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Research

Combined training is the most effective training modality to improve aerobic capacity and blood pressure control in people requiring haemodialysis for end-stage renal disease: systematic review and network meta-analysis

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KEY WORDS

Chronic kidney failure
Renal dialysis
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ABSTRACT

Questions: Do aerobic, resistance and combined exercise training improve aerobic capacity, arterial blood pressure and haemodialysis efficiency in people requiring haemodialysis for end-stage renal disease? Is one exercise training modality better than the others for improving these outcomes? **Design**: Systematic review with network meta-analysis of randomised trials. **Participants**: Adults requiring haemodialysis for end-stage renal disease. **Intervention**: Aerobic training, resistance training, combined training and control (no exercise or placebo). **Outcome measures**: Aerobic capacity, arterial blood pressure at rest, and haemodialysis efficiency. **Results**: Thirty-three trials involving 1254 participants were included. Direct meta-analyses were conducted first. Aerobic capacity improved significantly more with aerobic training (3.35 ml/kg/min, 95% CI 1.79 to 4.91) and combined training (5.00 ml/kg/min, 95% CI 3.50 to 6.50) than with control. Only combined training significantly reduced systolic (−9 mmHg, 95% CI −13 to −4) and diastolic (−5 mmHg, 95% CI −6 to −3) blood pressure compared to control. Only aerobic training was superior to control for haemodialysis efficiency (Kt/V 0.11, 95% CI 0.02 to 0.20). However, when network meta-analysis was conducted, there were some important different findings. Both aerobic training and combined training again elicited greater improvements in aerobic capacity than control. For systolic blood pressure, combined training was superior to control. For diastolic blood pressure, combined training was superior to aerobic training and control. No modality was superior to control for haemodialysis efficiency. Combined training was ranked as the most effective treatment for aerobic capacity and arterial blood pressure. **Conclusion**: Combined training was the most effective modality to increase aerobic capacity and blood pressure control in people who require haemodialysis. This finding helps to fill the gap created by the lack of head-to-head comparisons of different modalities of exercise in people with end-stage renal disease. **Registration**: PROSPERO CRD42015020531. **[Scapini KB, Bohlke M, Moraes OA, Rodrigues CG, Inácio JFS, Sbruzzi G, Leguisamo CP, Sanches IC, Tourinho Filho H, Irigoyen MC (2019) Combined training is the most effective training modality to improve aerobic capacity and blood pressure control in people requiring haemodialysis for end-stage renal disease: systematic review and network meta-analysis. *Journal of Physiotherapy* 65:4–15]**

Introduction

Chronic renal disease has been increasing in recent decades; it affects 8 to 16% of the population worldwide. This increase is mainly due to the increased prevalence of risk factors, such as diabetes mellitus and hypertension, and as result of aging of the population.[1–3]

People with end-stage renal disease present higher risk for cardiovascular disease and mortality,[4] which, as in other populations, may be aggravated by a sedentary lifestyle.[5,6] It is well documented that people with end-stage renal disease have reduced aerobic capacity, muscle strength and exercise tolerance, which are factors that contribute to higher levels of physical inactivity. In two cohorts of people requiring haemodialysis for end-stage renal disease, 35% and 43% did not exercise at all, and only 5% and 6% exercised 4 to 5 times per week.[6,7]

Several trials have demonstrated that exercise training improves functional capacity, arterial blood pressure, lipid profile, heart rate variability, and quality of life in people with end-stage renal disease;[8] therefore, exercise interventions could be an interesting non-pharmacological strategy to improve cardiovascular health in this population. Furthermore, some studies have evaluated the effect of intradialytic exercise on haemodialysis efficiency, measured, in most cases, using Kt/V, and revealed conflicting results.[9–11]

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Most published randomised clinical trials about the effects of exercise on people with end-stage renal disease have used aerobic exercise as the intervention. Resistance exercise or combined aerobic and resistance exercise have been investigated much less. Moreover, few randomised trials have compared the effects of different training modalities on the health outcomes of people with end-stage renal disease. The surveyed studies had small samples, short duration, different outcomes, and heterogeneous results.[10,12,13] This lack of solid and coherent evidence precludes any conclusion regarding the best training modality for people with end-stage renal disease.

While there is a broad consensus that exercise training promotes beneficial effects in end-stage renal disease, it is not routinely included in clinical practice and the comparative efficiency of different modalities of exercise training remains to be determined. To overcome the restrictions of limited available comparisons, this systematic review employed a network meta-analysis of randomised trials with the aim of assessing the effectiveness of different modalities of exercise training on aerobic capacity, arterial blood pressure and haemodialysis efficiency in adults with end-stage renal disease requiring haemodialysis treatment.

Therefore the research questions for this systematic review were:

1. Do aerobic, resistance, and combined exercise training improve aerobic capacity, arterial blood pressure and haemodialysis efficiency in people requiring haemodialysis for end-stage renal disease?
2. Is one exercise training modality better than the others for improving these outcomes?

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[14]

Identification and selection of studies

The following electronic databases were searched in May 2018: PubMed, EMBASE, Cochrane CENTRAL (Wiley InterScience), Web of Science and LILACS (Bireme), for articles published up to 5 January 2018. The following MeSH terms were used: 'Exercise', 'Resistance Training', 'Kidney Failure, Chronic' and 'Renal Dialysis', as well as their synonyms. For the search of the LILACS database, the equivalent terms in Portuguese were used. All these search terms were combined with a highly sensitive search strategy for the retrieval of reports of controlled trials.[15] The complete search strategy used in PubMed is shown in Appendix 1 (see eAddenda for Appendix 1). There was no restriction on the language or the status of the publication. Further eligible studies were sought by manually searching the reference lists of eligible articles and of review articles on end-stage renal disease.

Eligibility criteria were defined a priori. The inclusion criteria are presented in Box 1. We excluded: studies in which people with end-stage renal disease were undergoing a type of renal replacement therapy other than haemodialysis; studies with randomised co-interventions besides haemodialysis; studies in which interventions consisted of guidelines and educational measures for exercise practice, rather than exercise training; and studies where only a single exercise session was delivered to assess acute effects.

Titles and abstracts of all articles identified by the search strategy were evaluated in duplicate by two investigators working independently. All abstracts that did not provide sufficient information regarding the eligibility criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full-text articles and made their selection in accordance with the eligibility criteria. Disagreements between reviewers were resolved by discussion.

Box 1. Inclusion criteria.

Design
- Randomised controlled trial

Participants
- People with chronic renal disease requiring haemodialysis
- Adults (ie, $\geq$ 18 years old)

Intervention
- Aerobic training
- Resistance training
- Combined training (aerobic plus resistance training)

Comparator
- Control group (no exercise or placebo)

Outcome measures
- Aerobic capacity, measured by maximal oxygen uptake in ml/kg/min
- Systolic and diastolic arterial pressures at rest in mmHg
- Haemodialysis efficiency measured as single pool Kt/V[a]

Comparisons
- All interventions compared to the comparator and to each other

[a] See main text for explanation of Kt/V.

Assessment of characteristics of studies

Quality

Study quality assessment was conducted using the Cochrane Collaboration's tool for assessing risk of bias[16] and included random sequence generation, allocation concealment, blinding of outcome

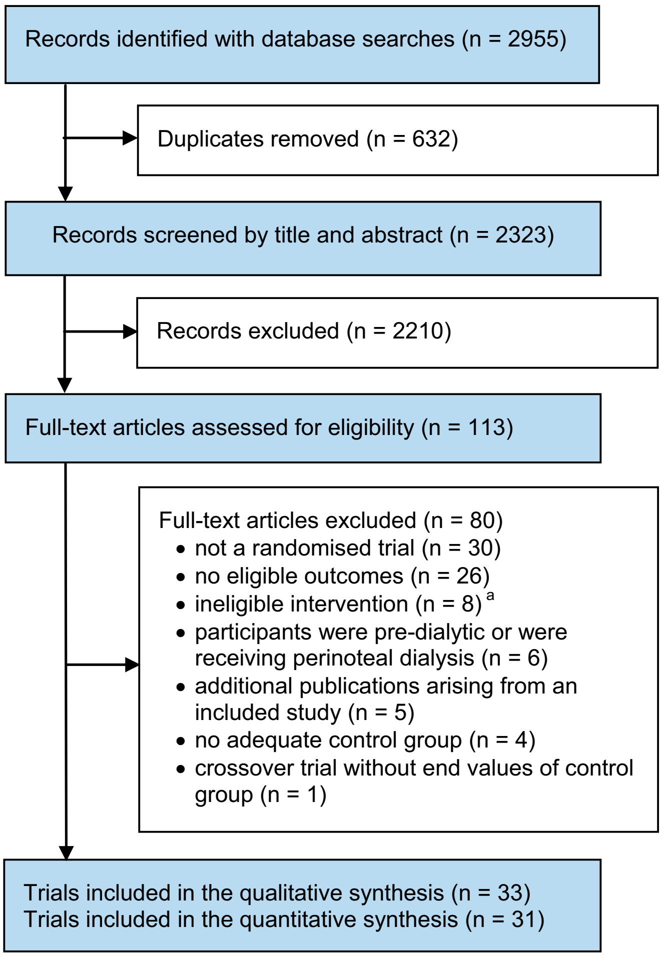

Figure 1. Flow of studies through the review.
[a] Reasons for ineligibility of interventions included: provision of only guidelines and educational measures for exercise practice; delivery of a single exercise session only; use of an ineligible modality of exercise; and inclusion of a co-intervention as part of the randomised intervention.

Table 1
Characteristics of the studies included in the review.

Study	Country	Group (n)	Interventions					Loss (%)
			Type	Period	Prescription	Program duration	Compliance (%)	
Abreu 2017[26]	Brazil	Exp = 32	RT	ID	3/week; 30 min: 3 sets of 10 reps, four lower limb exercises with ankle cuffs and elastic band resistance; intensity based on an adaptation of the 1RM test with the initial intensity set at 60% of 1RM	12 weeks	NR	19
		Con = 29	–	–	No exercise	12 weeks	–	35
Frih 2017[27]	Tunisia	Exp = 28	CT	ND	4/week; 60 min: 10 min warm up, dynamic closed- and open-chain strengthening exercises (quadriceps, pectoral, triceps, biceps and hamstrings, start at 50% 1RM and 12 to 15 reps for each exercise, load increased by 5% of the 1RM monthly), ergometer cycling and treadmill walking for 20 min at 5 to 6 RPE, 10 min cool down	16 weeks	NR	25
		Con = 22	–	–	No exercise	16 weeks	–	9
Liao 2016[28]	Taiwan	Exp = 20	AT	ID	3/week; 30 min: 5 min warm up, 20 min ergometer cycling at 12 to 15 RPE, 5 min cool down	12 weeks	NR	NR
		Con = 20	–	–	No exercise	12 weeks	–	NR
Thompson 2016[29]	Canada	Exp1 = 8	AT	ID	3/week; 5 min warm up, 15 min ergometer cycling at 12 to 14 RPE increased by 2.5 min/week, 5 min cool down	12 weeks	87	13
		Exp2 = 7	RT	ID	3/week; 3 sets of 10 to 15 reps, knee extension, knee flexion and hip flexion (with ankle weights) and hip abduction (with elastic resistance band) at 12 to 14 RPE	12 weeks	84	14
		Exp3 = 8	CT	ID	3/week; Exp1 followed by Exp2 at each session	12 weeks	88	13
		Con = 8	–	–	Stretching exercise	12 weeks	–	25
Groussard 2015[9]	France	Exp = 10	AT	ID	3/week; 30 min ergometer cycling at 50 rpm and 55 to 60% of peak power output	12 weeks	NR	20
		Con = 10	–	–	No exercise	12 weeks	–	0
Mohseni 2013[30]	Iran	Exp = 25	AT	ID	3/week; 15 min aerobic movement exercise of range of motion (rotating wrist 40 rpm, 20 times flexion and extension of the wrist, 20 times full flexion and extension of the elbow, 40 rpm of rotating the ankles, 20 times flexion and extension of the ankles)	8 weeks	NR	8
		Con = 25	–	–	No exercise	8 weeks	–	4
Dobsak 2012[11]	Czech Republic	Exp = 11	AT	ID	3/week; 2 sets of 20 min ergometer cycling at 60% of individual Wpeak determined by ergometric test	20 weeks	NR	NR
		Con = 10	–	–	No exercise	20 weeks	–	NR
Reboredo 2011[21]	Brazil	Exp = 14	AT	ID	3/week; 35 min supervised ergometer cycling at 4 to 6 modified RPE	12 weeks	77	14
		Con = 14	–	–	No exercise	12 weeks	–	14
Afshar 2010[12]	Iran	Exp1 = 7	AT	ID	3/week; 10 to 30 min ergometer cycling at 12 to 16 RPE	8 weeks	NR	NR
		Exp2 = 7	RT	ID	3/week; 3 sets of 8 reps at 60% of 3RM of knee extension-flexion and hip abduction-flexion at 15 to 17 RPE with ankle weights	8 weeks	NR	NR
		Con = 7	–	–	No exercise	8 weeks	–	NR
Koh 2010[31]	Australia	Exp = 27	AT	ID	3/week; 45 min ergometer cycling at 12 to 13 RPE	24 weeks	75	44
		Con = 22	–	–	Usual care	24 weeks	–	27
Kouidi 2010[32]	Greece	Exp = 25	CT	ID	3/week; 60 min ergometer cycling and 20 min strengthening exercises; 11 to 13 RPE; RT initially consisted of 2 sets of exercises for the lower limbs using elastic bands and free weights. The workload was gradually increased by increasing the number of reps (8 to 12) and the number of sets.	12 months	82	4
		Con = 25	–	–	No exercise	12 months	–	20

(Continued on next page)

Table 1 (*Continued*)

Study	Country	Group (n)	Interventions					Loss (%)
			Type	Period	Prescription	Program duration	Compliance (%)	
Reboredo 2010[33]	Brazil	Exp = 14	AT	ID	3/week; 35 min supervised ergometer cycling at 4 to 6 modified RPE	12 weeks	75	22
		Con = 14	–	–	Usual care	12 weeks	–	22
Wilund 2010[34]	USA	Exp = 8	AT	ID	3/week; 45 min ergometer cycling at 12 to 14 RPE	16 weeks	NR	13
		Con = 9	–	–	Usual care	16 weeks	–	11
Kouidi 2009[35]	Greece	Exp = 32	CT	ID	3/week; 40 min ergometer cycling and 30 min isotonic and isometric flexibility and strengthening exercises for the abdomen and lower limbs, with 3 sets of 15 reps using elastic bands and free weights; 13 RPE and 60 to 70% HRmax	10 months	88	6
		Con = 31	–	–	Usual care	10 months	–	6
Ouzoni 2009[36]	Greece	Exp = 20	CT	ID	3/week; 30 min ergometer cycling, 30 min of strengthening and flexibility exercises with elastic bands and limb weights; 13 to 14 RPE	10 months	NR	5
		Con = 15	–	–	No exercise	10 months	–	7
Petraki 2008[37]	Greece	Exp = 26	CT	ID	3/week; 60 min of cycling and 30 min strengthening and flexibility exercises at 13 RPE; RT consisted of sets of reps of isotonic and isometric exercises and the workload was gradually increased by using elastic bands and limb weights	7 months	NR	15
		Con = 24	–	–	No exercise	7 months	–	13
Toussaint 2008[38]	Australia	Exp = 10	AT	ID	3/week; 30 min ergometer cycling without exercise velocity, target HR or supervision	12 weeks	NR	10
		Con = 10	–	–	No exercise	12 weeks	–	0
Cheema 2007[19]	Australia	Exp = 24	RT	ID	3/week; 2 sets of 8 reps; five upper limb exercises using free-weight dumbbells, five lower limb exercises using ankle weights or elastic resistance bands, and one abdominal exercise; 15 to 17 RPE	12 weeks	85	16
		Con = 25	–	–	No exercise	12 weeks	–	4
Kopple 2007[10]	USA	Exp1 = 20	AT	ID	3/week; 40 min ergometer cycling at ~50% of maximal oxygen uptake	20.7 weeks	NR	50
		Exp2 = 20	RT	ND	3/week; apparatus for combined leg extension and flexion, and leg press and plantar flexion; 3 sets of 6 to 8 reps at 80% of 5RM	21.2 weeks	NR	25
		Exp3 = 20	CT	ID/ND	3/week; CT group performed a combination of approximately one half of the AT and RT work effort	21.5 weeks	NR	40
		Con = 20	–	–	No exercise	21 weeks	–	20
Van Vilsteren 2005[39]	Netherlands	Exp = 60	CT	ID/ND	2 to 3/week; 5 to 10 min warm up, 20 min of calisthenics exercises, step aerobics, flexibility and low-intensity resistance exercises, 5 to 10 min cool down, 20 to 30 min of cycling on pedals coupled to the haemodialysis chair; 12 to 16 RPE and ~60% of VO_2max	12 weeks	NR	12
		Con = 43	–	–	No exercise	12 weeks	–	0
Molsted 2004[40]	Denmark	Exp = 22	CT	ND	2/week; 10 min warm up, 20 to 30 min of strength exercises and aerobic exercises (such as step and circuit training), 15 to 20 min ergometer cycling; 14 to 17 RPE	20 weeks	74	50
		Con = 11	–	–	No exercise	20 weeks	–	18
Parsons 2004[41]	Canada	Exp = 9	AT	ID	3/week; 3 bouts of 15 minute cycle ergometry exercise at 40 to 50% of maximum work load	8 weeks	NR	33
		Con = 9	–	–	No exercise	8 weeks	–	22
Tsuyuki 2003[42]	Japan	Exp = 17	AT	ND	2 to 3/week; 30 min ergometer cycling, walking and running at 50 to 60% HRmax	20 weeks	NR	NR
		Con = 12	–	–	No exercise	20 weeks	–	NR

(*Continued on next page*)

Table 1 (*Continued*)

Study	Country	Group (n)	Interventions					Loss (%)
			Type	Period	Prescription	Program duration	Compliance (%)	
De Paul 2002[43]	Canada	Exp = 20	CT	ID/ND	3/week; 20 min egometer cycling at 13 to 14 RPE, at around 50 rpm; 3 sets of 10 reps of hamstring and quadriceps exercises on weight machines in the ND period, at 125% of 5RM	12 weeks	NR	25
		Con = 18	–	–	Sham (range of motion) exercises	12 weeks	–	22
Konstantinidou 2002[13]	Greece	Exp1 = 12	CT	ID	3/week; 30 min ergometer cycling, 30 min of stationary bike; 30 min of flexibility and strength exercises for the lower limbs. Progression via reps, sets, and elastic bands and limb weights; 70% HRmax	24 weeks	NR	17
		Exp2 = 21	CT	ND	3/week; 10 min warm ergometer cycling or treadmill, 50 min intermittent aerobic exercise program, including calistenics, steps and flexibility exercises, and 10 min cool down at 60 to 70% HR max. At 2 months, 10 min stretching and low-weight resistance program was added	24 weeks	NR	28
		Exp3 = 12	AT	ND	5/week; 30 min home ergometer cycling at 50 to 60% HRmax	24 weeks	NR	17
		Con = 13	–	–	No exercise	24 weeks	–	8
Painter 2002[44]	USA	Exp = 10	AT	ID	3/week; 30 min ergometer cycling at 12 to 14 RPE and 70% HRmax	20 weeks	NR	NR
		Con = 14	–	–	No exercise	20 weeks	–	NR
Deligiannis 1999[45]	Greece	Exp = 30	CT	ND	3 to 4/week; 50 min aerobic exercise (calisthenics exercises, step aerobics, swimming, or ball games); 20 min stretching and low-intensity resistance exercises; 60 to 70% HRmax	24 weeks	NR	NR
		Con = 30	–	–	No exercise	24 weeks	–	NR
Frey 1999[46]	USA	Exp = 11	AT	ID	3/week; 45 min ergometer cycling 60 to 80% HRmax and 11 to 16 RPE	8 weeks	NR	0
		Con = 11	–	–	No exercise	8 weeks	–	0
Kouidi 1997[47]	Greece	Exp = 24	AT	ND	3 to 4/week; 90 min of ergometer cycling, walking/jogging, calisthenics and aerobics, with swimming and/or ball sports in the last 8 to 12 weeks; 50 to 60% VO_2max or 60 to 70% HRmax	24 weeks	78	17
		Con = 12	–	–	No exercise	24 weeks	–	8
Akiba 1995[48]	Japan	Exp = 10	AT	ND	3/week; 20 min on a cycle ergometer at 16 RPE	12 weeks	NR	10
		Con = 10	–	–	No exercise	12 weeks	–	40
Moros 1995[25]	Spain	Exp = 9	AT	NR	Frequency NR; dynamic aerobic exercises adapted individually according to the individual capacity	18 weeks	NR	33
		Con = 7	–	–	No exercise	18 weeks	–	43
Carney 1987[49]	USA	Exp = 11	AT	ND	3/week; 45 to 60 min at 70 to 80% VO_2max including calistenics exercises, ergometer cycling, walking and jogging	24 weeks	NR	9
		Con = 10	–	–	Psychosocial support	24 weeks	–	30
Goldberg 1983[24]	USA	Exp = 14	AT	ND	3/week; 45 to 60 min at 70 to 75%VO_2max including cycling on a stationary bicycle ergometer, walking and jogging	12 months	NR	NR
		Con = 11	–	–	No exercise	12 months	–	

AT = aerobic training, Con = control group, CT = combined training, Exp = experimental group, HR = heart rate, HRmax = maximum heart rate, ID = intradialytic, min = minutes, ND = non-dialytic, NR = not reported, RM = repetition maximum, RPE = Borg rating of perceived exertion, rpm = rotations per minute, RT = resistance training, VO_2max = maximal oxygen uptake.

assessment, incomplete outcome data, and selective reporting. The same two reviewers independently performed the assessment. Disagreements between reviewers were resolved by discussion and, if necessary, the opinion of a third reviewer was sought.

Using standardised forms, the same two reviewers independently conducted data extraction regarding the methodological characteristics of the studies, interventions, and outcomes. Disagreements were again resolved by discussion.

Participants

The country of recruitment was extracted for each study. The initial sample sizes and the percentage of dropouts were extracted for

Table 2
Risk of bias of the included studies.

Study (Author, year)	Selection bias		Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Abreu 2017[26]	Unclear	Unclear	Unclear	Low risk	Low risk	None
Frih 2017[27]	Low risk	Unclear	Low risk	Low risk	Unclear	None
Liao 2016[28]	Unclear	Unclear	Unclear	Low risk	Unclear	None
Thompson 2016[29]	Low risk	Low risk	Unclear	Low risk	Low risk	None
Groussard 2015[9]	Unclear	Unclear	High risk	Low risk	Unclear	None
Mohseni 2013[30]	Low risk	High risk	Low risk	Low risk	Low risk	None
Dobsak 2012[11]	Unclear	Unclear	Low risk	Unclear	Unclear	None
Reboredo 2011[21]	Unclear	Unclear	Low risk	High risk	Low risk	None
Afshar 2010[12]	Unclear	Unclear	Low risk	Unclear	Unclear	High risk[a]
Koh 2010[31]	Low risk	Low risk	Unclear	High risk	Low risk	None
Kouidi 2010[32]	Unclear	Unclear	Unclear	High risk	Unclear	None
Reboredo 2010[33]	Unclear	Unclear	Low risk	High risk	Unclear	None
Wilund 2010[34]	Unclear	Unclear	Low risk	Low risk	Unclear	None
Kouidi 2009[35]	Low risk	Unclear	Low risk	Low risk	Low risk	None
Ouzoni 2009[36]	Unclear	Unclear	Unclear	Low risk	Unclear	None
Petraki 2008[37]	Unclear	Unclear	Unclear	Low risk	Unclear	None
Toussaint 2008[38]	Low risk	Low risk	Unclear	Low risk	Low risk	High risk[b]
Cheema 2007[19]	Low risk	Low risk	Unclear	Low risk	Low risk	None
Kopple 2007[10]	Low risk	Unclear	Unclear	High risk	Unclear	None
van Vilsteren 2005[39]	Unclear	Unclear	Unclear	High risk	Unclear	None
Molsted 2004[40]	Low risk	Low risk	Low risk	High risk	Unclear	None
Parsons 2004[41]	Unclear	Unclear	Unclear	Low risk	Unclear	None
Tsuyuki 2003[42]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk[c]
De Paul 2002[43]	Low risk	Low risk	Low risk	Low risk	Unclear	None
Konstantinidou 2002[13]	Unclear	Unclear	Unclear	Low risk	Unclear	None
Painter 2002[44]	Unclear	Unclear	Unclear	Unclear	Unclear	None
Deligiannis 1999[45]	Unclear	Unclear	Unclear	Unclear	Unclear	None
Frey 1999[46]	Unclear	Unclear	Unclear	Low risk	Unclear	None
Kouidi 1997[47]	Unclear	Unclear	Unclear	Unclear	Unclear	None
Akiba 1995[48]	Unclear	Unclear	Unclear	Unclear	Unclear	None
Moros 1995[25]	Unclear	Unclear	Unclear	Unclear	Unclear	None
Carney 1987[49]	Unclear	Unclear	Unclear	Low risk	Unclear	None
Goldberg 1983[24]	Unclear	Unclear	Unclear	Unclear	Unclear	None

[a] No women participants due to religious beliefs.
[b] Exercise was not supervised and there was no specific goal to duration and intensity.
[c] The primary cause of chronic kidney disease in all patients was chronic glomerulonephritis.

each group. The participants' compliance with the prescribed intervention was also noted.

Intervention

To characterise the experimental intervention, the following information was extracted: the modality of exercise training (aerobic, resistance or combined) including further details where available; the duration, frequency and intensity of the training sessions; when the exercise sessions occurred in relation to haemodialysis (intradialytic, non-dialytic or both); and the progression and total duration of the training.

Outcome measures

Exercise capacity data were extracted from formal cardiopulmonary exercise test results as maximum or peak oxygen uptake (VO_2max), with conversion to ml/kg/min where necessary. Blood pressure data were extracted as systolic and diastolic arterial pressure at rest, in mmHg. Haemodialysis efficiency was extracted as Kt/V, which is an index comprised of K (dialyser clearance of urea), t (dialysis time), and V (volume of distribution of urea, approximately equal to patient's total body water. A patient's average Kt/V should be at least 1.2.

Data analysis

For each outcome considered in this systematic review, effect sizes between different exercise modalities were calculated using mean and standard deviation of the outcome. When the data were unavailable in the required format (eg, number of participants, means and standard deviation), the authors of the primary studies were contacted. Pooled-effect estimates were obtained using the post-intervention values.[16] Calculations were performed using a random-effects model. A p value ≤ 0.05 was regarded as statistically significant. Statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the I^2 inconsistency test, in which values from 0 to 40% might not be important, 40 to 60% represents moderate heterogeneity, 60 to 75% substantial heterogeneity, and 75 to 100% considerable heterogeneity.[16]

A network meta-analysis using a random-effects model was performed, allowing comparison of all modalities of exercise in a connected network of trials, making indirect comparison from trials that have at least one treatment in common. The Bayesian Markov-chain Monte Carlo method was used with RStudio statistical software[a] and the RJAGS package[b]. The network meta-analysis code used in RStudio is shown in Appendix 2 (see eAddenda for Appendix 2). Inconsistency in the network meta-analysis was verified by node-splitting analysis of inconsistency that is shown in Appendix 3 (see eAddenda for Appendix 3). The results were expressed with mean differences with 95% credible intervals (CrI). Also, rank probabilities for each outcome were obtained using Markov-chain Monte Carlo.

Results

Flow of studies through the review

The search strategy yielded 2955 articles, from which 113 were deemed potentially relevant and retrieved for detailed analysis. Of these articles, 75 were excluded based on the eligibility criteria. The excluded studies are listed under the reasons for exclusion in Appendix 4 (see eAddenda for Appendix 4). A further five articles were eliminated as they were found to be duplicate publications: Deligiannis et al[17] was included together with the study by Konstantinidou et al[13], since the latter only added another intervention group to the former one; Cheema et al[18] was part of the study

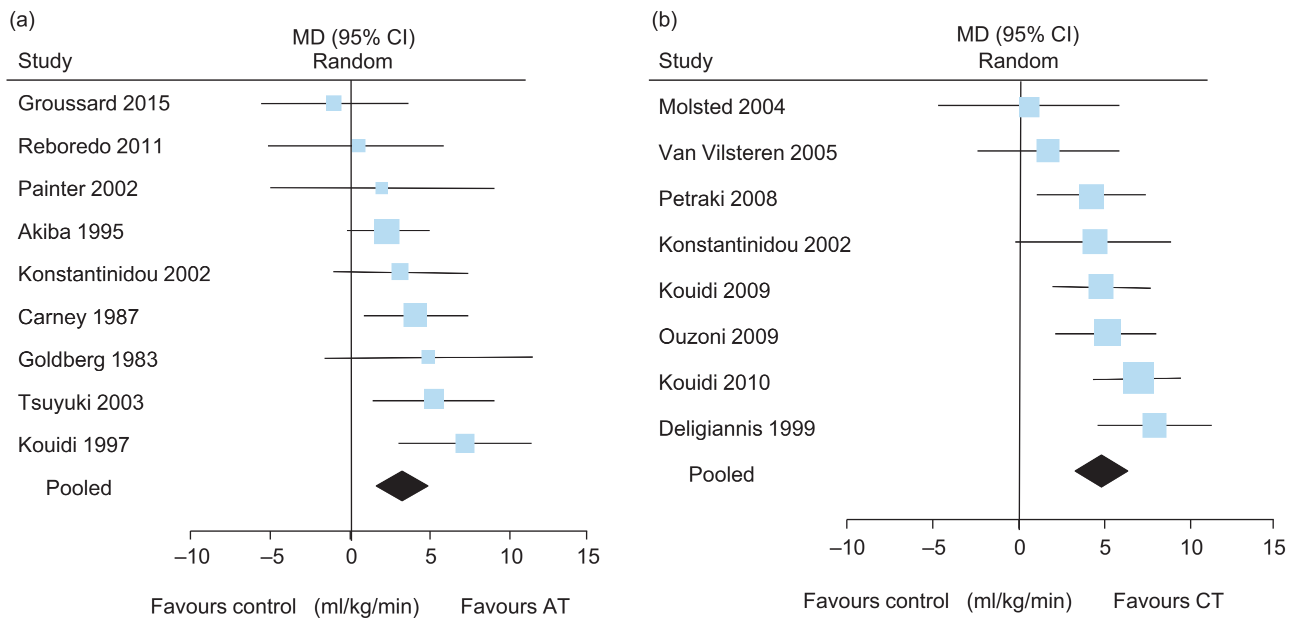

Figure 2. Direct meta-analysis of the effect of (a) aerobic training compared to control and (b) combined training compared to control on aerobic capacity (VO_2max). AT = aerobic training, CT = combined training, VO_2max = maximal oxygen uptake.

Cheema et al[19]; Reboredo et al[20] duplicated the oxygen consumption data of Reboredo et al[21]; Goldberg et al[22] and Harter et al[23] were addressed together in Goldberg et al,[24] in order not to duplicate data. Therefore, 33 studies were included in this review.[9–13,19,21,24–49] However, the study developed by Moros et al[25] was included only in the qualitative analyses because it did not present the values (mean and standard deviation) of control group for our outcomes of interest, and the authors did not respond to the request for data. Also, the study of Thompson et al[29] was not included in the meta-analysis because it presented values that not were similar between groups at baseline. Figure 1 shows the flow diagram of the studies included in this review and Table 1 summarises the characteristics of these studies.

Characteristics of included studies

The studies comprised 1254 participants with end-stage renal disease and on haemodialysis; 703 were allocated to an experimental intervention (301 aerobic training, 312 combined training and 90 resistance training) and 551 were allocated to a control group.

The main characteristics of the included studies are shown in Table 1. Most studies (64%) evaluated the effects of aerobic training,[9–13,21,24,28–31,33,34,38,41,42,44,46–49] 37% evaluated combined training[10,13,27,29,32,35–37,39,40,43,45] and 15% resistance training.[10,12,19,26,29] In most of the experimental groups (25/39, 64%), exercise sessions were scheduled during haemodialysis.[9–13,19,21,26,28–38,41,44,46] The duration of exercise protocol was 8 weeks in five groups (13%),[12,30,41,46] 12 weeks in 13 groups (33%),[9,19,21,26,28,29,33,38,39,43,48] 16 to 20 weeks in ten groups (26%)[10,11,25,27,34,40,42,44] and ≥24 weeks in 11 groups (28%).[13,24,31,32,35–37,45,47,49] The exercise training program was prescribed three times a week for most groups (80%).[9–13,19,21,24,26,28–38,41,43,44,46,48,49] Only nine studies (27%) reported compliance with the exercise training program,[19,21,29,31–33,35,40,47] with compliance being at least 74% in all experimental groups where it was reported.[40]

Risk of bias

The data concerning the assessment of the risk of bias for each study are shown in Table 2. Most included studies had poor methodological quality. Adequate randomisation was reported in only 10 studies (30%),[10,19,27,29–31,35,38,40,43] and allocation concealment in only six studies (18%).[19,29,31,38,40,43] This review did not evaluate blinding of patients and investigators who delivered the interventions due to the characteristics of intervention. Ten trials (30%) blinded assessors.[11,12,21,27,30,33–35,40,43] Slightly more than half of the studies (52%) properly described losses and exclusions.[9,13,19,26–30,34–38,41,43,46,49]

Synthesis of results – direct meta-analysis

Aerobic capacity

The effect of exercise training on aerobic capacity as estimated by direct meta-analysis is shown in Figure 2 (see Figure 3 on the eAddenda for a more detailed forest plot). Aerobic training significantly improved aerobic capacity (WMD 3.35 ml/kg/min, 95% CI 1.79 to 4.91, I^2 = 20%), as shown in Figure 2a. Combined training also significantly improved aerobic capacity (WMD 5.00 ml/kg/min, 95% CI 3.50 to 6.50, I^2 = 35%), as shown in Figure 2b.

Blood pressure

The effect of exercise training on blood pressure as estimated by direct meta-analysis is shown in Figure 4 (see Figure 5 on the eAddenda for a detailed forest plot). Aerobic training did not significantly improve systolic blood pressure (WMD −3 mmHg, 95% CI −11 to 6, I^2 = 38%), as shown in Figure 4a. However, combined training did significantly reduce systolic blood pressure (WMD −9 mmHg, 95% CI −13 to −4, I^2 = 56%), as shown in Figure 4b.

The results were similar for diastolic blood pressure. Aerobic training did not significantly improve diastolic blood pressure (WMD 1 mmHg, 95% CI −4 to 5, I^2 = 45%), as shown in Figure 4c. However, combined training did significantly improve diastolic blood pressure (WMD −5 mmHg, 95% CI −6 to −3, I^2 = 8%), as shown in Figure 4d.

Haemodialysis efficiency

The effect of exercise training on haemodialysis efficiency as estimated by direct meta-analysis is shown in Figure 6 (see Figure 7 on the eAddenda for a detailed forest plot). Aerobic training improved haemodialysis efficiency (WMD 0.11, 95% CI 0.02 to 0.20, I^2 = 45), as shown in Figure 6a. Haemodialysis efficiency was not significantly affected by resistance training (WMD −0.11, 95% CI −0.34 to 0.13, I^2 = 70%) or by combined training (WMD −0.01, 95% CI −0.18 to 0.16, I^2 = %), as shown in Figures 6b and 6c.

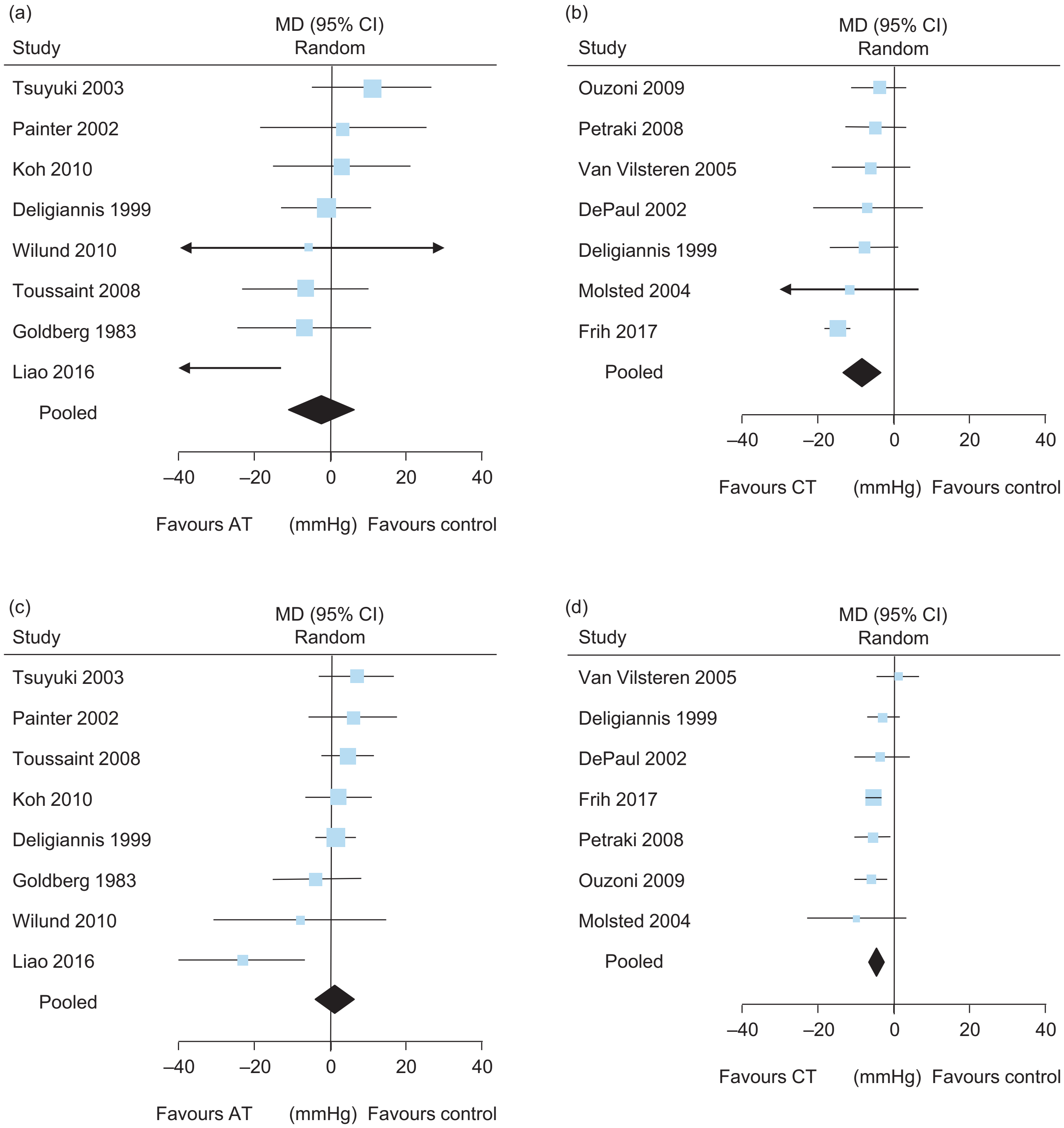

Figure 4. Direct meta-analysis of the effect of (a) aerobic training compared to control group on systolic arterial pressure, (b) combined training compared to control on systolic arterial pressure, (c) aerobic training compared to control on diastolic arterial pressure, and (d) combined training compared to control on diastolic arterial pressure.
AT = aerobic training, CT = combined training.

Heterogeneity

No significant heterogeneity ($I^2 > 60\%$) was observed for aerobic capacity and blood pressure; nevertheless, this review did investigate the possible reason for the heterogeneity amongst studies comparing the effects of combined training in aerobic capacity ($I^2 = 35\%$) (Figure 2b). To explain the source of heterogeneity, we could identify two articles[39,40] that differed in the frequency of the intervention (twice per week) from the others (three or more per week). The exclusion of these trials eliminated heterogeneity and did not affect the evidence that combined training significantly increases VO_2max (WMD 5.79 ml/kg/min, 95% CI 4.52 to 7.06, $I^2 = 0\%$).

In the meta-analyses of the effect of aerobic training on arterial blood pressure, we observed heterogeneity of 38% for systolic pressure and 45% for diastolic pressure. To explain the heterogeneity, we found that the study of Liao et al[28] showed a mean blood pressure reduction in the exercise group that was much higher than among the other studies: systolic pressure improved from 138 mmHg (SD 17) at baseline to 96 mmHg (SD 64) at the end of the training period; and diastolic pressure improved over the same period from 77 mmHg (SD 8) to 54 mmHg (SD 35). The study did not explain the reason for this major reduction and did not report whether the antihypertensive drug regimen was maintained during the protocol. The comparison between aerobic training and control group without the data of Liao et al[26] showed no heterogeneity for both the systolic and diastolic data, and did not affect the evidence that aerobic training does not improve systolic (0 mmHg, 95% CI −6 to 7, $I^2 = 0\%$) or diastolic (2 mmHg, 95% CI −1 to 6, $I^2 = 0\%$) arterial pressure.

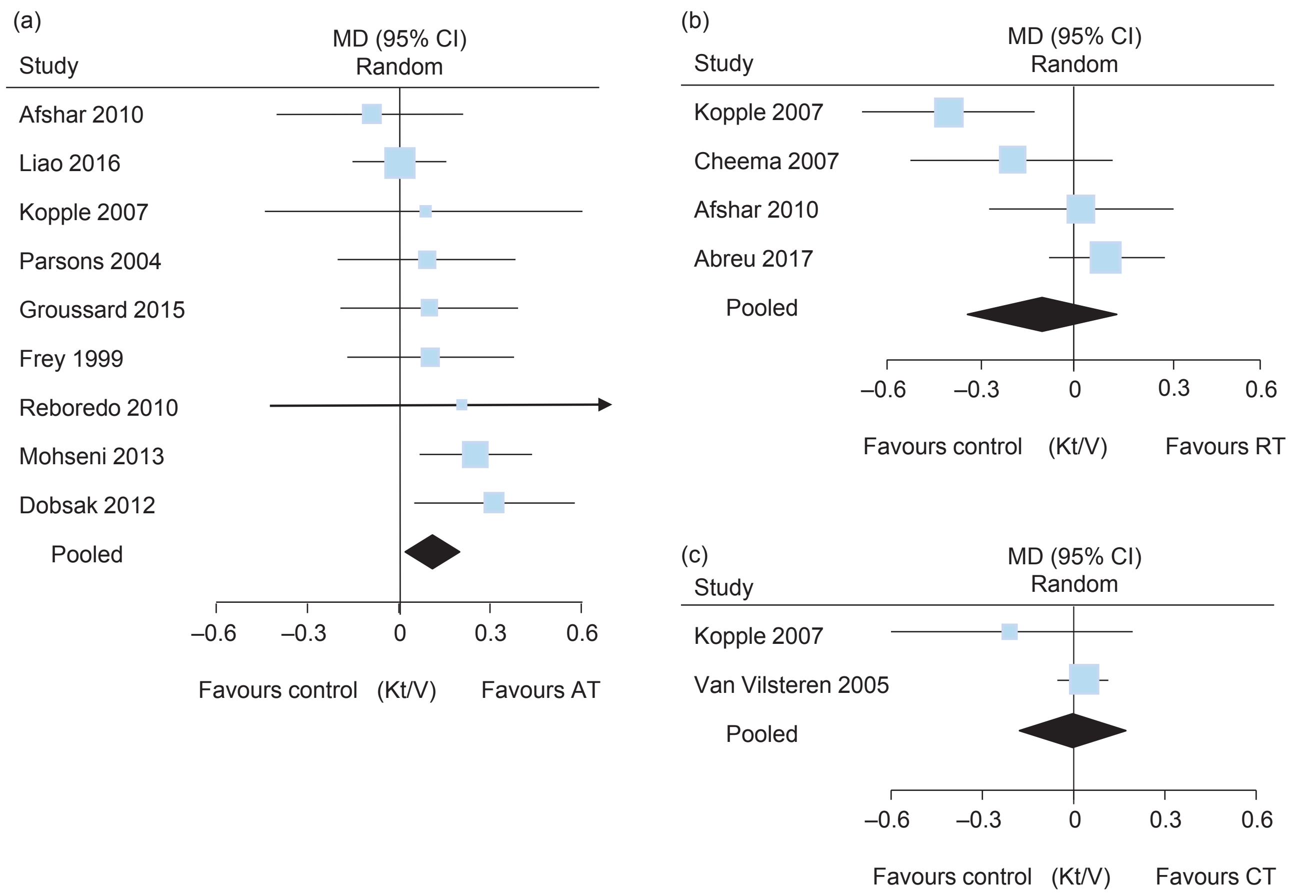

Figure 6. Direct meta-analysis of the effect of (a) aerobic training compared to control, (b) resistance training compared to control, and (c) combined training compared to control on Kt/V. See main text for explanation of Kt/V.
AT = aerobic training, CT = combined training, RT = resistance training.

Substantial heterogeneity was found in the meta-analysis of the effect of resistance training on haemodialysis efficiency (I^2 = 70%) (Figure 6b); however, only four studies[10,12,19,26] were included in this comparison.

Synthesis of results – network meta-analysis

Figure 8 shows the network of comparisons for each outcome measure in this review. Note that there is only one network of comparisons for blood pressure because all trials that measured blood pressure reported both systolic and diastolic data, so Figure 8b applies to both outcomes. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of participants. Table 3 shows the results of the network meta-analysis.

In the network analysis for aerobic capacity, 199 participants were allocated to a combined training group, 113 to an aerobic training group, and 271 to the control group, summing to a total of 583 participants. As in the results obtained using direct meta-analysis, aerobic training (3.34 ml/kg/min, 95% CrI 1.55 to 5.11) and combined training (5.01 ml/kg/min, 95% CrI 3.26 to 6.57) were both superior to the control group for aerobic capacity, as presented in Table 3. Although no significant difference was found between aerobic training and combined training, combined training had 92% probability of being ranked as the most effective treatment, as presented in Figure 9a.

In network meta-analyses of arterial blood pressure, 157 participants were allocated to a combined training group, 102 to an aerobic training group, and 237 to the control group, summing to a total of 496 participants. In the network meta-analysis for systolic arterial blood pressure, only combined training was superior to the control group (−9 mmHg, 95% CrI −14 to −3). In the network meta-analysis for diastolic arterial blood pressure, combined training was superior to control (−4 mmHg, 95% CrI −7 to −2) and to aerobic training (−6 mmHg, 95% CrI −10 to −1), as presented in Table 3. Moreover, combined training presented 91% probability of being the best treatment for systolic arterial pressure and 99% for diastolic arterial pressure, as presented in Figures 9c and 9d.

In the network meta-analysis for haemodialysis efficiency, 100 participants were allocated to an aerobic training group, 71 to a resistance training group, 65 to a combined training group, and 230 to a control group, summing to a total of 466 participants. Unlike direct meta-analysis, which demonstrated that aerobic training improves haemodialysis efficiency when compared to control group, none of exercise training modalities were superior to control treatment, as shown in Table 3. Aerobic training had the highest probability (76%) of being the best treatment for this outcome, as presented in Figure 9b.

Discussion

Network meta-analysis has been used to compare the effects of different exercise training modalities in a range of health conditions, such as overweight/obesity[50] and type 2 diabetes.[51] This is the first published network meta-analysis to compare exercise training modalities in people with end-stage renal disease who require haemodialysis. In doing so, it helps to overcome the absence of comparative data from head-to-head trials about the effects of different exercise modalities on aerobic capacity, blood pressure and dialysis efficiency in this population. The network meta-analysis results substantially progress understanding of the relative merits of the exercise training modalities beyond that obtained from the direct meta-analyses in this review and elsewhere.

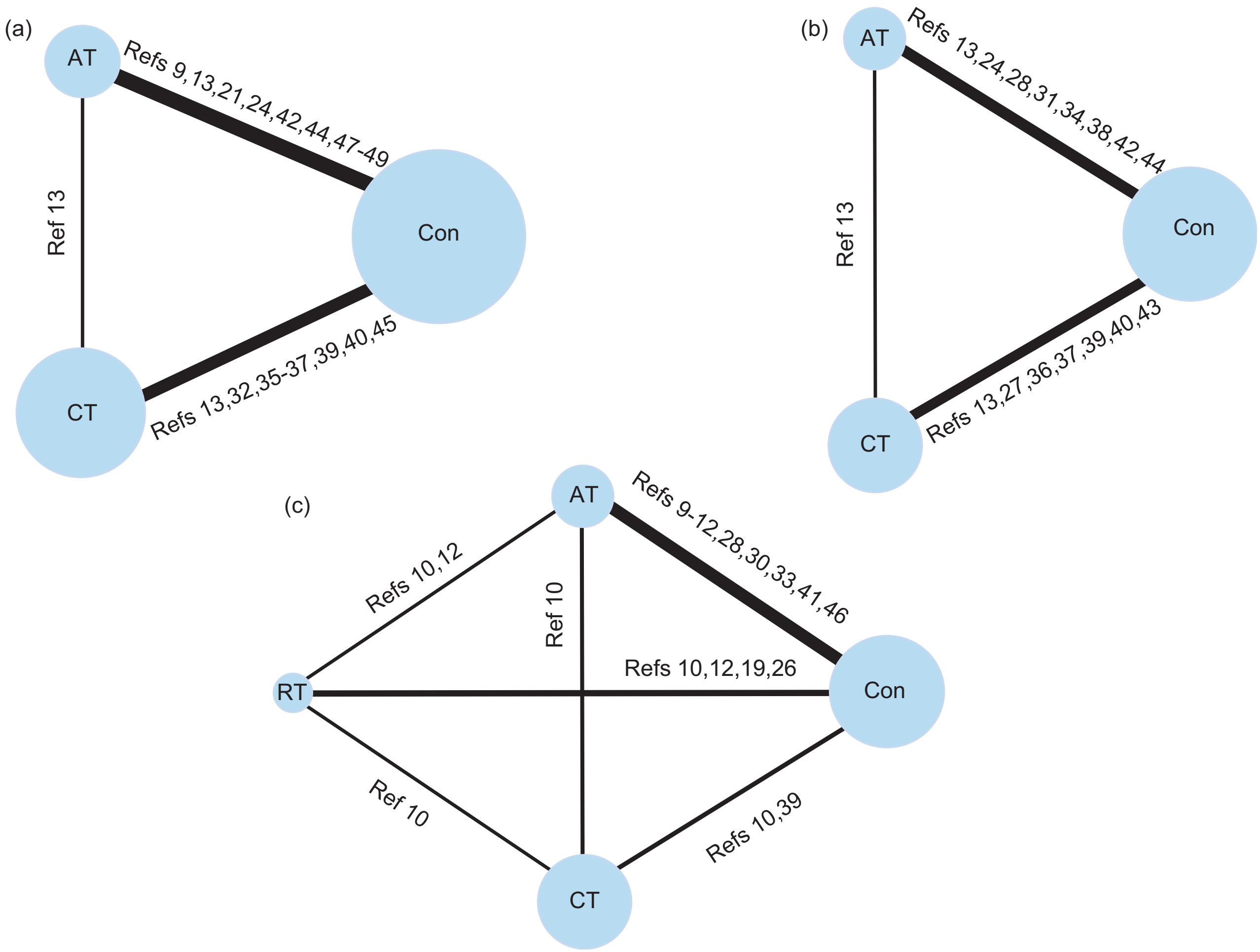

Figure 8. Network of clinical trials comparing different modalities of exercise to (a) aerobic capacity, (b) arterial blood pressure, and (c) haemodialysis efficiency. AT = aerobic training, Con = control, CT = combined training, R = resistance training.

Our direct meta-analyses found that aerobic training increased aerobic capacity and haemodialysis efficiency compared to control, but had no effect on blood pressure. Combined training increased aerobic capacity and reduced both diastolic and systolic arterial pressure compared to control. Resistance training had no effect on the studied outcomes. These findings corroborate those of a 2011 Cochrane systematic review,[8] which found that aerobic training significant improved aerobic capacity, but only combined training improved both aerobic capacity and blood pressure control. Although the Cochrane review[8] did not assess the effect of exercise on dialysis efficiency, this was estimated in a systematic review by Sheng et al,[52] which meta-analysed six studies with a total of 233 participants. That review found a significant effect of intradialytic exercise on haemodialysis efficiency (Kt/V 0.27, 95% CI 0.01 to 0.53), but they did not analyse that effect according to training modalities. Our direct meta-analysis is the first to separate the effects of different exercise modalities on Kt/V and to find a significant effect only for aerobic training.

Our network meta-analysis revealed some interesting findings. First, it evidenced the superiority of combined training (aerobic exercise plus resistance training) in improving aerobic capacity and controlling blood pressure in people with end-stage renal disease. Increasing aerobic capacity in people with end-stage renal disease is a significant goal, given that exercise capacity, characterised as VO_2peak, has been considered a powerful predictor of survival in this clinical population.[53] Furthermore, a cross-sectional study including more than 10 000 haemodialysis patients found that subjective physical function was the strongest predictor of death among all health-related quality of life measures.[7] The positive effect of combined training on blood pressure is also a noteworthy finding, given that the risk of cardiovascular disease has a direct, strong and continuous correlation with blood pressure levels.[54,55]

Table 3
Mean differences and credible intervals estimated from network meta-analysis model.

	VO_2max *(ml/kg/min)*	Systolic arterial pressure *(mmHg)*	Diastolic arterial pressure *(mmHg)*	Haemodialysis efficiency *(Kt/V)*[a]
AT versus Con	3.34 (1.55 to 5.11)	−2 (−10 to 5)	1 (−3 to 5)	0.11 (−0.02 to 0.25)
CT versus Con	5.01 (3.26 to 6.57)	−9 (−14 to −3)	−4 (−7 to −2)	0.01 (−0.24 to 0.25)
RT versus Con	–	–	–	−0.06 (−0.26 to 0.11)
CT versus AT	1.66 (−0.83 to 3.93)	−6 (−15 to 3)	−6 (−10 to −1)	−0.1 (−0.39 to 0.16)
AT versus RT	–	–	–	0.17 (−0.03 to 0.39)
CT versus RT	–	–	–	0.07 (−0.21 to 0.36)

AT = aerobic training, Con = control, CT = combined training, RT = resistance training, VO_2max = maximal oxygen uptake.
[a] See main text for explanation of Kt/V.

(a) VO_2max probability rank

	1st	2nd	3rd
AT	8%	92%	0%
Con	0%	0%	100%
CT	92%	8%	0%

(b) Kt/V probability rank

	1st	2nd	3rd	4th
AT	76%	20%	4%	1%
Con	2%	36%	49%	12%
CT	19%	32%	25%	24%
RT	3%	12%	22%	63%

(c) Systolic BP probability rank

	1st	2nd	3rd
AT	9%	65%	26%
Con	0%	26%	73%
CT	91%	9%	0%

(d) Diastolic BP probability rank

	1st	2nd	3rd
AT	1%	27%	72%
Con	0%	72%	28%
CT	99%	1%	0%

Figure 9. Rankograms of aerobic training, control, combined training and resistance training for (a) aerobic capacity, (b) haemodialysis efficiency, (c) systolic arterial pressure, and (d) diastolic arterial pressure.
AT = aerobic training, BP = blood pressure, Con = control, CT = combined training, RT = resistance training.
The cell transparency is proportional to the probability of the treatment to be ranked in that column. The columns represent the ranks; the first column represents the best treatment and the last column represents the worst treatment.

Since combined training seems more effective in increasing functional capacity and decreasing blood pressure, it may play a role in survival rates. This hypothesis awaits testing in additional clinical trials assessing long-term outcomes.

The network meta-analysis for haemodialysis efficiency was inconclusive. This may mean that exercise has limited effect on haemodialysis efficiency or, alternatively, Kt/V-urea may not be the best way to measure the impact of exercise on dialysis efficiency. Kt/V is based on the clearance of urea, a small solute that is distributed in total body water and that passively distributes across plasma membranes. However, some trials have assessed haemodialysis efficiency through measurement of the removal of solutes of higher molecular weight or that are more hydrophilic than urea in dialysate; most of these studies found positive results.[41,56–58]

This systematic review had several methodological strengths, including: focused review questions; a comprehensive and systematic literature search; and the collaboration of a multidisciplinary team of health researchers and methodologists who used explicit and reproducible eligibility criteria. Furthermore, it employed network meta-analysis to indirectly compare different modalities of exercise training for each outcome analysed, which allowed new findings to be derived from the literature. Despite advancing knowledge on the issue, this network meta-analysis had some limitations due the characteristics of the included studies. Most trials included in the analysis have uncertain or high risk of bias. Regarding haemodialysis efficiency, the review was limited by the fact that these are small trials measuring only single pool Kt/V. Although the validity of Kt/V-urea as a prognostic factor has been questioned,[59] this measure was chosen because it has largely been used in previous studies on dialysis efficiency. Moreover, the analysis did not consider training details, such as intensity and duration.

The main contribution of this network meta-analysis is the ranking of the potential benefits of different exercise training modalities on health outcomes in people who required haemodialysis for end-stage renal disease. This ranking shows that combined aerobic and resistance training is the most effective modality to increase aerobic capacity and control blood pressure in this population. This knowledge helps physiotherapists and other clinicians to advise people with end-stage renal disease about which exercise training modality is likely to be most beneficial for them, despite the lack of head-to-head trials comparing the different modalities.

Future research could examine the influence of the duration and intensity of the exercise training regimen on its clinical effects, to further guide clinical exercise prescription in this setting. Despite the need for further evidence, the findings of this review support the prescriptions of combined exercise training regimens in haemodialysis centres.

What was already known on this topic: People with end-stage renal disease present higher risk for cardiovascular disease and mortality, which may be aggravated by a sedentary lifestyle. Exercise training improves functional capacity, arterial blood pressure, lipid profile, heart rate variability, and quality of life in people with end-stage renal disease, but few head-to-head comparisons between different exercise modalities have been published.
What this study adds: Using network meta-analysis, the review identified that combined training is the most effective modality to increase aerobic capacity and control blood pressure in people who require haemodialysis for end-stage renal disease.

Footnotes: [a] RStudio Inc, Boston, USA. [b] R package version 2.2.0-3, http://CRAN.R-project.org/package=rjags.

eAddenda: Figures 3, 5 and 7, and Appendices 1, 2, 3 and 4 can be found online at DOI: https://doi.org/10.1016/j.jphys.2018.11.008.

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Competing interest: Nil.

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