Effect of exercise modality and intensity on endothelial function in patients with cardiovascular disease: a systematic review and network meta-analysis

Running title: Exercise modality and intensity on endothelial function

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Abstract

Aims: Endothelial dysfunction is a hallmark of cardiovascular disease (CVD). Exercise effectively improves endothelial function, yet the impact of different modalities and intensities remains unclear. This study evaluated the effect of aerobic (AE), resistance (RE), and combined exercise (CE), on endothelial function measured by flow-mediated dilation (FMD).

Methods: A systematic review and frequentist network meta-analysis of randomised and non-randomised trials in adults with coronary artery disease or chronic heart failure was conducted. Electronic databases were searched up to April 2025. Interventions were classified as usual care (UC), moderate-intensity AE (MAE), high-intensity interval AE (HIIE), moderate-intensity RE (MRE), high-intensity RE (HRE), moderate-intensity CE (MCE), and high-intensity CE (HCE). Mean differences (MD) with 95% confidence intervals (CI) were used as effect size index, and interventions ranked using surface under the cumulative ranking curve (SUCRA).

Results: Thirty-seven studies (80 groups; n = 6818) were included. Compared with UC, MAE (2.04%; 95% CI: 1.01–3.07), HIIE (3.47%; 95% CI: 2.02–4.92), MCE (2.71%; 95% CI: 0.05–5.36), and HCE (8.25%; 95% CI: 3.18–13.32) significantly improved brachial FMD, whereas MRE did not. HIIE outperformed MAE (1.43%; 95% CI: 0.09–2.78). Although HCE showed the highest surface under the cumulative ranking curve (SUCRA: 98.2%), this relied on a single group. Crucially, sensitivity analyses confirmed HIIE as the most robust high-performing intervention (84.0%) compared to MRE (61.6%) and MCE (61.3%).

Conclusion: Exercise significantly enhances endothelial function in in patients with CVD. HIIE emerged as the most robust and evidence-based modality, demonstrating superior efficacy over moderate continuous exercise. While high-intensity combined protocols (HCE) show significant theoretical potential, randomised trials are urgently needed to confirm their efficacy. Current evidence supports HIIE as a primary strategy for vascular adaptation in cardiac rehabilitation.

Lay Summary

This network meta-analysis confirms that structured exercise training effectively improves endothelial function in patients with cardiovascular disease.

- High-intensity interval training offers the most robust benefits across different ages and conditions, proving superior to moderate-intensity continuous exercise.
- A progressive training strategy is recommended to maximise long-term results, starting with moderate exercise for conditioning and advancing to high-intensity or resistance exercise.

Key words: endothelial-dependent dilation; exercise modality; FMD; high-intensity interval exercise; cardiac rehabilitation; cardiovascular disease.

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality globally, accounting for 32% of deaths worldwide [1,2]. It also contributes substantially to morbidity, impairs quality of life, and imposes a significant economic burden on healthcare systems [3]. A hallmark of CVD is endothelial dysfunction, characterised by impaired vasodilation due to reduced nitric oxide (NO) bioavailability, promoting a pro-inflammatory and pro-thrombotic state [4]. As a key regulator of vascular homeostasis, endothelium dysfunction contributes to the pathophysiology of various cardiovascular conditions, including coronary artery disease (CAD), and chronic heart failure (CHF) [5-7]. Flow-mediated dilation (FMD) is the most widely used method for assessing endothelial function. It quantifies the percentage increase in arterial diameter—typically brachial artery—in response to reactive hyperaemia. This vasodilation, triggered by shear stress-induced NO release, reflects endothelium-dependent function. To distinguish this from smooth muscle responsiveness, nitrate-mediated dilation (NMD) is used as a complementary measure, assessing endothelium-independent vasodilation via exogenous NO administration. Notably, FMD is recognised as an independent predictor of cardiovascular events in both asymptomatic individuals and patients with CVD [8,9].

Exercise is one of the most effective interventions for improving endothelial function. Cardiac rehabilitation (CR) offers a structured and cost-effective framework for delivering these benefits, with class I, level A recommendation for all patients with CAD or CHF, supported by strong evidence of reduced cardiovascular morbimortality and readmissions [10-12]. Exercise has also been shown to mitigate age-related vascular deterioration in healthy individuals [13] and restore endothelial function in CVD [14]. Exercise-induced enhancements in flow-mediated dilation (FMD) have been consistently observed across a wide range of populations, including those with cardiovascular risk factors [14], peripheral artery disease [15], CAD [16,17], CHF [18], and heart transplant recipients [19].

These vascular adaptations have been reported across different exercise modalities, highlighting the importance of exercise prescription in clinical practice. While aerobic exercise (AE) remains the most commonly prescribed exercise modality in CR, resistance exercise (RE) and combined aerobic and resistance exercise (CE) are also employed [20]. AE comprises moderate-intensity aerobic exercise (MAE) or high-intensity interval exercise (HIIE**)** [20]. MAE is characterised by long-term exercise bouts (e.g., 30 min) performed at moderate intensity (e.g., between the first [VT1] and second ventilatory thresholds [VT2] and can be carried out continuously or intermittently [21]. Conversely, HIIE comprises alternating periods of high-intensity AE (e.g., > 85% peak oxygen uptake [VO_2 peak] or > VT2) with active (e.g. < 60% VO_2 peak or < VT1) or passive recovery of shorter, equal, or longer duration [22]. RE intensity is defined as the percentage of one-repetition maximum (1RM), which represents the maximum load a person can lift once with proper technique. According to the American College of Sports Medicine, moderate-intensity resistance exercise (MRE) involves loads below 70% 1RM, whereas high-intensity resistance exercise (HRE) is performed at or above 70% 1RM [23,24], a classification is grounded in the physiology of motor unit recruitment

In recent years, HIIE has gained interest as a time-efficient and potentially superior AE method for CVD [25]. Previous meta-analyses have shown that HIIE elicits greater improvements in endothelial function than MAE across various clinical populations [26,27]. In patients with CHF, HIIE has been associated with a 2.4% increase in FMD [28]. In contrast, a separate meta-analysis in patients with CVD reported no overall superiority of HIIE over MAE in improving endothelial function [29]. However, subgroup analyses within that study revealed that long-interval HIIE (i.e., > 1 min) significantly improved brachial FMD compared to MAE, whereas short-interval HIIE (i.e., ≤ 1 min) showed no such benefit [29]. These findings underscore the importance of considering the duration of the high-intensity bouts when assessing AE-induced effects on endothelial function.

Regarding exercise modality, a meta-analysis in individuals at elevated cardiovascular risk demonstrated that AE, RE, and CE all significantly improved FMD [14]. Chen, Gao [30] reported that CE yielded superior outcomes compared to RE alone in patients with CAD and CHF. To date, no meta-analyses have examined the influence of RE intensity on FMD in patients with CVD. Moreover, in prior meta-analyses, AE intensity (e.g., MAE or HIIE) has only been considered when AE was the primary intervention, whereas AE intensity was not accounted for when CE was implemented [31]. Given the range of exercise modalities and intensities applicable within CR programmes, a more comprehensive analytical framework is required. Traditional pairwise meta-analyses are inherently limited in this context; thus, a network meta-analysis is warranted.

This systematic review and network meta-analysis aims to bridge this gap by evaluating the effects of exercise on endothelial function in patients with CVD. Specifically, it seeks to evaluate how variations in exercise modality, intensity, and duration influence endothelial adaptations, offering clinicians an evidence-based framework for optimising exercise prescriptions to maximise vascular benefits.

Method

Study design and protocol registration

This systematic review and network meta-analysis (NMA) was prospectively registered on the PROSPERO database (CRD42025641257). The protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines for network meta-analysis (PRISMA-NMA) [32]. A summary of the study design and main results can be found in the Graphical Abstract.

Data search

Electronic searches were performed in PubMed, Embase, and Web of Science Core Collection without language restriction, up to April 2025. Free-text terms were used to structure the searches, based on participants, interventions, and outcomes, and were applied to titles, abstracts, and keywords when available. Conference proceedings were also searched in the Web of Science Core Collection. Authors of relevant abstracts were contacted to obtain missing information; if no response was received, the abstract was excluded. In addition, systematic reviews, meta-analyses, and the reference lists of included studies were manually reviewed to identify further eligible studies. To identify unpublished or ongoing studies meeting the inclusion criteria, corresponding authors were also contacted by email.

Study selection

Eligibility criteria were established according to the PICOS (participants, interventions, comparisons, outcomes, and study design) guideline as follows: (a) participants: Adult patients (≥18 years), both male and female, with CVD, specifically CAD and CHF with either preserved (HFpEF; left ventricular ejection fraction [LVEF] $\geq$ 50%) or reduced (HFrEF; LVEF $<$ 50%). Those with implantable devices were also included. Conversely, patients with congenital cardiomyopathy or those who had undergone heart transplantation were excluded; (b) interventions: The main classification of the interventions was: (1) usual care (UC) (i.e., non-exercise groups); (2) MAE (i.e., AE performed below the VT2; (3) HIIE (i.e., AE bouts performed above VT2); (4) MRE (i.e., RE performed below 70% 1RM); (5) HRE (i.e., RE performed equal or above 70% 1RM); (6) moderate-intensity combined exercise (MCE) (i.e., MRE plus MAE); and (7) high-intensity combined exercise (HCE) (i.e., MRE plus HIIE). The classification of exercise intensity domains was based on physiological thresholds and relative intensity percentages (aligned with ACSM/ESC guidelines), as detailed in Table S1 [33]. Additionally, a secondary classification considering the length of high-intensity bouts (i.e., short HIIE [i.e., ≤ 1 min] and long HIIE [i.e., > 1 min]) was established. Exercise modality and intensity were carefully evaluated to ensure accurate classification. Studies involving other forms of exercise (e.g., yoga, pilates, stretching) were excluded. However, studies combining the defined exercise interventions with adjunct treatments (e.g., nutritional or psychological counselling, inspiratory muscle training, and blood flow restriction) were included. Only studies lasting at least four weeks were considered. Both supervised and unsupervised exercise interventions were included; (c) comparisons: Only studies comparing at least two of the predefined interventions were included; (d) outcomes: The primary outcome was endothelial function, measured by FMD via ultrasound in upper (e.g., brachial, radial) and/or lower (e.g., femoral, tibial) limb arteries, reported as relative (%) or absolute (mm) changes. Additional outcomes included endothelial-independent dilation, measured by NMD; (e) study design: Prospective randomised and non-randomised studies with two or more arms were included. Observational and retrospective studies were excluded.

Data extraction and coding study characteristics.

Two authors independently assessed all studies for inclusion. Data extraction was performed independently by two authors using a standardised form. Disagreements were resolved by consensus, or by involving a third reviewer when necessary. Extracted information included: (a) study characteristics: Year of publication and study design (i.e., randomised or non-randomised studies); (b) patient characteristics: Sample size, sex, age, baseline FMD, baseline cardiorespiratory fitness (CRF), medication, and pathology; (c) intervention characteristics: Setting (i.e., home-based, supervised, or mixed), training frequency, programme duration, and detailed session characteristics (e.g., modality, intensity, duration, and repetitions); (d) endothelial function assessment characteristics: Artery assessed, cuff placement (i.e., distal or proximal to the imaged artery), occlusion pressure, occlusion length, hyperaemia window, and device; and (e) statistical information: Mean and standard deviation (*SD*) pre- and post-intervention. Finally, adverse events and drop-outs across interventions were also extracted.

Dealing with missing data

When necessary, corresponding authors were contacted to retrieve missing data. Studies with unavailable information after contact attempts were excluded.

Methodological quality assessment

Methodological quality was assessed using the TESTEX scale, a 15-point tool specifically designed for exercise training studies. This tool evaluates study quality and reporting (see supplementary material [Table S2]) [34]. Based on total scores, studies were categorised as "excellent" (12–15 points), "good" (9–11 points), "fair" (6–8 points), or "poor" (<6 points). Two authors independently rated each study; disagreements were resolved by consensus or by involving a third reviewer.

Statistical analyses

Mean differences (MD) with 95% confidence intervals (CI) were used as the effect size index. Separate meta-analyses were conducted for each outcome (i.e., FMD and NMD). The artery measured was also considered to conduct network meta-analyses (e.g., brachial FMD). Network evidence plots were created to visualise relationships between interventions: nodes represented interventions, with node size proportional to sample size, and connecting lines indicating direct comparisons (with line thickness proportional to the number of comparisons). Closed loops allowed for mixed-treatment comparisons (direct and indirect). Consistency between direct and indirect comparisons was evaluated globally (Wald test) and locally (node-splitting method). Depending on results, either consistent or inconsistent models were applied. Random-effects multivariate network meta-analyses were conducted within a frequentist framework. Interventions were ranked based on the surface under the cumulative ranking curve (SUCRA). Additionally, to avoid over-reliance on mean ranks and better reflect statistical uncertainty, we calculated the cumulative probability of each intervention being among the top two most effective treatments [35]. On the other hand, we investigated the influence of potential effect modifiers on the relative treatment effects by fitting post hoc network meta-regression models within the consistency framework. We assessed both quantitative covariates (i.e., intervention length, frequency, mean age, and baseline CRF) and dichotomous characteristics (i.e., pathology [CAD vs. CHF], supervision [yes vs. no], distal occlusion [yes vs. no], and co-interventions [yes vs. no]). On the other hand, to assess the robustness of the findings, we performed sensitivity analyses by removing nodes with n = 1, non-randomised studies, and poor methodological quality studies based on the TESTEX scale results. Finally, the comparison-adjusted funnel plot and the Egger test were used to evaluate the potential for publication bias and small-study effects for the primary network meta-analysis (i.e., brachial FMD) [36]. All analyses were conducted for the primary and secondary treatment classifications and performed using Stata software (version 16; StataCorp LLC, College Station, TX, USA). Additionally, the certainty of the evidence for the primary outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [37].

Results

Study selection

The study selection process is shown in Figure 1. Briefly, 6818 studies were retrieved after removing duplicates (n = 3158). After reviewing title and abstract, 44 references were considered eligible for full-text analysis, of which, 37 were included in the qualitative synthesis [17,38-73] and seven excluded (see Figure 1 for exclusion reasons). No additional studies were identified via other sources. Therefore, despite efforts were made, unpublished studies were not included.

*****Insert Figure 1 near here**

Study and participant characteristics

Study and participant characteristics can be found in Table S3. The included studies were published between 2001 and 2023. Thirty (81%) studies were randomised [17,38-42,44-47,49-51,53,56,58-68,70-73] and seven (19%) non-randomised [43,48,52,54,55,57,69]. Regarding sex, 31 (84%) studies recruited both male and female patients [17,38,39,42-47,50-52,54-72], while six (16%) enrolled exclusively male patients [40,41,48,49,53,73]. Out of all the included studies, 19 (51%) included patients with CAD [17,44-48,52,55-57,60,61,64,65,67,68,70-72], 15 (41%) patients with HFrEF [38,40-43,49-

[51,53,54,59,62,63,69,73], two (5%) patients with HFpEF [39,58], and one (3%) recruited both HFrEF and HFpEF [66]. Group sample size ranged between six and 100 patients. The mean ± *SD* age was 60.9 ± 5.5 years (min – max: 52.0 – 76.5), while CRF, which was reported in 58 groups, was 19.1 ± 4.3 $ml^{-1}\cdot kg^{-1}\cdot min$ (min – max: 13.0 – 32.2).

Intervention characteristics and outcomes measured are reported in Table S4. Regarding exercise intervention characteristics, 23 (62%) studies conducted a supervised-exercise programme [17,38,40-46,52-56,59-61,63,66-68,72,73], one (3%) a home-based exercise programme [49], four (11%) combined supervised and home-based exercise sessions [47,50,64,65], and nine (24%) did not report this information [39,48,51,57,58,62,69-71]. The intervention duration ranged between four and 48 weeks, while training frequency ranged between two and seven sessions per week. Eighty groups were obtained from the 37 included studies, of which, 27 (34%) were UC groups, 31 (39%) MAE groups, 14 (17%) HIIE groups, three (4%) MRE groups, four (5%) MCE groups, and one (1%) HCE group. None of the included studies used HRE. Among the 14 HIIE groups, 10 (71%) used long HIIE and four (29%) short HIIE.

Regarding outcomes, all included studies measured endothelial-dependent dilation (i.e., FMD), while 18 (49%) also measured endothelial-independent dilation (i.e., NMD) [17,40,41,43,45-47,51-55,60,64,68,71,72]. Thirty-one (84%) studies measured endothelial function in the brachial artery [17,38-42,44-49,53-58,60,61,63-73], two (5%) in the brachial and tibial arteries [52,59], one (3%) in the brachial and femoral arteries [43], two (5%) in the radial artery [50,51], and one (3%) in the femoral artery [62]. Nineteen (51%) studies positioned the cuff distal to the evaluated artery [38,41,42,46,49,51,53,56-60,63,64,67-72], four (11%) proximal [44,55,61,73], and 14 (38%) did not specifically disclose this information [17,39-41,43,47,48,50,52,54,62,65,66,68]. Finally, adverse events and drop-outs across studies can be found in Table S5. No major exercise-related adverse events were reported across interventions and drop-out rates ranges from 0% to 31.7% with no consistent pattern favouring any exercise modality.

Methodological quality assessment

The results of the methodological quality assessment are reported in Table S6. The mean ± *SD* TESTEX score was 7.6 ± 2.3 (min – max: 3 – 11). Reviewers judged six studies (16%) to have poor quality [42,48,49,51,63,73], 16 (43%) to have fair quality [39,43,46,47,52,54-57,59,64,65,68-70,72], and 15 (40%) to have good quality [17,38,40,41,44,45,50,53,58,60-62,66,67,71].

A domain-level analysis revealed specific deficits. regarding randomisation, the generation of the random sequence and allocation concealment were not specified in 65% and 62% of the studies, respectively. Blinding of the outcome assessor was not implemented in 49% of the trials. Regarding attrition, intention-to-treat analysis was absent in 51% of the studies that reported experimental mortality. Furthermore, activity monitoring in the control group and adjustment of relative exercise intensity were not reported in 70% and 84% of the studies, respectively.

Network meta-analysis

Brachial flow-mediated dilation

The specific characteristics of brachial FMD measurement can be found in Table S7. The assumption of transitivity was supported by the balanced distribution of baseline characteristics and medication across intervention nodes (Table S8). Consistent with this, the results of the global inconsistency test did not reach statistical significance (p = .412). Additionally, the node-splitting results did not show statistical significance ($p \geq .219$) (see Table S9). However, no direct evidence was available for the comparisons of HIIE vs. MCE, MRE vs. HCE, and MCE vs. HCE. Therefore, estimates for these pairs rely exclusively on indirect evidence. Figure 2 depicts the network diagram for FMD for the primary treatment classification.

*****Insert Figure 2 near here**

The results of the comparative network meta-analysis for the primary classification for relative brachial FMD can be found in Figure 3. We found that MAE (2.04%: 95%CI = 1.01, 3.07), HIIE (3.47%: 95%CI = 2.02, 4.92), MCE (2.71%: 95%CI = 0.05, 5.36), and HCE (8.25%: 95%CI = 3.18, 13.32) improve brachial FMD to a greater extent than UC. Additionally, when comparing exercise treatments, the results showed that HIIE is better than MAE (1.43%: 95%CI = 0.09, 2.78), as well as that HCE better than MAE (6.21%: 95%CI = 1.17, 11.26) to enhance brachial FMD. There were no other significant differences between exercise treatments. The cumulative probability of each treatment for the network of FMD is shown in Figure 4.

Based on SUCRA values, the intervention hierarchy in the primary model was ordered as follows: HCE (98.2%), HIIE (67.5%), MCE (50.2%), MRE (49.9%), MAE (33.1%), and UC (1.2%). Additionally, HCE displayed the highest certainty, with a 97.8% likelihood of ranking in the top two. Among the standard exercise modalities, HIIE presented the most favorable profile, with a 51.9% probability of ranking in the top two, compared to MRE (26.0%) and MCE (23.8%). Notably, MAE had a near-zero probability (0.5%) of being a top-tier intervention. However, these rankings must be interpreted with caution; the confidence intervals for the mean differences overlapped substantially between the active treatments (see Figure 3), suggesting that while HIIE is the leading candidate based on probability, the statistical distinction between HIIE, MRE, and MCE entails a degree of uncertainty.

The results of univariate network meta-regressions are shown in Table S10. Between-study variance (τ^2) ranged from 5.46 to 6.49, comparable to the main consistency model (6.03), suggesting that these factors are not major drivers of global heterogeneity. However, significant treatment-specific interactions were identified: Pathology moderated MAE outcomes (p = .016), with smaller improvements in CHF patients than in CAD patients (–2.42%: 95% CI = –4.40, –0.45). For HIIE, older age was associated with larger improvements (p = .021; 0.28%: 95% CI = 0.04, 0.52), while supervision was associated with smaller effect sizes (p = .022; –6.39%: 95% CI = –11.87, –0.91).

The robustness of this hierarchy was assessed through three sensitivity scenarios (results detailed in Table S11). The primary findings remained largely consistent across all analyses. First, the exclusion of studies with poor methodological quality did not alter the primary hierarchy. Second, when the influential HCE node was removed, HIIE emerged as the highest-ranked intervention (SUCRA 84.0%), followed by MRE (61.6%) and MCE (61.3%). Finally, after removing non-randomised studies, the results showed a slight shift in the middle rankings; while HCE remained dominant (96.3%), MCE (62.7%) showed a marginally higher SUCRA value than HIIE (59.6%). Importantly, HIIE consistently achieved higher rankings than MAE across every sensitivity scenario (SUCRA range for HIIE: 59.6% to 84.0% vs MAE: 31.9% to 41.5%), indicating a robust probabilistic advantage of high-intensity intervals over moderate continuous aerobic exercise.

Regarding publication bias, visual inspection of the funnel plot revealed a generally symmetrical distribution of studies around the zero line (Figure S1). This was confirmed by the statistical test, which showed no significant evidence of small-study effects or publication bias across the network (p = .322).

The certainty of evidence was assessed using the GRADE framework (Table S12). For the primary comparisons involving substantial data (i.e., MAE vs UC, HIIE vs UC, and the head-to-head comparison HIIE vs MAE), the certainty was rated as moderate. These ratings were downgraded due to serious risk of bias, primarily driven by deficits in allocation concealment and the lack of intention-to-treat analyses. For comparisons with limited data or wide confidence intervals (e.g., HCE vs MAE, and comparisons involving MRE or MCE), the certainty was rated as low due to the combination of risk of bias and imprecision.

*****Insert Figures 3 and 4 near here**

The inconsistency analysis, network diagram, and comparative network meta-analysis for the secondary classification for relative brachial FMD can be found in Table S13, Figure S2, and Figure S3, respectively.

Network consistency assessments revealed no significant discrepancies between direct and indirect evidence in the closed loops available (p > .050). Notably, direct evidence was lacking for short vs long HIIE and short HIIE vs UC. Estimates for these pairs, as well as for HCE vs MCE/MRE, rely exclusively on indirect evidence.

Regarding exercise intervention comparisons, results showed that only long HIIE (MD = 5.69%; 95% CI = 0.02, 11.37) and MCE (MD = 1.59%; 95% CI = 0.04, 3.15) were significantly better than MAE for improving brachial FMD. No statistically significant differences were found between long and short HIIE (MD = 5.01%; 95% CI = –1.28, 11.29).

When specifically analysing the influence of interval duration, long HIIE showed a superior probability profile compared to short HIIE. The likelihood of being among the top two best interventions was 41.3% for long HIIE versus 25.0% for short HIIE. In fact, short HIIE clustered with moderate-intensity protocols, suggesting that shortening the intervals may dilute the superior efficacy observed with longer high-intensity bouts.

Brachial nitroglycerin-mediated dilation

The inconsistency analysis, network diagram, and comparative meta-analyses for the primary classification for relative brachial NMD can be found in Table S14, Figure S4, and Figure S5, respectively. No statistically significant differences were found between treatments for enhancing NMD. SUCRA plots for all treatments for NMD are showed in Figure S6.

Discussion

The current systematic review with network meta-analysis was conducted to evaluate the effects of exercise, while consider modality, intensity, and high-intensity bout duration on endothelial function in patients with CVD. The majority of studies performed supervised AE as training modality and used MAE as exercise method, followed by long and short HIIE. All studies measured FMD, mainly in the brachial artery, positioning the cuff distal to assessed artery.

Our key findings demonstrate that all exercise modalities, except for MRE, improve brachial FMD more than UC. This finding should be interpreted cautiously, as the mean effect size for MRE was comparable to that of other modalities, but the wide 95% CI suggests a lack of statistical power due to the small number of studies evaluating MRE. Moreover, previous research in healthy young men has indicated that shorter durations of MRE (e.g., six or 12 weeks) [78] are insufficient to improve FMD, whereas longer durations (e.g., six months) do confer a benefit [79]. In line with this, all three MRE studies included in our meta-analysis had intervention durations of less than twelve weeks, which may partly explain the absence of a significant effect [62,66,70]. These findings suggests that a more extended period of MRE training might be necessary for FMD improvement, potentially implying a distinct time course of FMD adaptation between resistance and aerobic training, though this requires further confirmation. While Ashor, Lara [14] identified a dose-dependent relationship between AE intensity and endothelial function improvement, enhancements in FMD following RE appear to be predicted more by exercise frequency than intensity. Therefore, heterogeneity in RE duration and frequency across studies could account for the absence of statistically significant differences in FMD compared to usual care within our analysis.

The mechanisms responsible for improved vascular function with exercise include hemodynamic stimuli such as shear stress, as well as improvements in autonomic regulation, oxidative stress, and modulation of cardiovascular risk factors, including blood pressure and lipid profiles [80-82]. Among these, increased shear stress—the frictional force exerted by flowing blood on the vascular endothelium—is a central mediator of endothelial health [83]. Physical activity elevates shear stress, promoting NO release, a potent vasorelaxant. In CAD patients, four weeks of supervised AE increased endothelial nitric oxide synthase (eNOS) expression and Akt-dependent phosphorylation at serine 1177 in internal mammary artery tissue sampled during bypass surgery, with phospho-eNOS levels directly correlating with improved FMD [84]. The pivotal role of shear stress is further supported by studies where its attenuation abolished FMD improvements. For instance, Tinken, Thijssen [85], conducted an eight-week bilateral handgrip exercise intervention where shear stress was selectively attenuated in one arm using a cuff; improvements in endothelial function were observed only in the uncuffed arm. Repeated exposure to elevated shear stress not only improves NO bioavailability but also upregulates atheroprotective endothelial gene expression [85-87]. Exercise also modulates oxidative stress through redox-dependent mechanisms. Excessive reactive oxygen species (ROS) production impairs NO bioavailability [88]. Although a single session of AE [89] or RE [90] can increase ROS production, regular exercise training has been shown to enhance endogenous antioxidant capacity by upregulating extracellular superoxide dismutase (SOD) expression, thereby reducing ROS accumulation and preserving NO bioactivity [91]. Supporting this, Donato, Uberoi [92] demonstrated that antioxidant administration pre-training improved FMD in sedentary older men, suggesting a redox-sensitive mechanism.

Importantly, the dissociation between enhanced FMD and unchanged NMD observed in our meta-analysis provides mechanistic insight into the site-specificity of these exercise-induced adaptations. FMD reflects endothelium-dependent vasodilation, predominantly mediated by NO release in response to shear stress, whereas NMD assesses endothelium-independent smooth muscle responsiveness to exogenous NO donors [75,93]. The paired observation of FMD improvement with stable NMD indicates that the vascular benefits of exercise training in patients with CVD are localised to the endothelium, whilst smooth muscle vasodilatory capacity remains unaltered. The stability of NMD across the 4-12 weeks intervention durations included in this meta-analysis is biologically plausible, as exercise-induced vascular adaptations follow a temporal hierarchy whereby functional endothelial changes precede structural vascular remodeling [94]. Changes in smooth muscle structure and function—including alterations in collagen-to-elastin ratio, intima-media thickness, and receptor sensitivity—require more prolonged stimuli and may not manifest within typical cardiac rehabilitation programme durations [95]. Collectively, these findings reinforce that the primary mechanism underlying exercise-induced vascular improvement in CVD patients is enhanced endothelium-dependent NO bioavailability, mediated through shear stress-induced eNOS upregulation and phosphorylation, coupled with improved redox balance—whilst vascular smooth muscle function remains preserved. Although the majority of exercise types improved endothelial function, the magnitude of this effect varied depending on exercise intensity and modality. Regarding AE intensity, HIIE was significantly more effective than MAE in improving brachial FMD (1.43%; 95%CI = 0.09, 2.78). This result is reinforced by our sensitivity analyses, which demonstrated that HIIE consistently outranked MAE across all methodological scenarios examined, whether excluding studies of poor quality, removing the influential HCE node, or restricting analysis to randomised trials. These findings suggest that the superiority of HIIE over MAE is not an artefact of specific methodological choices but rather a consistent signal across the evidence base, positioning HIIE as a robust evidence-based alternative to continuous training. The superior effect of HIIE has been replicated across diverse populations, including patients with CHF [77], individuals with type 2 diabetes or obesity [27], and at risk and healthy cohorts [26]. A possible explanation for these greater benefits lies in the fact that shear stress responses vary according to exercise modality, intensity, and the vascular territories involved [96]. Higher aerobic exercise intensities typically induce greater shear stress than moderate aerobic intensities, thereby enhancing NO production and potentially accounting for the superior endothelial effects observed with HIIE [97-99]. The result of our secondary analysis suggests that the duration of HIIE intervals also plays a critical role in vascular adaptation. Long-interval HIIE was found to be significantly more effective than MAE, aligning with our previous findings, which demonstrated that long-interval HIIE improved brachial FMD compared to MAE (1.46%; 95% CI = 0.35–2.57), whereas short-interval HIIE conferred no such benefit [29]. However, no statistically significant difference was observed between long and short HIIE in the current network meta-analysis. This may reflect limited statistical power or overlapping confidence intervals, rather than the absence of a true effect. Such limitations are inherent to network meta-analytic approaches, which synthesise both direct and indirect evidence from a broad range of studies, many of which may not have directly compared HIIE interval durations [38]. While this methodology enhances generalisability and allows for comprehensive comparisons across multiple interventions, it may also attenuate effect estimates and reduce sensitivity to detect subtle differences. Therefore, the nuanced impact of HIIE interval duration on endothelial function merits further investigation through well-powered, direct head-to-head trials.

Regarding exercise modality, we found that HCE appeared to yield even greater vascular benefits compared to MAE and HIIE. This was further supported by SUCRA rankings, which indicated that HCE had the highest probability of being the most effective intervention (98.2%), followed by HIIE (67.5%). These results suggest that combining MRE and HIIE may confer synergistic vascular benefits. Combined training may activate complementary pathways that enhance NO synthesis, which may explain the superior endothelial benefits of HCE protocols [85]. One proposed mechanism involves transient skeletal muscle ischaemia during contraction, followed by reactive hyperaemia upon relaxation, which markedly increases shear stress and stimulates endothelial function [85]. However, this result warrants careful consideration, as our findings are based on a single study evaluating HCE, and previous evidence has not consistently confirmed that CE offers superior improvements in endothelial function compared to single-modality exercise. For instance, a network meta-analysis by Chen, Gao [30] reported that MAE had the highest probability of being the best intervention for improving FMD in middle-aged and older adults (SUCRA = 68.9%), followed by HIIE, MRE, and MCE. Similarly, a randomised controlled trial in individuals with prehypertension or hypertension showed comparable improvements in FMD across exercise modalities, with MCE offering no statistically superior benefit, despite numerically higher gains in some cases [100]. Conversely, other studies have found CE to be particularly effective in specific populations, such as individuals with type 2 diabetes [101] and those recovering from COVID-19-related endothelial dysfunction [102]. These discrepancies likely reflect heterogeneity in exercise protocols (e.g., intensity, duration, and frequency), participant characteristics (e.g., age, comorbidities, and baseline vascular function), or methodological differences across studies. Moreover, most previous studies have not adequately considered or reported the intensity of the aerobic component within CE protocols, limiting the interpretation of their findings. While MCE may not always yield the largest improvements in FMD, it consistently offers broader cardiovascular benefits, including enhanced blood pressure control, increased CRF, muscular strength, and lean body mass—factors relevant for overall cardiovascular risk reduction [103,104].

Our exploratory meta-regression analyses revealed treatment-covariate interactions that may inform individualised exercise prescription. MAE yielded smaller improvements in patients with CHF compared to CAD suggesting that moderate-intensity protocols may be insufficient to overcome the more severe endothelial dysfunction in CHF [105]; in contrast, HIIE efficacy was not moderated by pathology, implying preserved benefit regardless of underlying cardiac condition. The positive association between age and HIIE-induced FMD improvements warrants particular attention. Older patients, who typically exhibit more pronounced baseline endothelial dysfunction [106], may paradoxically represent the subgroup with the greatest potential for vascular benefit from HIIE [107]. This finding challenges the conventional tendency to prescribe conservative, low-to-moderate intensity regimens for older adults and supports the growing body of evidence that appropriately supervised HIIE can be both safe and particularly effective in this population [108,109]. The paradoxical observation that supervised HIIE yielded smaller effect sizes than unsupervised programmes is counterintuitive and merits cautious interpretation. This finding may reflect residual confounding, rather than a true detrimental effect of supervision, and requires prospective validation given the post-hoc nature of these analyses [110].

The findings of this network meta-analysis carry significant clinical implications for the prescription of exercise in CR programmes. While AE is a cornerstone of current CR guidelines, our results suggest that the intensity and modality of exercise play a critical role in optimising endothelial benefits [111,112]. The superior effectiveness of HIIE in improving FMD suggests that this modality should be strongly considered in exercise prescriptions for patients with CVD. Importantly, HIIE has also been shown to be more cost-effective than MAE. This evidence provides an updated framework for clinicians, indicating that pushing beyond traditional MAE could lead to greater vascular adaptations. Incorporating RE alongside AE, especially at higher intensities, might offer additional benefits for endothelial health. These findings support a shift towards more tailored and intensified exercise prescriptions within CR to maximise the physiological benefits.

Strengths and limitations

To the best of our knowledge, this is the first systematic review and network meta-analysis to address the effect of exercise on endothelial function in patients with CVD. This methodological approach is a significant strength, as it allowed for simultaneous comparisons of multiple exercise interventions and their intensities, providing a more comprehensive understanding of their relative effectiveness than traditional pairwise meta-analyses. This is also the first meta-analysis to account for exercise intensity in the context of CE, and the first to explore the influence of high-intensity interval duration on vascular outcomes.

On the contrary, several limitations warrant consideration. First, substantial heterogeneity in exercise protocols and methodological flaws identified by TESTEX (e.g., lack of allocation concealment and intention-to-treat analyses) resulted in a low-to-moderate certainty of evidence according to GRADE. Second, the network structure contained sparse nodes; notably, HCE relied on a single intervention group, and comparisons regarding HIIE duration were derived exclusively from indirect evidence, necessitating cautious interpretation. Third, meta-regression analyses were post-hoc and restricted to univariate models due to collinearity. Finally, although cardiovascular medication was generally balanced, residual confounding cannot be fully excluded; a detailed analysis of the potential confounding effect of cardiovascular medications is provided in the supplementary material (see Supplementary Material).

Conclusion

This network meta-analysis confirms that structured exercise training improves endothelial function. HIIE appears to offer the most robust benefits, being significantly superior to moderate-intensity continuous training. While HCE showed the largest effect size, these findings rely on indirect evidence from a single group and must be viewed as preliminary. Specifically, the comparative efficacy between long and short HIIE remains inconclusive due to the absence of head-to-head trials. Exploratory post-hoc analyses further suggest that efficacy may be modulated by clinical characteristics; notably, MAE showed reduced benefits in patients with CHF compared to CAD, whereas high-intensity protocols appeared consistent across pathologies and particularly beneficial for older adults. Consequently, these findings support the integration of HIIE into CR programmes as a time-efficient alternative or complement to MAE. Future research should prioritize high-quality randomised trials to validate the promising potential of HCE, explore underrepresented interventions such as HRE, and directly compare long versus short HIIE protocols. If the ultimate goal is lifelong exercise adherence, a pragmatic strategy would be to initiate training with MAE as a conditioning phase, then progressively introduce HIIE and resistance exercise to sustain the training stimulus.

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Conflict of interest

The authors declare that they have no conflicts of interest related to this work.

Author Contributions

LF.K., A.M-R., and S.B. designed the systematic review, established the electronic search equation, and performed the searches. S.B., L.FK and A.M-R. performed the study selection, S.B., L.F.K, and A.M-R. carried out the data extraction, and A.M-R, and J.M.S performed the risk of bias assessment. A.M-R., C.B-P., and N.S-R. carried out analyses, and A.M-R. and L.F.K. wrote the first draft of the manuscript. C.B-P., N.S-R., and J.M.S. critically revised the content of the manuscript and wrote the final version of the manuscript, which was finally approved by all authors. All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

The dataset generated from the current study is available from the corresponding author on reasonable request.

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Figure legends

Figure 1. Flow chart of the study selection process.

Figure 2. Network evidence map for the primary classification for flow-mediated dilation. HCE, high-intensity combined exercise; HIIE, high-intensity interval exercise; MAE, moderate-intensity aerobic exercise; MCE, moderate-intensity combined exercise; MRE, moderate-intensity resistance exercise; UC, usual care.

Figure 3. Interval plot for the primary exercise classification for flow-mediated dilation. HCE, high-intensity combined exercise; HIIE, high-intensity interval exercise; MAE, moderate-intensity aerobic exercise; MCE, moderate-intensity combined exercise; MRE, moderate-intensity resistance exercise; UC, usual care.

Figure 4. Plots of the surface under the cumulative ranking curves for all treatments. HCE, high-intensity combined exercise; HIIE, high-intensity interval exercise; MAE, moderate-intensity aerobic exercise; MCE, moderate-intensity combined exercise; MRE, moderate-intensity resistance exercise; UC, usual care.

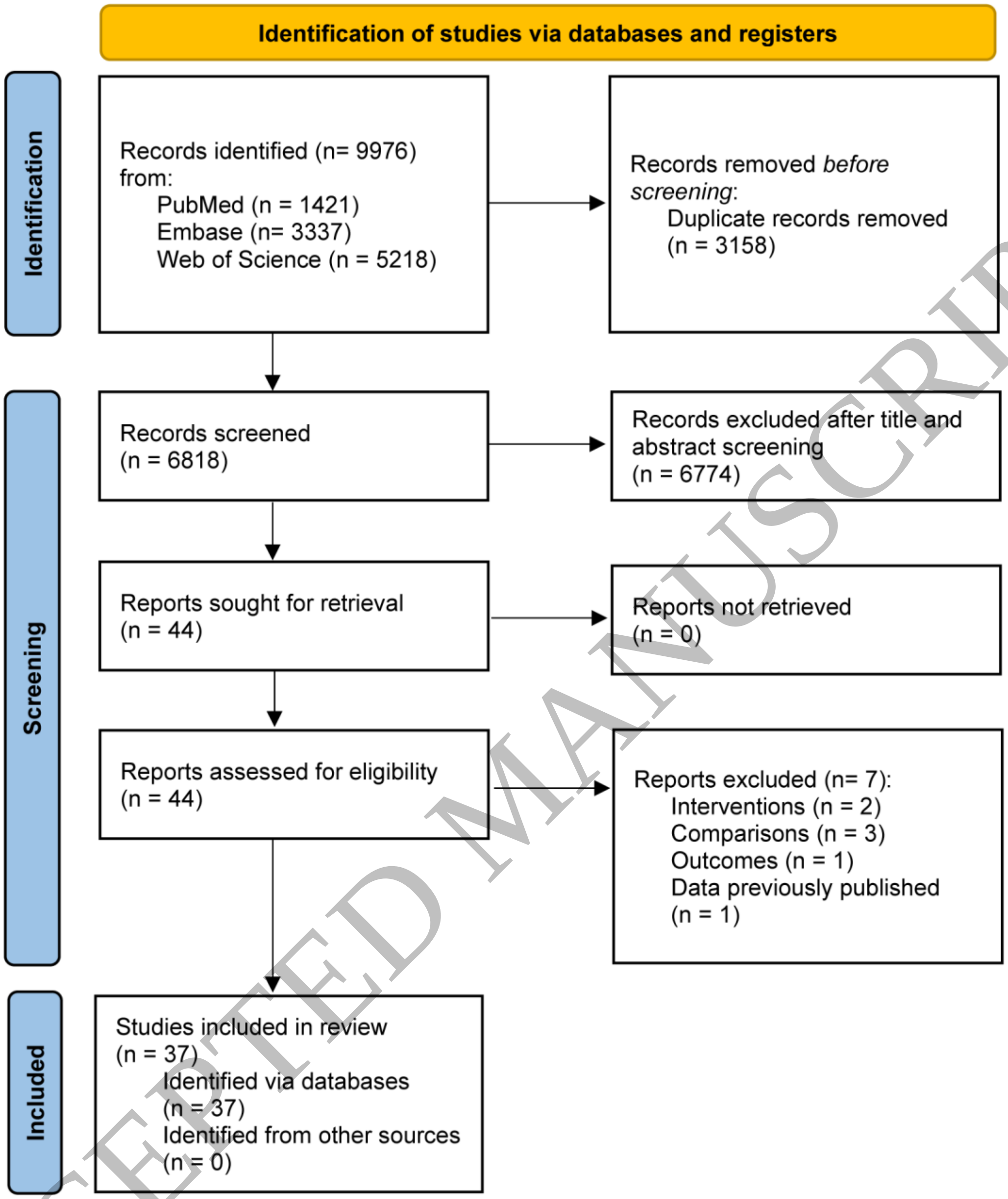

Figure 1
142x176 mm (x DPI)

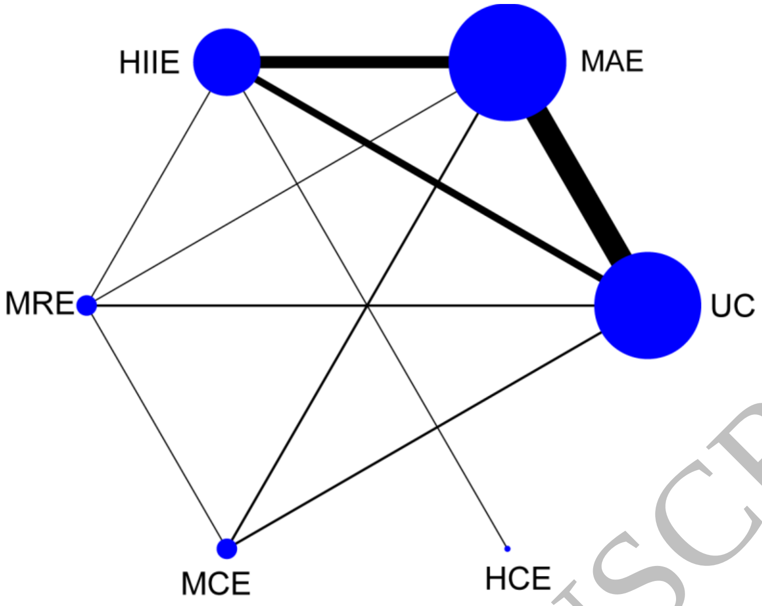

Figure 2
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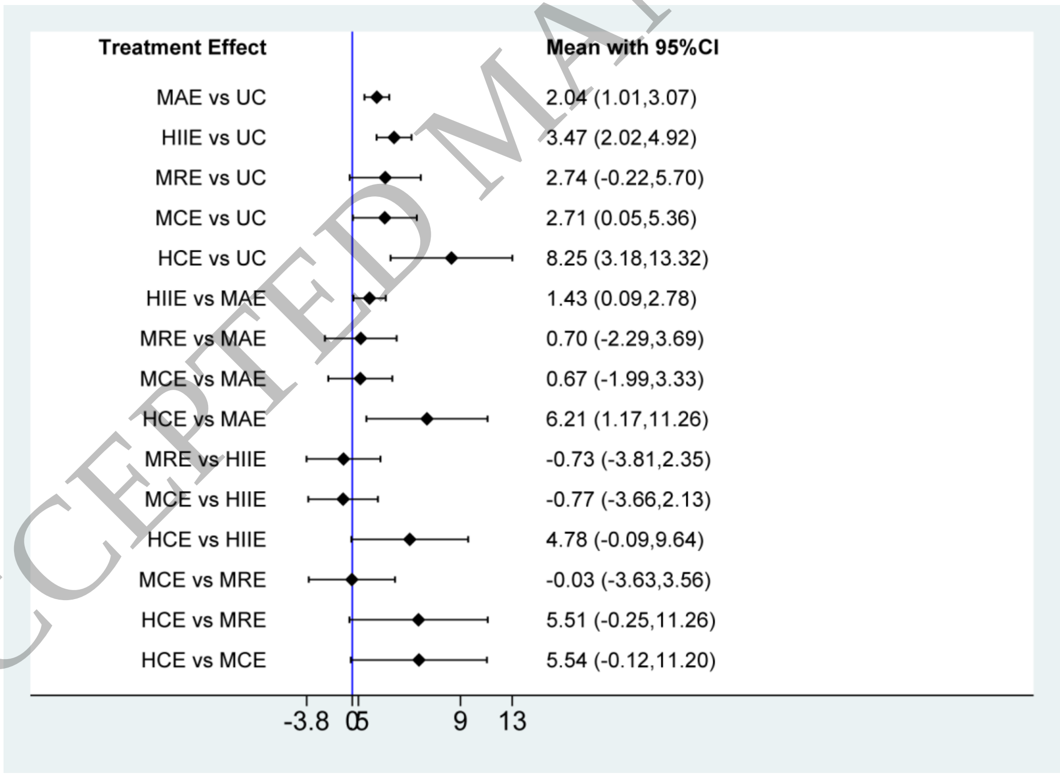


Treatment Effect	Mean with 95%CI
MAE vs UC	2.04 (1.01,3.07)
HIIE vs UC	3.47 (2.02,4.92)
MRE vs UC	2.74 (-0.22,5.70)
MCE vs UC	2.71 (0.05,5.36)
HCE vs UC	8.25 (3.18,13.32)
HIIE vs MAE	1.43 (0.09,2.78)
MRE vs MAE	0.70 (-2.29,3.69)
MCE vs MAE	0.67 (-1.99,3.33)
HCE vs MAE	6.21 (1.17,11.26)
MRE vs HIIE	-0.73 (-3.81,2.35)
MCE vs HIIE	-0.77 (-3.66,2.13)
HCE vs HIIE	4.78 (-0.09,9.64)
MCE vs MRE	-0.03 (-3.63,3.56)
HCE vs MRE	5.51 (-0.25,11.26)
HCE vs MCE	5.54 (-0.12,11.20)

Figure 3
140x102 mm (x DPI)

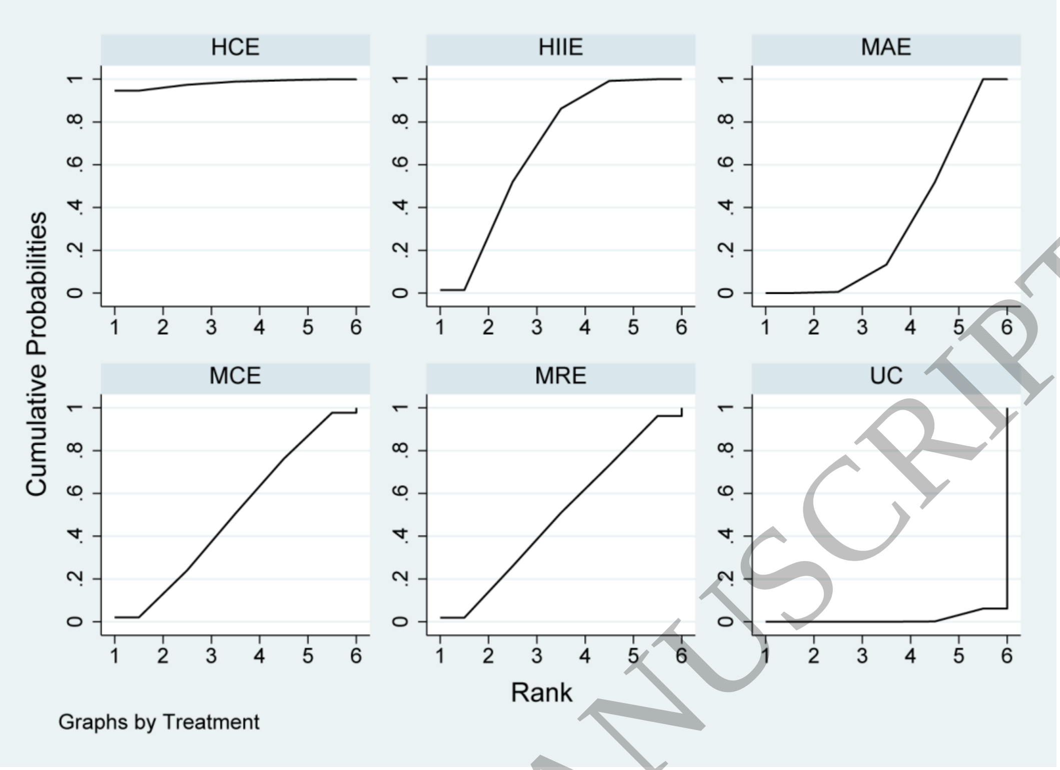
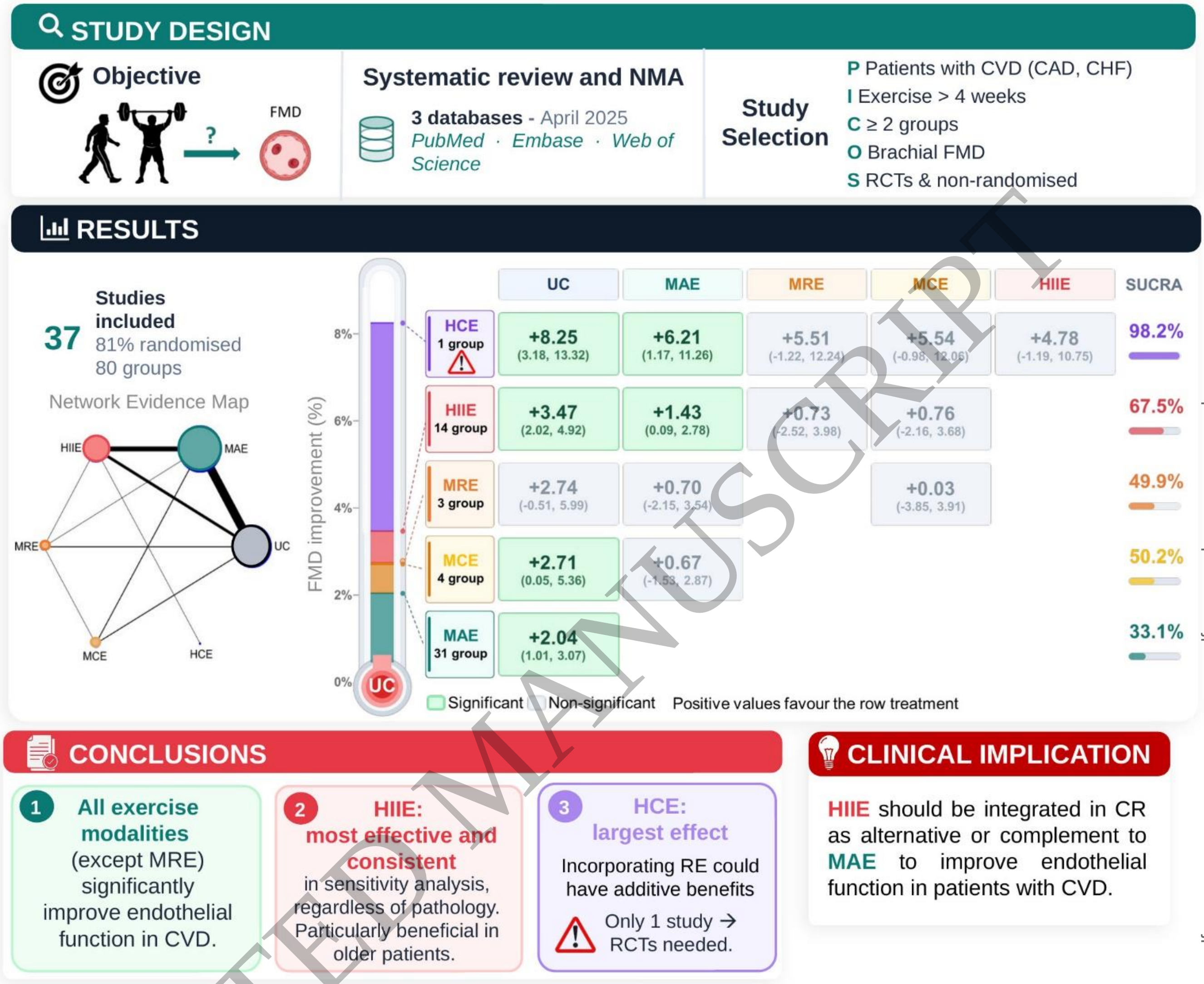


Figure 4
140x102 mm (x DPI)



STUDY DESIGN

Objective

Systematic review and NMA

3 databases - April 2025
PubMed · Embase · Web of Science

Study Selection

P Patients with CVD (CAD, CHF)
I Exercise > 4 weeks
C ≥ 2 groups
O Brachial FMD
S RCTs & non-randomised

RESULTS

37 **Studies included**
81% randomised
80 groups

Network Evidence Map

	UC	MAE	MRE	MCE	HIIE	SUCRA
HCE 1 group ⚠	+8.25 (3.18, 13.32)	+6.21 (1.17, 11.26)	+5.51 (-1.22, 12.24)	+5.54 (-0.98, 12.06)	+4.78 (-1.19, 10.75)	98.2%
HIIE 14 group	+3.47 (2.02, 4.92)	+1.43 (0.09, 2.78)	+0.73 (-2.52, 3.98)	+0.76 (-2.16, 3.68)		67.5%
MRE 3 group	+2.74 (-0.51, 5.99)	+0.70 (-2.15, 3.54)		+0.03 (-3.85, 3.91)		49.9%
MCE 4 group	+2.71 (0.05, 5.36)	+0.67 (-1.53, 2.87)				50.2%
MAE 31 group	+2.04 (1.01, 3.07)					33.1%

🟩 Significant ⬜ Non-significant Positive values favour the row treatment

CONCLUSIONS

① **All exercise modalities** (except MRE) significantly improve endothelial function in CVD.

② **HIIE: most effective and consistent** in sensitivity analysis, regardless of pathology. Particularly beneficial in older patients.

③ **HCE: largest effect**
Incorporating RE could have additive benefits
⚠ Only 1 study → RCTs needed.

CLINICAL IMPLICATION

HIIE should be integrated in CR as alternative or complement to **MAE** to improve endothelial function in patients with CVD.

CAD, coronary artery disease; CHF, chronic heart failure; CR, cardiac rehabilitation; CVD, cardiovascular disease; FMD, flow-mediated dilation; HCE, high-intensity combined exercise; HIIE, high-intensity interval exercise; MAE, moderate-intensity aerobic exercise; MCE, moderate-intensity combined exercise; MRE, moderate-resistance exercise; NMA, network meta-analysis; RCT, randomised controlled trials; RE, resistance exercise; UC, usual care.

Graphical Abstract
181x158 mm (x DPI)