**) OR (performance)]. References were also identified in the reference lists of previous systematic reviews in addition to the results of our electronic database search. Studies in this review were restricted to those conducted from the year 2000 onwards to highlight contemporary exercise interventions among dialysis patients (see 'Participants, Interventions, Comparators' below).

2.3 Participants, Interventions, Comparators

Database search results were imported into Endnote X8 (Thompson Reuters, Philadelphia, Pennsylvania, USA). Duplicates were removed, and screening was completed by title, abstract, and full text. Excluded articles were sorted into individual folders indicating the reason for exclusion until only articles for inclusion remained. This process was completed by two researchers independently. The relevant inclusion criteria are identified below and reasons for exclusions noted in the PRISMA flow chart (Figure 1):

1. Language: only studies published in English were included in this review.
2. Participants: patients aged at least 18 years of age with stage 5 chronic kidney disease (ESKD) undergoing either haemodialysis or peritoneal dialysis were included. Patients who had received kidney transplant or were affected by acute kidney failure or injury were excluded.

3. Study Design: only studies that employed a randomised control trial (RCT) design were included. Systematic reviews, narrative reviews, conference abstracts, editorials, letters or publications not-inclusive of original data were excluded.
4. Intervention: studies must have included an exercise intervention in the form of aerobic, resistance, combined, or alternative types of progressive exercise or significant muscular activation in the primary intervention group or groups.
5. Controls: control groups in these studies must have been usual care, non-exercising patients or undergoing only range of motion or passive exercises.
6. Outcomes: must have included at least one objective measure of physical function indicative of activities of daily living (ADL). Subjective measures associated with physical function (questionnaires or surveys) were excluded.

Examples of objective measures of physical function indicative of ADL include the 6MWT, variations of the sit-to-stand test, balance tests, or grip strength tests which have similarities in their execution to everyday activities. Measures excluded from this review include laboratory tests such as maximal strength testing, or graded exercise testing utilising measures of oxygen utilisation, ventilatory or lactate threshold, as these are not reflective of ADL.

2.4 Assessment of Risk Bias

The risk of bias of included studies was independently evaluated by two independent reviewers (MJC, PNB) using the Cochrane Collaboration's tool for assessing risk bias (32). The overall quality assessment of the RCTs included analysis of both selection bias, detection bias, and attrition bias. Selection bias was examined through method of recruitment, protocol for randomisation, concealment of treatment allocation, and similarity of groups' baseline characteristics. Detection bias included blinding of assessors to intervention groups and possible blinding of participants. Attrition bias explored level of adherence of participants, completeness of follow up, and reported reasons for attrition.

Contention between quality assessments was resolved through follow up consultation between reviewers. Each component of the bias assessment was assigned a rating of high, low, or unclear risk of bias, sufficient enough to notably impact results or the conclusions of the trial.

2.5 Data Extraction

Initial screening of information was based on titles and abstracts, and subsequent screening used the full text of identified articles. Information from identified studies that was extracted included basic study characteristics, mean participant age, dialysis vintage, dialysis type, sample size, intervention modality, duration and location, and measures of objective physical function.

2.6 Statistical Analysis

Sufficient data for a robust meta-analysis was only available for the 6MWT, although one study was excluded from the meta-analysis as data was unable to be obtained or estimated (52). All outcomes from the 6MWT were treated as continuous data. The absolute net differences for the change in mean distance walked on the 6MWT between intervention and control groups was used to combine study effect estimates (ES) in the meta-analysis. Outcomes of the 6MWT were analysed using a random-effects meta-analysis due to the variability in the samples and interventions used (31). Heterogeneity was assessed statistically using the I^2 statistic. Studies with an I^2 of less than 40% were considered to have low heterogeneity (32). Subgroup analyses were conducted by exercise modality, and by timing of delivery (interdialytic compared with intradialytic). A funnel plot was used to examine potential publication bias of the included studies for the 6MWT.

3. Results

3.1 Literature Search

We retrieved 1615 articles in searches between January 2000 to 16th January 2019 from MEDLINE (215), Embase (1186), the Cochrane Central Register of Controlled Trials (160), and CINAHL (54). Duplicates were removed to refine the number of articles for screening down to 1313. Of these 1313 articles screened for eligibility, 848 were excluded based on title or abstract. The full texts of the remaining 465 were evaluated based on the inclusion criteria for this review, of which 23 fulfilled the criteria and were included in the current review. An additional 4 studies were identified from the reference lists of the included studies and were added to the analyses for a total of 27 included studies.

3.2 Study Selection and Characteristics

Table 1 summarises the studies included in this review based on sample size, mode and duration of intervention, outcome measures, and main findings. The 27 studies included a total of 1156 participants. Individual studies generally included small sample sizes, with only four studies examining more than the mean number of participants for all studies included in this review (46 participants) (13, 53, 85, 90). Sample sizes ranged from n = 16 (23, 35) to n = 227 (53) inclusive of both intervention and control groups. Only one study used healthy participants as a comparison in addition to the control group required for inclusion in this review (18). One study included two additional groups besides the exercise intervention and non-exercising control that examined the addition of nandrolone decanoate to each condition, for the purpose of the present review the nandrolone decanoate was deemed an extraneous variable, and these two groups were excluded from the review (42). Most interventions ranged from 8 weeks to 26 weeks with none lasting longer than six months in duration. While most studies examined the effects of traditional aerobic or resistance exercise interventions, or a combination of the two, three studies utilised neuromuscular electrical stimulation (20, 74, 77), two studies utilised respiratory muscle training using resistance training principles (60, 69), one study employed whole body vibration training (23), and one study employed Yoga as an exercise intervention (92). Similarly, eight of the included studies included an exercise intervention that was performed interdialytically (23, 45, 53, 60, 76, 81, 89, 92), while the remaining exercise interventions were performed intradialytically. Twenty-one of the 27 included studies were published during or after 2010 (Table 1).

3.3 Risk of Bias Assessment

Risk of bias was summarised for all included studies (Figure 2). Nineteen studies were rated as low to moderate risk of bias, primarily due to insufficient blinding procedures leading to possible detection bias. The remaining eight studies were rated as moderate to high risk of bias predominately due to insufficient reporting (20, 22, 27, 35, 52, 69, 85, 89).

3.3.1 Selection bias

As it was a requirement of the review that included studies be randomised control trials, most studies had adequate randomisation or participant allocation (13, 14, 16, 18, 23, 42, 45, 50, 55, 60, 62, 74, 76, 77, 81, 84, 90, 92). Concealment of the randomisation method was only described in 18 of the included studies (13, 14, 16, 18, 23, 42, 45, 50, 53, 55, 60, 62, 74, 76, 77, 81, 84, 92). One study allocated participants to intervention or control group by dialysis shift, which appeared to provide a random representation of the whole sample as there was no significant difference in baseline characteristics between groups (22).

3.3.2 Detection bias

The blinding process of participants, nurses, or other health professionals was adequately described in only four of the included studies (18, 23, 42, 60). In total, only eight studies used blinded assessors for the outcome assessment (13, 18, 23, 60, 62, 84, 89, 92).

3.3.3 Attrition bias

Most of the 27 studies adequately reported attrition of participants. However, in one study this reduced the size and power of the intervention group compared with control (55). In another of these studies all attrition (approximately 7%) was solely from the intervention group, of which 5 were for reasons relating to the intervention (85). Ten of the 27 included studies reported compliance as a percentage of the total exercise sessions possible (13, 14, 35, 42, 45, 53, 62, 76, 81, 84). Compliance ranged from 71% (45) to 93% (76). Only six of the studies identified the intention-to-treat principle when conducting their analysis (13, 18, 23, 53, 60, 84).

3.3.4 Reporting Bias

One study only presented the mean and variance of the change in measures of physical function from before to after the intervention, and did not report the means and variance for both before and after the intervention (84). One study reported baseline means and standard deviations but only the change data and not post-intervention means and standard deviations (13). Two studies presented data on their single measure of physical function as a figure but did not state the mean or standard deviation for either group at baseline or after the intervention (52, 89).

3.3.5 Other sources of Bias

Sample size calculations were presented in only ten of the included studies (13, 18, 23, 42, 45, 55, 60, 74, 77, 81). This makes interpretation of the findings for the remainder of studies difficult, especially with varying levels of attrition and multiple studies noting the limitation of having small sample sizes. The funnel plot included with the meta-analysis (Figure 3) indicated the existence of some publication bias as the minor asymmetry appears to be due to the impact of smaller studies (35, 84), one identified as a higher risk of bias (22), and one with a markedly different modality of exercise compared with other included studies (76).

3.4 Modality and Duration of Interventions

The primary modality of intervention was aerobic exercise for at least one intervention group in twelve studies, usually as cycling performed intradialytically, with main sets ranging from 10 to 45 min duration per session (16, 20, 27, 35, 45, 50, 52, 53, 76, 84, 89, 90). The intensities of these aerobic sessions were primarily measured by rating of perceived exertion (RPE) at an equivalent of 9-17 RPE on a 6-20 Borg scale (9, 15, 16, 35, 45, 52, 76, 84, 89, 90). Two studies used an intensity equivalent to 60% of peak power from a baseline cardiorespiratory fitness test (20, 27). One study used 90% of ventilatory threshold (50). One home-based study utilised an intermittent walking protocol, progressing over the training program towards continuous walking, totalling to 10 minutes, twice per day at a speed dictated by their performance on the 6MWT during pre-testing (53). One study utilised 20 to 40 min duration swimming sessions as the aerobic exercise modality (76).

Resistance training was the primary intervention modality for at least one intervention group in nine of the included studies, predominately lower limb exercises using low-to-moderate loads for 1 to 3 sets of 8 to 15 repetitions (13, 14, 16, 22, 42, 55, 69, 81, 84). Intensity or load used by participants in these studies was often evaluated by RPE which ranged from 9 to 17 on a 6-20 Borg scale (9, 13-16, 81), or by a percentage of either a 1-repetition maximum (69) or a 3-repetition maximum strength test (42).

A combination of aerobic and resistance exercise was used as a single intervention in four of the included studies, combining the same parameters as the individual aerobic and resistance interventions (18, 62, 84, 85). Neuromuscular electrical stimulation was utilised in three studies for between 20 and 60 min, with a pulse width ranging from 200 to 400 ms, at 10 to 80 Hz applied over 2 to 20 s, followed by 10 to 50 s rest (20, 74, 77). Respiratory training was used in a second intervention group utilising the same resistance training variables as their resistance training intervention group: 3 sets of 15 repetitions at 50% maximal effort (maximal inspiratory pressure) (69). Another study utilised respiratory training twice per day as 3 sets of 30 repetitions inhalation at 50% maximum inspiratory power (60). One study used 30 min of Yoga and relaxation exercise as their primary intervention (92). Finally, one study used whole body vibration training involving 10 to 20 minutes (as 1 minute active and 30 second rest cycles) whereby a static semi-squat position was held during active periods under vibration at 35 Hz and an amplitude of 2 to 4 mm (23).

3.5 Outcome Measures

Six-minute walk test: of the 27 included studies, 18 assessed the 6MWT (13, 18, 20, 22, 23, 27, 35, 45, 52, 53, 55, 60, 69, 74, 76, 77, 84, 90). Eight of these studies examined only an aerobic intervention (18, 27, 35, 45, 52, 53, 76, 90), three utilised a resistance training intervention only (13, 22, 55), two studies used only electromyostimulation to increase muscle activity (74, 77), two studies examined more than one of the previously stated intervention types and/or a combination of them (20, 84), one study consisted of both a resistance training group and a respiratory muscle training group (69), one study primarily used a respiratory training group (60), and one study consisted of a whole body vibration training group (23). A statistically and clinically significant increase in 6MWT distance was observed for the intervention groups in eleven of these studies (20, 22, 27, 35, 52, 53, 55, 69, 70, 74, 76, 90) with a mean increase of 51.2 ± 111.6 m (7 - 26% increase). Of the eleven studies demonstrating statistically significant increases in their intervention groups, there were seven aerobic exercise groups (20, 27, 35, 52, 53, 76, 90), three resistance training groups (22, 55, 69), two electromyostimulation groups (20, 74), and one group using respiratory muscle training (69). While most control groups displayed no significant change in 6MWT distance from baseline to post-testing, a statistically significant decrease was observed in the control groups of two of the 16 studies assessing 6MWT, with a mean decrease of 39.9 ± 147.2 m (10 - 11% decrease) (22, 76).

The results of the meta-analysis for the 6MWT indicate that overall exercise, regardless of modality and timing of delivery, improves distance walked on the 6MWT among patients with ESKD (ES = 33.64 m, 95% CI [23.74, 43.54], $P < 0.001$; P for heterogeneity = 0.64, and $I^2 = 0\%$) (Figure 4a). A subgroup analysis for exercise modality was performed for resistance, aerobic, combined aerobic and resistance, respiratory and electromyostimulation (Figure 4b). Aerobic exercise interventions (ES = 47.80 m, 95% CI [31.74, 63.87], $P < 0.001$; P for heterogeneity = 0.42 and $I^2 = 1.9\%$), resistance exercise interventions (ES = 23.62 m, 95% CI [6.45, 40.79], $P = 0.007$; P for heterogeneity = 0.79, and $I^2 = 0\%$) and respiratory exercise interventions (ES = 22.82 m, 95% CI [0.39, 45.26], $P = 0.046$; P for heterogeneity = 0.36, and $I^2 = 0\%$) were the only interventions to elicit significant improvements in distance walked on the 6MWT. A subgroup analysis was also performed for the timing of exercise delivery for interventions between interdialytic and intradialytic exercise sessions (Figure 4c). Both interdialytic (ES = 29.88 m, 95% CI [11.31, 48.45], $P = 0.002$; P for heterogeneity = 0.36, and $I^2 = 8.3\%$) and intradialytic (ES = 36.11 m, 95% CI [23.82, 48.40], $P < 0.001$; P for heterogeneity = 0.64, and $I^2 = 0\%$) exercise interventions improved distance walked on the 6MWT, although this appeared to be slightly in favour of intradialytic exercise.

Sit to stand tests: eleven studies assessed at least one version of a sit-to-stand test (22, 42, 50, 53, 55, 62, 76, 77, 84, 85, 90). Intervention groups in these studies included aerobic exercise (50, 53, 76, 84, 90), resistance training (22, 42, 55, 84), a combination of both aerobic and resistance exercise (62, 84, 85), or electromyostimulation (77). The types of sit to stand test administered varied between the 5-times sit to stand (42, 50, 53), 10-times sit to stand (22, 62, 76, 85, 90), Max-repetition sit to stand (55), 30-second sit to stand (77, 84), and the 60-second sit to stand (50, 90). Only two studies did not produce a significant improvement in sit to stand performance in their intervention groups (42, 84), while the other studies showed improvements between 6% and 70%, with a median improvement of 15%. Conversely, only one study reported a significant reduction in sit to stand performance in their control group (16%) (22), while there was no significant change in performance seen in the other control groups.

Grip Strength: six studies with interventions consisting of aerobic exercise (45, 76, 92), resistance exercise (22, 81), or Yoga (92) assessed grip strength. Four studies reported a significant increase in the grip strength of participants in their intervention group compared to controls (22, 76, 90, 92). Of these four studies, three measured grip strength in kilograms, with intervention groups significantly improving by 3.6 ± 13.0 kg (8 - 17% increase), while the one study measuring grip strength in mmHg reported a 22.3 ± 46.4 mmHg, or 14.9% improvement in the Yoga intervention group (92). Of the two studies that did not report a significant improvement in grip strength, one utilised only lower limb aerobic exercise either on or off dialysis as an intervention (45), and the other used moderate intensity resistance exercise using elastic bands and sand bags (81).

Timed up and go: two of the included studies measured timed up and go (TUG) performance following aerobic interventions (45, 76). Only Samara et al. found a significant improvement in TUG performance following 16 weeks of swimming, with time to completion decreasing by 0.9 ± 1.4 s compared with no significant change in time to completion for the control group (76). Koh et al. found no significant difference in TUG performance for either home-based or HD unit based aerobic exercise groups or controls (45).

Step and stair climb tests: step tests were examined in four of the included studies (16, 42, 62, 90). However, no two studies examined the same step test. One study demonstrated significant increases in the number of step ups achieved in 4 minutes compared with controls, for both resistance training (69 ± 25 to 131 ± 31 steps) and aerobic exercise training (86 ± 36 to 142 ± 32 steps) interventions (16). Wu et al. also found improved stair climbing performance following 12 weeks of aerobic exercise with a reduction in the time taken to climb 22 steps (total height 3.3 m) decreasing from 29.1 ± 7.2 s to 27.3 ± 7.3 s, while there was no change in the performance of the control group (90). Neither of the other two studies measuring stepping or stair climb performance showed a significant improvement in performance or a difference from the control groups (42, 62).

Balance tests: of the three studies that explored the effect of exercise intervention on balance performance among dialysis patients (23, 35, 81), none found a significant improvement in balance performance following intervention. However, Hristea et al. reported a decrease in balance performance, measured as centre of pressure on a force plate in millimetres squared, in the non-exercising control group, which was significantly worse than the level of balance maintained by the intervention group (35). Song et al. found no difference in the duration of single leg balancing with eyes closed for either the intervention or control groups (81), and Fuzari et al. found no significant difference in measures of either static or dynamic balance (23).

Sit and Reach: Two studies reported functional hamstring flexibility as measured by the sit and reach test (76, 81). Samara et al. demonstrated a significant improvement in sit and reach performance of 5.3 ± 8.8 cm following 16 weeks swimming compared with a significantly decreased performance of 3.2 ± 12.4 cm from the control group (76). However, Song et al. reported no change in sit and reach performance following 12 weeks of moderate intensity resistance exercise compared with controls (81).

Short Physical Performance Battery: two studies examined the Short Physical Performance Battery (SPPB) (14, 84). Both studies found that exercise intervention significantly improved SPPB scores regardless of modality (Aerobic, Resistance, or a combination of both) (14, 84), while control groups showed no change in SPPB scores in either study. Chen et al. showed the largest improvement of 2.0 ± 6.4 in SPPB score following 24 weeks of a whole-body resistance exercise program (14).

Incremental Shuttle Walk Test: Wilund et al. was the only study to examine the Incremental Shuttle Walk Test (ISWT) (89). Following 16 weeks of intradialytic aerobic exercise, the intervention group improved their distance walked during the ISWT by 45 ± 16 m, compared with no change in the control group (89).

Other measures of physical function: Additional measures of physical function were reported by three studies (42, 50, 81). These included the North Staffordshire Royal Infirmary (NSRI) walk test (50), a 20 ft gait speed assessment (42), and a shoulder mobility assessment (81). Koufaki et al. reported no significant improvement in the NSRI walk test following 12 weeks of aerobic exercise (50). Johansen et al. showed no significant increase in gait speed following 12 weeks resistance training (42). Song et al. showed no significant increase in shoulder mobility following 12 weeks resistance training (81).

3.6 Intradialytic compared with Interdialytic exercise

The majority of the intervention groups among the included studies underwent intradialytic exercise. Of 33 intervention groups that completed exercise, 8 performed interdialytic exercise outside the dialysis unit (23, 45, 53, 60, 76, 81, 89, 92), while the remaining 25 completed intradialytic exercise during their regular dialysis sessions. Overall, intervention groups improved objectively measured physical function following exercise training on 57% of measurements. However, when examining these as intradialytic and interdialytic exercise, interdialytic intervention groups increased physical function on 47% of measurements, compared with 61% of measurements for intradialytic exercise groups.

For the most consistently used measure of physical function, the 6MWT, there were five interdialytic intervention groups (23, 45, 53, 60, 76), and only two (40%) elicited a significant increase in distance walked (by ~12% each) (53, 76). Conversely, there were 18 intradialytic intervention groups who underwent the 6MWT (13, 18, 20, 22, 27, 35, 45, 52, 55, 69, 74, 77, 84, 90), 11 of which (61%) elicited a significant increase in distance walked (by 7-26%) (20, 22, 27, 35, 52, 55, 69, 74, 90). As detailed in section 3.5, meta-analysis comparing interdialytic and intradialytic interventions for the 6MWT appeared to slightly favour intradialytic exercise for improving distance walked on the 6MWT. The only other measure of physical function for which a comparison between interdialytic and intradialytic exercise can be made was grip strength. Among the included studies, there were four interdialytic intervention groups (45, 76, 81, 92) and three intradialytic exercise groups examining grip strength (22, 45, 90). Two of the four interdialytic (76, 92), and two of the three intradialytic exercise groups (22, 90) elicited a significant increase in grip strength following exercise intervention.

4. Discussion

This systematic review consistently demonstrated that both aerobic and resistance exercise as well as similar means of muscular activation such as electromyostimulation and respiratory exercise had beneficial effects on objectively measured physical function indicative of activities of daily living (ADL) in ESKD patients on dialysis. Subsequent meta-analyses further supported the efficacy of exercise specifically for improving performance on the 6MWT. This is important for patients with ESKD, as there is a markedly higher prevalence of ADL disability (an inability to perform at least one key domain of everyday activities) among patients with ESKD when compared with community dwelling older adults (57). This is notable as ADL disability has been shown to be independently associated with a greater than three-fold increase in mortality for patients with ESKD of all ages (57). However, despite the notable association of physical function with mortality for patients with ESKD, physical function is not commonly assessed among these patients (67). Further, despite physical activity being strongly associated with improvements in physical function, exercise is not a component of the routine management of patients with ESKD on dialysis (66).

Interestingly, measures of physical function that are more commonly associated with a specific physiological response, such as sit-to-stand tests with muscular strength or the 6MWT with aerobic capacity, also improved with exercise intervention modalities not traditionally associated with those physiological responses (21, 43, 58, 73). For example, of the thirteen intervention groups showing significant improvement in distance walked during the 6MWT compared with controls, three used resistance training interventions (22, 55, 69), two used electromyostimulation (20, 74), and one used only respiratory muscle training (69). Furthermore, the meta-analysis in the present review indicated that resistance and respiratory interventions improved distance walked during the 6MWT similar to aerobic based exercise interventions. In studies measuring shorter duration sit-to-stand tests more closely associated with lower limb strength, intervention groups showing significant improvement included four aerobic exercise interventions (50, 53, 76, 90) and one electromyostimulation group (77). This was also true for the intervention groups for which grip strength improved compared with controls, which included two aerobic exercise interventions (76, 90), and one yoga intervention (92).

Comparing interdialytic exercise with intradialytic exercise in the present review suggested not only was intradialytic exercise more commonly employed, but it demonstrated more frequent improvements in measures of physical function. This was evident with intradialytic exercise increasing physical function for 61% of measurements compared with 47% for interdialytic exercise. Distance walked on the 6MWT may have been the best indicator for this, as it significantly increased for 40% compared with 61% of measurements for interdialytic versus intradialytic exercise, respectively. Additionally, for the 6MWT the magnitude of the increases in distance walked appear to be larger for intradialytic (up to 26%) compared with interdialytic interventions (12%), although a greater number of interdialytic exercise interventions would be required to validate this comparison. Indeed, this was supported by the meta-analyses included with the present review, whereby the increase in distance walked during the 6MWT following exercise intervention was approximately 21% greater following intradialytic exercise interventions compared with interdialytic exercise interventions (increasing by 36.11 ± 6.21 m, and 29.88 ± 9.38 m, respectively). This may be influenced by known issues with reduced compliance for interdialytic exercise programs (19), although this is difficult to determine in the present review, with only ten of the included studies reporting compliance.

Collectively, this review indicates that exercise regardless of modality is beneficial for improving physical function among dialysis patients, it also suggests that physical function is a multi-faceted domain that may require multi-modal exercise to attain the greatest benefit. This aligns with the broad exercise recommendations for patients with ESKD, which recommend a combination of aerobic, resistance and flexibility exercises for up to 540 minutes per week, including exercise during and outside of dialysis (80).

The results of this systematic review support the effectiveness of exercise for improving physical function, yet it remains an ongoing concern that clinical pathways for the delivery of physical therapy are largely non-existent (6). This was underscored by a recent editorial published in the *British Journal of Sports Medicine (BJSM)*, calling for clinicians to adopt exercise programmes into standard practice for patients undergoing dialysis (19). The editorial further elucidated that improvements in physical function among patients undergoing dialysis contribute to the prevention of some clinical and functional disabilities, reduces hospitalisations and mortality, and increases patient transplant eligibility (19). Additionally, the editorial highlights that not only is exercise during dialysis feasible regardless of age, it also displays notably higher compliance compared with exercise programmed outside of dialysis (19).

A Cochrane review and subsequent update by Heiwe and Jacobsen (29, 30) also found improvements in physical function as well as other measures such as aerobic capacity and muscular strength in patients across the full spectrum of chronic kidney disease following various exercise interventions. The findings of our review support these findings for physical function, specifically for ESKD patients on dialysis. However, one limitation for both reviews, is the lack of consistency in the measures of physical function used by the included studies. While the 6MWT was employed by 16 of the 27 (64%) studies included in the present review (13, 18, 20, 22, 27, 35, 45, 52, 53, 55, 69, 74, 76, 77, 84, 90), no other single measure of physical function was used in any more than 6 of the 27 (24%) included studies. Similarly, the inconsistencies in exercise prescription variables for the training components of these studies creates another limitation when trying to determine the effectiveness of specific exercise modalities or the effect of exercise on specific measures of physical function.

A subsequent letter supporting the *BJSM* editorial also highlighted the paucity of high-quality RCTs of adequate power with any consistency in exercise prescription (54). This makes attempts to standardise intradialytic exercise prescription difficult. The studies included in the present review are examples of such high quality RCTs, but the broad prescription used in conjunction with overarching improvements in physical function may suggest that there is no single exercise prescription that is ideal among this population. Indeed, prescribing any exercise that is feasible to conduct during dialysis and can be tolerated by patients with ESKD is likely to provide significant benefit, and should therefore be incorporated into standard practice.

4.1 Limitations of the included studies

While this review included robust, contemporary evidence of the effect of exercise, moderate risk of bias in some studies was still present (Figure 2). Namely, randomisation and concealment, and blinding of participants and personnel were of concern (78). Indeed, many studies were excluded from this review due to having no control group and/or a non-randomised allocation of participants. Even amongst those included in the review, randomisation and concealment was only sufficiently reported in 16 of the 27 included studies (13, 14, 16, 18, 42, 45, 50, 53, 55, 62, 74, 76, 77, 81, 84, 92). Additionally, only 4 studies indicated use of the intention-to-treat principle (13, 18, 53, 84); only 8 included sample size calculations (13, 18, 42, 45, 55, 74, 77, 81); and only 10 reported compliance (13, 14, 35, 42, 45, 53, 62, 76, 81, 84), which is a noted concern for dialysis patients completing exercise programs (46, 88). While only 2 of the included studies adequately addressed blinding of participants, included studies were largely comparing exercise to, in most cases, a non-exercising control making blinding difficult as participants are able to determine when they are active compared to inactive. With regards to meta-analyses, the lack of consistent measures of objective physical function between studies made it difficult to present other meaningful meta-analyses of objective measures of physical function.

4.2 Future directions for research

As there appears to be benefits across multiple modalities of exercise, future research should aim to determine which exercise prescriptions provide the best value for time spent exercising. This is especially relevant due to the previously established reluctance of dialysis patients to commit time to exercising (17). Similarly, direct comparisons of exercise interventions delivered both intradialytically and interdialytically in conjunction with reporting of compliance for each method of delivery may help determine which method of delivery is more effective. Importantly, a continued emphasis should be placed on objective measures of physical function due to its relevance to dialysis patients. This should incorporate a holistic battery of physical function measures as it is apparent from this review that a single modality of exercise may improve physical function indicative of multiple physiological outcomes, which may not be traditionally associated with that exercise modality. Finally, greater measures to account for the notably elevated levels of participant attrition seen among dialysis patients need to be made in future research in order to avoid the commonly reported limitation of studies being underpowered. This may potentially warrant greater allowances for dropout when calculating sample size, increased study recruitment times, or adopting multi-centre approaches to these types of training studies.

4.3 Conclusions

Physical function is a poorly examined and under treated area of patient care among people with ESKD undergoing dialysis. The results of this review indicate that exercise, regardless of modality, is indeed useful for improving physical function as measured by tasks reflective of everyday activities. Additionally, the meta-analysis provides evidence to support the value of intradialytic compared with interdialytic exercise for dialysis populations. However, despite the known impact that poor physical function has on the health outcomes of patients with ESKD undergoing dialysis, there is no established pathway for exercise delivery to these patients. Moderate intensity exercise can be delivered in numerous forms both during and outside of dialysis and this review demonstrates that such moderate intensity exercise improves physical function. However, the absence of clinical implementation of such programs is an area of concern in the overall management of patients undergoing dialysis.

5. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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9. Figure Legends

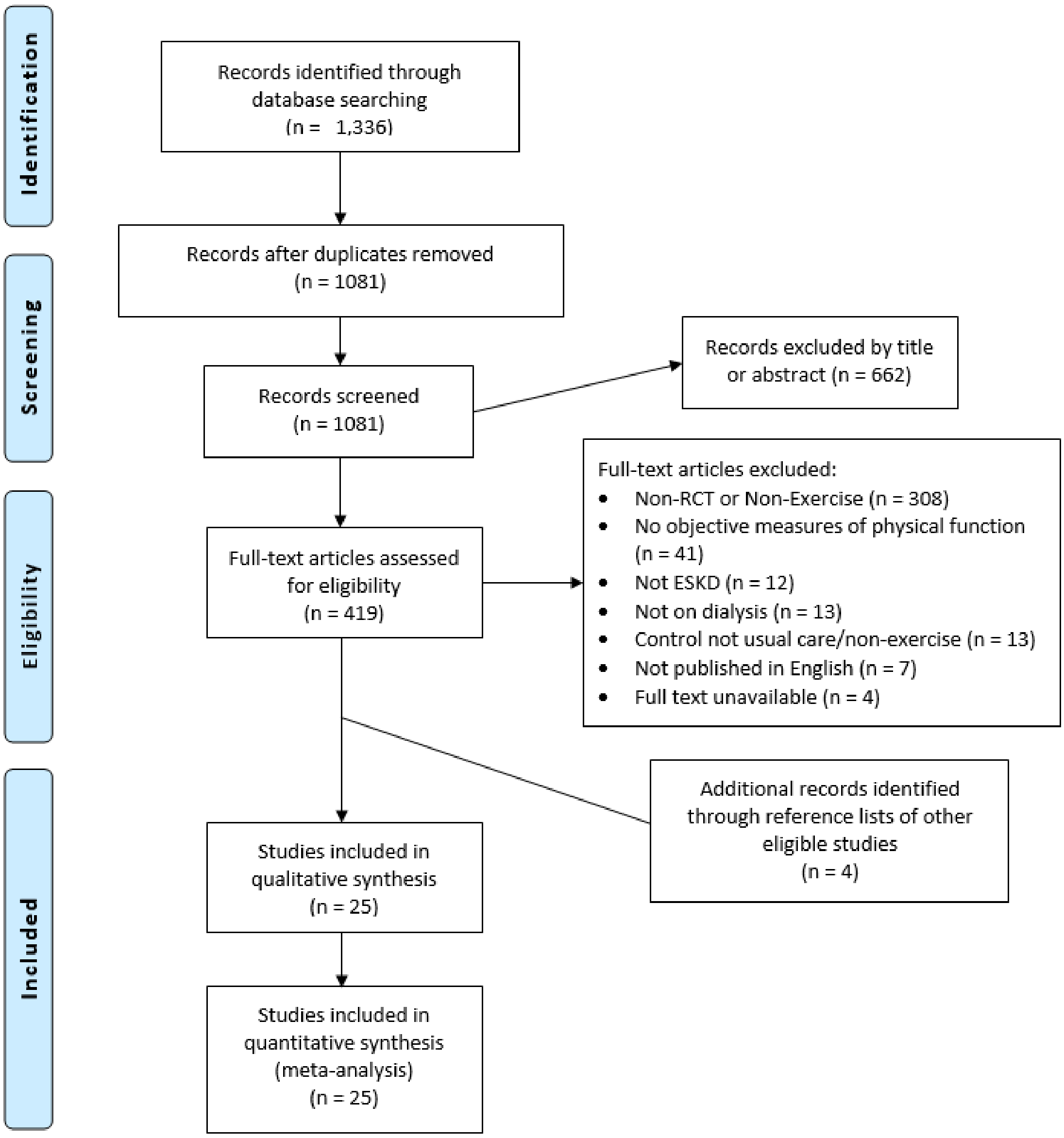


Figure 1. PRISMA flow chart of study selection process.

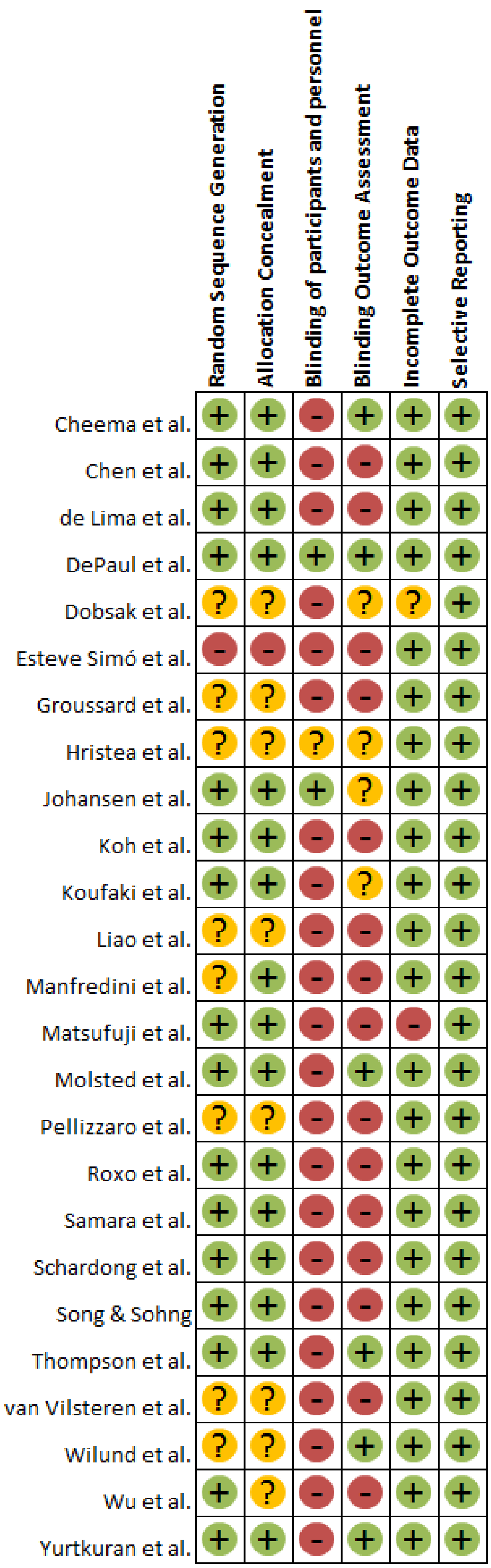


Figure 2. Risk of bias assessment for included studies evaluating changes in objective measures of physical function following exercise intervention among patients with end-stage kidney disease.

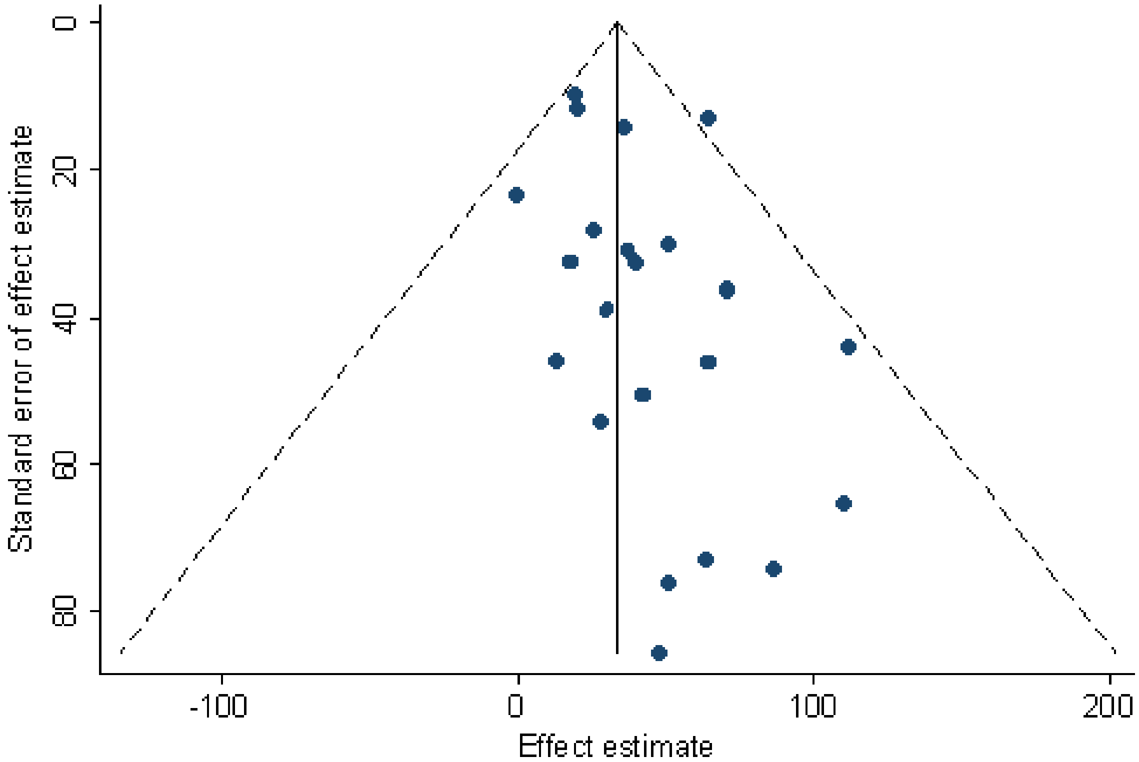
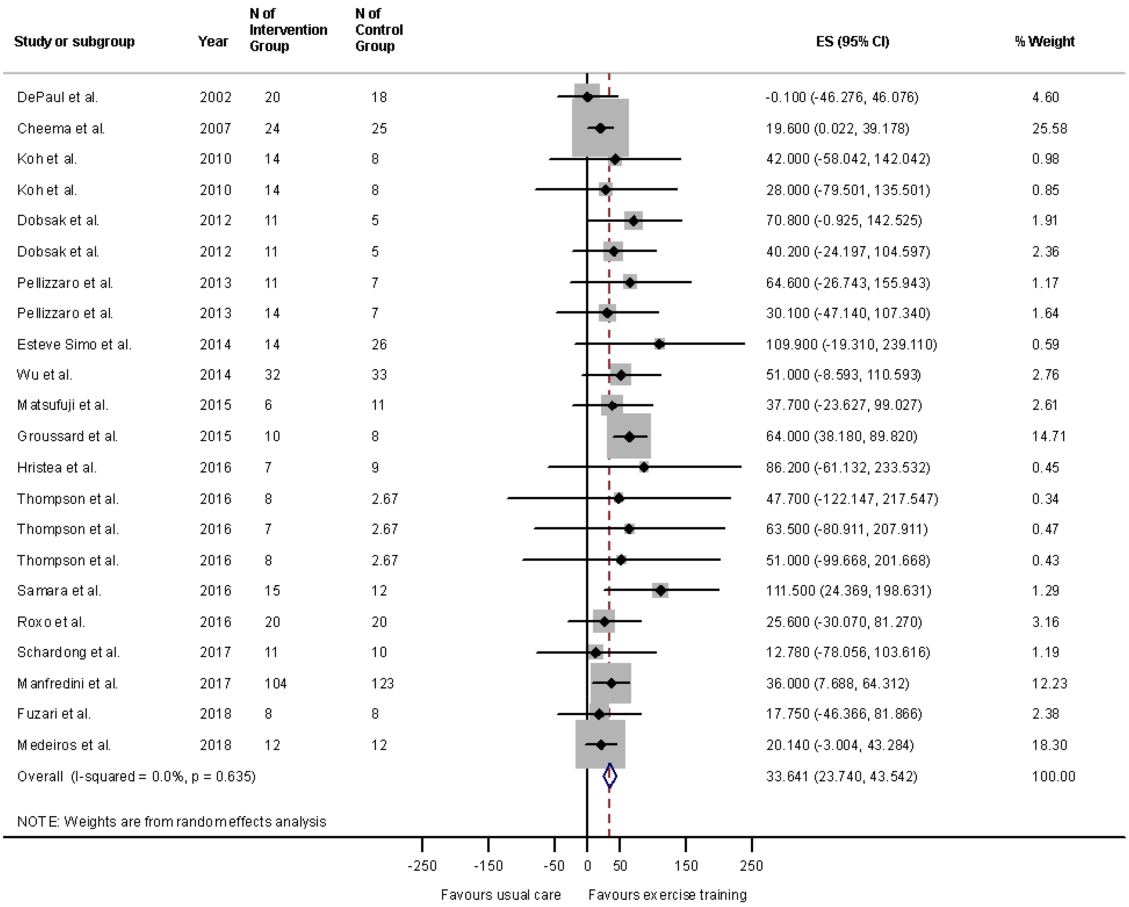
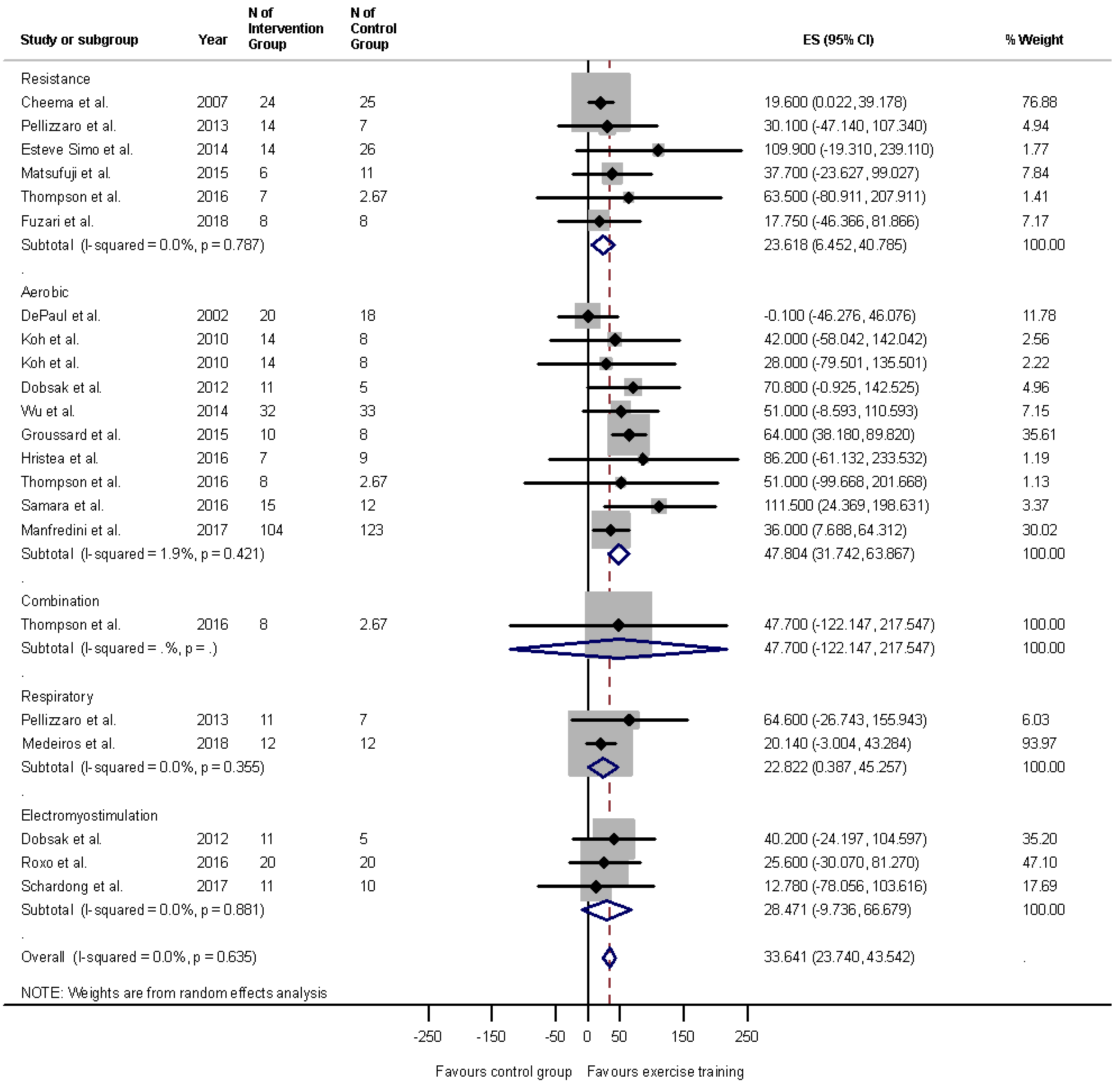


Figure 3. Funnel plot for the effect estimates on distance walked during the six-minute walk test among patients with end-stage kidney disease following exercise intervention compared with usual care controls.

a)


Study or subgroup
Year
N of Intervention Group
N of Control Group
ES (95% CI)
% Weight
DePaul et al. 2002 20 18 -0.100 (-46.276, 46.076) 4.60
Cheema et al. 2007 24 25 19.600 (0.022, 39.178) 25.58
Koh et al. 2010 14 8 42.000 (-58.042, 142.042) 0.98
Koh et al. 2010 14 8 28.000 (-79.501, 135.501) 0.85
Dobsak et al. 2012 11 5 70.800 (-0.925, 142.525) 1.91
Dobsak et al. 2012 11 5 40.200 (-24.197, 104.597) 2.36
Pellizzaro et al. 2013 11 7 64.600 (-26.743, 155.943) 1.17
Pellizzaro et al. 2013 14 7 30.100 (-47.140, 107.340) 1.64
Esteve Simo et al. 2014 14 26 109.900 (-19.310, 239.110) 0.59
Wu et al. 2014 32 33 51.000 (-8.593, 110.593) 2.76
Matsufuji et al. 2015 6 11 37.700 (-23.627, 99.027) 2.61
Groussard et al. 2015 10 8 64.000 (38.180, 89.820) 14.71
Hristea et al. 2016 7 9 86.200 (-61.132, 233.532) 0.45
Thompson et al. 2016 8 2.67 47.700 (-122.147, 217.547) 0.34
Thompson et al. 2016 7 2.67 63.500 (-80.911, 207.911) 0.47
Thompson et al. 2016 8 2.67 51.000 (-99.668, 201.668) 0.43
Samara et al. 2016 15 12 111.500 (24.369, 198.631) 1.29
Roxo et al. 2016 20 20 25.600 (-30.070, 81.270) 3.16
Schardong et al. 2017 11 10 12.780 (-78.056, 103.616) 1.19
Manfredini et al. 2017 104 123 36.000 (7.688, 64.312) 12.23
Fuzari et al. 2018 8 8 17.750 (-46.366, 81.866) 2.38
Medeiros et al. 2018 12 12 20.140 (-3.004, 43.284) 18.30
Overall (I-squared = 0.0%, p = 0.635) 33.641 (23.740, 43.542) 100.00
NOTE: Weights are from random effects analysis
-250 -150 -50 0 50 150 250
Favours usual care
Favours exercise training

b)


Study or subgroup
Year
N of Intervention Group
N of Control Group
ES (95% CI)
% Weight
Resistance
Cheema et al. 2007 24 25 19.600 (0.022, 39.178) 76.88
Pellizzaro et al. 2013 14 7 30.100 (-47.140, 107.340) 4.94
Esteve Simo et al. 2014 14 26 109.900 (-19.310, 239.110) 1.77
Matsufuji et al. 2015 6 11 37.700 (-23.627, 99.027) 7.84
Thompson et al. 2016 7 2.67 63.500 (-80.911, 207.911) 1.41
Fuzari et al. 2018 8 8 17.750 (-46.366, 81.866) 7.17
Subtotal (I-squared = 0.0%, p = 0.787) 23.618 (6.452, 40.785) 100.00
Aerobic
DePaul et al. 2002 20 18 -0.100 (-46.276, 46.076) 11.78
Koh et al. 2010 14 8 42.000 (-58.042, 142.042) 2.56
Koh et al. 2010 14 8 28.000 (-79.501, 135.501) 2.22
Dobsak et al. 2012 11 5 70.800 (-0.925, 142.525) 4.96
Wu et al. 2014 32 33 51.000 (-8.593, 110.593) 7.15
Groussard et al. 2015 10 8 64.000 (38.180, 89.820) 35.61
Hristea et al. 2016 7 9 86.200 (-61.132, 233.532) 1.19
Thompson et al. 2016 8 2.67 51.000 (-99.668, 201.668) 1.13
Samara et al. 2016 15 12 111.500 (24.369, 198.631) 3.37
Manfredini et al. 2017 104 123 36.000 (7.688, 64.312) 30.02
Subtotal (I-squared = 1.9%, p = 0.421) 47.804 (31.742, 63.867) 100.00
Combination
Thompson et al. 2016 8 2.67 47.700 (-122.147, 217.547) 100.00
Subtotal (I-squared = .%, p = .) 47.700 (-122.147, 217.547) 100.00
Respiratory
Pellizzaro et al. 2013 11 7 64.600 (-26.743, 155.943) 6.03
Medeiros et al. 2018 12 12 20.140 (-3.004, 43.284) 93.97
Subtotal (I-squared = 0.0%, p = 0.355) 22.822 (0.387, 45.257) 100.00
Electromyostimulation
Dobsak et al. 2012 11 5 40.200 (-24.197, 104.597) 35.20
Roxo et al. 2016 20 20 25.600 (-30.070, 81.270) 47.10
Schardong et al. 2017 11 10 12.780 (-78.056, 103.616) 17.69
Subtotal (I-squared = 0.0%, p = 0.881) 28.471 (-9.736, 66.679) 100.00
Overall (I-squared = 0.0%, p = 0.635) 33.641 (23.740, 43.542)
NOTE: Weights are from random effects analysis
-250 -150 -50 0 50 150 250
Favours control group
Favours exercise training

c)

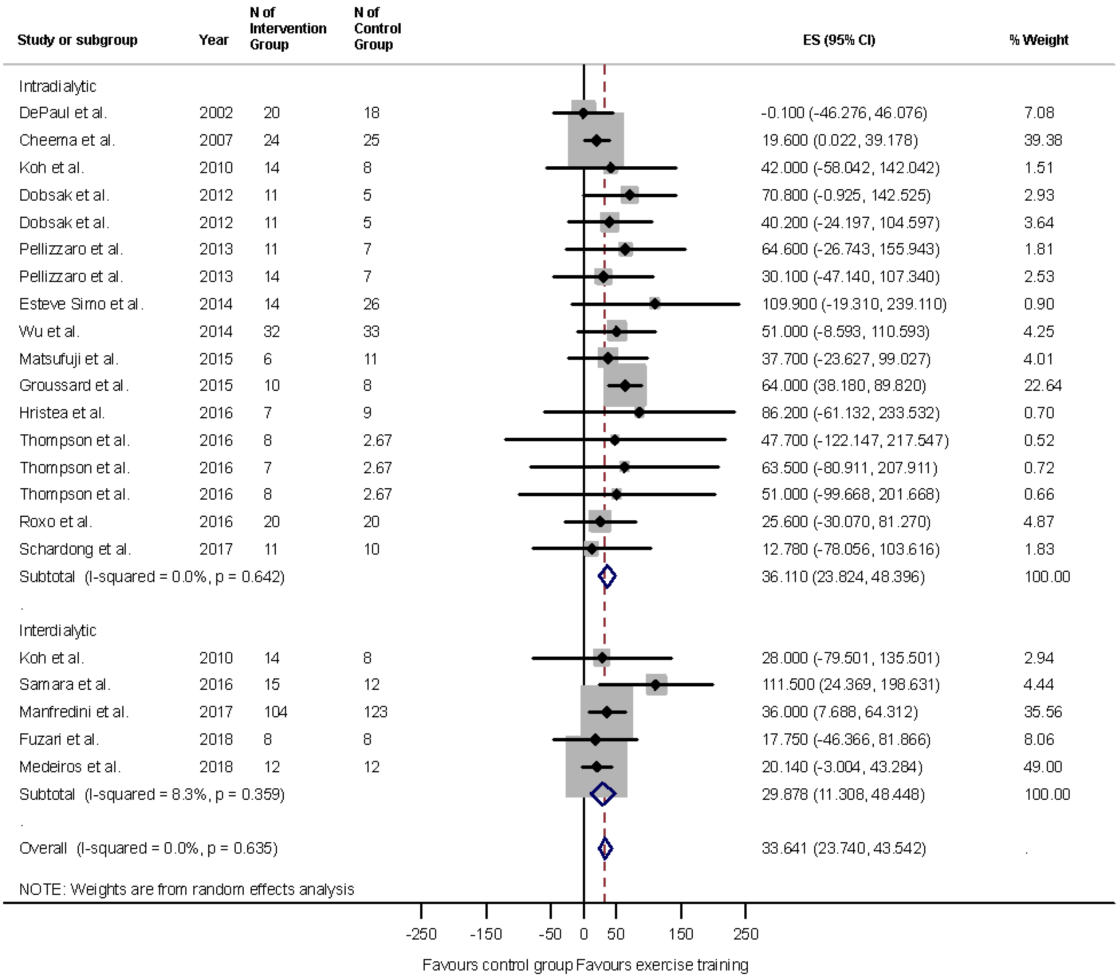


Figure 4. Forest plots of the effect estimates with 95% confidence intervals for the distance walked during the six-minute walk test between exercise interventions and usual care control groups for a) all included studies b) subgroup analysis by exercise modality; c) subgroup analysis by timing of exercise intervention delivery (interdialytic versus intradialytic).

Table 1. Summary of studies evaluating changes in objective measures of physical function following exercise intervention among patients with end-stage kidney disease (values presented are means ± SD).

Authors	Year	Sample (dialysis type, mean age, location, other)	Dialysis Vintage (years)	Study *N*	Intervention Details				Control Group	Physical Function Outcome (exercise vs control)
					Duration	Modality	Location	Prescription		
Cheema et al.(12)	2007	Haemodialysis Age: 62.6 ± 14.2 Australia	5.4 ± 4.1	49	12 weeks	Resistance	HD Unit	Free-weight exercises: (dumbbells for upper body, ankle weights for lower body), 3 times per week, 2 sets of 8 repetitions of 10 exercises (5 upper body, 5 lower body) at intensity of 15 – 17 on Borg's RPE scale.	Usual care	↔ 6MWT
Chen et al. (14)	2010	Haemodialysis Age: 69 ± 13	3.7 ± 4.1	44	24 weeks	Resistance	HD Unit	Free-weight exercises: (ankle weights from 0.5 – 20 lbs). 2 times per week, 2 sets of 8 repetitions of 5 exercises (4 lower limb, 1 core) at intensity of 6 out of 10 on a modified OMNI scale.	5 Light flexibility exercises in semi-recumbent position held for 20-30 sec each, repeated twice.	↑ SPPB
de Lima et al. (16)	2013	Haemodialysis Age: 45.5 ± 11.2	6.1 ± 4.2	32	8 weeks	Aerobic	HD Unit	Progressive cycle ergometry 3 times per week, for 20 min at intensity of 2 – 3 on the modified 1-10 Borg's RPE scale	Usual care	↑ 4 min step test
					8 weeks	Resistance	HD Unit	Free-weight exercises: (ankle weights equivalent to 40% 1RM knee-extension). 3 times per week, 3 sets of 15 repetitions of 2 lower limb exercises.		↑ 4 min step test
DePaul et al. (18)	2002	Haemodialysis Age: 54.5 ± 15.1	4.4 ± 4.7	38	12 weeks	Aerobic & Resistance	HD Unit	Progressive cycle ergometry, 3 times per week for 20 min at intensity of 13 on Borg's RPE scale.	30 min non-resisted range of motion exercises	↔ 6MWT

DePaul et al. (cont.)								Resistance exercises: (seated knee flexion/extension machine) 3 times per week, 1-3 sets of 10 repetitions of 2 knee flexion/extension exercises at 50-125% baseline 5RM over 12 weeks		
Dobsak et al. (20)	2012	Haemodialysis Age: 61 ± 7.8	4.0 ± 2.1	32	20 weeks	Aerobic	HD Unit	Cycle ergometry, 3 times per week for 1-2 sets of 20 min at intensity of 60% of the watts determined in an ergometric test.	Usual care	↑ 6MWT
					20 weeks	Electromyo-stimulation	HD Unit	Neuromuscular electrical stimulation (dual channel battery-powered stimulators) 3 times per week, for 60 min, with 200 µs pulse width, at a frequency of 10Hz (20 sec on, 20 sec rest) for both quadriceps and calves.		↑ 6MWT
Esteve Simó et al. (22)	2014	Haemodialysis Age: 68.4 ± 16.4	5.5 ± 6.3	40	26 weeks	Resistance	HD Unit	Resistance exercises (resistance bands, medicine balls, ankle weights, and dumbbells) 2 times per week, maximal repetitions and sets of 12 exercises (5 upper limb, 7 lower limb).	Usual care	↑ 6MWT ↑ Grip Strength ↑ STS-10
Fuzari et al. (23)	2018	Haemodialysis Age: 57.6 ± 8.9	N/A	16	12 weeks	Whole Body Vibration	Off-HD	Whole body vibration: 10-20 min (1min vibration 30 sec off) Static semi-squat during vibration; 35Hz, 2-4mm amplitude	Usual care	↔ 6MWT ↔ Balance
Groussard et al. (27)	2015	Haemodialysis Age: 67.6 ± 4.1	3.3 ± 0.7	18	12 weeks	Aerobic	HD Unit	Progressive cycle ergometry, 3 times per week for 15-30 min at intensity of 55-60% of the watts determined in an ergometric test.	Usual care	↑ 6MWT
Hristea et al. (35)	2016	Haemodialysis Age: 69.8 ± 11.8	9.6 ± 14.9	16	26 weeks	Aerobic	HD Unit	Progressive cycle ergometry, 3 times per week for up to 30 min at an intensity of 3 on the modified 1-10 Borg's RPE scale	Usual care and dietary advice from a nutritionist	↑ 6MWT ↑ Balance

Johansen et al. (41)	2006	Haemodialysis Age: 55.6 ± 13.7	4.0 ± 2.7	40	12 weeks	Resistance	HD Unit	Free-weight exercises: (ankle weights), 3 times per week, 2 sets of 10 repetitions of 3 lower limb exercises at 60% 3RM.	Usual care	↔ Stair Climb ↔ Gait Speed ↔ STS-5
Koh et al. (45)	2010	Haemodialysis Age: 51.9 ± 12.8	2.7 ± 2.3	44	26 weeks	Aerobic	HD Unit	Progressive cycle ergometry, 3 times per week for 15-45 min at an intensity of 12-13 on Borg's RPE scale.	Usual care	↔ 6MWT ↔ TUG ↔ Grip Strength
					26 weeks	Aerobic	Home	Home-based unsupervised walking, 3 times per week for 15-45 min at an intensity of 12-13 on Borg's RPE scale.		↔ 6MWT ↔ TUG ↔ Grip Strength
Koufaki et al. (50)	2002	Continuous Ambulatory Peritoneal Dialysis & Haemodialysis Age: 54.2 ± 16.6	3.5 ± 4.0	33	12 weeks	Aerobic	HD Unit	Progressive cycle ergometry, 3 times per week progressing from 3 sets of 6-8 min, to 1 set of 30-35 min at an intensity 90% of the watts corresponding to ventilatory threshold determined in an ergometric test.	Usual Care	↔ *WALK* Test ↑ STS-5 ↑ 60STS
Liao et al. (52)	2016	Haemodialysis Age: 62 ± 9	6.4 ± 5.0	40	12 weeks	Aerobic	HD Unit	Cycle ergometry, 3 times per week for 30 min at an intensity of 12-15 on Borg's RPE scale.	Usual Care	↑ 6MWT
Manfredini et al. (53)	2016	Continuous Ambulatory Peritoneal Dialysis & Haemodialysis Age: 63.5 ± 13.6	N/A	227	26 weeks	Aerobic	Home	Home-based walking program, twice daily always on non-dialysis days, 3 times per week for 10 min at a metronome dictated speed equating to between 1.4 and 2.8 $km.h^{-1}$ depending on 6MWT performance.	Usual Care	↑ 6MWT ↑ STS-5
Matsufuji et al. (55)	2015	Haemodialysis Age: 69.8 ± 4.3	13.6 ± 3.4	17	12 weeks	Resistance	HD Unit	Repeated sit-to-stand exercise on 40cm chair (3 sec stand time and 3 sec sit time), 3 times per week for 5 sets of half participants' maximum repetitions.	Passive upper and lower body stretching exercises	↑ 6MWT ↑ Max STS

Medeiros et al. (60)	2018	Haemodialysis Age: 36.4 ± 3.6	6.8 ± 1.7	24	8 weeks	Respiratory	Off-HD	Inspiratory muscle training: twice per day; 3 sets of 30 inspirations at 50% of maximal inspiratory pressure.	Usual Care	↔ 6MWT
Molsted et al.(62)	2004	Haemodialysis Age: 48.3 ± 8.4	3.9 ± 3.1	33	22 weeks	Aerobic & Resistance	HD Unit	Progressive cycle ergometry, 2 times per week for 15-20 min at an intensity of 17 on Borg's RPE scale. Supervised resistance exercises: Step and circuit training, high and low impact aerobics, 2 times per week for 20-30 min, at an intensity of 14-17 on Borg's RPE scale.	Usual Care	↔ Stair Climb ↑ STS-10
Pellizzaro et al. (69)	2013	Haemodialysis Age: 48.3 ± 11.8	4.9 ± 2.0	39	10 weeks	Resistance	HD Unit	Free-weight exercises: (ankle weights) for knee extension, 3 times per week, for 3 sets of 15 repetitions at an intensity of 50% 1RM	Usual Care	↑ 6MWT
					10 weeks	Respiratory	HD Unit	Inspiratory muscle training using a unidirectional flow limiter, 3 times per week, 3 sets of 15 inspirations at an intensity of 50% of maximal inspiratory pressure.		↑ 6MWT
Roxo et al. (74)	2016	Haemodialysis Age: 50.5 ± 17.8	4.8 ± 3.7	40	8 weeks	Electromyo-stimulation	HD Unit	Neuromuscular electrical stimulation (four channel battery-powered stimulators) 3 times per week, for 30 min, with 350 µs pulse width, at a frequency of 50Hz (2 sec on, 10 sec rest) for quadriceps.	Usual Care	↑ 6MWT
Samara et al. (76)	2016	Haemodialysis Age: 48.3 ± 13.3	N/A	27	16 weeks	Aerobic	Pool	Aquatic training on non-dialysis days (various swimming strokes with and without floatation aids), 3 times per week, up to 60 min, at an intensity of 13-14 on Borg's RPE scale.	Usual Care	↑ 6MWT ↑ TUG ↑ Grip Strength ↑ STS-10 ↑ Sit-and-Reach

Schardong et al. (77)	2017	Haemodialysis Age: 61.1 ± 5.2	4.3 ± 4.4	21	8 weeks	Electromyo-stimulation	HD Unit	Neuromuscular electrical stimulation (four channel battery-powered stimulators) 3 times per week, for 20-36 min, with 400 µs pulse width, at a frequency of 50Hz (10 sec on, 50-10 sec rest) for quadriceps.	Usual Care	↔ 6MWT ↑ 30STS
Song & Sohng (81)	2012	Haemodialysis Age: 53.4 ± 11.3	3.5 ± 3.7	40	12 weeks	Resistance	Off-HD	Free-weight exercises: (resistance bands and sand bags), 3 times per week. 3 sets of 10-15 repetitions of 12 exercises (6 lower body and 6 upper body exercises), at an intensity of 11-15 on Borg's RPE scale.	Usual Care	↔ Balance ↔ Grip Strength ↔ Sit-and-Reach ↔ Shoulder Mobility
Thompson et al. (84)	2016	Haemodialysis Age: 59.9 ± 6.5	3.1 ± 0.7	31	12 weeks	Aerobic	HD Unit	Progressive cycle ergometry, 3 times per week for 15-45 min at an intensity of 12-14 on Borg's RPE scale.	Non-progressive stretching exercises (2 sets of 4 exercises)	↔ 6MWT ↔ 30STS ↑ SPPB
					12 weeks	Resistance	HD Unit	Free-weight exercises: (ankle weights and Thera-Band), 3 times per week, for 1-3 sets of 4 exercises (all lower body), at an intensity of 12-14 on Borg's RPE scale.		↔ 6MWT ↔ 30STS ↑ SPPB
					12 weeks	Aerobic & Resistance	HD Unit	Progressive cycle ergometry, 3 times per week for 15-45 min at an intensity of 12-14 on Borg's RPE scale. Free-weight exercises: (ankle weights and Thera-Band), 3 times per week, for 1-3 sets of 4 exercises (all lower body), at an intensity of 12-14 on Borg's RPE scale.		↔ 6MWT ↔ 30STS ↑ SPPB

van Vilsteren et al. (85)	2005	Haemodialysis Age: 54.7 ± 15.5	4.5 ± 0.9	96	12 weeks	Aerobic & Resistance	HD Unit	Pre-dialysis resistance exercises: (calisthenics, steps, free weights), 2-3 times per week, 20 min at 60% maximum (determined by RPE) Intradialytic cycling ergometry, 2-3 times per week for 20-30 min at an intensity of 60% maximal capacity (determined by RPE)	Usual Care	↑ STS-10
Wilund et al. (89)	2010	Haemodialysis Age: 59.8 ± 4.2	4.5 ± 0.9	17	16 weeks	Aerobic	Off-HD	Progressive cycle ergometry, 3 times per week up to 45 min at an intensity of 12-14 on Borg's RPE scale.	Usual Care	↑ ISWT
Wu et al. (90)	2014	Haemodialysis Age: 44.3 ± 2.5	4.0 ± 2.8	65	12 weeks	Aerobic	HD Unit	Intradialytic cycling ergometry, 3 times per week for 15-20 min at an intensity of 12-16 on Borg's RPE scale.	Non-progressive stretching exercises for 10-15 min	↑ Stair Climb ↑ 6MWT ↑ Grip Strength ↑ 60STS ↑ STS-10
Yurtkuran et al. (92)	2007	Haemodialysis Age: 39.5 ± 12.3	1.8 ± 1.2	37	12 weeks	Yoga	Off-HD	Yoga (modified exercises – 7 postures and relaxation), 2 times per week for 15-30 min	Usual care and home-based active range of motion exercises for upper limbs and spine	↑ Grip Strength