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ORIGINAL ARTICLE

Home-based exercise in patients on maintenance dialysis: a systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Background. The impact of home-based exercise on physical performance and quality of life (QoL) in patients on maintenance dialysis has not yet been fully established.

Methods. We searched four large electronic databases to identify randomized controlled trials (RCTs) reporting the impact of home-based exercise interventions vs. usual care or intradialytic exercise interventions, on physical performance and QoL in patients on dialysis. The meta-analysis was performed using fixed effects modeling.

Results. We included 12 unique RCTs involving 791 patients of various ages on maintenance dialysis. Home-based exercise interventions were associated with an improvement of walking speed at the 6 Minutes Walking Test [6MWT; nine RCTs; pooled weighted mean differences (WMD): 33.7 m, 95% confidence interval (CI) 22.8–44.5; $P < 0.001$; $I^2 = 0\%$) and in aerobic capacity as assessed by the peak oxygen consumption (VO_2 peak; 3 RCTs; pooled WMD: 2.04 ml/kg/min, 95% CI 0.25–3.83; $P = 0.03$; $I^2 = 0\%$). They were also associated with improved QoL, as assessed by the Short Form (36) Health (SF-36) score. Stratifying the RCTs by control groups, no significant difference was found between home-based exercise and intradialytic exercise interventions. Funnel plots did not reveal any significant publication bias.

Conclusions. Our systematic review and meta-analysis showed that home-based exercise interventions for 3–6 months were associated with significant improvements in physical performance in patients on maintenance dialysis. However, further RCTs with a longer follow-up should be conducted to assess the safety, adherence, feasibility, and effects on QoL of home-based exercise programs in dialysis patients.

Keywords: end-stage kidney disease, home-based exercise, maintenance dialysis, physical performance, quality of life

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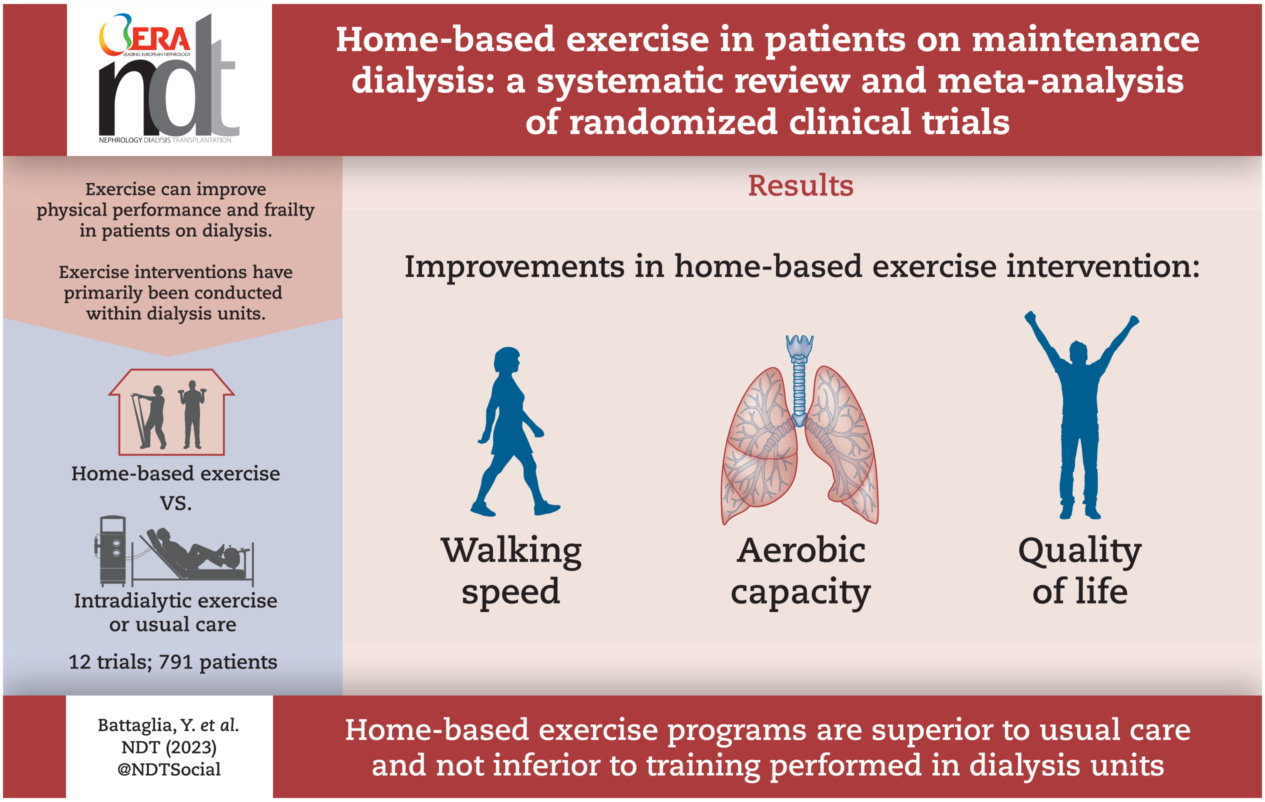
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Physical inactivity, frequent in maintenance dialysis patients, leads to a state of frailty and increased mortality.
- Aerobic exercise and/or resistance training programs to improve the physical performance of dialysis patients have mostly been conducted in dialysis units, but are limited by many environmental barriers.
- Specific systematic reviews and meta-analyses evaluating the impact of home exercise on physical performance and quality of life in dialysis patients have not yet been published.

This study adds:

- Our systematic review and meta-analysis including 12 unique randomized clinical trials showed that the prescription of home-based exercise programs from 3 to 6 months in end-stage kidney disease (ESKD) patients on dialysis had a beneficial impact on physical function that was superior to usual care and not inferior to training performed in dialysis units.
- Home-based exercise interventions were also associated with improved quality of life, as assessed by the Short Form (36) Health (SF-36) score. Funnel plots did not reveal any significant publication bias.
- The impact of home-based exercise programs was similar in dialysis patients, regardless of their demographic characteristics and the presence of the exercise supervisor.

Potential impact:

- The findings of this systematic review and meta-analysis should lead to increased awareness regarding the positive impact of home-based exercise programs for 3–6 months on physical performance in dialysis patients.
- These data suggest that supervised home-based exercise programs could be routinely prescribed in dialysis patients as good daily clinical practice.

INTRODUCTION

Dialysis is the most common renal replacement therapy (RRT) in patients with end-stage kidney disease (ESKD) [1] However, there is still compelling evidence regarding the adverse effects of hemodialysis (HD) or peritoneal dialysis (PD) on quality of life (QoL) as well as regarding the higher risk of malnutrition, hospitalization, and even mortality in ESKD patients on dialysis [2, 3]. Indeed, in particular, the detection of skeletal muscle atrophy, functional limitations, weakness, slow walking, and disability, resulting in physical inactivity [4], lead to a frailty state in more than 40% of HD patients [5]. Therefore, to prevent and treat frailty, exercise is seen as the most feasible way, improving physical performance [6–8]. A large number of studies, including randomized clinical trials (RCTs), have been published in recent years involving aerobic exercise and/or resistance training interventions conducted primarily within dialysis units among HD patients [9–11]. However, to reduce healthcare costs [12] and overcome common barriers to physical activity [13], there has been growing interest in developing home-based exercise programs [14–18].

To our knowledge, to date there is no specific systematic review and meta-analysis investigating the impact of home-based exercise programs on physical performance and QoL in ESKD patients on dialysis. Thus, the aim of this systematic review and meta-analysis of RCTs was to evaluate, primarily, changes in the walking speed, aerobic capacity, muscle strength, and, secondarily, in QoL between patients randomly assigned to usual care or intradialytic exercise interventions and those randomly assigned to home-based exercise interventions.

MATERIALS AND METHODS

Protocol registration

The present systematic review and meta-analysis was registered in advance on Open Science Frameworks (registration DOI: https://doi.org/10.17605/OSF.IO/ZPN3U).

Search strategy and selection criteria

We systematically searched PubMed, Scopus, Google Scholar, and Web of Science databases from inception to 13 August 2022 to identify RCTs reporting the impact of home-based exercise interventions on physical performance and QoL in ESKD adult patients (≥18 years of age) on maintenance HD or PD. The free text search terms were: "exercise," AND "home," AND "dialysis," OR physical capacity," OR "muscle," OR "quality of life." No language restriction was applied. We also reviewed references from original papers and review articles to identify additional suitable studies not covered by our original database searches. This systematic review and meta-analysis were performed according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [19]. Exclusion criteria were: (i) meeting abstracts, case reports, reviews, practice guidelines, case-control or cross-sectional or longitudinal studies; (ii) RCTs that did not report any estimates of the outcomes of interest; (iii) RCTs conducted in the pediatric population (<18 years of age); and (iv) RCTs conducted in adults with kidney failure, but not on dialysis.

Data extraction and quality assessment

Data from eligible RCTs were independently extracted by two authors (Y.B. and M.A.). Disagreements at this level were resolved by consensus and a third author if needed (A.M.). For all RCTs, we extracted data on first author, publication year, study country, sample size, population characteristics, duration of the trial, intervention type, as well as outcomes as far as efficacy or harm are concerned. Specifically, the primary outcome measures of interest were changes in the walking speed as assessed by means of the 6 Minutes Walking Test (6MWT), aerobic capacity as assessed by the peak oxygen consumption (VO_2 peak) and muscle strength as assessed by the hand grip strength test (HGST) between patients randomly assigned to usual care or intradialytic exercise interventions and those randomly assigned to home-based exercise interventions. As secondary outcome measures of interest, we extracted data on QoL by Short Form Health Survey 36 (SF-36), when available. We did not contact any corresponding authors of the included RCTs to obtain additional information for the meta-analysis. In case of multiple publications, we included the most current or complete information.

Two investigators (Y.B. and M.A.) independently assessed the risk of bias for each eligible RCT. We used the Cochrane Collaboration tool, which assesses seven potential sources of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and staff (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. For each of these domains, we classified each eligible RCT into one of three categories: low, unclear, or high risk of bias [20].

Data synthesis and analysis

The effect sizes of the primary outcome measures of interest for each RCT were displayed as weighted mean difference (WMD) and 95% confidence intervals (CI) for changes in the walking speed (as assessed by the 6MWT), aerobic capacity (as assessed by VO_2 peak) and muscle strength (as assessed by the HGST) between patients randomly assigned to usual care or intradialytic exercise interventions and those randomly assigned to home-based exercise interventions. The estimate of the overall effect size was calculated using a fixed effects model, as there was no heterogeneity among the eligible RCTs (see below) [20]. The outcome measures of interest were reported as median, range, or 25th–75th percentiles, mean, and standard deviation (SD) values were estimated using validated formulas [21]. Additionally, if unavailable, the SDs of the mean differences were estimated using the following formula: $SD = [(\text{pre-treatment SD})^2 + (\text{post-treatment SD})^2 - (2R \times \text{pre-treatment SD} \times \text{post-treatment SD})]^{½}$ [22]. An R value of 0.5 was assumed in this meta-analysis because the pretest–posttest correlation coefficients I were not reported in the eligible RCTs [22]. Visual inspection of the forest plots was used to estimate heterogeneity. Heterogeneity among the included RCTs was also tested by means of the I^2-statistics. The interpretation of the I^2-statistics is as follows: I^2-values of ∼25% show low heterogeneity, I^2-values of ∼50% show medium heterogeneity, whereas I^2-values of ∼75% show high heterogeneity [23]. Publication bias was assessed both by the visual inspection of the funnel plots and by Egger's regression test [24]. Univariate meta-regression analyses were also performed to test the potential effect of specific moderator variables [such as age, gender, body mass index (BMI), percentage of patients with type 2 diabetes (T2DM) and dialysis vintage] on the effect size for the changes in the walking speed between patients randomly assigned to usual care or intradialytic exercise interventions and those randomly assigned to home-based exercise interventions. Finally, we tested for possible excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies one at a time.

All statistical tests were two-sided and used a significance level of P-value < 0.05. All statistical analyses were performed using the STATA® 16.1 software with the meta-analysis package (STATA, College Station, TX, USA) and R software V.4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with "meta" and "metafor" packages.

RESULTS

Figure 1 summarizes the results of the literature search and study selection. Based on the titles and abstracts of 112 selected papers (after excluding duplicates), we initially identified 38 potentially

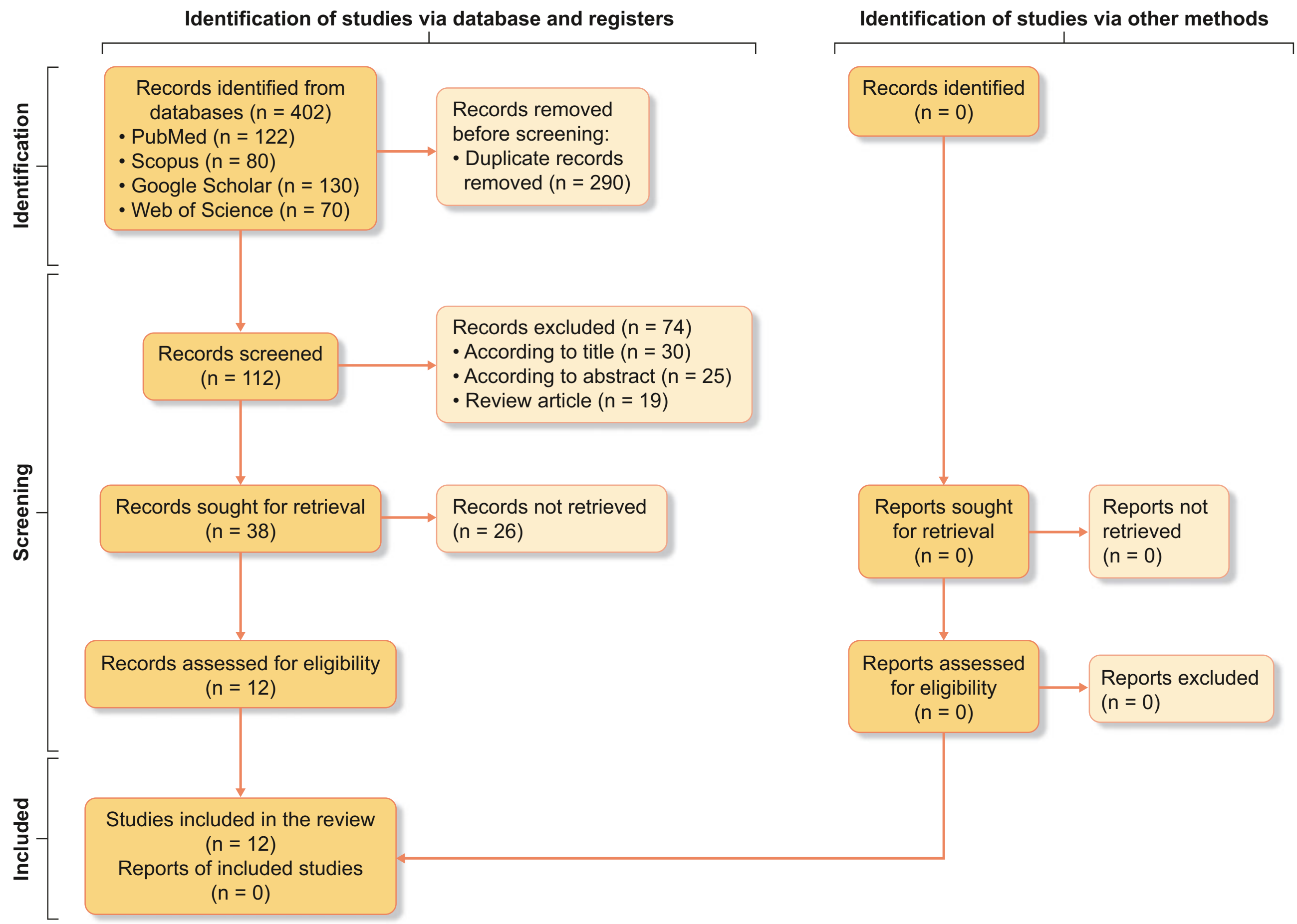


Figure 1: PRISMA flow diagram.

eligible studies from PubMed, Scopus, Google Scholar, and Web of Science databases [16, 25–61]. After reviewing the full text of these potentially eligible studies, we excluded 26 studies [25, 29, 31, 33–35, 38–40, 42–49, 51–55, 57, 59–61] due to unsatisfactory inclusion criteria, such as patients with kidney failure not on dialysis, kidney transplant recipients, mixed (in-center and home-based) exercise programs, and/or unsatisfactory outcome measures, such as biochemistry, questionnaires, echocardiographic indices, and adherence. Therefore, in our meta-analysis, we included a total of 12 unique RCTs. Their main characteristics are shown in Table 1: 40.8% were men; mean age was 63 ± 6 years, mean BMI was 26.5 ± 1.8 kg/m^2, mean dialysis vintage was 57.2 ± 20.7 months, and 22.3% patients had T2DM (pooled data of 791 patients of various ages). Nine RCTs reported data on changes in the walking speed as assessed by the 6MWT [16, 26–28, 30, 37, 41, 56, 58]; three RCTs had data on changes in aerobic capacity as assessed by VO_2 peak [41, 50, 56]; two RCTs showed data regarding changes in muscle strength as assessed by handgrip [32, 37], and four RCTs also had data on QoL as assessed by SF-36 score [28, 32, 36, 58]. Seven studies were conducted in Europe (Italy, Greece, and Spain), one in Australia, two in Japan, and two in North America (USA and Canada). Most RCTs had an unsupervised aerobic exercise three times a week or more. Among eligible RCTs, exercise intensity was assessed by several methods, such as the Borg scale [62], percentage of maximum heart rate, and patient tolerance (Table 1). Incomparable measures of adherence to home-based exercise programs were taken in six studies, of which three had >70% of patients achieving the exercise program goal [16, 26, 27, 37, 56, 58]. Supplementary Table 1 (Supplementary Material) reports the risk of bias assessed by the Cochrane RCT Quality Scale, which was low for most domains in all eligible studies.

Figure 2 shows the forest plot and pooled estimates of the impact of home-based exercise interventions on walking speed. Compared with usual care or intradialytic exercise interventions, home-based exercise interventions were associated with significant improvement in the 6MWT (nine RCTs; pooled WMD 33.7 m, 95% CI 22.8–44.5; Z-test = 6.08, $P < 0.001$; $I^2 = 0\%$). By dividing the controls in two different subgroups, no significant difference was found between home-based exercise and intradialytic exercise interventions (Supplementary Fig. 1). However, this analysis should be taken with caution, as only two eligible studies were used to compare home-based exercise and intradialytic exercise interventions in terms of 6MWT improvement. Stratifying eligible RCTs by countries, we observed that the strength of the association was mainly driven by studies conducted in Europe (Supplementary Fig. 2). We also tested for the possibility of excessive influence of individual RCTs, using a sensitivity test that eliminates each of the eligible RCTs one at a time. Of note, removing each of the nine RCTs from the pooled primary analysis, no effect on the observed significant improvements in the 6MWT provided by home-based exercise interventions was shown (Supplementary Fig. 3).

Figure 3 shows the forest plot and pooled estimates of the impact of home-based exercise interventions on aerobic capacity. Compared with usual care or intradialytic exercise

Table 1: Main characteristics of the eligible 12 RCTs assessing the impact of home-based exercise interventions on physical performance and QoL.

	Sample		Intervention	
Authors, year, country [PMID] (Ref.)	Inclusion/exclusion criteria	Sample characteristics	Duration of the RCT Groups	Adherence
Koh *et al.* 2010 Australia [19 932 545] [58]	Inclusion: • age ≥18 years • on HD > 3 months Exclusion: • unstable angina • lower-limb amputation • >120 minutes of moderate intensity physical activity per week	Home-based: *n*.15 (age 52.1 ± 13.6 years, 73.3% male) Intradialytic: *n*.15 (age 52.3 ± 10.9 years, 66.6% male) Usual care: *n*.16 (age 51.3 ± 14.4 years, 50.0% male)	24 weeks Home-based: • 30-45 min aerobic walking • 3 times/week • intensity Borg scale 12–13 Intradialytic: • 30-45 min aerobic ergometer cycling • 3 times/week • intensity Borg scale 12–13 Usual care • generic advice to maintain active lifestyle	Home-based: 71.0% sessions completed (by diaries) Intradialytic: 75.0% session completed (by diaries)
Bohm *et al.* 2014 Canada [25 061 127] [56]	Inclusion: • age ≥18 years • on HD >3 months with KT/V > 1.2 over the month prior to study entry • English comprehension Exclusion: • clinical or physical limitation to ambulate	Home-based: *n*.30 (age 53.0 ± 16.9 years, 60.0% male) Intradialytic: *n*.30 (age 52.0 ± 14.5 years, 63.0% male)	24 weeks Home-based: • 10–60 min aerobic walking • 7 times/week, 10 000 steps/day • intensity Borg scale 12–14 Intradialytic: • aerobic ergometer cycling • 3 times/week • intensity Borg scale 12–14	Home-based: 0 participants met the goal of >10 000 steps/day Intradialytic: 6 participants met the goal of >180 min cycling/week
Konstantinidou *et al.* 2002 Greece [11 900 261] [50]	Inclusion: • age 21–65 years • on HD > 6 months Exclusion: • clinical or physical limitation to ambulate	Home-based: *n*.10 (age 51.4 ± 12.5 years, 80.0% male) Center-based: *n*.16 (age 46.4 ± 13.9 years, 69.0% male) Intradialytic: *n*.10 (age 48.3 ± 12.1 years, 80.0% male) Usual care: *n*.12 (age 50.2 ± 7.9 years, 33.0% male)	24 weeks Home-based • 30 min exercise training program with cycle-ergometer, flexibility, and muscular extension exercises • 5 times/week • intensity 50%–60% of max HR Center-based • 10 min warm-up, 30 min, aerobic cycle-ergometer, flexibility, muscle extension exercise, 10 min cool down period • 3 times/week • intensity 60%–70% of max HR Intradialytic • 30 min bed ergometer, 30 min strength and flexibility exercises with therabands • 3 times/week • intensity 70% of max HR Usual care • generic advice to maintain active lifestyle	Not measured

Table 1: Continued

	Sample		Intervention	
Authors, year, country [PMID] (Ref.)	**Inclusion/exclusion criteria**	**Sample characteristics**	**Duration of the RCT Groups**	**Adherence**
Baggetta *et al.* 2018 Italy [30 342 464] [26]	Inclusion: • age ≥65 years • on HD or PD > 6 months Exclusion: • physical or clinical limitations to ambulate • high degree of fitness (ability to walk a distance >550 m in 6 min)	Home-based: *n*.53 (age 73.0 ± 5.0 years, 54.0% male) Usual care: *n*.62 (age 75.0 ± 6.0 years, 56.0% male)	24 weeks Home-based • 20 min, aerobic walking • 3 times/week, 2 times/day • intensity individualized and gradually increased Usual care • generic advice to maintain active lifestyle	Home-based: exercise session completed ≧ 60% of the prescribed sessions: 27 participants
Manfredini *et al.* 2017 Italy [27 909 047] [16]	Inclusion: • age ≥18 years • on HD or PD > 6 months Exclusion: • physical or clinical limitation to ambulate • high degree of fitness (ability to walk a distance >550 m in 6 min)	Home-based: *n*.104 (age 63.0 ± 13.0 years, 64.0% male) Usual care: *n*.123 (age 64.0 ± 14.0 years, 68.0% male)	24 weeks Home-based • 20 min, aerobic walking • 3 times/week, 2 times/day • intensity individualized and gradually increased Usual care • generic advice to maintain active lifestyle	Home-based: mean exercise session completed 119 out of total 144 prescribed sessions (83.0%)
Manfredini *et al.* 2015 Italy [26 067 552] [27]	Inclusion: • age ≥18 years • on HD or PD > 6 months Exclusion: • physical or clinical limitations to ambulate • high degree of fitness (ability to walk a distance >550 m in 6 min)	Home-based: *n*.28 (age 66.0 ± 14.0 years, 71.0% male) Usual care: *n*.26 (age 68.0 ± 13.0 years, 58.0% male)	24 weeks Home-based • 20 min aerobic walking • 3 times/week, 2 times/day • intensity individualized and gradually increased Usual care • generic advice to maintain active lifestyle	Home-based: exercise session completed ≧ 60% of the prescribed sessions: 20 participants
Malagoni *et al.* 2008 Italy [19 034 871] [28]	Inclusion: • age ≥18 years • on HD 3×/week > 1 year Exclusion: • active smokers • patients with acute illness or infections • recent surgery or vascular intervention • recent myocardial infarction or unstable angina	Home-based: *n*.13 (age 62.0 ± 10.0 years, 77.0% male) Usual care: *n*.7 (age 66.0 ± 14.0 years, 57.0% male)	12 weeks Home-based • 10 min aerobic walking • 7 times/week, 2 times/day • intensity individualized and gradually increased Usual care • generic advice to maintain active lifestyle	Not measured
Watanabe *et al.* 2021 Japan [33 736 592] [30]	Inclusion: • age ≥18 years • on PD or HD + PD > 3 months Exclusion: • physical or clinical limitations to ambulate • cognitive disorders • change in hemodialysis type	Home-based: *n*.26 (age 66.2 ± 13.1 years, 76.9% male) Usual care: *n*.27 (age 64.0 ± 13.0 years, 77.8% male)	24 weeks Home-based • 20–30 min, walking, resistance exercises and stretching • 3–5 times/week • intensity Borg scale 11–13 Usual care • generic advice to maintain active lifestyle	Not measured
Uchiyama *et al.* 2019 Japan [30 796 338] [32]	Inclusion: • age 20–90 years • on PD > 3 months Exclusion: • severe clinical limitations	Home-based: *n*.24 (age 64.9 ± 9.2 years, 79.0% male) Usual care: *n*.23 (age 63.2 ± 9.5 years, 16.0% male)	12 weeks Home-based • 20–30 min walking training program • 3 times/week • intensity Borg scale 11–13, 40–60% HR pea Usual care • generic advice to maintain active lifestyle	Not measured

Table 1: Continued

Authors, year, country [PMID] (Ref.)	Sample: Inclusion/exclusion criteria	Sample: Sample characteristics	Intervention: Duration of the RCT Groups	Intervention: Adherence
Perez-Domoniguez *et al.* 2021 Spain [33 826 277] [36]	Inclusion: • age ≥18 years • on HD > 3 months • clinically stable patients Exclusion: • unstable cardiovascular diseases or heart attack in the previous 6 weeks • lower-limb amputation • ischemic brain disease or severe muscle-skeletal or respiratory conditions • clinical limitations to ambulated • language barrier	Home-based: *n*.34 (age 67.2 ± 15.9 years, 65.0% male) Intradialytic: *n*.36 (age 67.2 ± 13.3 years, 67.0% male)	16 weeks Home-based • 1 hour, combined generic strengthening and aerobic resistance training program • 3 times/week • intensity Borg scale 12 Intradialytic • 1 hour, combined generic strengthening and aerobic resistance training program • 3 times/week • intensity Borg scale 12	Not measured
Ortega-Pérez de Villar *et al.* 2020 Spain [32 427 935] [37]	Inclusion: • age ≥18 years • on HD > 3 months • clinically stable patients Exclusion: • unstable cardiovascular diseases or heart attack in the previous 6 weeks • lower-limb amputation • ischemic brain disease or severe muscle-skeletal or respiratory conditions • clinical limitations to ambulated • language barrier	Home-based: *n*.12 (age 61.9 ± 12.1 years, 30.4% male) Intradialytic: *n*.11 (age 65.3 ± 15.2 years, 32.6% male)	16 weeks Home-based • lower-limb stretching, strength training and walking exercise • 3 times/week • intensity Borg scale 12–15 Intradialytic: • assisted lower-limb stretching • 3 times/week • intensity Borg scale 12–15	Home-based: adherence defined by the number of sessions performed divided by the number of sessions offered, multiplied by 100 = 53.0% Intradialytic: adherence reported on a diary by physical therapist in the HD unit = 80.8%
Myers *et al.* 2021 USA [33 774 634] [41]	Inclusion: • age 55–80 years • on HD > 3 months with Kt/V ≥ 1.2 • impaired exercise capacity (VO_2 peak 10–20 ml/kg/min) Exclusion: • severe clinical conditions • high degree of fitness (>2 h/week of moderate intensity exercise) • use of anabolic, catabolic or cytotoxic medications in the past 3 months	Home-based: *n*.13 (age 66.3 ± 7.6 years, 46.4% male) Usual care: *n*.15 (age 66.2 ± 6.7 years, 53.5% male)	12 weeks Home-based • ≥45 min, therabands for resistance exercises and cycle-ergometer for aerobic exercises • 7 times/week • intensity Borg scale 12–14, 70–80% HR reserve Usual care • generic advice to maintain active lifestyle	Not measured

Abbreviations: HD = hemodialysis, PD = peritoneal dialysis.

interventions, home-based exercise interventions were associated with improvement in aerobic capacity, albeit it was statistically borderline (three RCTs; pooled WMD 2.04 ml/kg/min, 95% CI 0.25–3.83; Z-test = 1.90, P = 0.03; I^2 = 0%). Figure 4 shows the forest plot and pooled estimates of the impact of home-based exercise interventions on muscle strength as assessed by handgrip. Compared with usual care or intradialytic exercise interventions, home-based exercise interventions were not significantly associated with improvement in muscle strength (two RCTs; pooled WMD 1.06 kg, 95% CI −2.23–4.35; Z-test = 0.63, P = 0.53; I^2 = 0%). We also performed univariate meta-regression analyses to test the potential effects of specific moderator variables (e.g. age, gender, BMI, percentage of patients with T2DM, and dialysis vintage) on observed changes in the 6MWT provided by home-based exercise interventions (Supplementary Fig. 4). Specifically, these analyses did not show a significant effect of age, gender, BMI, T2DM, or dialysis vintage on the improvement in the 6MWT provided by home-based exercise interventions. Supplementary Table 2 reports the comparison of several scales of SF-36 score between patients randomly assigned to usual care and those randomly assigned to home-based exercise interventions. Home-based exercise interventions were significantly associated with improvements in SF-36 scores as far as physical role, emotional role, social functioning (SF), bodily pain, and vitality (VT) are concerned, thus

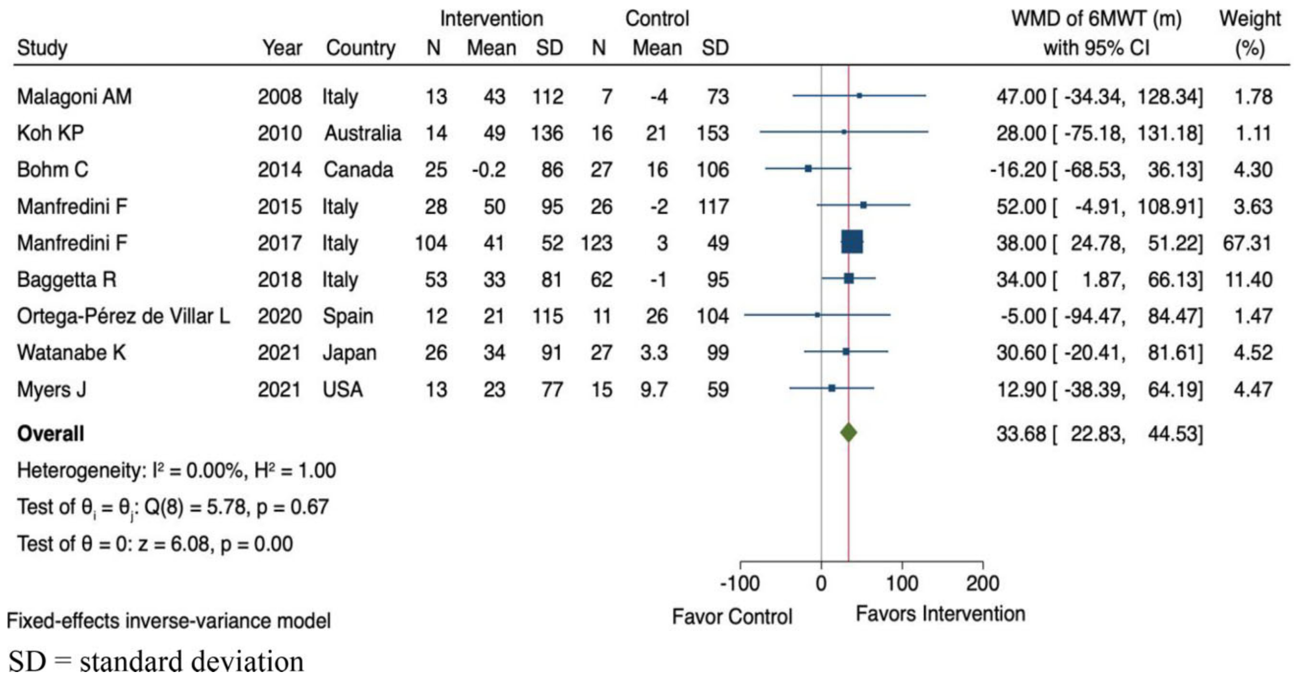


Figure 2: Forest plot and pooled estimates of the impact of home-base exercise interventions on the 6-minute-walking test (6MWT) compared with usual care or intradialytic exercise interventions. The pooled (green diamond) and individual effect sizes for all RCTs included were expressed as WMD and 95% CI.

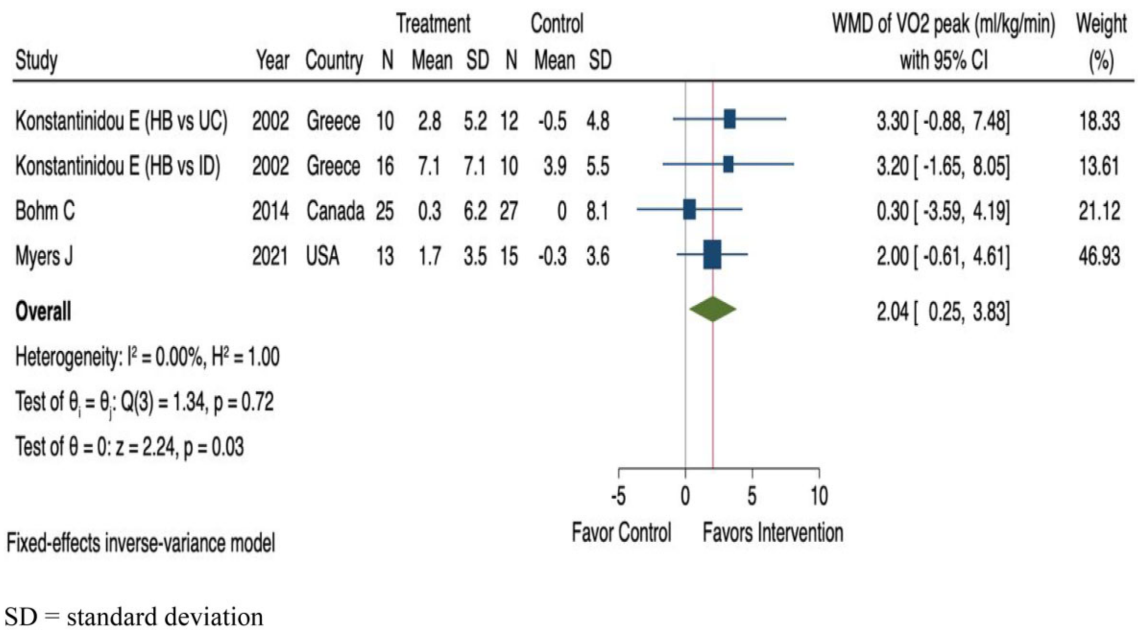
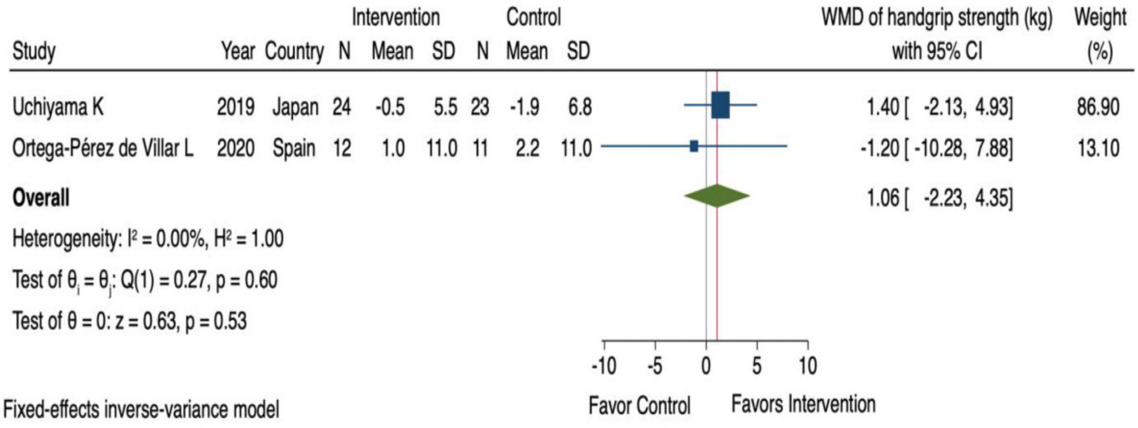


Figure 3: Forest plot and pooled estimates of the impact of home-based (HB) exercise interventions on VO_2 peak compared with usual care (UC) or intradialytic exercise (ID) interventions. The pooled (green diamond) and individual effect sizes for all RCTs included were expressed as WMD and 95% CI.

suggesting improved QoL. As shown in Supplementary Fig. 5, Egger's regression test showed no statistically significant asymmetry of the funnel plots of the eligible RCTs (reported in Fig. 2), examining the impact of home-based exercise interventions on walking speed ($P = 0.258$), thus indicating that a publication bias was unlikely.

DISCUSSION

This is the first systematic review and meta-analysis of RCTs evaluating the impact of home-based exercise programs, compared to usual care or intradialytic exercise programs, on specific clinical outcomes (physical performance and QoL) in ESKD patients undergoing dialysis. In particular, 12 RCTs, of which seven placebos



SD = standard deviation

Figure 4: Forest plot and pooled estimates of the effects of home-base exercise interventions on handgrip compared with usual care or intradialytic exercise interventions. The pooled (green diamond) and individual effect sizes for all RCTs included were expressed as WMD and 95% CI.

controlled, two intradialytic controlled, and two placebo and intradialytic controlled, tested walking speed with the 6MWT (nine RCTs), muscular strength with handgrip (two RCTs), aerobic capacity with VO_2 peak (three RCTs), and QoL with SF-36 score (four RCTs). Notably, other measures of exercise capacity and disability assessed by multiple heterogenous tests, likely a short physical performance battery and an incremental walk test, were excluded from this meta-analysis. Pooled data on home-based exercise interventions for a median period ranging from 3 to 6 months, were obtained in 791 patients of various ages with ESKD undergoing HD or PD. To date, only one recent systematic review of 8 RCTs and five quasi-experimental studies [63], addressed the issue of the impact of home-based exercise interventions on frailty indicators, namely weakness, sluggishness, low physical activity, perceived exhaustion, and shrinkage in ESKD patients undergoing dialysis [60]. However, some quasi-experimental studies conducted in a mixed renal population, such as patients with kidney failure not on dialysis and/or kidney transplant recipients, were also included in the meta-analysis [36, 47].

Therefore, compared to others, our selected RTCs are uniquely characterized by both the site of exercise training (home-based) and the stage of kidney failure (maintenance dialysis). Interestingly, when examining the impact of home-base exercise interventions on the 6MWT, we found greater distance, expressed in meters, covered by patients in active home-based groups, when compared to controls at the end of study period (nine RCTs; pooled WMD 33.7 m, 95% CI 22.8–44.5; $P < 0.001$). Furthermore, programs of home-based exercising scheduled 3–7 days a week, were found to result in enhancement of walking capacity. Notably, only few studies (two RCTs) conducted a supervised home-based exercise program, despite the fact that a wide range of professionals, including nurse and kinesiologists, could act as supervisors. Indeed, the presence of exercise facilitator may be crucial not only to improve exercise adherence but also to ensure exercise safety [7]. However, there is considerable variation in safety precautions published in different guidelines with low grade of evidence [29, 64]. Additionally, the potential role of online exercise platforms which could improve adherence and motivation for optimal results should be explored adequately with larger multicenter RCTs.

Furthermore, when analyzing intradialytic exercise subgroups, compared with baseline, no difference in walking distance between intradialytic and home-based exercise interventions at 4–6 follow-up months was found. However, given the relatively small number of patients included in this analysis, this result should be interpreted with caution. To specifically address this important issue, we think that additional and larger RCTs are needed.

Collectively, however, our findings provide compelling evidence for prescribing home-based exercise programs in ESKD patients on dialysis for their beneficial impact on physical function that are superior to usual care, but not inferior to those of training performed in dialysis units. Indeed, the positive impact on 6MWT of intradialytic and interdialytic exercise programs, regardless of physical activity modality, was previously demonstrated in a meta-analysis by Clarkson *at al.* of 27 RCTs (11 aerobic training, eight resistance, four both) [65]. By contrast, in other meta-analyses, because of poor quality trials, no sufficient evidence was found to show whether exercise during HD improved patient outcomes [66].

It is worth noting that some RCTs, excluded from our analysis, implemented the home-based exercise program with additional in-center training sessions, obtaining encouraging results on physical performance and QoL [29, 52, 55]. In addition, a complete physical fitness program should include, along with endurance and muscle strengthening exercises, flexibility and balance so as to prevent falls [67]. Therefore, we think that additional and larger RCTs assessing the feasibility, balance and efficacy of combined inpatient and home-based exercise interventions are needed in HD patients. Regarding the relationship of QoL with home-based exercise, compared to controls, an increased score of five SF-36 domains was found. These findings are in agreement with a systematic review of 11 RCTs, four uncontrolled trials and one trial involving a within-subjects control period plus RCT, evaluating the application of interdialytic and intradialytic progressive resistance training (PRT). In five of seven RCTs, the multiple scores of health related QoL domains were increased in PRT groups [63]. Recently, Ferreira *et al.* conducted a meta-analysis of eight RCTs, demonstrating that exercise interventions were effective for mitigating symptoms of depression and anxiety in kidney failure patients [64]. In addition to traditional psychiatric diagnoses, evidence from experimental and observational studies suggests that the psychosocial dimensions and subthreshold syndromes found in patients on RRT may further compromise QoL [65–68]. Therefore, further investigations with a follow-up period of one or more years should be planned primarily to evaluate the non-pharmacological impact of home-based exercise programs on psychosocial determinants in dialysis patients.

The main strength of this meta-analysis is the use of stringent predefined inclusion/exclusion criteria in identifying RCTs originally designed to investigate the impact of home-based exercise interventions in patients on maintenance dialysis. Additionally, to provide the highest reliability, two reviewers conducted an independent selection process of literature search, data extraction and bias assessment moderated by a third reviewer, basing on a prespecified and preregistered review protocol.

Despite this, our meta-analysis has also some important limitations: (i) it includes a relatively low number of RCTs with a small sample size and short duration of treatment (from 3 to 6 months). Only few RCTs have specifically evaluated the impact of home-based exercise programs on clinical outcomes compared to intradialytic exercise programs. It is also important to note that in most of the eligible RCTs the physical activity was unsupervised, and that physical activity intensity was assessed by different methods. Furthermore, in half of RCTs, the adherence to exercise programs was not assessed; (ii) the restriction to RCTs might have limited generalizability to 'real-world' populations of ESKD patients on dialysis; and (iii) most of the eligible RCTs included patients of various ages, mostly White and overweight. Therefore, future large RCTs conducted in other specific ESKD populations are urgently awaited.

In conclusion, our systematic review and meta-analysis of 12 RCTs showed that the prescription of home-based exercise programs for 3–6 months in ESKD patients on dialysis has a beneficial impact on physical function that is superior to usual care and not inferior to training performed in dialysis units. In most studies, the prescribed home-based activity was fairly simple, unsupervised, and did not require specific devices, such as 30–45 minutes of aerobic walking, three times a week, at moderate intensity [58]. We believe that these data might be useful to promote the prescription of home-based exercise programs in ESKD patients on maintenance dialysis as good daily clinical practice. However, supervision of home-based exercise programs is crucial for promoting adherence, ensuring safety, and assessing feasibility in HD patients [68]. Moreover, multicenter RCTs with follow-up period of one or more years should be planned to assess the impact of home-based exercise programs on QoL in ESKD patients on dialysis.

SUPPLEMENTARY DATA

Supplementary data is available at *ndt* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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