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# Exercise Training in Elderly People Undergoing Hemodialysis: A Systematic Review and Meta-analysis

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**Introduction:** Previous reviews have indicated the effectiveness of exercise in people undergoing hemodialysis. However, these analyses did not take into account whether the subjects were elderly. We performed a systematic review of the effects of exercise training in elderly people undergoing hemodialysis and updated the evidence of exercise for people undergoing hemodialysis by adding recent research data.

**Methods:** We searched 8 electronic databases up to June 2016. Inclusion criteria were as follows: randomized controlled trial, English publication, subjects aged 18 and older undergoing hemodialysis, evaluation of physical function as an outcome of exercise intervention. We defined elderly as age 60 years and older. The main outcomes were exercise tolerance (peak/maximum oxygen consumption) and walking ability (6-minute walk distance). Secondary outcomes were lower extremity muscle strength and quality of life.

**Results:** After screening of 10,923 references, 30 comparisons were entered into the analysis. However, because we found only 1 study in which elderly subjects were treated, we could not perform a meta-analysis for these people. For the general population undergoing hemodialysis, supervised exercise training was shown to significantly increase peak/maximum oxygen consumption (standard mean difference, 0.62; 95% confidence interval 0.38–0.87; $P < 0.001$), 6-minute walk distance (standard mean difference, 0.58; 95% confidence interval 0.24–0.93; $P < 0.001$), lower extremity muscle strength (standard mean difference, 0.94; 95% confidence interval 0.67–1.21; $P < 0.001$), and quality of life (standard mean difference, 0.53; 95% confidence interval 0.52–0.82; $P < 0.001$).

**Discussion:** Our analysis on the effectiveness of exercise training in elderly people undergoing hemodialysis as compared with nonelderly people was somewhat inconclusive. Future studies should be carried out for elderly people to identify the most favorable exercise program for this population.

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An aging population and the increasing prevalence of lifestyle-related diseases, such as diabetes, hypertension, and cardiovascular disease, have led to a worldwide increase in the rate of chronic kidney disease requiring renal replacement therapy, including hemodialysis.[1] The mean age of people undergoing dialysis has been on the rise because of improved survival in this patient population, as well as the reduced availability of transplants for elderly patients. Significant increases in age of people undergoing dialysis were observed in almost all 12 nations included in the Dialysis Outcomes and Practice Patterns Study, an international cohort study.[2] Other studies from the United States, Europe, and Japan also report a significant proportion of elderly patients undergoing dialysis.[3–5] In particular, the mean age in the Japanese dialysis population was 66.9 years in 2012, showing an 11.6-year increase since the end of 1991. Furthermore, the proportions of people aged 60 years and older

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were 78.1% of patients who started undergoing dialysis in 2012 and 75.4% of the entire dialysis population.[5]

Elderly people undergoing hemodialysis have a high prevalence (70%) of physical frailty, characterized by lower levels of physical functioning.[6] However, physical frailty, a well-known indicator of disability and poor prognosis among the elderly,[7–10] could be prevented, postponed, or even reversed with specific interventions and health strategies. Physical exercise has been shown to have positive effects on physical function among frail older adults[11] and is recommended for those with kidney disease.[12] Previous meta-analyses indicated the effectiveness of exercise interventions on exercise tolerance, physical function, and quality of life (QoL) for people undergoing hemodialysis[13,14]; however, these analyses did not take into consideration whether subjects were elderly. Elderly patients face an array of barriers to exercise such as self-efficacy, discomfort, disability, fear of injury, habits, environmental factors, cognitive decline, and fatigue.[15] Hence, the concept of exercise intervention for young to middle-aged people undergoing hemodialysis is not entirely applicable to elderly people, and whether exercise training improves physical function, exercise tolerance, or QoL in elderly people undergoing hemodialysis remains unclear. Moreover, how best to manage this patient population is still poorly understood in the field of nephrology. Therefore effectiveness of exercise interventions on patient outcomes needs to be evaluated with patient age in mind, and conclusions regarding the effectiveness of exercise training must be updated with the latest data from new trials targeting elderly people undergoing hemodialysis.[16,17]

The main goals of this systematic review and meta-analysis were (i) to compare the benefits of supervised exercise training programs on exercise tolerance (peak/maximum oxygen consumption [$VO_2$]), walking ability (6-minute walk distance), lower extremity muscle strength, and health-related QoL (short-form health survey [SF-36]) between nonelderly and elderly people undergoing hemodialysis, especially those aged 60 years and older and (ii) to update the evidence base for recommendation of supervised exercise interventions for hemodialysis populations by adding data from recent research studies.

## MATERIALS AND METHODS

This review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance[18] (Supplementary Appendix S1) and is one of a series of systematic reviews regarding the effectiveness of exercise training in elderly patients undergoing hemodialysis. 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: CRD42015020701), and our protocol has already been published (http://bmjopen.bmj.com/content/6/5/e010990.long).[19]

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. The search was performed with the following terms: dialysis, renal replacement therapy, exercise, physical fitness, cycling, walk, physical therapy. The full strategy is described in Supplementary Appendix S2. To identify any articles missed by the initial search, we also evaluated the reference lists of previously reported systematic reviews.

We used EndNote X7 for Windows (Thompson Reuters, Philadelphia, Pennsylvania) to manage literature records and data. Reviewers screened all titles, abstracts, and the full texts. When required data were not available, the study authors were contacted by e-mail.

### Inclusion and Exclusion Criteria

We included only randomized controlled trials (RCTs) published in English that evaluated the effects of supervised exercise training on at least 1 of the outcome measures included for this review and were a measure of physical function. Supervised exercise included resistance training, aerobic exercise, and combined exercise. Only RCTs that included subjects at least 18 years of age who were undergoing hemodialysis were included in this meta-analysis. Patients affected by acute kidney failure were excluded. In the present study, we defined elderly as age 60 years and older. The main outcomes of the study were exercise tolerance (peak/maximum $VO_2$) and walking ability (6-minute walk distance). Secondary outcomes were lower extremity muscle strength measured by using a dynamometer and health-related QoL (short-form health survey: physical component summary score and mental component summary score).

### Risk of Bias

The methodological quality of trials included in the review was evaluated independently by using the

Cochrane Collaboration tool[20] for assessment of risk of bias by 2 reviewers. Studies were graded as having a "low risk," "high risk," or "unclear risk" of bias across the following 7 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, we assessed the risk of bias of references using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX),[21] which consists of 15 different items and has been shown to be a reliable tool for performing a comprehensive review of exercise training trials.

### Data Analysis and Statistical Methods

Our statistical analysis strategy involved finding the average absolute change in the included patient measures from baseline to endpoint (including SD) in the intervention and control groups. We evaluated the standardized mean difference for exercise training. An analysis was performed according to whether study subjects were elderly (defined as $\geq$ 60 years old) or nonelderly. The effect consistency across studies was assessed using the $I^2$ statistic,[22] with $I^2 > 25\%$ and 50% considered to indicate moderate and substantial heterogeneity, respectively. We used the random-effects model as the default method of analysis because of the expected clinical heterogeneity between studies, since the alternative fixed-effects model assumes that the true treatment effect of each trial is the same and that any observed differences are caused by chance. We assessed publication bias by plotting the inverse of the SE of the effect estimates using funnel plots to explore symmetry, which was assessed visually and using Egger's regression test in analyses including 10 or more studies. The analysis was performed using Review Manager Software (RevMan V.5.3; Cochrane Collaboration, Oxford, UK) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Of the total of 10,923 references that were initially screened, 7640 had no duplicates and 7306 were rejected at the title and abstract stage. We analyzed 334 studies that were identified for potential inclusion and full-text review, and 30 comparisons were entered into the analysis[16,17,23–49] (Figure 1). Of the 30 comparisons, only 1 study targeted elderly people undergoing hemodialysis.

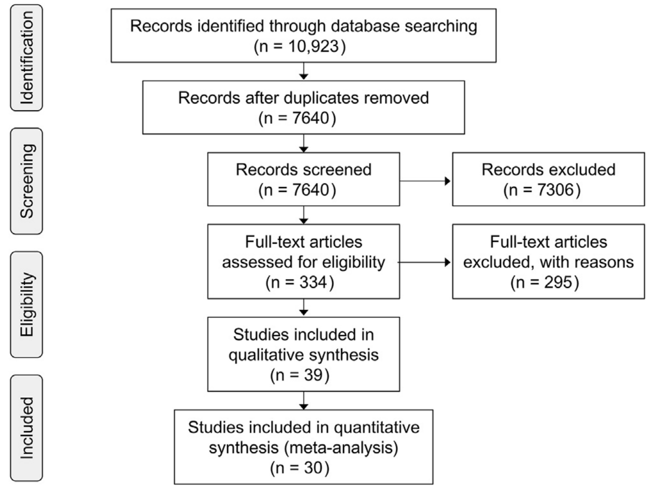


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing selection of randomized controlled trials.

### Participants and Interventions

Table 1 presents a summary of the trials.[16,17,23–58] In 21 studies intradialytic exercise was adopted, and interventions ranged from 8 weeks to 12 months in duration, with most lasting for 3 to 6 months. A combination of aerobic exercise and strength exercise training was used in 10 studies, and interventions were performed 3 times per week in most of the studies. There was no trial in which peak/maximum $VO_2$ was reported for elderly participants undergoing hemodialysis, and only 1 trial included reports of 6-minute walk distance, lower extremity muscle strength, and QoL in elderly people.

### Treatment Outcomes

#### *Exercise Tolerance*

Eighteen trials included measurement of peak/maximum $VO_2$, with a total of 313 subjects in the intervention group and 269 control subjects.[17,23,26,27,30,31,35–40,43–45,47,48] Supervised exercise training was shown to significantly increase exercise tolerance in the total patient population. The standardized mean difference (SMD) of peak/maximum $VO_2$ was 0.62 (95% confidence interval [CI], 0.38–0.87; $P < 0.001$) in the total patient population. There was a moderate degree of heterogeneity in exercise tolerance across studies ($I^2 = 49\%$). However, because there was no study involving elderly participants, we were not able to analyze the efficacy of exercise training on exercise tolerance among elderly patients undergoing hemodialysis (Figure 2).

#### *Walking Ability*

Ten trials assessed 6-minute walk distance with a total of 161 subjects in the intervention group and 165 subjects in the control group.[16,17,24,27,33,34,42,45,49,53] Only 1 of these 11 trials included elderly participants.[16] Supervised exercise training was shown to

**Table 1.** Characteristics of included studies

| Studies | Location | Mean age (SD), yr | Mean duration of HD (SD), yr | No. of patients | Duration of intervention | Type of intervention | Training program | Intensity of program | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Akiba *et al.* (1995)[50] | Japan | Ex: 38.4 (9.5)<br>Con: 40.6 (10.8) | Ex: 6.15 (3.9)<br>Con: 5.69 (3.5) | Ex: 10<br>Con: 10 | 3 mo | Cycle ergometer before hemodialysis session (+treatment for anemia) | Aerobic for 20 min using cycle ergometer 3 times per wk | No data | Exercise tolerance ($VO_{2\ max}$) |
| Carmack *et al.* (1995)[23] | USA | All: 44.1 | No data | Ex: 23<br>Con: 25 | 10 wk | Intradialytic | Aerobic exercise for 20–30 min using cycle ergometer 3 times per wk | No data | Exercise tolerance ($VO_2$ peak)<br>Depression |
| Carney *et al.* (1987)[51] | USA | Ex: 36.1 (3.2)<br>Con: 40.7 (5.3) | Ex: 2.5 (0.7)<br>Con: 3.3 (1.1) | Ex: 11<br>Con: 7 | 6 mo | Track walking, bicycle ergometer | Aerobic exercise for 45–60 min using indoor track and bicycle ergometer 3 times per wk | 70%–80% of $VO_{2max}$ | Exercise tolerance ($VO_{2max}$)<br>Depression |
| Cheema *et al.* (2007)[24] | Australia | All: 62.6 (14.2) | 2.2 | Ex: 24<br>Con: 25 | 24 wk | Intradialytic | High-intensity progressive resistance training: 2 sets of 8 repetitions of 10 types using weighted ankle cuffs or Thera-Band tubing[a] 3 times per wk | Borg scale 15 to 17 ("hard" to "very hard") | Lower extremity muscle strength<br>Muscle mass (CT)<br>Walking ability (6MWT) |
| Chen *et al.* (2010)[25] | USA | Ex: 71.1(12.6)<br>Con: 66.9(13.4) | Ex: 2.6 (2.6)<br>Con: 4.8 (5.2) | Ex: 25<br>Con: 25 | 24 wk | Intradialytic | Progressive resistance training 2 sets of 8 repetitions of 8 types using ankle weights 2 times per wk | OMNI scale 6 (somewhat hard) out of 10 (extremely hard), equivalent to 60% of a 1-repetition maximum | ADL level<br>Lower extremity muscle strength<br>Physical performance (SPPB)<br>Physical activity<br>QoL |
| de Lima *et al.* (2013)[52] | Brazil | Ex: 49.6 (9.1)<br>Con: 43.5 (11.1) | Ex: 5.4 (4.0)<br>Con: 6.5 (4.2) | Ex: 11<br>Con: 11 | 8 wk | Intradialytic | Developed peripheral musculature training using anklets consisting of 3 series of 15 repetitions 3 times per wk | 40% of 1RM | QoL |
| de Lima *et al.* (2013)[52] | Brazil | Ex: 43.1 (13.3)<br>Con: 43.5 (11.1) | Ex: 6.4 (4.4)<br>Con: 6.5 (4.2) | Ex: 10<br>Con:11 | 8 wk | Intradialytic | Progressive ergometric bicycle exercise 20 min 3 times per wk | Modified Borg scale 2–3 | QoL |
| Deligiannis *et al.* (1999)[26] | USA | Ex: 46.4 (13.9)<br>Con: 50.2 (7.9) | Ex: 6.5 (5.2)<br>Con: 6.6 (7.2) | Ex: 16<br>Con: 12 | 6 mo | Nonintradialytic | Aerobic and low-weight resistance training for 90 min (including 10-min warm- up using cycle ergometer or treadmill, 50-min intermittent aerobic exercise, and 10-min cool-down) 3 times per wk<br>After the first 3 months, the younger patients were playing basketball and football, whereas the older patients were swimming. | 60%–70% of the $HR_{max}$ | Exercise tolerance ($VO_{2max}$) |
| DePaul *et al.* (2002)[27] | Canada | Ex: 55 (16)<br>Con: 54 (14) | Ex: 4.2 (4.8)<br>Con: 4.6 (4.5) | Ex: 20<br>Con: 18 | 12 wk | Intradialytic<br>Before and after the dialysis session | Aerobic training 20 min 3 times per wk, progressive strength training: 1 set of 10 repetitions; number of sets: 1–3 | Borg scale 13 ("somewhat strong")<br>5-repetition maximum | Lower extremity muscle strength<br>Walking ability (6MWT)<br>QoL |
| Dobsak *et al.* (2002)[53] | France | Ex: 58.2 (7.2)<br>Con: 60.1 (8.2) | Ex: 4.1 (2.1)<br>Con: 4.1 (2.3) | Ex: 11<br>Con: 10 | 20 wk | Intradialytic | Progressive ergometric bicycle exercise 20–40 min 3 times per wk | 60% peak workload | Exercise tolerance (peak workload)<br>Walking ability (6MWT)<br>QoL |
| Dong *et al.* (2010)[28] | USA | Ex: 46.5 (12.1)<br>Con: 40.2 (13.5) | Unknown | Ex: 15<br>Con: 17 | 6 mo | Intradialytic | 3 sets of 12 repetitions of leg press, under supervision of study personnel, within 30 min 3 times per wk | 70% of the 1-RM | Lower extremity muscle strength<br>Muscle mass (DEXA) |
| Giannaki *et al.* (2013)[29] | Cyprus | Ex: 59.2 (11.8)<br>Con: 58.0 (10.7) | Ex: 2.0 (1.25)<br>Con: 2.5 (2.2) | Ex:12<br>Con:12 | 6 mo | Intradialytic | Ex: progressive aerobic exercise training using a recumbent cycle ergometer for 45 min 3 times per wk | Ex: 60%–65% of the patient's maximal exercise capacity (in Watts) | Depression<br>Lower extremity muscle strength (STS)<br>Sleep quality |

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**Table 1.** Characteristics of included studies (Continued)

| Studies | Location | Mean age (SD), yr | Mean duration of HD (SD), yr | No. of patients | Duration of intervention | Type of intervention | Training program | Intensity of program | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Giannaki *et al.* (2013)[29] | Greece | Ex: 56.4 (12.5)<br>Con: 55.7 (10.4) | Ex: 3.9 (1.3)<br>Con: 4.0 (1.7) | Ex: 15<br>Con: 7 | 6 mo | Intradialytic | Progressive aerobic exercise training using a recumbent cycle ergometer 3 times per wk | 60%–65% of the patient's maximal exercise capacity (in Watts) | Depression<br>Lower extremity muscle strength (STS)<br>Muscle mass (CT)<br>QoL<br>Walking speed |
| Goldberg *et al.* (1983)[31] | USA | Ex: 38.5 (15.4)<br>Con: 37.1 (12.1) | Ex: 1.9 (1.4)<br>Con: 3.3 (2.5) | Ex: 14<br>Con: 11 | No data | Indoor training | Progressive treadmill walking or jogging 45–60 min included 5–10 min low-intensity walking | Initial training: 50–60 $VO_{2max}$<br>By 9 mo: 70–80 $VO_{2max}$ | Exercise tolerance ($VO_{2max}$)<br>Depression |
| Goldberg *et al.* (1986)[30] | USA | Ex: 40.0 (14.0)<br>Con: 36.0 (10.0) | Ex:1.9 (1.5)<br>Con: 3.3 (2.6) | Ex: 13<br>Con: 12 | 12 mo | Unknown | Endurance training for 45 min (cycling using bicycle ergometer and walking-jogging) | 70%–80% of $VO_{2max}$ | Exercise tolerance ($VO_{2max}$)<br>Depression |
| Groussard *et al.* (2015)[17] | France | Ex: 66.5 (4.6)<br>Con: 68.4 (3.7) | Ex: 36.6 (8.2)<br>Con: 41.2 (8.1) | Ex: 8<br>Con: 10 | 3 mo | Intradialytic | Aerobic exercise consisting of cycling 3 times per wk (5-min warm-up, 15–30 min at a tolerable pace and 5-min cool-down) | 55%–60% of the peak power output | Exercise tolerance ($VO_2$ peak)<br>Walking ability (6MWT) |
| Guadalupe *et al.* (2016)[54] | Mexico | Ex: 28.5<br>Con: 29 | Ex: 1.0<br>Con: 1.5 | Ex: 30<br>Con: 31 | 12 wk | Intradialytic | Resistance training 2 times per wk using ankle weights and bands<br>Four series of 30 repetitions were performed for each of the 4 exercises. | 500-g weight | Grip strength |
| Johansen *et al.* (2006)[32] | USA | Ex: 54.4 (13.6)<br>Con: 56.8 (13.8) | Ex: 2.8<br>Con: 2.1 | Ex: 20<br>Con: 20 | 12 wk | Intradialytic | Progressive resistance training using ankle weights 2–3 sets of 10 repetitions | 60% of 3RM | Lower extremity muscle strength<br>Lower extremity muscle strength (STS)<br>Muscle mass (MRI)<br>Physical activity<br>QoL<br>Walking speed |
| Kirkman *et al.* (2014)[33] | UK | Ex: 48 (18)<br>Con: 58 (15) | Ex: 3.8 (4.5)<br>Con: 5.5 (3.9) | Ex: 12<br>Con: 11 | 12 wk | Intradialytic | Progressive resistance training: 8 sets of 10 repetitions of 10 types using resistance bands 3 times a wk | 3 sets of 8–10 repetitions at 80% of their predicted 1RM with 2-min rest period between sets | Lower extremity muscle strength<br>Muscle mass (MRI)<br>QoL<br>Walking ability (6MWT)<br>Walking speed |
| Koh *et al.* (2010)[34] | Australia | Ex: 52.3 (10.9)<br>Con: 51.3 (14.4) | Ex: 2.7 (2.2)<br>Con: 2.2 (1.9) | Ex: 15<br>Con: 16 | 6 mo | Intradialytic | Aerobic exercise training for 30–45 min using cycle ergometer 3 times per wk | Borg scale 12–13 | Grip strength<br>QoL<br>Walking ability (6MWT)<br>Walking speed (TUG) |
| Konstantinidou *et al.* (2002)[35] | Greece | Ex: 46.4 (13.9)<br>Con: 50.2 (7.9) | Ex: 6.5 (5.2)<br>Con: 6.6 (7.2) | Ex: 16<br>Con: 12 | 6 mo | Nondialysis days | Aerobic and strengthening training for 60 min 3 times per wk (10 min warm-up, 30 min intermittent aerobic exercise, 10 min stretching, low-weight resistance training and 10 min cool-down) | 60%–70% of the $HR_{max}$ | Exercise tolerance ($VO_2$ peak) |
| Konstantinidou *et al.* (2002)[35] | Greece | Ex: 48.3 (12.1)<br>Con: 50.2 (7.9) | Ex: 6.0 (5.5)<br>Con: 6.6 (7.2) | Ex: 10<br>Con: 12 | 6 mo | Intradialytic | Aerobic and strength training for 60 min program 3 times per wk (30 min with a bed bicycle ergometer and 30 min for strength and flexibility) | 70% of the $HR_{max}$ | Exercise tolerance ($VO_2$ peak) |

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**Table 1.** (Continued)

| Studies | Location | Mean age (SD), yr | Mean duration of HD (SD), yr | No. of patients | Duration of intervention | Type of intervention | Training program | Intensity of program | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Koufaki *et al.* (2002)[36] | UK | Ex: 57.3 (14.3)<br>Con: 50.5 (19) | Ex: 3.1 (3.8)<br>Con: 4.0 (4.2) | Ex: 26<br>Con: 22 | 12 wk | CAPD: in the Renal Rehabilitation Gym<br>HD: Intradialytic | Progressive aerobic training on a cycle ergometer 3 times per wk | 90% of VT | Exercise tolerance ($VO_2$ peak)<br>Lower extremity muscle strength (STS)<br>Physical activity |
| Kouidi *et al.* (1997)[55] | Greece | Ex: 49.6 (12.1)<br>Con: 52.8 (10.2) | Ex: 5.9 (4.9)<br>Con: 6.2 (5.4) | Ex: 20<br>Con: 11 | 6 mo | Nondialysis days | Supervised exercise (stationary cycling, walking or jogging, calisthenics, aerobics, swimming and/or game sports) 90 min 3–4 times per wk | 50%–60% of their $VO_{2max}$ or 60%–70% of their $HR_{max}$ | Exercise tolerance ($VO_{2max}$)<br>QoL |
| Kouidi *et al.* (2009)[37] | USA | Ex: 54.6 (8.9)<br>Con: 53.2 (6.1) | Ex: 6.3 (3.7)<br>Con: 6.2 (3.9) | Ex: 32<br>Con: 31 | 10 mo | Intradialytic | Supervised training (40 min: cycling ergometer; 30 min: progressive muscle strengthening 3 sets of 15 repetitions using Thera-Band tubing[a] and weights to the limbs)<br>3 times per wk | Borg scale 13 (somewhat hard) | Exercise tolerance ($VO_2$ peak) |
| Matsufuji *et al.* (2015)[16] | Japan | Ex: 69 (61–78)<br>Con: 69 (64–79) | Ex: 14<br>Con: 15 | Ex: 12<br>Con: 15 | 12 wk | On dialysis day | 5 sets chair stand exercise as resistance training<br>3 times per wk | 5 sets of half of the maximum duration for each participant with 4 short breaks | Lower extremity muscle strength<br>QoL<br>Walking ability (6MWT) |
| Matsumoto *et al.* (2007)[56] | Japan | Ex: 60.8 (9.5)<br>Con: 57.2 (8.3) | Ex: 12.4 (6.8)<br>Con:12.7(7.5) | Ex: 17<br>Con: 32 | 12 mo | Endurance training before each hemodialysis treatment | 20 min of continuous cycling 3 times per wk | Borg scale 11–13 (60%– 70% of peak heart rate) | QoL |
| Molsted *et al.* (2004)[38] | Denmark | Ex: 59.0<br>Con: 48.0 | Ex: 2.0<br>Con: 1.4 | Ex: 22<br>Con: 11 | 5 mo | Unknown | Strength and aerobic exercises for 1 h twice a wk (10 min of warm-up, 20–30 min of strength and aerobic exercises, 20 min of interval cycling, and 10 min cooling down) | Borg scale 14–17 | Exercise tolerance ($VO_{2max}$)<br>Lower extremity muscle strength (STS)<br>QoL |
| Ouzouni *et al.* (2009)[39] | Greece | Ex: 47.4 (15.7)<br>Con: 50.5(11.7) | Ex: 7.7 (7.0)<br>Con: 8.6 (6.0) | Ex: 19<br>Con: 14 | 10 mo | Intradialytic | 60–90 min 3 times per wk (cycling: 30 min, strengthening: 30 min, flexibility exercise: 30 min) | Borg scale 13–14 ("somewhat hard") | Exercise tolerance ($VO_2$ peak)<br>QoL |
| Painter *et al.* (2002)[40] | USA | Ex: 43.5 (10.5)<br>Con: 50.1 (13.8) | Ex: 5.0 (6.7)<br>Con: 5.7 (4.5) | Ex: 12<br>Con: 12 | 5 mo | Intradialytic<br>(+ Normalized hematocrit) | Continuous cycling 30 min 3 times per wk<br>Interval exercise 20 min 3 times per wk | Borg scale 12–14 (70% of peak heart rate)<br>Borg scale 15–17 | Exercise tolerance ($VO_2$ peak)<br>QoL |
| Parsons *et al.* (2004)[41] | Canada | Ex: 60.0 (17.0)<br>Con: 49.0(25.0) | Ex: 2.9 (2.1)<br>Con: 4.1 (2.2) | Ex: 6<br>Con: 7 | 8 wk | Intradialytic | Cycle ergometry exercise for 15 min 3 times per wk | 40%–50% maximal work capacity | QoL |
| Pellizzaro *et al.* (2004)[42] | Brazil | Ex: 48.9 (10.1)<br>Con: 51.9 (11.6) | Ex: 4.5<br>Con: 4.5 | Ex: 14<br>Con: 14 | 10 wk | Intradialytic | Resistance training using leg weights 3 sets of 15 knee extension repetitions | 50% of 1RM | Walking ability (6MWT)<br>QoL |
| Pellizzaro *et al.* (2004)[42] | Brazil | Ex: 43.0 (13.8)<br>Con: 51.9 (11.6) | Ex: 5.0<br>Con: 4.5 | Ex: 11<br>Con: 14 | 10 weeks | Intradialytic | Inspiratory muscle training using the *Threshold Loader* 3 sets of 15 inspirations<br>Resistance training using leg weights: 3 sets of 15 knee extension repetitions | 50% of $PI_{max}$<br>50% of 1RM | Walking ability (6MWT)<br>QoL |
| Petraki *et al.* (2008)[43] | Greece | Ex: 50.05 (13.2)<br>Con: 50.52 (1.4) | Ex: 6.4 (0.6)<br>Con: 6.1 (0.4) | Ex: 22<br>Con: 21 | 7 mo | Intradialytic | Progressive 60 min cycling using specific bed cycles (including 5-min warm -up and terminated 5-min recovery) and 30 min strengthening and flexibility exercises 3 times per wk | Borg scale 13 | Exercise tolerance ($VO_2$ peak) |

*(Continued on next page)*

**Table 1.** Characteristics of included studies (Continued)

| Studies | Location | Mean age (SD), yr | Mean duration of HD (SD), yr | No. of patients | Duration of intervention | Type of intervention | Training program | Intensity of program | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Reboredo *et al.* (2011)[44] | Brazil | Ex: 50.7 (10.7)<br>Con: 42.2 (13.0) | Ex: 3.3 (3.4)<br>Con: 4.8 (4.4) | Ex: 12<br>Con: 12 | 12 wk | Intradialytic | Warmed up for 10 min (lower-limb stretching exercise, low work rate cycling)<br>Aerobic training program for 40 min 3 times per wk | No data<br>Modified Borg scale 4–6 | Exercise tolerance ($VO_2$ peak) |
| Reboredo *et al.* (2015)[57] | Brazil | Ex: 50.7 (10.7)<br>Con: 42.2 (13.0) | Ex: 3.3 (3.4)<br>Con: 4.8 (4.4) | Ex: 12<br>Con: 12 | 12 wk | Intradialytic | Aerobic exercise at moderate exertion for 43 min 3 times per wk (10 min warm-up by lower limb stretching, 5 min low-intensity cycling, 35 min moderate intensity cycling, and 3 min cool-down) | Modified Borg scale 4–6 | Exercise tolerance ($VO_2$ peak) |
| Segura-Orti *et al.* (2009)[45] | Spain | Ex: 53.5 (18.0)<br>Con: 60.1(16.9) | Ex: 3.1 (2.9)<br>Con: 4.5 (3.5) | Ex: 17<br>Con: 8 | 24 wk | Intradialytic | Progressive resistance training that targeted major muscle groups of lower extremities, 3 sets of 4 exercises using weights and elastic bands | Borg scale 12–15 | Exercise tolerance ($VO_2$ peak)<br>Lower extremity muscle strength<br>Lower extremity muscle strength (STS)<br>QoL<br>Walking ability (6MWT) |
| Song *et al.* (2012)[46] | Korea | Ex: 52.1 (12.4)<br>Con: 54.6 (10.1) | Ex: 3.2 (2.2)<br>Con: 3.8 (4.7) | Ex: 20<br>Con: 20 | 12 wk | Predialysis resistance training | 5 min warm-up and cool-down; progressive resistance training consisted of upper and lower body exercise using elastic bands and sandbags for 30 min 3 times per wk | Borg Scale 11–15 (moderate to hard) | Grip strength<br>Lower extremity muscle strength<br>Lower extremity muscle strength (STS)<br>Balance function<br>QoL |
| Tsuyuki *et al.* (2003)[47] | Japan | Ex: 40.1 (11.9)<br>Con: 39.7(10.7) | Ex: 2.1 (2.5)<br>Con: 2.7 (2.6) | Ex:17<br>Con: 12 | 20 wk | Nondialysis days | Combination training of bicycle ergometry, walking, and jogging for 30 min 2–3 times per wk | 50%–60% of the peak heart rate | Exercise tolerance ($VO_2$ peak) |
| van Vilsteren *et al.* (2005)[48] | Netherlands | Ex: 52 (15)<br>Con: 58 (16) | Ex: 3.2 (4.1)<br>Con: 3.9 (4.4) | Ex: 53<br>Con: 43 | 12 wk | Predialysis strength training<br>Intradialytic<br>Exercise counseling | A 5- to 10-min warm-up and cool-down; a 20-min exercise program including calisthenics, steps, flexibility, and low weight resistance training<br>Cycling 20–30 min 2–3 times per wk<br>The techniques based on the transtheoretical model, motivational interviewing, and health counseling | Borg scale 12–16<br>($<$ 60% maximal capacity) | Exercise tolerance ($VO_2$ peak)<br>Lower extremity muscle strength (STS)<br>QoL |
| Wilund *et al.* (2010)[58] | USA | Ex: 60.8 (3.2)<br>Con: 59.0 (4.9) | Ex: 5.3 (8.7)<br>Con: 3.7 (1.0) | Ex: 7<br>Con: 8 | 4 months | Intradialytic | Endurance exercise training for 45 min using cycle ergometer 3 times per wk | Borg scale 12–14 | Walking ability (shuttle walk test) |
| Wu *et al.* (2014)[49] | China | Ex: 45<br>Con: 44 | Ex: 4.6 (3.1)<br>Con: 3.3 (2.5) | Ex: 32<br>Con: 33 | 12 weeks | Intradialytic | 15–20 min of recumbent cycling (including 5-min warm-up) | Energy consumption of 70–100 calories, Borg scale 12–16 and an increase in heart rate of 20 beats/min (optimum individualized exercise load) | Grip strength<br>Lower extremity muscle strength (STS)<br>Walking ability (6MWT)<br>QoL |

ADL, activities of daily living; Con, control; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; Ex, exercise; HD, hemodialysis; $HR_{max}$, maximum heart rate; MRI, magnetic resonance imaging; $PI_{max}$, maximum inspiratory pressure; RM, repetition maximum; QoL, quality of life; SPPB, short physical performance battery; STS, sit-to-stand; TUG, timed up & go test; $VO_{2max}$, maximum oxygen consumption; VT, ventilatory threshold; 6MWT, 6-minute walk test.
[a]Thera-Band tubing is manufactured by Performance Health (Akron, OH).

| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.2.1 Nonelderly** | | | | | | | | |
| Carmack 1995 | 3.7 | 6.3 | 10 | 0.9 | 4.5 | 11 | 4.8% | 0.50 [-0.38, 1.37] |
| Deligiannis 1999 | 7.1 | 9.9 | 16 | -0.5 | 6.7 | 12 | 5.4% | 0.85 [0.06, 1.63] |
| DePaul 2002 | 20 | 18 | 15 | 6 | 13 | 14 | 5.5% | 0.86 [0.10, 1.63] |
| Goldberg 1983 | 4 | 11.4 | 14 | 0 | 10.6 | 11 | 5.3% | 0.35 [-0.45, 1.15] |
| Goldberg 1986 | 17.5 | 16 | 14 | 7.7 | 11 | 11 | 5.2% | 0.67 [-0.14, 1.49] |
| Groussard 2015 | -0.4 | 3.1 | 8 | 1.9 | 1.3 | 10 | 4.0% | -0.96 [-1.96, 0.03] |
| Konstantinidou 2002a | 7.1 | 9.9 | 16 | -0.5 | 6.7 | 12 | 5.4% | 0.85 [0.06, 1.63] |
| Konstantinidou 2002b | 3.9 | 7.7 | 10 | -0.5 | 6.7 | 12 | 4.9% | 0.59 [-0.27, 1.45] |
| Koufaki 2002 | 1.1 | 4.8 | 18 | -1 | 4.7 | 15 | 6.1% | 0.43 [-0.26, 1.12] |
| Kouidi 2009 | 4.8 | 3.7 | 30 | -0.2 | 2.6 | 29 | 7.1% | 1.54 [0.95, 2.12] |
| Molsted 2004 | 2.16 | 2 | 9 | 0.12 | 2.4 | 9 | 4.1% | 0.88 [-0.10, 1.86] |
| Ouzouni 2009 | 4.4 | 7.6 | 19 | -0.2 | 5 | 14 | 6.0% | 0.68 [-0.04, 1.39] |
| Painter 2002 | 1.16 | 11.4 | 13 | -0.49 | 6.2 | 13 | 5.5% | 0.17 [-0.60, 0.94] |
| Petraki 2008 | 4.6 | 8 | 22 | -1.1 | 6.4 | 21 | 6.8% | 0.77 [0.15, 1.39] |
| Reboredo 2011 | 3.2 | 8.9 | 12 | -2.9 | 9.6 | 12 | 5.1% | 0.64 [-0.19, 1.46] |
| Segura-Orti 2009 | 3.15 | 6.7 | 17 | 1.4 | 5.3 | 8 | 5.0% | 0.27 [-0.58, 1.11] |
| Tsuyuki 2003 | 5.6 | 3.6 | 17 | -0.2 | 3.2 | 12 | 4.8% | 1.64 [0.77, 2.50] |
| van Vilsteren 2005 | 2.58 | 10.8 | 53 | 0.12 | 15.3 | 43 | 9.0% | 0.19 [-0.22, 0.59] |
| **Subtotal (95% CI)** | | | **313** | | | **269** | **100.0%** | **0.62 [0.38, 0.87]** |
| Heterogeneity: Tau² = 0.13; chi² = 33.19, *df* = 17 (*P* = 0.01); *I*² = 49% | | | | | | | | |
| Test for overall effect: *Z* = 4.95 (*P* < 0.00001) | | | | | | | | |
| **3.2.2 Elderly** | | | | | | | | |
| **Subtotal (95% CI)** | | | **0** | | | **0** | | **Not estimable** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Not applicable | | | | | | | | |
| **Total (95% CI)** | | | **313** | | | **269** | **100.0%** | **0.62 [0.38, 0.87]** |
| Heterogeneity: Tau² = 0.13; chi² = 33.19, *df* = 17 (*P* = 0.01); *I*² = 49% | | | | | | | | |
| Test for overall effect: *Z* = 4.95 (*P* < 0.00001) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |

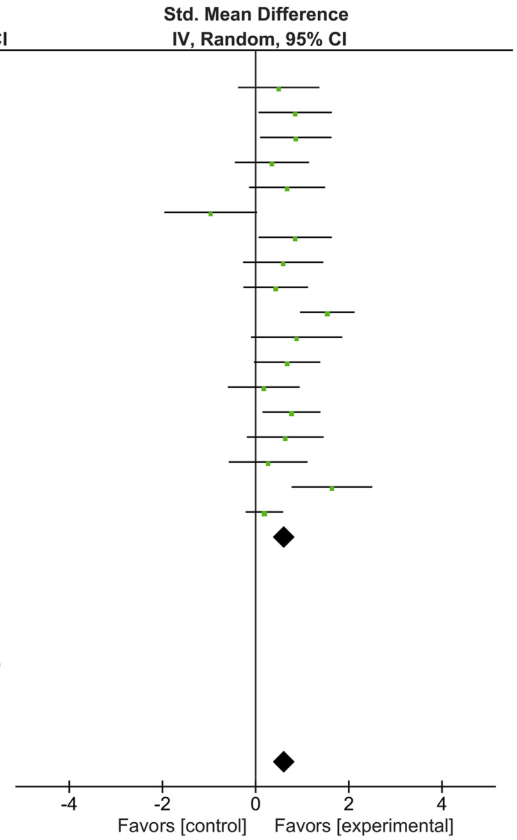


**Figure 2.** Forest plot showing the effects of supervised exercise training compared with usual care on changes in exercise tolerance (peak/maximum oxygen consumption). CI, confidence interval; IV, inverse variance; Std., standard.

significantly increase walking ability, as determined by 6-minute walking test, in subjects undergoing hemodialysis, with SMD of 0.58 (95% CI, 0.24–0.93; $P < 0.001$) in the total patient population. There was a moderate degree of heterogeneity across studies in walking ability ($I^2 = 53\%$). In elderly subjects undergoing hemodialysis, exercise training did not significantly increase 6-minute walking distance (SMD, 0.23; 95% CI, -0.76 to 1.23; $P = 0.65$) (Figure 3).

## Muscle Strength

In 9 trials with 142 subjects in the intervention group and 139 control subjects, lower extremity muscle strength was measured by using a dynamometer.[16,24,25,27,28,32,33,45,46] Only 1 of these 9 trials included elderly participants.[16] Supervised exercise training was shown to significantly increase lower extremity muscle strength in patients undergoing hemodialysis, with SMD of 0.94 (95% CI, 0.67–1.21; $P < 0.001$) in the total patient population. There was a low degree of heterogeneity across studies for muscle strength ($I^2 = 10\%$). In elderly subjects undergoing hemodialysis, exercise training was shown to significantly increase muscle strength (SMD, 1.99; 95% CI, 0.73–3.24; $P = 0.002$) (Figure 4).

## Quality of Life

Nine trials with 143 subjects in the intervention group and 121 subjects in the control group assessed the physical component summary of the short-form health survey.[16,25,29,32,34,38,39,45,46] Only 1 of these 9 trials included elderly participants.[16] Supervised exercise training was shown to significantly increase physical component summary score in patients undergoing hemodialysis, with SMD of 0.53 (95% CI, 0.52–0.82; $P < 0.001$) in the total patient population. There was only a low level of heterogeneity across studies for the physical component summary ($I^2 = 19\%$). Exercise training was not shown to significantly increase the physical component summary score in elderly subjects undergoing hemodialysis (SMD, 1.02; 95% CI, -0.04 to 2.09; $P = 0.06$) (Figure 5).

The mental component summary score of short-form health survey was measured in 8 trials, which included 124 subjects in the intervention group and 104 subjects in the control group.[16,25,29,34,38,39,45,46] Only 1 of these 8 studies included elderly participants.[16] There were no increases in the mental component summary score associated with supervised exercise training in elderly, nonelderly, or all subjects undergoing hemodialysis ($P = 0.13$, $P = 0.13$,

| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.3.1 Nonelderly** | | | | | | | | |
| Cheema 2007a | 16.7 | 40.5 | 24 | -2.9 | 25.8 | 25 | 12.1% | 0.57 [-0.00, 1.14] |
| DePaul 2002 | 3.3 | 45.7 | 15 | 3.4 | 86.7 | 14 | 10.0% | -0.00 [-0.73, 0.73] |
| Dobsak 2012 | 58.2 | 113.5 | 11 | -12.6 | 107.3 | 10 | 8.3% | 0.61 [-0.27, 1.50] |
| Groussard 2015 | 94 | 35 | 8 | 30 | 35.2 | 10 | 6.1% | 1.74 [0.61, 2.87] |
| Kirkman 2014 | 39 | 138.7 | 9 | 60 | 227.7 | 10 | 8.1% | -0.10 [-1.01, 0.80] |
| Koh 2010 | 63 | 160 | 14 | 21 | 215.3 | 16 | 10.1% | 0.21 [-0.51, 0.93] |
| Pellizzaro 2013a | 65.5 | 29.8 | 11 | -0.5 | 30.3 | 14 | 7.0% | 2.12 [1.10, 3.14] |
| Pellizzaro 2013b | 30.8 | 29.9 | 14 | -0.5 | 30.3 | 14 | 9.2% | 1.01 [0.22, 1.80] |
| Segura-Orti 2009 | 48.5 | 60.8 | 17 | 20.6 | 36.6 | 8 | 8.6% | 0.49 [-0.36, 1.35] |
| Wu 2014 | 33 | 166.2 | 32 | -18 | 166.8 | 33 | 13.3% | 0.30 [-0.19, 0.79] |
| **Subtotal (95% CI)** | | | **155** | | | **154** | **92.8%** | **0.61 [0.24, 0.98]** |
| Heterogeneity: Tau² = 0.19; chi² = 20.78, *df* = 9 (*P* = 0.01); *I*² = 57% | | | | | | | | |
| Test for overall effect: *Z* = 3.25 (*P* = 0.001) | | | | | | | | |
| **3.3.2 Elderly** | | | | | | | | |
| Matsufuji 2015 | 16.6 | 43.2 | 6 | 4.5 | 51.7 | 11 | 7.2% | 0.23 [-0.76, 1.23] |
| **Subtotal (95% CI)** | | | **6** | | | **11** | **7.2%** | **0.23 [-0.76, 1.23]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: *Z* = 0.46 (*P* = 0.65) | | | | | | | | |
| **Total (95% CI)** | | | **161** | | | **165** | **100.0%** | **0.58 [0.24, 0.93]** |
| Heterogeneity: Tau² = 0.17; chi² = 21.10, *df* = 10 (*P* = 0.02); *I*² = 53% | | | | | | | | |
| Test for overall effect: *Z* = 3.31 (*P* = 0.0009) | | | | | | | | |
| Test for subgroup differences: chi² = 0.48, *df* = 1 (*P* = 0.49), *I*² = 0% | | | | | | | | |

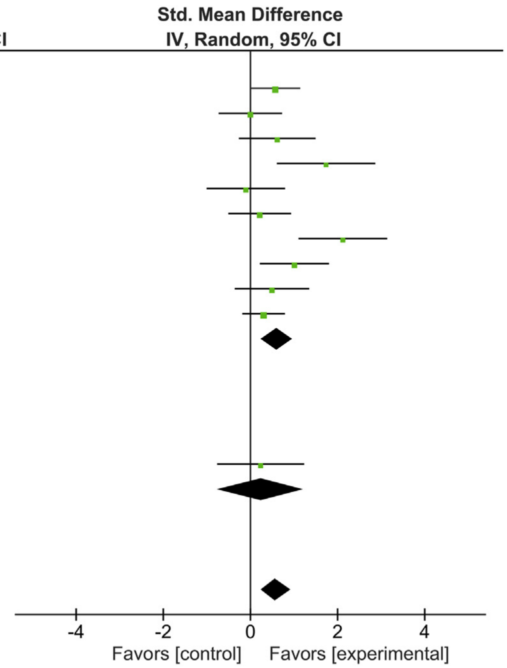


**Figure 3.** Forest plot showing the effects of supervised exercise training compared with usual care on changes in walking ability (6-minute walking distance). CI, confidence interval; IV, inverse variance; Std., standard.

and $P = 0.34$, respectively). There was a low degree of heterogeneity with regard to the mental component summary score across studies ($I^2 = 10\%$) (Figure 6).

### *Assessment of Risks of Bias and Publication Bias*

The risks of bias were frequently high or unclear in the studies (Table 2).[16,17,23–58] In 10 studies (33.3%) low-risk methods for random sequence generation were reported, and allocation was adequately concealed in 8 studies (26.7%). The assessor was blinded to patient allocation in 5 studies (16.7%), and both participants and investigators were masked and blinded in only 1 study (3.3%). Outcome data were incomplete or were reported only selectively in 4 (13.3%) and 7 (23.3%) studies, respectively. In 3 studies (10.0%) the analyses were reported as intention-to-treat. The total Tool for the assEssment

| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.1.1 Nonelderly** | | | | | | | | |
| Cheema 2007a | 15.2 | 15.4 | 24 | -2.4 | 13.8 | 25 | 16.4% | 1.19 [0.57, 1.80] |
| Chen 2010 | 4.4 | 7.0713 | 22 | -2.7 | 8.5563 | 22 | 15.9% | 0.89 [0.27, 1.51] |
| DePaul 2002 | 46.7 | 49.3 | 15 | 1.4 | 44.7 | 14 | 10.9% | 0.93 [0.16, 1.71] |
| Dong 2010 | 123 | 187.8776 | 10 | 52 | 223.4862 | 12 | 9.2% | 0.33 [-0.52, 1.17] |
| Johansen 2006 | 8.6 | 6.9 | 19 | 0.8 | 2 | 17 | 11.6% | 1.47 [0.72, 2.21] |
| Kirkman 2014 | 108 | 138.8 | 9 | 50 | 110.3176 | 10 | 8.0% | 0.44 [-0.47, 1.36] |
| Segura-Orti 2009 | 1.5 | 4.2 | 17 | -2.3 | 4.8 | 8 | 8.6% | 0.84 [-0.04, 1.71] |
| Song 2012 | 4.3 | 8.7 | 20 | -1.4 | 7 | 20 | 15.1% | 0.71 [0.07, 1.35] |
| **Subtotal (95% CI)** | | | **136** | | | **128** | **95.6%** | **0.89 [0.64, 1.15]** |
| Heterogeneity: Tau² = 0.00; chi² = 6.13, *df* = 7 (*P* = 0.53); *I*² = 0% | | | | | | | | |
| Test for overall effect: *Z* = 6.80 (*P* < 0.00001) | | | | | | | | |
| **3.1.2 Elderly** | | | | | | | | |
| Matsufuji 2015 | 0.04 | 0.06 | 6 | -0.1 | 0.07 | 11 | 4.4% | 1.99 [0.73, 3.24] |
| **Subtotal (95% CI)** | | | **6** | | | **11** | **4.4%** | **1.99 [0.73, 3.24]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: *Z* = 3.11 (*P* = 0.002) | | | | | | | | |
| **Total (95% CI)** | | | **142** | | | **139** | **100.0%** | **0.94 [0.67, 1.21]** |
| Heterogeneity: Tau² = 0.02; chi² = 8.93, *df* = 8 (*P* = 0.35); *I*² = 10% | | | | | | | | |
| Test for overall effect: *Z* = 6.84 (*P* < 0.00001) | | | | | | | | |
| Test for subgroup differences: chi² = 2.81, *df* = 1 (*P* = 0.09), *I*² = 64.4% | | | | | | | | |

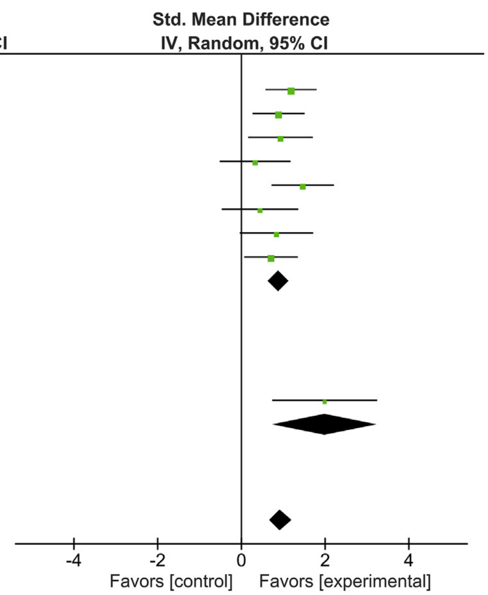


**Figure 4.** Forest plot showing the effects of supervised exercise training compared with usual care on changes in muscle strength (lower-extremity muscle strength). CI, confidence interval; IV, inverse variance; Std., standard.

| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.8.1 Nonelderly** | | | | | | | | |
| Chen 2010 | 21 | 36 | 22 | -2 | 24 | 22 | 15.8% | 0.74 [0.13, 1.35] |
| Giannaki 2013b | 11.5 | 18.4 | 15 | 6.1 | 5.7 | 7 | 8.5% | 0.33 [-0.57, 1.23] |
| Johansen 2006 | 11.5 | 15.4 | 19 | -5.9 | 24.3 | 17 | 13.3% | 0.85 [0.16, 1.53] |
| Koh 2010 | -6 | 29.7 | 15 | 0 | 38.2 | 15 | 12.4% | -0.17 [-0.89, 0.55] |
| Molsted 2004 | 4.7 | 4.5 | 10 | 5 | 6.3 | 7 | 7.5% | -0.05 [-1.02, 0.91] |
| Ouzouni 2009 | 4 | 7.8 | 19 | -0.1 | 7.9 | 14 | 12.8% | 0.51 [-0.19, 1.21] |
| Segura-Orti 2009 | 2 | 12.1 | 17 | -1.4 | 11.1 | 8 | 9.5% | 0.28 [-0.57, 1.12] |
| Song 2012 | 7.9 | 9.9 | 20 | -2.1 | 9.1 | 20 | 14.0% | 1.03 [0.37, 1.69] |
| **Subtotal (95% CI)** | | | **137** | | | **110** | **93.7%** | **0.50 [0.20, 0.80]** |
| Heterogeneity: Tau² = 0.04; chi² = 9.03, *df* = 7 (*P* = 0.25); *I*² = 22% | | | | | | | | |
| Test for overall effect: *Z* = 3.26 (*P* = 0.001) | | | | | | | | |
| **3.8.2 Elderly** | | | | | | | | |
| Matsufuji 2015 | 9.6 | 12.1 | 6 | -1.8 | 9.7 | 11 | 6.3% | 1.02 [-0.04, 2.09] |
| **Subtotal (95% CI)** | | | **6** | | | **11** | **6.3%** | **1.02 [-0.04, 2.09]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: *Z* = 1.88 (*P* = 0.06) | | | | | | | | |
| **Total (95% CI)** | | | **143** | | | **121** | **100.0%** | **0.53 [0.25, 0.82]** |
| Heterogeneity: Tau² = 0.04; chi² = 9.86, *df* = 8 (*P* = 0.27); *I*² = 19% | | | | | | | | |
| Test for overall effect: *Z* = 3.67 (*P* = 0.0002) | | | | | | | | |
| Test for subgroup differences: chi² = 0.87, *df* = 1 (*P* = 0.35), *I*² = 0% | | | | | | | | |

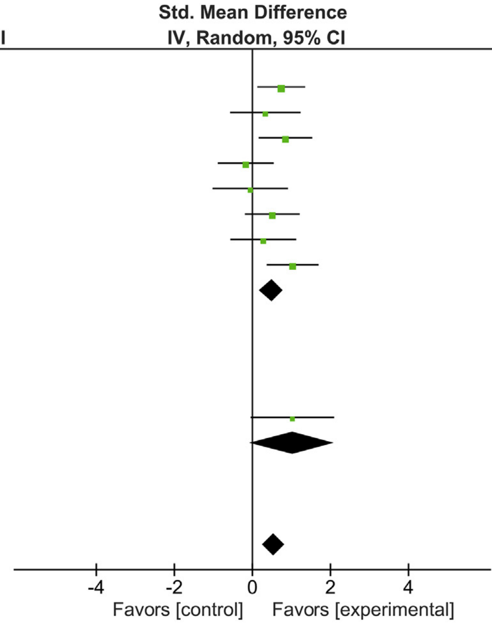


**Figure 5.** Forest plot showing the effects of supervised exercise training compared with usual care on changes in quality of life (short-form health survey: physical component summary). CI, confidence interval; IV, inverse variance; Std., standard.

of Study qualiTy and reporting in EXercise score, study quality score, and study reporting score of the studies were 7.9 ± 2.3, 2.5 ± 1.1, and 5.4 ± 1.5, respectively.

Egger's regression test for publication bias was not significant for exercise tolerance ($P = 0.27$) or walking ability ($P = 0.93$). Funnel plots were symmetrical for each outcome (Figures 7 and 8), and we did not detect evidence of publication bias for other outcomes because fewer than 10 studies dealt with muscle strength and QoL.

## DISCUSSION

We conducted a systematic review of the literature to evaluate the effects of supervised exercise training on exercise tolerance, walking ability, muscle strength, and QoL in elderly people undergoing hemodialysis

| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3.9.1 Nonelderly** | | | | | | | | |
| Chen 2010 | 6 | 27 | 22 | 1 | 23 | 22 | 19.4% | 0.20 [-0.40, 0.79] |
| Giannaki 2013b | 9.3 | 26.7 | 15 | 3.1 | 9.8 | 7 | 9.2% | 0.26 [-0.64, 1.16] |
| Koh 2010 | -2 | 29.7 | 15 | -2 | 36.1 | 15 | 14.0% | 0.00 [-0.72, 0.72] |
| Molsted 2004 | -1.3 | 8.3 | 10 | -2.7 | 14.1 | 7 | 8.1% | 0.12 [-0.85, 1.09] |
| Ouzouni 2009 | 0 | 14.2 | 19 | -0.2 | 9.7 | 14 | 14.9% | 0.02 [-0.67, 0.71] |
| Segura-Orti 2009 | 1.4 | 16.6 | 17 | 3.2 | 10.3 | 8 | 10.5% | -0.12 [-0.96, 0.72] |
| Song 2012 | 6.5 | 11.6 | 20 | -1.9 | 8.9 | 20 | 16.7% | 0.80 [0.15, 1.44] |
| **Subtotal (95% CI)** | | | **118** | | | **93** | **92.9%** | **0.21 [-0.06, 0.49]** |
| Heterogeneity: Tau² = 0.00; chi² = 4.42, *df* = 6 (*P* = 0.62); *I*² = 0% | | | | | | | | |
| Test for overall effect: *Z* = 1.51 (*P* = 0.13) | | | | | | | | |
| **3.9.2 Elderly** | | | | | | | | |
| Matsufuji 2015 | 0.14 | 5.4 | 6 | 5.2 | 6.3 | 11 | 7.1% | -0.80 [-1.84, 0.24] |
| **Subtotal (95% CI)** | | | **6** | | | **11** | **7.1%** | **-0.80 [-1.84, 0.24]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: *Z* = 1.50 (*P* = 0.13) | | | | | | | | |
| **Total (95% CI)** | | | **124** | | | **104** | **100.0%** | **0.14 [-0.15, 0.42]** |
| Heterogeneity: Tau² = 0.02; chi² = 7.81, *df* = 7 (*P* = 0.35); *I*² = 10% | | | | | | | | |
| Test for overall effect: *Z* = 0.95 (*P* = 0.34) | | | | | | | | |
| Test for subgroup differences: chi² = 3.39, *df* = 1 (*P* = 0.07), *I*² = 70.5% | | | | | | | | |

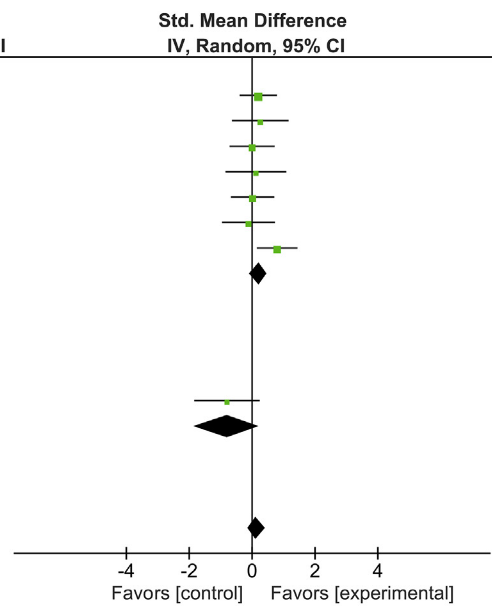


**Figure 6.** Forest plot showing the effects of supervised exercise training compared with usual care on changes in quality of life (short-form health survey: mental component summary). CI, confidence interval; IV, inverse variance; Std., standard.

**Table 2.** Summary of risk of bias assessment

| Studies | The 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) | Study quality score (/5) | Study reporting score (/10) |
| Akiba *et al.* (1995)[50] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 4 | 1 | 3 |
| Carmack *et al.* (1995)[23] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 6 | 3 | 4 |
| Carney *et al.* (1987)[51] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 7 | 3 | 5 |
| Cheema *et al.* (2007)[24] | Low bias | Low bias | High bias | High bias | Low bias | Low bias | Unclear | 10 | 3 | 7 |
| Chen *et al.* (2010)[25] | Unclear | Low bias | High bias | Low bias | High bias | High bias | Low bias | 13 | 4 | 8 |
| de Lima *et al.* (2013)[52] | Low bias | Low bias | Unclear | Unclear | High bias | Unclear | Low bias | 9 | 4 | 5 |
| Deligiannis *et al.* (1999)[26] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 6 | 3 | 4 |
| DePaul *et al.* (2002)[27] | Low bias | Low bias | High bias | Low bias | Low bias | Unclear | Unclear | 10 | 4 | 6 |
| Dobsak *et al.* (2012)[53] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 6 | 1 | 5 |
| Dong *et al.* (2011)[28] | Low bias | Low bias | Unclear | Unclear | Low bias | Low bias | Low bias | 9 | 4 | 5 |
| Giannaki *et al.* (2013)[29] | Unclear | Low bias | High bias | Unclear | Unclear | Low bias | Unclear | 10 | 3 | 7 |
| Giannaki *et al.* (2013)[29] | Unclear | Unclear | High bias | Unclear | Low bias | Low bias | Unclear | 7 | 3 | 5 |
| Goldberg *et al.* (1983)[31] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 4 | 1 | 3 |
| Goldberg *et al.* (1986)[30] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 5 | 1 | 4 |
| Groussard *et al.* (2015)[17] | Unclear | Unclear | High bias | Unclear | Unclear | Unclear | Low bias | 6 | 3 | 4 |
| Guadalupe *et al.* (2016)[54] | Low bias | Low bias | Low bias | Low bias | Unclear | Unclear | Low bias | 10 | 5 | 5 |
| Johansen *et al.* (2006)[32] | Unclear | Low bias | Unclear | Unclear | Unclear | Unclear | Unclear | 9 | 3 | 7 |
| Kirkman *et al.* (2014)[33] | Unclear | Unclear | High bias | Unclear | Unclear | Low bias | Low bias | 7 | 3 | 5 |
| Koh *et al.* (2010)[34] | Low bias | Low bias | High bias | High bias | High bias | High bias | Low bias | 10 | 4 | 6 |
| Konstantinidou *et al.* (2002)[35] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 8 | 3 | 6 |
| Koufaki *et al.* (2002)[36] | Low bias | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 9 | 3 | 6 |
| Kouidi *et al.* (2009)[37] | Low bias | Unclear | Unclear | Low bias | Unclear | Low bias | Low bias | 13 | 4 | 8 |
| Kouidi *et al.* (1997)[55] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 8 | 3 | 6 |
| Matsufuji *et al.* (2015)[16] | Low bias | Low bias | Unclear | Unclear | High bias | Low bias | Unclear | 8 | 4 | 4 |
| Matsumoto *et al.* (2007)[56] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 7 | 3 | 5 |
| Molsted *et al.* (2004)[38] | Low bias | Unclear | Unclear | Low bias | Unclear | Unclear | Unclear | 10 | 4 | 6 |
| Ouzouni *et al.* (2009)[39] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 8 | 3 | 6 |
| Painter *et al.* (2002)[40] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 7 | 3 | 5 |
| Parsons *et al.* (2004)[41] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 6 | 3 | 4 |
| Pellizzaro *et al.* (2013)[42] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Low bias | 8 | 3 | 6 |
| Petraki *et al.* (2008)[43] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 7 | 3 | 5 |
| Reboredo *et al.* (2011)[44] | Unclear | Unclear | Unclear | Unclear | Unclear | Low bias | Unclear | 8 | 3 | 6 |
| Roboredo *et al.* (2015)[57] | Unclear | Unclear | Unclear | Unclear | Unclear | Low bias | Low bias | 7 | 3 | 5 |
| Segura-Orti *et al.* (2009)[45] | Low bias | Unclear | Low bias | Low bias | Unclear | Unclear | Unclear | 11 | 3 | 8 |
| Song and Sohng (2012)[46] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 7 | 3 | 5 |
| Tsuyuki *et al.* (2003)[47] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | 3 | 1 | 1 |
| van Vilsteren *et al.* (2005)[48] | Unclear | Unclear | Unclear | Unclear | High bias | Unclear | Low bias | 8 | 1 | 7 |
| Wilund *et al.* (2010)[58] | Unclear | Unclear | Unclear | Low bias | High bias | Unclear | Low bias | 9 | 3 | 6 |
| Wu *et al.* (2014)[49] | Low bias | Low bias | Unclear | Unclear | Unclear | Unclear | Low bias | 10 | 4 | 6 |

TESTEX, Tool for the assEssment of Study qualiTy and reporting in Exercise.

and to provide an update of recent studies regarding the effects of exercise training on functional status. Only 1 study targeted people aged 60 years and older undergoing hemodialysis, and thus we could not perform a meta-analysis to confirm the effects of exercise training in elderly people undergoing hemodialysis. There is still insufficient evidence regarding the effectiveness of exercise training for elderly people undergoing hemodialysis. Further RCTs will be needed to clarify the effectiveness of exercise training on exercise tolerance, walking ability, muscle strength, and QoL in elderly people undergoing hemodialysis. On the other hand, our findings suggest that supervised exercise training has significant beneficial effects on exercise tolerance, walking ability, muscle strength, and QoL (physical component summary score) in the general hemodialysis population.

In 2016, the European Renal Best Practice Guideline Development Group published new clinical practice guidelines for elderly patients with chronic kidney disease,[59] recommending the use of physical functional assessment tools and interventions aimed at increasing functional status in older patients with renal failure. Given the importance of these recommendations in

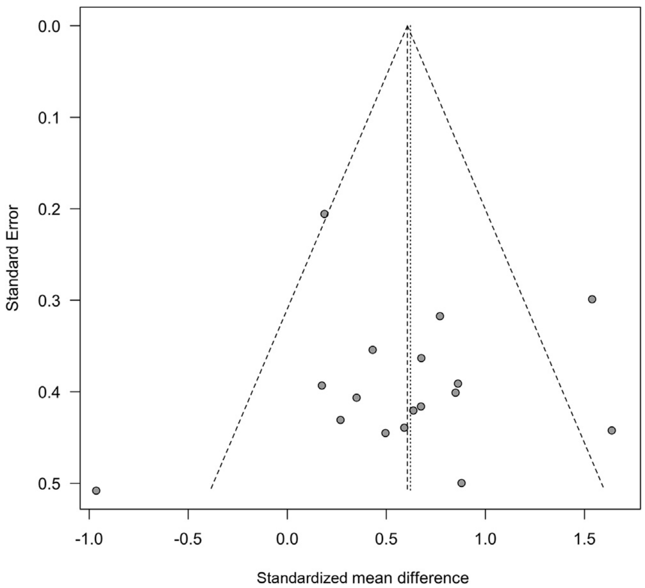


**Figure 7.** Funnel plot test exploring publication bias (exercise tolerance: peak/maximum oxygen consumption).

clinical settings, the present study assessed the impact of supervised exercise on functional status in elderly patients undergoing hemodialysis.

Although the findings of the present study were generally in agreement with those of previous meta-analyses,[13,14,60] our analysis of the effectiveness of exercise training in elderly people as compared with nonelderly people was somewhat inconclusive. In particular, we found no studies in which the association between exercise training and exercise tolerance was evaluated in elderly people undergoing hemodialysis. Groussard *et al*.[17] reported that an intradialytic aerobic exercise training program significantly

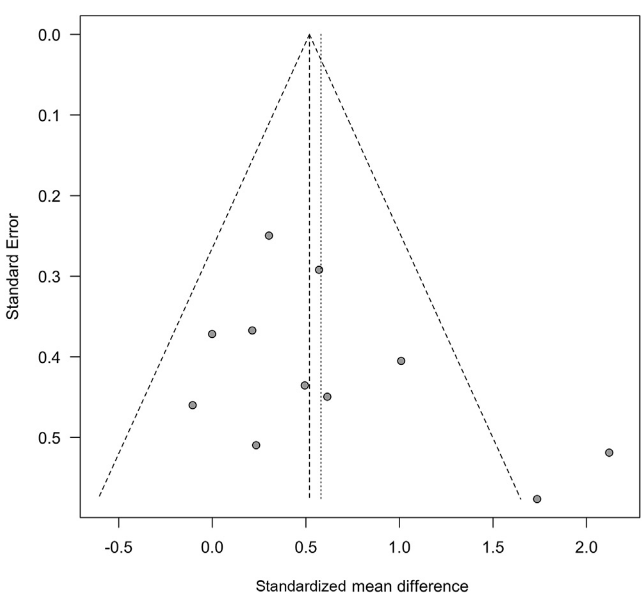


**Figure 8.** Funnel plot test exploring publication bias (walking ability: 6-minute walk distance).

improved 6-minute walking distance in middle-aged and elderly people, although no changes were observed in peak $VO_2$. They postulated that this discrepancy was due to the short duration of the intervention program and the use of aerobic training alone, rather than a combination of aerobic and strength training. Moreover, people undergoing hemodialysis might not achieve maximum $VO_2$ because of functional limitations caused by bone, joint, and/or muscle pain and muscle fatigue. Because elderly patients are likely to experience difficulty participating in combined, prolonged exercise training, peak or maximum $VO_2$ evaluated by cardiopulmonary exercise testing might not provide appropriate outcome measurements in most elderly patients. On the other hand, 6-minute walking distance—which has proven relative and absolute reliability in elderly people undergoing hemodialysis,[61] is used in clinical settings as an index of exercise tolerance, and provides prognostic information comparable to that of peak $VO_2$ in elderly patients with heart failure[62]—is an appropriate outcome measure for exercise training in elderly people undergoing hemodialysis.

The prevalence of frailty is higher among elderly people with end-stage renal disease compared with community-dwelling elderly people. In a previous study, 85.9% of elderly people undergoing hemodialysis were found to be frail or intermediately frail.[63] Given that muscle weakness is an important component of frailty, our review of the effects of exercise training on physical function in these populations could be of clinical significance.

Matsufuji *et al*. evaluated the effects of chair stand exercise on physical performance among elderly people (≥60 years old) undergoing hemodialysis and reported improvements in their activities of daily living by strengthening the quadriceps.[16] Chair stand exercise is suitable for elderly patients, because it does not require any special equipment or place. Low-intensity strength training with ankle weights was also shown to improve physical performance in elderly patients.[25] Because reduced physical performance is a strong predictor of poor prognosis in people undergoing hemodialysis,[7,8] participation in chair stand exercise or low-intensity weight training may not only increase QoL but also improve prognosis in elderly people undergoing hemodialysis. In a recent multicenter RCT, Zoccali *et al*.[64] revealed that a low-intensity, home-based walking program improved functional status compared with usual care in patients with end-stage renal disease. These interventions are inexpensive, safe, and feasible for elderly people undergoing hemodialysis.

This study has several limitations. First, because our literature searches were restricted to studies published in English, some articles might have been overlooked. Second, the number of studies that included elderly people (≥60 years old) undergoing hemodialysis was too small for performance of meta-analysis. Barriers to exercise (e.g. self-efficacy, discomfort, disability, fear of injury, habits, environmental factors, cognitive decline, and fatigue)[15] could explain why elderly patients were not often recruited for exercise trials. Studies targeting elderly patients can be helpful in designing exercise programs and exercise goals that take into consideration patient barriers. Although the optimal program has yet to be identified, it might be more effective to implement programs such as chair stand exercise[16] and electromyostimulation[53] that are affordable and more feasible for older patients. A recent non-RCT showed that low-intensity physical exercise improved muscle strength, functional capacity, and QoL in subjects aged 80 years and older.[65] Further RCTs in elderly people undergoing hemodialysis will be necessary to confirm these findings. Third, the present review focused on the effects of supervised exercise training, without taking into consideration the effects of home-based exercise training. However, Konstantinidou *et al*. compared the effects of home-based exercise and supervised exercise training in people undergoing hemodialysis and reported that the former did not show a greater improvement in exercise tolerance compared with the latter.[35] On the other hand, another study suggested greater benefits of independent home-based exercise compared with intradialytic exercise in people undergoing hemodialysis. Therefore further studies will be needed to compare the effectiveness of home-based exercise and supervised exercise training in this patient population.

In conclusion, our meta-analysis confirmed the positive effects of supervised exercise training on exercise tolerance, walking ability, muscle strength, and QoL in the general hemodialysis population. However, there still is insufficient evidence regarding the effectiveness of exercise training for elderly people undergoing hemodialysis, despite a strong rationale for the use of exercise in the population. Future studies should investigate whether supervised exercise training leads to similar improved outcomes in elderly people undergoing hemodialysis and identify the most favorable exercise program for this patient population.

## DISCLOSURE

All the authors declared no competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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## SUPPLEMENTARY MATERIAL

**Appendix S1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist.

**Appendix S2.** Search strategy.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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