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Effects of aerobic training on brachial artery flow-mediated dilation in healthy adults: a meta-analysis of inter-individual response differences in randomized controlled trials

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Abstract

Background This study aimed to investigate: (a) the effects of aerobic training (AT) on brachial artery endothelial function, measured by flow-mediated dilatation ($_{ba}$FMD) and whether changes in $_{ba}$FMD are associated with changes in other cardiovascular health markers in healthy adults; (b) whether intra-individual response differences (IIRD) in $_{ba}$FMD improvement exist following AT; and (c) the association between participants' baseline characteristics and exercise-induced changes in $_{ba}$FMD.

Methods The search conducted across six databases (PubMed, Web of Science, CINAHL, EMBASE, the Cochrane Central Register of Controlled Trials, and EBSCOhost) identified 12 eligible studies. We conducted both traditional meta-analyses identifying the effects of the intervention and IIRD. IIRD meta-analysis was performed to assess if true IIRD between AT and the control group exists for $_{ba}$FMD. The methodological quality of included studies was assessed by the PEDro scale, while GRADE assessment was used for certainty of evidence evaluation.

Results In total, 12 studies with 385 participants (51% male, 46.3 ± 17.3 [years]) were included in the current review. Meta-analysis revealed improvement in $_{ba}$FMD post-AT (*small* MD = 1.92%, 95% CI 0.90 to 2.94, $p = 0.001$). The standard deviation of change scores in the intervention and control groups suggests that most of the variation in the observed change from pre-to-post intervention is due to other factors (e.g., measurement error, biological variability etc.) unrelated to the intervention itself. However, subgroup meta-analysis revealed that significantly trivial IIRD exists following AT in prehypertensive individuals.

Conclusions The study found small improvements in $_{ba}$FMD, suggesting an average 19.2% reduction in cardiovascular disease (CVD) risk, with some individuals—such as prehypertensive individuals—potentially experiencing even greater benefits from AT. However, a meta-analysis based on IIRD suggests that factors unrelated to AT predominantly explain $_{ba}$FMD changes. Further research is needed to better understand response variability in individuals with cardiovascular risk factors, and longer studies are required to assess IIRD in the general population.

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Key points

- In this meta-analysis of 12 randomized controlled trials, aerobic training (AT) intervention revealed small improvements in brachial artery endothelial function measured by flow-mediated dilatation ($_{ba}$FMD) technique in the healthy adult population.
- Based on prior evidence indicating that a 1% increase in $_{ba}$FMD is associated with a 10% reduction in cardiovascular disease (CVD) risk, the pooled results demonstrate an average 19.2% decrease in CVD risk following AT. Notably, some individuals may experience even greater benefits from AT.
- Conversely, meta-analysis based on intra-individual response difference (IIRD) suggests that factors unrelated to the intervention itself mostly contribute to the observed changes in $_{ba}$FMD, whereas prehypertension appeared to moderate the IIRD in $_{ba}$FMD improvement following AT.
- Current evidence indicates that response heterogeneity following AT can be expected in individuals with increased cardiovascular risk factors, such as elevated systolic blood pressure, and this warrants further investigation.

Keywords Brachial artery reactive hyperemia, Endothelial dysfunction, Cardiovascular health, Adults, Exercise, Intra-individual response, Responders, Non-responders

Introduction

Brachial artery flow-mediated dilatation ($_{ba}$FMD) is a non-invasive and widely used measure of endothelial function, reflecting the artery's capacity to dilate in response to increased blood flow-induced shear stress. Reduced $_{ba}$FMD signifies endothelial dysfunction, an important marker of vascular health and a robust predictor of future cardiovascular events [1, 2]. This response is mediated by endothelial nitric oxide bioavailability, a key regulator of vascular tone and health. Clinically, even modest improvements in $_{ba}$FMD are associated with reduced cardiovascular risk [1], underscoring its value as a therapeutic target for interventions aimed at vascular health.

As part of a comprehensive health management program, aerobic training (AT) is recommended to maintain optimal cardiovascular health [3] and improve endothelial function [4, 5]. While both continuous (CAT) and interval (IAT) aerobic modalities improve traditional cardiovascular risk factors (e.g., body mass, body mass index (BMI), percent body fat, blood pressure, lipid profile, glucose level, resting heart rate) [6, 7] and $_{ba}$FMD [8–13], their comparative efficacy remains debated due to high interindividual response variability [5, 7, 14–17]. Emerging evidence suggests IAT may induce superior vascular adaptations in certain populations, however optimal exercise prescriptions (intensity, duration) likely depend on individual factors such as baseline fitness level and cardiovascular disease (CVD) risk [5, 6]. Identifying strategies to maximize $_{ba}$FMD responsiveness is critical, as improved endothelial function may delay atherosclerosis progression and reduce morbidity.

In every intervention, either exercise, pharmacological, or psychological, there is a subset of people who do not respond to the treatment the same way as the general population. These individuals are commonly referred to as "non-responders" or "low-responders" as they do not experience significant improvements in their fitness level, body composition, or other health-related benefits after a period of structured exercise training [18]. The lack of response can be attributed to various factors such as age, sex, baseline fitness level, health status, exercise adherence, genetics, and lifestyle [18]. This highlights the need for personalized exercise regimens to ensure vascular benefits across diverse populations.

There are several published reports aimed at investigating the inter-individual variation of vascular function response to exercise [5, 19–21], including observations that exercise may lead to less-than-expected improvements in endothelial function for some individuals [20]. For example, Green and colleagues [20] aggregated data from their previous investigations and conducted an individual participant meta-analysis on 182 subjects to investigate vascular responsiveness to supervised endurance training. Despite improvements in cardiorespiratory fitness, accompanied by reductions in participants' body mass, BMI, cholesterol, and mean arterial pressure after training, 25% of participants exhibited no improvement in $_{ba}$FMD. Moreover, authors found that the training-induced changes in $_{ba}$FMD were predicted by lower baseline body mass (β = -0.212), lower baseline $_{ba}$FMD (β = -0.469), lower training frequency (β = -0.256), and longer training duration (β = 0.367) (together: $P < 0.001$, $r = 0.63$). Notably, changes in traditional cardiovascular risk factors (except total cholesterol; $r = 0.243$, $P < 0.01$) showed no significant associations with $_{ba}$FMD adaptations. While this study represents a significant step towards a better understanding of the $_{ba}$FMD response to the AT, the study failed to account for potential confounders.

The premise that inter-individual response differences (IIRD) to AT interventions exist is a cornerstone of exercise precision medicine [22, 23]. However, this assumption requires scrutiny due to potential confounding

factors such as random variation, measurement error, and biological fluctuations within- and between days. An innovative approach to assessing true IIRD involves comparing changes in outcome standard deviations between the intervention and control groups in randomized controlled trials [22]. Greater variability in the outcomes of the intervention group indicates the presence of IIRD attributable to the intervention [22]. Identifying clinically relevant differences in IIRD between intervention and control groups can facilitate the development of tailored exercise prescriptions, thereby optimizing individual health benefits.

To our knowledge, no prior research has employed a meta-analytical approach to examine true IIRD in the context of AT effects on $_{ba}$FMD. Given the significance of $_{ba}$FMD as an independent predictive marker of cardiovascular health, the present study aims to address this gap by conducting a meta-analysis of the standard deviation of individual response (SD_{IR}) besides conventional meta-analysis. An IIRD analysis seeks to determine the existence of true effects of AT on $_{ba}$FMD when accounting for potential confounders as outlined previously. Thus, the present study aimed to investigate (a) the effects of AT on $_{ba}$FMD and whether changes in $_{ba}$FMD are associated with changes in other cardiovascular health markers in healthy adults; (b) whether IIRD in $_{ba}$FMD improvement exists following AT; and (c) the association between participants' baseline characteristics and exercise-induced changes in $_{ba}$FMD.

Methods

Eligibility criteria, literature search and study selection

This review study has been conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [24]. The protocol was prospectively registered in the Open Science Framework online registry (https://osf.io/4xht5/metadata/osf).

The systematic search of PubMed, Web of Science, CINAHL, EMBASE, the Cochrane Central Register of Controlled Trials and EBSCOhost was preliminarily conducted from inception to the 15th of September, 2023 within a scope of a greater project (ID: CRD42023453202). Additionally, an updated search of all databases was conducted once again on the 15th of February, 2025. The following terms and their combinations were used as search strings: adult, vascular endothelium, endothelial function, endothelial dysfunction, flow-mediated dilatation, endothelium-dependent vasodilatation, vascular reactivity, exercise, physical exercise, exercise training, and randomized controlled trial. Additionally, relevant medical subject heading (MeSH) terms were combined using the Boolean operators "OR," "AND," and "NOT" when possible. Furthermore, the reference lists of the retrieved articles, as well as those from systematic literature reviews and meta-analyses, were hand-searched for additional eligible articles.

Eligibility criteria were selected in accordance with the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework (Table 1).

Table 1 Eligibility criteria for inclusion defined by population, intervention, comparison, outcomes and study (PICOS) framework

PICOS criteria	
Population	- Studies recruiting asymptomatic adult subjects (≥ 18 years of age), with no restriction to sex and ethnicity.
Intervention	- Aerobic training (AT) with an eligible non-intervention control group;
Comparison	- Change in FMD was compared between AT and passive control group.
Outcome	Primary: - brachial artery endothelial function measured by the FMD technique and reported as percentage (%) Secondary: Anthropometric measures: - body mass in kilograms - body mass index in kg/m^2 - percentage of body fat Measures of cardiorespiratory fitness: - aerobic capacity (VO_{2max}) reported in relative or absolute values from different tests - heart rate at rest in beats per minute Haemodynamic parameters: - Systolic blood pressure (mmHg) - Diastolic blood pressure (mmHg) Blood derived parameters: - Total cholesterol - Low density lipoprotein - High density lipoprotein - Triglycerides - Glucose
Study design	Randomized controlled trials (RCTs).

Screening strategy and data extraction

As outlined above, this study is part of a larger project involving multiple researchers. Thus, the literature search and study identification were initially performed by two authors (AHP and NL), while six reviewers (AHP, EA, SI, KD, FM, NL) independently screened the articles for eligibility in pairs. In the secondary literature search focusing on IIRD analysis, AHP and KD performed the search and study identification alone. During the preliminary phases, the online platform Nested Knowledge (https://nested-knowledge.com) was used. First, titles and abstracts were screened for eligibility. Then, AHP and KD thoroughly reviewed the full text of the articles, leading to a final decision on their inclusion in the synthesis. Any disagreements between the reviewers were resolved by consensus or consultation with GT if needed. If the full text was not available online, the corresponding author was contacted by e-mail or through the ResearchGate platform. The entire process of study selection is presented in Fig. 1. Criteria for data extraction were discussed and accepted by the authors. Data extraction according to the predefined criteria was undertaken by AHP and checked by KD independently. Any uncertainties were discussed between the authors until an agreement was reached.

Credibility assessment

The methodological quality of the included studies was assessed using the Physiotherapy Evidence Database (PEDro) scale, while the quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [25]. The PEDro scores ≥ 3, 4 to 5 and from 6 to 10 were categorized as poor quality, fair quality and high quality studies, respectively [26].

The GRADE system classifies evidence as high, moderate, low, or very low quality [25]. However, several factors can lead to a downgrade in the quality of evidence. In this study, we considered the following criteria when assessing confidence in the evidence: design limitations (if most studies in the meta-analysis had a PEDro score below 6), imprecision (based on a small sample size of fewer than 300 participants for each pooled outcome), and inconsistency of results (substantial heterogeneity with $I^2 \geq 50\%$). The review did not account for the indirectness criterion, as the eligibility criteria ensured a specific population with relevant outcomes.

Statistical analysis

The pairwise meta-analyses were performed with SPSS statistical software (version 29.0, IBM Inc, Chicago, United States of America). Both fixed and random meta-analysis methods were used for the analysis. In case of large heterogeneity within the included studies and for each meta-analysis, data were analyzed using a random effect model. Thus, the restricted maximum likelihood with Knap–Hartung standard error adjustment was used for all random effect model analyses [27]. Egger's test was performed on the collected data to provide statistical evidence of publication bias ($p < 0.10$), together with a funnel asymmetry plot [28]. As $_{ba}$FMD was measured by standardized procedures and reported as a percentage, the mean difference (MD) with 95% confidence intervals was calculated for all outcome measures. Except for body mass, BMI, resting heart rate, systolic blood pressure, diastolic blood pressure, body fat percentage (BF%), and brachial artery diameter, a standardized mean difference (SMD) was used because the unit of measurement differed and/or the methods of assessment varied substantially between studies for the majority of secondary outcomes, as reported in Table 1. 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) [29]. In addition, 95% prediction intervals (PI) were calculated for each outcome to identify what results one might expect if a new randomized controlled trial (RCT) was conducted in a population similar to those studies included in the meta-analysis. Furthermore, heterogeneity was assessed using 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 [30]. IIRD meta-analysis was performed to assess if true IIRD between AT and the control group exists for $_{ba}$FMD. Thus, standard deviations of individual response differences (SD_{IR}^2) for each outcome were used as point estimates and calculated for each study [23]. To further quantify the clinical significance of the observed results (i.e., minimal clinically important difference [MCID]), a threshold of 1% of $_{ba}$FMD improvement was chosen [1] and interpreted as *trivial* or not clinically relevant (if the effect was smaller than 1%), *small* but clinically relevant (effect > 1% but < 3%), *moderate* (effect > 3% but < 6%), and *large* (effects ≥ 6%) [31]. A level of $p \leq 0.05$ was adopted as statistically significant for all analyses performed.

Results

Study selection process

A search conducted across six databases yielded 1818 reports, of which 556 duplicates were excluded. In total, 1262 reports were screened, and 1097 were excluded for reasons outlined in Fig. 1. Among the remaining 165 reports, all were assessed for eligibility, and 153 were excluded for one or more of the following reasons: the report combined several treatments ($n = 6$); endothelial function was assessed by other means than $_{ba}$FMD ($n = 29$); the symptomatic population was investigated ($n = 35$), interventions other than AT ($n = 23$); irrelevant

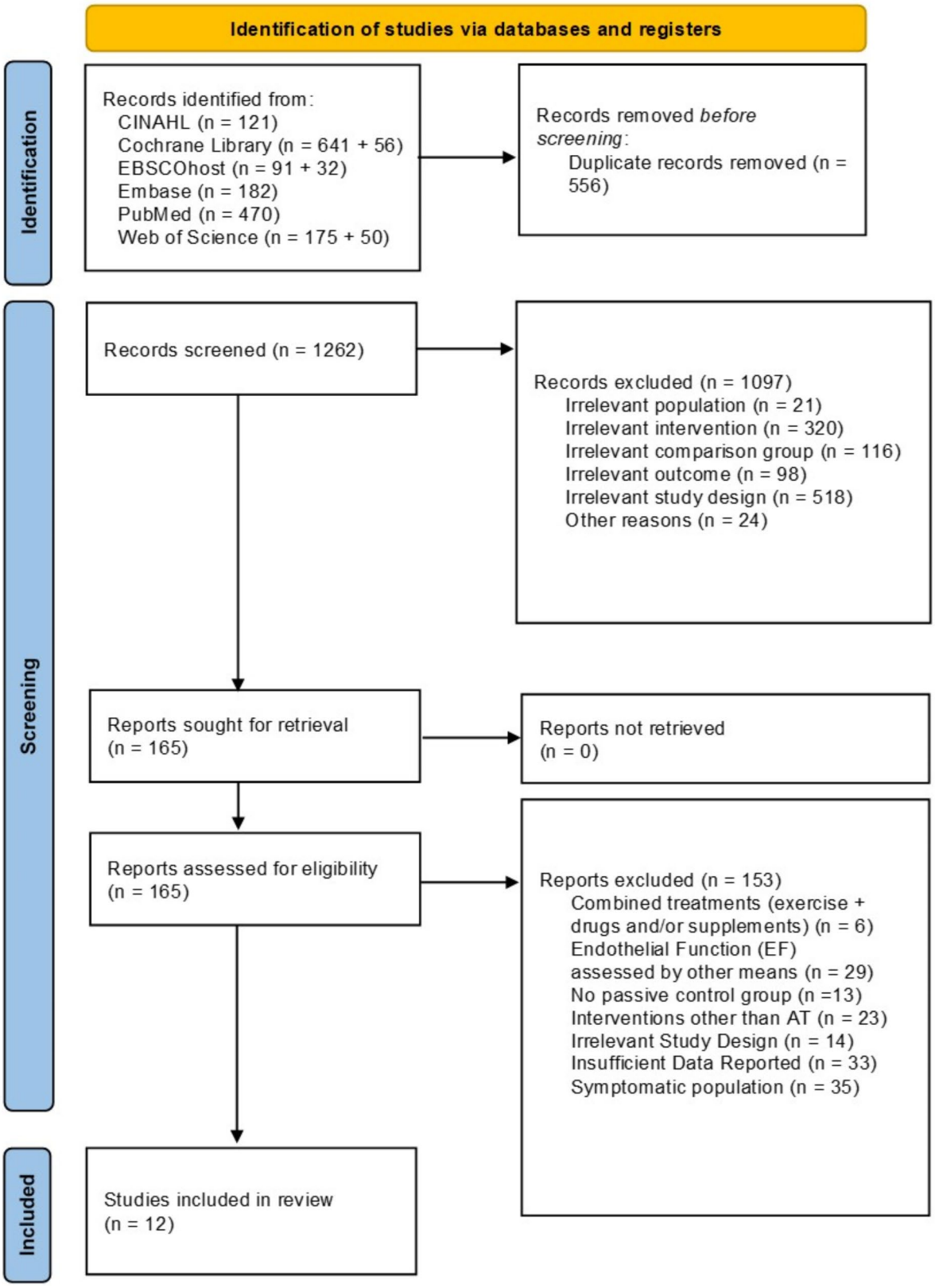

Fig. 1 Flow diagram of the study selection process

study design ($n = 14$); no passive control group ($n = 13$); and insufficient data reported for assessing the eligibility criteria or effect size calculation ($n = 33$) (Fig. 1).

Study and participants' characteristics

In total, 12 studies with 385 participants (51% male, 46.3 ± 17.3 [years], range: 20.1 to 74.3 [years]) were included in the current review (Tables 2 and 3). The average study duration was 11.3 weeks (range: 8 to 24 weeks). From 12 included studies, data from 18 AT interventions were derived from 12 CAT and 7 IAT interventions, while the participants in the control groups were passive (not engaged in any form of physical training or other type of treatment). Among all included participants, 4 interventions consisted of subjects with normal body mass as measured by BMI, while three and 11 were classified as obese or overweight. A baseline value of systolic blood pressure could be derived from 15 intervention groups on which basis participants were classified as normotensive ($n = 8$) and prehypertensive ($n = 7$), whereas 6 studies [32–36] reported values of brachial artery diameter. For the purpose of the current meta-analysis, normotensive individuals were defined as those with optimal blood pressure (< 120/80 mmHg), while prehypertensive individuals were classified as those with blood pressure values of 120–139 mmHg systolic and/or 80–89 mmHg diastolic [37].

Methodological quality assessment of the individual studies

The methodological quality of the included studies showed that they were, on average, of fair quality, with an average PEDRO score of 5.3 (range: 3 to 7). Most of the studies failed to report whether the group allocation

Table 2 Systematic overview of the included studies in the meta-analysis with their characteristics and relevant outcomes

Study name	Number of participants	Type on intervention	M/F ratio	Participants Age	Participants BMI	BP classification	Results on FMD
Hovespian et al. 2021	26	IAT	0/26	EXP: 20.2; CON: 20.7	EXP: 29.7; CON: 32.1	Normotensive	baFMD EXP: 1.38%; CON: -1.2%
Shenouda et al. 2017 a	15	IAT	15/0	EXP: 27; CON: 26	EXP: 26; CON: 25	Normotensive	baFMD EXP: -0.7%; CON: 0.4%
Shenouda et al. 2017 b	16	CAT	16/0	EXP: 28; CON: 26	EXP: 27; CON: 26	Normotensive	baFMD EXP: -1.4%; CON: 0.4%
Robinson et al. 2016	19	CAT	3/7	EXP: 34; CON: 28	EXP: 32; CON: 33	Prehypertensive	baFMD EXP: -0.9%; CON: 0%
Almenning et al. 2015	17	IAT	0/17	EXP: 25.5; CON: 27	EXP: 23.8; CON: 26.3	NR	baFMD EXP: 2%; CON: -1.2%
Beck et al. 2013	28	CAT	9/4	EXP: 20.1; CON: 21.6	EXP: 28.7; CON: 27	Prehypertensive	baFMD EXP: 3.72%; CON: -0.35%
Azadpour et al. 2017	24	CAT	0/24	EXP: 57.6; CON: 56.6	EXP: 32.15; CON: 33.71	Prehypertensive	baFMD EXP: 5.18%; CON: -0.47%
Bouaziz et al. 2019	56	IAT	16/44	EXP: 72.9; CON: 74.3	EXP: 28.7; CON: 28.8	Prehypertensive	baFMD EXP: 0.8%; CON: -0.4%
Haynes et al. 2021 a	33	CAT	7/26	EXP: 61.9; CON: 61.8	EXP: 26.6; CON: 27.3	NR	baFMD EXP: 2.38%; CON: -0.09%
Haynes et al. 2021 b	34	CAT	8/25	EXP: 62.2; CON: 61.8	EXP: 27.6; CON: 27.3	NR	baFMD EXP: 0.45%; CON: -0.09%
Collins et al. 2023 a	29	CAT	29/0	EXP: 51.1; CON: 51.2	EXP: 30.6; CON: 28.7	Prehypertensive	baFMD EXP: 3.4%; CON: 0.8%
Collins et al. 2023 b	29	IAT	29/0	EXP: 49.1; CON: 51.2	EXP: 29.7; CON: 28.7	Prehypertensive	baFMD EXP: 4%; CON: 0.8%
Collins et al. 2023 c	29	IAT	29/0	EXP: 47.3; CON: 51.2	EXP: 29.7; CON: 28.7	Prehypertensive	baFMD EXP: 5%; CON: 0.8%
Yoshizawa et al. 2010	20	CAT	0/20	EXP: 57; CON: 58	EXP: 23.7; CON: 22.2	Normotensive	baFMD EXP: 1.1%; CON: -0.23%
Pierce et al. 2011	36	CAT	11/15	EXP: 63; CON: 60	EXP: 25.3; CON: 25.1	Normotensive	baFMD EXP: 1.24%; CON: 0.2%
He et al. 2022 a	30	CAT	0/30	EXP: 57.6; CON: 58.33	EXP: 23.9; CON: 24.8	Normotensive	baFMD EXP: 0.56%; CON: 0.06%
He et al. 2022 b	23	CAT	0/23	EXP: 24.3; CON: 58.33	EXP: 25.1; CON: 24.8	Normotensive	baFMD EXP: 2.09%; CON: 0.06%
He et al. 2022 c	25	IAT	0/25	EXP: 55.8; CON: 58.33	EXP: 23.1; CON: 24.8	Normotensive	baFMD EXP: 4.63%; CON: 0.06%

Table 3 Training variables

Study name	Training mode	Duration in weeks	Weekly frequency (times)	Single session duration (min)	Weekly duration (min)	Total number of training sessions
Hovespian et al. 2021	Ergometer-based	10	4	40	160	40
Shenouda et al. 2017 a	Cycling	12	3	10	27	32
Shenouda et al. 2017 b	Cycling	12	3	45	121.5	32
Robinson et al. 2016	Treadmill	8	3	37.5	112.5	24
Almenning et al. 2015	Walk/run/cycle	10	3	40	120	30
Beck et al. 2013	Treadmill	8	3	60	180	24
Azadpour et al. 2017	Treadmill walking/jogging	10	3	32.5	97.5	30
Bouaziz et al. 2019	Cycling	9.5	2	30	60	19
Haynes et al. 2021 a	Land walking	24	3	32.5	75	72
Haynes et al. 2021 b	Water walking	24	3	32.5	82.5	72
Collins et al. 2023 a	Cycling	12	3	55	165	36
Collins et al. 2023 b	Cycling	12	3	26	78	36
Collins et al. 2023 c	Cycling	12	3	26.5	78.5	36
Yoshizawa et al. 2010	Walking or cycling	8	4–5	35	157.5	36
Pierce et al. 2011	Walking	8	4	45	295	52
He et al. 2022 a	Treadmill running	8	5	50	250	60
He et al. 2022 b	Treadmill running	8	3	40	120	24
He et al. 2022 c	Treadmill running	8	3	30	90	24

was concealed (100%), blinding of the subjects (100%), blinding of the therapist (100%), and whether the subjects for whom outcome measures were available received the treatment or control condition as allocated (100%) (Table 4). Here, we emphasize that blinding participants is challenging to achieve in studies using physical exercise interventions as a treatment. Moreover, as FMD is a clinically important measure requiring adherence to standardized protocols to ensure valid and reliable measurements, all relevant methodological details are provided in Supplementary Table 1.

The grading of recommendations, assessment, development, and evaluations (GRADE)

The quality of evidence for $_{ba}$FMD was downgraded from high to low due to the high heterogeneity and low methodological quality of the included studies.

Effects of aerobic exercise intervention on brachial artery flow-mediated dilatation (traditional meta-analysis)

Meta-analysis of 18 ES studies with a total of 385 participants demonstrated a significant improvement of $_{ba}$FMD after AT (*small* MD = 1.92%, 95% CI 0.90 to 2.94, $p = 0.001$, $I^2 = 89$). Additionally, sub-analyses revealed that the effect of AT was moderated by form of AT, participants' age, sex, BMI, and hypertension status; however, none of the between-group comparisons reached statistical significance (all $p > 0.05$) (Table 5). It is interesting to note that a significant difference ($Q = 62.750$, $p < 0.001$) in the magnitude of increase in $_{ba}$FMD was observed between initially normotensive (*small* MD = 1.20%, 95% CI 0.64 to 1.75, $p < 0.001$) and prehypertensive participants (*moderate* MD = 4.43%, 95% CI 3.86 to 5.01, $p < 0.001$). The Egger's test was performed to provide statistical evidence of funnel plot asymmetry (Fig. 2). The results indicated no publication bias for this meta-analysis ($p = 0.963$).

Separate group meta-analysis on the standard deviation of change scores

Pooled analysis of standard deviation (SD) of change score estimates for both experimental and control arms of individual studies are presented in Figs. 3 and 4. Results revealed similar estimates for the SD of change in both the experimental (SD change = 1.62%, 95% CI 1.13 to 2.10) and control (SD change = 1.40%, 95% CI 0.83 to 1.97) groups. Based on the SD change scores, standard error of measurement (SEM) values were calculated for both the control (average SEM = 0.99%, ranging from 0.59 to 1.40%) and experimental groups (average SEM = 1.44%, ranging from 0.80 to 1.49%). The best estimate for the SD of change scores for both groups is between 0.83% and 2.10%, suggesting that much of the variation in observed change scores within a single intervention is likely attributable to measurement error.

Meta-analysis of intra-individual response difference for brachial artery flow-mediated dilatation

The pooled mean group difference in pre- to post-changes in $_{ba}$FMD from 12 studies with 385 participants was *trivial* (SD_{IR}^2 = 0.03%, 95% CI -0.11 to 0.17). If similar future studies were conducted, we estimate a 95%

Table 4 Fulfilment of physiotherapy evidence database (PEDro) criteria for each of the studies included in the present meta-analysis

Study reference	PEDro criteria											PEDro score
	1	2	3	4	5	6	7	8	9	10	11	
Almenning et al. 2015	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	YES	4
Azadpour et al. 2017	YES	YES	NO	YES	NO	NO	NO	YES	NO	YES	YES	5
Beck et al. 2013 a	YES	YES	NO	YES	NO	NO	NO	YES	NO	YES	YES	5
Bouaziz et al. 2019	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	7
Collins et al. 2023	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	7
Haynes et al. 2021	YES	YES	NO	YES	NO	NO	YES	YES	NO	YES	YES	6
He et al. 2022	YES	YES	NO	YES	NO	NO	YES	YES	NO	YES	YES	6
Hovespian et al. 2021	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	7
Pierce et al. 2011	YES	YES	NO	YES	NO	NO	YES	NO	NO	YES	YES	5
Robinson et al. 2016	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES	YES	3
Shenouda et al. 2017	YES	NO	YES	YES	NO	NO	NO	YES	NO	YES	YES	5
Yoshizawa et al. 2010	NO	YES	NO	YES	NO	NO	NO	NO	NO	YES	YES	4

PEDro criteria: 1—eligibility criteria were specified, 2—subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received), 3—allocation was concealed, 4—the groups were similar at baseline regarding the most important prognostic indicators, 5—there was blinding of all subjects, 6—there was blinding of all therapists who administered the therapy, 7—there was blinding of all assessors who measured at least one key outcome, 8—measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups, 9—all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analysed by "intention to treat", 10—the results of between-group statistical comparisons were reported for at least one key outcome, 11—the study provided both point measures and measures of variability for at least one key outcome. YES—criterion fulfilled, NO—criterion not fulfilled

likelihood that the difference in $_{ba}$FMD improvement between groups would fall between −0.11% and 0.17% (Table 6). Importantly, there is a 0% chance that a future study would find a clinically meaningful improvement (defined as ≥ 1% increase in $_{ba}$FMD) from aerobic exercise training. The results showed that there is no strong evidence that the SD_{IR}^2 of $_{ba}$FMD following AT is influenced by the form of AT (CAT: SD_{IR}^2 = 0.03; IAT: SD_{IR}^2 = 0.23), participants' age (18–39 years: SD_{IR}^2 = 0.14; 40–59 years: SD_{IR}^2 = 0.19; 60–75 years: SD_{IR}^2 = -0.01), sex (Both: SD_{IR}^2 = -0.01; Men: SD_{IR}^2 = 0.49; Women: SD_{IR}^2 = 0.18), or BMI (Normal body mass: SD_{IR}^2 = -0.06; Overweight: SD_{IR}^2 = -0.01; Obese: SD_{IR}^2 = 0.38). Finally, the SD_{IR}^2 of $_{ba}$FMD following AT was shown to be influenced by participants' blood pressure status (Prehypertensive: SD_{IR}^2 = 0.37, vs. Normotensive: SD_{IR}^2 = 0.32). For the prehypertensive individuals, neither the confidence nor predictive intervals crossed 0, suggesting there is trivial evidence that individual trainability for $_{ba}$FMD exists following AT in this population. In both cases (for BMI and blood pressure categorization), the between-study heterogeneity (τ) was 0; thus, the probability that the mean $_{ba}$FMD increase in a future study in similar settings will exceed MCID could not be calculated.

Meta-regression analysis

Through the meta-regression analysis, we investigated whether the effects of AT on $_{ba}$FMD were moderated by the baseline participants' characteristics, pre-to-post intervention changes in anthropometric, hemodynamic, hematological parameters and training-related variables (Supplementary Table 2). Results demonstrate that the effects of AT on $_{ba}$FMD were not moderated by the selected variables. Pre-to-post changes in BF% only showed a possible moderating effect (β = −2.160, $p = 0.055$), with a negative association suggesting that a greater reduction of BF% leads to greater improvements in $_{ba}$FMD following AT. When Robinson and colleagues' study [38] was excluded for the purpose of sensitivity analysis, the predictive value of changes in participants' body mass became significant (β = −1.181, $p = 0.042$), whereas the predictive value for changes in BMI improved slightly towards significance (β = −1.810, $p = 0.077$). These results suggest that reducing participants' body mass and BF% may explain the benefits of AT on $_{ba}$FMD. No other significant associations were observed for other parameters.

Discussion

Principal findings

The present meta-analysis aimed to investigate (a) the effects of AT on $_{ba}$FMD, and whether changes in $_{ba}$FMD are associated with changes in other cardiovascular health markers in healthy adults; (b) whether IIRD in

Table 5 The effects of aerobic training on brachial artery flow-mediated dilatation (results from traditional meta-analysis)

Independent variables	Effect size	SE	t value	*p* value	95% CI		95% pCI		I^2 (%)	df	Q value and (*p*) between groups
Brachial artery flow-mediated dilatation											
All studies	1.92	0.48	3.971	**0.001**	0.90	2.94	-2.03	5.86	89	17	NA
Subcategory (form of AT)											
CAT	1.66	0.64	2.610	**0.026**	0.24	3.07	-2.88	6.19	93	10	0.457 (0.499)
IAT	2.36	0.77	3.077	**0.022**	0.48	4.24	-2.56	7.29	72	6	
Subcategory (Age)											
18–39	0.94	1.04	0.911	**0.404**	-1.72	3.61	-5.72	7.61	75	5	3.544 (0.170)
40–59	2.94	0.67	4.350	**0.003**	1.34	4.53	-1.80	7.68	86	7	
60–75	1.38	0.46	2.975	**0.059**	-0.10	2.85	-2.97	5.73	83	3	
Subcategory (Sex)											
Both	1.38	0.54	2.567	**0.050**	0.00	2.77	-1.66	4.43	78	5	3.00 (0.223)
Men	1.00	1.22	0.820	**0.458**	-2.38	4.37	-7.07	9.06	68	4	
Women	2.85	0.71	3.987	**0.007**	1.10	4.59	-2.15	7.84	89	6	
Premenopausal	3.03	0.27	11.06	0.057	-0.45	6.52	NA	NA	0.00	1	0.029 (0.865)
Postmenopausal	2.82	0.99	2.83	0.047	0.06	5.58	-4.72	10.35	93.5	4	
Subcategory (BMI)											
Normal	2.00	0.86	2.340	**0.101**	-0.72	4.73	-5.48	9.49	84	3	0.523 (0.770)
Overweight	1.50	0.56	2.667	**0.024**	0.25	2.75	-1.95	4.95	83	10	
Obese	2.69	1.91	1.406	**0.295**	-5.53	10.91	-43.76	49.13	88	2	
Subcategory (SBP)											
Normotensive (RE)	1.17	0.70	1.667	**0.140**	-0.49	2.83	-3.31	5.65	80	7	2.250 (0.134)
Prehypertensive (RE)	2.93	0.86	3.384	**0.015**	0.81	5.04	-2.72	8.57	79	6	
Normotensive (FE)	1.20	0.28	4.233	$p < 0.001$	0.64	1.75	NA	NA	76	7	**62.750 ($p < 0.001$)**
Prehypertensive (FE)	4.43	0.29	15.090	$p < 0.001$	3.86	5.01	NA	NA	87	6	

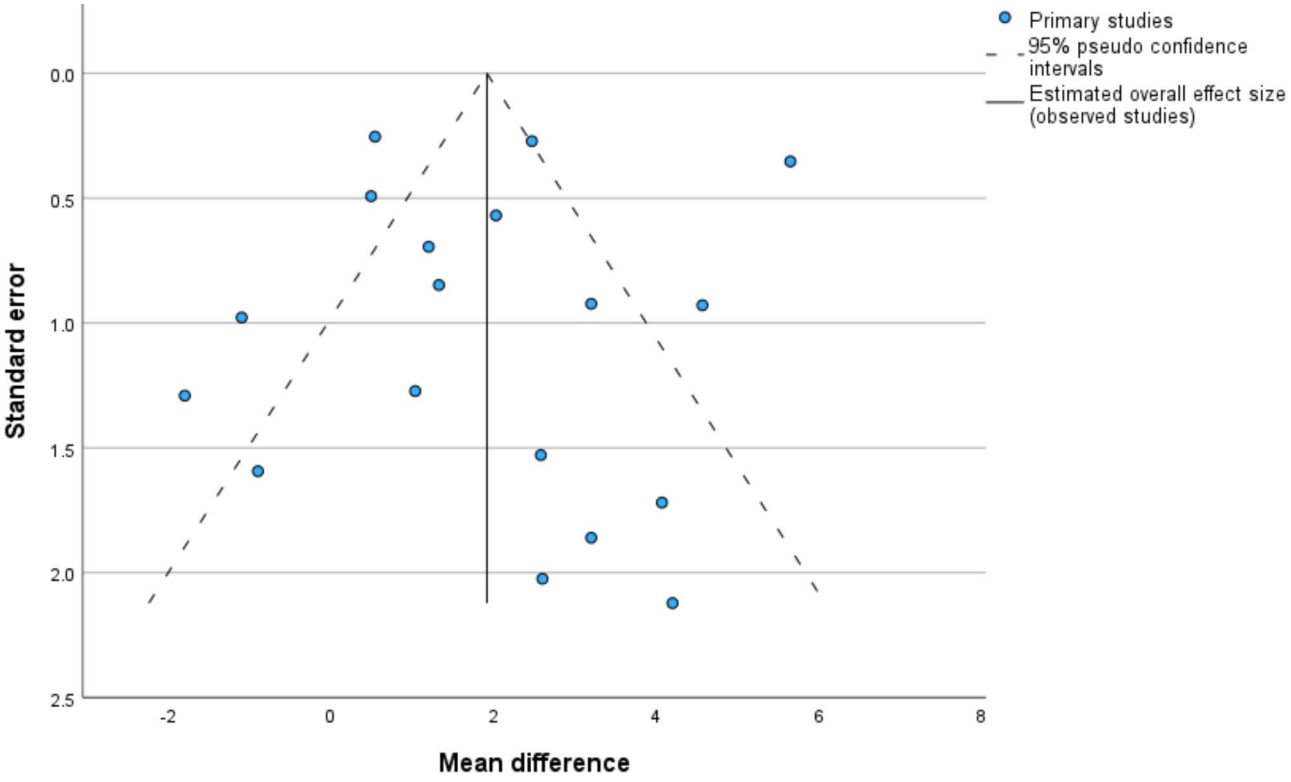

Fig. 2 Funnel plot of the mean differences vs. standard errors for flow-mediated dilatation

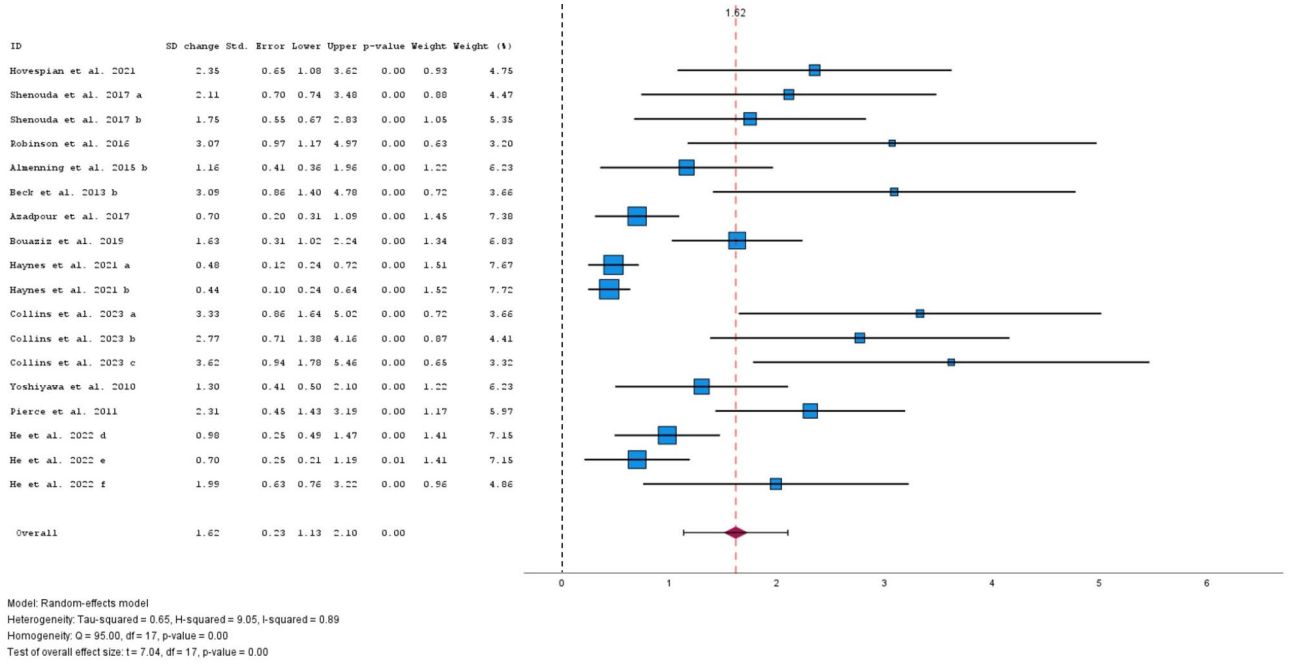

Fig. 3 Standard deviation of change scores across intervention groups only

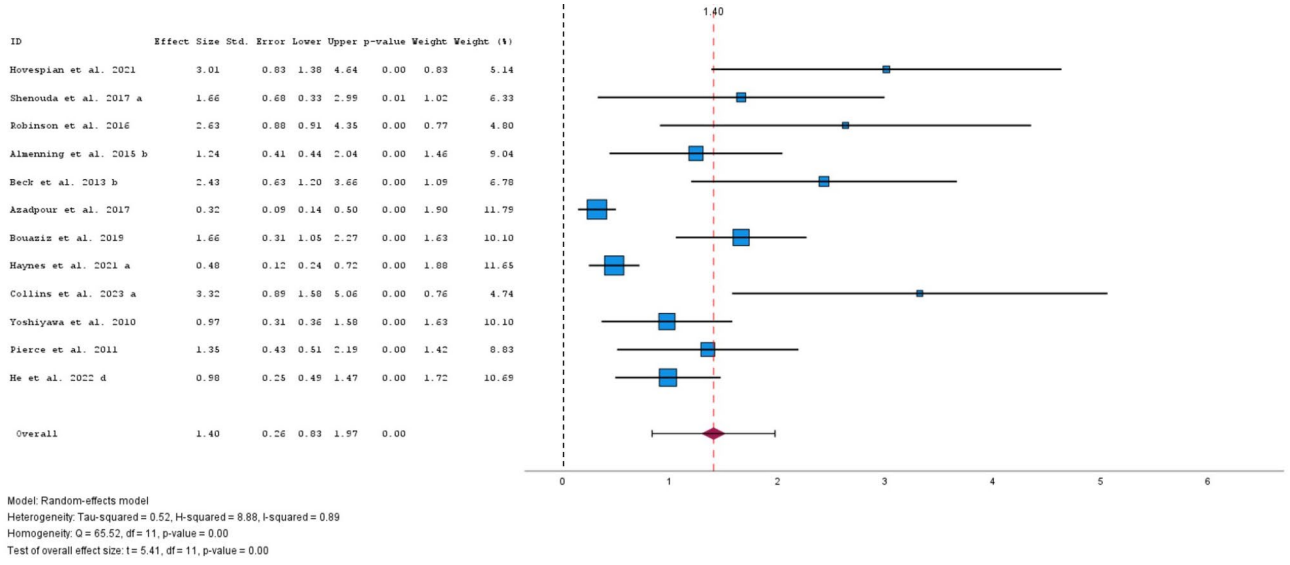

Fig. 4 Standard deviation of change scores across passive control groups only

$_{ba}$FMD improvement exists following AT; and (c) the association between participants' baseline characteristics and exercise-induced changes in $_{ba}$FMD.

The present study revealed a statistically significant improvement in $_{ba}$FMD following AT with a *small* mean difference of 1.92% (95% CI 0.90 to 2.94, $p = 0.001$), suggesting an average 19.2% reduction in CVD risk, with some individuals potentially experiencing even greater benefits from AT. The magnitude of $_{ba}$FMD improvements was moderated by form of AT, participant age, sex, BMI, and hypertension status. Notably, prehypertensive individuals exhibited a greater benefit from AT compared to normotensive participants. Variability in pre-to-post intervention changes, as indicated by the SD of change scores, was primarily attributed to factors unrelated to the intervention itself, such as measurement error or biological variability. The subgroup meta-analysis revealed statistically significant but clinically trivial IIRD exists following AT in prehypertensive individuals (SD_{IR}^2 < 1%). The results of the meta-regression analysis suggested that reductions in participants' body mass, BMI and BF% following AT may predict improvements in

Table 6 The results of the intra-individual response difference meta-analysis for brachial artery flow-mediated dilatation

Independent variables	SDir^2	SE	t value	*p* value	95% CI		95% pCI		Q statistic for ind. MA	df	Sig.	Tau-squared	H-squared	I-squared (%)	Q statistic for subgroups
$_{ba}$FMD															
Experimental group only	1.62*	0.23	7.04	$p < 0.001$	1.13	2.10	-0.16	3.39	95.00	17	$p < 0.001$	0.65	9.05	88.95	NA
Control group only	1.41*	0.22	6.38	$p < 0.001$	0.94	1.88	-0.22	3.04	91.61	17	$p < 0.001$	0.54	10.01	90.01	NA
All studies	0.03	0.07	0.48	0.639	-0.11	0.17	-0.11	0.17	14.08	17	0.66	0.00	1.00	0.00	
Subgroup analysis for form of aerobic training															
CAT	0.03	0.07	0.40	0.700	-0.13	0.19	-0.14	0.20	10.05	10	0.44	0.00	1.00	0.00	0.090 (0.764)
IAT	0.23	0.53	0.43	0.684	-1.07	1.52	-1.13	1.59	3.95	6	0.68	0.00	1.00	0.00	
Subgroup analysis for participants' age															
18–39	0.14	0.53	0.26	0.807	-1.22	1.49	-1.33	1.60	1.90	5	0.86	0.00	1.00	0.00	0.753 (0.686)
40–59	0.19	0.20	0.97	0.363	-0.28	0.67	-0.55	0.94	6.16	7	0.52	0.05	1.12	11.10	
60–75	-0.01	0.10	-0.15	0.889	-0.32	0.29	-0.43	0.40	4.21	3	0.24	0.00	1.00	0.26	
Subgroup analysis for participants' sex															
Both	-0.01	0.08	-0.16	0.880	-0.22	0.20	-0.24	0.21	5.08	5	0.41	0.00	1.00	0.00	0.746 (0.689)
Men	0.49	0.70	0.70	0.522	-1.46	2.45	-1.75	2.73	0.81	4	0.94	0.00	1.00	0.00	
Women	0.18	0.21	0.83	0.440	-0.35	0.70	-0.61	0.96	6.49	6	0.37	0.05	1.14	12.12	
Subgroup analysis participants' body mass index															
Normal	-0.06	0.37	-0.16	0.884	-1.24	1.12	-1.65	1.53	4.21	3	0.24	0.00	1.00	0.01	3.106 (0.212)
Overweight	-0.01	0.06	-0.21	0.835	-0.15	0.12	-0.15	0.13	5.82	10	0.83	0.00	1.00	0.00	
Obese	0.38	0.14	2.61	0.121	-0.24	1.00	-1.46	2.21	0.95	2	0.62	0.00	1.00	0.00	
Subgroup analysis for participants' blood pressure categorization															
Normotensive (RE)	0.32	0.45	0.72	0.496	-0.74	1.38	-1.50	2.14	9.37	7	0.23	0.35	1.37	26.82	0.010 (0.921)
Prehypertensive (RE)	0.37	0.10	3.64	**0.011**	0.12	0.62	0.11	0.63	1.47	6	0.96	0.00	1.00	0.00	

SDir - standard deviations of individual response; SE – standard error; **$_{ba}$FMD -** brachial artery flow-mediated dilation; * – pooled analysis was conducted for SDir; CI – confidence interval; pCI – predicted confidence interval

$_{ba}$FMD. However, these findings emerged from sensitivity analysis after excluding one study, precluding definitive conclusions.

Traditional meta-analysis on the effects of aerobic training on brachial artery FMD

In addition to investigating IIRD, our review and meta-analysis aimed to examine the effects of AT on various health-related parameters, with a particular focus on $_{ba}$FMD. The results of our meta-analysis revealed a significant improvement in $_{ba}$FMD post-AT (*small* MD = 1.92%, $p = 0.001$), which is in line with previous studies investigating similar questions in the adult population regardless of health status [17, 21], or overweight and obese adults [39]. Based on prior evidence linking a 1% FMD increase to a 10% lower CVD risk [1], this improvement could translate to roughly a 19.2% reduction in CVD risk for participants following AT. The actual benefit likely falls between a 9% lower risk (if the true improvement is at the lower end of the range, 0.90%) and a 29.4% lower risk (if it's at the higher end, 2.94%). Although the 1% FMD change itself may seem small and clinically trivial, the pooled results highlight an average 19.2% reduction in CVD risk, with some individuals potentially experiencing even greater benefits from AT.

To investigate sources of variability among the studied population, several sub-analyses were conducted. These indicated that the form of AT, participants' age, sex, BMI, and hypertension status moderated the effects, though between-group differences were not statistically significant. Notably, prehypertensive participants exhibited greater improvements in $_{ba}$FMD after AT compared to normotensive participants (*moderate* MD = 4.43% vs. *small* MD = 1.20%). The robustness of our findings was further confirmed by random-effects model meta-analysis. The results of meta-regression analysis showed that reductions in participants' body mass, BMI and BF% could be potential predictors of beneficial effects of AT on $_{ba}$FMD. However, given that these results were derived from a sensitivity analysis after the removal of one study, a firm conclusion on the causal relationship of this question cannot be drawn.

AT improves endothelial function primarily through structural and functional adaptations, which can be viewed through hemodynamic, biochemical, and anti-inflammatory pathways. Indeed, AT-induced shear stress during exercise stimulates endothelial nitric oxide synthase (eNOS) activity, boosting nitric oxide production, a key vasodilator that enhances arterial elasticity and reduces vascular resistance [40]. This shear stress is sensed by mechanoreceptors on endothelial cells, triggering signaling pathways that upregulate eNOS expression and reduce oxidative stress by suppressing nicotinamide-adenine dinucleotide phosphate oxidase [41], thereby preserving nitric oxide bioavailability [42, 43]. Exercise also mitigates endothelial dysfunction by reducing systemic inflammation; it lowers pro-inflammatory cytokines (e.g., TNF-α, IL-6) while elevating anti-inflammatory mediators like adiponectin and IL-10, which counteract endothelial activation and leukocyte adhesion [44, 45]. Additionally, AT improves insulin sensitivity, reducing hyperglycemia-induced oxidative stress and advanced glycation end-products that impair endothelial NO signaling [12, 46]. Enhanced mitochondrial biogenesis in vascular endothelial cells, driven by exercise-induced AMPK activation, further reduces reactive oxygen species and improves endothelial redox balance [47]. Finally, exercise may promote endothelial repair via increased circulating endothelial progenitor cells, which are mobilized by VEGF and stromal-derived factor-1 to replace damaged cells and restore vascular homeostasis [48]. Although many of the physiological mechanisms underlying endothelial function improvements following exercise, as discussed earlier, were not directly investigated in the studies included in this meta-analysis, our findings underscore the beneficial effects of AT on vascular function. Additionally, the results highlight the need for more rigorous studies to confirm these findings and further investigate the observed heterogeneities. Our evidence suggests that significant response heterogeneity following AT can be expected in individuals with increased cardiovascular risk factors, such as elevated systolic blood pressure, which is combined with other comorbidities (e.g., increased BMI, lower cardiorespiratory function as indicated by higher resting heart rate and lower aerobic capacity).

Intra-individual response difference for brachial artery flow-mediated dilatation

To the best of our knowledge, this is the first study aimed at investigating whether true IIRD in $_{ba}$FMD improvement occurs in response to AT in healthy adults. We found a trivial, non-significant result favoring AT over the control group in terms of IIRD. This suggests that most of the variation in the observed change scores is likely attributable to factors unrelated to the intervention itself such as measurement error, biological variability, and uncontrolled lifestyle factors (e.g., habitual physical activity [49, 50], dietary patterns [51], or stressors [52, 53]) that were not systematically accounted for in the original studies. This was further confirmed by several subgroup meta-analyses, which showed that other demographic characteristics such as body mass, BMI, sex and participants' age are not moderating factors of the observed IIRD, reinforcing the notion that these variables do not explain heterogeneity in responses. These findings align with prior meta-analytic research examining IIRD in various settings [54–59]. These studies

investigated whether true IIRD exists for $VO_{2max,}$ BMI, body mass reduction, or other body composition indices following AT [54, 60] or resistance training [58] interventions. Given the lack of evidence supporting the existence of IIRD for the parameters previously mentioned, the authors suggested it is unlikely that clinically relevant predictors for VO_{2max} trainability or decreases in body mass can be identified within a single study intervention. Some authors even recommended reallocating resources from investigating IIRD in future studies.

Nevertheless, while our results and existing literature highlight the challenges of detecting IIRD—particularly when variability is dominated by uncontrolled confounders—they also underscore the need for large-scale, methodologically rigorous studies to differentiate responders from non-responders. Future research should prioritize controlled designs that systematically account for other confounding variables we were not able to assess in this meta-analysis (e.g., habitual physical activity [49, 50], dietary patterns [51], or stressors [52, 53]) and employ rigorous endothelial functions assessment methodology with larger sample sizes to isolate true intervention effects from noise. Until such studies are conducted, the clinical relevance of IIRD in $_{ba}$FMD—and its potential utility for personalizing AT interventions in apparently healthy adult populations—remains speculative.

An interesting finding from this meta-analysis was that a subgroup meta-analysis revealed greater IIRD following AT in prehypertensive individuals compared to normotensive controls. Endothelial dysfunction is an early marker of CVD [1], often presented in prehypertensive individuals [61–63]. This dysfunction is characterized by a reduced availability of nitric oxide, increased oxidative stress, and elevated levels of inflammatory markers [64–66]. The endothelium, which lines the blood vessels, plays a crucial role in maintaining vascular health, including the regulation of blood vessel dilation and, consequently, blood pressure. In prehypertensive individuals, endothelial function is typically impaired [61–63], providing a lower baseline [33, 67] from which improvements can be more easily observed compared to normotensive individuals. A thorough comparison of individual participants' characteristics classified as prehypertensive or normotensive revealed higher initial values in the prehypertensive group for body mass (81.8 kg vs. 70.0 kg), BMI (29.0 kg/m^2 vs. 25.5 kg/m^2), BF% (37.5% vs. 36.2%), resting heart rate (69.6 bpm vs. 64.9 bpm), and systolic blood pressure (131.1 mmHg vs. 112.9 mmHg). Although our inclusion criteria aimed to investigate the effects of AT on certain health-related parameters in healthy adults, it appears that the prehypertensive group exhibited some degree of CVD risk compared to the normotensive group, which may have led to them experiencing greater benefits from the intervention [20, 68, 69]. For example, Joris and colleagues [69] found that each 10 kg decrease in body mass increased the FMD by 1.11%, with the effects being more pronounced in individuals with coexisting obesity-related morbidities. Similar findings were replicated in patients diagnosed with coronary heart disease [68]. The authors found a greater increase in $_{ba}$FMD in patients who lost more body mass, advocating a dose–response relationship between the amount of body mass lost and endothelial function improvements. Moreover, the association was higher between body mass loss and $_{ba}$FMD ($R^2 = 0.18$, $p = 0.005$) than between changes in other health-related measures, including abdominal fat ($R^2 = 0.08$, $p = 0.05$), fat mass ($R^2 = 0.11$, $p = 0.02$), insulin ($R^2 = 0.08$, $p = 0.05$), lipid measures or cardiorespiratory fitness [68]. Although the mechanisms behind the beneficial effects of mass reduction on endothelial function are not yet fully understood, reduced secretion of adipose tissue-derived adipokines and other vasoactive factors may play a significant role [70–74]. Adipose tissue, a metabolically active endocrine organ, contributes to the production of proinflammatory and proatherogenic cytokines, which have detrimental effects on the endothelium [70–72]. Reducing adipose tissue lowers the levels of these harmful cytokines, potentially improving endothelial function. In fact, adipocytokine levels, such as retinol-binding protein-4 and resistin, have been recognized as independent predictors of FMD in healthy individuals [73]. On the other hand, adiponectin, one of the primary hormones secreted from the adipose tissue and the liver, plays several important roles in homeostasis through its anti-inflammatory, anti-fibrotic, and antioxidant effects by regulating glucose levels, lipid metabolism, and insulin sensitivity. Several studies have shown positive associations between adiponectin levels and improved endothelial function, suggesting that increased circulating adiponectin is positively linked to enhanced endothelial function, as demonstrated in a study included in this meta-analysis [75]. Hovsepian and colleagues [75] observed a 6.9% increase in adiponectin levels, accompanied by reductions in body mass, waist circumferences and BF%, along with improved $_{ba}$FMD following a high-intensity interval training in overweight and obese women. Thus, based on the current evidence, we believe several mechanisms may be responsible for the observed changes in $_{ba}$FMD in the subgroup of prehypertensive individuals.

Limitations and future directions

We believe this study has some limitations worth mentioning. Firstly, we introduced several inclusion criteria for this review, which limits our ability to generalize the findings to other forms of exercise (e.g., resistance training, combined aerobic and resistance training), combined interventions (e.g., exercise plus diet or education on

healthy lifestyle), symptomatic populations (e.g., diagnosed CVD or metabolic syndrome), or other markers of endothelial function beyond $_{ba}$FMD. While this can be viewed as a limitation, it can also be considered a strength, as we narrowed our focus to specific settings, minimizing the influence of other moderating factors that would be difficult to interpret. Secondly, the included studies varied in duration, ranging from 8 to 24 weeks (with only one study extending beyond 12 weeks, i.e., at 24 weeks [34]), and showed substantial differences in training frequency, session duration, overall training duration, and the equipment used to conduct the interventions. Therefore, we believe these findings should be interpreted within the context of short-term intervention studies. Further research with longer intervention periods is needed before concluding that there is no evidence of IIRD in $_{ba}$FMD following AT in healthy adults. Additionally, the methodological quality of the included studies was fair, and the certainty of evidence for most primary and secondary outcomes was low or very low, indicating a low level of confidence in the recommendations that can be drawn from these studies. While only two studies explicitly referenced established guidelines for FMD assessment, the majority provided sufficient methodological detail in their reports (Supplementary Table 1). This mitigates—though does not fully eliminate—concerns that variability in FMD protocols significantly skewed the observed results. Nevertheless, the scarcity of adherence to standardized guidelines highlights a critical gap. Future studies should prioritize strict compliance with contemporary consensus recommendations for FMD methodology to enhance methodological rigor, reduce inter-study variability, and improve the reliability of conclusions. Such efforts would be particularly valuable given that key methodological parameters (e.g., measurement protocols, cuff placement, and analysis criteria) were inconsistently reported across the literature despite their importance to result interpretation. We would also like to highlight the importance of calculating both traditional effects and IIRD in the included studies, as this provides deeper insights into the true impact of the intervention. We encourage future researchers to account for these factors in both original studies and when conducting meta-analyses of already published data.

Conclusions

When summarizing findings by traditional meta-analysis, the present study found small improvements in $_{ba}$FMD, suggesting an average 19.2% reduction in CVD risk, with some individuals potentially experiencing even greater benefits from AT. On the contrary, a meta-analysis based on IIRD suggests that factors unrelated to the intervention itself mostly contribute to the observed changes in $_{ba}$FMD. However, prehypertension appeared to moderate the IIRD in $_{ba}$FMD improvement following AT, though the results were not clinically significant. Current evidence indicates that response heterogeneity following AT can be expected in individuals with increased cardiovascular risk factors, such as elevated systolic blood pressure, and this warrants further investigation. However, these findings should be considered within the context of short-term intervention studies, and further research with high methodological rigor and longer intervention periods is warranted before concluding that there is no evidence of IIRD in $_{ba}$FMD following AT in the generally healthy adult population.

Abbreviations

$_{ba}$FMD	brachial artery flow–mediated dilatation
PEI	Physical exercise interventions
IIRD	Intra–individual response differences
REML	Restricted maximum likelihood
CI	Confidence interval
pCI	Predicted confidence interval
SDir	Standard deviations of individual response
SE	Standard error
PEDro	Physiotherapy Evidence Database
AT	Aerobic training
CAT	Continuous AT
IAT	Interval AT

Supplementary Information

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Supplementary Material 1

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Author contributions

Author contributions: AHP was involved in the initial idea and the conceptualization of current review. AHP and KD collaborated on the literature review. AHP performed the meta-analysis and wrote the manuscript draft. Both authors collaborated on interpreting the results and reviewing the manuscript. Both authors contributed to the article, approved the submitted version, and read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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