Effect of Intradialytic Exercise on Cardiovascular Outcomes in Maintenance Hemodialysis: A Systematic Review and Meta-Analysis

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Key Points

- Individuals receiving hemodialysis have high rates of cardiovascular disease not explained by traditional cardiovascular risk factors.
- Intradialytic exercise improves cardiovascular outcomes, including arterial resistance, BP, and heart rate variability.
- Clinicians should consider including intradialytic aerobic exercise programs in hemodialysis care to supplement broader treatment plans.

Abstract

Background Cardiovascular disease is the leading cause of death among people with kidney failure on hemodialysis, for whom improving cardiovascular health is a research priority. Intradialytic myocardial stunning is common and associated with adverse cardiovascular events. Intradialytic exercise may mitigate intradialytic myocardial stunning and improve cardiovascular structure and function. This systematic review investigated the effect of intradialytic exercise on cardiovascular outcomes in adults undergoing maintenance hemodialysis (PROSPERO CRD42018103118).

Methods Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we systematically searched MEDLINE, Embase, Cochrane CENTRAL, SportDiscus, and PEDro databases from 1960 until June 2022, for randomized and nonrandomized studies investigating the effect of intradialytic exercise programs on objective cardiovascular outcomes, prespecified as primary or secondary outcomes. The primary outcome was arterial resistance.

Results Of 10,837 references identified, 32 met eligibility criteria. These studies investigated the effect of intradialytic exercise on arterial resistance (eight studies), BP (20 studies), myocardial structure and function (seven studies), endothelial function (two studies), sympathetic overactivity (nine studies), biomarkers of cardiac injury (three studies), and cardiovascular hospitalization and mortality (two studies). Most studies used aerobic exercise as the intervention and usual care (no exercise) controls. Meta-analysis of intradialytic exercise versus usual care resulted in a statistically significant reduction in arterial resistance measured by pulse wave velocity with mean difference −1.63 m/s (95% confidence interval, −2.51 to −0.75). Meta-analyses for diastolic BP, left ventricular ejection fraction, and low-frequency/high-frequency ratio measure of heart rate variability also showed statistically significant improvements with exercise. There was no significant difference in change in systolic BP, augmentation index, and left ventricular mass index between groups.

Conclusions Intradialytic exercise programming resulted in a clinically meaningful improvement to pulse wave velocity, a component of arterial resistance. Improvements in several physiologic measures of cardiovascular health, including diastolic BP, left ventricular ejection fraction, and heart rate variability measured by the low-frequency/high-frequency ratio were also observed. The effects of intradialytic exercise on major adverse cardiovascular events remains uncertain.

Kidney360 5: 390–413, 2024. doi: https://doi.org/10.34067/KID.0000000000000361

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Received: August 24, 2023 **Accepted:** January 11, 2024
Published Online Ahead of Print: February 2, 2024

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Introduction

Although considered life-sustaining therapy for people with kidney failure, many individuals on maintenance hemodialysis experience severe disease-related complications, including adverse cardiovascular events.[1] Half of all patients die within the first 3 years of hemodialysis initiation, and half of all deaths are related to cardiovascular diseases.[2] Individuals receiving hemodialysis have strikingly low physical activity levels and poor physical function, which decline over time and are associated with higher risks of cardiovascular and all-cause hospitalizations and death.[3–13]

Intradialytic hypotension is common. Present in 20%–30% of hemodialysis treatments, it can result from abnormal underlying cardiovascular physiology, volume removal and the hemodialysis procedure itself, or the compounded effects of both these factors.[14] Regardless of its cause, intradialytic hypotension can lead to decreased cardiac output and decreased coronary perfusion, which contributes to temporary decreases in regional contraction of the myocardium during dialysis, known as myocardial stunning.[14–18] Hemodialysis-related myocardial stunning is associated with decreased organ perfusion[19–21] and contributes to the high rates of heart failure, cardiac events, and mortality observed in people receiving hemodialysis.[17,22–25]

In the general population, the cardioprotective benefits of exercise have been noted to exceed those gained from pharmacological interventions.[26–28] Increased physical activity through exercise programming improves physical function in individuals receiving hemodialysis.[29] Exercise during hemodialysis (intradialytic exercise) is convenient and has been associated with the highest exercise program adherence rates.[30] Recent studies suggest such programs decrease hemodialysis-related cardiac stunning and improve aspects of cardiovascular structure and function. This may be through an ischemic preconditioning effect, in which minor ischemic insults provide cardioprotection by enhancing the ability of the tissue to respond to larger ischemic events.[31–34]

To summarize the evidence and identify knowledge gaps, we conducted a systematic review and meta-analysis to evaluate the effect of intradialytic aerobic and/or resistance exercise on objective measures of cardiovascular health in adults with kidney failure receiving maintenance hemodialysis.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered the protocol with PROSPERO International Prospective Register of Systematic Reviews (CRD42018103118).[35] Our search strategy aimed to identify randomized controlled trials (RCTs) and quasiexperimental studies that measured the effect of intradialytic exercise programs (aerobic, resistance, or both) on objectively measured cardiovascular outcomes associated with major adverse cardiovascular events as compared with a nonexercise/sham exercise control group in adults (18 years and older) on maintenance hemodialysis. Studies in which the intervention consisted of exercise sessions that occurred two or more times per week for at least 20 minutes of duration per session and for 2 weeks or longer were eligible for inclusion. Exclusion criteria were publication before 1960, inclusion of individuals who were younger than 18 years, no intradialytic exercise intervention, and no prespecified cardiovascular outcomes (Table 1).

We prespecified arterial resistance as the primary outcome of this review given that increased arterial resistance is associated with vascular calcification in people receiving dialysis,[36] and both vascular calcifications and increased arterial resistance are associated with episodes of intradialytic hypotension.[37,38]

Table 1. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population/ participants	Adults (18 yr or older) on chronic hemodialysis	Children (younger than 18 yr) and animals
Intervention	Exercise interventions performed during hemodialysis (intradialytic exercise) that include aerobic exercise, resistance exercise, or both	Studies including exercise interventions that do not include intradialytic aerobic exercise, resistance exercise, or both
Comparison	Nonexposed control group receiving standard/usual care or sham exercise (*e.g.*, breathing exercises)	—
Outcome	Studies that report changes in relevant prespecified cardiovascular outcomes, including arterial resistance; BP; myocardial function as measured by changes in LVEF, shortening fraction, number of regional wall motion abnormalities, or myocardial blood flow; endothelial function; sympathetic overactivity as measured by change in baroreflex sensitivity and/or HRV; biomarkers of cardiac injury (*e.g.*, troponin, brain-natriuretic peptide); cardiac structure as measured by changes in myocardial thickness and/or LVM; hospitalization and death for cardiovascular causes	Studies that do not include cardiovascular outcomes as mentioned in inclusion criteria
Other	Study design: randomized controlled or quasiexperimental design	Date: studies before 1960

HRV, heart rate variability; LVEF, left ventricular ejection fraction; LVM, left ventricular mass.

Secondary outcomes included systolic BP (SBP) and diastolic BP (DBP), cardiac structure and function, endothelial function, sympathetic overactivity, biomarkers of cardiac injury, and cardiovascular-related hospitalization and mortality rates. For inclusion in this review, studies needed to include at least one objective measure of a cardiovascular outcome as a prespecified primary or secondary outcome (Table 1).

The systematic search strategy was designed in collaboration with a medical librarian (A. Iansavitchene) and conducted using MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases (all through Ovid interface), SportDiscus (through EBSCO platform), and PEDro databases from 1960 or inception using a combination of medical subject headings (*i.e.*, MeSH in MEDLINE) and free-text terms, such as "intradialytic," "kinesiotherapy," "exercise," "aerobic," "physical training," and "resistance training." Optimized high-sensitivity filters were used to refine search results for dialysis and chronic kidney disease content.[39,40] Search strategies were modified using appropriate thesaurus terms and fields as indicated for each database (Supplemental Table 1). No language restrictions were applied. We reviewed reference lists of key review articles and the studies selected for inclusion. Ongoing trials, conference proceedings, and other gray literature were not searched separately. The initial database search was conducted on June 18, 2018, with the last updated search on June 14, 2022.

Study Screening and Selection

We used Covidence (Melbourne, Australia) software to upload and deduplicate citations, for abstract screening, full-text review, and data abstraction.[41] Pairs of two blinded independent reviewers screened abstracts and reviewed full-text articles for inclusion, meeting after their independent review to obtain consensus (A. Sharma/D. Verrelli, K. Rossum/E. Ford, M. Sharma/J. Alexiuk, Q. Tays/D. Verrelli). A third reviewer (C. Bohm) adjudicated discrepancies when necessary. Data extraction from studies selected for inclusion was performed by the same paired reviewers in duplicate, with discrepancies resolved similarly.

Data extracted included characteristics of each study (first author, year, contact information, and country of publication), study design, sample size (if applicable), type of exercise (aerobic, resistance, or both), duration and frequency of intervention, target exercise dose/intensity, inclusion/exclusion criteria, study dropouts, reasons for attrition, patient characteristics (age, sex, time on dialysis, exercise adherence), and review-relevant outcomes.

Pairs of independent reviewers (A. Sharma/D. Verrelli, J. Alexiuk/D. Verrelli) evaluated studies for individual and cumulative risk of bias using the Cochrane Collaboration's Risk of Bias Assessment Tool for RCTs and Newcastle Ottawa Scale for non-RCTs.[42] Discrepancies were resolved by consensus or third-party adjudication (C. Bohm).

Data Synthesis

For summative review, studies were grouped by outcome categories.[43] We performed a thematic analysis using study and intervention characteristics, such as study design, type of exercise, and duration of intervention to identify patterns and similarities in outcome results within the studies.[44] Although results reporting was variable, we used mean change of the outcome within the intervention and control groups over the study period as our principal summary measure and when available, also incorporated between group difference.

We proceeded with meta-analysis for outcomes for which more than two randomized controlled studies with required data were available for the *same* outcome measure. We performed meta-analysis for arterial resistance, DBP and SBP, left ventricular ejection fraction (LVEF), left ventricular mass, and heart rate variability (HRV) using random effects models. We did not impute missing data but attempted to contact corresponding authors for missing data as needed. In addition, when required, methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions were used to calculate mean difference (MD), SD, and SEM difference.[45] Statistical heterogeneity was quantified using the I^2 statistic and considered unimportant for I^2 <40%, with statistical significance assessed using the chi-squared test. Review Manager (version 5.3) was used for the analysis.[46]

Results

Our search strategy identified 10,837 unique citations, of which 192 were selected for full-text review, and 32 studies published between 1992 and 2022 were included in this review (Figure 1). Studies were from North America (n=6), Australia (n=3), Asia (n=7), Europe (n=8), South America (n=6), and the Middle East (n=2).

Studies selected include 18 parallel arm RCTs, two randomized cross-over studies, seven nonrandomized studies that included an intervention and control group, and five single-group pre-post studies.[32,47–77] In total, 1817 individuals participated in these 32 studies, with sample sizes ranging from 6 to 174 participants (Table 2).

Twenty-two studies evaluated the effects of intradialytic aerobic exercise.[32,47,48,50,51,53,55–59,62,64–66,68–70,72,74–76] Four studies examined the effects of resistance exercise.[54,61,73,77] Five studies included both aerobic and resistance exercise.[49,52,60,63,67] One study did not state the type of exercise used in the intervention (Table 2).[71]

Quality of Reporting and Risk of Bias of Included Studies

In included RCTs, risk of bias was high in domains of performance bias and other bias (*e.g.*, contamination bias). However, risk of bias was low or unclear in selection, detection, attrition, and reporting bias. Most studies before 2018 had high or unclear risk of bias, whereas studies published after 2018 generally had larger sample sizes, better quality reporting, and moderate to low risk of bias (Table 3 and Supplemental Figure 1).

Risk of bias for nonrandomized studies was high or unclear for the comparability of cohorts but was relatively low for selecting outcome measures (Supplemental Table 2).

Arterial Resistance

Arterial resistance was measured by pulse wave velocity (PWV) and/or augmentation index (AI) in eight studies

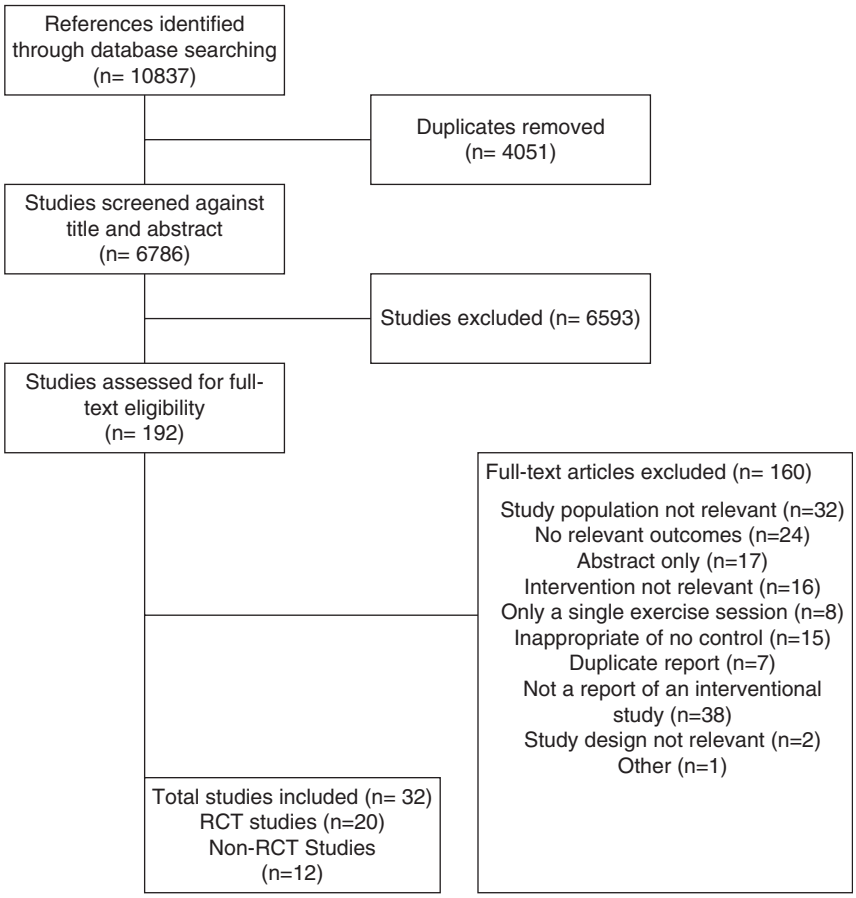


Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.

(total n=653).[47,48,54,64,66,67,69,73] Meta-analysis of four studies demonstrated a statistically significant mean difference in PWV with 13–26 weeks of intradialytic cycling (n=95) as compared with 95 controls of −1.63 m/s; 95% confidence interval [CI], −2.51 to −0.75; I^2=93%; $P < 0.001$ (Figure 2A).[47,64,66,69] By contrast, meta-analysis of three studies showed no statistically significant difference in AI with intradialytic cycling (n=46) as compared with 48 controls (MD –3.29%; 95% CI, −7.88 to 1.30; I^2=88%; $P < 0.001$) (Figure 2B).[47,64,69]

BP

Twenty studies (n=984), including nine RCTs, reported BP measures. Most (13 studies) studied predialysis BP measured peripherally using automated BP machines.[47,51,52,57,61–63,66,69,73–76] One study measured interdialytic BP, one study measured BP preintradialytic exercise, two studies measured ambulatory BP (24 and 44 hour), and in three studies, the timing of BP measurement was unclear[50,54,58,59,66,71,77] (Table 4).

Of the seven RCTs eligible for meta-analysis, five studies used intradialytic cycling for the exercise intervention, one study used resistance exercise, and one study used combined resistance and aerobic exercise.[47,50,52,61–63,66,69] Intervention duration ranged from 8 to 104 weeks but was more than 24 weeks in most studies. All but one study reported predialysis BP. In a total of 263 individuals who participated in the exercise intervention as compared with 78 controls, we observed no statistically significant between-group MD in SBP of –3.23 mm Hg (95% CI, −6.76 to 0.29; I^2=95%; $P < 0.001$) but a statistically significant MD in DBP of –1.57 mm Hg (95% CI, −2.94 to −0.21; I^2=86%; $P < 0.001$) (Figure 3).

Myocardial Function

Five studies (n=236) examined LVEF, measured using echocardiography or cardiac MRI.[32,53,55,60,66] Meta-analysis of four studies (n=222), which involved intradialytic cycling for 30–90 minutes per session and intervention duration of 12–44 weeks, demonstrated a small statistically significant MD in LVEF of 3.29% (95% CI, 2.48 to 4.11; I^2=0%; P = 0.72) with exercise as compared with nonexercise controls (Figure 4A).[32,53,60,66]

Myocardial Structure

In total, six studies (total n=315) examined outcomes related to myocardial structure (Table 4).[32,53,55,60,64,66] Only left ventricular mass index (LVMI) was eligible for meta-analysis, including four RCTs (n=210) which demonstrated no statistically significant change in LVMI in individuals who completed 12–44 weeks of intradialytic cycling for 30–90 minutes per session as compared with no exercise

Table 2. Characteristics of included studies

Author, Year	Country	Study Design	Type of Exercise Type of Control	*N* (Control/ Exercise) (Attrition%)	Eligibility Criteria: Inclusion Criteria	Eligibility Criteria: Exclusion Criteria	% Female	Months on Hemodialysis (Mean [SD]/Median [IQR]): Control	Months on Hemodialysis (Mean [SD]/Median [IQR]): Exercise	Participant Age (yr) (Mean [SD]): Control	Participant Age (yr) (Mean [SD]): Exercise	Comorbidities (%)	Outcomes Assessed
	Indonesia	Single-group pre/ post	Not stated Usual care	30 (15/15) (0%)	Hemodialysis 2 times/wk Able to exercise during hemodialysis SBP >180 mm Hg DBP >120 mm Hg	Asthma, IHD No completion of any exercise sessions	43	Not stated	Not stated	51.03	51.03	—	BP
Anderson *et al.*,[59] 2004	United States	Single-group pre/ post	Aerobic NA	19 (32% at 3 mo) (53% at 6 mo)	Hemodialysis 3 times/wk	AKI; type 1 DM; active cerebral ischemia Severe arrhythmia, IHD, CHF, or valve disease Unable to cycle	21	—		49.1 (13.6)		—	BP, HTN medications
Chan *et al.*,[54] 2017	Australia	Single-group pre/ post	Resistance Usual care	22 (22/18) (18%)	40 yr and older; medically stable Hemodialysis >3 mo Ambulate independently <120 min moderate PA/wk	Amputation Unable to exercise during hemodialysis No previous resistance training	41	42.5 (7–163)		71.3 (11.0)		DM: 36 HT: 23 MI: 10 CVA: 10 PVD: 5	Arterial resistance, BP
Cheng *et al.*,[61] 2019	China	RCT	Resistance Usual care	132 (65/67) (49%)	18–80 yr old Hemodialysis 3 times/wk for ≥3 mo Kt/V >1.2	Severe CVD, MSK, or other medical problems Dyspnea or chest pain during exercise Instability during hemodialysis BP ≥180/100, or <90/ 60 mm Hg	40	47 (26–78)	43 (23–91)	55.8 (12)	54.6 (12.6)	—	BP
Cooke *et al.*,[48] 2018	Canada	RCT	Aerobic Usual care	32 (16/16) (38%)	Hemodialysis 3 times/wk for ≥12 wk Stable cardiac workup	Serum PTH >250 pmol/L Severe arrhythmia, CVD, or PVD K >6.5 mmol/L in last 2 wk; active cancer Posthemodialysis SBP ≥160 mm Hg or DBP ≥100 mm Hg Planned major surgery during study	30	—	—	52.5 (15.4)	58.2 (17.2)	DM: 35 HT: 100 Smoking: 45 CAD: 10 MI: 5 CHF: 20 CVA: 10 PVD: 5 COPD: 15	Arterial resistance, BP
Fernandes *et al.*,[62] 2019	Brazil	RCT	Aerobic Usual care	44 (22/22) (11%)	18 yr and older Hemodialysis >6 mo Clinically stable No lung, MSK, neurological issues	Planned surgical intervention during study IHD event <3 mo Severe IHD, valve disease, or arrhythmia Require home oxygen Require mobility assist device	50	85.9 (45.4)	79.8 (56.4)	42.6 (11.2)	44.3 (11.3)	—	BP

Table 2. (Continued)

Author, Year	Country	Study Design	Type of Exercise Type of Control	*N* (Control/ Exercise) (Attrition%)	Eligibility Criteria		% Female	Months on Hemodialysis (Mean [SD]/Median [IQR])		Participant Age (yr) (Mean [SD])		Comorbidities (%)	Outcomes Assessed
					Inclusion Criteria	Exclusion Criteria		Control	Exercise	Control	Exercise		
Graham-Brown *et al.*,[66] 2021	United Kingdom	Cluster RCT	Aerobic Usual care	130 (65/65) (22%)	18 yr and older Hemodialysis >3 mo	Unable/unfit to participate in exercise Unable to undergo MRI scanning	27	15.6 (4.8–38.4)	14.4 (6–44.4)	58.9 (14.9)	55.5 (15.5)	AFib: 3.1 IHD: 13.8	LVM, arterial resistance
Greenwood *et al.*,[67] 2021	United Kingdom	RCT	Combined Usual care	335 (160/175) (16.42%)	Older than 18 yr Hemodialysis >3 mo	Planned hemodialysis for >6 mo Hemodialysis <3 mo; clinically unstable Bilateral lower-limb amputations Dementia or severe cognitive impairment Unstable psychiatric disorders; pregnant	40	Not stated	Not stated	59.8 (14.1)	60.5 (15.0)	DM: 40 HT: 78 CVD: 20	Arterial resistance, cardiovascular mortality
Guio *et al.*,[55] 2017	Brazil	Single-group pre/ post	Aerobic Usual care	24 (24/24) (42%)	18 yr and older Hemodialysis 3 times/wk for ≥6 mo Arteriovenous fistula	CVD; MSK, neurological reasons unable to exercise Active inflammatory/ infectious disease <6 mo Hospitalization	57	23 (10)		50.2 (15.2)		—	BP, LVF
Huang *et al.*,[63] 2020	China	RCT	Combined Sham exercise	47 (23/24) (32%)	18 yr and older Hemodialysis 3 times/wk for ≥3 mo	Severe MSK pain; need assist sit, stand, or walk Dyspnea at rest or with ADLs; mental disease	28	43 (89)	26 (30)	37.6 (10.3)	43.8 (10.3)	—	BP
Isnard-Rouchon *et al.*,[72] 2017	France	Prospective interventional cohort; nonrandomized	Aerobic Usual care	80 (40/40) (18%)	Hemodialysis	None stated	38	—	—	67.65 (13.4)	66.8 (10.6)	DM: 36 HT: 84 IHD: 13	BP medications, CV hospitalizations
Koh *et al.*,[47] 2010	Australia	RCT	Aerobic Usual care	49 (22/27) (44%)	Older than 18 yr, stable dialysis Urea reduction ratio >70% for >3 mo	Unstable angina, lower-limb amputation Current moderate exercise ≥120 min/wk	42	—	—	51.3 (14.4)	52.3 (10.9)	DM: 5 HT: 29 MI: 2 Mitral regurgitation: 1 Other arterial disease: 2 Angina: 3	Arterial resistance, BP
Kouidi *et al.*,[60] 2009	Greece	RCT	Combined Usual care	63 (31/32) (6%)	Hemodialysis ≥6 mo Able to reach target workload	Bundle branch block; unstable HTN; DM; severe CHF; recent MI; unstable angina	42	74.4 (46.8)	75.6 (44.4)	53.2 (6.1)	54.6 (8.9)	HT: 71 CAD: 12 CHF: 29	LVF, HRV
Kouidi *et al.*,[49] 2010	Greece	RCT	Combined Usual care	44 (20/24) (12%)	Hemodialysis	Severe psychiatric, neurological, cardiac, lung, MSK issues DM; significant electrolyte instability Undisciplined patients	41	75.6 (58.8)	73.2 (55.2)	45.8 (10.9)	46.3 (11.2)	—	HRV

Table 2. (Continued)

Author, Year	Country	Study Design	Type of Exercise Type of Control	*N* (Control/ Exercise) (Attrition%)	Eligibility Criteria: Inclusion Criteria	Eligibility Criteria: Exclusion Criteria	% Female	Months on Hemodialysis (Mean [SD]/Median [IQR]): Control	Months on Hemodialysis (Mean [SD]/Median [IQR]): Exercise	Participant Age (yr) (Mean [SD]): Control	Participant Age (yr) (Mean [SD]): Exercise	Comorbidities (%)	Outcomes Assessed
Liao *et al.*,[50] 2016	Taiwan	RCT	Aerobic Usual care	40 (20/20) (—)	Hemodialysis 3 times/wk for ≥6 mo	Severe HTN, lung issues, DM; high PTH levels Moderate CHF, arrhythmia; recent MI; unstable angina; active liver dysfunction; MSK problems Inflammation/infection; cancer; autoimmune disease Emotional instability Hospitalization in last mo; BMI >25 kg/m^2 Lower-extremity arterial–venous access	58	83 (71)	71 (46)	62 (9)	62 (8)	DM: 43 Cardiomyopathy: 28 CVD: 20 PAD: 13 TIA: 8	BP, EPC count
Martínez-Olmos *et al.*[70] 2021	Spain	Randomized cross-over	Aerobic Usual care	56 (56/56) (37.5%)	Hemodialysis >3 mo	MI in last 6 wk, BKA Cerebrovascular disease Chest pain, dyspnea with exertion Inability to perform functional tests	39	58.8 (—)	52.8 (—)	66.5 (14.8)	68 (13.5)	DM: 41	HTN medications
Mihaescu *et al.*,[73] 2013	Romania	Prospective interventional cohort; nonrandomized	Resistance Usual care	35 (16/19) (9%)	Hemodialysis 3 times/wk ≥3 mo	None stated	69	55.2 (52.8)	54 (56.4)	55.1 (10.5)	55.6 (8.9)	—	Arterial resistance, BP, HTN medications
Miller *et al.*,[74] 2002	United States	Prospective interventional cohort; nonrandomized	Aerobic Usual care	75 (35/40) (24%)	Hemodialysis >1 mo	Angina, CVD requiring oxygen; MI, CABG Stroke or TIA <3 mo Unable to pedal a bike	57	28.7 (25.5)	20.7 (27.5)	56.1 (15.2)	52.8 (16.0)	DM: 23 CAD/CHF: 25	BP, HTN medications
Momeni *et al.*,[32] 2014	Iran	RCT	Aerobic Usual care	40 (20/20) (—)	Older than 18 years Hemodialysis >3 mo	Older than 60 years; IHD; LVEF <40% Using antiarrhythmic agents; unable to exercise Dyspnea/chest pain during exercise BP ≥160/100 mm Hg	25	—	—	43.1 (10.5)		—	LVF
Moore *et al.*,[56] 1993	United States	Nonrandomized single-group cross-over	Aerobic Unloaded cycling (<50 rpm)	23 (23/23) (61%)	Achieve 6/10 on Borg RPE.	Angina; IHD, MSK disease-limiting exercise Ability to complete study	43	—	—	—	—	—	Stroke volume, CO
Musavian *et al.*,[57] 2015	Iran	Single-group pre/post	Aerobic Passive cycling (electric bike)	18 (18/18) (11%)	15–80 years Hemodialysis 3 times/wk for ≥3 mo	CVD, IHD <6 mo; Stroke/TIAs Pulmonary, MSK, and immune disorders Severe HTN or SBP <90 mm Hg); severe DM; nonadherence	19	27.24 (25.08)		51.98 (1.57)		DM: 0	BP

Table 2. (Continued)

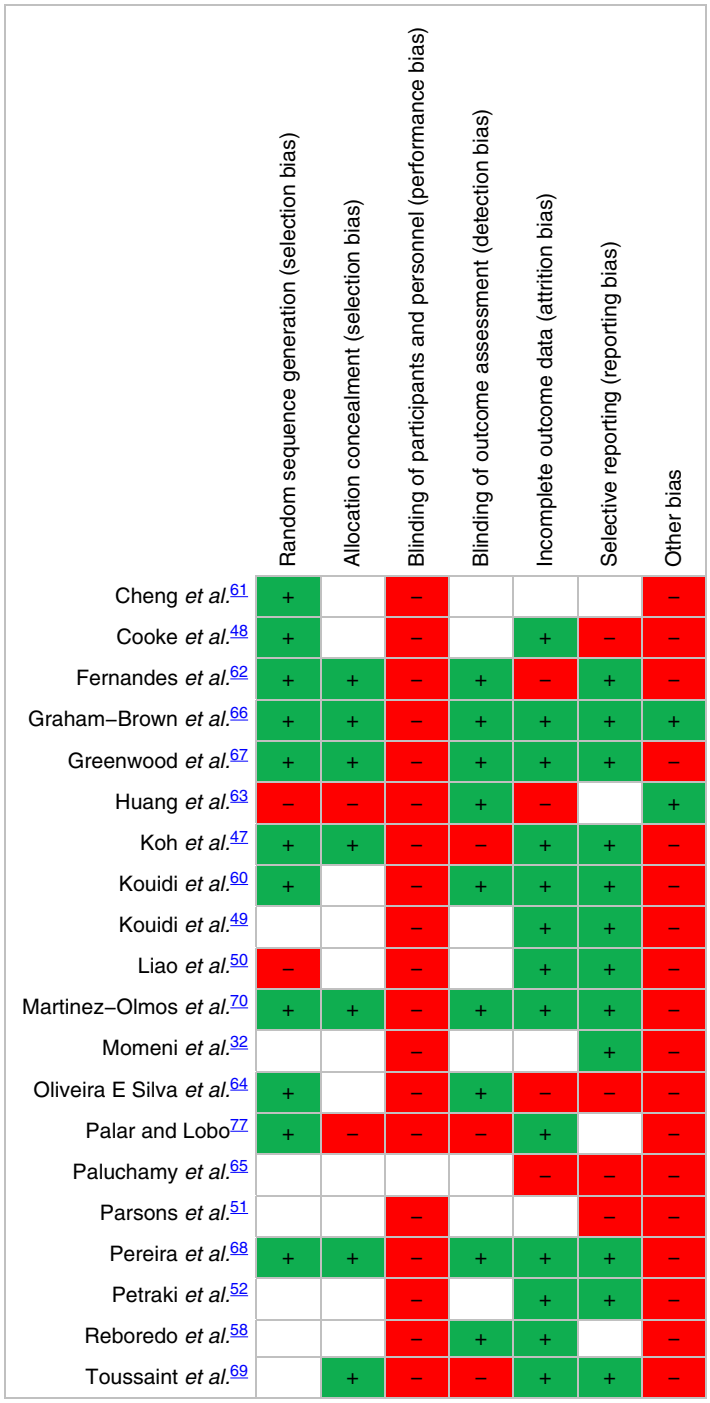
Author, Year	Country	Study Design	Type of Exercise Type of Control	*N* (Control/ Exercise) (Attrition%)	Eligibility Criteria		% Female	Months on Hemodialysis (Mean [SD]/Median [IQR])		Participant Age (yr) (Mean [SD])		Comorbidities (%)	Outcomes Assessed
					Inclusion Criteria	Exclusion Criteria		Control	Exercise	Control	Exercise		
Oliveira E Silva *et al.*,[64] 2019	Brazil	RCT	Aerobic Usual care	30 (15/15) (17%)	Older than 18 years Hemodialysis ≥3 mo Stable medication Able to exercise	Already physically active; IHD; stroke; cancer; liver failure; active infection BP >160/100 mm Hg during treadmill test	50	21 (27.1)	26 (14.58)	58 (15)	50 (17.2)	DM: 30 HT: 83	Arterial resistance, LVM, LVF
Painter *et al.*,[75] 1986	United States	Prospective interventional cohort; nonrandomized	Aerobic Usual care	27 (7/20) (30%)	Hemodialysis	None stated	—	62.4 (46.8)	45.6 (36.0)	42 (16)	42 (10)	DM: 11	BP, HTN medications
Palar and Lobo,[77] 2022	India	Prospective interventional cohort; nonrandomized	Resistance Usual care	40 (20/20) (12.5%)	20–80 years Hemodialysis >3 mo	Uncontrolled HTN Unstable angina, recent MI Lower limb amputation	29	3–6 mo: n=0 6–12 mo: n=0 1–3 years: n=5 >3 years: n=11	3–6 mo: n=6 6–12 mo: n=1 1–3 years: n=7 >3 years: n=5	20–35: n=7 36–50: n=6 51–65: n=3 66–90: n=0	20–35: n=2. 36–50: n=6. 51–65: n=9. 66–90: n=2	DM: 13	BP
Paluchamy *et al.*,[65] 2018	India	RCT	Aerobic Usual care	20 (10/10) (0%)	None stated	Unstable angina, recent MI, grade II CHF Fever (≥101°F); persistent prehemodialysis hyperkalemia Active liver disease; MSK limitations Severe peripheral neuropathy Dementia/other mental disorders; unstable during hemodialysis Lower limb amputee; already in exercise program	10	<6 mo: 20% 6 mo to 1 yr: 20% 1–3 yr: 60% >3 yr: 0	<6 mo: 30% 6 mo to 1 yr: 10% 1–3 yr: 50% >3 yr: 10%	18–30: 0% 31–50: 30% 51–70: 70%	18–30: 20% 31–50: 30% 51–70: 50%	—	Baroreflex sensitivity
Parsons *et al.*,[51] 2004	Canada	RCT	Aerobic Usual care	18 (7/6) (28%)	Hemodialysis	CVD, MSK, neurological issue, and unable to exercise	46	49 (26)	35 (25)	49 (25)	60 (17)	DM: 15	BP
Petraki *et al.*,[52] 2008	Greece	RCT	Combined Usual care	50 (24/26) (14%)	Hemodialysis ≥6 mo	Unstable HTN, grade II CHF Lown's grade III arrhythmia; recent MI; unstable angina DM; active liver disease; established cause of syncope	25	72.8 (5.3)	76.32 (7.0)	50.52 (14.4)	50.05 (13.2)	—	BP, baroreflex sensitivity

Table 2. (Continued)

Author, Year	Country	Study Design	Type of Exercise Type of Control	*N* (Control/ Exercise) (Attrition%)	Eligibility Criteria: Inclusion Criteria	Eligibility Criteria: Exclusion Criteria	% Female	Months on Hemodialysis (Mean [SD]/Median [IQR]): Control	Months on Hemodialysis (Mean [SD]/Median [IQR]): Exercise	Participant Age (yr) (Mean [SD]): Control	Participant Age (yr) (Mean [SD]): Exercise	Comorbidities (%)	Outcomes Assessed
Pereira *et al.*,[68] 2022	Brazil	RCT	Aerobic Usual care	98 (49/49) (18.4%)	50–70 years Hemodialysis ≥6 mo	Previously hospitalized for CKD MSK diseases that prevent exercise Drugs that influenced HR Cognitive impairment; BMI >30 Pacemakers or cardiac surgery <6 mo	38	5.77 (1.56)	5.8 (3.42)	71.55 (6.76)	69.1 (6.17)	DM: 35 HT: 90	HRV
Reboredo *et al.*,[53] 2010 (a)	Brazil	Nonrandomized single-group cross-over	Aerobic Usual care	18 (18/18) (22%)	None stated	Unstable angina; uncontrolled arrhythmia or DM Uncompensated CHF SBP ≥200 mm Hg and/or DBP ≥120 mm Hg; systemic infection; severe renal osteodystrophy Neurological, pulmonary, or MSK disturbances	31	93.7 (43.9)		47.6 (12.8)		HT: 86 LVH: 57 CHF: 28	BP
Reboredo *et al.*,[58] 2010 (b)	Brazil	RCT	Aerobic Usual care	28 (14/14) (21%)	Older than 18 years No regular exercise for ≥6 mo	DM; unstable angina; uncontrolled HTN On antiarrhythmic drugs; severe pneumopathies Acute systemic infection; severe renal osteodystrophy Disabling neurological and MSK disorders	36	60.1 (54.4)	41.9 (42.4)	43.5 (12.8)	49.6 (10.6)	—	LVF, HRV
Thenmozhi *et al.*,[76] 2018	India	Prospective interventional cohort; nonrandomized	Aerobic Usual care	130 (65/65) (—)	25–65 years Hemodialysis ≥3 mo Clinically stable	Unstable angina, recent MI, CHF grade II Fever (≥101°F); persistent prehemodialysis hyperkalemia Active liver disease; MSK limitations Severe peripheral neuropathy; lower limb amputee Dementia or other mental disorders Participation in other exercise program; unstable hemodialysis	15	6 mo to 1 yr: 49% 1–3 yr: 46% >3 yr: 5%	6 mo to 1 yr: 53% 1–3 yr: 42% >3 yr: 5%	18–30: 11% 31–50: 34% 51–65: 55%	18–30: 9% 31–50: 31% 51–65: 60%	—	BP
Toussaint *et al.*,[69] 2008	Australia	Randomized cross-over	Aerobic Usual care	20 (10/10) (5%)	Hemodialysis >3 mo Able to exercise for 3 mo	Symptomatic CVD Respiratory or MSK issue-limiting exercise	53	72 (56)	35 (51)	70 (28–77)	67 (60–83)	DM: 32 CAD: 47	Arterial resistance, BP, brain natriuretic peptide

ADL, activities of daily living; AFib, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CMRI, cardiac magnetic resonance imaging; CO, cardiac output; Combined, aerobic and resistance exercise; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular attack; CVD, cardiovascular disease; DBP, diastolic BP; DM, diabetes mellitus; EPC, endothelial progenitor cell; HF, heart failure; HR, heart rate; HRV, heart rate variability; HTN, hypertension; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; LVF, left ventricular function; LVH, left ventricular hypertrophy; LVM, left ventricular mass; MRI, magnetic resonance imaging; MSK, musculoskeletal; N/A, not applicable; MI, myocardial infarction; PVD, peripheral vascular disease; RCT, randomized controlled trial; SBP, systolic BP; TIA, transient ischemic attack.

Table 3. Risk of bias for randomized controlled trials



controls (MD –1.62 g/m^2; 95% CI, −7.46 to 4.22; I^2=91%; $P < 0.001$) (Figure 4B).[53,60,64,66]

Cardiac Autonomic Dysfunction/Increased Sympathetic Activity

Four RCTs (total n=205) assessed the effect of intradialytic cycling for 30–90 minutes, thrice weekly over 12–52 weeks of duration on various measures of HRV (Table 4).[49,53,60,68] Meta-analysis of these studies showed no statistically significant difference in the SD of normal R-R intervals during a 24-hour period (SD of N-N intervals [SDNN]) in the exercise group as compared with the control group (MD 16.05 ms; 95% CI, −14.60 to 46.70; I^2=99%; $P < 0.001$). By contrast, meta-analysis of three

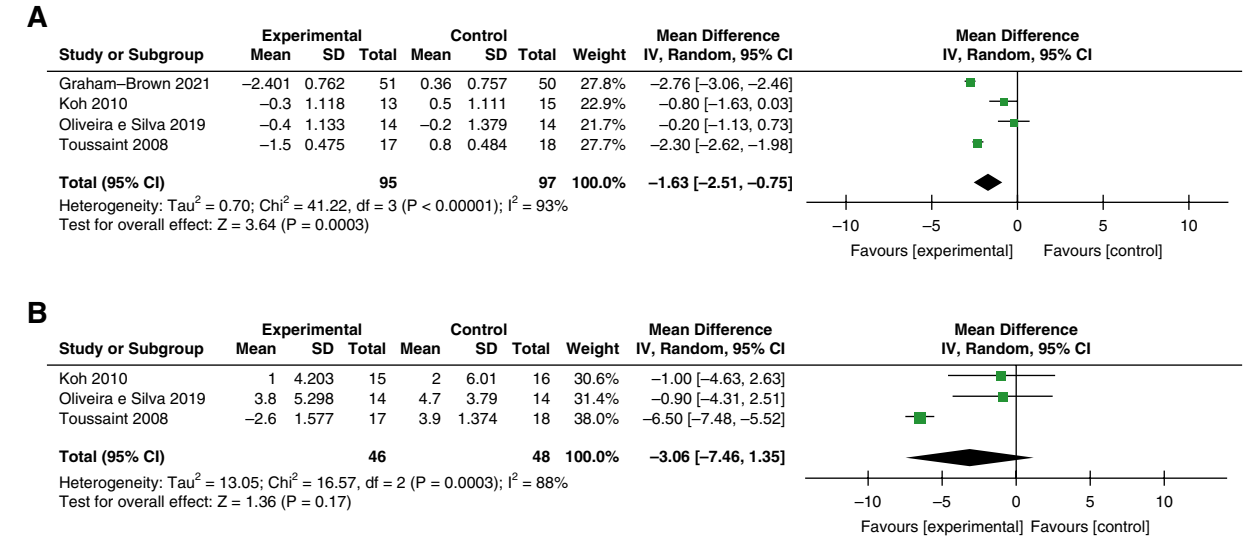


Figure 2. Meta-analysis of studies examining the effect of intradialytic exercise on arterial resistance. (A) PWV and (B) AI. AI, augmentation index; CI, confidence interval; IV, inverse variance; PWV, pulse wave velocity.

RCTs demonstrated a statistically significant between-group difference in low-frequency/high-frequency (LF/HF) ratio of 0.38 (95% CI, 0.32, 0.44; I^2=0%; P = 0.90) (Supplemental Figure 2).[49,53,60]

Summative review of studies not included in the meta-analysis for each outcome above is provided in Supplemental Appendix.

Endothelial Function

In a single RCT (n=40), Liao *et al.* demonstrated a statistically significant increase in circulating endothelial progenitor cell count after 12 weeks of aerobic exercise compared with no exercise ($P < 0.05$; no change measure reported).[50] By contrast, a pre/post study (n=22) showed no significant change in endothelial progenitor cell count with 12 weeks of resistance exercise MD −0.024 (95% CI, −0.043 to 0.005; P = 0.53).[54]

Biomarkers of Cardiac Injury

No changes were observed in predialysis *N*-terminal pro-B-type natriuretic peptide and high-sensitivity troponin I levels in two RCTs evaluating intradialytic cycling for 6 months (n=101) and 3 months of (n=19) duration (Table 4).[66,69]

Cardiovascular Hospitalization and Mortality

One cohort study (n=66) of intradialytic cycling for 30 minutes twice weekly for 2 years demonstrated fewer cardiovascular hospitalizations with exercise (n=5) than in controls (n=14) in unadjusted analysis.[72] One RCT of intradialytic cycling for 6 months showed a decline in overall number of cardiovascular hospital admissions during (n=8) and 6 months after (n=5) the intervention period as compared with the pretrial period (n=9) in the exercise group, while admissions increased during (n=3) and after (n=7) the trial period compared with pretrial in controls (n=1) (Table 4).[78]

An RCT studying a 6-month combined intradialytic cycling and resistance program demonstrated no significant difference in number of cardiovascular deaths in the exercise group (n=2; 1%) as compared with nonexercise controls (n=3; 2%) (Table 4).[67]

Adverse Events, Adherence, and Study Attrition

Only 19/32 studies reported adverse events.[47–50,52,53,58,60,61,65–70,72,74,75,77] Across these studies, 248 adverse events occurred, with 135 (54.4%) occurring in the intervention groups and 113 (45.6%) in the control groups. Of the adverse events in the intervention group, only one was identified to be related to exercise.[67]

Attrition ranged from 0% to 61%, with only 4/32 studies reporting no withdrawals.[50,65,71,76] Of 1817 participants in all studies, 367 withdrew (20%). One study did not report attrition.[32]

Adherence to exercise intervention was reported in 44% of studies (14/32). Adherence was variable in these 14 studies, ranging from 28% to 92% of total possible exercise sessions completed. Overall, participants completed a mean 74.9% of prescribed exercise sessions and between 21 and 60 minutes of exercise per session.[47–49,53,54,58–60,66,67,69,70,74,75]

Discussion

This systematic review and meta-analysis of the effect of intradialytic exercise on cardiovascular outcomes in hemodialysis demonstrated significant improvements in multiple physiological cardiovascular outcomes, including PWV, DBP, LVEF, and HRV measured by the LF/HF ratio.

Mean change observed in PWV (−1.64 m/s) was statistically and clinically significant. Multiple studies have established a minimal clinically important difference of >1 m/s for PWV in people with kidney failure.[79,80] One study of 242 people receiving hemodialysis with a follow-up time of 78±46 months demonstrated a 14% increase in

Table 4. Summary of study outcomes and results

First Author (Year)	Meta-Analysis (Yes/No)	Intervention	Exercise Frequency (per week)	Goal Intensity	Goal Session Length (min)	Duration (wk)	Control	Measurement Tool (Primary/Secondary Outcome)	Mean Change		MD Exercise Control (SD or 95% CI)	Effect Size (95% CI)	*P* Value
									Control	Exercise			
Arterial resistance													
Chan *et al.*[54] (2017)	No	Ten muscle groups using free weights, tubing, resistance machine	3	Week 1–4 RPE 12–14; 12–15 rep Week 5–12 RPE 14–15; 10–12 rep	30	13	Usual care	PWV peripheral (m/s) (primary)	BL: 12.3 (9.1–20.8) Post: 11.5 (9.7–20.0)	BL: 11.5 (9.7–20.0) Post: 13.0 (9.3–26.7)	0 (−0.1 to 0.1)	0.02 (−0.61 to 0.57)	0.6
								AI (%) (secondary)	−1.4	0.4	1.9 (−5.9 to 9.7)	0.14 (−0.45 to 0.74)	0.9
								AI×75 (%) (secondary)	−0.3	2.3	2.7 (−3.9 to 9.4)	0.24 (−0.35 to 0.84)	0.5
Cooke *et al.*[48] (2018)	Yes	Stationary cycling	3	RPE 12–16	Not stated	16	Usual care	PWV central (m/s) (primary)	0.20 (−0.1 to 0.9)	−1.0 (−2.0 to 0.5)	—	—	0.03
								AI×75 (%) (secondary)	3.5 (1.0–8.5)	−2 (−4.5 to 1.0)	—	—	0.01
Graham-Brown *et al.*[66] (2021)	Yes	Stationary cycling	3	RPE 12–14	30	26	Usual care	PWV central (m/s)	0.36 (0.76)	−2.4 (0.76)	−2.8 (0.15)	−2.07 (−3.2 to −0.99)	<0.001
Greenwood *et al.*[67] (2021)	Yes	Stationary cycling, lower-extremity muscular strengthening	Aerobic 3×, resistance 2×	7	21–30 min aerobic; three sets of lower extremity muscular conditioning exercises	26	Usual care	PWV central (m/s) (secondary)	−0.32	−0.04	−0.28	—	—
Koh *et al.*[47] (2010)	Yes	Stationary cycling	3	RPE 12–13	Progress from 15 to 45	26	Usual care	PWV central (m/s) (primary)	0.5 (1.1)	−0.3 (1.1)	−0.8 (−2.1 to 0.5)	—	0.4
								PWV peripheral (m/s) (secondary)	0.7 (0.7)	−0.3 (0.42)	1.0 (0.2)	—	0.2
								AI (%) (secondary)	2 (6)	1 (4)	−1 (−10.2 to 8.1)	—	0.8
								AI×75 (%) (secondary)	2 (6)	1 (4)	−1 (−9.5 to 6.6)	—	0.7
Mihaesu *et al.*[73] (2013)	No	Elastic bands, dumbbells, ankle weights	3	RPE 12–14 and increase of exercise HR of 15–30 bpm	40	12	Usual care	PWV central (m/s) (primary)	1.3 (0.9)	−1.0 (0.7)	−2.3 (0.3)	—	0.03
		AI (%) (secondary)							−3.8 (6.7)	−3.5 (5.4)	−0.4 (2.2)	—	0.1
Oliveira E Silva *et al.*[64] (2019)	Yes	Stationary cycling	3	RPE 13; 65%–75% maximum HR	30	17	Usual care	PWV central (m/s) (primary)	−0.2 (1.4)	−0.4 (1.1)	−0.2 (0.5)	—	0.3
								AI (%) (primary)	4.7 (3.8)	3.8 (5.3)	−0.9 (1.7)	—	0.06
Toussaint *et al.*[69] (2008)	Yes	Stationary cycling	3	None stated	None stated	13	Usual care	PWV central (m/s) (primary)	10.2 (0.7)	9.0 (0.6)	2.3 (0.2)	—	—
								AI (%) (secondary)	33.9 (2.9)	28.4 (2.4)	6.5 (0.5)	—	—
BP													
Agustin *et al.*[71] (2022)	No	Not stated (? aerobic)	2	Not stated	30–45	8	Usual care	SBP (primary)	4.2	−9.07	13.27	—	—
								DBP (primary)	0.8	−9.34	10.14	—	—
Anderson *et al.*[59] (2004)	No	Stationary cycling	3	RPE somewhat hard	30	13	Usual care periods	44-h ambulatory SBP (primary)	N/A	−12.5 (9.37)	—	—	<0.05 (repeated measures ANOVA 0, 3, 6 mo time points)
								44-h ambulatory DBP (primary)	N/A	−9.3 (4.85)	—	—	0.05 (repeated measures ANOVA at 0, 3, 6 mo time points)

Table 4. (Continued)

First Author (Year)	Meta-Analysis (Yes/No)	Intervention	Exercise Frequency (per week)	Goal Intensity	Goal Session Length (min)	Duration (wk)	Control	Measurement Tool (Primary/Secondary Outcome)	Mean Change		MD Exercise Control (SD or 95% CI)	Effect Size (95% CI)	*P* Value
									Control	Exercise			
Chan *et al.*[54] (2017)	No	Ten muscle groups using free weights, tubing, and resistance machine	3	Week 1–4 RPE 12–14; 12–15 rep Week 5–12 RPE 14–15; 10–12 rep	30	12	Usual care	SBP (secondary)	−6 (7.98)	−7 (9.88)	1 (3.17)	Relative ES: 0.05 (−0.64 to 0.54)	Week 13 versus week 0: 0.28 Week 26 versus week 0: 0.25 Whole time: 0.17
								DBP (secondary)	−1 (3.04)	−1 (3.69)	0 (1.19)	Relative ES: 0.02 (−0.61 to 0.57)	Week 13 versus week 0: 0.55 Week 26 versus week 0: 0.54 Whole time: 0.16
								Central PP (secondary)	−4 (7.31)	−4 (9.04)	0 (2.90)	Relative ES: 0.03 (−0.62 to 0.56)	Week 13 versus week 0: 0.39 Week 26 versus week 0: 0.4 Whole time: 0.22
								Central SBP (secondary)	−6 (8.12)	−5 (10.29)	−1 (3.27)	Relative ES: 0.04 (−0.55 to 0.63)	Week 13 versus week 0: 0.31 Week 26 versus week 0: 0.48 Whole time: 0.19
								Central DBP (secondary)	−1 (3.18)	−1 (3.89)	0 (1.25)	Relative ES: 0.08 (−0.51 to 0.67)	Week 13 versus week 0: 0.4 Week 26 versus week 0: 0.71 Whole time: 0.17
								Peripheral PP (secondary)	−4 (7.17)	−5 (8.63)	1 (2.80)	Relative ES: 0.05 (−0.64 to 0.54)	Week 13 versus week 0: 0.32 Week 26 versus 0: 0.28 Whole time: 0.16
Cheng *et al.*[61] (2019)	Yes	Weight-bearing arm curl, arm raise, and leg raises	3	RPE 11–12 6-(6–20 scale)	20	104	Usual care	Predialysis SBP (primary)	4.83 (3.19)	1.26 (3.42)	3.57 (0.66)	—	$P = 0.413$ (control group) $P = 0.597$ (exercise group) $P = 0.694$ (baseline) $P = 0.510$ (year 1)
								Predialysis DBP (primary)	−0.33 (2.15)	−1.58 (2.54)	1.25 (0.47)	—	$P = 0.117$ (control group) $P = 0.234$ (exercise group) $P = 0.497$ (baseline) $P = 0.328$ (year 1)

Table 4. (Continued)

First Author (Year)	Meta-Analysis (Yes/No)	Intervention	Exercise Frequency (per week)	Goal Intensity	Goal Session Length (min)	Duration (wk)	Control	Measurement Tool (Primary/Secondary Outcome)	Mean Change		MD Exercise Control (SD or 95% CI)	Effect Size (95% CI)	*P* Value
									Control	Exercise			
Fernandes *et al.*[62] (2019)	Yes	Stationary cycling	3	—	50	8	Usual care	Predialysis SBP (primary)	2.63 (5.16)	1.5 (4.57)	1.13 (1.56)	—	0.738
								Predialysis DBP (primary)	2.9 (3.56)	3.5 (2.90)	−0.6 (1.04)	—	0.864
Graham-Brown *et al.*[66] (2021)	Yes	Stationary cycling	3	RPE 12–14	30	26	Usual care	Interdialytic SBP (mm Hg)	−4.9 (4.41)	−6 (4.22)	1.1 (0.65)	−6.8 (−17.2 to 3.6)	0.2
								Interdialytic DBP (mm Hg)	0.6 (2.46)	−2 (2.33)	2.6 (0.36)	−1.95 (−7.6 to 3.7)	0.5
								Predialysis SBP (mm Hg)	−6.7 (3.93)	−4 (2.91)	−2.7 (0.47)	1.32 (−10.5 to 13.2)	0.8
								Predialysis DBP (mm Hg)	−2.5 (2.26)	−3.2 (1.81)	0.7 (0.28)	0.5 (−5.7 to 6.7)	0.9
Guio *et al.*[55] (2017)	No	Stationary cycling	3	Mean modified Borg RPE 1.1±1.1 to 1.4±0.9	≤30	17	Usual care	Central SBP (secondary)	—	2.1 (4.06)	—	—	0.951 (ANOVA)
								Central DBP (secondary)	—	4.1 (3.26)	—	—	0.328 (ANOVA)
Huang *et al.*[63] (2020)	Yes	Progressively increasing combined aerobic and resistance stationary cycling	3	RPE of 12–14	40	24	Sham exercises	Predialysis SBP (secondary)	−1.63 (6.06)	−8.42 (5.20)	6.79 (2.00)	—	>0.05 (control group) <0.05 (exercise group)
								Predialysis DBP (secondary)	−2.32 (3.02)	3.57 (2.62)	−5.89 (1.00)	—	>0.05 (control group) <0.05 (exercise group)
Koh *et al.*[47] (2010)	Yes	Stationary cycling	3	RPE 12–13	Progress from 15 to 45	26	Usual care	Predialysis SBP (secondary)	−9 (8.53)	−9 (8.03)	0 (2.98)	—	0.7
								Predialysis DBP (secondary)	−5 (4.37)	1 (5.84)	−6 (1.86)	—	0.9
								PP (secondary)	−4 (6.54)	−3 (7.30)	−1 (2.50)	—	0.9
								MAP (secondary)	−6 (6.18)	−6 (4.93)	0 (2.00)	—	0.9
								Central SBP (secondary)	−7 (8.11)	−8 (8.22)	1 (2.94)	—	0.9
								Central DBP (secondary)	−4 (4.72)	−7 (4.02)	3 (1.57)	—	0.8
								Central PP (secondary)	−2 (5.13)	−2 (7.49)	0 (2.32)	—	0.9
Liao *et al.*[50] (2016)	No[a]	Stationary cycling	3	RPE 12–15	30	12	Usual care	Pre-exercise SBP (secondary)	1.3 (5.43)	−42.1 (14.85)	43.4 (3.53)	—	<0.05
								Pre-exercise DBP (secondary)	2.5 (4.24)	−23.1 (8.11)	25.6 (2.05)	—	>0.05
Mihaescu *et al.*[73] (2013)	No	Elastic bands, dumbbells, ankle weights	3	RPE 12–14 and HR increase by 15–30 bpm with exercise	40	12	Usual care	Predialysis SBP (secondary)	−14.4 (12.97)	−8.9 (6.29)	−5.5 (3.77)	—	0.697
								Predialysis DBP (secondary)	−2.81 (8.98)	−6 (4.55)	3.19 (2.63)	—	0.578
								Predialysis PP (secondary)	−11.63 (5.71)	−1.68 (3.28)	−9.95 (1.71)	—	0.926
								Predialysis MAP (secondary)	−6.6 (10.12)	−8.16 (4.90)	1.56 (2.94)	—	0.618
								Central SBP (secondary)	−5 (11.04)	−11.2 (7.17)	6.2 (3.40)	—	0.302
Miller *et al.*[74] (2002)	No	Stationary cycling	3	Exercise as long as possible; increase time by 1–5 min/session. At 30 min, increase resistance	30	26	Usual care	Predialysis SBP (secondary)	2.4	0	2.4	—	>0.05
								Predialysis DBP (secondary)	0	−2.4	2.4	—	>0.05

Table 4. (Continued)

First Author (Year)	Meta-Analysis (Yes/No)	Intervention	Exercise Frequency (per week)	Goal Intensity	Goal Session Length (min)	Duration (wk)	Control	Measurement Tool (Primary/Secondary Outcome)	Mean Change		MD Exercise Control (SD or 95% CI)	Effect Size (95% CI)	*P* Value
									Control	Exercise			
Musavian *et al.*[57] (2015)		Stationary cycling	3	Not stated	30 min; three 10-min bouts of exercise, 20-min recovery between each bout	8	Passive cycling with electrically powered bike	Predialysis SBP (secondary)	−0.07 (0.77)	1.06 (0.70)	−1.13 (0.26)	—	$P = 0.058$ (control group) $P = 0.255$ (exercise group)
								Predialysis DBP (secondary)	−0.37 (0.25)	0.48 (0.29)	−0.85 (0.10)	—	$P = 0.039$ (control group) $P = 0.296$ (exercise group)
Painter *et al.*[75] (1986)		Stationary cycling	3 (one participant cycled 2x/wk)	65% of VO2 max initially, 75%–85% of VO2max after 30 min/session reached	5 min/session start; increase by 2–5 min/session until 30 min/session	26	Usual care	Predialysis SBP (secondary)	0 (8.57)	−14 (12.90)	14 (4.94)	—	3 mo >0.05 (control group) >0.05 (exercise group) 6 mo <0.05 (exercise group)
Palar and Lobo,[77] (2022)		Resistance and ROM for upper and lower extremities	2: n=11 (57.9%). 3: n=8 (42.1%)	Not stated	25	13.0357	Usual care	SBP (secondary)	−5 (3.292)	−7.9 (4.801)	2.9 (1.375)	—	0.383
								DBP (secondary)	−0.59 (2.675)	0 (3.163)	−0.59 (0.987)	—	0.990
Parsons *et al.*[51] (2004)		Stationary cycling	3	40–50% maximal work capacity	45 min (15-min increments in first 3 h of dialysis)	8	Usual care	Predialysis SBP (secondary)	—	—	—	—	>0.05 (control group) >0.05 (exercise group)
								Predialysis DBP (secondary)	—	—	—	—	>0.05 (control group) >0.05 (exercise group)
								Predialysis PP (secondary)	3	−3	6	—	>0.05 (control group) >0.05 (exercise group)
Petraki *et al.*[52] (2008)		Stationary cycling, strengthening exercises, flexibility exercises	3	RPE 13	90	30	Usual care	Predialysis SBP (primary)	−2 (4.79)	−8.3 (4.54)	6.3 (1.42)	—	<0.05
								Predialysis DBP (primary)	−1.17 (2.30)	−6 (2.60)	4.83 (0.75)	—	<0.05
Reboredo *et al.*[53] (a) (2010)		Stationary cycling	3	RPE 11–13	Not stated	12	Usual care	24-h ambulatory SBP (secondary)	−4.8 (7.16)	−7.1 (6.29)	2.3 (2.55)	—	<0.05
								24-h ambulatory DBP (secondary)	−1.8 (4.10)	−3.2 (3.82)	1.4 (1.50)	—	<0.05
Thenmozhi *et al.*[76] (2018)		Stationary cycling	3/wk, except 33.85% of exercise patients exercised 2×/wk	"According to t he tolerance of the (patients)" No other info	10–15	12	Usual care	Predialysis SBP (secondary)	0.16 (0.30)	−8.75 (0.27)	8.91 (0.05)	—	<0.001
								Predialysis DBP (secondary)	0.88 (0.27)	−2.46 (0.24)	3.34 (0.04)	—	$P < 0.001$
Toussaint *et al.*[69] (2008)		Stationary cycling	3	None stated	None stated	13	Usual care	Predialysis SBP (secondary)	−0.42 (5.44)	−8.21 (5.94)	7.78 (1.85)	—	0.99
								Predialysis DBP (secondary)	−1.25 (2.65)	0.19 (2.83)	−1.44 (0.89)	—	—
								Predialysis PP (secondary)	1.19 (4.44)	−9.06 (4.52)	10.25 (1.45)	—	—

Table 4. (Continued)

First Author (Year)	Meta-Analysis (Yes/No)	Intervention	Exercise Frequency (per week)	Goal Intensity	Goal Session Length (min)	Duration (wk)	Control	Measurement Tool (Primary/Secondary Outcome)	Mean Change		MD Exercise Control (SD or 95% CI)	Effect Size (95% CI)	*P* Value
									Control	Exercise			
Left ventricular structure and function (echocardiogram/CMRI)													
Graham-Brown *et al.*[66] (2021)	Yes	Stationary cycling	3	RPE 12–14	30	26	Usual care	LV Mass (g) (primary)	1.6 (7.3)	−10 (8.6)	−11.6	−11.1 (−15.8 to −6.4)	<0.001
								LV Mass index (g/m^2) (secondary)	1.1 (3.7)	−5.5 (4.3)	−6.6	−6.3 (−9.2 to −3.4)	<0.001
								LV end diastolic volume (ml) (secondary)	0.9 (11.7)	3.0 (12.7)	2.1	0.5 (−14.2 to 21.2)	0.6
								LV ejection fraction (%)[a] (secondary)	0.1 (11.3)	2.5 (2.3)	2.4	0.03 (−0.8 to 4.8)	0.9
Guio *et al.*[55] (2017)	No	Ergometer	3	Target HR (no specifics)	30	17	Usual care Single-group	LV ejection fraction (%) (secondary)	65.7 (10.2)[a]	73.6 (10.1)	7.9 (4.0)	—	0.03
								LV systolic diameter (mm) (secondary)	32.4 (6.7)	29.8 (4.6)	−2.6 (2.2)	—	0.3
								LV diastolic diameter (mm) (secondary)	54.5 (49.0–56.0)	56 (53.0–58.0)	—	—	0.03
								LV posterior wall (mm) (secondary)	12.2 (1.8)	13.3 (3.3)	1.1 (1.0)	—	0.9
Kouidi *et al.*[60] (2009)	Yes	Stationary cycling, strengthening exercises	3	RPE 13	90	44	Usual care	LV ejection fraction (primary)	0.2 (7.7)	3.4 (3.9)	3.2 (1.0)	—	0.05
								LV mass index (g/m2) (secondary)	1.2 (4.2)	3.4 (6.3)	2.2 (0.8)	—	0.1
Momeni *et al.*[32] (2014)	Yes	Stationary cycling	3	Not stated	30	13	Usual care	LV ejection fraction (primary)	0.3 (1.8)	3.5 (1.03)	3.2 (0.5)	—	0.01
								LV systolic diameter (mm) (secondary)	2.5 (2.7)	1.8 (1.8)	−0.7 (0.7)	—	0.1
								LV diastolic diameter (mm) (secondary)	1. 2 (2.1)	−0.1 (2.4)	−1.3 (0.7)	—	0.9
								Severe LVH (% participants) (secondary)	0	0	0	—	—
Moore *et al.*[56] (1993)	No	Stationary cycling	3	RPE 6/10; 70% peak HR	30–60	12	Unloaded cycling at <50 rpm	Stroke volume (secondary)	3 (2.9)	3 (2.3)	0 (1.2)	—	—
								CO (L/min)	0.3 (0.5)	0.0 (0.5)	−0.3 (0.2)	—	—
Oliveira E Silva *et al.*[64] (2019)	Yes	Stationary cycling	3	RPE 13; 65%–75% of maximum HR	30	17	Usual care	LV mass index (g/m^2) (secondary)	−1.2 (6.5)	−3.6 (6.7)	−2.4 (2.5)	—	0.2
								LV mass (g) (secondary)	−4 (22.1)	−13 (20.5)	−9 (8.2)	—	0.2
								LV systolic diameter (mm) (secondary)	−0.1 (1.2)	0.3 (2.3)	0.4 (0.7)	—	0.7
								LV diastolic diameter (mm) (secondary)	0.1 (1.7)	0.4 (1.9)	0.3 (0.7)	—	0.4
								LV posterior wall (mm) (secondary)	−0.2 (0.7)	−0.7 (0.7)	−0.5 (0.3)	—	0.07

Table 4. (Continued)

First Author (Year)	Meta-Analysis (Yes/No)	Intervention	Exercise Frequency (per week)	Goal Intensity	Goal Session Length (min)	Duration (wk)	Control	Measurement Tool (Primary/Secondary Outcome)	Mean Change		MD Exercise Control (SD or 95% CI)	Effect Size (95% CI)	*P* Value
									Control	Exercise			
Reboredo *et al.*[58] (2010)b	Yes	Stationary cycling, stretches	3	RPE 4–6	15-min warmup; ≤35-min conditioning; 1–3 min of cool-down	12	Usual care	LV mass index (g/m^2) (secondary)	−1.3 (19.6)	2.2 (10.6)	3.5 (6.7)	—	—
								LV ejection fraction (%) (secondary)	−2.2 (3.2)	2.9 (5.0)	5.1 (1.8)	—	—
								Stroke volume (ml) (secondary)	−2.2 (9.9)	13.9 (8.1)	16.1 (3.8)	—	—
								LV end systolic volume (ml) (secondary)	2.6 (7.8)	2.4 (11.3)	−0.2 (4.1)	—	—
								LV end diastolic volume (ml) (secondary)	0.4 (15.6)	20 (16.5)	19.6 (6.8)	—	—
HRV													
Kouidi *et al.*[60] (2009)	Yes	Stationary cycling, strengthening exercises	3	RPE 13	90	44	Usual care	SDNN (ms) (secondary)	−1.1 (10.2)	12.6 (16.3)	14.0 (1.3)	—	<0.001
								Mean RR interval (ms) (secondary)	−11.4 (68.2)	23.1 (61.4)	34.6 (7.4)	—	0.05
								LF/HF ratio	−0.1 (0.3)	0.3 (0.4)	0.5 (0.042)	—	<0.001
Kouidi *et al.*[49] (2010)	No[a]	Stationary cycling, strengthening exercises with increasing workload and repetitions	3	RPE 11–13	60–90	52	Usual care	SDNN (ms) (secondary)	−1.4 (7.8)	60.9 (6.7)	62.3 (1.9)	—	<0.001
								MSSD (ms) (secondary)	−0.2 (0.2)	15.8 (2.19)	16.0 (0.6)	—	<0.001
								NN50 (ms) (secondary)	−0.2 (0.2)	0.8 (0.2)	1.0 (0.1)	—	<0.001
								LF/HF ratio	−0.1 (0.1)	0.2 (0.1)	0.4 (0.03)	—	<0.001
Pereira *et al.*[68] (2022)	Yes	Stationary cycling	3	Warmup and cool-down: 60%–70% maximal HR RPE 1–2/10 Conditioning Phase 70–80% maximal HR RPE 3–4/10	30 (5 min warmup and cool-down, 20 conditioning)	13.036	Usual care	RMSSD (not stated primary or secondary)	−3.2 (1.096)	5 (3.054)	−8.20 (0.513)	1.2	0.562
								SDNN (not stated primary or secondary)	−2.6 (1.336)	8.3 (2.567)	−10.90 (0.458)	1.2	0.49
								SD1 (SD of instantaneous beat-to-beat variability) (not stated primary or secondary)	−1.9 (0.767)	0.7 (2.006)	−2.60 (0.340)	1.2	0.383
								SD2 (long-term SD of continuous RR intervals) (not stated primary or secondary)	−5 (3.125)	7.7 (3.030)	−12.70 (0.688)	1.2	0.448
Reboredo *et al.*[58] (2010)b	Yes	Stationary cycling, stretches	3	RPE 4–6	15-min warmup ≤35-min conditioning 1–3 min of cool-down	12	Usual care	SDNN (ms) (primary)	13.4 (11.7)	−7.27 (10.9)	−20.63 (4.83)	—	Reported as NS
								RMSSD (ms) (secondary)	1.4 (3.19)	1.5 (4.20)	0.10 (1.60)	—	Reported as NS
								pNN50 (%) (secondary)	N/A (median and IQR)	N/A (median and IQR)	N/A (median and IQR)	—	Reported as NS
								LF/HF ratio	0.1 (0.94)	0.3 (1.08)	0.20 (0.43)	—	Reported as NS
Endothelial function													
Chan *et al.*[54] (2017)	No	Ten muscle groups using free weights, tubing, and resistance machine	3	Week 1–4 RPE 12–14; 12–15 rep Week 5–12 RPE 14–15; 10–12 rep	30	13	Usual care	EPC count (secondary)	Pre: 0.044 (0.028)	Post: 0.039 (0.033)	−0.024 (−0.043 to 0.005)	0.77 (−1.38 to −0.16)	0.53

Table 4. (Continued)

First Author (Year)	Meta-Analysis (Yes/No)	Intervention	Exercise Frequency (per week)	Goal Intensity	Goal Session Length (min)	Duration (wk)	Control	Measurement Tool (Primary/Secondary Outcome)	Mean Change		MD Exercise Control (SD or 95% CI)	Effect Size (95% CI)	*P* Value
									Control	Exercise			
Liao *et al.*[50] (2016)	No	Stationary cycling	3	RPE 12–15	30	12	Usual care	EPC count (secondary)	No accurate numbers reported	No accurate numbers reported	No accurate numbers reported	No accurate numbers reported	<0.05
Cardiac biomarkers													
Graham-Brown *et al.*[66] (2021)	No	Stationary cycling	3	RPE 12–14	30	26	Usual care	NT-pro-brain natriuretic peptide (pg/ml) (secondary)	BL: 3566.0 (1220–11,121) Post: 2597 (1173–11,319)	BL: 2515 (1015–11,443) Post: 3721 (1151–11,801)	—	0.2 (−0.2 to 0.5)	0.9
Toussaint *et al.*[69] (2008)	No	Stationary cycling	3	No scaled target	None stated	13	Usual care	Brain natriuretic peptide (pg/ml) (secondary)	351 (102)	−57 (70)	408 (29)	—	—
Graham-Brown *et al.*[66] (2021)	No	Stationary cycling	3	RPE 12–14	30	26	Usual care	Troponin I (ng/L) (secondary)	−4.4 (7.347)	−37.3 (23.778)	−32.9 (3.087)	0.86 (−10.8 to 12.5)	0.9
Baroreflex sensitivity													
Petraki *et al.*[52] (2008)	No	Stationary cycling, strengthening exercises, flexibility exercises	3	RPE 13	90	30	Usual care	Baroreflex sensitivity (ms/mm Hg) (primary)	0.2 (0.5)	1.4 (0.5)	1.6 (0.2)	—	<0.05
Cardiovascular-related hospitalization													
Graham-Brown *et al.*[66] (2021)		Stationary cycling	3	RPE 12–14	30	26	Usual care						
Isnard-Rouchon *et al.*[72] (2017)	No	Aerobic virtual reality exercise	2	40–80 rpm without resistance	30	104	Usual care period	Number of cardiovascular hospitalizations (secondary)	14	5	−9	—	Not reported
Cardiovascular mortality													
Greenwood *et al.*[67] (2021)	No	Stationary cycling, lower-extremity muscular strengthening	Aerobic 3×, resistance 2×	40%–75% VO2 reserve	21–30 min of aerobic; three sets of lower-extremity muscular conditioning exercises	26.07	Usual care	Number of cardiovascular deaths (secondary)	3/160 (1.9/100 person-years)	2/174 (1.3/100 person-years)	N/A	N/A	N/A

AI, augmentation index; CI, confidence interval; CO, cardiac output; DBP, diastolic BP; EPC, endothelial progenitor cell; HR, heart rate; HRV, heart rate variability; IQR, interquartile range; LF/HF, low-frequency/high-frequency; LV, left ventricular; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; MD, mean difference; pNN50, percentage of adjacent NN intervals that differ from each other by more than 50 ms; PP, pulse pressure; PWV, pulse-wave velocity; RMSSD, root mean square of successive differences; RPE, rating of perceived exertion; rpm, repetitions per minute; SBP, systolic BP; SDNN, SD of NN intervals; VO2, rate of oxygen consumption.

[a]Not included in meta-analysis because of concerns regarding heterogeneity (magnitude of change reported much greater than all other studies).

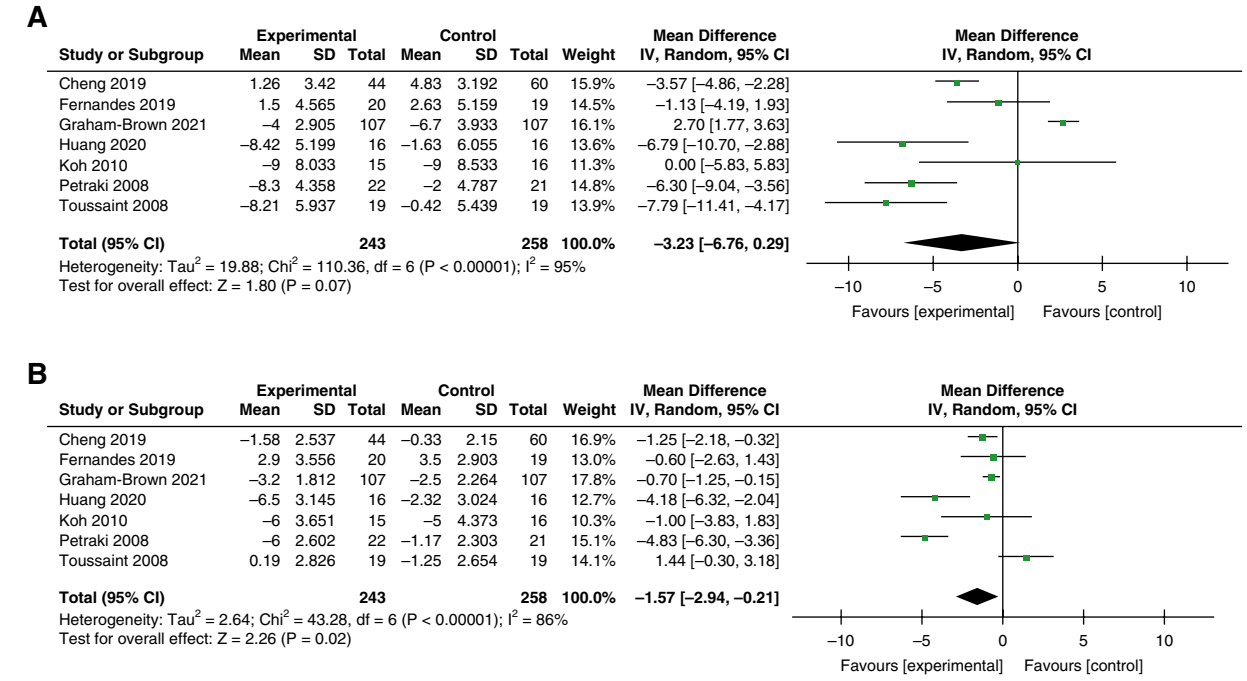


Figure 3. Meta-analysis of studies examining the effect of intradialytic exercise. (A) SBP and (B) DBP. DBP, diastolic BP; SBP, systolic BP.

cardiovascular and overall mortality with each 1 m/s increase in PWV.[80] Similarly, in a study involving 1497 kidney transplant recipients with a median follow-up of 4.2 years (interquartile range, 3.0–5.3), each 1 m/s increase in PWV measured 8 weeks post-transplant was associated with a 36% increase in mortality risk.[79]

Conversely, meta-analysis showed no statistically significant change in arterial resistance when measured by AI. Discordant results between AI and PWV measures of arterial resistance have been observed previously.[81] PWV measures the speed at which the arterial pulse travels between two distant major arterial sites and is considered the gold standard.[82] AI, a surrogate measure of arterial resistance, is less sensitive and specific than PWV and is affected by multiple clinical factors, including LVEF and peripheral hemodynamics, which were not adjusted for in included studies.[81] In addition, insulin resistance has been shown to attenuate decreases in arterial resistance.[83,84]

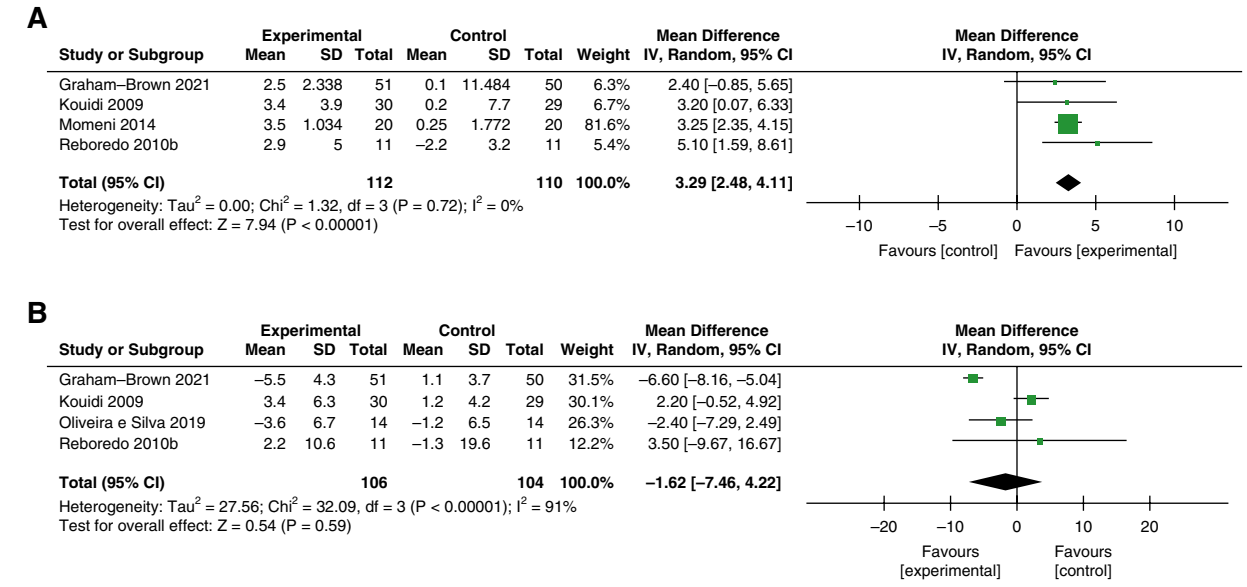


Figure 4. Meta-analysis of studies examining the effect of intradialytic exercise on myocardial function and structure. (A) LVEF and (B) LVMI. LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

When considering that diabetes is common in people receiving hemodialysis, this may explain why the observed change in AI was attenuated as compared with PWV. Consistent with this hypothesis, although not significant, the observed change in AI seen in our meta-analysis was overall in the same direction as PWV.

Similarly, meta-analysis of the LF/HF measure of HRV showed a statistically significant change, while SDNN did not. This may be due to inclusion of studies with relatively short intervention durations, which may not be a sufficient exercise dose to affect SDNN. This is supported by the 13-week intervention in the study of Pereira *et al.* that demonstrated minimal increase in measures of HRV, while increases in prolonged (44-week and 52-week) interventions were more pronounced.[49,60,68] Importantly, this dose-response effect with longer intradialytic exercise interventions has been demonstrated for other outcomes, such as depression.[29,85]

In contrast to our findings for DBP, although meta-analysis for SBP showed a clear trend for clinically significant decrease with exercise, it did not reach statistical significance. The reason for this discrepancy is unclear, but increased heterogeneity identified in the meta-analysis for SBP as compared with that for DBP (I^2 95% versus 86%, respectively) may have contributed. Studies included different populations, intervention designs (exercise type, intensity, session duration, and program length) and outcome measures, which contributed to increased heterogeneity. For instance, the 8-week duration in the study by Fernandes *et al.* may have been of insufficient in length to detect a measurable change in SBP, biasing its results and those of the meta-analysis toward the null.[62]

PWV and BP are closely related. Although arterial stiffness has traditionally been considered a consequence of arterial hypertension, a growing body of literature suggests that arterial stiffness is also an independent predictor of hypertension.[86] Exercise may improve both PWV and BP through vasodilation, improvements in endothelial function, and increased arterial compliance in arteries of skeletal muscle.[87]

Notably, PWV improvements in the exercise group reversed after a 3–4-month washout period in two of our included studies.[48,59,69] A similar reversion to preintervention BP levels after a post-training control period was seen in the study of Anderson *et al.*[59] Other studies have demonstrated that the beneficial effects of acute exercise on PWV last 24 hours.[87] Together, these findings suggest that the observed improvements in PWV and BP are likely attributable to intradialytic exercise and demonstrate a need for continued participation in regular exercise to maintain exercise-related benefits to cardiovascular health.

Meta-analysis for LVMI demonstrated no significant change. Interestingly, of the four studies included in the meta-analysis, two studies observed no significant change in LVMI. These included participants who had been receiving hemodialysis for longer (mean 3–7 years) compared with the two other studies that observed a significant difference in LVMI (mean 1–2 years). This observation suggests that people who are newer to hemodialysis may have greater improvement in LVMI with intradialytic exercise than those who have been on hemodialysis for many years.

Unmeasured heterogeneity could have additionally biased our overall findings related to SBP and LVMI. Depending on the setting and population, discrepancies in prevalence of unmeasured comorbidities, low adherence to exercise intensity targets, and low activity levels outside of dialysis because of geographic environment could have biased results toward the null.

Qualitative synthesis of studies measuring outcomes not eligible for meta-analysis was not substantially different from meta-analyses. The effect of intradialytic exercise was inconclusive because of few studies and low power for endothelial function, baroreflex function, biomarkers of myocardial injury, and cardiovascular mortality/hospitalization.

Earlier reviews exclusively included RCTs with small sample sizes and high risk of bias. Our review updates the effect of exercise on several important surrogate cardiovascular outcomes, including arterial resistance and BP, by including recently published large RCTs with improved reporting of methods of randomization, allocation concealment, and blinding of outcome assessors. We present meta-analysis results of the effect of intradialytic exercise on several outcomes that have not been explored in previous studies, including LVEF and LVMI, and summarize recent data regarding antihypertensive medication use, cardiac biomarkers, and cardiovascular hospitalization and mortality. Our findings expand on the findings of the benefits of intradialytic exercise to DBP and HRV observed in previous reviews.[33,88–90]

Strengths of this review include a robust search strategy including validated high-sensitivity filters and inclusion of studies that prespecified outcomes and were performed in diverse international settings. Compared with previous reviews, our updated review includes recent studies, a broader range of cardiovascular outcomes, and studies of resistance and combined aerobic and resistance training rather than solely aerobic exercise.[30,88,90,91] Finally, we include qualitative analysis of non-RCTs to complement and support meta-analysis results.

Limitations include lack of important adherence outcomes in most studies. The number of completed exercise sessions was only reported in 44% of studies. Mean/median exercise intensity and exercise duration achieved per session was only reported in 3.1% and 15.6% studies, respectively. Earlier studies included have high risks of bias because of lack of information on randomization methods, allocation, and blinding. Many studies reported within-group change requiring estimation of SD for across group change, potentially reducing the accuracy of final meta-analysis results. Metaregression using patient and study-level factors, such as sex, exercise type, and intervention details including exercise intensity and duration, was not possible for most outcomes because of lack of data and small number of studies. Despite excluding studies with outlier results, meta-analyses for some outcomes demonstrated high heterogeneity, likely the result of heterogenous populations, interventions, and outcome measures.

As with many clinical trials in nephrology, most participants included were male (<50% female in 24 studies, ranging as low as 10%), younger (mean age 54.6 rather than 60 years) and healthier than most individuals receiving hemodialysis limiting the generalizability of our findings

in female individuals, older individuals, and those with multiple comorbidities as is common in the hemodialysis population.[91,92]

This study, which demonstrates the benefits of intradialytic exercise on outcomes associated with major adverse cardiovascular event, has both clinical and research implications. First, because most studies included in this review implemented an aerobic exercise program, clinicians should consider including intradialytic aerobic exercise programs in hemodialysis care to supplement broader treatment plans aimed at improving cardiovascular health. Furthermore, our observation that cardiovascular gains regressed with cessation of exercise participation suggests the need for long-term exercise participation to maintain these health benefits.

Future RCTs with standardized outcomes validated in kidney failure that incorporate clinical outcomes, such as cardiovascular events and hospitalization, are required. As well, the cardiovascular effects of intradialytic resistance exercise are understudied and require further characterization. Moreover, given our observations in changes to outcomes associated with myocardial stunning (*e.g.*, PWV and BP) with exercise, rigorous interventional trials are required to investigate the effect of exercise on myocardial stunning. Finally, there is an ongoing need for better information on exercise program design and implementation strategies that promote sustainability and adherence in diverse environments and populations, including incorporating individualized exercise plans or wearable technologies during hemodialysis.[93]

In conclusion, our findings suggest that intradialytic aerobic exercise effectively improves several physiological cardiovascular outcomes, including arterial resistance, BP, and HRV. Larger RCTs are required to determine whether such benefits lead to improvement in cardiovascular events and mortality in individuals receiving maintenance hemodialysis.

Disclosures

C. Bohm reports the following: Consultancy: GuidePoint; and Ownership Interest: Precision Advanced Digital Manufacturing. A.X. Garg reports the following: Employer: London Health Sciences Centre; Research Funding: Astellas and Baxter; Advisory or Leadership Role: Currently on the Editorial Boards of *American Journal of Kidney Diseases* and *Kidney International*; and Other Interests or Relationships: Served as the Medical Lead Role to Improve Access to Kidney Transplantation and Living Kidney Donation for the Ontario Renal Network (government funded agency located within Ontario Health). This position ended October 2022. C.W. McIntyre reports the following: Consultancy: Baxter, Intellomed, Sequana Medical, Spiden AG, and Vascular Dynamics; Research Funding: Baxter and Sequana; Honoraria: Baxter; and Advisory or Leadership Role: Baxter, Sequana Medical, and Spiden AG. R. Whitlock reports the following: Consultancy: Tricida Inc. All remaining authors have nothing to disclose.

Funding

Canadian Institutes of Health Research (MYG 151209). C. Bohm: Manitoba Medical Service Foundation (F.W. DuVal Clinical Research Professorship).

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Data Sharing Statement

All data are included in the manuscript and/or supporting information.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A428, http://links.lww.com/KN9/A429.

Summary of studies not included in meta-analysis
Supplemental Table 1. Search strategy for each database.
Supplemental Table 2. Risk of bias for non-RCT studies.
Supplementary Figure 1. Risk of bias for RCTs.
Supplemental Figure 2. Meta-analysis of studies examining the effect of intradialytic exercise on heart rate variability using SDNN and LF/HF.

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