Exercise Modalities and Endothelial Function: A Systematic Review and Dose– Response Meta-Analysis of Randomized Controlled Trials

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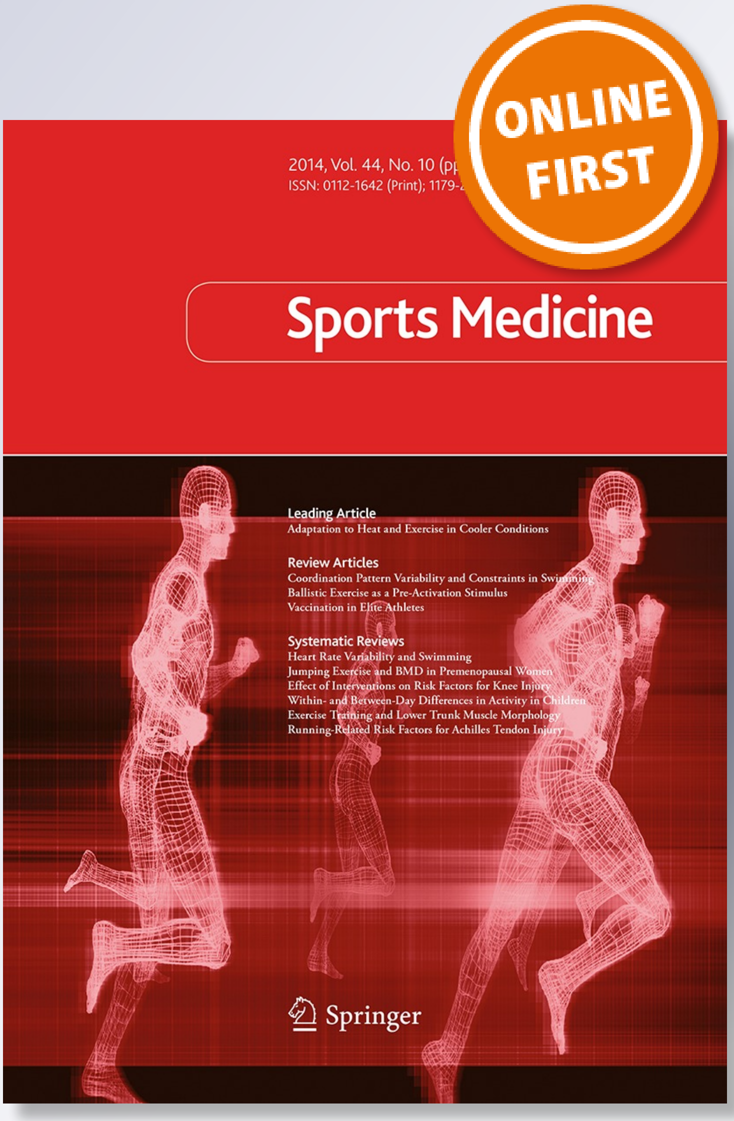

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SYSTEMATIC REVIEW

Exercise Modalities and Endothelial Function: A Systematic Review and Dose–Response Meta-Analysis of Randomized Controlled Trials

**Ammar W. Ashor · Jose Lara · Mario Siervo ·
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Abstract

Background Regular exercise is associated with enhanced nitric oxide (NO) bioavailability. Flow-mediated dilation (FMD) is used widely to assess endothelial function (EF) and NO release.

Objectives The aims of this systematic review and meta-analysis were to (i) investigate the effect of exercise modalities (aerobic, resistance or combined) on FMD; and (ii) determine which exercise and participant characteristics are most effective in improving FMD.

Methods We searched the MEDLINE, Embase, Cochrane Library, and Scopus databases for studies that met the following criteria: (i) randomized controlled trials of exercise with comparative non-exercise, usual care or sedentary groups; (ii) duration of exercise intervention ≥4 weeks; (iii) age ≥18 years; and (iv) EF measured by FMD before and after the intervention. Weighted mean differences (WMDs) with 95 % confidence interval were entered into a random effect model to estimate the pooled effect of the exercise interventions.

Results All exercise modalities enhanced EF significantly: aerobic (WMD 2.79, 95 % CI 2.12–3.45, $p = 0.0001$), resistance (WMD 2.52, 95 % CI 1.11–3.93, $p = 0.0001$) and combined (WMD 2.07, 95 % CI 0.70–3.44, $p = 0.003$). A dose–response relationship was observed between aerobic exercise intensity and improvement in EF. A 2 metabolic equivalents (MET) increase in absolute exercise intensity or a 10 % increase in relative exercise intensity resulted in a 1 % unit improvement in FMD. There was a positive relationship between frequency of resistance exercise sessions and improvement in EF (β 1.14, CI 0.16–2.12, $p = 0.027$).

Conclusions All exercise modalities improve EF significantly and there was a significant, positive relationship between aerobic exercise intensity and EF. Greater frequency, rather than intensity, of resistance exercise training enhanced EF.

Key Points

All exercise modalities improved endothelial function significantly.

There was a significant positive relationship between aerobic exercise intensity and endothelial function.

Greater frequency, rather than intensity, of resistance exercise training enhanced endothelial function.

1 Introduction

Epidemiological evidence suggests that physical activity is associated with a 35 % reduction in cardiovascular

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mortality and a 33 % reduction in all-cause mortality [1]. Moreover, there is an inverse dose–response relationship between physical activity and cardiovascular mortality or risk of coronary artery disease [2].

Despite the reported beneficial effect of physical activity on cardiovascular health, some evidence also suggests that different exercise modalities may have different effects on markers of cardiovascular diseases [3]. For example, studies have shown that resistance training reduced blood pressure and enhanced insulin sensitivity and glycaemic control significantly [4, 5]. However, a recently published meta-analysis demonstrated that resistance exercise intervention had adverse effects on vascular stiffness [6]. Furthermore, whilst aerobic exercise improved endothelial function (EF) significantly in individuals with diabetes mellitus [7], it failed to improve arterial stiffness indices in obese and hypertensive participants [8, 9].

Moreover, the intensity of exercise training further complicates the relationship between physical activity and cardiovascular markers. While some researchers suggested a higher threshold for aerobic exercise training to improve EF [10], other researchers advocate low-rather than high-intensity resistance exercise training for improved vascular function [11].

Enhancement of nitric oxide (NO) bioavailability is one of the most important molecular consequences of regular exercise and physical activity [12], and exercise-induced increases in shear stress enhances the synthesis and release of NO [13]. Furthermore, regular exercise increased NO availability by reducing its degradation by free radicals [14]. The assessment of coronary and brachial EF is associated with prediction of short- and long-term atherosclerotic progression and cardiovascular events rate [15]. Flow mediated dilation (FMD) is currently the most common method used to assess EF. This method involves measurement of brachial artery diameter at baseline and after reactive hyperaemia secondary to temporary occlusion of the upper or lower arm [16].

In the present systematic review, we aimed to investigate the effect of exercise modalities (aerobic, resistance or combined) on EF measured by FMD. Our secondary aim was to determine which exercise and participant characteristics are most effective in improving FMD.

2 Methods

This systematic review was conducted according to the Cochrane guidelines and is reported according to PRISMA guidelines [17, 18].

2.1 Data Sources

The search for relevant studies was conducted via electronic search of four databases (MEDLINE, Embase, Scopus and Cochrane library). Additionally, we searched for eligible studies in the reference lists of the relevant articles and reviews. The following keywords were used to search the above databases from inception until March 2014: ‘physical activity’, ‘training’, ‘exercise’, ‘endothelial function’, and ‘flow mediated dilation’ (see electronic supplementary material [ESM], Table S1).

2.2 Study Selection

The selection of eligible studies was conducted by two reviewers independently (AA, JL). Disagreements were resolved by a third reviewer (CCM). The inclusion criteria for eligible studies were as follows: (i) randomized controlled trials (RCTs) of exercise with comparative non-exercise, usual care or sedentary groups; (ii) prescribed structured exercise intervention of $\geq$4 weeks duration; (iii) adult humans aged $\geq$18 years; and (iv) studies that measured EF by FMD in response to reactive hyperaemia before and after intervention. We excluded studies of $<$4 weeks duration because animal and experimental studies showed that the beneficial adaptive effect of exercise on vascular function required at least 3 weeks to be detected [14, 19].

2.3 Data Abstraction and Quality Assessment

Data were extracted by one reviewer (AA) using a specific data extraction sheet and checked by an independent reviewer (CCM). Disagreements were resolved by discussion. The following information was extracted from eligible articles: (i) study design, quality, sample size; (ii) participants’ characteristics (age, sex, health status, body mass index [BMI], baseline FMD, systolic and diastolic blood pressure); (iii) characteristics of exercise intervention (type, duration and frequency of sessions, intensity and duration of intervention); (iv) outcome measures (instrument, position, duration and pressure of the occluding cuff; and (v) indices of study quality which was assessed by the modified Jadad score (range 0–5) using three main items related to randomization, blinding and description of dropout or withdrawals. Because it is difficult (if not impossible) to blind participants to an exercise intervention, we considered the blinding of the outcome assessment by the operator as a quality criterion. Two points were given if the study reported randomization with an appropriate random sequence generation, another two points were given if the study reported was blinded and described an appropriate method of blinding, and the fifth point was given if the study adequately described, and gave reasons for, dropout from the study. A Jadad score of <3 indicates a low quality study [20].

2.4 Statistical Analyses

Statistical analyses were performed by using STATA 12 (StataCorp. 2011. College Station, TX, USA). The outcome of the meta-analysis is the net difference between the intervention and control group in FMD. The FMD was calculated by subtracting the peak diameter after reactive hyperaemia from the baseline diameter divided by the baseline diameter and multiplied by 100. The secondary outcome was change in FMD in response to administration of nitroglycerin; that is, nitrate mediated dilation (NMD). Missing values (mean and SD) were imputed according to the Cochrane Handbook for Systematic Review [17]. The effect size was estimated as weighted mean differences (WMDs) with 95 % confidence intervals. Random effect models were used to take account of between-study heterogeneity for population characteristics, study design and methods used to assess EF. Data not provided in the main text or tables were extracted from the figures. For crossover trials, we used the mean and SD separately for the intervention and control conditions. In trials with multiple treatment arms and a single control group, the sample size of the control group was divided by the number of treatment groups to avoid over-inflation of the sample size [17].

Subgroup analyses were undertaken to investigate the role of potential factors influencing the effect of exercise modalities on EF and accounting for the heterogeneity of the models. These factors included the health status (whether healthy subjects or specific disease conditions), age of participants, baseline values for BMI, blood pressure and FMD. The values for age, BMI, blood pressure and FMD were dichotomized to ensure equal distribution of the studies in the subgroup analyses. Moreover, these values represent the mean values at baseline which were reported by the published studies, not the individual participants' data. Meta-regression analyses were conducted to examine possible dose-response relationships between exercise characteristics (intensity, frequency and duration of sessions) and changes in EF. Where studies reported a range of intensities across different time periods, the maximum exercise intensity before the end of intervention was chosen. Both relative (aerobic exercise: peak oxygen consumption [$VO_{2\mathrm{peak}}$]; resistance exercise: repetition maximum [% 1 RM]) and absolute (metabolic equivalents [METs]) exercise intensities were calculated by using the methods and formulae described by Howley [21]. Where studies used both aerobic and resistance exercise interventions, we estimated the exercise intensities for each type separately and then calculated the average of both exercise intensities.

Publication bias was evaluated by visual inspection of the funnel plot and by Egger's regression test [22]. Heterogeneity between studies was evaluated using Cochrane Q statistics; $p > 0.1$ indicates significant heterogeneity. The I^2 test was also used to evaluate consistency between studies where a value <25 % indicates low risk of heterogeneity, 25–75 % indicates moderate risk of heterogeneity and >75 % indicates high risk of heterogeneity [23].

3 Results

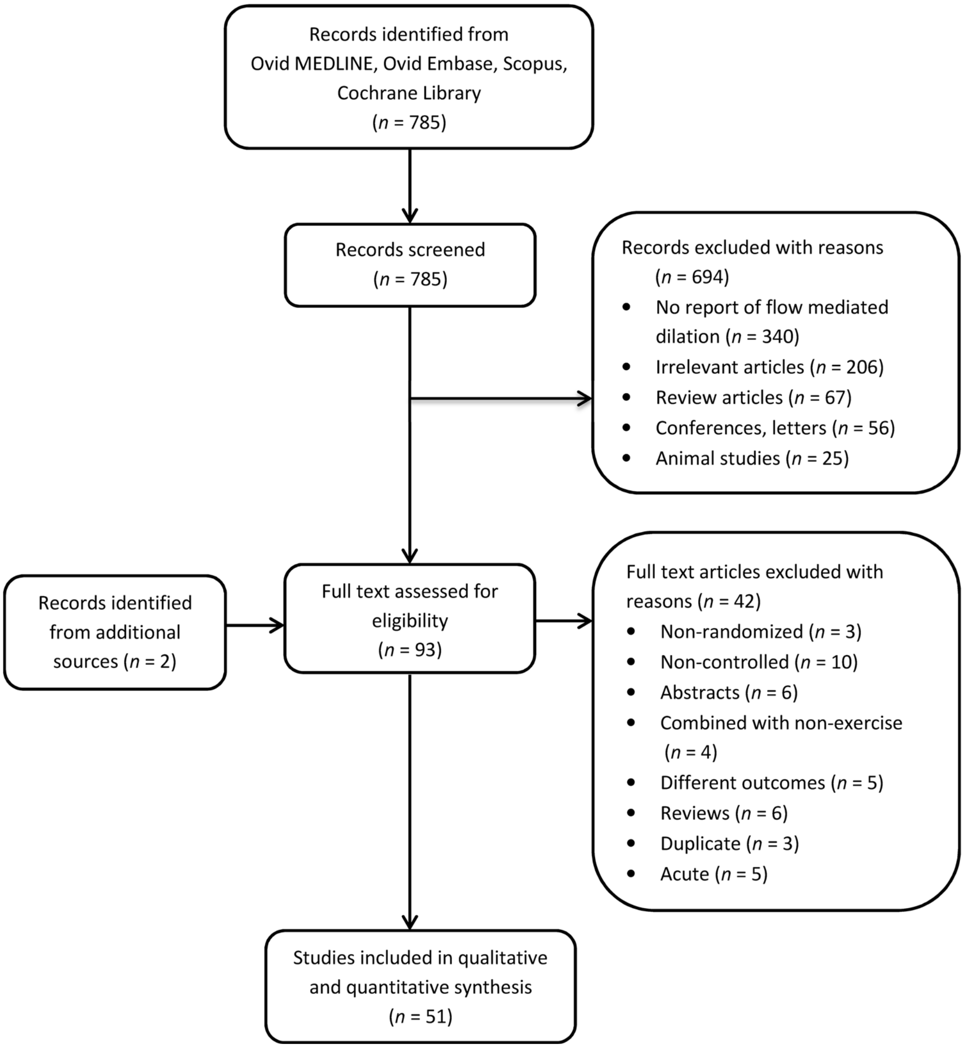
3.1 Search Results

The process followed in the selection of eligible studies is summarized in Fig. 1. After full text examination, 51 RCTs were included in the final analysis.

3.2 Study Characteristics

Characteristics of the studies included in the systematic review and meta-analysis are summarized in Tables 1 and 2. The total number of participants was 2,260 (1,378 males, 882 females) with a median sample size of 28 participants per study (range 10–112). Participant age ranged from 18 to 76 years (median 56 years). Twelve studies included males only while five studies included females only. The median duration of the studies was 12 weeks (range 4–52 weeks). The quality of the included studies ranged from 2 to 5 with a median quality score of 4. The study design comprised 39 parallel, 9 factorial and 3 crossover studies. Some of the articles included results from separate, independent trials testing the effects of two or more exercise modalities on EF, so the 51 articles yielded a total of 65 trials for the final analysis. Of these, 42 trials investigated aerobic exercise [24–61], 12 investigated resistance exercise [24, 42, 45, 46, 53, 56, 62–66] and 11 investigated a combination of aerobic and resistance exercise [53, 56, 67–74]. The relative intensity of exercise ranged from 38 to 85 % with a median of 60 % $VO_{2\mathrm{peak}}$ while the median of absolute intensity was 7.2 (range 3.2–9.9 METs). The duration of exercise sessions ranged from 15 to 60 minutes (median 40 min) and the frequency from 1 to 7 sessions per week (median 3 per week). Two studies reported the occurrence of minor adverse effects, hypoglycaemia [40] and diarrhoea [27]. The methods for quantification of FMD varied considerably between studies, including the specific instruments used and site of reading (proximal vs distal to the occluding cuff). The duration of cuffing ranged from 3 to 8 minutes and the pressure of the occluding cuff ranged from 50 mmHg above systolic pressure to 300 mmHg (ESM, Tables S2 and S3).

Fig. 1 Flow diagram of the process used in selection of the randomized controlled trials included in this systematic review and meta-analysis



3.3 Meta-Analyses of Aerobic Exercise Studies

Data synthesis from aerobic exercise trials (1,591 participants) revealed a significant improvement in FMD with exercise (WMD 2.79, 95 % CI 2.12–3.45, $p = 0.0001$). However, these studies were characterized by significant heterogeneity ($\chi^2 = 342.3, p < 0.001, I^2 = 88$ %) (Fig. 2). Analysis of the studies according to the health status of participants showed that larger improvements of EF were observed in participants with cardio-metabolic disorders (Table 3). Moreover, subgroup analyses showed significantly greater improvement in FMD after aerobic exercise intervention in non-obese compared with obese participants (Table 3 and ESM, Table S4).

Meta-regression analyses demonstrated significant positive relationships between both absolute (β 0.51, CI 0.01–1.00, $p = 0.046$) and relative exercise intensity (β 0.06, CI 0.002–0.12, $p = 0.042$) and improvement in FMD (Fig. 3). The meta-regression coefficient showed that every 2-MET increase in absolute intensity or 10 % increase in relative intensity of aerobic exercise resulted in approximately 1 % unit improvement in FMD.

Visual inspection of the funnel plot for the aerobic exercise studies indicated slight asymmetry (ESM, Figure S1), which, together with Egger's regression test outcomes (β 1.17, $p = 0.122$), suggested low likelihood of publication bias.

3.4 Meta-Analyses of Resistance Exercise Studies

Meta-analysis of resistance exercise studies (396 participants) demonstrated significant improvement in FMD (WMD 2.52, 95 % CI 1.11–3.93, $p = 0.0001$), but there was also significant heterogeneity between studies ($\chi^2 = 130.5, p < 0.001, I^2 = 91.6$) (Fig. 4).

Subgroup analyses of resistance exercise studies showed non-significant differences across various groups (Table 3 and ESM, Table S5). Meta-regression analyses showed no evidence of a dose–response relationship between the intensity of resistance exercise and EF (Fig. 5), but the

Table 1 Characteristics of aerobic exercise studies included in the systematic review and meta-analysis

References	Health status	Sample size	Age (years)	Male (%)	Basal BMI (kg/m^2)	Baseline FMD (%)	Type of exercise	Intensity of exercise	Session duration (min)	Frequency of sessions (per week)	Duration of intervention (weeks)	Jadad score
Beck et al. [24]	Prehypertension	28	20	68	29	6	W/R	65–85 % HR_{max}	60	3	8	3
Belardinelli et al. [27]	CAD	56	60	84	29	4	C	60 % of VO_{2peak}	40	3	8	2
Belardinelli et al. [26]	CHF	59	57	100		2	C	60 % of VO_{2peak}	40	3	8	4
Belardinelli et al. [25]	CHF	52	55	100		4	C	60 % of VO_{2peak}	40	3	8	4
Bhutani et al. [28]	Obese	40	42	95	35	7	C	60–75 % HR_{max}	25–40	3	12	2
Blumenthal et al. [30]	CAD	90	62	70	30	5	W/J	70–85 % HRR	35	3	16	3
Blumenthal et al. [29]	CAD	59	65	75	31	4	W/J	70–85 % HR_{max}	30	3	16	3
Braith et al. [31]	Heart transplant	16	54	81	26	5	W	12–14/20 Borg scale	30–40	3	12	4
Choi et al. [32]	Type 2 diabetes	75	54	0		6	W	3.6–6 MET	60	5	12	5
Desch et al. [33]	CAD	27	62	70	30	10	C	75 % HR_{max}	45	7	24	4
Edwards et al. [34]	CAD	18	63	100	30	8	W/C	45–85 % HRR	20–50	3	12	2
Erbs et al. [35]	CHF	37	60	100	27	6	C	60 % of VO_{2peak}	40	7	12	5
Giannattasio et al. [36]	CHF	22	61	82		7	C		30	3	8	2
Herman et al. [37]	Heart transplant	27	53	81	26	8	C/R	80–90 % of VO_{2peak}	42	3	8	5
Hill et al. [38]	Overweight	32	51	41	33	19	W/R	75 % HR_{max}	45	3	12	3
Jones et al. [39]	Prostatectomy	35	58	100	28	3	W	55–100 % of VO_{2peak}	30–45	5	24	5
Kitzman et al. [40]	CHF	54	70	26	32	4	W/C	70 % HRR	40	3	16	2
Kobayashi et al. [41]	CHF	28	55	71		4	C	13/20 Borg scale	15	3	12	4
Kwon et al. [42]	Type 2 diabetes	28	56	0	27	4	W	4–6 MET	60	5	12	2
Lavrenčič et al. [43]	Polymetabolic syndrome	29	53	100	32	5	C	80 % HR_{max}	30	3	12	4
Linke et al. [44]	CHF	22	58	100		4	C	70 % of VO_{2peak}	60	6	4	2
Maiorana et al. [45]	CHF	24	61	92	30	4	W/C	50–70 % of VO_{2peak}	45	3	12	2
McDermott et al. [46]	PAD	65	72	52	30	6	W	12–14/20 Borg scale	40	3	24	5
Munk et al. [47]	CAD	40	57	83	27	3	C	80–90 % HR_{max}	30	3	24	5
Pierce et al. [48]	Healthy	36	63	39	25	5	W	70–75 % HR_{max}	40–50	6–7	8	4
Ramírez-Vélez et al. [49]	Pregnancy	50	20	0		14	?	50–65 % HR_{max}	60	3	16	5
Schmidt et al. [50]	Heart transplant	13	60	100	27	5	C	60 % HR_{max}	40	2–3	24	2
Sixt et al. [51]	Prediabetes + CAD	23	64	74	29	9	C	70 % HR_{max}	45	3	4	4
Sonnenschein et al. [52]	Metabolic syndrome	24	58	92	33	7	C	50–70 % of VO_{2peak}	30	3	8	4
Stensvold et al. [53]	Metabolic syndrome	22	50	64	31	7	W/R	90–95 % HR_{max}	30	3	12	4
Swift et al. [54]	Postmenopausal obese	155	57	0	32	4	C	4,8,12 kcal/kg/week		3–4	24	4
Tjønna et al. [55]	Metabolic syndrome	28	55	46	30	5	W/R	90 % HR_{max}	30	3	16	4
Vona et al. [57]	CAD	52	56	77		2	C	75 % HR_{max}	40	3	12	4
Vona et al. [56]	CAD	102	56	75	27	5	C	75 % HR_{max}	40	3	4	4

Table 1 continued

References	Health status	Sample size	Age (years)	Male (%)	Basal BMI (kg/m^2)	Baseline FMD (%)	Type of exercise	Intensity of exercise	Session duration (min)	Frequency of sessions (per week)	Duration of intervention (weeks)	Jadad score
Westhoff et al. [59]	Hypertension	24	66	46	29	4	C	2 ± 0.5 lactate	10–30	3	12	4
Westhoff et al. [58]	Hypertension	52	68	50	28	6	W	2 ± 0.5 lactate	20–36	3	12	4
Wisløff et al. [60]	CHF	27	77	74	25	4	W	90–95 % HR_{max}	25	3	12	4
Yoshizawa et al. [61]	Postmenopausal	20	57	0	24	5	W/C	60–75 % HR_{max}	25–45	3–5	8	3

BMI body mass index, *C* cycling, *CAD* coronary artery disease, *CHF* congestive heart failure, *FMD* flow mediated dilation, HR_{max} maximum heart rate, *HRR* heart rate reserve, *J* jogging, *MET* metabolic equivalent, *PAD* peripheral arterial disease, *R* running, VO_{2peak} peak oxygen consumption, *W* walking

frequency of resistance exercise sessions was significantly, and positively, associated with FMD (β 1.14, CI 0.16–2.12, $p = 0.027$) (Fig. 5).

Visual inspection of the funnel plot did not show evidence of publication bias for the resistance exercise studies included in the meta-analysis (ESM, Figure S2) and Egger's regression test outcomes (β −0.31, $p = 0.104$) confirmed the likely absence of publication bias.

3.5 Meta-Analyses of Combined (Aerobic and Resistance) Exercise Studies

Analysis of data from combined exercise trials (449 participants) showed significant improvement in EF (WMD 2.07, 95 % CI 0.70–3.44, $p = 0.003$) with significant heterogeneity between studies ($\chi^2 = 71.8$, $p < 0.001$, $I^2 = 86$) (Fig. 6). Subgroup analyses of combined (aerobic and resistance) exercise studies demonstrated a significantly greater improvement of FMD in those participants with lower baseline FMD values (Table 3 and ESM, Table S6). However, meta-regression analyses did not show any significant relationships between characteristics of the combined exercise interventions and EF (ESM, Figure S3).

Neither funnel plot (ESM, Figure S4) nor Egger's regression test (β 3.17, $p = 0.602$) suggested evidence of publication bias for the studies included in the combined exercise meta-analysis.

3.6 Effect of Exercise Modalities on Nitrate Mediated Dilation (NMD)

There was a tendency for improved NMD after exercise intervention (26 trials, 1,159 participants) when compared with the corresponding control groups but this effect was not statistically significant (WMD 0.47, 95 % CI −0.009 to 0.95, $p = 0.055$) (ESM, Figure S5).

4 Discussion

The main finding of our systematic review and meta-analysis was that all exercise modalities (aerobic, resistance or combined exercise) enhanced EF significantly in comparison with the control groups. Furthermore, there was a significant dose–response relationship between both the relative and absolute aerobic exercise intensity and FMD. In contrast, exercise frequency, not exercise intensity, was positively associated with FMD in resistance exercise studies.

The following potential mechanisms may explain the beneficial effects of exercise on EF. First, exercise increases NO bioavailability, which occurs secondary to enhanced expression/stabilization of endothelial nitric

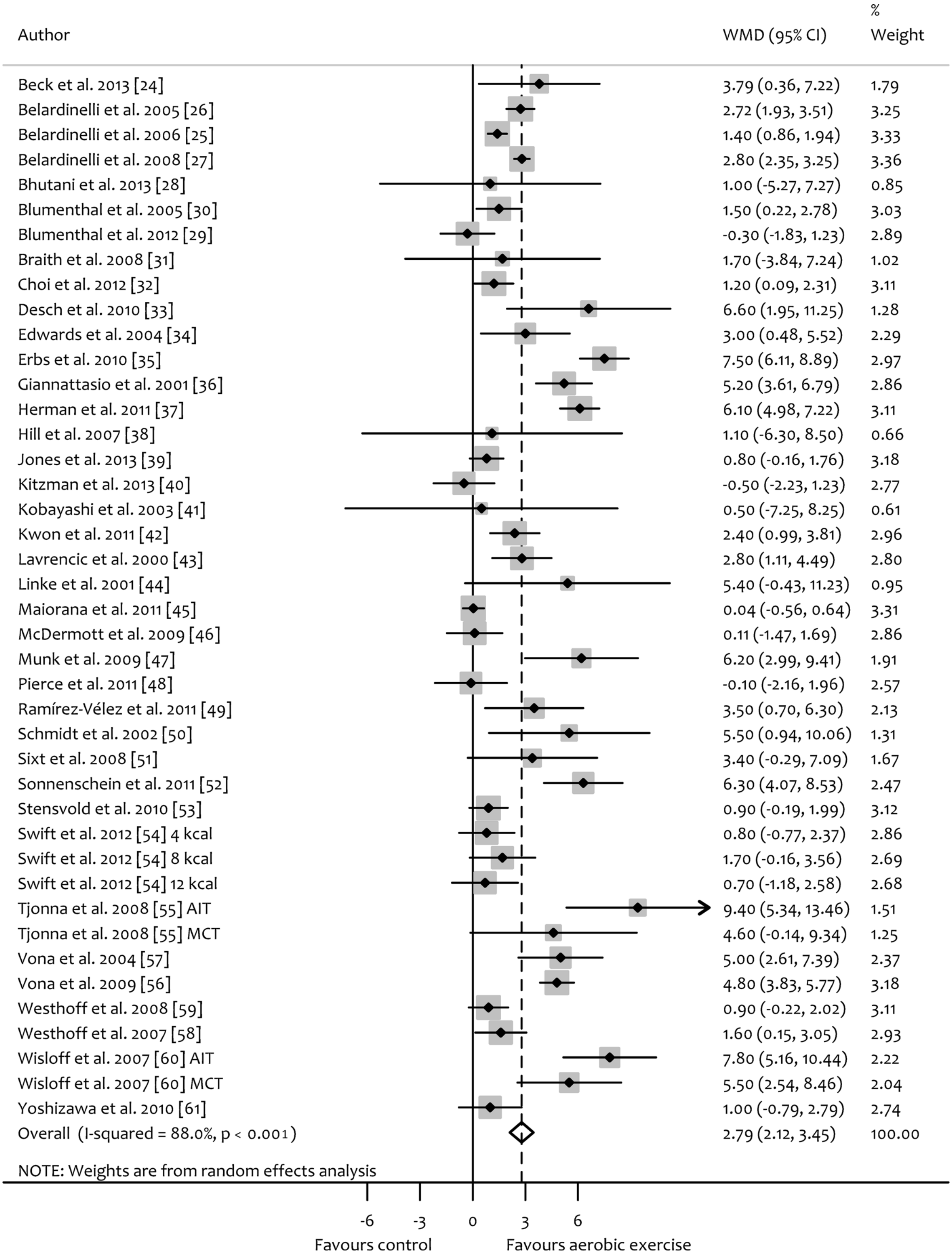


Fig. 2 Forest plot showing the effect of aerobic exercise on endothelial function. The pooled estimates were obtained by using random effect models. *Diamonds* indicate the effect size of each study summarized as weighted mean difference (WMD). The size of the *shaded squares* is proportional to the percentage weight of each study. *Horizontal lines* represent the 95 % confidence interval and the *vertical broken line* represents the overall effect. *AIT* acute interval training, *MCT* moderate continuous training

oxide synthase enzyme (eNOS) or reduced inactivation/degradation of NO by free radicals [75]. Second, regular exercise increases expression of the antioxidant enzymes, superoxide dismutase, glutathione peroxidase and catalases and so enhances the antioxidant capacity [26]. Moreover, exercise reduces expression of the oxidant enzymes,

Table 2 Characteristics of resistance/combined exercise studies included in the systematic review and meta-analysis

Author	Health status	Sample size	Age (years)	Male (%)	Basal BMI (kg/m^2)	Baseline FMD (%)	Type of exercise	Intensity of exercise	Session duration (min)	Frequency of sessions (per week)	Duration of intervention (weeks)	Jadad score
Barone Gibbs et al. [67]	Type 2 diabetes	112	58	62	32	6	Aerobic and resistance (2 sets of 12–15 reps of pull down, leg extension, leg curl, leg press, bench press, shoulder press and seated mid-rowing)	60–90 % HR$_{max}$/ 50 % 1 RM	45	3	26	2
Beck et al. [24]	Prehypertension	30	21	70	27	6	All major muscle groups; 2 sets of 8–12 reps	50 % 1 RM	60	3	8	3
Hambrecht et al. [62]	CHF	20	55	100		3	Dynamic handgrip exercise		?	7	4	2
Haykowsky et al. [68]	Heart transplant	43	57	81		4	Treadmill, cycling (aerobic) and resistance (chest press, pull down, arm curls, leg press)	60–80 % HR$_{max}$/ 50 % 1 RM	45	7	12	2
Kwon et al. [42]	Type 2 diabetes	27	56	0	27	5	Biceps curls, triceps extensions, upright rows, shoulder chest press, seated rows		40	3	12	2
Luk et al. [69]	CAD	64	68	75	25	4	Treadmill, ergometry, rowing, steps, arm ergometry, resistance (dumbbell or weights)	80 % HR$_{max}$	50	3	8	3
Maiorana et al. [70]	Type 2 diabetes	16	52	88		2	Circuits of hand gripping, forearm exercise, cycle ergometry, treadmill walking and resistance training of major muscle groups	70–85 % HR$_{max}$/ 60 % 1 RM	60	1	8	3
Maiorana et al. [45]	CHF	24	59	88	28	4	3 Sets of 9 weight exercises with 3-min rest period between each set	50–70 % 1 RM	45	3	12	2
McDermott et al. [46]	PAD	64	72	55	30	6	3 Sets of 8 reps of knee extension, leg press, leg curl	50–80 % 1 RM	40	3	24	5
Okada et al. [71]	Type 2 diabetes	38	62	55	26	7	Aerobic dance, stationary bicycle riding, resistance training		60	3–5	12	3
Okamoto et al. [72]	Healthy	22	19	32	22	8	Running (aerobic) and resistance (chest and shoulder press, arm curls, seated rows, leg curls, leg press and sit-ups)	60 % HR$_{max}$/80 % 1 RM		2	8	3
Okamoto et al. [63]	Healthy	19	19	100		9	Chest and shoulder press, arm curls, lateral pull down, seated rows, leg extension, leg curls, leg press and sit-ups	40 % 1 RM		2	8	3
Okamoto et al. [64]	Healthy	30	20	100	21	14	Chest press, arm curls, seated rows, leg curls, leg press and sit-ups	80 % 1 RM		2	10	3
Okamoto et al. [65]	Healthy	26	19	73	23	10	Chest press, arm curls, lateral pull down, seated rows, leg extension, leg curls, leg press and sit-ups	50 % 1 RM		2	10	3
Olson et al. [66]	Overweight	30	38	0	28	6	3 Sets of 8–10 reps isotonic resistance machines to major muscle groups			2–3	52	2

Table 2 continued

Author	Health status	Sample size	Age (years)	Male (%)	Basal BMI (kg/m^2)	Baseline FMD (%)	Type of exercise	Intensity of exercise	Session duration (min)	Frequency of sessions (per week)	Duration of intervention (weeks)	Jadad score
Stensvold et al. [53]	Metabolic syndrome	22	51	64	32	8	2–3 Sets of 8–12 reps to major muscle groups (deltoid, triceps, biceps, curl, low-row and core exercise)	60–80 % 1 RM	45	3	12	4
Stensvold et al. [53]	Metabolic syndrome	21	53	62	30	8	W/R (2/week) and the above resistance programme once per week	90–95 % HR$_{max}$/ 70 % 1 RM	45	3	12	4
Vona et al. [56]	CAD	104	57	73	26	4	4 Sets of 10–12 reps with weights and rubber bands, major muscle groups	60 % 1 RM	40	4	4	4
Vona et al. [56]	CAD	103	55	75	26	4	Cycling and 4 sets of 10–12 reps with weights and rubber bands, major muscle groups	75 % HR$_{max}$/60 % 1 RM	40	4	4	4
Walsh et al. [74]	Hypercholesterolaemia	10	52	70		4	Circuit of resistance training cycle ergometry and treadmill walking	70–85 % HR$_{max}$	45–60	2	8	2
Walsh et al. [73]	CAD	10	55	100	29	3	Circuit of resistance training (leg press, standing calf raise, hip flexion, pectoral exercise, abdominal flexion and shoulder extension), cycle ergometry and treadmill walking	70–85 % HR$_{max}$/ 60 % 1 RM	45–60	3	8	3

1 RM one repetition maximum, *BMI* body mass index, *CAD* coronary artery disease, *CHF* congestive heart failure, *FMD* flow mediated dilation, *HR$_{max}$* maximum heart rate, *PAD* peripheral arterial disease, *R* running, *reps* repetitions, *W* walking

Table 3 Subgroup analyses of the effects of exercise modalities on endothelial function using a random-effects model

	No. of subgroups	Aerobic exercise			No. of subgroups	Resistance exercise			No. of subgroups	Combined (aerobic and resistance)		
		FMD % (95 % CI)	I^2 %	*p* Value		FMD % (95 % CI)	I^2 %	*p* Value		FMD % (95 % CI)	I^2 %	*p* Value
Health status				0.098				0.484				0.200
Congestive heart failure	10	3.51 (1.84–5.17)	94.3		2	3.46 (−4.20 to 11.12)	96.3					
Coronary artery disease	9	3.25 (2.01–4.49)	82.5		1	5.0 (4.02–5.98)	–		3	3.48 (0.68–6.29)	90.8	
Type 2 diabetes	2	1.72 (0.55–2.88)	41.7		1	1.60 (−0.25 to 3.45)	–		3	3.50 (−0.06 to 7.06)	68.9	
Healthy	2	1.57 (−1.95 to 5.09)	75.7		4	1.87 (0.18–3.56)	75.7		1	−0.90 (−2.41 to 0.61)	–	
Heart transplantation	3	5.64 (3.94–7.34)	15.3						1	1.40 (−1.62 to 4.42)	–	
Hypercholesterolaemia									2	1.71 (−1.29 to 4.71)	49.9	
Hypertension	2	1.16 (0.27–2.05)	0									
Metabolic syndrome	5	4.44 (1.68–7.19)	87.3		1	3.0 (1.84–4.16)	–		1	1.10 (0.07–2.13)	–	
Overweight/obese	2	1.04 (−3.74 to 5.83)	0		1	3.80 (1.68–5.92)	–					
Peripheral arterial disease	1	0.11 (−1.47 to 1.69)	–		1	0.85 (−0.99 to 2.69)	–					
Postmenopausal	4	1.03 (0.15–1.91)	0									
Prehypertension	1	3.79 (0.37–7.22)	–		1	2.45 (−0.44 to 5.34)	–					
Prostatectomy	1	0.80 (−0.16 to 1.76)	–									
Age of participants (years)				0.718				0.714				0.689
≤55	12	2.59 (1.24–3.93)	83.5		8	2.84 (1.58–4.10)	66		7	2.25 (0.29–4.21)	80.1	
>55	30	2.87 (2.06–3.68)	89.5		4	1.79 (−1.20 to 4.78)	95.5		4	1.57 (0.64–2.50)	85.9	
Body mass index (kg/m^2)				0.009				0.727				0.423
≤29.9	21	3.71 (2.68–4.73)	88.5		8	2.21 (0.33–4.10)	90.5		5	2.54 (−0.15 to 5.24)	86.9	
≥30	13	1.22 (0.33–2.10)	72.3		2	2.05 (−0.04 to 4.14)	94		2	0.97 (0.08–1.85)	91.2	
Baseline systolic pressure (mmHg)				0.745				0.426				0.049
≤120	7	3.23 (0.56–5.90)	92.2		5	3.16 (0.97–5.34)	84.4		1	−0.90 (−2.40 to 0.60)	0	
>120	22	2.33 (1.50–3.16)	88.8		3	1.60 (−1.04 to 4.24)	92.7		5	1.45 (0.77–2.14)	0.2	

Table 3 continued

	No. of subgroups	Aerobic exercise			No. of subgroups	Resistance exercise			No. of subgroups	Combined (aerobic and resistance)		
		FMD % (95 % CI)	I^2 %	*p* Value		FMD % (95 % CI)	I^2 %	*p* Value		FMD % (95 % CI)	I^2 %	*p* Value
Baseline diastolic pressure (mmHg)				0.650				0.914				0.935
≤80	17	2.52 (1.27–3.78)	90.4		6	2.52 (0.36–4.68)	91.9		5	1.23 (−0.22 to 2.69)	66.1	
>80	11	2.89 (1.58–4.20)	87.4		2	2.92 (1.84–4.00)	0		1	1.10 (0.07–2.12)	–	
Baseline FMD (%)				0.112				0.826				0.024
≤4.6	21	2.23 (1.45–3.00)	87.8		3	3.91 (−0.60 to 8.42)	95.2		6	3.21 (1.62–4.79)	79.9	
>4.6	21	3.40 (2.17–4.63)	87.1		9	2.13 (1.23–3.03)	68.2		5	0.59 (−0.48 to 1.67)	45.1	
Duration of the study (weeks)				0.294				0.292				0.490
≤10	12	3.42 (2.37–4.47)	89.6		7	3.10 (1.40–4.80)	85.4		7	2.38 (0.45–4.30)	0	
>10	30	2.51 (1.67–3.36)	84.8		5	1.70 (−0.07 to 3.48)	89.0		4	1.13 (0.31–1.96)	89.6	
Quality of studies (Jadad score)				0.653				0.798				0.432
<3	9	2.43 (0.97–3.89)	90.2		4	2.93 (−0.13 to 5.99)	92.6		4	1.03 (−0.17 to 2.24)	0	
≥3	33	2.91 (2.11–3.71)	87.6		8	2.41 (1.11–3.70)	82.0		7	2.42 (0.64–4.21)	90.7	

FMD flow mediated dilation, *p* value for the meta-regression analyses between subgroups

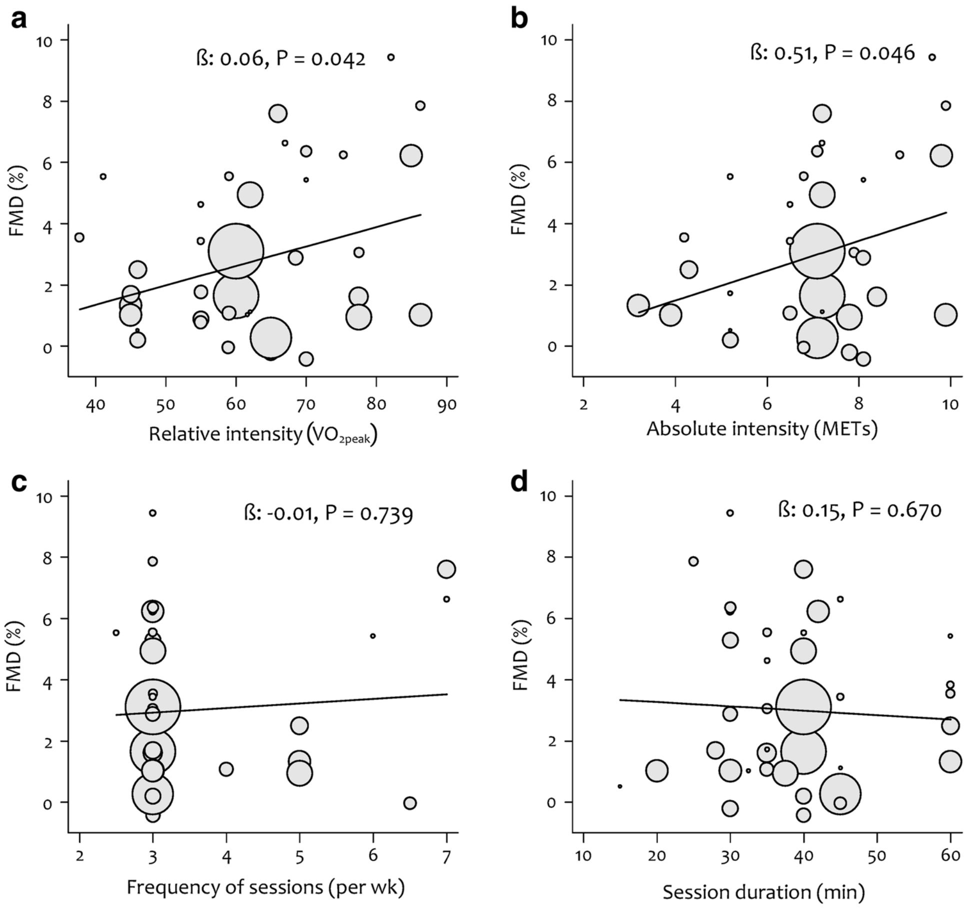


Fig. 3 Associations between aerobic exercise intervention characteristics and endothelial function measured by FMD: **a** relative intensity; **b** absolute intensity; **c** session frequency; **d** session duration. Each study is depicted by a *circle* where the *circle size* represents the degree of weighting for the study based on participant numbers. *FMD* flow mediated dilation, VO_{2peak} peak oxygen consumption, *MET* metabolic equivalent

nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase [13]. Third, regular exercise provides anti-inflammatory effects through reduced expression of pro-inflammatory molecules such as interleukins, adhesion molecules, selectin and C-reactive protein [76]. The fourth mechanism involves the ability of exercise to increase the number of endothelial progenitor cells (EPCs) which could contribute to vascular regeneration and angiogenesis [77].

We found a significant dose–response relationship between aerobic exercise intensity and FMD which may be due to the greater release of NO because of the higher shear stress on the endothelium caused by greater exercise intensity [78]. These findings support the emerging evidence that high-intensity physical training may be more beneficial for cardiovascular health than low-intensity physical training [79]. Physical activity guidelines published by the American College of Sports Medicine emphasize the benefit of high-intensity exercise training for maintaining and improving cardiovascular health [80]. For each MET increase in exercise intensity, cardiovascular and all-cause mortality are reduced by 8–17 % [81]. Moreover, in comparison with moderate-intensity exercise, high-intensity exercise training was superior in improving cardiorespiratory fitness (CRF) [82, 83]. CRF is a strong, negative predictor of cardiovascular mortality and morbidity and improvements in CRF improve the prognosis of patients with chronic diseases [84].

Despite the evident benefits from regular exercise on cardiovascular and other aspects of health, physical inactivity is highly prevalent in the general population. The most common barrier associated with inactivity and non-compliance with regular exercise is lack of time [85]. Therefore, high-intensity interval training (HIIT) might be a useful alternative to conventional moderate-intensity, longer-duration exercise and might enhance both compliance and efficacy [86]. Research suggests that HIIT improves compliance and is superior in improving major cardio-metabolic outcomes including insulin sensitivity, glucose metabolism, high-density lipoproteins, oxidized low-density lipoproteins, left ventricular dysfunction, NO bioavailability and EF [55, 60, 83, 86, 87].

Aerobic exercise significantly improved EF in both obese and non-obese participants. However, the beneficial effect was significantly greater in non-obese than in obese individuals (Table 3). This adiposity-related difference was not explained by differences in baseline blood pressure, age, health status of participants or in the intensity,

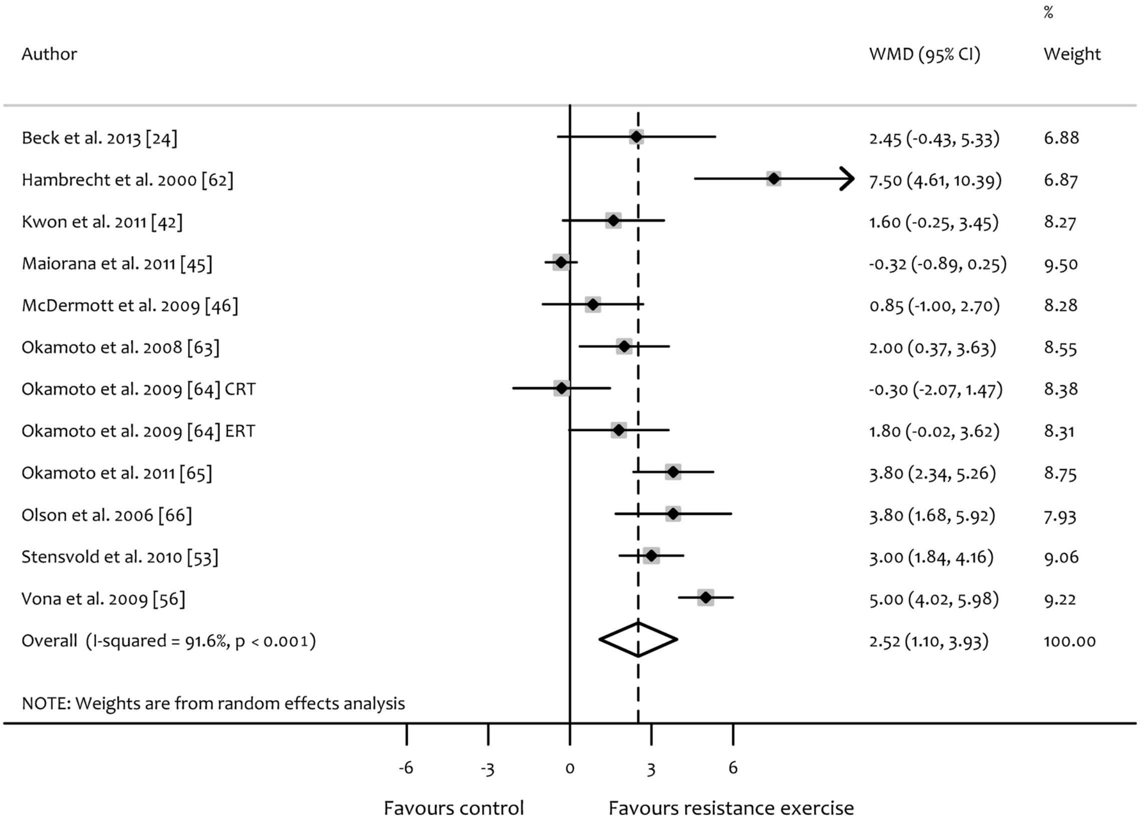


Fig. 4 Forest plot showing the effect of resistance exercise on endothelial function. The pooled estimates were obtained by using random effect models. *Diamonds* indicate the effect size of each study summarized as weighted mean difference (WMD). The size of the *shaded squares* is proportional to the percentage weight of each study. *Horizontal lines* represent the 95 % confidence interval and the *vertical broken line* represents the overall effect. *ERT* eccentric resistance training, *CRT* concentric resistance training

duration or frequency of the intervention. Therefore, we speculate that aerobic exercise alone may not be the best method to enhance EF in obese individuals. Future studies are required to discover whether the effects of aerobic exercise plus weight loss intervention are superior to those of aerobic exercise alone in improving EF in obese people.

In subgroup analysis of combined exercise studies, we observed a significantly greater improvement of EF in populations with low baseline FMD. This may indicate that combined (aerobic and resistance) exercise interventions are more beneficial in populations at greater cardiovascular risk.

In the present meta-analysis, we observed that exercise improved NMD marginally. In studies of EF, NMD is used as a measure of smooth muscle function compared with the hyperaemic FMD which is a proxy for EF. Deterioration in NMD function is found in several cardio-metabolic disorders [7] and is a strong predictor of cardiovascular disease (CVD) [88]. Animal studies showed that regular exercise may involve changes in protein kinase C-α expression and phosphorylation, which augment intracellular calcium concentration and eventually smooth muscle contraction [30]. Therefore, NMD improvement might be an additional beneficial effect of exercise on cardiovascular outcomes which requires confirmation in future studies.

4.1 Implications

In this systematic review and meta-analysis we aimed to investigate the effect of exercise modalities (aerobic, resistance or combined) on EF and to determine which exercise and participant characteristics are most effective in improving EF. Epidemiological studies have suggested that changes in known CVD risk factors explain a large proportion (59 %) of the observed beneficial effect of exercise on major cardiovascular outcomes [89]. The remaining 40 % of risk reduction may be attributed to effects on vascular haemodynamics (including EF, arterial remodelling, and vessel compliance) [19]. A recently conducted meta-analysis involving data from more than 5,000 participants showed that every 1 % unit improvement in FMD (typical values for FMD are 8–12 %) [1] may reduce the risk of cardiovascular events by 13 % [15]. In the present meta-analysis, exercise modalities (aerobic, resistance or combined) increased FMD by 2–2.8 % units, which could translate into a reduction in CVD risk of 26–36 %.

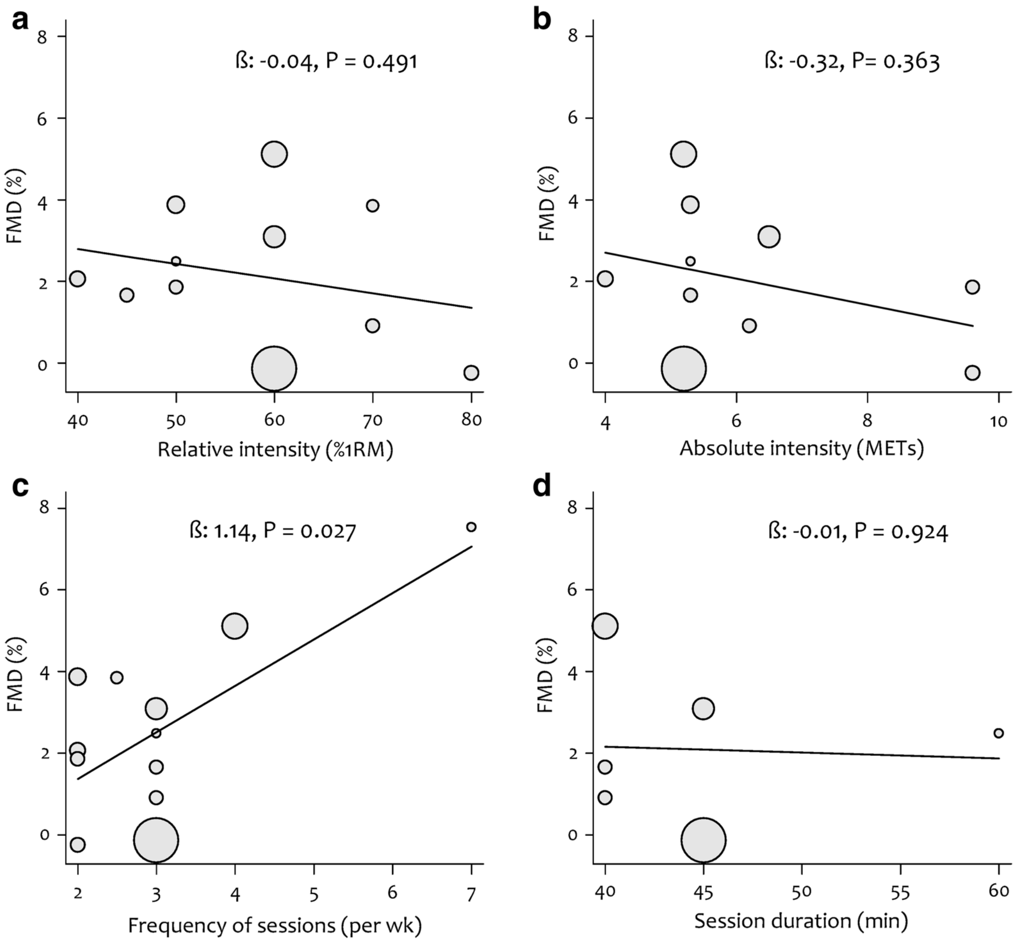


Fig. 5 Associations between aerobic exercise intervention characteristics and endothelial function measured by FMD: **a** relative intensity; **b** absolute intensity; **c** session frequency; **d** session duration. Each study is depicted by a *circle* where the *circle size* represents the degree of weighting for the study based on participant numbers. *FMD* flow mediated dilation, *RM* repetition maximum, *MET* metabolic equivalent

We found that all intensities (light, moderate and vigorous) of aerobic exercise enhance EF significantly and there was a dose–response relationship between relative/absolute exercise intensities and EF. Every 2-MET increase in absolute exercise intensity was associated with approximately 1 % unit improvement in FMD. This suggests that more intensive exercise may have greater CVD benefits and that the focus should be on intervention modalities which enhance compliance with the exercise intervention [90].

4.2 Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis examining the effect of different exercise modalities on EF. A total number of 2,260 participants (1,378 males, 882 females) from 51 studies were included in this meta-analysis. The generalizability of findings from our study is enhanced by our inclusion of a wide range of participants from trials in several geographical locations. We included participants with normal health, those suffering from cardiac, hypertensive and diabetic diseases, obese participants and those with the metabolic syndrome. The included trials were conducted in North America, Europe, Asia, Australia and South America. Further strengths of our study include the comprehensive search of major databases with no language or time restrictions and the rigorous way in which the review was conducted and the results are reported. However, the study has limitations including the high levels of heterogeneity among the studies and therefore our findings should be treated with caution until further research reveals the sources of this heterogeneity. For example, several factors such as smoking, food and alcohol intakes and the diverse health status of the participants may have influenced the results and contributed to the high levels of heterogeneity observed. In previous studies of healthy participants, FMD ranged from 2.2 to 19.1 %, while in coronary artery disease patients, the

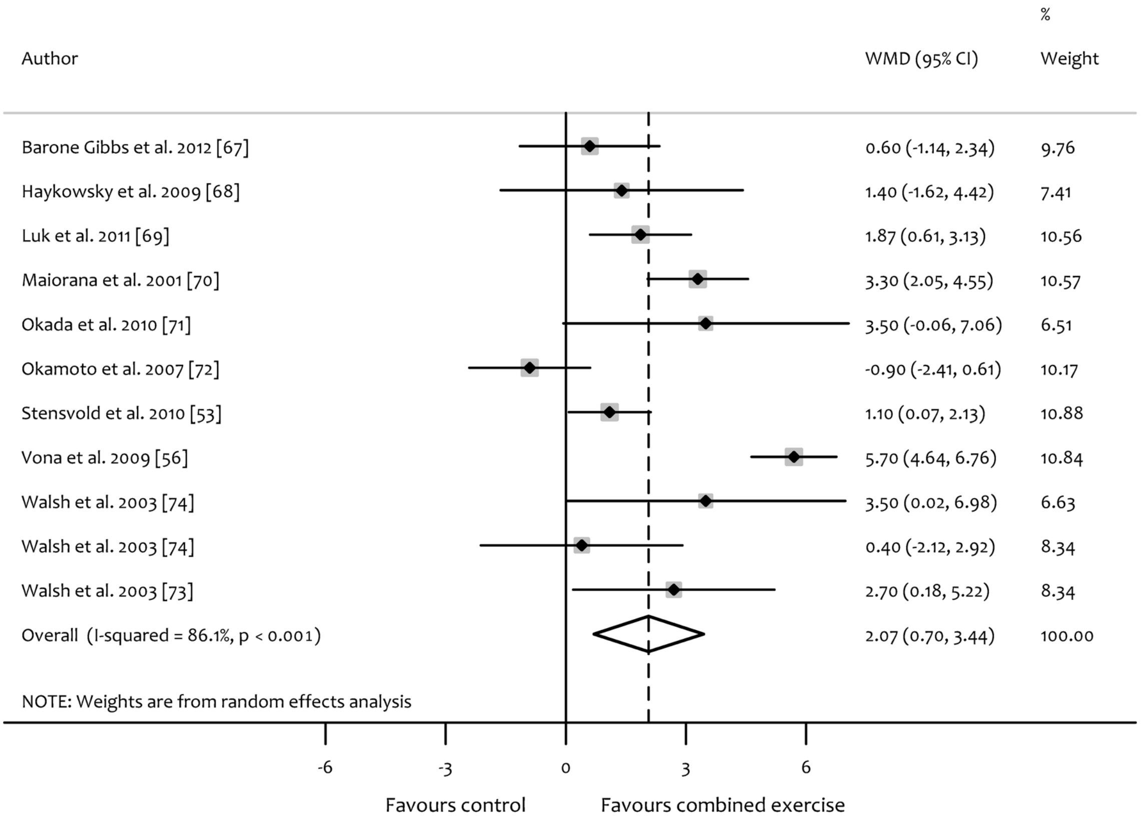


Fig. 6 Forest plot showing the effect of combined (aerobic and resistance) exercise on endothelial function. The pooled estimates were obtained by using random effect models. *Diamonds* indicate the effect size of each study summarized as weighted mean difference (WMD). The size of the *shaded squares* is proportional to the percentage weight of each study. *Horizontal lines* represent the 95 % confidence interval and the *vertical broken line* represents the overall effect

range was 1.6–5.7 % [91]. This suggests that even within groups sharing similar characteristics, the outcome measure of interest maybe highly variable. For example, BP or EF will vary according to stage of the disease, and in response to other treatments, or other adjuvant therapies (e.g., use of dietary supplements), which are not addressed adequately in some research studies. Inter-laboratory differences in reporting FMD and technical differences in the protocols for FMD measurement (location, duration and pressure of cuffing) may contribute significantly to this heterogeneity in FMD measurement [92] but are unlikely to have important effects on the detection of effects of exercise interventions.

5 Conclusions

A review of RCTs has shown that all exercise modalities improve EF significantly. Larger effects were observed with aerobic than with resistance or combined exercise training. There was a significant dose–response relationship between relative/absolute aerobic exercise intensity and EF. Every 2-MET increase in absolute intensity or 10 % increase in relative intensity (VO_{2peak}) was associated with a 1 % unit improvement in FMD. The frequency rather than the intensity of resistance exercise training enhanced EF.

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