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Review article

Quantifying the dose-response relationship between exercise and health-related quality of life in patients undergoing haemodialysis: A meta-analysis

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ABSTRACT

Objective: This meta-analysis aims to explore the dose–response relationship of aerobic exercise or aerobic combined resistance exercise on cardiopulmonary function in maintenance hemodialysis (MHD) , with the goal of aiding in the formulation of precise exercise prescriptions.
Methods: A literature search up to August 18, 2023, was conducted in databases including Web of Science, among others, focusing on the effects of exercise interventions on cardiopulmonary function in hemodialysis patients. Two researchers independently conducted literature screening, data extraction, and an assessment of study methodology quality. A dose–response *meta*-analysis was carried out using a one-stage cubic spline mixed-effects model, followed by stratified analyses based on intervention period, intervention method, and exercise environment.
Results: A nonlinear dose–response relationship was observed between exercise and 6-minute walk test (6WMT) as well as peak oxygen uptake (VO_2Peak) in hemodialysis patients. The optimal exercise dose for the 6WMT across the full exposure range was 922 METs-min/week, with VO_2Peak increasing with the dose. The effects were influenced by the type of exercise, intervention period, and exercise environment. An exercise dose of 500 METs-min/week and 619 METs-min/week was found sufficient to achieve the minimal clinically important differences (MCID) for 6WMT and VO_2Peak, respectively.
Conclusion: There is a significant association between the dose of exercise and its effects. With appropriate adjustment of variables, even low-dose exercise can lead to clinically significant improvements in cardiopulmonary function.

1. Introduction

Chronic kidney disease (CKD) includes a spectrum of kidney diseases, not limited to end-stage conditions, characterized by high morbidity and mortality rates, thus emerging as a significant public health concern that demands widespread attention(Gallo Marin et al., 2023). Current estimates suggest that approximately 759 out of every million individuals require renal replacement therapy due to CKD(See et al., 2021). Maintenance hemodialysis (MHD) serves as a primary renal replacement therapy for CKD patients. While MHD technology effectively extends patients' lifespan, it also leads to declines in muscle mass and exercise tolerance, markedly impacting quality of life and physical functionality(Locatelli and Del Vecchio, 2023). Moreover, with the progression of the disease, CKD patients' VO_2Peak significantly decreases, further indicating compromised cardiopulmonary function.

Nowadays, the goals for CKD patients undergoing MHD have expanded beyond mere survival and lifespan prolongation to emphasize improvements in quality of life and social engagement(Hsiao et al., 2023). The American Kidney Foundation highlights the importance of exercise training as a critical component in managing and treating complications in MHD patients(Cheung et al., 2021). Exercise increasingly plays a pivotal role in enhancing the cardiopulmonary function of

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MHD patients. Not only can it reduce resting heart rate and blood pressure, diminish arteriosclerosis markers, and promote physiological cardiac hypertrophy, but it can also enhance myocardial perfusion and increase cardiac blood flow(Pinckard et al., 2019).

Clinical practice guidelines for CKD suggest formulating appropriate exercise prescriptions for MHD patients to boost their physical capabilities, thereby enhancing their quality of life(Eckardt et al., 2023). However, there is currently a lack of high-level evidence-based medical evidence to provide precise and effective exercise programs and dosage guidelines for MHD patients. In response to this, we have introduced a first-order mixed effects framework suitable for integrating data (Recchia et al., 2023). The first-order mixed effects model operates on the principle that the observed data comprise layers of variability that can be dissected into predictable (fixed) and unpredictable (random) components. Fixed effects in our context refer to the specific exercise interventions under examination, while random effects capture the unobserved heterogeneity among the included studies, such as differences in study design, participant characteristics, and measurement methods. Its key advantage includes incorporating studies that perform single comparisons, considering heterogeneity and potential dose–response relationships simultaneously. Following this approach, we designed a dose–response *meta*-analysis to conduct stratified analysis on the intervention period, intervention method, and exercise environment, further exploring the relationship between exercise dose and cardiopulmonary function in MHD patients. Given the focus of this study on the cardiorespiratory function of hemodialysis patients, aerobic exercise is considered. This excludes transportation, household chores, or occupational activities. Aerobic exercise, also known as cardiovascular exercise or cardio, is a form of physical activity that increases heart rate and breathing for an extended period. Unlike anaerobic exercise, which involves short bursts of intense activity, aerobic exercise is characterized by continuous, rhythmic movements that engage large muscle groups. Examples include walking, running, cycling, swimming, and dancing. This study aims to elucidate the dose–response relationship between exercise and cardiopulmonary function in MHD patients, seeking to establish optimal exercise dosages for enhancing their health and quality of life. This effort is expected to significantly contribute to the formulation of precise and effective exercise prescriptions, thereby elevating the standard of care for MHD patients.

2. Materials and Methods

This *meta*-analysis adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions(Higgins and Green, 2008) and reported following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). The detailed PRISMA checklist is presented in Appendix A. The protocol for this study has been proactively registered with the PROSPERO international prospective register of systematic reviews, under the registration ID: CRD42023455557.

2.1. Search strategy

In defining the search strategy, we adopted the PICOS framework. Two independent researchers(WZ, SW) systematically conducted a comprehensive literature search across multiple databases, including PubMed, OVID, Web of Science, the Cochrane Library, Embase, SPORTDiscus, SinoMed, China National Knowledge Infrastructure, Wanfang Data, and the VIP database, to ensure a rigorous and exhaustive review of the available literature. The search timeline was from the establishment of these databases to August 18, 2023. Detailed search strategy can be found in Appendix B. Furthermore, potential unpublished trials were searched through both the US and China clinical trial registries.

2.2. Study selection

Inclusion criteria: (1) Study design: Randomized Controlled Trials (RCTs); (2) Participants: Patients undergoing MHD ($\geq$18 years old); (3) Interventions: Aerobic Exercise (AT) or combined aerobic and resistance exercise (CT); (4) At least one of the following outcomes must be reported in the studies: 6-minute walk test (6WMT), peak oxygen uptake (VO_2Peak); (5) Language: English or Chinese.

Exclusion criteria: (1) Studies involving participants under the age of 18 years, encompassing both children and adolescents, as our focus is on adult patients undergoing MHD treatment; (2) Patients not undergoing MHD treatment; (3) Data not presented in the required format and the authors did not respond to our request; (4) Low quality studies(those with significant flaws in design, implementation, reporting, or risk of bias, which may compromise the reliability of their findings) or those containing data errors.

2.3. Literature screening and data extraction

Two researchers(WZ, SW) independently screened titles and abstracts and determined studies to be included through full-text assessment. Any disagreements during the entire literature screening and assessment process were resolved through discussion or adjudication by a third researcher(MF). The extracted information included the first author's name, year of publication, sample size, baseline information of hemodialysis patients, methods of generating random sequences, interventions in the experimental and control groups, exercise prescriptions, measured outcomes, adverse reactions, as well as mean values and standard deviations (SDs) of outcomes.

2.4. Quality assessment of included studies

Two researchers(WZ, SW) independently assessed the quality of studies using the Cochrane's second edition of the Risk of Bias tool (ROB2)(Sterne et al., 2019). In the case of disagreement, a third researcher(MF) made the final decision. We considered the following five domains of bias risk: (1) Bias arising from the randomization process; (2) Bias due to deviations from intended interventions; (3) Bias due to missing outcome data; (4) Bias in the measurement of the outcome; (5) Bias in the selection of the reported results. Each domain could be described as having a low risk of bias, some concerns, or a high risk of bias. When there were some concerns in at least one domain, the study was assigned a moderate risk of bias. If all domains were judged to have a low risk, the overall risk of bias for the study was considered low.

2.5. Statistical analysis

We conducted a dose–response *meta*-analysis with random effects, analyzing the influence of exercise dose on 6WMT and VO_2Peak using a one-stage mixed-effects model(Sera et al., 2019). The data were presented as the mean and standard deviation of the difference between post-intervention and baseline values. Under fixed percentiles (10 %, 50 %, and 90 %), parameters were estimated using a restricted cubic spline model and maximum likelihood method, with no pre-set assumptions about the shape of the relationship. This approach was chosen because cubic spline models offer the capacity to effectively capture complex, non-linear relationships present in the data. By employing smooth and easily interpretable curves, these models accurately represent the underlying patterns without imposing restrictive assumptions. Interventions were divided into three levels: the first level was coded as "exercise" or "control"; the second level was coded according to exercise type as "aerobic exercise", "combined aerobic and resistance exercise", or "control". The third level coded the intervention based on specific type and dose (intensity coding refers to the "Physical Activity Guidelines")(Ainsworth et al., 2011), resulting in metabolic equivalent tasks, or METs, represented by METs-min/week. The METs were the energy expenditure caused by the product of the duration, frequency, and intensity of a certain type of exercise. In the dose–response evaluation, 0 METs-min/week was taken as the reference, showing the differences in 6WMT and VO_2Peak under different exercise doses (increment units of 200 METs-min/week, ranging from 600 to 1800 METs-min/week). We conducted subgroup analysis according to the mode of exercise, intervention period, and exercise environment. The MCID, estimated using the distribution method, differentiates statistical from clinical significance(Watt et al., 2021). This provides a quantified evaluation of treatment effectiveness. By doing so, it offers stakeholders, including patients, physicians, and policymakers, a deeper understanding and interpretation of the study results, specifically regarding the impact of exercise on the cardiopulmonary function of MHD patients. We assessed publication bias using a funnel plot and the trim and fill method was used to correct small sample effects based on the asymmetry of the funnel plot(Lin et al., 2020). Data analysis was performed using the dosresmeta and meta packages in R(4.1.3), with statistical inferences primarily based on the pooled dose–response relationship.

3. Results

3.1. Literature search results and process

The initial search yielded 3,407 studies, of which 3,211 came from ten databases, 196 from reviews of published reviews, and three from ongoing studies at clinical trial registries. After removing 2,011 duplicates, 52 studies(Carmack et al., 1995; DePaul et al., 2002; Konstantinidou et al., 2002; Koufaki et al., 2002; Tsuyuki et al., 2003; Storer et al., 2005; van Vilsteren et al., 2005; Petraki et al., 2008; Kouidi et al., 2009; Ouzouni et al., 2009; Koh et al., 2010; Kouidi et al., 2010; Mustata et al., 2011; Reboredo et al., 2011; Dobsak et al., 2012; Pellizzaro et al., 2013; Baria et al., 2014; Bohm et al., 2014; Wu et al., 2014; Esteve Simo et al., 2015; Greenwood et al., 2015; Groussard et al., 2015; Huang et al., 2015; Manfredini et al., 2015; Reboredo et al., 2015; Tang, 2015;

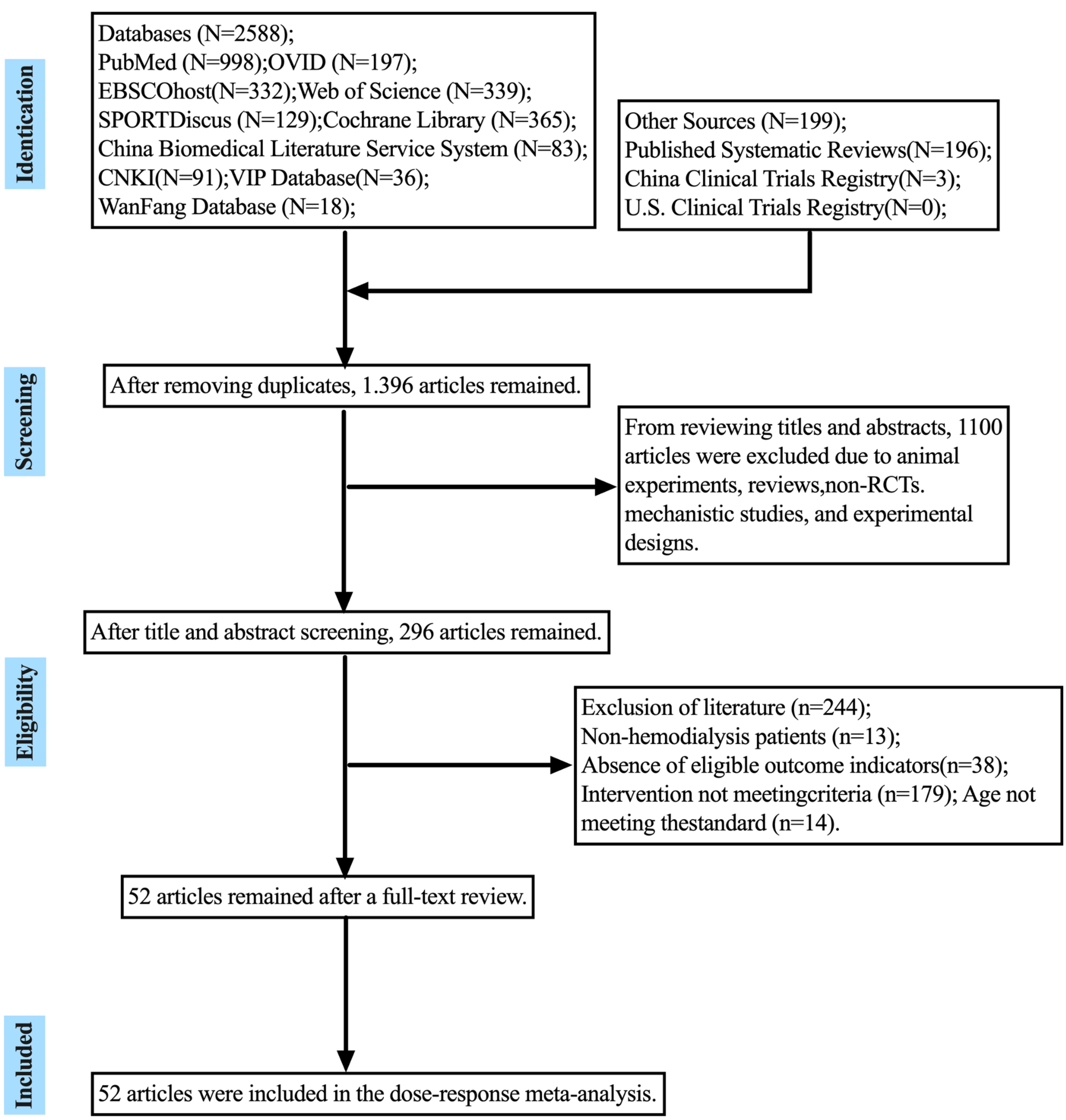

Fig. 1. Flowchart of Literature Screening for Meta-Analysis on Exercise and Health Outcomes in Hemodialysis Patients.

Anastasia et al., 2016; Li and Wang, 2016; Marchesan et al., 2016; Pomidori et al., 2016; Chang et al., 2017; Frih et al., 2017; Tao et al., 2017; Wang, 2017; Campos et al., 2018; McGregor et al., 2018; Fernandes et al., 2019; Nilsson et al., 2019; Cardoso et al., 2020; Huang et al., 2020; Jamshidpour et al., 2020; Liao and Sun, 2020; Ortega-Pérez de Villar et al., 2020; Yeh et al., 2020; Dornelas and Lima, 2021; Myers et al., 2021; Yu et al., 2021; Andrade et al., 2022; Krase et al., 2022; Liu and Xu, 2022; Wang et al., 2022; Ye et al., 2022) were ultimately included in the *meta*-analysis following standard screening. The screening process is shown in Fig. 1.

3.2. Characteristics of the included

Studies Of the 52 included studies, 29 independently examined the effects of exercise on 6WMT in hemodialysis patients, 17 independently reported on the effects on VO_2Peak, and the remaining six addressed both. The studies spanned both developed and developing countries, with a total of 2,258 hemodialysis patients involved. For details, see Table1 in the Appendix A.

3.3. Quality assessment of the included studies

Due to the difficulty in implementing blinding, the methodological quality of exercise trials is often not high. Only 30.8 % of the studies provided a complete randomization process, and only 3.8 % of the studies were assessed as having low risk of bias. Summaries and specific evaluations of bias risk can be viewed in Appendix A (Figs. 1 and 2).

3.4. Dose-Response meta-analysis results

3.4.1. Dose-Response relationship between exercise and 6WMT

Fig. 2(A) and Table 1 depict an inverted U-shaped non-linear dose–response relationship between exercise dose and 6WMT, with 6WMT peaking at an exercise dose of 922 METs-min/week. The predicted values for the WHO's recommended lower limit (600 METs-min/week), upper limit (1200 METs-min/week), and double (1800 METs-min/week) exercise doses correspond to 43.92 (95 %CI [30.62,57.22]), 46.46 (95 %CI [34.56,58.36]), and 39.7 (95 %CI [10.07,69.34]), respectively.

The results of the stratified analysis are as follows. Fig. 3(A) displays the effect of two exercise modes on the dose–response relationship with 6WMT; the effect of AT is optimal at 778 METs-min/week and decreases thereafter, whereas CT increases with the dose. Fig. 3(B) demonstrates the effect of intervention duration on 6WMT, showing an inverted U-shape for ≤ 12 weeks, with the best effect at 752 METs-min/week, and a positive correlation for > 12 weeks. Fig. 3(C) indicates continuous improvement with exercise during dialysis, whereas non-dialysis exercise peaks at 813 METs-min/week and then weakens.

3.4.2. Dose-Response relationship between exercise and VO_2Peak

Fig. 2(B) and Table 2 present a non-linear dose–response relationship between exercise dose and VO_2Peak. Within the exposure range, VO_2Peak shows a continuous positive correlation with dose. The predicted values at the WHO's recommended lower limit (600 METs-min/week), upper limit (1200 METs-min/week), and double (1800 METs-min/week) exercise doses are 2.6 (95 %CI [1.36,3.85]), 3.88 (95 %CI [2.74,5.01]), and 4.74 (95 %CI [3.28,6.2]), respectively.

The stratified analysis results are as follows. Fig. 3(D) shows that the effect of AT on VO_2Peak strengthens with increasing dose, while the effect of CT peaks at 659 METs-min/week and then decreases. Fig. 3(E) reveals that for intervention durations of ≤ 12 weeks, the effect peaks at 901 METs-min/week and then gradually weakens, while for > 12 weeks, the effect continues to strengthen with increasing dose. Fig. 3(F) demonstrates that the effect of exercise during dialysis gradually strengthens with dose, while the effect of non-dialysis exercise peaks at 562 METs-min/week and then weakens.3.4.3 Exercise Dose and MCID.

Table 1
Dose-Response Relationship between Exercise Dosage and 6-Minute Walking Test in Hemodialysis Patients.

subject	n	600METS-min/week		800METS-min/week		1000METS-min/week		1200METS-min/week		1400METS-min/week		1600METS-min/week		1800METS-min/week	
		MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)
Overall	35	43.95	30.66,57.25	47.75	35.99,59.52	48.09	37.86,58.34	46.45	34.54,58.36	44.21	27.42,60.99	41.95	18.97,64.92	39.69	10.03,69.36
Mode															
Aerobic	26	52.88	34.75,70.99	55.09	40.77,69.41	52.42	41.43,63.41	46.87	31.42,62.31	40.50	15.33,65.68	34.12	−2.1,70.32	27.73	−19.9,75.37
Combined	14	29.90	17.51,42.29	24.76	37.04,49.32	43.28	3.35,55.21	40.01	36.18,61.83	54.58	39.15,69.99	60.14	41.03,79.25	65.7	42.31,89.09
Period															
≤12 weeks	21	57.51	38.53,76.48	59.46	44.24,74.68	54.86	43.31,66.41	45.99	29.06,62.95	35.12	6.3,63.94	24.00	−18.3,66.27	12.88	−43.3,69.01
>12 weeks	14	24.97	11.11,38.82	31.12	17.44,44.79	36.44	22.69,50.2	41.24	24.8,57.66	45.78	23.95,67.60	50.28	21.69,78.87	54.78	18.83,90.73
Environment or Setting															
Dialysis	19	37.81	23.86,51.76	43.12	29.47,56.76	46.09	31.54,60.63	47.72	29.22,66.24	48.97	24.23,73.69	50.19	18.25,82.14	51.42	11.82,91.02
Non-dialysis	17	51.08	29.92,72.24	53.92	37.17,70.68	52.26	40.71,64.04	47.97	32.86,63.09	42.92	17.45,68.38	37.85	0.36,75.34	32.77	−17.2,82.78

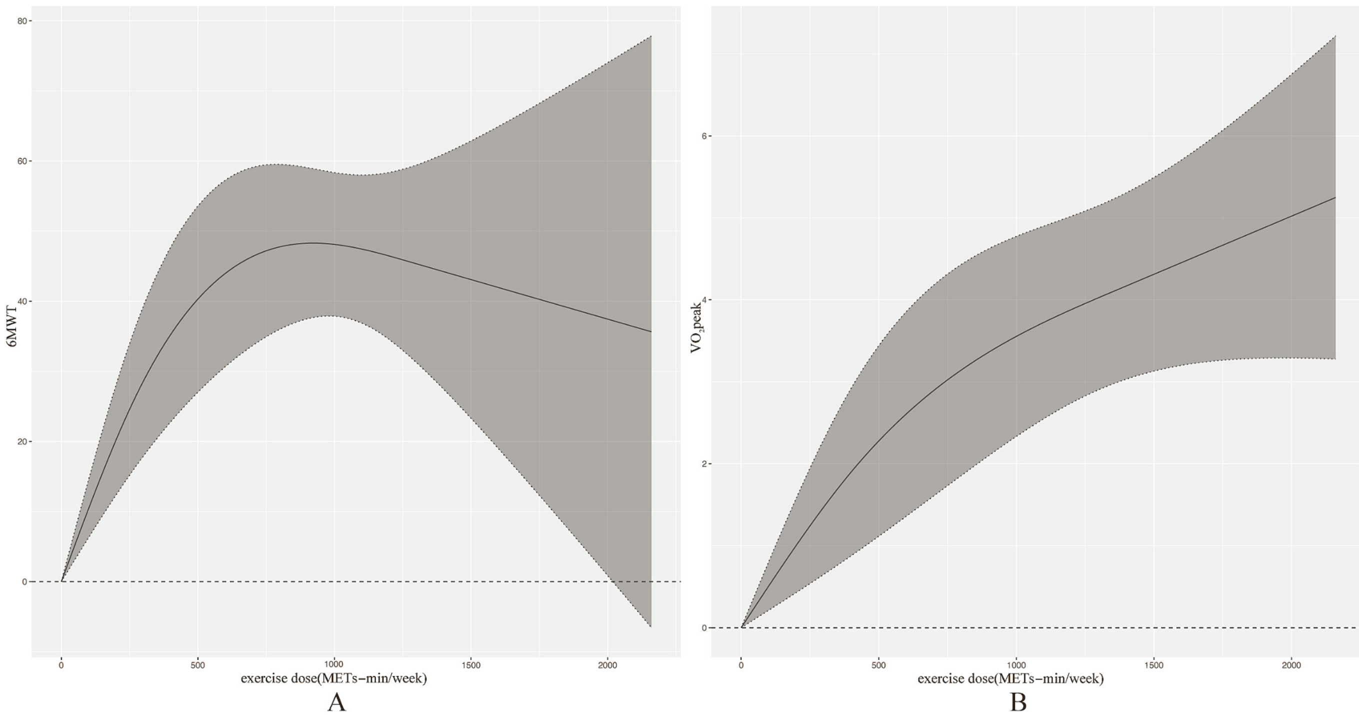

Fig. 2. Dose-Response Relationship of Exercise on 6-Minute Walking Capacity (A) and Peak Oxygen Uptake (B) in Hemodialysis Patients.

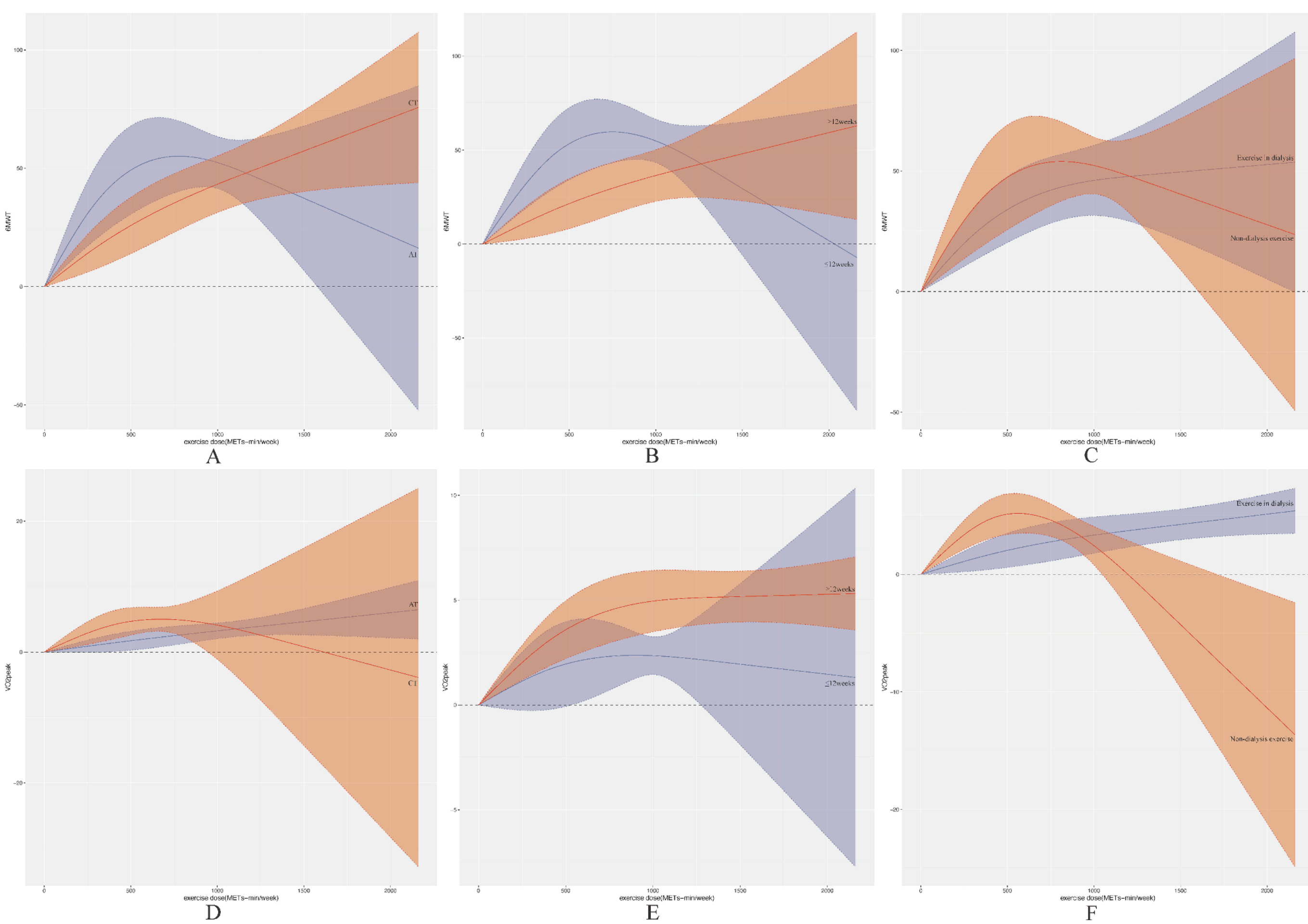

Fig. 3. Subgroup Analysis of Dose-Response Relationship between Exercise Intensity and 6-Minute Walking Ability and Peak Oxygen Uptake in Hemodialysis Patients.

Table 2
Dose-Response Relationship between Exercise Dosage and Peak Oxygen Uptake in Hemodialysis Patients.

subject	N	600METS-min/week MD	(95 % CI)	800METS-min/week MD	(95 % CI)	1000METS-min/week MD	(95 % CI)	1200METS-min/week MD	(95 % CI)	1400METS-min/week MD	(95 % CI)	1600METS-min/week MD	(95 % CI)	1800METS-min/week MD	(95 % CI)
Overall	23	2.60	1.35,3.85	3.14	1.85,4.43	3.55	2.33,4.77	3.88	2.74,5.01	4.17	3.02,5.3	4.45	3.20,5.70	4.73	3.28,6.19
Mode															
Aerobic	21	2.04	0.54,3.53	2.65	1.26,4.04	3.23	2.03,4.43	3.79	2.53,5.05	4.35	2.64,6.06	4.91	2.54,7.26	5.46	2.37,8.54
Combined	7	4.96	3.08,6.84	4.87	2.36,7.37	4.11	−1.11,9.33	2.91	−6.01,11.84	1.51	−11.5,14.53	0.09	−17.8,17.24	−1.32	−22.6,20.03
Period															
≤12 weeks	12	2.15	0.19,4.10	2.34	0.89,3.79	2.35	1.45,3.25	2.22	0.58,3.87	2.04	−1.03,5.12	1.85	−2.7,6.46	1.65	−4.52,7.84
>12 weeks	11	4.02	2.53,5.51	4.62	3.08,6.17	4.95	33.48,6.41	5.09	3.76,6.41	5.14	3.92,6.37	5.19	3.96,6.42	5.23	3.88,6.58
Environment or Setting															
Dialysis	16	2.35	0.78,3.91	2.88	1.26,4.51	3.33	1.79,4.87	3.71	2.31,5.11	4.06	2.76,5.37	4.41	3.08,5.74	4.76	3.29,6.23
Non-dialysis	7	5.15	3.51,6.790	4.28	2.97,5.59	2.43	0.80,4.05	−0.07	−2.96,2.83	−2.86	−7.4,1.68	−5.69	−11.96,0.58	−8.52	−16.56,-0.49

The minimum clinically important difference (MCID) estimated by the combined effect size for 6WMT is 40.244 m, with the minimal predicted exercise dose being 500 METs-min/week. The corresponding values for CT and AT are 900 METs-min/week and 354–1409 METs-min/week respectively. For intervention durations of $\leq$ 12 weeks and $>$ 12 weeks, the corresponding values are 328–1307 METs-min/week and 1158 METs-min/week, respectively. For exercise in non-dialysis and dialysis conditions, the values are 378–1505 METs-min/week and 679 METs-min/week, respectively.

For VO_2Peak, the MCID estimated by the combined effect size is 2.66 ml/kg/min, and the minimal predicted exercise dose required is 619 METs-min/week. The corresponding values for combined aerobic and resistance exercise and aerobic exercise alone are 288–1238 METs-min/week and 803 METs-min/week, respectively. For intervention durations of $\leq$ 12 weeks, any dose does not reach MCID, while $>$ 12 weeks corresponds to 340 METs-min/week. For exercise in non-dialysis and dialysis conditions, the values are 192–979 METs-min/week and 710 METs-min/week, respectively. Table 3 presents exercise recommendations based on these results.

3.5. Publication bias

The funnel plot (Fig. 3 in the Appendix.) displays slight asymmetry, suggesting possible publication bias. The trim and fill method further confirms this: before trimming, the random effects model for 6WMT was 42.2119 [32.2316,52.1921] ($p < 0.0001$), and after trimming it was 36.9808 [25.1540,48.8076] ($p < 0.0001$); for VO_2Peak, the values were 3.6068 [2.7576,4.4559] ($p < 0.0001$) and 2.4379 [1.4578,3.4180] ($p < 0.0001$) before and after trimming, respectively. The results may be slightly affected by publication bias, but the impact is relatively small.

4. Discussion

4.1. Synthesis of evidence

In this comprehensive dose–response *meta*-analysis, we elucidate the intricate nonlinear association between physical activity and cardiopulmonary health in individuals undergoing hemodialysis. Our results underscore a salient point in line with the WHO's 2020 proclamation that even modest amounts of physical activity serve beneficial purposes for cardiopulmonary function(Bull et al., 2020). Such a standpoint is bolstered by contemporary literature indicating that even minimal-intensity physical engagements can yield marked cardiopulmonary advantages in those grappling with metabolic syndrome(Bahgat et al., 2022). Intriguingly, we discern that a regimen involving 500 METs-min/week suffices to elicit clinically significant cardiopulmonary enhancements, slightly trailing behind the WHO's endorsed minimal activity threshold of 600 METs-min weekly, which equates to 150 min of moderate exertion or a mere 75 min of intense physical activity(Bull et al., 2020). Such a modest weekly goal, we posit, might be more pragmatic and achievable for a broad swath of chronic disease patients, thereby serving as an impetus for wider exercise adoption to harness its manifold health dividends. It's noteworthy that exceeding the WHO's stipulated upper echelon of physical activity (i.e., surpassing 1200 METs-min weekly or the equivalent of 300 min of moderate or 150 min of intense activity)(Bull et al., 2020)doesn't seem to proffer incremental cardiopulmonary benefits. This observation is, however, at variance with certain studies suggesting amplified cardiopulmonary gains with escalated exercise dosages(Ismail et al., 2013). This incongruence might stem from diverse study methodologies, encompassing variances in participant demographics, exercise modalities, and intervention frequencies, heralding a clarion call for more nuanced investigations in forthcoming research.

In our study, we utilized a more adaptable methodology, allowing a detailed examination of exercise dosage. Previous investigations into the effects of exercise dosage on disease outcomes have been limited by rigid

Table 3
Exercise Recommendations for Improving Cardiopulmonary Function in Hemodialysis Patients.

type	subgroup analysis	MICD(METs-min/ week)	Intensity	Energy expenditure(METs-min)	Recommended Accumulation (minutes/week)		Exercise Prescription Suggestion (sessions x minutes/week)	
					Minimum	Optimal	Minimum	Optimal
–	Overall	500 ~ 1751	Moderate	4.3(codes 02035)	~115	~215	3x ~ 35 6x ~ 20	5x ~ 45
			Vigorous	8.0(codes02040)	~65	~115	2x ~ 30 5x ~ 15	3x ~ 35 6x ~ 20
Mode	Aerobic	354 ~ 1409	Moderate	4.3(average of codes02105、02017、02120、02160)	~85	~185	2x ~ 40 5x ~ 20	3x ~ 50 6x ~ 30
			Vigorous	7.6(average of codes02005、02110、02019、02062)	~50	~105	2x ~ 25	3 x ~ 35 5 x ~ 20
	Combined	288 ~ 1238	Moderate	4.8(average of codes02052、02054、03015、05193)	~60	~140	2x ~ 30 3x ~ 20	3x ~ 40 5x ~ 30
			Vigorous	7.2(average of codes02040、02050、02020、15546)	~40	~100	2x ~ 20 4x ~ 10	3x ~ 30 5x ~ 20
Period	≤12 weeks	328 ~ 1307	Moderate	4.3(codes02035)	~80	~185	2x ~ 40 4x ~ 20	3x ~ 50 6x ~ 30
			Vigorous	8.0(codes02040)	~45	~100	2x ~ 20 3x ~ 15	3x ~ 30 5x ~ 20
	>12 weeks	340	Moderate	4.3(codes02035)	~80	~280	2x ~ 40 4x ~ 20	4x ~ 70
			Vigorous	8.0(codes02040)	~30	~150	2x ~ 15	3x ~ 50 5x ~ 30
Environment or Setting	Dialysis	679	Moderate	4.3(codes02035)	~160	~280	4x ~ 40	4x ~ 70
			Vigorous	8.0(codes02040)	~85	~150	2x ~ 40 5x ~ 20	3x ~ 50 5x ~ 30
	Non-dialysis	192 ~ 1505	Moderate	4.3(codes02035)	~45	~135	2x ~ 20 3x ~ 15	3x ~ 40 5x ~ 30
			Vigorous	8.0(codes02040)	~30	~75	2x ~ 15	2x ~ 35 4x ~ 20

methodologies. For example, Sanders categorized high-dosage interventions as exceeding 150 min weekly, while designations below this were considered low-dosage(Groot et al., 2016). Groot, on the other hand, made distinguished based on intensity, equating 45-minute interventions with those of 200 min(Groot et al., 2016). Such classifications may obscure true dose–response relationships. Diverging from these, our approach incorporated a dose–response *meta*-analytical technique. This not only permitted a refined segmentation of exercise dosages but also considered intensity, establishing a clearer dose–response relationship. The benefits of exercise are influenced by both volume and intensity; neglecting either can skew findings. Whereas Sanders and Groot may have overlooked the interplay between these factors, our study addressed them comprehensively. Conventional linear models prove inadequate when defining optimal dose brackets. We've adopted sophisticated models to better define the relationship between exercise dosage and its outcomes. While minimal dosages have limited effects, there's a risk of reduced patient adherence at excessive levels (Sanders et al., 2019). Acknowledging this balance, our study also recognizes the potential impact of high dosages on adherence, thus ensuring our recommendations are both effective and feasible.

This study elucidates that the modality of exercise, intervention duration, and the exercise setting substantially influence the outcomes of physical activity. Stratified analysis of two pivotal outcome metrics—6WMT and VO_2Peak—revealed that, when interventions are classified as aerobic training (AT), last for 12 weeks or less, and are conducted outside the dialysis phase, a dose of 378 METs-min/week is required to achieve the MCID for the 6WMT. In contrast, for combined training (CT) interventions that exceed 12 weeks and are undertaken outside the dialysis environment, a weekly dose of merely 340 METs-min is sufficient to attain the MCID for VO_2Peak. Among various combinations of modulating variables required to achieve the MCID, the minimum exercise dosage for both outcomes—6WMT and VO_2Peak—was consistently observed outside the dialysis setting. This may indicate that exercises performed during dialysis necessitate a higher dose for equivalent outcomes, possibly attributed to the inherent physiological impacts of the dialysis process. The optimal exercise dosage is modulated by a myriad of factors. Hence, when devising exercise intervention strategies, it is imperative to consider these determinants comprehensively to maximize the benefits of physical activity.

4.2. Clinical implications of Dose-Response analysis

This study underscores the salient belief that health thrives on exercise; even low-dose activity offers discernible health advantages. In real-world clinical settings, patients debilitated or encumbered by movement impairments may find it challenging to commit to high-dose exercise regimens right from the outset. In these contexts, moderate low-dose exercises become crucial, fostering a patient-friendly acceptance and adaptation to exercise therapy. This phased approach can safely amplify their physical capabilities, thereby enhancing the quality of life, a sentiment corroborated by numerous investigations(Coelho-Júnior et al., 2021). Furthermore, the effective dosages for various exercise modes are notably lower than the minimums endorsed by the WHO (Bernier-Jean et al., 2022), suggesting that non-specific modalities might confer substantial auxiliary benefits to clinical treatments, even at reduced intensities. The insights from this research pave the way for tailoring exercise dosage recommendations, subsequently amplifying cardiopulmonary wellness in patients undergoing hemodialysis, marking a pivotal stride toward precision exercise prescription for chronic ailment sufferers. Furthermore, it's imperative to consider the distinction between weight-bearing and non-weight-bearing exercises when prescribing physical activity regimens for these patients. Incorporating a combination of weight-bearing and non-weight-bearing exercises into rehabilitation programs can offer a comprehensive approach to improving cardiopulmonary health while accommodating individual needs and limitations. Additionally, the data fortify the notion of bespoke exercise advisories, tailored to individual proclivities, requirements, and resource availability(Pomidori et al., 2016), potentially steering the medical community toward a more patient-centric caregiving paradigm(Wu et al., 2014). Although evidence-based medicine is gaining traction in the realm of exercise rehabilitation, manifold research gaps persist. Investigations elucidating the efficacy of specific exercise modalities, or sub-group analyses against particular covariates, don't yet satiate the clinical appetite. Hence, dose–response analyses play a pivotal role, probing for more nuanced outcomes. In conclusion, this study aspires to provide methodological guidance for practitioners within the rehabilitation domain.

4.3. Strengths and limitations

While several studies have attempted to evaluate the effects of exercise on cardiopulmonary function(Bernier-Jean et al., 2022; Zang et al., 2022), the predominant focus has been on the efficacy of exercise or distinctions between different types of exercise, neglecting to elucidate the relationship between exercise dosage and cardiopulmonary outcomes. Building upon a synthesis of large-sample clinical data, the present study boasts advantages in statistical power and evidence quality. We have delineated an "optimal" exercise dosage that meaningfully corresponds to clinical cardiopulmonary alterations, thereby enhancing its clinical applicability to some extent. However, due to data constraints, the study did not appraise the relationship between other cardiopulmonary indices (e.g., blood pressure) and exercise. It also excluded exercise modalities beyond AT or CT and didn't factor in patient-specific characteristics such as the degree of frailty. Addressing these shortcomings in future research endeavors will refine our dose predictions and further aid clinical practice.

5. Conclusion

Our study demonstrates that low-dose exercises effectively improve the cardiopulmonary function of hemodialysis patients. The mode of exercise, duration of intervention, and exercising environment are crucial in influencing the effectiveness of these exercises. These findings provide practical insights for clinicians to develop personalized exercise plans, considering patient preferences and feasibility, thus potentially enhancing their quality of life. However, our analysis was limited to the impact of aerobic and combined aerobic-resistance training, and future research should explore a wider range of exercise types and patient characteristics to refine clinical guidelines.

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CRediT authorship contribution statement

Wanli Zang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation. **Mingqing Fang:** Writing – review & editing, Writing – original draft. **Ningkun Xiao:** Writing – review & editing, Writing – original draft. **Xianzuo Zhang:** Writing – review & editing, Writing – original draft. **Changchun Lin:** Writing – review & editing, Writing – original draft. **Su Wang:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

Ainsworth, B.E., Haskell, W.L., Herrmann, S.D., Meckes, N., Bassett Jr., D.R., Tudor-Locke, C., et al., 2011. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med. Sci. Sports Exerc. 43 (8), 1575–1581. https://doi.org/10.1249/MSS.0b013e31821ece12.

Anastasia, S., Evangelia, K., Konstantinos, F., Serafeim, A., Asterios, D., 2016. The effects of aquatic exercise on functional capacity and health-related quality of life in hemodialysis patients. J Clin Exp Nephrol 1 (15), 1–6.

Andrade, F.P., Borba, G.C., da Silva, K.C., Ferreira, T.S., de Oliveira, S.G., Antunes, V.V.H., et al., 2022. Intradialytic periodized exercise improves cardiopulmonary fitness and respiratory function: A randomized controlled trial. Semin. Dial. 35 (2), 181–189. https://doi.org/10.1111/sdi.13020.

Bahgat, N., Abdel-Salam, M., Abdel-Latif, M., Abdel-Hady, E.A., 2022. Low-intensity exercise improves cardiac tolerance to ischemia/reperfusion injury in aged female rats with metabolic syndrome. Exp. Gerontol. 160, 111711 https://doi.org/10.1016/j.exger.2022.111711.

Baria, F., Kamimura, M.A., Aoike, D.T., Ammirati, A., Rocha, M.L., de Mello, M.T., et al., 2014. Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients. Nephrol. Dial. Transplant. 29 (4), 857–864. https://doi.org/10.1093/ndt/gft529.

Bernier-Jean, A., Beruni, N.A., Bondonno, N.P., Williams, G., Teixeira-Pinto, A., Craig, J.C., et al., 2022. Exercise training for adults undergoing maintenance dialysis. Cochrane Database Syst Rev 1 (1), Cd014653. https://doi.org/10.1002/14651858.Cd014653.

Bohm, C., Stewart, K., Onyskie-Marcus, J., Esliger, D., Kriellaars, D., Rigatto, C., 2014. Effects of intradialytic cycling compared with pedometry on physical function in chronic outpatient hemodialysis: a prospective randomized trial. Nephrol. Dial. Transplant. 29 (10), 1947–1955. https://doi.org/10.1093/ndt/gfu248.

Bull, F.C., Al-Ansari, S.S., Biddle, S., Borodulin, K., Buman, M.P., Cardon, G., et al., 2020. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br. J. Sports Med. 54 (24), 1451–1462. https://doi.org/10.1136/bjsports-2020-102955.

Campos, N.G., Marizeiro, D.F., Florêncio, A.C.L., Silva Í, C., Meneses, G.C., Bezerra, G.F., et al. (2018). Effects of respiratory muscle training on endothelium and oxidative stress biomarkers in hemodialysis patients: A randomized clinical trial. *Respir Med* 134, 103-109. doi: 10.1016/j.rmed.2017.12.005.

Cardoso, R.K., Araujo, A.M., Del Vechio, F.B., Bohlke, M., Barcellos, F.C., Oses, J.P., et al., 2020. Intradialytic exercise with blood flow restriction is more effective than conventional exercise in improving walking endurance in hemodialysis patients: a randomized controlled trial. Clin. Rehabil. 34 (1), 91–98. https://doi.org/10.1177/0269215519880235.

Carmack, C.L., Amaral-Melendez, M., Boudreaux, E., Brantley, P.J., Jones, G.N., Franks, B.D., et al., 1995. Exercise as a component of the physical and psychological rehabilitation of hemodialysis patients. Int. J. Rehabilitat. Health 1, 13–23.

Chang, J.H., Koo, M., Wu, S.W., Chen, C.Y., 2017. Effects of a 12-week program of Tai Chi exercise on the kidney disease quality of life and physical functioning of patients with end-stage renal disease on hemodialysis. Complement. Ther. Med. 30, 79–83. https://doi.org/10.1016/j.ctim.2016.12.002.

Cheung, A.K., Chang, T.I., Cushman, W.C., Furth, S.L., Hou, F.F., Ix, J.H., et al., 2021. Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 99 (3), 559–569. https://doi.org/10.1016/j.kint.2020.10.026.

Coelho-Júnior, H.J., Uchida, M.C., Picca, A., Bernabei, R., Landi, F., Calvani, R., et al., 2021. Evidence-based recommendations for resistance and power training to prevent frailty in community-dwellers. Aging Clin. Exp. Res. 33 (8), 2069–2086.

DePaul, V., Moreland, J., Eager, T., Clase, C.M., 2002. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. Am. J. Kidney Dis. 40 (6), 1219–1229. https://doi.org/10.1053/ajkd.2002.36887.

Dobsak, P., Homolka, P., Svojanovsky, J., Reichertova, A., Soucek, M., Novakova, M., et al., 2012. Intra-dialytic electrostimulation of leg extensors may improve exercise tolerance and quality of life in hemodialyzed patients. Artif. Organs 36 (1), 71–78. https://doi.org/10.1111/j.1525-1594.2011.01302.x.

Dornelas, B.R., Lima, F.A., 2021. Effects of daily inspiratory muscle training on respiratory muscle strength and chest wall regional volumes in hemodialysis patients: a randomized clinical trial. Disabil. Rehabil. 43 (19), 2828. https://doi.org/10.1080/09638288.2019.1709566.

Eckardt, K.U., Delgado, C., Heerspink, H.J.L., Pecoits-Filho, R., Ricardo, A.C., Stengel, B., et al., 2023. Trends and perspectives for improving quality of chronic kidney disease care: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. https://doi.org/10.1016/j.kint.2023.05.013.

Esteve Simo, V., Junqué Jiménez, A., Moreno Guzmán, F., Carneiro Oliveira, J., Fulquet Nicolas, M., Pou Potau, M., et al., 2015. Benefits of a low intensity exercise programme during haemodialysis sessions in elderly patients. Nefrologia 35 (4), 385–394. https://doi.org/10.1016/j.nefro.2015.03.006.

Fernandes, A.O., Sens, Y., Xavier, V.B., Miorin, L.A., Alves, V., 2019. Functional and Respiratory Capacity of Patients with Chronic Kidney Disease Undergoing Cycle Ergometer Training during Hemodialysis Sessions: A Randomized Clinical Trial. Int J Nephrol 2019, 7857824. https://doi.org/10.1155/2019/7857824.

Frih, B., Jaafar, H., Mkacher, W., Ben Salah, Z., Hammami, M., Frih, A., 2017. The Effect of Interdialytic Combined Resistance and Aerobic Exercise Training on Health Related Outcomes in Chronic Hemodialysis Patients: The Tunisian Randomized Controlled Study. Front. Physiol. 8, 288. https://doi.org/10.3389/fphys.2017.00288.

Gallo Marin, B., Aghagoli, G., Hu, S.L., Massoud, C.M., Robinson-Bostom, L., 2023. Calciphylaxis and Kidney Disease: A Review. Am. J. Kidney Dis. 81 (2), 232–239. https://doi.org/10.1053/j.ajkd.2022.06.011.

Greenwood, S.A., Koufaki, P., Mercer, T.H., MacLaughlin, H.L., Rush, R., Lindup, H., et al., 2015. Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: a pilot randomized controlled trial. Am. J. Kidney Dis. 65 (3), 425–434. https://doi.org/10.1053/j.ajkd.2014.07.015.

Groot, C., Hooghiemstra, A.M., Raijmakers, P.G., van Berckel, B.N., Scheltens, P., Scherder, E.J., et al., 2016. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res. Rev. 25, 13–23. https://doi.org/10.1016/j.arr.2015.11.005.

Groussard, C., Rouchon-Isnard, M., Coutard, C., Romain, F., Malardé, L., Lemoine-Morel, S., et al., 2015. Beneficial effects of an intradialytic cycling training program in patients with end-stage kidney disease. Appl. Physiol. Nutr. Metab. 40 (6), 550–556. https://doi.org/10.1139/apnm-2014-0357.

Higgins, J.P., and Green, S. (2008). Cochrane handbook for systematic reviews of interventions.

Hsiao, L.L., Shah, K.M., Liew, A., Abdellatif, D., Balducci, A., Haris, Á., et al., 2023. Kidney health for all: preparedness for the unexpected in supporting the vulnerable. Kidney Int. 103 (3), 436–443. https://doi.org/10.1016/j.kint.2022.12.013.

Huang, L., Huang , Y., Li, J., Teng, Y. (2015). Effects of aerobic exercise on motor function of lower limb and fatigue status in maintenance hemodialysis patients. *Guangxi Med. J.* 37(04), 476-478+484.

Huang, M., Lv, A., Wang, J., Zhang, B., Xu, N., Zhai, Z., et al., 2020. The effect of intradialytic combined exercise on hemodialysis efficiency in end-stage renal disease patients: a randomized-controlled trial. Int. Urol. Nephrol. 52 (5), 969–976. https://doi.org/10.1007/s11255-020-02459-1.

Ismail, H., McFarlane, J.R., Nojoumian, A.H., Dieberg, G., Smart, N.A., 2013. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. JACC Heart Fail 1 (6), 514–522. https://doi.org/10.1016/j.jchf.2013.08.006.

Jamshidpour, B., Bahrpeyma, F., Khatami, M.R., 2020. The effect of aerobic and resistance exercise training on the health related quality of life, physical function, and muscle strength among hemodialysis patients with Type 2 diabetes. J. Bodyw. Mov. Ther. 24 (2), 98–103. https://doi.org/10.1016/j.jbmt.2019.10.003.

Koh, K.P., Fassett, R.G., Sharman, J.E., Coombes, J.S., Williams, A.D., 2010. Effect of intradialytic versus home-based aerobic exercise training on physical function and vascular parameters in hemodialysis patients: a randomized pilot study. Am. J. Kidney Dis. 55 (1), 88–99. https://doi.org/10.1053/j.ajkd.2009.09.025.

Konstantinidou, E., Koukouvou, G., Kouidi, E., Deligiannis, A., Tourkantonis, A., 2002. Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. J Rehabil Med 34 (1), 40–45. https://doi.org/10.1080/165019702317242695.

Koufaki, P., Mercer, T.H., Naish, P.F., 2002. Effects of exercise training on aerobic and functional capacity of end-stage renal disease patients. Clin. Physiol. Funct. Imaging 22 (2), 115–124. https://doi.org/10.1046/j.1365-2281.2002.00405.x.

Kouidi, E.J., Grekas, D.M., Deligiannis, A.P., 2009. Effects of exercise training on noninvasive cardiac measures in patients undergoing long-term hemodialysis: a randomized controlled trial. Am. J. Kidney Dis. 54 (3), 511–521. https://doi.org/10.1053/j.ajkd.2009.03.009.

Kouidi, E., Karagiannis, V., Grekas, D., Iakovides, A., Kaprinis, G., Tourkantonis, A., et al., 2010. Depression, heart rate variability, and exercise training in dialysis patients. Eur. J. Cardiovasc. Prev. Rehabil. 17 (2), 160–167. https://doi.org/10.1097/HJR.0b013e32833188c4.

Krase, A.A., Terzis, G., Giannaki, C.D., Stasinaki, A.N., Wilkinson, T.J., Smith, A.C., et al., 2022. Seven months of aerobic intradialytic exercise training can prevent muscle loss in haemodialysis patients: an ultrasonography study. Int. Urol. Nephrol. 54 (2), 447–456. https://doi.org/10.1007/s11255-021-02931-6.

Li, P., and Wang, D. (2016). Effects of aerobic exercise on 6-minute walk distance and serum level of omentin-1 in hemodialysis patients. *Tianjin Medical Journal* 44(08), 1014-1017.

Liao, L., Sun, G., 2020. Effect of low intensity aerobic training on quality of life in maintenance hemodialysis patients. RENOWNED DOCTOR 08, 270–271.

Lin, L., Shi, L., Chu, H., Murad, M.H., 2020. The magnitude of small-study effects in the Cochrane Database of Systematic Reviews: an empirical study of nearly 30 000 meta-analyses. BMJ Evid Based Med 25 (1), 27–32. https://doi.org/10.1136/bmjebm-2019-111191.

Liu, Y., and Xu, F. (2022). Application effect of treadmill exercise combined with breathing training in elderly patients with maintenance hemodialysis. *Clinical medical research and practice* 7(18), 176-178. doi: 10.19347/j.cnki.2096-1413.202218050.

Locatelli, F., Del Vecchio, L., 2023. Quality of life: a crucial aspect for the patients, a neglected goal in the treatment of anemia in patients with CKD. Kidney Int. 103 (6), 1025–1027. https://doi.org/10.1016/j.kint.2023.03.026.

Manfredini, F., Lamberti, N., Malagoni, A.M., Felisatti, M., Zuccalà, A., Torino, C., et al., 2015. The role of deconditioning in the end-stage renal disease myopathy: physical exercise improves altered resting muscle oxygen consumption. Am. J. Nephrol. 41 (4–5), 329–336. https://doi.org/10.1159/000431339.

Marchesan, M., Krug, R.d.R., Silva, J.R.L.d.C., Barbosa, A.R., Rombaldi, A.J., 2016. Physical exercise modifies the functional capacity of elderly patients on hemodialysis. Fisioterapia Em Movimento 29, 351–359.

McGregor, G., Ennis, S., Powell, R., Hamborg, T., Raymond, N.T., Owen, W., et al., 2018. Feasibility and effects of intra-dialytic low-frequency electrical muscle stimulation and cycle training: A pilot randomized controlled trial. PLoS One 13 (7), e0200354.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and Group*, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med.* 151(4), 264-269.

Mustata, S., Groeneveld, S., Davidson, W., Ford, G., Kiland, K., Manns, B., 2011. Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: a pilot study. Int. Urol. Nephrol. 43 (4), 1133–1141. https://doi.org/10.1007/s11255-010-9823-7.

Myers, J., Chan, K., Chen, Y., Lit, Y., Patti, A., Massaband, P., et al., 2021. Effect of a Home-Based Exercise Program on Indices of Physical Function and Quality of Life in Elderly Maintenance Hemodialysis Patients. Kidney Blood Press. Res. 46 (2), 196–206. https://doi.org/10.1159/000514269.

Nilsson, B.B., Bunæs-Næss, H., Edvardsen, E., Stenehjem, A.E., 2019. High-intensity interval training in haemodialysis patients: a pilot randomised controlled trial. BMJ Open Sport Exerc. Med. 5 (1), e000617.

Ortega-Pérez de Villar, L., Martínez-Olmos, F.J., Pérez-Domínguez, F.B., Benavent-Caballer, V., Montañez-Aguilera, F.J., Mercer, T., et al., 2020. Comparison of intradialytic versus home-based exercise programs on physical functioning, physical activity level, adherence, and health-related quality of life: pilot study. Sci. Rep. 10 (1), 8302. https://doi.org/10.1038/s41598-020-64372-y.

Ouzouni, S., Kouidi, E., Sioulis, A., Grekas, D., Deligiannis, A., 2009. Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients. Clin. Rehabil. 23 (1), 53–63. https://doi.org/10.1177/0269215508096760.

Pellizzaro, C.O., Thomé, F.S., Veronese, F.V., 2013. Effect of peripheral and respiratory muscle training on the functional capacity of hemodialysis patients. Ren. Fail. 35 (2), 189–197. https://doi.org/10.3109/0886022x.2012.745727.

Petraki, M., Kouidi, E., Grekas, D., Deligiannis, A., 2008. Effects of exercise training during hemodialysis on cardiac baroreflex sensitivity. Clin. Nephrol. 70 (3), 210–219. https://doi.org/10.5414/cnp70210.

Pinckard, K., Baskin, K.K., Stanford, K.I., 2019. Effects of Exercise to Improve Cardiovascular Health. Front Cardiovasc Med 6, 69. https://doi.org/10.3389/fcvm.2019.00069.

Pomidori, L., Lamberti, N., Malagoni, A.M., Manfredini, F., Pozzato, E., Felisatti, M., et al., 2016. Respiratory muscle impairment in dialysis patients: can minimal dose of exercise limit the damage? A Preliminary study in a sample of patients enrolled in the EXCITE trial. J. Nephrol. 29 (6), 863–869. https://doi.org/10.1007/s40620-016-0325-2.

Reboredo, M.M., Neder, J.A., Pinheiro, B.V., Henrique, D.M., Faria, R.S., Paula, R.B., 2011. Constant work-rate test to assess the effects of intradialytic aerobic training in mildly impaired patients with end-stage renal disease: a randomized controlled trial. Arch. Phys. Med. Rehabil. 92 (12), 2018–2024. https://doi.org/10.1016/j.apmr.2011.07.190.

Reboredo, M.M., Neder, J.A., Pinheiro, B.V., Henrique, D.M., Lovisi, J.C., Paula, R.B., 2015. Intra-dialytic training accelerates oxygen uptake kinetics in hemodialysis patients. Eur. J. Prev. Cardiol. 22 (7), 912–919. https://doi.org/10.1177/2047487314543079.

Recchia, F., Leung, C.K., Yu, A.P., Leung, W., Yu, D.J., Fong, D.Y., et al., 2023. Dose-response effects of exercise and caloric restriction on visceral adiposity in overweight and obese adults: a systematic review and meta-analysis of randomised controlled trials. Br. J. Sports Med. https://doi.org/10.1136/bjsports-2022-106304.

Sanders, L.M.J., Hortobágyi, T., la Bastide-van Gemert, S., van der Zee, E.A., van Heuvelen, M.J.G., 2019. Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. PLoS One 14 (1), e0210036.

See, E.J., Bello, A.K., Levin, A., Lunney, M., Osman, M.A., Ye, F., et al., 2021. Availability, coverage, and scope of health information systems for kidney care across world countries and regions. Nephrol. Dial. Transplant. 37 (1), 159–167. https://doi.org/10.1093/ndt/gfaa343.

Sera, F., Armstrong, B., Blangiardo, M., Gasparrini, A., 2019. An extended mixed-effects framework for meta-analysis. Stat. Med. 38 (29), 5429–5444. https://doi.org/10.1002/sim.8362.

Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., et al., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898. https://doi.org/10.1136/bmj.l4898.

Storer, T.W., Casaburi, R., Sawelson, S., Kopple, J.D., 2005. Endurance exercise training during haemodialysis improves strength, power, fatigability and physical performance in maintenance haemodialysis patients. Nephrol. Dial. Transplant. 20 (7), 1429–1437. https://doi.org/10.1093/ndt/gfh784.

Tang, D., 2015. Dynamic resistance exercise training for chronic and terminal heart failure Improving the quality of life in patients with kidney disease. Shandong Medicine 55 (31), 46–48.

Tao, H., Lu, Y., Chen, Y., 2017. Effect of low-intensity aerobic rehabilitation exercise on lipid metabolism and dialysis-related fatigue in hemodialysis patients with chronic renal insufficiency. Shanxi Medical Journal 46 (07), 857–859.

Tsuyuki, K., Kimura, Y., Chiashi, K., Matsushita, C., Ninomiya, K., Choh, K., et al., 2003. Oxygen uptake efficiency slope as monitoring tool for physical training in chronic hemodialysis patients. Ther. Apher. Dial. 7 (4), 461–467. https://doi.org/10.1046/j.1526-0968.2003.00084.x.

van Vilsteren, M.C., de Greef, M.H., Huisman, R.M., 2005. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. Nephrol. Dial. Transplant. 20 (1), 141–146. https://doi.org/10.1093/ndt/gfh560.

Wang, H., 2017. Effects of low-intensity aerobic training combined with health education on the incidence of complications and quality of life in patients with maintenance hemodialysis. Nursing Practice and Research 14 (19), 31–33.

Wang, T., Chen, X., Liang, Y., 2022. Effect of low intensity aerobic rehabilitation exercise on mental state and lower limb motor function of uremic hemodialysis patients. Jilin Medical College 43 (02), 565–566.

Watt, J.A., Veroniki, A.A., Tricco, A.C., Straus, S.E., 2021. Using a distribution-based approach and systematic review methods to derive minimum clinically important differences. BMC Med. Res. Method. 21 (1), 41. https://doi.org/10.1186/s12874-021-01228-7.

Wu, Y., He, Q., Yin, X., He, Q., Cao, S., Ying, G., 2014. Effect of individualized exercise during maintenance haemodialysis on exercise capacity and health-related quality of life in patients with uraemia. J. Int. Med. Res. 42 (3), 718–727. https://doi.org/10.1177/0300060513509037.

Ye, X., Jiang, L., Jun, C., Jiang, J., Chen, Y., 2022. Effects of aerobic resistance exercise on physiological function and quality of life in elderly hemodialysis patients. Chin. J. Gerontol. 42 (06), 1399–1402.

Yeh, M.L., Wang, M.H., Hsu, C.C., Liu, Y.M., 2020. Twelve-week intradialytic cycling exercise improves physical functional performance with gain in muscle strength and endurance: a randomized controlled trial. Clin. Rehabil. 34 (7), 916–926. https://doi.org/10.1177/0269215520921923.

Yu, X., Cao, S., Ji, X., Chang, M., Xu, J., 2021. Effect of intradialytic exercise program in maintenance hemodialysis patients. Journal of Nursing 36 (17), 5–8.

Zang, W., Fang, M., He, H., Mu, L., Zheng, X., Shu, H., et al., 2022. Comparative efficacy of exercise modalities for cardiopulmonary function in hemodialysis patients: A systematic review and network meta-analysis. Front. Public Health 10, 1040704. https://doi.org/10.3389/fpubh.2022.1040704.