Journal of Exercise Science & Fitness 21 (2023) 313–325

Contents lists available at ScienceDirect

Journal of Exercise Science & Fitness

journal homepage: www.elsevier.com/locate/jesf

Effects of regular aerobic exercise on vascular function in overweight or obese older adults: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 22 January 2023
Received in revised form
16 April 2023
Accepted 21 June 2023
Available online 22 June 2023

Keywords:
Aerobic exercise
Meta-analysis
Older adults
Obesity
Overweight
Vascular function

ABSTRACT

Background: Overweight and obese older adults have a high risk for developing cardiovascular disease. Aerobic exercise is a valuable strategy to improve vascular health, but the effects of aerobic exercise on vascular endothelial function in obese and overweight older adults remain controversial. The purpose of this meta-analysis was to investigate the effects of aerobic exercise on vascular function in obese and overweight older adults with or without comorbidity.
Methods: A systematic literature search for related studies published in English was conducted between January 1989 and October 30, 2022, in the PubMed, Embase, and Cochrane Library databases. A random effects model was chosen for meta-analysis, which calculated the effect sizes of control and intervention groups after exercise intervention using standardized mean differences (SMDs) corrected for Hedges' g bias and 95% confidence intervals (95% CIs).
Results: Twenty-six studies containing 1418 participants were included in the study. After excluding three studies contributing to higher heterogeneity by sensitivity analysis, there are small effects of regular aerobic exercise on vascular function of obese and overweight older adults, including flow-mediated dilation (FMD) [SMD = 0.21, 95% CI (0.02, 0.41), z = 2.16, df = 19, I^2 = 52.2%, P = 0.031] and pulse wave velocity (PWV) [SMD = −0.24, 95% CI (−0.46, −0.02), z = 2.17, df = 10, I^2 = 8.6%, P = 0.030], and no significant effect was observed on augmentation index (Aix). Subgroup analysis showed small effects of regular aerobic exercise on FMD [SMD = 0.37, 95% CI (0.13, 0.61), z = 3.05, df = 9, I^2 = 52.6%, P = 0.002] in the overweight not obese subgroup (25 = BMI <30 kg/m^2), but no significant effect on the obese subgroup (BMI ≥30 kg/m^2). Regular aerobic exercise for more than 24 weeks improved FMD by small effect sizes [SMD = 0.48, 95% CI (0.04, 0.93), z = 2.12, df = 5, I^2 = 56.4%, P = 0.034] and for more than three times per week improved FMD by moderate effect sizes [SMD = 0.55, 95% CI (0.12, 0.98), z = 2.50, df = 3, I^2 = 31.1%, P = 0.012] in obese and overweight older adults with or without CVD.
Conclusion: In obese and overweight older adults with or without comorbidity, regular aerobic exercise for more than 24 weeks improved FMD by small effect sizes and exercise for more than three times per week improved FMD by moderate effect sizes and regular aerobic exercise reduced PWV by small effect sizes and had no influence on Aix. Taken together, it was recommended that obese and overweight older adults should adhere to regular aerobic exercise, training at least 3 times per week for better results.

1. Introduction

Vascular dysfunction is one of the most important causes of cardiovascular disease (CVD), which is the leading cause of mortality worldwide, and vascular health status is associated with CVD risk.[1,2] Older adults are one of the high-risk groups for cardiovascular disease.[2–4] Age-related decline in vascular function occurs

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https://doi.org/10.1016/j.jesf.2023.06.002

throughout the vascular tree, ranging from coronary arteries to peripheral conduit, resistance and microvessels in humans.[5] Elevated levels of oxidative stress and inflammation in endothelial cells due to aging are possible causes of vascular dysfunction.[5] In addition, in a previous meta-analysis, it was shown that vascular smooth muscle function was lower in older adults, particularly women, compared with younger adults.[6] These findings suggested that the impairment of vascular function due to aging is not limited to vascular endothelium, but also includes vascular smooth muscle.

Obesity is a significant factor in the increased risk of CVD.[7,8] There is considerable evidence that overweight and obesity and their comorbidities increase CVD and overall morbidity and mortality rates.[9] The appearance of vascular dysfunction in obese people is a complex process. There is evidence that obesity accelerates age-related damage to blood vessel function.[9] Currently, obesity rates are increasing among older adults,[10] and the co-existence of obesity and aging poses a significant threat that will increase the risk of CVD.[7]

Aerobic exercise can effectively reduce the risk of CVD[8,11–14] and improve endothelial function[15–17] and arterial stiffness.[18–20] The positive effects of aerobic exercise on improving vascular function in older or obese individuals are well established.[4,8,15,21] Previous systematic reviews and meta-analyses have investigated the impact of regular aerobic exercise on flow-mediated dilation (FMD) and pulse wave velocity (PWV) in middle-aged and older adults.[22–24] It has been reported that aerobic exercise significantly increases FMD[22] and decreases PWV in middle-aged and older adults, but PWV improvement in older adults is less pronounced.[23] A meta-analysis of obese individuals showed that aerobic exercise did not significantly improve arterial stiffness in obese middle-aged and older adults.[24]

In conclusion, previous meta-analyses have focused only on obese or middle-aged and older individuals. For obese and overweight older adults with co-existent risk factors, there is insufficient evidence on whether regular aerobic exercise plays a role in improving vascular function, and systematic reviews of older adults who are obese or overweight are warranted. Therefore, the purpose of this meta-analysis was to investigate the effects of aerobic exercise on vascular function in obese and overweight older adults, and to identify appropriate aerobic exercise programs through subgroup analysis. To expand the search results of studies, subjects were included in this meta-analysis regardless of whether they had complications. We hope that this meta-analysis will serve as a reference and recommendation for obese and overweight older adults with or without comorbidities who wish to prevent and recover from CVD through regular aerobic exercise.

2. Methods

This meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] We registered our work in the PROSPERO database (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023389112, identifier: CRD42023389112).

2.1. Search strategy

A systematic literature search for related studies published in English was conducted between January 1989 and April 6, 2023, in the PubMed, Embase, and Cochrane Library databases. Full search items used in the databases are summarized in Supplementary Table 1. Systematic reviews and meta-analyses related to this meta-analysis were examined, and the reference list was searched to include studies that met the criteria. All retrieved results were imported into EndNote X9.1 software (Thomson ResearchSoft, Stanford, CA, USA) for further screening.

2.2. Study selection

Two reviewers (PL and ZL) independently assessed all studies for potential eligibility. In case of disagreement, a third reviewer (KW) determined whether a study met the inclusion criteria.

2.3. Eligibility criteria

The criteria for including studies were as follows: (1) Aerobic exercise was used as the intervention. (2) Older adults ($\geq$60 years) who were overweight (body mass index [BMI] ≥ 25 kg/m^2) or obese (BMI $\geq$30 kg/m^2) were studied. (3) Outcome indicators included at least one of these measurements of vascular function: FMD, PWV, or augmentation index (Aix). The following exclusion criteria were used: (1) There were baseline differences between the exercise and control groups. (2) An acute aerobic exercise intervention was used. (3) No detailed exercise protocol was reported, or subjects received inconsistent exercise intervention protocols. (4) Selection of non-randomized controlled trials. (5) Mean age or BMI not reported. (6) Intervention programs that included resistance training or excessively intense anaerobic interval training for the experimental group. As described by Billat in a review,[26,27] aerobic interval training was defined as repeated (high intensity) exercise sessions with a focus on aerobic metabolism interspersed with recovery periods. In his review, Billat summarized interval training with different modalities of intensity and interval duration and differentiated interval training into aerobic and anaerobic intervals.[26,27] Based on this review and in combination with the description of the exercise protocol in each study, studies utilizing aerobic interval training were included, and studies utilizing anaerobic interval training were excluded.

2.4. Risk of bias

Two authors (PL and ZL) independently assessed the risk of bias according to Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2),[28] which includes five aspects. Any disagreements were resolved through discussion between the reviewers and consultation with a third party on the review team.

2.5. Data extraction

Two investigators (PL and ZL) independently extracted all data. The focus remained primarily on the mean and standard deviation of the primary outcome measures after intervention for each group, including FMD, PWV, Aix, ankle-brachial index (ABI) and endothelial progenitor cells (EPCs). When reported as standard errors or confidence intervals, the data were converted to estimated standard deviations following the method provided in the *Cochrane Handbook for Systematic Reviews of Interventions*.[29] To prevent bias caused by different PWV measurement sites, carotid femoral PWV (cfPWV) data were used during data extraction if reported; if no cfPWV data were reported, other peripheral PWV data were extracted for meta-analysis. To explore the potential factors influencing the effect of exercise, the duration of exercise intervention, intensity and form of exercise, and characteristics of the subjects were extracted as the basis for subgroup analysis. Subgroups were created for the following items: BMI (overweight not obese: $25 \leq$ BMI $<$30 kg/m^2 and obese: BMI $\geq$30 kg/m^2), maximum oxygen uptake [VO_2 max $\leq$20 mL/(min $\times$ kg) and VO_2 max $>$20 mL/(min $\times$ kg)], sex (male or female), age (65 $>$ age $\geq$60, 70 $>$ age $\geq$60 and age $\geq$70), intervention duration ($<$12 weeks, 12–24 weeks, or

24 ≥ weeks) and frequency of weekly exercise (<3 times, 3 times, or > 3 times). In addition, to broaden the search, several studies on older adults with comorbidities were included, most of which suffered from CVD. In addition, CVD may have an impact on the effectiveness of regular aerobic exercise. Therefore, to explore whether CVD affects the effectiveness of exercise interventions, subgroups were created based on the health status of the subjects (without CVD and obesity, only CVD, or with CVD and obesity). Of these, older adults with mild cognitive impairment and sedentary lifestyles were considered to have no CVD, while other disorders (Heart transplantation, ischemic heart disease, diabetes mellitus type 2, etc.) were considered to have CVD. Although diabetes mellitus type 2 is a metabolic disease, it increases the risk of CVD and can cause vascular dysfunction and even more serious cardiovascular complications.[30–32] Therefore, in this meta-analysis, diabetes mellitus type 2 was split into CVD subgroups.

2.6. Data analysis

Data extracted from the included literature were statistically analyzed using Stata12.0 (Stata Corporation, College Station, TX, USA) software, including pooled effect sizes for outcome indicators, heterogeneity tests, Egger's tests, sensitivity analyses, and subgroup analyses. Statistical heterogeneity (I^2) was classified as low (0–25%), moderate (26–50%), substantial (50–75%), or high (>75%).[33] When heterogeneity was present, a random-effects model was chosen for analysis, and subgroup analysis and publication bias analysis were used to identify sources of heterogeneity. In the presence of publication bias, the stability of the results was examined using the trim-and-fill method. The outcome measures for this meta-analysis were continuous variables that may fluctuate in value depending on the method and location of the measurement. Therefore, to eliminate the effect of different units or measurement methods, this meta-analysis was calculated the effect sizes of control and intervention groups after exercise intervention using standardized mean differences (SMDs) corrected for Hedges' g bias and 95% confidence intervals (95% CIs). The magnitude of the SMD value was interpreted as the extent of the effect, with absolute values up to 0.2, 0.5, and 0.8 indicating small, medium, and large effect sizes.[34]

3. Results

3.1. Study search results

The search was conducted on October 30, 2022, according to the specified search terms and search method (see Fig. 1). After importing all articles into EndNote software, a total of 2781 search results were obtained after removing duplicate articles. Studies using ABI and endothelial nitric oxide synthase (eNOS) as indicators were not included. Three articles using EPC flow cytometry counts as an indicator were selected.[35–37] However, a pooled effect size analysis could not be performed due to the different cell markers and result presentations used in each paper. In the end, ABI, eNOS and EPC were excluded as outcome metrics for discussion in this meta-analysis.

3.2. Study characteristics

All included studies were randomized controlled trials. The characteristics of the participants are summarized in Table 1. The earliest publication date was 2002, and the most recent study was performed in 2021. Studies using only EPC flow cytometry counts as outcome measures were excluded.[37] Of the remaining 26 studies, including 1418 participants (654 males and 764 females), there were 22 continuous training (CT) studies[22,35,36,38–49] and 5 interval training (IT) studies.[45,50–53] One study used taekwondo training as an aerobic intervention.[54]

3.3. Risk of bias

The quality of the 26 included studies was assessed, see Supplementary Fig. 1 for the results of the quality assessment. Four studies were assessed as having a high risk of bias. Two studies[22,47] had a lack of follow-up related to the participants' health status, and the likelihood of missingness in the outcome was affected by its true value; one study[35] did not provide information on whether appropriate analyses were used to estimate the effect of assignment to the intervention; one study,[43] for ethical reasons, assigned seven patients with untreated hypercholesterolemia to an exercise intervention instead of a full randomization. Twelve studies were rated as of some concern because they provided incomplete information, but this was unlikely to affect outcomes or had only a small effect on outcomes. The randomization and the allocation concealment were not described in 10 studies.[22,36,38,40,42,44,47,49–51,59,61] In two studies, the rates of loss to follow-up differed between the intervention groups.[36,53] No blinding for the outcome assessment was performed in four studies.[42,49,54,56] No information was available on planned outcome measures and analyses in four studies.[36,45,49,51] Ten studies were assessed as having a low risk of bias and were considered to have a true effect size close to the estimate of the effect size.[39,41,44,46,48,50,52,55,57,60]

3.4. Meta-analyses

3.4.1. Meta-analysis of exercise effects

The effect sizes were aggregated using a random effects model. A total of twenty-two studies assessing FMD were included (see Fig. 2). Compared to that of the control group, FMD was significantly improved at a small effect level in the exercise group [SMD $= 0.46$, 95% CI (0.16, 0.75), $z = 3.02$, df $= 21$, $I^2 = 80.1\%$, $P = 0.002$]. However, there was a high heterogeneity among the included studies.

A total of twelve studies assessing PWV were included (see Fig. 3). There was a significant difference in PWV between the two groups after exercise intervention [SMD $= -0.88$, 95% CI (-1.70, -0.06), $z = 2.10$, df $= 11$, $I^2 = 93.6\%$, $P = 0.036$], suggesting that exercise intervention can significantly reduce PWV to a high degree. Importantly, heterogeneity existed among studies using PWV as an indicator, and the source of the high heterogeneity should be further explored.

A total of five studies assessing Aix were included (see Fig. 4). The results of Aix [SMD $= -1.61$, 95% CI (-3.79, 0.58), $z = 1.44$, df $= 4$, $I^2 = 97.5\%$, $P = 0.150$] between the exercise group and the control group were statistically significant. This finding indicates that exercise can significantly reduce Aix, but there was high heterogeneity, which needs further analysis.

3.4.2. Sensitivity analyses of meta-analysis

Sensitivity analyses showing that the previous results were stable and statistically significant are shown in Table 2. Specifically, the heterogeneity was reduced after Jo et al. 2020[36] and Erbs et al. 2010[35] were excluded (from 80.1% to 52.2%), thereby suggesting that these two studies contributed to the higher pooled effect size for FMD. Consequently, two studies[35,36] were excluded from the subsequent analysis. After excluding Wong et al., 2018 [57], the pooled effect size for PWV changed from −0.88 to −0.24, going from a large effect size to a small effect size, but causing little change in the P-values (from 0.036 to 0.030). However, the decrease

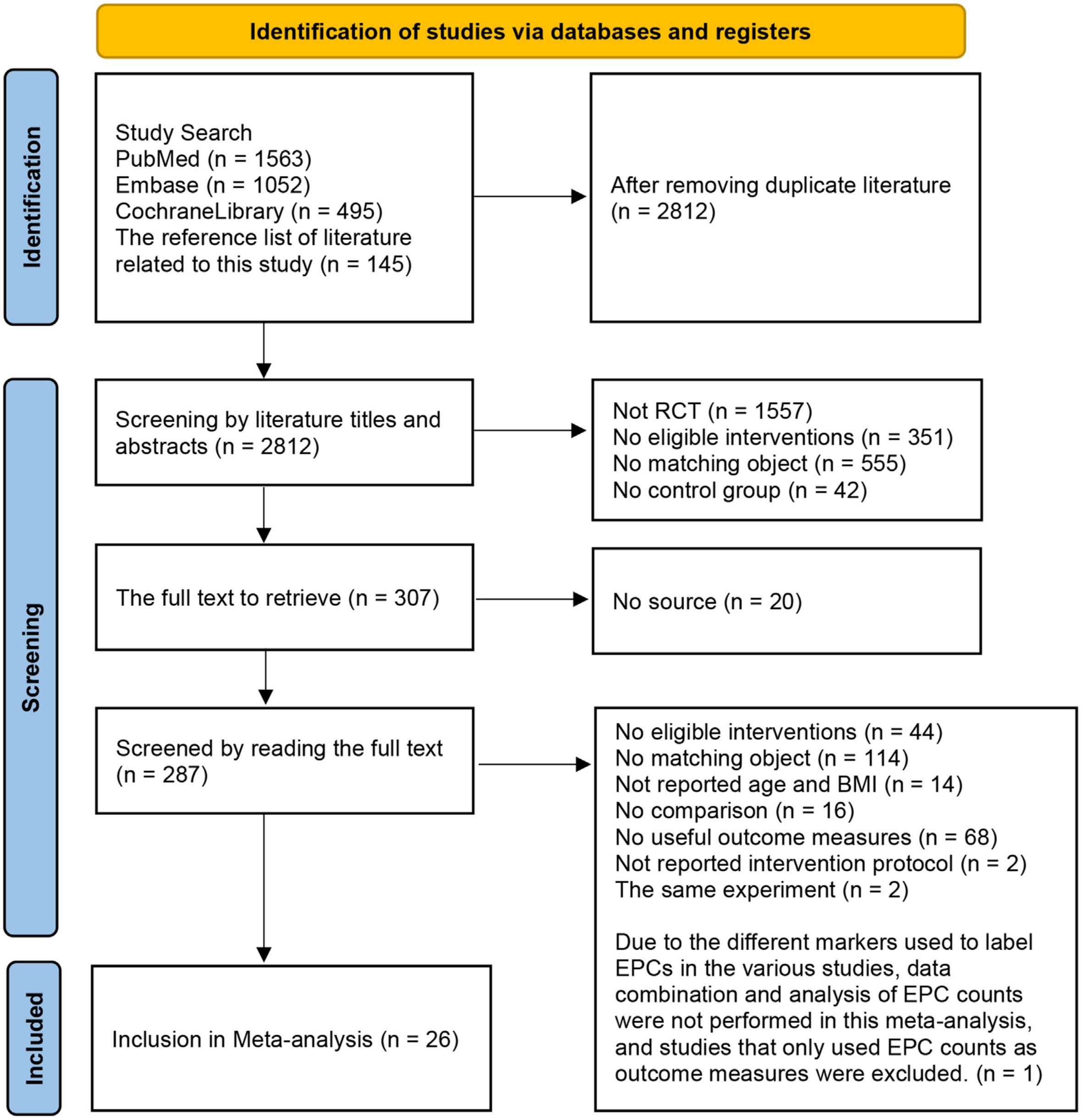

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews, including searches of databases and registers only1.

in I^2 from 93.6% to 8.6% indicated a substantial reduction in the heterogeneity of PWV, which originated mainly from Wong et al. 2018.[56] For Aix, the pooled effect size changed from −1.61 to −0.03, the *P*-value became 0.864, and I^2 decreased from 97.5% to 0%. This indicates that the Aix results are not stable. The disappearance of heterogeneity for Aix indicates that this heterogeneity originated from Wong et al. 2018.[56] In summary, these three studies were tentatively excluded and not included in the subsequent analysis following discussion and consultation among the researchers.

3.4.3. *Publication bias analysis*

Egger's test for FMD, PWV, and Aix excluded three studies.[35,36,56] This result suggests that there is no significant publication bias (see Supplementary Table 2).

3.4.4. *Subgroup analysis*

For the included studies, subgroup analysis was performed to identify appropriate aerobic exercise programs and to explore the source of heterogeneity, and the results are shown in Table 3. Regular aerobic exercise significantly improved FMD with small effect size in overweight not obese older adults [SMD = 0.37, 95% CI (0.13, 0.61), z = 3.05, df = 9, I^2 = 52.6%, P = 0.002], but no significant difference was observed for the obese older adult subgroup. In addition, regular aerobic exercise improved FMD in older adults with CVD and without obesity [SMD = 0.44, 95% CI (0.19, 0.70), z = 3.36, df = 4, I^2 = 0.0%, P = 0.001] with small effect sizes, and PWV in older adults without CVD and without obesity [SMD = −0.41, 95% CI (−0.70, 0.12), z = 2.75, df = 5, I^2 = 0.0%, P = 0.006] with small effect sizes. Exercise protocol with an intervention duration of more than 24 weeks [SMD = 0.48, 95% CI (0.04, 0.93), z = 2.12, df = 5, I^2 = 56.4%, P = 0.034] and a frequency of exercise greater than 3 times per week [SMD = 0.55, 95% CI (0.12, 0.98), z = 2.50, df = 3, I^2 = 31.1%, P = 0.012] significantly increased FMD in obese and overweight older adults. The effect size levels

Table 1
Description of studies included in the meta-analysis.

Author and year	Group	N1	N2	M/F	Age	BMI (kg/m^2)	VO2max [mL/(kg·min)]	Health status	Exercise strategy	Exercise protocol	Main findings
Bruno et al. 2018[46]	Training	53	51	24/29	75.0 (4.6)	26.5 (3.7)		Mild cognitive impai rment (MCI)		7 months, 3 times/week for 1 h Each class includes the first set of callisthenic exercise, a second set of aerobic exercise on an exercise bicycle, and a third set of cool down.	FMD ↑ Aix -
	Control	32	28	15/17	75.8 (5.4)	27.0 (4.0)		Mild cognitive impairment (MCI)			
Schmidt et al. 2002[38]	Training	7	7	7/0	60.0 (6.0)	27.3 (4.4)	16.7 (1.6)	Heart transplantation (HTx)	CT	6 months, 2 times/week (the first 2 w) and 3 times/week (the remaining period) for 60 min 3–5 min warm up, 60% HRmax maintained over 40 min on a bicycle. The last five 5 min was for cool down and stretching.	FMD ↑
	Control	6	6	6/0	63.0 (8.0)	28.9 (4.8)	16.7 (1.6)	Heart transplantation (HTx)			
Blumenthal et al. 2005[39]	Training	48	48	31/17	62.0 (10.5)	29.9 (5.7)	19.1 (6.0)	Ischemic heart disease (IHD)	CT	16 w, 3 times/week for 45 min 10 min warm-up (50%–70% HRR); 35 min walking and jogging (70%–85% HRR); 10 min cooldown stretching.	FMD ↑
	Control	42	42	32/10	63.0 (9.0)	29.8 (4.0)	20.2 (5.2)	Ischemic heart disease (IHD)			
Bouaziz et al. 2019[52]	Training	30	27	9/21	72.9 (2.5)	28.7 (5.6)		Sedentary	IT	9.5 w, 2 times/week for 30 min Each session involved six 5-min bouts of exercise combining 4 min cycling at the measured pre-intervention VT1 workload (called "BASE") and 1 min cycling at 40% of the pre-intervention VT1 workload (called "RECOVERY"). Every session started with a 3-min warm-up and finished with a 3-min recovery.	FMD ↑ cfPWV -
	Control	30	29	7/23	74.3 (3.4)	28.8 (5.1)		Sedentary			
Westhoff et al. 2007[50]	Training	27	24	13/14	67.2 (4.2)	27.7 (4.4)		Ischemic heart disease (IHD)	IT	12 w, 3 times/week. During the first week, training consisted of 5 workloads of 3 min; between workloads, patients walked on a treadmill at half-speed for 3 min. Exercise time gradually increases, reaching 30, 32 and 36 min in the sixth week and beyond, and is carried out uninterrupted. A capillary lactate concentration of 2.5 ± 0.5 mmol/l, slightly above the aerobic threshold, was reached.	FMD ↑
	Control	27	27	13/14	68.9 (5.2)	29.8 (4.3)		Ischemic heart disease (IHD)			
Sixt et al. 2008[40]	Training	13	13	10/3	64.0 (6.0)	29.2 (4.3)	21.5 (6.0)	Prediabetic with coronary disease	CT	4 w; 6 times/day for 15 min at 70% HR max by ergometer (first week). Thereafter, home-based ergometer training of 30 min a day was continued for another 3 weeks, in addition to 1 h supervised group exercise sessions twice a week.	FMD ↑
	Control	10	10	7/3	64.0 (6.0)	31.7 (4.0)	21.1 (4.7)	Prediabetic with coronary disease			
Westhoff et al. 2008[51]	Training	11	11	4/7	66.1 (4.0)	28.6 (4.4)		Ischemic heart disease (IHD)	IT	12 w, 3 times/week 15 workloads of 1 min; between workloads, patients rested for 1 min (first week); 10 × 2 min (second week); 8 × 3 min (third and fourth weeks); 2 × 12 min (seventh and eighth weeks); 2 × 15 min (ninth and 10th weeks); 30 min without interruption (11th and 12th weeks). The intensity was to reach a lactate concentration of 2.0 ± 0.5 mmol/l in capillary blood.	FMD - Aix -
	Control	12	12	6/6	68.4 (9.7)	26.5 (3.0)		Ischemic heart disease (IHD)			
Mcdermott et al. 2009[41]	Training	51	37	24/27	71.7 (8.7)	30.4 (6.2)		Peripheral arterial disease (PAD)	CT	24 w, 3 times/week, participants began with 15 min of exercise and increased to 40 min by week 8. Initial treadmill walking speed was 2.0 mph per hour or lower. Between weeks 8 and 24, attempts were made to increase exercise intensity.	FMD -
	Control	53	28	25/28	68.5 (11.9)	29.9 (7.1)		Peripheral arterial disease (PAD)			
Desch et al. 2010[42]	Training	14	14	11/3	62.3 (6.2)	29.8 (4.0)	21.7 (5.6)	Prediabetic with coronary disease	CT	24 w, 4 times/day for 30 min at 75% HR max (first week). Thereafter, patients took part in an intense exercise program with daily home-based sessions on a stationary bicycle (30 min each at 75% of the maximum heart rate) and additional supervised in- and outdoor group exercise sessions twice a week (90 min each).	FMD ↑
	Control	12	12	8/4	62.3 (6.5)	31.3 (3.9)	19.3 (3.8)	Prediabetic with coronary disease			
Mustata et al. 2011[55]	Training	10	10	4/6	64.0 (55, 73)	27.5 (25, 32)	15.8 (10.9, 17.4)	Chronic kidney disease (CKD)	CT	1 year, combining supervised and home-based exercise. Supervised training: 2 times/week (treadmill, stationary cycle and elliptical trainer). Home training (walking) in the second month: progressed over 3 months to 3 times/week.	Aix ↓
	Control	10	10	3/7	72.5 (59, 79)	29.0 (25, 30)	15.0 (13.2, 19.5)	Chronic kidney disease (CKD)			

(*continued on next page*)

Table 1 (*continued*)

Author and year	Group	N1	N2	M/F	Age	BMI (kg/m^2)	VO2max [mL/(kg·min)]	Health status	Exercise strategy	Exercise protocol	Main findings
										Initial intensity of 40–60% VO2 max and duration of 5–20 min. Exercise duration was increased by 5–10% weekly (to a maximum of 60 min).	
Pierce et al. 2011[43]	Training	26	26	11/15	63.0 ± 1.0	25.3 ± 0.7	27.8 ± 1.1	Sedentary and healthy	CT	Subjects in the exercise group were asked to walk for 8 weeks, 6–7 days/week for 40–50 min/day at 70–75% of HR max measured during the maximal treadmill exercise test.	FMD -
	Control	10	10	4/6	60.0 ± 1.0	25.1 ± 0.8	25.7 ± 1.5	Sedentary and healthy			
Blumenthal et al. 2012[44]	Training-PLACEBO	37	37	24/13	64.7 (11.0)	31.0 (5.7)	19.5 (4.8)	Coronary heart disease (CHD)	CT	16 w, 3 times/week, 30 min at 70%–85% HR max. Walking or jogging on a treadmill.	FMD -
	Control-PLACEBO	24	24	20/4	63.5 (11.4)	30.8 (5.1)	20.1 (7.4)	Coronary heart disease (CHD)			
Kitzman et al. 2013[22]	Training	32	24	9/23	70.0 (7.0)	32.2 (6.7)	14.2 (2.8)	Heart failure with preserved ejection fraction (HFpEF)	CT	16 w, 3 times/week,1 h Each session had 3 phases: 10-min warm-up, stimulus, and 10-min recovery. Patients exercised initially at 40%–50% of heart rate reserve for 5–10 min for both walking and ergometry. The intensity increased gradually until 70% heart rate reserve was maintained for at least 20 min for both walking and ergometry.	FMD -
	Control	31	30	6/25	70.0 (7.0)	32.0 (6.6)	14.0 (3.2)	Heart failure with preserved ejection fraction (HFpEF)			
Ha et al. 2018[49]	Training	11	11	0/11	74.64 (4.59)	26.39 (3.26)	38.23 (4.16)	Sedentary and healthy	CT	12 w, 3 times/week, 50 min 5-min warm-up, 40-min main exercise period, and 5-min wrap-up. Exercise intensity was measured using the rating of perceived exertion (RPE): RPE 9–10 for weeks 1–4, RPE 11–12 for weeks 4–8, and RPE 13–14 for weeks 9–12.	caPWV -Aix -
	Control	10	10	0/10	74.11 (4.65)	25.94 (2.38)	35.50 (3.69)	Sedentary and healthy			
Mitranun et al. 2014[45]	Training-CT	14	14	5/9	61.7 ± 2.7	29.4 ± 0.7	23.8 ± 1.0	Diabetes mellitus type 2 (T2D)	CT	12 w, 3 times/week exercising on a treadmill INT program: Phase 1: 5-min warm up to 50% VO2max, maintain for 20 min, and 5-min cool down. Phase 2: 5-min warm up to 50% VO2max, 4 × 1 min at 80% VO2max with 4 × 4 min at 50% VO2max, and 5-min cool down. Phase 3: 5-min warm up to 60% VO2max, 6 × 1 min at 85% VO2max with 6 × 4 min at 60% VO2max, and 5-min cool down. CON program: Phase 1: 5-min warm up to 50% VO2max, maintain for 20 min, and 5-min cool down. Phase 2: 5-min warm up to 60% VO2max, maintain for 20 min, and 5-min cool down. Phase 3: 5-min warm up to 65% VO2max, maintain for 30 min, and 5-min cool down.	FMD ↑
	Training-IT	14	14	5/9	61.2 ± 2.8	29.6 ± 0.5	24.2 ± 1.6	Diabetes mellitus type 2 (T2D)	IT		FMD ↑
	Control	15	15	5/10	60.9 ± 2.4	29.7 ± 0.4	24.4 ± 1.3	Diabetes mellitus type 2 (T2D)			
Wong et al. 2018[56]	Training	52	52	0/52	74.0 (4.0)	26.0 (2.8)	22.0 (2.0)	Stage 2 hypertension	CT	20 w training combination of freestyle, breaststroke, and backstroke swimming. 3-4 times/week for 30–40 min at 60% HR max for the first 5 weeks. Thereafter, 3–4 times/week for 40–45 min at 70–75% HR max for the remaining weeks.	crPWV ↓ Aix ↓
	Control	48	48	0/48	73.0 (4.0)	26.9 (2.9)	24.0 (3.0)	Stage 2 hypertension			
Mcdermott et al. 2017[47]	Training + GM-CSF	53	51	33/20	66.6 (9.5)	29.7 (6.5)		Peripheral arterial disease (PAD)	CT	Outcomes were measured before randomization and at 6 weeks, 12 weeks, and 6 months after randomization by an individual blinded to group assignment. Treadmill exercise with an exercise physiologist was provided 3 times weekly. Walking exercise duration was increased gradually until 50 min of exercise per session was achieved. GM-CSF (250 μ g/m^2/d) or placebo was administered subcutaneously 3 times weekly for 2 weeks in a double-blinded fashion.	FMD -
	Training + Placebo	53	53	30/23	67.5 (8.7)	31.7 (6.0)		Peripheral arterial disease (PAD)	CT		FMD -
	Control + GM-CSF	53	53	34/19	67.9 (7.5)	30.7 (6.9)		Peripheral arterial disease (PAD)			
	Control + Placebo	51	51	31/20	66.0 (8.6)	29.9 (6.8)		Peripheral arterial disease (PAD)			
Madden et al. 2013[57]	Training	25	25	13/12	68.5 ± 0.9	30.9 ± 1.0	22.2 ± 0.9	Hypertension complicated by Type 2 diabetes (T2DM) and hyperlipidemia	CT	24 w training consisted of moderate to vigorous intensity exercise on a treadmill and a cycle ergometer, 3 times/week at 60–70% HRR. The aerobic training sessions were 60 min in duration and consisted of 10 min warm-up, 40 min aerobic training and 10 min cool down/stretching.	cfPWV ↓
	Control	27	27	17/10	70.0 ± 0.8	28.6 ± 0.8	23.4 ± 1.0	Hypertension complicated by Type 2 diabetes (T2DM) and hyperlipidemia			
	Training + Alagebrium	11	11	6/5	69.0 (3.0)	26.9 (3.5)	36.4 (6.7)		CT		cfPWV -

Table 1 (*continued*)

Author and year	Group	N1	N2	M/F	Age	BMI (kg/m²)	VO2max [mL/(kg·min)]	Health status	Exercise strategy	Exercise protocol	Main findings
Oudegeest et al. 2013[58]								Sedentary and healthy		16 months using a cycle ergometer, 3 times/week. Each exercise session consisted of 10 min warm up, followed by 30 min cycling exercise at 70–85% of the individual heart rate reserve, and ended with 5 min cool down.	
	Control + Alagebrium	11	11	8/3	70.0 (3.0)	26.6 (3.0)	36.0 (5.1)	Sedentary and healthy			
Kim et al. 2017[53]	Training-CT	18	11	8/10	65.0 ± 2.0	28.7 ± 1.0	26.0 ± 1.8	Sedentary and healthy	CT	Exercise sessions were conducted 4 times/week for 8 weeks under supervision. CT consisted of 47 min at 70% HRpeak and included a 10-min warm-up and 5-min cool down at the same intensity. IT consisted of 40 min of 4 × 4 min at 90% HRpeak alternated with 3 × 3 min active recovery at 70% HRpeak and a 10-min warm-up and 5-min cool down at 70% HRpeak.	cfPWV (CT) ↓
	Training-IT	17	13	4/13	65.0 ± 1.0	28.1 ± 1.2	22.9 ± 0.8	Sedentary and healthy	IT		cfPWV (IT) -
	Control	14	14	4/10	63.0 ± 2.0	25.3 ± 1.4	25.1 ± 1.7	Sedentary and healthy			
Lee et al. 2018[54]	Training	10	10	0/10	70.0 (4.0)	25.0 (1.6)		Stage 2 hypertension		12 w taekwondo training, 3 times/week for 60 min Exercise intensity was set at 30–40% HRR for the first four weeks and gradually increased up to 50–60% HRR during the last four weeks of training.	baPWV ↓
	Control	10	10	0/10	70.0 (4.0)	25.4 (3.4)		Stage 2 hypertension			
Vasic et al. 2019[48]	Training	30	30	21/9	62.4 (7.6)	29.0 (26.5–31.6)	13.1 (2.8)	Coronary artery disease (CAD)	CT	The exercise programs consisted of 30-min training sessions twice daily, 6 days a week (24 sessions in total). Bicycle ergometer training (5 min warm-up, 20 min at 60–80% HR max, and 5 min cooldown) and calisthenics (5 min warm-up, 20 min exercises at 60–80% HR max with a progressive increase), and cooldown.	FMD ↑
	Control	30	30	24/6	60.6 (8.3)	29.3 (26.8–30.9)	16.6 (3.6)	Coronary artery disease (CAD)			
Haynes et al. 2021[59]	Training-Land walking	17	17	3/14	61.9 (5.4)	26.7	28.4 (7.9)	Sedentary and healthy	CT	3 × 50 min supervised and individually tailored walking sessions per week for 24 consecutive weeks. The exercise intervention initially comprised 15 min of exercise at an HRR of 40%–45%, progressing to 50 min at 55%–65% HRR.	FMD ↑
	Training-Water walking	18	18	5/13	62.2 (7.4)	27.8	28.8 (5.1)	Sedentary and healthy	CT		
	Control	16	16	4/12	61.8 (7.3)	27.4	29.7 (4.4)	Sedentary and healthy			
Jo et al. 2020[36]	Training	22	21	0/22	61.8 (10.1)	27.7 (3.0)		High CVD risk patients		During the 12-week training period, the participants exercised at a self-selected pace for 40 min per day. The range of exercise intensity for exergaming was between 42% and 82% of HRR	FMD ↑
	Control	21	13	0/21	62.5 (13.9)	27.3 (4.6)		High CVD risk patients			
Tomoto et al. 2021[60]	Training	22	18	10/12	64.8 (6.4)	27.3 (4.8)		Mild Cognitive Impairment (MCI)	CT	1 year of training using a treadmill. For weeks 1–10, 3 times/week for 25–30 min at 75–80% HR max. For weeks 11–25, 3–4 times/week for 30–35 min; a high intensity exercise session, which consisted of 30 min of exercise at an intensity of 85–90% of maximal HR (e.g., brisk uphill walking), was introduced. For weeks 26–48, 4–5 times/week for 30–40 min, including two high intensity sessions. Each exercise session included a 5 min warm-up and a 5 min cooldown.	cfPWV -
	Control	30	28	14/16	66.1 (6.8)	28.2 (4.2)		Mild Cognitive Impairment (MCI)			
Erbs et al. 2010[35]	Training	18	18	18/0	60.0 (11.0)	26.5 (2.3)	15.3 (3.3)	Chronic heart failure (CHF)	CT	During the first 3 weeks, 3–6 times/week for 5–20 min at 50% VO2 max. Participants were encouraged to exercise close to their target heart rate daily for 20–30 min for a period of 12 weeks, and they were expected to participate in 1 supervised group training session, consisting of walking, calisthenics, or noncompetitive ball games, for 60 min each week.	FMD ↑
	Control	19	19	19/0	62.0 (10.0)	25.8 (3.2)	15.4 (3.8)	Chronic heart failure (CHF)			

N1, the sample size that underwent randomization in the study; N2, the sample size of the study that completed the intervention and was included in the data analysis; M/F, the sex ratio; xxx (xx), the mean (standard deviation); xxx ± xx, the mean (standard error); xxx (xx, xx), the median (25%, 75%); xxx (xx-xx), the mean (95% CI); ↑, a significant rise in the exercise group compared with the control group after the exercise intervention; ↓, a significant decrease in the exercise group compared with the control group after the exercise intervention; -, no significant difference between the exercise group and the control group after the exercise intervention; BMI, body mass index; VO2max, maximal oxygen consumption; IT, interval training; CT, continuous training; FMD, flow mediated dilation; PWV, pulse wave velocity; Aix, augmentation index.

were small and medium, respectively. In addition, sex differences emerged for the effect of regular aerobic exercise on PWV. Regular aerobic exercise was small effect on improving PWV in obese and overweight older adults who were female [SMD = -0.41, 95% CI (−0.69, −0.13), z = 2.83, df = 5, I^2 = 7.8%, P = 0.005], but not in male [SMD = 0.01, 95% CI (−0.32, 0.33), z = 0.03, df = 3, I^2 = 0.0%, P = 0.976].

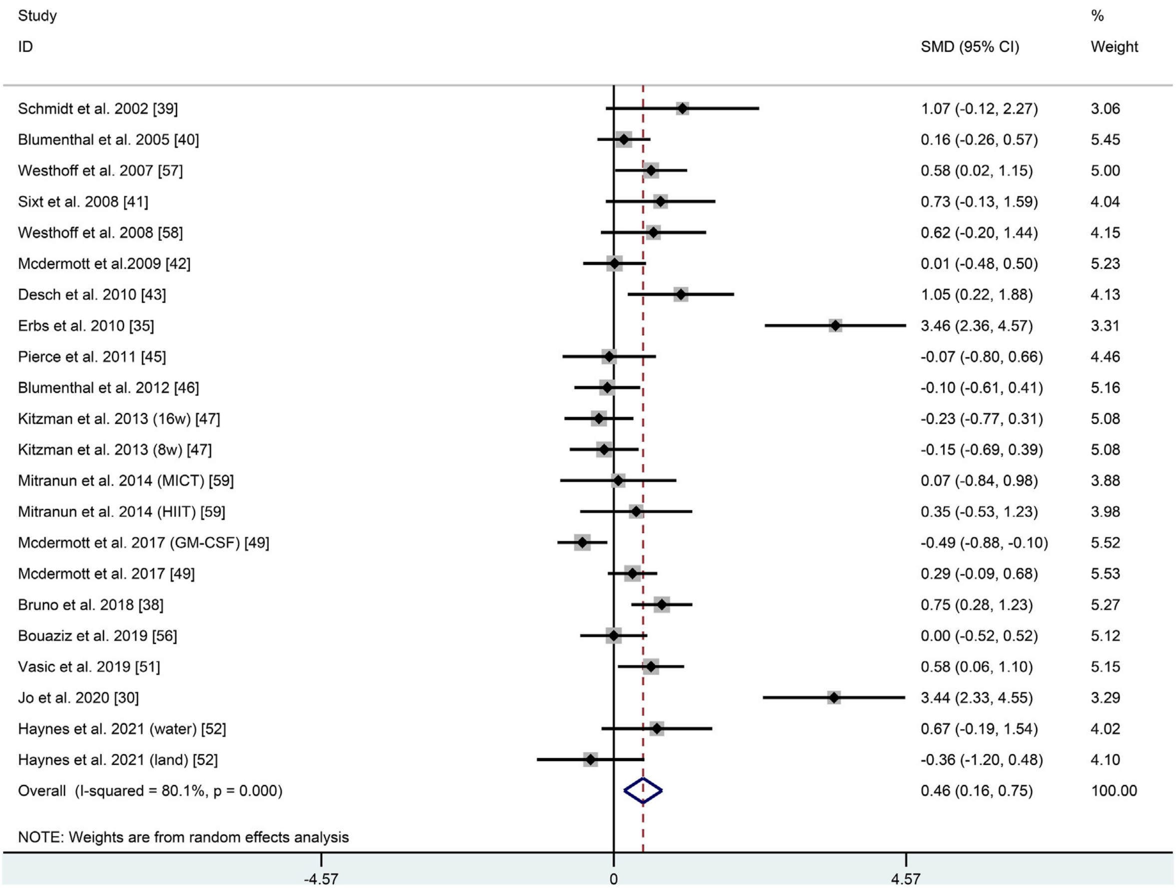

Fig. 2. Forest plot for FMD.

4. Discussion

To the best of our knowledge, this is the first meta-analysis of the effects of regular aerobic exercise on vascular function in obese and overweight older adults. After excluding three studies contributing to higher heterogeneity by sensitivity analysis, it was found that regular aerobic exercise for more than 24 weeks improved FMD by small effect sizes and for more than three times per week improved FMD by moderate effect sizes in obese and overweight older adults with or without comorbidity. However, for obese and overweight older adults, regular aerobic exercise reduced PWV by small effect sizes and had no influence on Aix. The present meta-analysis revealed that the longer the duration period of exercise intervention and the higher the frequency of weekly intervention are, the more significant the effect on vascular function improvement and the higher the effect level are. Based on the results of this meta-analysis, obese and overweight older adults are recommended to perform aerobic exercise more than three times a week for better vascular function.

FMD was used to assess vascular endothelial function by measuring brachial artery reactive congestion.[62] The principle is that endothelial release of NO is induced by increased wall shear stress to induce endothelium-dependent vasodilation.[63] Aging and obesity-mediated endothelial dysfunction are associated with excess ROS production.[64,65] It has been shown that older men who perform regular aerobic exercise do not exhibit age-related increases in ROS.[66] These findings suggest that regular aerobic exercise may improve endothelial function in obese and overweight older adults by reducing endothelial oxidative stress levels. Furthermore, PWV and Aix are methods available to assess arterial stiffness in clinical and research settings based on ultrasound measurements.[67] The mechanisms leading to increased arterial stiffness are more complex and are not only influenced by the endothelial status, but also related to smooth muscle function.[68,69] In addition to the role of oxidative stress, aging-induced arterial stiffness may also be associated with an increase or decrease in circulating bioactive factors, including advanced glycation end-products,[70] endothelin-1 [71], oxidized low-density lipoprotein,[72] and aldosterone.[73] The results of this meta-analysis show that regular aerobic exercise had little effect on PWV in obese and overweight older adults. It is possible that aerobic exercise interventions in obese and overweight older adults only alleviate arterial stiffness to a certain extent by improving endothelial function, but do not have a positive effect on vascular smooth muscle dysfunction. However, the effect of exercise on vascular smooth muscle in obese and overweight older adults remains unclear and further experiments are needed to confirm this conjecture.

The results of the subgroup analysis show some of the factors that may influence the effect of regular aerobic exercise on vascular function. Moreover, subgroup analysis by BMI expressed that regular aerobic exercise had little effect on improving endothelial function in overweight not obese older adults, but no significant effect in obese older adults. To avoid differences in the health status of older adults as a potential factor influencing the results, studies were grouped according to their health status. In patients with CVD, endothelial function was still not significantly improved after

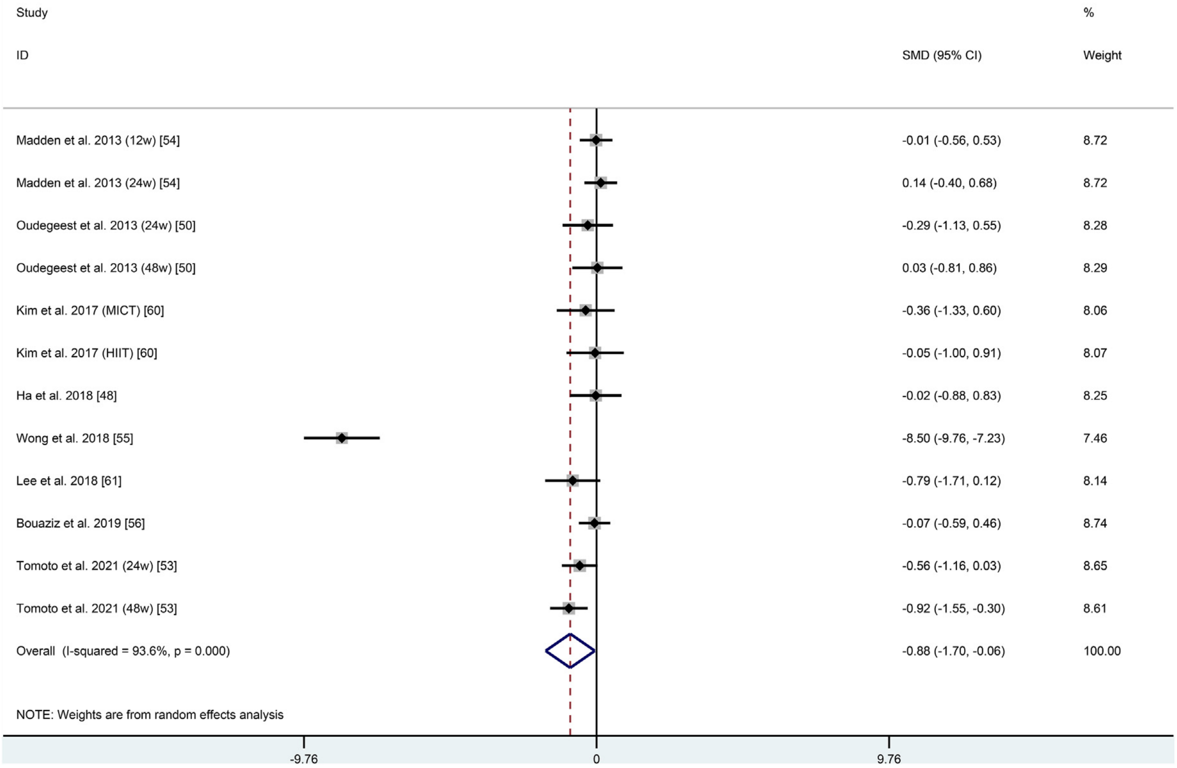

Fig. 3. Forest plot for PWV.

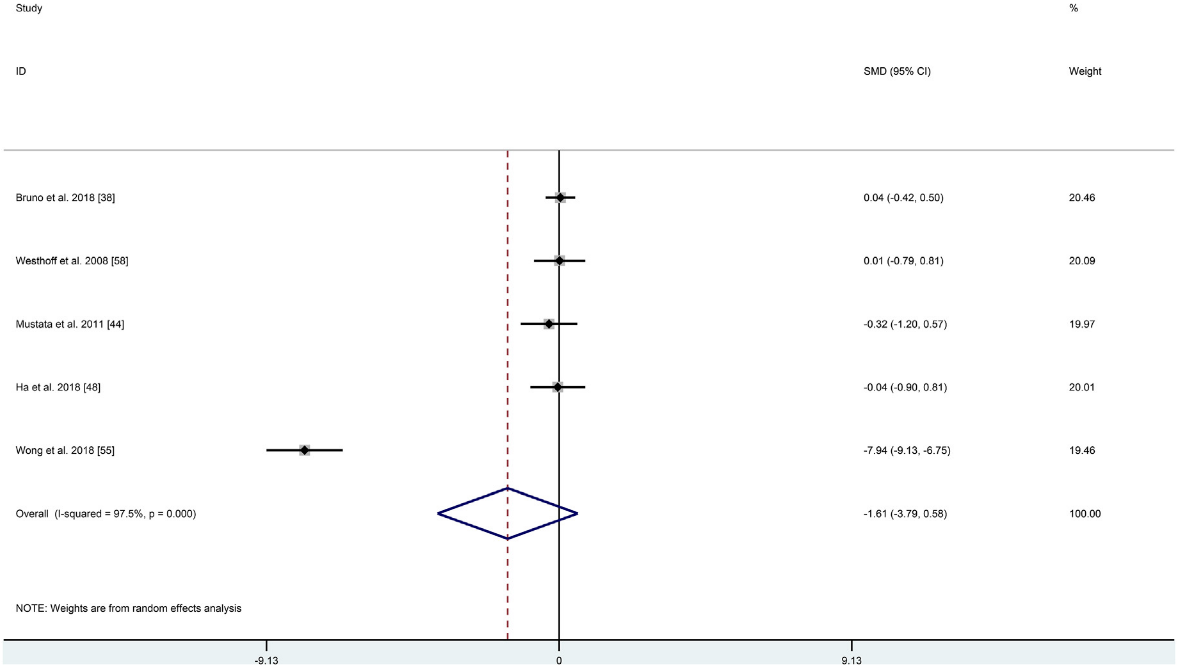

Fig. 4. Forest plot for Aix.

exercise intervention in obese older adults, while it was improved in overweight not obese older adults. The above-mentioned results indicated that obesity may blunt the beneficial effects of aerobic exercise in older adults. Pedrinolla et al. recruited a cohort of physically active older adults for a cross-sectional study and found poorer vascular function in older adults who were obese and

Table 2
Sensitivity analysis results.

Indicators	Dimension of the analysis	K	SMD	95% CI	Z	*P*	Heterogeneity
FMD	NA	22	0.46	0.16, 0.75	3.02	0.002	$I^2 = 80.1\%$
	Erbs et al. 2010[35]	21	0.33	0.08, 0.59	2.56	0.010	$I^2 = 72.5\%$
	Jo et al. 2020[36]	21	0.34	0.08, 0.59	2.57	0.010	$I^2 = 72.8\%$
	Erbs et al. 2010[35] AND Jo et al. 2020[36]	20	0.21	0.02, 0.41	2.16	0.031	$I^2 = 52.2\%$
PWV	NA	12	−0.88	−1.70, −0.06	2.10	0.036	$I^2 = 93.6\%$
	Wong et al. 2018[56]	11	−0.24	−0.46, −0.02	2.17	0.030	$I^2 = 8.6\%$
Aix	NA	5	−1.61	−3.79, 0.58	1.44	0.150	$I^2 = 97.5\%$
	Wong et al. 2018[56]	4	−0.03	−0.36, 0.31	0.17	0.864	$I^2 = 0\%$

Studies with large deviations were excluded, and meta-analysis results were analyzed. Studies excluded are listed in dimension of analysis. NA, no studies were excluded. FMD, flow mediated dilation. PWV, pulse wave velocity. Aix, augmentation index. SMD, standardized mean difference.

Table 3
Summary of the subgroup analysis results.

Variable	Measurement	Subgroup	K	SMD	95% CI	Z	*P*	Heterogeneity (I^2)
BMI	FMD	Obese	10	0.07	−0.20, 0.33	0.48	0.628	31.0%
		Overweight not obese	10	0.37	0.13, 0.61	3.05	0.002*	52.6%
	PWV	Obese	0	–	–	–	–	–
		Overweight not obese	11	−0.24	−0.30, 0.26	2.10	0.036*	8.6%
Health status	FMD	Without CVD and obesity	5	0.23	−0.21, 0.67	1.03	0.304	54.5%
		Only CVD	5	0.44	0.19, 0.70	3.36	0.001*	0.0%
		With CVD and obesity	10	0.07	−0.20, 0.33	0.48	0.628	52.6%
	PWV	Without CVD and obesity	7	−0.41	−0.70, −0.12	2.75	0.006*	0.0%
		Only CVD	4	−0.07	−0.36, 0.23	0.44	0.660	0.1%
		With CVD and obesity	0	–	–	–	–	–
Vo$_2$ max	FMD	Vo$_2$ max ≤20	7	0.22	−0.11, 0.55	1.29	0.196	55.6%
		Vo$_2$ max >20	6	0.21	−0.13, 0.56	1.20	0.230	1.3%
Sex	FMD	Male	8	0.29	−0.06, 0.65	1.61	0.107	69.6%
		Female	12	0.18	−0.05, 0.41	1.55	0.122	34.1%
	PWV	Male	4	0.01	−0.32, 0.33	0.03	0.976	0.0%
		Female	7	−0.41	−0.69, −0.13	2.83	0.005**	7.8%
Age	FMD	60–70	14	0.20	−0.04, 0.44	1.64	0.101	51.3%
		70+	6	0.25	−0.12, 0.61	1.33	0.183	59.9%
	PWV	60–70	8	−0.26	−0.54, 0.02	1.82	0.337	21.1%
		70+	3	−0.20	−0.60, 0.21	0.96	0.068	0.9%
Duration	FMD	<12 w	5	0.19	−0.15, 0.53	1.07	0.283	36.2%
		12-24 w	9	0.09	−0.17, 0.35	0.67	0.500	50.9%
		≥24 w	6	0.48	0.04, 0.93	2.12	0.034*	56.4%
	PWV	<12 w	3	−0.12	−0.53, 0.30	0.56	0.577	0.0%
		12-24 w	3	−0.18	−0.62, 0.26	0.82	0.412	9.1%
		≥24 w	5	−0.33	−0.75, 0.08	1.58	0.114	47.6%
Weekly frequency	FMD	<3	2	0.40	−0.62, 1.41	0.77	0.444	61.5%
		3	14	0.13	−0.09, 0.35	1.15	0.251	52.8%
		>3	4	0.55	0.12, 0.98	2.50	0.012*	31.1%
	PWV	<3	1	−0.07	−0.59, 0.46	0.25	0.801	–
		3	8	−0.29	−0.58, 0.01	1.93	0.054	31.5%
		>3	2	−0.20	−0.88, 0.48	0.59	0.557	0.0%
Risk of bias	FMD	High risk	4	0.09	−0.40, 0.60	0.37	0.712	68.7%
		Low-to-medium risk	16	0.24	0.03, 0.46	2.20	0.012*	50.2%
Measurement site	PWV	Aortic PWV	9	−0.23	−0.46, 0.01	1.84	0.065	13.7%
		Peripheral PWV	2	−0.39	−1.15, 0.36	1.02	0.309	30.8%

The subgroup analysis results are summarized in the table because there are many subgroups. Subgroup analyses of VO$_2$ max and risk of bias were not performed for PWV, as the included studies reporting VO$_2$ max were all classified as high-level groups and none of the studies were assessed as high-risk for bias. FMD, flow mediated dilation. PWV, pulse wave velocity, Aix, augmentation index, SMD, standardized mean difference, K, number of studies in subgroup. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

overweight compared to older adults with normal BMI.[74] This finding implies that the adverse effects of obesity on vascular function counterbalance the positive effects of regular aerobic exercise. The pathogenesis of obesity leads to perivascular adipose tissue (PVAT) dysfunction and reduced nitric oxide (NO) bioavailability,[75] both of which are harmful to vascular health. NO is an endogenous gas with vasodilative properties,[75] while obesity leads to reduce NO production in PVAT.[58] PVAT dysfunction induces vascular function dysregulation by increasing peripheral resistance and vascular tone.[76] However, the mechanisms by which aerobic exercise improves vascular function are primarily through protection against systemic oxidative stress and inflammation and induction of increased NO production.[77] Therefore, regular aerobic exercise alone may not improve vascular function in obese older adults, for whom a combination of other types of intervention may be necessary to achieve the goal of improved vascular function, including aerobic and resistance exercise, a proper diet, and nutritional supplements.[20,78–81]

In addition, our subgroup analysis revealed that the exercise intervention significantly reduced PWV in obese and overweight older female adults. Sex independently affects carotid structure and function, with females being more vulnerable to the progression of arterial aging.[82] This sex-specific difference may be related to estrogen levels in postmenopausal women.[83,84] In addition, a study by Scuteri et al. suggests a potentially greater effect of obesity in raising CVD risk in women than in men.[85] The effect of exercise

Table 4
Acronyms list.

Acronyms List	Full name
CVD	cardiovascular disease
FMD	flow-mediated dilation
PWV	pulse wave velocity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
BMI	body mass index
Aix	augmentation index
RoB 2	Version 2 of the Cochrane risk-of-bias tool for randomized trials
ABI	ankle-brachial index
EPCs	endothelial progenitor cells
cfPWV	carotid femoral PWV
VO_2 max	maximal oxygen consumption
SMDs	standardized mean differences
95% CIs	95% confidence intervals
eNOS	endothelial nitric oxide synthase
IT	interval training
CT	continuous training
PVAT	perivascular adipose tissue
NO	nitric oxide

interventions on improving arterial stiffness in obese and overweight older adults appears to be better in females than in males.

Subgroup analysis of the health status demonstrated that regular aerobic exercise improved endothelial function but not arterial stiffness in older CVD patients who were overweight but not obese. However, regular aerobic exercise improved arterial stiffness in patients without CVD with a small effect size. Due to the difference in pathogenesis of various diseases, the effects of exercise interventions on vascular function will vary. However, if subgroups are divided by disease, the number of studies in each subgroup will be small and results with low confidence will be obtained. Therefore, this was not analyzed in the current meta-analysis, which was also one of the limitations of this meta-analysis.

Sensitivity analyses were performed with three studies that had a large effect on the results, and were therefore excluded to avoid false results due to bias. In this meta-analysis, BMI was used to determine the degree of obesity of the subjects. However, BMI does not adequately represent the fat distribution for an individual.[86] In short, an increase in BMI may be due to an increase in lean mass, or it may be due to an increase in fat mass. For this meta-analysis, it was not possible to distinguish between the two conditions, which makes the results somewhat limited. Furthermore, although most of the included studies used heart rate as an indicator to monitor exercise intensity, some of them used other indicators, such as maximal oxygen uptake or lactate, or did not monitor intensity; consequently, a comparison of exercise intensity could not be made in this meta-analysis, but this limitation will be improved in subsequent studies.

5. Conclusion

Regular aerobic exercise for more than 24 weeks improved FMD by small effect sizes and for more than three times per week improved FMD by moderate effect sizes in obese and overweight older adults with or without comorbidities. However, for obese and overweight older adults with or without comorbidities, regular aerobic exercise reduced PWV by small effect sizes and had no influence on Aix. Therefore, it is recommended that obese and overweight older adults adhere to regular aerobic exercise, training at least 3 times per week for the better results. The longer the duration of training, the better the effect, but excessive training intensity should not be pursued for older people and should be adjusted according to their physical condition. Obesity and CVD may prevent regular aerobic exercise from improving vascular function. In obese older adults, aerobic exercise alone is not enough and must be combined with other methods to improve vascular health. This review provides updated and valuable information for improving vascular health by daily exercise in obese and overweight older adults.

Nomenclature

(See Table 4).

Funding

Financial support was received from the National Natural Science Foundation of China (31600969).

Conflicts of interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jesf.2023.06.002.

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