



THE EFFECT OF PHYSICAL EXERCISE INTERVENTIONS ON CARDIOVASCULAR HEALTH, PHYSICAL PERFORMANCE MEASURES, AND QUALITY OF LIFE IN PEOPLE LIVING WITH CARDIOVASCULAR DISEASE: A META-ANALYSIS AND META-REGRESSION OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Purpose: The aim of this meta-analysis was to examine the effect of physical exercise interventions on endothelial function, Quality of life (QoL), and various markers of cardiovascular health and in patients with cardiovascular disease. A meta-regression analysis was performed to elucidate the moderating effects of intervention and the participants' endothelial function characteristics.

Methods: Relevant databases were searched from the beginning until February, 2025. Primary outcomes were endothelial function measured by brachial artery flow-mediated dilatation ($_{ba}$ FMD) and QoL using appropriate questionnaires.

Results: Physical exercise interventions exhibited a moderate effect on $_{ba}$ FMD (standardized mean difference [SMD] = 1.04, 95% CI 0.38 – 1.70, $p = 0.005$) and peak oxygen uptake (VO_{2peak}) (SMD = 0.76, 95% CI 0.3 – 1.22, $p = 0.004$), whereas a small effect was observed for the 6-minute walking test (SMD = 0.31, 95% CI 0.10 – 0.53, $p = 0.019$). Finally, a large but non-significant effect was observed on QoL (SMD = 1.24, 95% CI 0.25 – 2.74, $p = 0.088$). Meta-regression results revealed $_{ba}$ FMD was moderated by the participants' initial body mass index value ($\beta = -0.233$, $p = 0.026$).

Conclusions: *QoL seems to mirror endothelial function and VO_{2peak} improvements in cardiovascular patients following physical exercise interventions.*

Keywords: *Exercise, Quality of life, Endothelium, Vascular, Resistance training, Endurance training*

UČINEK VADBENIH INTERVENCIJ NA SRČNO-ŽILNO ZDRAVJE, KAZALNIKE TELESNE ZMOGLJIVOSTI IN KAKOVOST ŽIVLJENJA PRI LJUDEH S SRČNO-ŽILNIMI BOLEZNIMI: METAANALIZA IN METAREGRESIJA RANDOMIZIRANIH KONTROLIRANIH RAZISKAV

IZVLEČEK

Namen: Cilj te metaanalize je bil proučiti učinek vadbenih intervencij na endotelijsko funkcijo, kakovost življenja in različne označevalnike srčno-žilnega zdravja pri bolnikih z različnimi srčno-žilnimi boleznimi. Dodatno je bila izvedena metaregresija za ovrednotenje vpliva značilnosti posameznih intervencij in izhodiščnih lastnosti preiskovancev na endotelijsko funkcijo.

Metode: Sistematičen pregled relevantnih podatkovnih baz je vključeval literaturo, ki je bila na voljo do februarja 2025. Primarni spremenljivki sta bili endotelijska funkcija, merjena z od pretoka odvisno dilatacijo na brahialni arteriji (ang. Flow-mediated dilation [FMD]), in kakovost življenja (ang. Quality of life [QoL]), merjena z vprašalniki. Sekundarne spremenljivke so vključevale različne spremenljivke, povezane s srčno-žilnim zdravjem, in značilnosti vadbenih intervencij.

Rezultati: Ugotovili smo zmeren, statistično značilen učinek vadbenih intervencij na FMD (standardized mean difference [SMD] = 1,04, 95-odstotni interval zaupanja (IZ) 0,38 – 1,70, $p = 0,005$) in maksimalni privzem kisika (VO_{2peak}) (SMD = 0,76, 95-odstotni IZ 0,3 – 1,22, $p = 0,004$) ter majhen učinek na rezultat 6-minutnega testa hoje (SMD = 0,31, 95-odstotni IZ 0,10 – 0,53, $p = 0,019$). Ugotovljen je bil velik, toda neznačilen učinek na QoL (SMD = 1,24, 95-odstotni IZ 0,25 – 2,74, $p = 0,088$). Metaregresijska analiza je pokazala značilen učinek izhodiščnega indeksa telesne mase na stopnjo izboljšanja endotelijske funkcije.

Zaključek: Pri bolnikih s srčno-žilnimi boleznimi se kakovost življenja po vadbeni intervenciji izboljšuje z izboljšanjem endotelijske funkcije in aerobno zmogljivostjo. Osnovne značilnosti preiskovancev pomembno vplivajo na odziv endotelijske funkcije na vadbo.

Ključne besede: vadba, endotelijska funkcija, kakovost življenja, vadba za moč, vzdržljivostna vadba

INTRODUCTION

Cardiovascular diseases (CVD) remain the most common cause of death in Europe, responsible for 45% (i.e., 4.5 million) of all deaths per year (Townsend, Nichols, Scarborough, & Rayner, 2015). Worldwide, CVD deaths accounted for around one-third of all global cases in 2021 (Roth et al., 2020). CVD is estimated to cost the European Union €282 billion annually, with health and long-term care accounting for €155 billion, equaling 11% of the European Union's health expenditure (Luengo-Fernandez et al., 2023).

Regular physical exercise (PE) has a positive effect on general health and helps lower the risk of CVD and mortality (Löllgen, Böckenhoff, & Knapp, 2009). PE has been shown to have an independent association between the volume of physical activity and overall mortality in healthy individuals with epidemiological evidence (Adams & Linke, 2019). PE elicits changes on the physiological and molecular level, including various organic and systemic adaptations.

Regular PE plays an important role in the reduction of mortality risk, with the benefits of higher levels of physical activity (>500 MET-min/week) eliciting a 4-7% risk reduction in mortality in individuals with and without CVD (Jeong et al., 2019). CVD patients experience a reduction in cardiovascular health. In the presence of cardiovascular risk factors, the endothelium undergoes functional and structural alterations resulting in impaired endothelial-dependent vasodilation (Versari, Daghini, Viridis, Ghiadoni, & Taddei, 2009).

Endothelial function measured by flow-mediated dilatation (FMD) is thought to be an independent predictor of cardiac events and restenosis in numerous studies and is therefore a prognostic factor in the assessment of cardiovascular health (Green, Jones, Thijssen, Cable, & Atkinson, 2011). Brachial artery FMD ($_{ba}$ FMD) and common femoral artery FMD ($_{cf}$ FMD) are most commonly used in the evaluation of endothelial function (Stout, 2009). Endothelial function can be significantly improved by regular exercise training, regardless of exercise mode (Shivgulam et al., 2023). There seems to be a dose-response relationship between exercise intensity and improvement in endothelial function, where every 2-MET increase in aerobic exercise intensity increases the FMD by 1% (Ashor et al., 2015). An increase in endothelial function after exercise has been shown in both healthy (Seals, Nagy, & Moreau, 2019) and symptomatic populations (Qiu et al., 2018).

Various other measures are connected to a decline in cardiovascular health, such as maximal oxygen uptake (VO_{2peak}), blood pressure, muscle strength, etc. A 6% increase in VO_{2peak} after 3 months of exercise training has been shown

to lower the risk of all-cause mortality by 5% in chronic heart failure (CHF) patients (Swank et al., 2012). Similarly, a 10-year exercise training study in CHF patients has shown a sustained improvement in VO_{2peak} and mortality risk, as well as improved QoL (Belardinelli, Georgiou, Cianci, & Purcaro, 2012). Similar improvements in blood pressure can be observed following regular exercise. For example, systolic and diastolic blood pressure are lowered by regular exercise, regardless of the exercise mode (Edwards et al., 2023). Hypertension is both a cardiovascular disease and an independent risk factor for mortality, with lower blood pressure being strongly associated with better health outcomes (Brunström & Carlberg, 2018).

In light of the numerous positive adaptations induced by regular PE, it is considered to play a major role in public health, as well as the primary and secondary prevention of CVD (Tucker et al., 2022). So far, various forms of PE have been shown to improve cardiovascular function, physical performance, and various cardiovascular health markers (Jeong et al., 2019; Schmidt-Trucksäss, 2021; Silva, Menêses, Parmenter, Ritti-Dias, & Farah, 2021; Valenzuela et al., 2023).

An improvement in cardiovascular markers and general health can also be translated into an increased quality of life (QoL). Health-related QoL is a multi-dimensional concept that measures the individual's perception of life by measuring functional status in the domains of physical, cognitive, emotional, and social health (Shibata, Oka, Nakamura, & Muraoka, 2007). QoL can be measured with various general health and disease-specific QoL questionnaires (Bilbao, Escobar, García-Perez, Navarro, & Quirós, 2016; Cong et al., 2022; Dempster, Donnelly, & O'Loughlin, 2004; Gonzalez-Saenz De Tejada et al., 2019; Green, Porter, Bresnahan, & Spertus, 2000; Höfer et al., 2012; Mogle, Buck, Zambroski, Alvaro, & Vellone, 2017; Nassif et al., 2022). The effect of physical exercise on QoL has been studied extensively in both healthy and clinical populations (Gillison, Skevington, Sato, Standage, & Evangelidou, 2009; Veskovic et al., 2023). Shepherd and While (2012) found QoL measurements to be of value in managing patients with cardiac disease, supporting the use of a 36-Item Short Form Survey Instrument (SF-36), as well as the Minnesota Living with Heart Failure Questionnaire (MLHFQ). They recommend using general health questionnaires in combination with disease-specific QoL questionnaires (Berry & McMurray, 1999; Shephard & Franklin, 2001). Various studies have examined the relationship between exercise and QoL in frail older adults (Chou, Hwang, & Wu, 2012), patients with multiple sclerosis (Latimer-Cheung et al., 2013), chronic obstructive pulmonary disease and heart failure (Berkhof, Metzemaekers, Uil, Kerstjens, & van den Berg, 2014), coronary heart

disease (Anderson et al., 2016), myocardial infarction (Campo et al., 2020) and type 2 diabetes (Cai, Li, Zhang, Xu, & Chen, 2017), among others.

While exercise as a tool has been shown to improve health-related QoL in various populations, the relationship between improvements in different CVD markers through exercise and their association with QoL remains unclear. Although recent studies highlight the effectiveness of exercise in different clinical populations, it is important to distinguish between improvements in specific CVD markers and their direct effect on health-related QoL. While there is substantial evidence supporting a link between improved aerobic capacity and better QoL, there is limited research investigating the association between endothelial function and QoL. Therefore, the aim of this meta-analysis was to investigate the association between endothelial function, aerobic capacity, and QoL following physical exercise interventions (PEI) in CVD patients; with the hypothesis that QoL will mirror improvements in endothelial function and other measures of cardiovascular health.

Objectives

The aim of this meta-analysis and meta-regression of randomized controlled trials was to provide an overview of the effectiveness of different training interventions on endothelial function measured by FMD_{ba} , the physiological parameters of cardiovascular health, objective measures of performance, and overall QoL. Additionally, we aimed to differentiate the effects of different training modalities based on the above parameters to inform clinical practice on both the QoL and objective health measures.

METHODS

This meta-analysis and meta-regression were conducted in line with the 2021 PERSiST guidance (implementing Prisma in Exercise, Rehabilitation, Sport medicine and Sports science) (Arden et al., 2022) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement items for systematic reviews in sport and exercise medicine (Page et al., 2021). The protocol of the current study was prospectively registered at the Open Science Framework online registry: doi.org/10.17605/OSF.IO/B6QPC.

Search Strategy

Relevant studies using FMD on a range of healthy and clinical adult populations were searched for using online databases in the scope of a broader meta-analysis project. The PubMed, Web of Science, Embase, CINAHL, and EBSCO host databases were searched on 7/9/2023. A Cochrane Library database search was conducted on 12/10/2023. Additionally, a PubMed database was searched on 6/2/2024. An additional search was conducted on 14/2/2025 to ensure up-to-date results. Online databases were searched using a combination of relevant medical subject heading terms and words such as “adults”, “vascular”, “endothelium”, “endothelial function”, “endothelial dysfunction”, “flow-mediated dilatation”, “FMD”, “endothelium-dependent vasodilatation”, “vascular reactivity”, “exercise”, “physical exercise” and “training” with the Boolean search terms “OR” and “AND”. The Boolean search term “NOT” was included where possible, including the words “review” and/or “systematic literature review”. Records in English with abstracts were obtained and subsequently screened for inclusion/exclusion in the systematic review (Supplementary Table 4).

Inclusion and Exclusion Criteria

PICO framework criteria were used to define the inclusion criteria. Population: recruited subjects were adults (≥ 18 years of age) with no restrictions on the age or sex of the participants. Only cardiovascular disease patients were eligible for inclusion (New York Heart Association (NYHA) functional class I-III), with no restrictions on the type of cardiovascular disease. Intervention: randomized controlled trials with physical exercise intervention. Comparison: the studies included exercise vs. non-intervention control. Outcome: endothelial function measured by FMD_{ba} (%) and QoL using appropriate questionnaires measured as a primary or secondary outcome.

The exclusion criteria were as follows: 1) studies utilizing underage participants; 2) no control groups; 3) utilized pharmacological treatment with no exercise-only group and untreated control group; 4) comparisons between different exercise treatments with no control group; 5) crossover studies; 6) systematic literature reviews, narrative reviews and meta-analyses; 7) abstracts in journals, symposium abstracts or reports; 8) study protocols; 9) endothelial function assessed by other means; 10) structured interview for measuring the quality of life.

Selection Process

The selection of studies was conducted by two reviewers independently (SI and AP). The first stage consisted of an evaluation of the titles and abstracts of the studies, as described above. The article was included in the first screen if the title and abstract satisfied the inclusion criteria. Full-text articles of the included abstracts were retrieved, independently evaluated by the two reviewers, and assessed for inclusion in the study. Disagreements were resolved by consensus between the two reviewers.

Data Collection

The Cochrane Consumers and Communication Review Group's data extraction protocol was used to extract primary outcome data, study protocol, study design, and participant information. Means and standard deviations were extracted for primary outcome data (FMD , QoL questionnaires), as well as secondary outcome data (systolic and diastolic blood pressure, body mass index (BMI), maximal oxygen uptake ($\text{VO}_{2\text{peak}}$), 6-minute walking test (6-MWT), and one-repetition maximum (1RM) strength). Data extracted from graphs was extracted using Plot Digitizer (*Plot Digitizer*, 2024). Data reported as 95% confidence intervals, interquartile ranges, or standard error means were transformed to means and standard deviations according to the Cochrane handbook. Participant characteristics (sample size, age, health status, gender, gender ratio, and BMI) and study protocol characteristics were extracted. Primary outcomes reported in tables only were extracted. A second reviewer (AP) independently compared the extracted data with full-text articles, and any disagreement was resolved by evaluation and consensus between the two reviewers. If consensus was not reached, a third reviewer was included. If data was not reported in the results sections or tables, the authors were contacted by email, with one reminder after two weeks if the authors failed to respond in time.

Outcomes of Interest

The primary outcomes were flow-mediated dilatation (FMD), and general and disease-specific health-related QoL scores. Secondary outcomes were systolic and diastolic blood pressure, and BMI. Secondary performance outcomes

included $\text{VO}_{2\text{peak}}$ and 6-MWT for studies utilizing aerobic exercise protocols, and 1RM strength measured by isometric grip, knee extensor strength, or 1-repetition maximal testing. If the studies reported two or more performance outcomes, we extracted all the outcomes. For QoL questionnaires, all the available data was extracted, including the total values and values for specific subgroups of given questionnaires. General study participant characteristics were extracted: age, sex, BMI, NYHA functional class, and left ventricular ejection fraction (LVEF%). For study intervention assessment, the study duration, weekly training frequency, single session duration, weekly training duration, and exercise modality and intensity were extracted. We used pre-determined criteria for study protocol assessment. For different intensity outcomes, we used pre-determined intensity criteria for different variables to stratify training intensity in different subgroups. Studies were also stratified based on subject health status.

Risk of Bias Assessment

The Cochrane ROB 2.0 (Sterne et al., 2019) was used for the risk of bias assessment of selected studies. Two researchers (SI and GT) independently assessed the risk of bias for each included study against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel, and outcomes; incomplete outcome data; selective outcome reporting and other sources of bias, in accordance with the methods recommended by the Cochrane Collaboration. Another reviewer (AP) independently assessed all risk of bias assessments and any disagreement was resolved between the reviewers. Studies were subsequently labeled as having a low, moderate, or high risk of bias. ^{ba}FMD and QoL outcomes were assessed for the risk of bias. Studies were assessed for primary outcomes only, namely ^{ba}FMD and QoL. The methodological quality of the included studies was assessed using the PEDro scale by one reviewer (SI). The study methodology was subsequently graded as poor (0-3), fair (4-5), good (6-8), and excellent (9-10), according to the authors (Cashin & McAuley, 2020).

Effect Measures

We assessed the outcomes based on values before and after the cessation of interventions. Study participants were stratified into categories by age: 18-39

years – young or early adulthood, 40-59 years – middle adulthood, 60-75 years – old age (young old), and >75 years – old age (old old) (Lachman, 2001). Training protocols were divided into subgroups based on the exercise modality (resistance or aerobic training) and the type of exercise. Aerobic training was further divided into continuous aerobic training (CAT) and interval aerobic training (IAT). Resistance training was classified as dynamic resistance training (DRT) or static resistance training (SRT). All interventions were divided into subgroups based on the intensity of exercise based on the 2020 ESC Guidelines on Sports Cardiology and Exercise in patients with cardiovascular disease (Pelliccia et al., 2021). Resistance training was also divided into intensity categories based on the maximal voluntary isometric contraction (MViC), 1RM, and the rate of perceived exertion (RPE) (Day, McGuigan, Brice, & Foster, 2004; DeWeese, Hornsby, Stone, & Stone, 2015).

Synthesis Methods

The primary outcome means and estimates were extracted for each variable. When confidence intervals or standard errors were reported, the measures were extracted and converted to means (M) and standard deviations (SD), if possible, as suggested in the Cochrane handbook. Data for exercise intervention and participant information was extracted for analysis. Continuous variables are presented as M and SD, while discrete variables are presented as median (Me) and interquartile range (IQR).

Statistical Analysis

Statistical analysis was performed using the SPSS statistical software (version 29.0, IBM Inc, Chicago, United States of America). Due to the large heterogeneity observed for each meta-analysis, the data was analyzed using a random effect model. The method of restricted maximum likelihood (REML) with Knap-Hartung standard error adjustment was used for all analyses (Langan et al., 2019). Egger's test was performed on collected data to provide statistical evidence of publication bias. Given the variability of the methods used to analyze the majority of variables of interest, along with the variability of the units reported, a standardized mean difference (SMD) along with 95% confidence intervals (CI) were calculated for all outcome measures. SMD was set as

trivial (<0.20), small ($0.21-0.60$), moderate ($0.61-1.20$), large ($1.21-2.00$), very large ($2.01-4.00$), or extremely large (>4.00) (Hopkins, Marshall, Batterham, & Hanin, 2009). Heterogeneity was assessed with the I^2 statistic, which indicates the percentage of variability across studies due to heterogeneity rather than chance. Values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity. Furthermore, random-effects meta-regression using the REML was performed to examine whether the effects of PEI on $\dot{V}_{O_{2ba}}$ and $\dot{V}_{O_{2peak}}$ were moderated by the age of the participants and their BMI, together with training-related variables including intervention duration, weekly training frequency, single session duration, weekly training volume, total number of training sessions, and overall training volume. To minimize the risk of overfitting, a meta-regression was performed when a minimum of 10 studies were eligible per examined covariate (Nasser, 2020). A level of $p < 0.05$ was adopted as statistically significant.

RESULTS

Study Selection Process and Patient Characteristics

The initial literature search was conducted in the PubMed, Cochrane Library, EBSCOhost, CINAHL, Web of Science, and Embase databases. A search yielded 1861 references in total, of which 1300 were screened for selection after the removal of duplicates. We assessed 24 full-text articles for eligibility based on the pre-specified inclusion and exclusion criteria. Nine randomized controlled trials were included in the systematic review (Figure 1) with a total of 592 participants and 13 treatment groups. Of the included studies, five studies used general health-related quality of life questionnaires, four studies used the SF-36 questionnaire, and one study used the General Health Questionnaire (GHQ). 6 studies used disease-specific QoL measurements, with 5 studies using the MLHFQ questionnaire and 1 study using the MacNew Questionnaire (MacNew). One study used both general health (SF-36) and disease-specific (MLHFQ) QoL questionnaires.

The mean age of the participants in the individual studies ranged between 51.9 and 76 years. The gender ratio (male/female) ranged from 7 to 0.4, with one study utilizing only male participants (Belardinelli, Lacalaprice, Faccenda, Purcaro, & Perna, 2005). Five out of nine studies reported the NYHA functional class of participants, with all the participants falling within functional class II or III. The mean left ventricular ejection fraction (LVEF%) ranged from 26.2

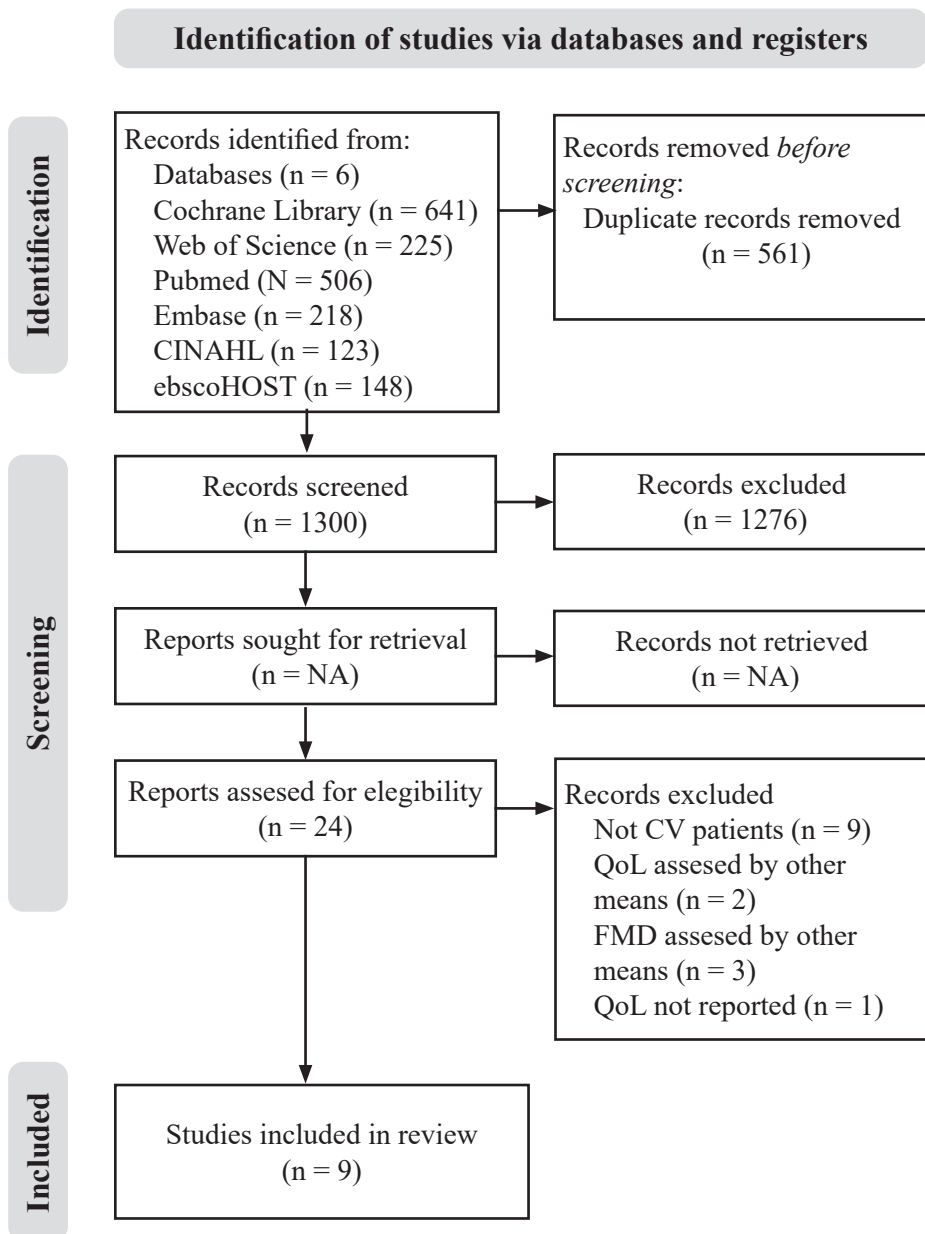


Figure 1. PRISMA flowchart. (Haddaway, Page, Pritchard, & McGuinness, 2022)

to 59.5 %, with five out of nine studies reporting this measure. The majority of the included studies were done on patients with chronic heart failure ($n = 5$), ischemic heart disease ($n = 1$), peripheral arterial disease ($n = 1$), and hypertension ($n = 1$). One study (Claes et al., 2020) included general CVD patients with various CVD diseases.

All the QoL instruments used in the included trials were validated for the relevant patient population. General health QoL instruments were used mainly in the form of the SF-36 ($n = 4$) and GHQ ($n = 1$). Disease-specific QoL instruments were applied using the MLHFQ questionnaire ($n = 4$) and the MacNew questionnaire ($n = 1$). One study (Karavidas et al., 2006) used both the SF-36 and MLHFQ questionnaires.

The most common mode of exercise interventions was center-based supervised training ($n = 7$), with one study (Wisløff et al., 2007) utilizing a combined center-based and home-based supervised approach to training and one study using a home-based Technology-Enabled Cardiac Rehabilitation Platform (Claes et al., 2020). As mentioned earlier, 13 different exercise intervention groups were assessed, of which 11 used aerobic training and 2 resistance training. The type of exercise was mostly continuous aerobic ($n = 9$), with two study groups using interval aerobic training ($n = 2$) (Molmen-Hansen et al., 2012; Wisløff et al., 2007). Dynamic resistance training was used in one group (McDermott et al., 2009) and functional electrical stimulation in one group (Karavidas et al., 2006).

Regarding the intensity of exercise of the aerobic training protocols, medium ($n = 7$), high ($n = 1$), and very high ($n = 2$) intensities were used according to pre-specified intensity classification, while one study failed to report the exercise intensity (Claes et al., 2020). Both interval aerobic training groups used very high intensity exercise, while continuous aerobic training groups used medium and high intensity exercise. Resistance training protocols were characterized as light intensity according to the pre-specified criteria. One resistance training group used functional electrical stimulation for exercise intervention (Karavidas et al., 2006) and was therefore left out of the resistance exercise intensity classification (Table 1).

Intervention duration ranged from 6 to 24 weeks ($Me = 12$), with all groups training three times a week. The mean weekly training duration was 126 ($SD = 23.6$) min, and the median of the total number of training sessions was 36 (24 – 48). The median of the total training volume was 1404 (960 – 1692) min.

Table 1. Study characteristics, intervention information, and main findings of the included studies.

Reference	Population	Health status / diagnosis	Intervention	Frequency, weekly volume, intensity	Main findings (Primary)
Belardinelli et al. (2005)	Mean age: 56.9	Stable chronic heart failure	Aerobic – CAT	3x/week, 120 min, medium intensity	MLHFQ: ↑, C: ↓ FMD: ↑, C: NS
Blumenthal et al. (2005)	Mean age: 62.5 Mean BMI: 29.8	Ischemic heart disease	Aerobic – CAT	3x/week, 105 min, high intensity	GHQ: ↑, C: ↑ FMD: ↑, C: NS
Belardinelli et al. (2006) ^a	Mean age: 54.2	Chronic heart failure + ICD	Aerobic – CAT	3x/week, 120 min, medium intensity	MLHFQ: ↑, C: NS FMD: ↑, C: NS
Belardinelli et al. (2006) ^b	Mean age: 54.3	Chronic heart failure + ICD + CRT	Aerobic – CAT	3x/week, 120 min, medium intensity	MLHFQ: ↑, C: NS FMD: ↑, C: NS
Karavidas et al. (2006)	Mean age: 59.5 Mean BMI: 27.1	Chronic heart failure	Resistance – FES	5x/week, 150 min, functional electrical stimulation	MLHFQ: ↑, C: NS FMD: ↑, C: NS
Wisløff et al. (2007) ^a	Mean age: 76 Mean BMI: 25	Chronic heart failure	Aerobic – IAT	3x/week, 115 min, very high intensity	MacNew: ↑, C: NS FMD: ↑, C: NS
Wisløff et al. (2007) ^b	Mean age: 75 Mean BMI: 25.1	Chronic heart failure	Aerobic – CAT	3x/week, 140 min, medium intensity	MacNew: ↑, C: NS FMD: ↑, C: NS
McDermott et al. (2009) ^a	Mean age: 70.3 Mean BMI: 30.2	Peripheral arterial disease	Aerobic – CAT	3x/week, 120 min, medium intensity	SF-36 (PF): ↑, C: NS FMD: ↑, C: NS

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Reference	Population	Health status / diagnosis	Intervention	Frequency, weekly volume, intensity	Main findings (Primary)
McDermott et al. (2009) ^b	Mean age: 70.3 Mean BMI: 30.2	Peripheral arterial disease	Resistance – DRT	3x/week, 120 min, low intensity	SF-36 (PF): ↑, C: NS _{ba} FMD: NS, C: NS
Molmen-Hansen et al. (2012) ^a	Mean age: 52.4 Mean BMI: 28.4	Hypertension	Aerobic – CAT	3x/week, 140 min, medium intensity	SF-36 (GH): ↑, C: NS _{ba} FMD: NS, C: NS
Molmen-Hansen et al. (2012) ^b	Mean age: 51.9 Mean BMI: 27.8	Hypertension	Aerobic – IAT	3x/week, 115 min, very high intensity	SF-36: (GH, SF, PF): ↑, C: NS _{ba} FMD: ↑, C: NS
Kitzman et al. (2013)	Mean age: 70 Mean BMI: 32.1	Chronic heart failure	Aerobic – CAT	3x/week, 180 min, medium intensity	MLHFQ: NS, C: NS SF-36 (EM, PF): ↑, C: NS _{ba} FMD: NS, C: NS
Claes et al. (2020)	Mean age: 60.7 Mean BMI: 28.1	Cardiovascular diseases	Aerobic – CAT	3x/week, 150 min, not reported	SF-36: NS, C: NS _{ba} FMD: NS, C: NS

Legend: a and b denote different subgroups analyzed within one study. ICD – implantable cardioverter defibrillator, CRT – cardiac resynchronization therapy, CAT – continuous aerobic training, IAT – interval aerobic training, FES – functional electrical stimulation, DRT – dynamic resistance training, MLHFQ – the Minnesota Living with Heart Failure Questionnaire, MacNew – the MacNew Quality of Life Questionnaire, GHQ – the General Health Questionnaire, SF-36 – the 36-Item Short Form Health Survey questionnaire, _{ba}FMD – flow-mediated dilatation, ↑ – statistically significant improvement, ↓ – statistically significant decrease, NS – not statistically significant.

Risk of Bias Assessment

The overall methodological quality of the assessed studies was good, with an average grade of 6 (SD = 1), based on the PEDro scale. 6 studies were graded as *good* while 3 studies were graded as *fair*. The overall risk of bias for $_{ba}$ FMD, assessed using the Cochrane Risk of Bias 2.0 Assessment Tool, was low (n = 5) or expressing some concerns (n = 4). Concerns were raised mainly due to deviations from the intended protocols (n = 3) and randomization process (n = 1), as outlined in Supplementary Table 1. No concerns were raised in other categories for the risk of bias assessment. The overall risk of bias for general health QoL was low (n = 2) or high (n=3). Additional concerns compared to the previously described concerns relating to the randomization process and deviations from the intended interventions arising from the study methodology were raised due to problems in the measurement of the outcome (n = 1) and the selection of the reported results (n = 2) (Supplementary Table 2). The overall risk of bias for disease-specific QoL was low (n = 2), and expressing some concerns (n = 3), although those concerns were raised based on the above outlined questionable randomization processes and deviations from the intended interventions. No additional risk was introduced due to missing outcome data, the measurement of the outcome, or selective reporting regarding disease-specific QoL measurements (Supplementary Table 3).

Meta-Analyses of the Effects of PEI on Different Markers of Cardiovascular Health

Meta-analysis of 13 studies with a total of 592 participants showed a *moderate* effect on $_{ba}$ FMD (SMD = 1.04, 95% CI 0.38 – 1.70, p = 0.005) and VO_{2peak} (SMD = 0.76, 95% CI 0.3 – 1.22, p = 0.004), whereas a *small* effect was observed on 6-MWT (SMD = 0.31, 95% CI 0.10 – 0.53, p = 0.019). Although the effect on CV QoL was *large* (SMD = 1.24, CI -0.25 – 2.74, p = 0.088), it did not reach statistical significance. Similarly, when the effects of PEI on the overall QoL were assessed, a non-significant moderate effect was observed (SMD = 0.66, 95% CI -0.13 to 1.45, p = 0.093). (Table 2)

Table 2. Effect of physical exercise interventions on different variables of interest.

Independent variables	SMD	SE	t value	P value	95 % CI		95% predicted CI		I ² (%)	n
baFMD	1.04	0.30	3.45	0.005	0.38	1.70	-1.22	3.30	91	13
VO_{2peak}	0.76	0.21	3.66	0.004	0.30	1.22	-0.48	2.00	72	11
6-MWT	0.31	0.07	4.61	0.019	0.10	0.53	0.02	0.60	0	4
Strength	0.22	0.21	1.05	0.404	-0.68	1.12	-4.22	4.65	58	3
SBP at rest	-0.35	0.14	-2.50	0.13	-0.96	0.26	-2.15	1.45	0	3
CV QoL	1.24	0.61	2.04	0.088	-0.25	2.74	-2.77	5.26	92	7

Legend: FMD – flow-mediated dilatation, VO_{2peak} – maximal oxygen uptake, 6-MWT – 6-minute walking test, SBP – systolic blood pressure, CV QoL – cardiovascular-disease-specific quality of life.

Meta-Regression Analysis

Table 3 presents the results of a meta-regression analysis, investigating whether the effects of PEI on FMD_{ba} and $\text{VO}_{2\text{peak}}$ were moderated by the age of the participants and their BMI, together with training-related variables including intervention duration, weekly training frequency, single session duration, weekly training volume, total number of training sessions, and overall training volume. The results demonstrate that the effect of PEI on the participants' FMD_{ba} of the brachial artery depended upon their BMI ($\beta = -0.233$, $p = 0.0260$), with a negative association observed (the smaller the initial participants' BMI, the larger the effect of PEI) (Fig. 2). No other significant associations were observed for the other parameters.

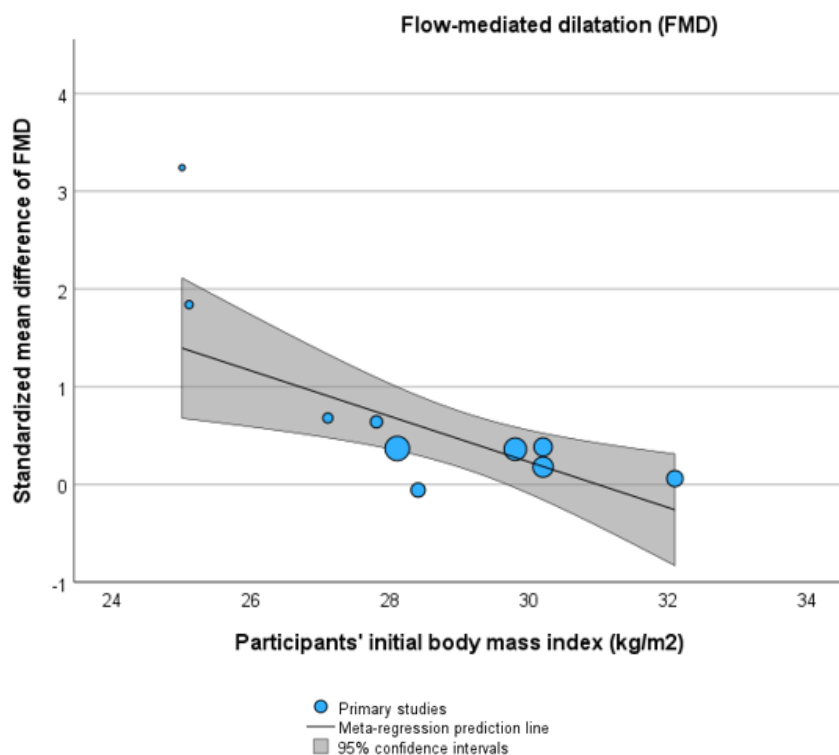


Figure 2. Results of the meta-regression analysis on whether the effects of physical exercise intervention on flow-mediated dilatation were predicted by the participants' initial body mass index.

Table 3. Meta-regression analysis for different variables to predict the effects of PEI on flow-mediated dilatation and $\dot{V}O_{2peak}$

	Coefficient	Standard error	t value	P value	95 % lower CI	95 % upper CI
$\dot{V}O_{2peak}$						
Age (years)	0.002	0.0388	0.052	0.96	-0.083	0.088
Body mass index (kg/m ²)	-0.233	0.0856	-2.72	0.026	-0.43	-0.035
Intervention duration (weeks)	-0.102	0.0479	-2.12	0.06	-0.208	0.005
Weekly frequency (times)	-0.238	0.6199	-0.38	0.709	-1.619	1.143
Single session duration (min)	-0.013	0.0416	-0.32	0.753	-0.107	0.081
Weekly training volume (min)	-0.023	0.0159	-1.41	0.195	-0.059	0.014
Total No. of training sessions	-0.044	0.0208	-2.14	0.061	-0.092	0.003
Overall training volume (min)	-0.001	0.0005	-1.98	0.083	-0.002	0
FMD						
Age (years)	0.035	0.0261	1.352	0.209	-0.024	0.094
Body mass index (kg/m ²)	-0.132	0.132	-1	0.354	-0.455	0.191
Intervention duration (weeks)	-0.006	0.0675	-0.09	0.935	-0.161	0.15
Weekly frequency (times)	-0.424	0.3632	-1.17	0.276	-1.262	0.413
Single session duration (min)	-0.009	0.0277	-0.34	0.744	-0.073	0.055
Weekly training volume (min)	-0.011	0.0088	-1.3	0.23	-0.032	0.009
Total No. of training sessions	-0.013	0.0247	-0.53	0.61	-0.07	0.044
Overall training volume (min)	0	0.0004	-0.59	0.573	-0.001	0.001

Legend: FMD – brachial artery flow-mediated dilatation, $\dot{V}O_{2peak}$ – maximal oxygen uptake

DISCUSSION

This review aimed to examine the association between changes in QoL and objective measures of cardiovascular health, with a particular focus on $baFMD$ following PEI in CVD patients. We identified a total of nine studies measuring both FMD and QoL with exercise interventions in CVD patients.

PEI resulted in an improvement in $baFMD$ and improved physical performance, as indicated by the significantly improved VO_{2peak} and 6-MWT. Muscular strength remained unaltered in the selected studies, whereas systolic BP and QoL showed a trend toward improvement, although not reaching statistical significance. This is consistent with the findings of other studies showing that exercise interventions can increase endothelial function in CVD patients (de Souza et al., 2020; Liang et al., 2024; Manresa-Rocamora et al., 2022). An increase in endothelial function is especially significant in CVD patients, as endothelial function is an important biomarker of cardiovascular health (Fuentes-Kenneally et al., 2023). Similar to the endothelial function, aerobic capacity was increased in almost all groups that utilized aerobic training of any modality lasting from 6 to 24 weeks. This suggests a concurrent improvement in cardiovascular health parameters and functional aerobic capacity measures following structured AT. An improvement in aerobic capacity is critical in CVD patients, as there is significant evidence supporting improved prognosis and outcomes in patients who manage to increase aerobic capacity (Tutor, Lavie, Kachur, Dinshaw, & Milani, 2022). An increase in endothelial function should also be in line with an increase in the overall Quality of life. Even though QoL measures did not reach statistical significance, a strong improvement in QoL scores was observed. QoL seems to mirror improvements in physical performance and endothelial function in CVD patients. Not reaching the level of significance in the QoL analysis may be due to the different measures used to assess the patients' QoL and the fact that we focused on studies investigating $baFMD$ as the primary outcome of our investigation. Thus, many studies that only investigated QoL in CVD patients might be excluded. A network meta-analysis by Gomes-Neto et al. (2024) found an improvement in VO_{2peak} following different types of PEI, as well as improved QoL in patients with coronary heart disease. Yoga has been found to have the greatest effect on QoL, with similar enhancement after CAT, AIT, and COM modalities, respectively. Interestingly, RT was not superior compared to the usual care in terms of improving QoL. Similarly, a meta-analysis by Slimani et al. (Slimani et al., 2018) found that PEI had a small effect on QoL and aerobic capacity measured by 6-MWT in older heart failure patients. An interesting finding was that shorter PEI (12 weeks) was shown to

be more effective in improving QoL compared to longer duration studies in heart failure patients (Slimani et al., 2018). Another meta-analysis found similar improvements in $\text{VO}_{2\text{peak}}$, 6-MWT, and QoL measured using the MLHFQ in heart failure patients with preserved ejection fraction (Zhuang et al., 2021). There is a growing body of evidence supporting a concomitant increase in aerobic capacity and QoL in CVD patients (Gomes-Neto et al., 2024; Slimani et al., 2018; Zhuang et al., 2021). Our study has shown similar results compared to the above-mentioned studies in terms of QoL and aerobic capacity, with confirmed increases in vascular endothelial function, measured by baFMD in line with aerobic capacity and QoL improvement.

Only two studies used resistance training as an exercise protocol, with the study by Karavidas et al. (Karavidas et al., 2006) using functional electrical stimulation as an intervention. Interestingly, functional electrical stimulation has been tied to improvements in QoL in other studies (Xiao et al., 2019), although the small number of studies limits the ability to draw a firm conclusion on its effectiveness. In terms of conventional resistance training, only McDermott et al. (McDermott et al., 2009) used a comparison between CAT and DRT in patients with peripheral arterial disease. FMD was only increased in the CAT group, suggesting a greater effect on endothelial function with the use of aerobic training, as shown previously in other studies on healthy adults (Ashor et al., 2015). Muscular strength did not generally increase in the selected studies, but this may be due to the low number of reported strength measures in eligible studies. Other studies have found increases in QoL following resistance training (Slimani et al., 2018) in older patients with heart failure. Thus, our findings on this particular question must be interpreted with caution.

Meta-regression results revealed that baFMD was moderated by the participants' initial BMI value. Interestingly, participants with smaller initial BMI experienced greater improvements in FMD, irrespective of age or differences in training prescription. These results are consistent with previous findings by Green et al. (2014), who reported greater FMD improvement in participants with a lower initial body weight. Other studies on patients with metabolic syndrome found lower values of FMD in patients with greater metabolic syndrome severity (Sprung et al., 2020). Another study found that weight loss is the best predictor of the improvement of FMD in CHD patients, exhibiting a dose-response relationship (Ades et al., 2011). Although weight loss was the best predictor of FMD improvement, related measures such as fat mass, visceral fat, or waist circumference also exhibited correlations to FMD improvement (Ades et al., 2011).

Although similar observations can be found in the literature, further studies investigating a similar question, by including other measures such as the percentage of body fat, lean body mass, and skeletal muscle mass are needed to gain a better insight into how body composition might influence the effectiveness of endothelial adaptation. This observation might be attributable to the fact that obese or overweight individuals are at an elevated risk of CVD, even when classified as metabolically healthy (Opio et al., 2020). Consequently, increased body weight, coupled with CVD, may induce adverse endothelial adaptations, impairing the endothelium's capacity to respond to PEI. Similarly to the aforementioned findings on QoL, we observed a trend toward a negative association between changes in baFMD from pre-to-post PEI and PEI duration ($\beta = -0.102$, $p = 0.06$), suggesting that greater benefits might be expected from shorter PEI durations. However, given the trivial magnitude of the observed association, with only 1% explained variance, this finding warrants further investigation before it can be used in clinical practice on PEI guidelines for improving baFMD . No associations were observed for $\text{VO}_{2\text{peak}}$.

QoL seems to mirror improvements in cardiovascular health and aerobic capacity in exercise interventions in cardiovascular patients. Improvements measured using the SF-36 questionnaire seem to come mostly in subdomains connected to physical functioning and general health, although some studies also report changes in social functioning and role/emotional. This is in line with previous research, comparing the effects of exercise on QoL or other measures of cardiovascular health (Yu et al., 2023). Even though most studies report an improvement in at least one subdomain and the effect itself was large, statistical significance was not reached. Further research is required for an informed decision regarding specific improvements in different subdomains, as the reporting of items in QoL measurements was generally poor in the included studies, as shown in the risk of bias analysis of the reported studies.

Study Limitations

This study has several limitations that should be mentioned. Firstly, endothelial function was measured solely by utilizing FMD, even though other measurement options could have been included. Additionally, to ensure more consistency in the reporting, the authors chose to include FMD at a single location (the brachial artery). While this could be seen as a limitation, it may also be considered a strength of the current study. Secondly, the use of meta-regression led to the inclusion of studies that reported both FMD and QoL as primary

outcomes. As a result, the findings of the meta-regression are limited to studies that assessed FMD, QoL, and other secondary parameters. This approach restricted our ability to provide a comprehensive overview of changes in these parameters across all available studies. However, it allowed us to examine how variations in these parameters may moderate improvements in FMD. Thirdly, the risk of bias was high for reporting QoL due to the incomplete reporting of different QoL subdomains, especially using the SF-36 questionnaire. This limits the practical implications of this meta-analysis in terms of improvements in QoL. We recommend reporting all data for different subdomains of the given questionnaire to enhance the quality of data, reduce the risk of bias, and enable better analysis of QoL-related measures.

CONCLUSION

The current study findings show that PEIs are an effective method for improving maximal aerobic capacity and endothelial function, as measured by baFMD in CVD patients, while their effectiveness on QoL remains questionable. PEIs had a moderate effect on baFMD and $\text{VO}_{2\text{peak}}$, a small effect on 6MWT, and a large effect on QoL, though the latter did not reach statistical significance. Meta-regression analysis revealed a negative association between the participants' initial BMI and improvement in baFMD with PEI, suggesting that the participants' initial characteristics might influence the effectiveness of PEI in improving endothelial function. The results of this meta-analysis show concurrent improvements in measures of cardiovascular health, as well as patients' QoL following PEI. These findings underscore the need for further research to explore the dose-response relationship of PEIs to endothelial function and to identify subgroups who may derive greater benefits across a broad spectrum of health-related outcomes.

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Appendix

Supplementary Table 1. Risk of bias assessment for FMD

Study ID	Outcome	Weight	D1	D2	D3	D4	D5	Overall	
Claes et al 2020	FMD	1	+	+	+	+	+	+	Low risk
Kitzman et al 2013	FMD	1	+	!	+	+	+	!	Some concerns
Molmen-Hansen et al 2012	FMD	1	+	!	+	+	+	!	High risk
Mcdermott et al 2009	FMD	1	+	+	+	+	+	+	
Wisloff et al 2007	FMD	1	+	!	+	+	+	!	
Karavidas et al 2006	FMD	1	+	+	+	+	+	+	
Belardinelli et al 2006	FMD	1	+	+	+	+	+	+	
Blumenthal et al 2005	FMD	1	+	+	+	+	+	+	
Belardinelli et al 2005	FMD	1	!	+	+	+	+	!	

Legend: D1 – randomization process, D2 – deviations from intended interventions, D3 – missing outcome data, D4 – measurement of the outcome, D5 – selection of the reported result.

Supplementary Table 2. Risk of bias assessment for general health QoL measures.

Study ID	Outcome	Weight	D1	D2	D3	D4	D5	Overall	
Claes et al 2020	SF-36	1	+	+	+	-	+	-	+
Kitzman et al 2013	SF-36	1	+	!	+	+	-	-	!
Molmen-Hansen et al 2012	SF-36	1	+	!	+	+	-	-	-
McDermott et al 2009	SF-36	1	+	+	+	+	+	+	
Blumenthal et al 2005	GHQ	1	+	+	+	+	+	+	

Legend: D1 – randomization process, D2 – deviations from intended interventions, D3 – missing outcome data, D4 – measurement of the outcome, D5 – selection of the reported result.

Supplementary Table 3. Risk of bias assessment for disease-specific QoL measures.

Study ID	Outcome	Weight	D1	D2	D3	D4	D5	Overall	
Wisloff et al 2007	MacNew	1	+	!	+	+	+	!	+
Kitzman et al 2013	MLHFQ	1	+	!	+	+	+	!	!
Karavidas et al 2006	MLHFQ	1	+	+	+	+	+	+	-
Belardinelli et al 2006	MLHFQ	1	+	+	+	+	+	+	
Belardinelli et al 2005	MLHFQ	1	!	+	+	+	+	!	

Legend: D1 – randomization process, D2 – deviations from intended interventions, D3 – missing outcome data, D4 – measurement of the outcome, D5 – selection of the reported result.

Supplementary Table 4. Database search word syntax.

Database searched	Date	Word syntax	Number of articles
Cochrane Library	12.10.2023	(„endothelial function index“ OR „flow-mediated dilation“ OR „vascular endothelium“) AND („exercise“ OR „Physical activity“) AND randomized controlled trial in All Text (Word variations have been searched)	641
Web of Science	7.9.2023	(„endothelial function index“ OR „flow-mediated dilation“ OR „vascular endothelium“) AND („exercise“ OR „Physical activity“) AND randomized controlled trial in All Text (Word variations have been searched)	175
PubMed	7.9.2023	((adult[MeSH Terms] OR (adult[Title/Abstract])) AND ((vascular endothelium[MeSH Terms] OR (vascular endothelium[Title/Abstract]) OR (endothelial function[Title/Abstract]) OR (endothelial dysfunction[Title/Abstract]) OR (flow-mediated dilatation[Title/Abstract]) OR (endothelium-dependent vasodilatation[Title/Abstract]) OR (vascular reactivity[Title/Abstract])) AND ((exercise[MeSH Terms] OR (exercise[Title/Abstract]) OR (physical exercise[MeSH Terms] OR (physical exercise[Title/Abstract]) OR (exercise training[MeSH Terms] OR (exercise training[Title/Abstract])) AND (randomized controlled trial[Publication Type]))	470
CINAHL	7.9.2023	(„endothelial function index“ OR „flow-mediated dilation“ OR „vascular endothelium“) AND („exercise“ OR „Physical activity“) AND randomized controlled trial in All Text (Word variations have been searched)	121
EBSCOhost	7.9.2023	AB ((adult) AND (vascular endothelium OR endothelial function OR endothelial dysfunction OR endothelium-dependent vasodilatation OR vascular reactivity OR flow-mediated dilatation OR FMD) AND (exercise OR physical exercise OR training)) AND TX (randomised controlled trial or randomized controlled trial or rct)	91

Database searched	Date	Word syntax	Number of articles
EmBase	7.9.2023	adult/exp AND (exercise/exp OR ,physical activity'/exp) AND ((,vascular endothelium'/exp OR ,blood vessel endothelium' OR ,endangium' OR ,endothelium, blood vessel' OR ,endothelium, vascular' OR ,endovascular' OR ,vascular endothelium') OR ,endothelial function'/exp OR (,flow-mediated dilation test'/exp OR ,FMD technique' OR ,FMD test' OR ,flow-mediated dilatation assessment' OR ,flow-mediated dilatation technique' OR ,flow-mediated dilatation test' OR ,flow-mediated dilatation assessment' OR ,flow-mediated dilatation technique' / OR ,flow-mediated dilation test') OR ,endothelium dependent vasodilation' / exp OR ,endothelium dependent relaxation'/exp OR ,endothelium dependent vasodilatation'/exp) AND (,randomized controlled trial'/exp OR ,controlled trial, randomized' OR ,randomised controlled study' OR ,randomised controlled trial' OR ,randomized controlled trial')	182
PubMed	6.2.2024	Same as original search	7
Web of Science	14.2.2025	Same as original search	50
PubMed	14.2.2025	Same as original search	29
Embase	14.2.2025	Same as original search	36
CINAHL	14.2.2025	Same as original search	2
EBSCOhost	14.2.2025	Same as original search	57