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Effects of Exercise on the Microvascular Response, Endothelial Health, and NO Bioavailability: A Systematic Review and Meta-Analysis

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Abstract

Purpose: Mechanistic evidence from animal models is essential for understanding exercise-induced vascular adaptations, yet the translatability of these findings to clinical settings remains uncertain. This systematic review and meta-analysis quantified the effects of exercise training on endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) levels in animal models. **Method:** A systematic search of PubMed, Scopus, Web of Science, and Cochrane Library (January 2000–September 2025) was done. The review protocol was registered with PROSPERO (CRD420251144669). A random-effects model (REML) was used for meta-analysis, and SYRCLE's Risk of Bias tool assessed study quality.

Results: Exercise training significantly increased eNOS levels (SMD = 0.99, 95% CI: 0.55–1.44, $p < 0.001$). In contrast, no significant effects were observed for NO (SMD = −1.26, 95% CI: −2.89–0.37, $p = 0.13$). Subgroup analyses showed that longer exercise duration (≥5 weeks; SMD = 2.25, $p < 0.001$) and specific modalities such as treadmill running (SMD = 1.92) and swimming (SMD = 4.59) were associated with substantially greater eNOS upregulation. Considerable heterogeneity was observed across most outcomes ($I^2 > 85\%$). **Conclusion:** Exercise training effectively upregulates eNOS expression in animal models, particularly with interventions lasting five weeks or longer and with structured modalities like treadmill and swimming. However, the absence of significant effects on NO level, despite increased eNOS, reveals a translational gap that warrants further mechanistic investigation.

Keywords: Exercise training; Endothelial nitric oxide synthase; Nitric oxide bioavailability; Systematic review; Animal models.

Introduction

Endothelial dysfunction is an early hallmark of cardiometabolic and vascular disorders, including atherosclerosis, type 2 diabetes, hypertension, and heart failure (Deanfield et al., 2007; Shojah-anzabi et al., 2026; Widlansky et al., 2003). It reflects a phenotypic shift toward reduced vasodilation, increased oxidative stress, and a pro-inflammatory, pro-thrombotic state. Central to this process is diminished NO bioavailability, driven by impaired endothelial nitric oxide synthase (eNOS) activity and enhanced nitric oxide (NO) degradation by reactive oxygen species (ROS) (Cai & Harrison, 2000; Landmesser et al., 2004). Given NO's critical role in regulating vascular tone, inhibiting platelet aggregation, and preserving endothelial integrity, its dysfunction promotes both functional abnormalities and structural vascular remodeling(Forstermann & Münzel, 2006). Consequently, endothelial dysfunction has emerged as a key therapeutic target and an early predictor of adverse cardiovascular outcomes.

Exercise training is widely recognized as an effective non-pharmacological intervention for improving vascular function(Green et al., 2017; Hassanzadeh et al., 2022). Mechanistic insights from animal models have substantially advanced our understanding of exercise-induced vascular adaptations at the molecular level(Laughlin et al., 2012). Repetitive increases in laminar shear stress during exercise stimulate eNOS expression and activation, augmenting NO production(Balligand et al., 2009). Additionally, exercise attenuates oxidative stress by reducing ROS generation and enhancing antioxidant systems such as superoxide dismutase (SOD), thereby preserving NO bioavailability(Nosrati et al., 2022; Powers & Jackson, 2008; ShojaAnzabi et al., 2023). Key signaling pathways involved include PI3K/Akt/eNOS and AMP-activated protein kinase (AMPK)(Robinson et al., 2018).

Despite these advances, the magnitude and consistency of exercise-induced vascular benefits vary according to exercise modality, intensity, and duration, highlighting important sources of heterogeneity

across animal studies(Karisa et al., 2026). Moreover, the translation of these mechanistic findings to clinical applications remains incomplete. Although a substantial body of animal literature has examined the vascular effects of exercise, findings remain fragmented and inconsistent due to heterogeneity in study design, animal models, and endpoints. Notably, few efforts have systematically quantified the effects of exercise on eNOS, and NO within a unified analytical framework.

Despite growing interest in the effects of exercise on endothelial function and vascular health, the existing animal literature is diverse and results are often inconsistent. Various factors, including exercise type, intensity, frequency, duration, and animal characteristics, may influence the impact of exercise on endothelial function and NO bioavailability. Therefore, a comprehensive synthesis of preclinical evidence is crucial to clarify these relationships and guide future translational research. Accordingly, this systematic review and meta-analysis was designed to address four specific research questions: (1) What is the pooled effect of exercise training on eNOS expression and NO bioavailability in animal models? (2) Does exercise duration (categorized as <5 weeks vs. ≥5 weeks) moderate the magnitude of exercise-induced changes in eNOS expression? (3) Do exercise characteristics, including frequency (<3 vs. ≥3 days/week), intensity (low, moderate, high), and modality (treadmill, swimming, general aerobic), significantly influence eNOS and NO responses? and (4) Does exercise frequency and intensity moderate the NO response to exercise training? By addressing these questions, we aim to identify key sources of heterogeneity and provide evidence-based recommendations for optimizing exercise protocols in preclinical vascular research.

Methodology

Research protocol registration and PICO framework

This systematic review and meta-analysis was conducted following the PRISMA 2020 guidelines and the PROSPERO protocol for systematic reviews(Page et al., 2021). The review protocol was registered with

PROSPERO (CRD420251144669) and adhered to throughout the review process. The research question was structured using the PICO(s) framework to define eligibility criteria for animal studies as follows: population included animal models (rats, mice, and other experimental animals) undergoing exercise training; intervention comprised exercise training protocols such as aerobic exercise, treadmill running, swimming, and voluntary wheel running; comparison involved control groups including sedentary animals, non-intervention; outcomes were changes in eNOS and NO levels; and study design required controlled experimental animal studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) original, peer-reviewed quantitative research articles published in English between January 2000 and September 2025; (2) studies involving animal models (including rats, mice, and other experimental animals) that participated in structured exercise training interventions such as aerobic exercise, treadmill running, swimming, voluntary wheel running, or combined exercise programs; (3) studies that included a control or comparison group (sedentary animals, non-intervention, or sham interventions); and (4) studies reporting outcomes related to eNOS and NO.

Exclusion criteria were: (1) studies not examining exercise training or the specified outcomes (eNOS, NO); (2) studies focusing solely on pharmacological, dietary, or non-exercise interventions; (3) studies without an appropriate control group (e.g., before-after designs without comparison); (4) reviews, editorials, case reports, conference abstracts, or non-English publications without available English translations; and (5) in vitro studies or studies using non-mammalian models unless specifically justified.

Search strategy and study selection

A systematic search was performed in PubMed, Scopus, Web of Science, and Cochrane Library for studies published from January 2000

to September 2025. The search strategy combined MeSH terms and keywords related to physical activity, exercise interventions, endothelial function, NO bioavailability, and animal models using Boolean operators (AND, OR). An example PubMed search string is provided in the supplementary materials. All records were imported into EndNote 2025 for duplicate removal. Two independent reviewers (R. F. and F. S.) screened titles and abstracts against eligibility criteria, with discrepancies resolved by a third reviewer. Full texts of potentially eligible studies were then assessed for inclusion. Reference lists of included articles were manually searched, and a snowballing approach was applied to identify additional studies. The selection process is illustrated in the PRISMA 2020 flow diagram (Fig. 1).

Data extraction

All retrieved records were imported into EndNote 2025.19000 for reference management. One author (R. F.) conducted the initial screening after duplicate removal and exclusion of review articles. Studies without an exercise intervention or those irrelevant to animal models were excluded. Titles and abstracts were screened individually to confirm relevance.

Two independent reviewers (R. F. and F. S.) performed full-text data extraction using a standardized form. Extracted data included: (1) study characteristics (author, year, country, design); (2) animal characteristics (species, strain, age, sex, weight, sample size, health status); (3) intervention details (type, frequency, intensity, session duration, total weeks); (4) control group details; (5) primary outcomes (eNOS, NO) with measurement methods and tissue source; (6) secondary outcomes (e.g., blood pressure, oxidative stress, inflammatory markers); and (7) study limitations (namely, small sample size, lack of blinding). Discrepancies were resolved through discussion.

Quality assessment

Risk of bias was assessed using the SYRCLE Risk of Bias tool, specifically designed for preclinical animal studies. The tool evaluates

six domains: selection bias (random sequence generation, allocation concealment, baseline characteristics), performance bias (random housing, blinding of caregivers/investigators), detection bias (random outcome assessment, blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other biases (namely, commercial funding, unit of analysis issues)(Hooijmans et al., 2014). Each domain was rated as low, high, or unclear risk. Two independent reviewers (R. F. and F. S.) assessed each study, with discrepancies resolved by consultation. The potential influence of bias on study outcomes was considered during data synthesis.

Statistical analysis

Meta-analysis model

A quantitative meta-analysis was performed using random-effects models (Restricted Maximum Likelihood [REML] method) with 95% confidence intervals (CIs) and Standardized Mean Difference (SMD) effect size. All analyses were conducted using CMA version 4 for overall meta-analysis, subgroup analysis, meta-regression (with Hartung-Knapp adjustment), and publication bias assessment(Dargel et al., 2015). Python was used for leave-one-out sensitivity analyses. Statistical significance was set at $p < 0.05$ (two-tailed). When numerical values were not directly reported, data were extracted from figures using WebPlotDigitizer. For studies reporting multiple measurements from the same animal model (e.g., different tissues or time points), a nested random-effects approach was used to avoid unit-of-analysis errors.

Subgroup analyses

Subgroup analyses explored potential sources of heterogeneity based on exercise frequency (sessions/week), intensity (low, moderate, high), type (aerobic, treadmill, swimming, voluntary wheel running), and animal age (young vs. aged). Subgroups were analyzed only when at least three studies were available per category.

Heterogeneity assessment

Heterogeneity was assessed using I^2 statistic, tau-squared (τ^2), and Cochran's Q test. I^2 values were interpreted as: 0–40% (not important), 30–60% (moderate), 50–90% (substantial), and 75–100% (considerable). For outcomes with $I^2 > 50\%$, prediction intervals (PIs) were calculated alongside Cis (Petitti, 2001).

Publication bias

Publication bias was evaluated using funnel plots, Egger's test, and Begg's test (for outcomes with ≥10 studies). When asymmetry was detected ($p < 0.10$), Trim and Fill adjustment was applied. Classic fail-safe N analysis calculated the number of null studies needed to nullify significant effects(Thornton & Lee, 2000).

Results

Study selection

A systematic search of PubMed, Scopus, Web of Science, and Cochrane Library databases (January 2000 – September 2025) identified 1,247 records. After removing 421 duplicates, 826 titles and abstracts were screened, and 712 were excluded for the following reasons: non-original research (namely, reviews, conference abstracts, editorials), human studies, in vitro studies, non-mammalian models, studies without an exercise intervention, and studies not reporting outcomes of interest (eNOS and NO). Subsequently, 114 full-text articles were assessed for eligibility, of which 80 were excluded due to: lack of extractable data for meta-analysis (n = 34), absence of an appropriate control group (n = 21), inappropriate study design (e.g., single bout only, no training intervention) (n = 15), and data overlap with another included study (n = 10). Ultimately, 34 studies met the inclusion criteria for the systematic review, of which 16 contained sufficient quantitative data for meta-analysis. From these 16 independent studies, a total of 34 separate effect sizes were extracted across the three outcomes. The

study selection process is illustrated in the PRISMA 2020 flow diagram (Fig. 1).

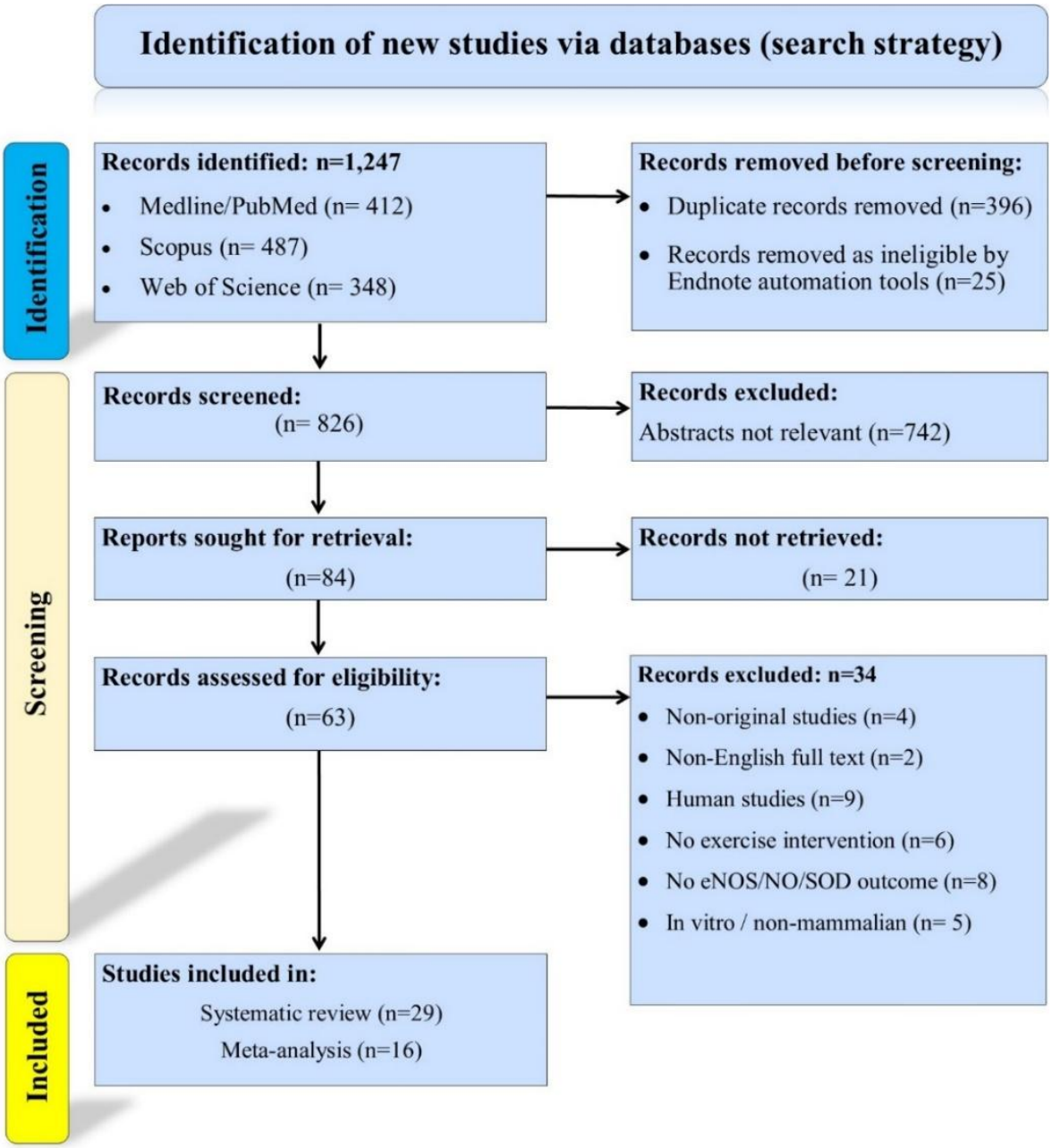


Fig. 1. PRISMA 2020 flow diagram of the study selection process.

Study characterization

A comprehensive summary of included studies is provided in Table 1. A total of 29 preclinical studies met the inclusion criteria for systematic review, comprising 34 independent effect sizes for meta-analysis. All studies were original, peer-reviewed articles published between 2014 and 2025. Animal models predominantly consisted of male rats (Wistar, Sprague-Dawley, and SHR) and male mice. The mean sample size per group ranged from 8 to 12 animals. Exercise interventions primarily included treadmill running (23 studies), swimming (2 studies), resistance training (3 studies), and voluntary wheel running (1 study). Intervention duration ranged from a single acute session to 12 weeks, with a mean of 6.5 ± 3.2 weeks. Exercise intensity was moderate (50–70% of maximum capacity) in most studies, with a frequency of 5 sessions per week. Primary outcomes included eNOS (immunoblotting, Western blot), NO (Griess assay, DAF-2 fluorescence), measured across various tissues such as aorta, mesenteric arteries, coronary arteries, and cardiac tissue. Considerable variability was observed in exercise protocols, disease models (hypertension, diabetes, heart failure, obesity, ovariectomy), and measurement techniques, which contributed to the substantial heterogeneity observed in the meta-analysis.

Table 1. Characteristics of included animal studies examining the effects of exercise training on endothelial function, nitric oxide bioavailability, and microvascular response.

First Author, Year	Animal Model	Sample Size (M/F)	Intervention Type	Duration	Intensity	Key Outcomes (Endothelial Function / NO / Microvascular)
(Braga et al., 2015)	OVX rat	40 F	Aerobic (treadmill)	8 wk	Low-moderate	↑ ACh-induced relaxation; ↑ NO; ↓ ROS
(Guizoni et al., 2016)	LDLr mouse	80 M	Aerobic (treadmill)	4 wk	Moderate	↑ ACh relaxation; ↑ eNOS phosphorylation; ↑ NO; ↓ superoxide

(Mendonça et al., 2019)	T. cruzi-infected rat	45 M	Aerobic (treadmill)	4 wk	Moderate	↑ NO (but ↑ inflammation); ↓ microvascular ratio
(Sun et al., 2017)	High-fructose rat	50 M	Treadmill test	3-30 d	Normal	Short-term: ↑ NO; Long-term: ↓ NO, ↑ superoxide
(Monnier et al., 2017)	SHR (hypertensive)	49 M	Aerobic (treadmill)	7 d	Moderate	↑ eNOS phosphorylation; ↑ BDNF (NO-dependent)
(Mota et al., 2017)	Healthy rat	24 M	Resistance (single bout)	1 session	High-volume	↑ Insulin-induced vasodilation; ↑ NO (volume-dependent)

(Battault et al., 2016)	SHR	34 M	Aerobic (treadmill)	6 wk	High vs. moderate	Moderate ↑ sensitivity; HIET → eNOS uncoupling, no benefit
(Tanaka et al., 2015)	Healthy rat	Not reported	Acute aerobic	1 session	Moderate	↑ ACh relaxation; ↑ eNOS Ser1177; ↑ NO without oxidative stress
(Zimmer et al., 2017)	MCT-PAH rat	24 M	Aerobic (treadmill)	5 wk	Moderate	No improvement; ↑ iNOS, nitrotyrosine; disease severity overrides

(Oliveira et al., 2020)	2K1C (hypertensive)	123 M	Aerobic (treadmill)	10 wk	Low-moderate	NO-mediated modulation in normotensive; blunted in hypertensive
(de Oliveira et al., 2019)	OVX + MI rat	60 F	Aerobic (treadmill)	8 wk	Low-moderate	↑ Endothelial relaxation; ↑ NO; ↓ gp91phox, ↓ ROS
(Couto et al., 2018)	HF (post-MI) rat	~60 M	Aerobic (treadmill)	8 wk	Moderate	Restored coronary relaxation; ↑ NO via GCH1/eNOS coupling
(Lavier et al., 2021)	Healthy mouse	58 M	Hypoxic treadmill	4 wk	Various	Hypoxic-high intensity ↑ ACh relaxation; ↑ NO; ↓ nitrotyrosine

(Nogueira et al., 2022)	Healthy rat	18 M	Resistance (ladder)	12 wk	Progressive	HPD+RT ↑ NO; ↓ TNF-α; ↑ MMP-2 activity
(van Deel et al., 2018)	Post-MI / TAC mouse	99 M/F	Voluntary wheel	8 wk	Self-paced	Post-MI: ↑ NO, ↓ eNOS uncoupling; TAC: worsening
(Wang et al., 2017)	TAC mouse	105 M	Swimming	9 wk	Progressive	↑ NO via β3-AR–nNOS; ↓ ROS; improved cardiac function
(Luo et al., 2023)	db/db (diabetic)	~30	Aerobic (treadmill)	4 wk	Moderate	↑ EDR, FMD; ↑ eNOS phosphorylation/dimerization; ↑ NO

(Farah et al., 2017)	Healthy rat	90 M	Aerobic (treadmill)	5 wk	Moderate	↑ eNOS-pSer1177; ↑ NO; cardioprotection via endothelial NO
(Garcia et al., 2022)	Healthy rat	52 M	Low-load RT ± BFR	4 wk	Low (50% MLW)	Training ↑ NO (71%); ↓ ROS; BFR alone impaired function
(Al-Dhuhli et al., 2022)	Healthy rat (F344)	52 M	Aerobic (treadmill)	10 wk	Moderate	↓ ACh relaxation in small arteries; ↑ PE contraction
(Guzzoni et al., 2018)	Healthy + nandrolone	24 M	Resistance (water jump)	6 wk	High	Nandrolone + RT ↓ NO, ↑ ROS; endothelial dysfunction

(Burgos et al., 2017)	Transgenic mouse	Multiple	Swimming	6 wk	Moderate	NO–CaMKII activation essential for contractile adaptation
(Ren et al., 2015)	ISO-induced hypertrophy	~48 F	Aerobic (treadmill)	4 wk	Moderate	↑ eNOS phosphorylation; ↑ NO; L-NAME blocked protection
(Sousa et al., 2021)	Diet-induced obese	36 M	Aerobic (treadmill)	8 wk	Moderate	↑ peNOS; ↑ NO; PVAT function restored
(Cheang et al., 2017)	db/db (diabetic)	Multiple M	Aerobic (treadmill)	4 wk	Moderate	↑ EDR, FMD; ↑ NO via AMPK–PPARδ–eNOS; ↓ ER stress

(Brooks et al., 2018)	Obese Zucker + UCMS	64 M	Aerobic (treadmill)	8 wk	Moderate	Restored MCA dilation; ↑ NO; prevented microvascular rarefaction
(Araujo et al., 2021)	Healthy rat	16 M	Resistance (squat)	8 wk	Moderate (60% 1RM)	↑ Insulin-induced dilation; ↑ NO via PI3K/eNOS
(La Favor et al., 2014)	-	32 (8/group)	Cycling	7 d / 8 wk	Moderate	↑ NOS activity; ↑ nutritive flow
(Faria et al., 2017)	SHR	22 M	Acute resistance	1 session	50% 1RM	↑ ACh relaxation (50→80%); ↑ p-eNOS (38%); ↑ NO

Abbreviations: ACh, acetylcholine; BFR, blood flow restriction; BDNF, brain-derived neurotrophic factor; d, days; eNOS, endothelial nitric oxide synthase; EDR, endothelium-dependent relaxation; F, female; FMD, flow-mediated dilation; HF, heart failure; HIET, high-intensity endurance training; HPD, high-protein diet; ISO, isoproterenol; M, male; MCA, middle cerebral artery; MCT, monocrotaline; MI, myocardial infarction; MLW, maximum lifting weight; NO, nitric oxide; OVX, ovariectomized; PAH, pulmonary arterial hypertension; PE, phenylephrine; PVAT, perivascular adipose tissue; RT, resistance training; ROS, reactive oxygen species; SHR, spontaneously hypertensive rat; TAC, transverse aortic constriction; UCMS, unpredictable chronic mild stress; wk, week(s).

Rob assessment findings

Quality assessment of the included studies using the SYRCLE Risk of Bias tool revealed low risk of bias in most domains. Specifically, in the domains of sequence generation, baseline characteristics, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias, approximately 100% of the studies were rated as having low risk of bias.

In contrast, in the domain of random housing, approximately 55% of the studies were rated as having unclear risk and approximately 45% as high risk. Furthermore, the highest proportion of high risk was observed in the domain of blinding for detection bias, where approximately 76% of studies were rated as high risk and approximately 24% as unclear risk. In the domain of blinding for performance bias, nearly 100% of studies were rated as having unclear risk. For random outcome assessment, approximately 72% of studies were rated as low risk and approximately 28% as unclear risk.

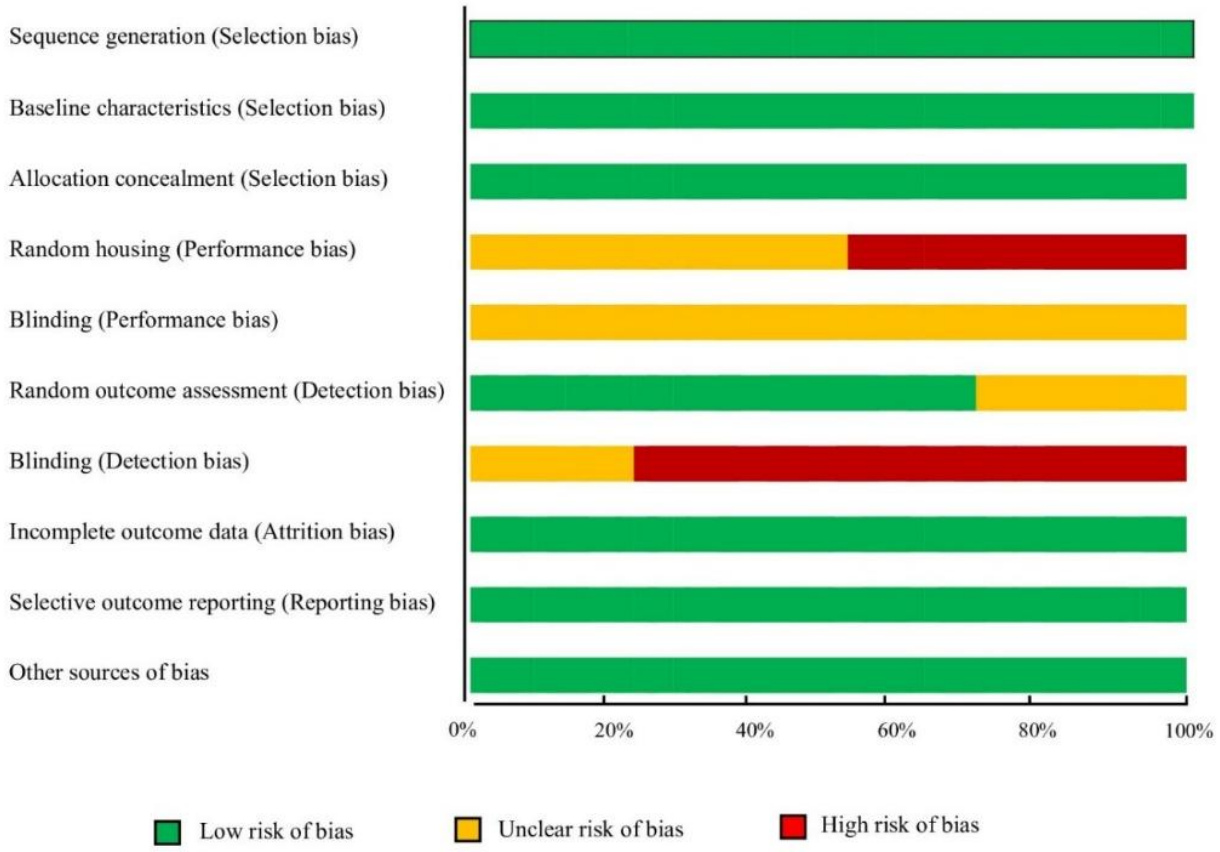


Fig. 2. SYRCLE Risk of Bias summary for the included animal studies (n = 29). Green (low risk), yellow (unclear risk), and red (high risk) represent the proportion of studies across each domain.

Meta-analysis findings

Effect of exercise training on eNOS

A random effects meta analysis of 34 studies showed that exercise training significantly increased eNOS levels, with a pooled effect size

of 0.99 (95% CI: 0.55,1.44; p = 0.001), as presented in the forest plot (Fig. 3). Substantial heterogeneity was observed across studies (I^2 = 89.36%, τ^2 = 1.39), with a wide 95% prediction interval ranging from −1.45 to 3.44. Assessment of publication bias using the funnel plot (Fig. 4) suggested possible asymmetry; Egger's test indicated significant small study effects (p = 0.001), whereas Begg and Mazumdar's test was not significant (p = 0.52). The robustness of the findings was supported by a large fail safe N (n = 793). Trim and fill analysis identified five potentially missing studies, and the adjusted effect size slightly increased to 1.30 (Fig. 5), indicating that the overall positive effect remained stable.

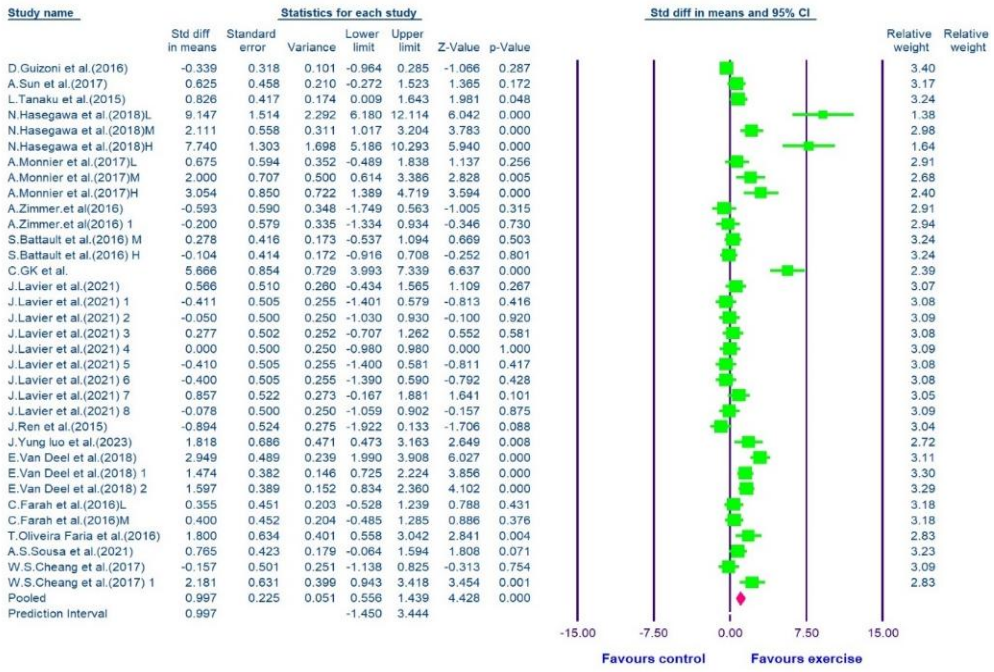


Fig. 3. Forest plot of the effect of exercise training on endothelial nitric oxide synthase (eNOS) levels in animal models. The plot displays standardized mean differences (SMD) with 95% confidence intervals (CIs) for 34 studies.

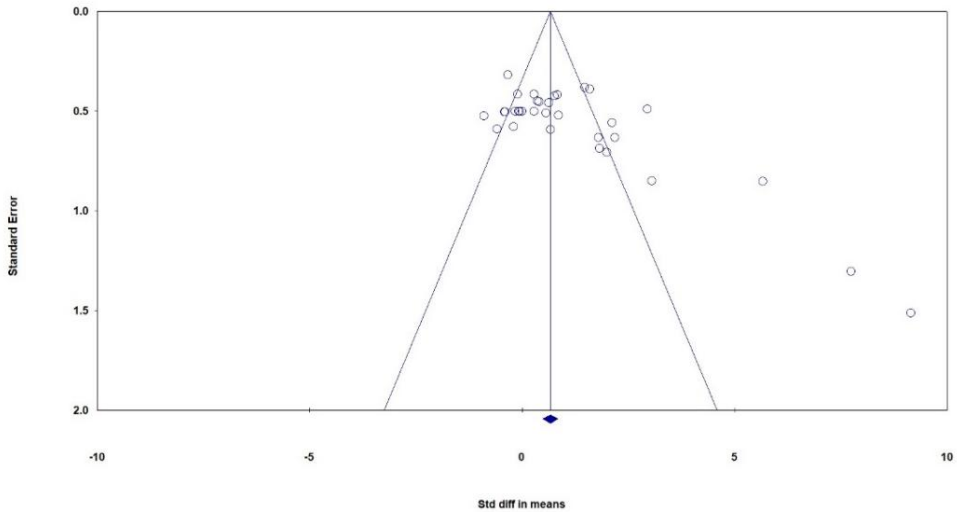


Fig. 4. Funnel plot of standard error by standardized mean difference for eNOS studies. The funnel plot illustrates the distribution of the 34 included studies to assess publication bias. Visual inspection reveals asymmetry, particularly with a lack of small studies showing negative or null results in the lower-left quadrant.

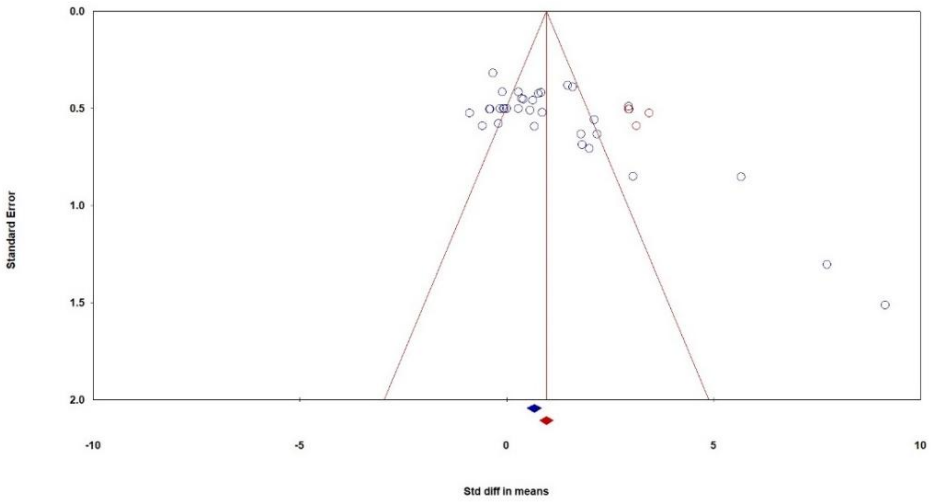


Fig. 5. Funnel plot with Duval and Tweedie's trim and fill adjustment for eNOS meta-analysis. To account for potential publication bias, the

trim and fill method identified five potentially missing studies (indicated by open red circles) on the left side of the distribution.

Subgroup analysis: impact of exercise duration on eNOS

A subgroup analysis was performed using a mixed-effects model to determine whether the duration of exercise training influenced its impact on eNOS expression. Studies were categorized into two subgroups: short-term (<5 weeks) and long-term (≥5 weeks) interventions. In the short-term subgroup (k=19), exercise training did not lead to a statistically significant increase in eNOS levels (SMD = 0.159; 95% CI: −0.155 to 0.474; p=0.321), with moderate heterogeneity (I2=49.36%) and a prediction interval ranging from −0.920 to 1.238. In contrast, long-term interventions (k=15) yielded a substantial and highly significant increase in eNOS expression (SMD = 2.247; 95% CI: 1.430 to 3.064; p<0.001), although high heterogeneity was observed (I2=88.19% 95% PI: −1.045 to 5.538). Crucially, the test for subgroup differences revealed a significant moderator effect for exercise duration (Q=21.844, df=1,p<0.001), indicating that the physiological adaptations in eNOS expression are significantly more pronounced when exercise interventions are sustained for 5 weeks or longer.

Subgroup analysis: Impact of exercise frequency on eNOS

To investigate the potential moderating effect of training volume, a subgroup analysis was conducted based on exercise frequency, categorized into < days per week and ≥ 5 days per week. Both subgroups demonstrated significant increases in eNOS expression following exercise training. Specifically, interventions involving < 3 days per week (k=16) yielded a significant pooled effect size (SMD = 0.855; 95% CI: 0.158 to 1.552; p=0.016), albeit with substantial heterogeneity (I2=84.13% 95% PI: −1.985 to 3.695). Similarly, more frequent training protocols of ≥ 3 days per week (k=14) resulted in a significant elevation of eNOS levels (SMD = 0.965; 95% CI: 0.300 to 1.630; p=0.004), also accompanied by high heterogeneity

(I2=83.6995% PI: −1.624 to 3.554). However, the test for subgroup differences indicated no statistically significant difference between the two frequency categories (Q=2.702, df=2,p=0.259), suggesting that the frequency of exercise days per week does not significantly moderate the magnitude of the eNOS response to training.

Subgroup analysis: impact of exercise intensity on eNOS

To investigate potential sources of heterogeneity, a subgroup analysis was conducted according to exercise intensity (high, moderate, and low). The mixed effects model indicated that exercise training significantly increased eNOS expression across all intensity levels, with no significant differences between subgroups (Q = 0.79, df = 2, p = 0.67). The largest effect size was observed in the low intensity subgroup (k = 9, SMD = 1.351, 95% CI: 0.181–2.521, p = 0.024), followed by high intensity (k = 9, SMD = 1.169, 95% CI: 0.200–2.139, p = 0.018) and moderate intensity interventions (k = 16, SMD = 0.84, 95% CI: 0.321–1.364, p = 0.002). However, substantial residual heterogeneity persisted within all subgroups (I^2 range: 79.34%–90.18%), accompanied by wide 95% prediction intervals (high: −2.212 to 4.551; low: −2.826 to 5.52; moderate: −1.242 to 2.92). Overall, these findings indicate that although exercise training consistently upregulates eNOS expression, the magnitude of this effect does not appear to depend on exercise intensity.

Subgroup analysis: moderating effect of type of exercise on eNOS

A subgroup analysis was conducted to examine whether exercise modality influenced the magnitude of eNOS upregulation, categorizing interventions as aerobic, swimming, and treadmill exercise. The mixed effects model demonstrated a significant difference between exercise modalities (Q = 20.52, df = 3, p = 0.001), indicating that training type significantly moderated the eNOS response. Treadmill training (k = 4, SMD = 1.92, 95% CI: 1.25–2.59, p = 0.001) and swimming (k = 4, SMD = 4.59, 95% CI: 1.48–7.70, p = 0.004) produced significant increases in eNOS levels. In contrast, general aerobic interventions

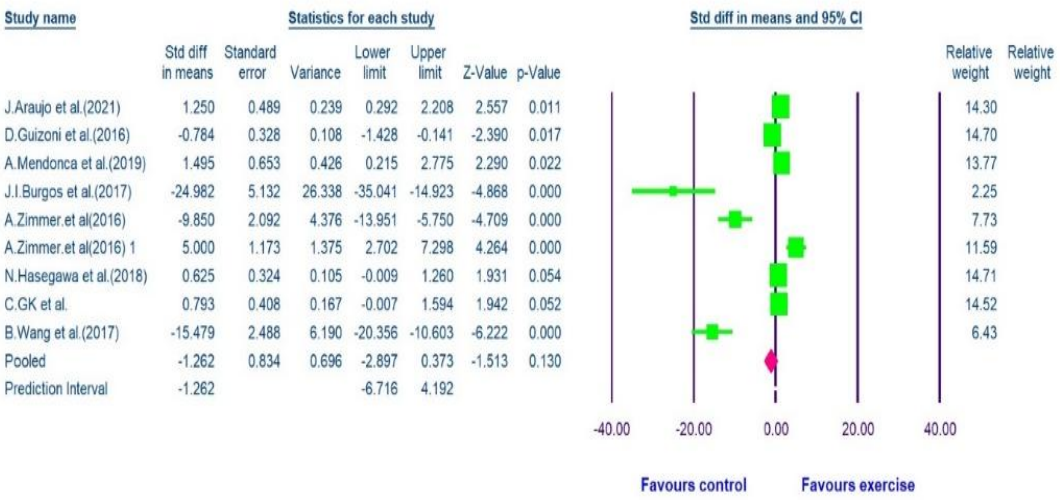
showed a smaller, non significant effect (k = 22, SMD = 0.38, 95% CI: −0.02–0.79, p = 0.067). Substantial heterogeneity was observed within subgroups, particularly for swimming (I^2 = 94.08%) and aerobic exercise (I^2 = 73.47%), accompanied by wide 95% prediction intervals (swimming: −10.04 to 19.23; aerobic: −1.40 to 2.17). Overall, these findings suggest that structured exercise modalities such as treadmill and swimming may elicit greater improvements in eNOS bioavailability compared with general aerobic protocols.

Effect of exercise training on NO

A random effects meta analysis of nine animal studies evaluated the effect of exercise training on nitric oxide (NO) levels. The pooled analysis indicated a non significant reduction in NO levels following exercise training, with an overall effect size of −1.26 (95% CI: −2.89 to 0.37; p = 0.13), as shown in the forest plot (Fig. 6). Substantial heterogeneity was observed among studies (I^2 = 93.58%, τ^2 = 4.624), with a wide 95% prediction interval ranging from −6.72 to 4.19. Assessment of publication bias using the funnel plot (Fig. 7) showed mixed evidence; Egger's regression test was not statistically significant (p = 0.16), whereas Begg and Mazumdar's rank correlation test indicated potential bias (p = 0.04). The fail safe N analysis suggested that five additional null studies would be required to raise the overall p value above 0.05. Trim and fill analysis did not identify any potentially

missing studies, and therefore the pooled estimate remained unchanged (Fig. 8).

Fig. 6. Forest plot illustrating the effect of exercise training on Nitric Oxide (NO) levels in animal models. The plot displays the standardized mean differences (SMDs) and 95% confidence intervals (CIs) for each study.



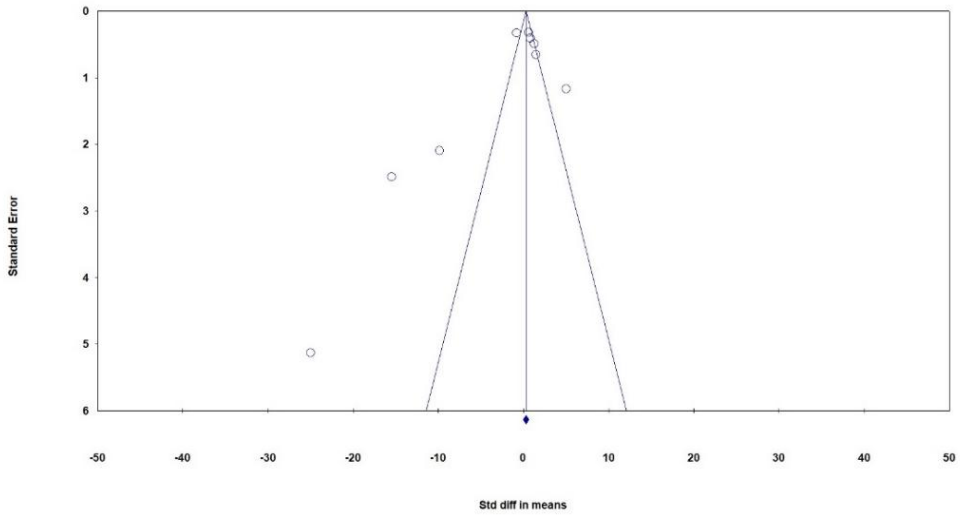


Fig. 7. Funnel plot of standard error by standardized mean difference (SMD) for publication bias assessment in NO studies. The vertical line represents the pooled effect size, and the diagonal lines define the 95% confidence pseudo-limits.

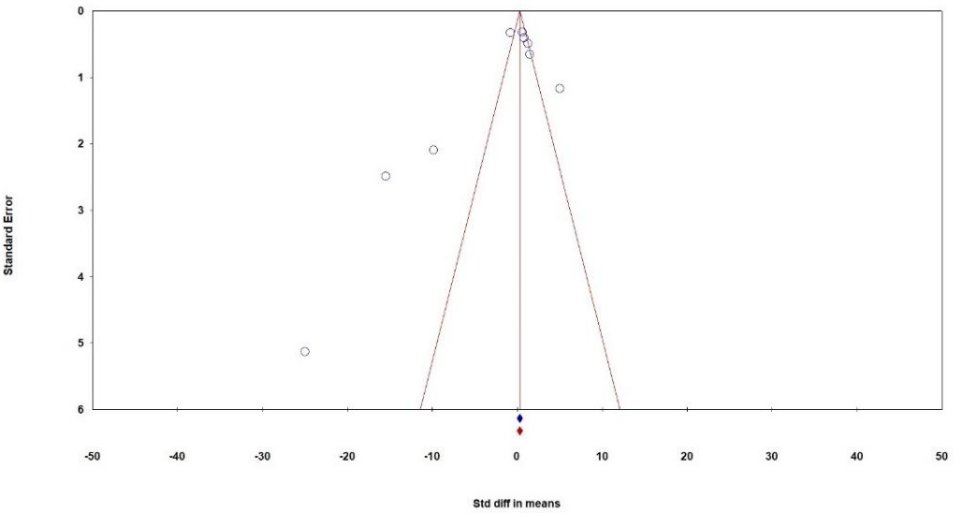


Fig. 8. Funnel plot after Trim and Fill adjustment for Nitric Oxide (NO). This plot evaluates the impact of potentially missing studies on the overall estimate. The blue diamond represents the original pooled

effect, while the red diamond (overlapping in this case) indicates the adjusted effect.

Subgroup analysis of exercise duration on NO

To determine the moderating influence of intervention length on nitric oxide (NO) bioavailability, a subgroup analysis was conducted comparing shorter (<5 weeks) and longer (≥5 weeks) exercise programs. The mixed-effects analysis revealed no significant differences between the two duration strata ($Q = 0.95$, $df = 1$, $p = 0.32$). Specifically, interventions lasting <5 weeks ($k = 4$) yielded a pooled SMD of -0.57 (95% CI: -2.92 to 1.77; $p = 0.63$), while longer-duration programs ($k = 5$) showed a larger but non-significant effect size (SMD = -2.40; 95% CI: -5.24 to 0.43; $p = 0.097$). High levels of residual heterogeneity were observed in both the <5-week ($I^2 = 92.71\%$) and ≥5-week subgroups ($I^2 = 95.06\%$), further evidenced by broad 95% prediction intervals (-10.83 to 9.69 and -12.80 to 7.98, respectively). These results indicate that exercise duration does not significantly moderate the training-induced changes in NO levels, with the observed variability likely driven by substantial between-study inconsistency.

Subgroup analysis of exercise frequency on NO

To evaluate the moderating role of training frequency on nitric oxide (NO) outcomes, a mixed-effects subgroup analysis was performed, comparing interventions of <3 days per week and ≥3 days per week. The analysis revealed a statistically significant difference between frequency categories ($Q = 22.66$; $p = 0.001$), indicating that exercise frequency is a critical moderator of the NO response. Specifically, interventions with <3 days per week ($k = 4$) showed a negligible and non-significant pooled effect (SMD = 0.14; 95% CI: −2.31 to 2.58; $p = 0.91$), characterized by substantial heterogeneity ($I^2 = 92.47\%$) and a

wide 95% prediction interval (−10.95 to 11.22). In contrast, programs with ≥3 days per week (k = 4) demonstrated a more pronounced, albeit within-group non-significant, effect size (SMD = −1.62; 95% CI: −3.97 to 0.73; p = 0.17), with very high heterogeneity (I^2 = 94.37%; prediction interval: −12.31 to 9.07). These findings suggest that while high between-study variability persists, exercise frequency significantly influences the magnitude of training-induced changes in NO bioavailability, with higher frequencies potentially eliciting stronger physiological adaptations.

Subgroup analysis of exercise intensity on NO

A mixed effects subgroup analysis was conducted to examine whether exercise intensity (high, low, and moderate) moderated the effects of exercise training on NO outcomes, as illustrated in. The high intensity subgroup included one study (k = 1) and demonstrated a positive effect size (SMD = 0.62; 95% CI: −0.009 to 1.26; p = 0.054), with no observed heterogeneity (I^2 = 0.00%), although the estimate approached but did not reach statistical significance. In the low intensity subgroup (k = 3), the pooled analysis indicated a non significant effect (SMD = −12.62; 95% CI: −27.58 to 2.33; p = 0.098), accompanied by very high heterogeneity (I^2 = 96.96%) and a wide prediction interval (−202.32 to 177.07), suggesting substantial variability across studies. Similarly, moderate intensity interventions (k = 5) produced a small and non significant pooled effect (SMD = 0.097; 95% CI: −2.09 to 2.28; p = 0.093), with considerable heterogeneity (I^2 = 93.03%) and a broad prediction interval (−7.99 to 8.18). The formal test for subgroup differences indicated no statistically significant moderating effect of exercise intensity on NO outcomes (Q = 3.19; p = 0.20), suggesting that variations in training intensity did not significantly influence the magnitude of exercise induced changes in nitric oxide across the included studies.

Discussion

The present systematic review and meta-analysis quantified the effects of exercise training on eNOS, NO bioavailability levels in animal models. Our key findings demonstrate that exercise training significantly upregulates eNOS expression (SMD = 0.99, 95% CI: 0.55–1.44, $p < 0.001$), particularly with interventions lasting ≥5 weeks (SMD = 2.25) and with structured modalities such as treadmill running (SMD = 1.92) and swimming (SMD = 4.59). In contrast, no significant effects were observed for NO (SMD = −1.26, $p = 0.13$) revealing a notable disconnect between eNOS expression and functional NO bioavailability in preclinical models.

Exercise training upregulates eNOS expression

Our finding that exercise increases eNOS expression aligns with the established mechanotransduction paradigm whereby laminar shear stress during exercise activates the PI3K/Akt pathway, leading to eNOS phosphorylation and increased expression. This is supported by multiple studies in our review.

Treadmill running consistently increased eNOS expression across various disease models. Guizoni et al. (Guizoni et al., 2016) showed that 4 weeks of moderate-intensity treadmill training restored eNOS phosphorylation and dimerization in $LDLr^{-/-}$ mice, a model of familial hypercholesterolemia. Similarly, Farah et al. (Farah et al., 2017) demonstrated that 5 weeks of treadmill training increased eNOS-pSer1177 phosphorylation and S-nitrosylation in healthy rats, providing cardioprotection against ischemia-reperfusion injury. Sousa et al.(Sousa et al., 2021) reported that 8 weeks of treadmill exercise partially restored peNOS^Ser1177 expression in obese mice, normalizing NO bioavailability and reducing PVAT-derived oxidative stress. Cheang et al. (Cheang et al., 2017)further confirmed that 4 weeks of treadmill running restored endothelial function in db/db diabetic mice via AMPK–PPARδ–eNOS pathway activation.

Swimming exercise produced the largest effect size in our subgroup analysis (SMD = 4.59). Wang et al. (Wang et al., 2017) demonstrated

that 9 weeks of swimming increased NO bioavailability via β3-AR–nNOS activation in pressure-overloaded mice, independent of eNOS. Burgos et al.(Burgos et al., 2017) showed that 6 weeks of swim training enhanced cardiac contractility via NO-dependent CaMKII activation.

Resistance training also showed benefits. Araujo et al. (Araujo et al., 2021) reported that 8 weeks of squat training increased insulin-induced vasodilation via PI3K/eNOS pathway activation, with increased plasma NO_2 levels. Nogueira et al.(Nogueira et al., 2022) found that 12 weeks of ladder climbing combined with high-protein diet increased NO bioavailability and reduced inflammation.

However, some studies reported no effect or even detrimental outcomes. Al-Dhuhli et al. (Al-Dhuhli et al., 2022) found that 10 weeks of treadmill training unexpectedly reduced ACh-induced relaxation in small mesenteric arteries of healthy rats, with no change in eNOS expression. Zimmer et al. (Zimmer et al., 2017) reported that 5 weeks of aerobic training failed to improve RV function in severe pulmonary arterial hypertension, with increased iNOS and nitrotyrosine. Battault et al. (Battault et al., 2016) showed that high-intensity endurance training in SHR caused eNOS uncoupling, increased ROS production, and failed to improve ACh-induced relaxation despite increased eNOS expression. These contradictory findings explain the substantial heterogeneity ($I^2 = 89.36\%$) observed in our meta-analysis.

Why does eNOS increase without significant NO elevation?

The most striking and novel finding of our meta-analysis is the absence of significant NO elevation (SMD = −1.26, p = 0.13) despite robust eNOS upregulation. This paradox warrants mechanistic explanation. The dissociation between eNOS upregulation and NO bioavailability can be mechanistically explained through several interrelated pathways. First, eNOS uncoupling represents a critical mechanism wherein the enzyme shifts from producing NO to generating superoxide ($O_2^{\bullet -}$) under conditions of oxidative stress. This phenomenon occurs when the essential cofactor tetrahydrobiopterin (BH4) becomes oxidized to dihydrobiopterin (BH2), destabilizing the eNOS dimer and favoring

monomer formation. Several studies in our review directly demonstrated this mechanism; Battault et al. demonstrated that high-intensity training in spontaneously hypertensive rats (SHR) increased eNOS expression but simultaneously induced uncoupling, evidenced by elevated eNOS-dependent reactive oxygen species (ROS) production that was reversed by BH4 or N-acetylcysteine supplementation (Battault et al., 2016). Similarly, van Deel et al. showed that voluntary wheel running in pressure-overloaded mice exacerbated eNOS uncoupling through increased S-glutathionylation and monomerization, reducing NO bioavailability despite preserved eNOS expression (van Deel et al., 2018).

Second, rapid oxidative scavenging of NO by superoxide to form peroxynitrite ($ONOO^-$) represents another critical pathway. This reaction is exceptionally rapid (rate constant ~6.7×10^9 $M^{-1}s^{-1}$), effectively outcompeting NO's physiological targets (Sun et al., 2017). Sun et al. demonstrated that high-fructose diet-induced superoxide production reduced NO bioavailability despite preserved eNOS expression (Sun et al., 2017). Braga et al. similarly showed that exercise restored NO bioavailability primarily through ROS reduction rather than eNOS upregulation alone, emphasizing that the NO/ROS ratio is more physiologically relevant than absolute NO levels (Braga et al., 2015).

Third, methodological limitations in NO measurement warrant careful consideration. NO has an extremely short half-life (1-5 seconds) in biological tissues, making direct quantification challenging. Most included studies measured NO metabolites (nitrite/nitrate via Griess assay or DAF-2 fluorescence), which reflect cumulative production but may miss rapid fluctuations and compartmentalized signaling (Farah et al., 2017). As demonstrated by Farah et al., endothelial-derived NO acts in a paracrine fashion on cardiomyocytes, suggesting that whole-tissue NO measurements may fail to detect localized changes (Farah et al., 2017).

Fourth, tissue-specific and disease-state-dependent effects significantly influence the eNOS-NO relationship. Oliveira et al. demonstrated that

exercise improved NO-mediated modulation in normotensive rats but this effect was blunted in hypertensive models due to oxidative stress (Oliveira et al., 2020). Mendonça et al. reported that exercise during acute infection increased NO levels but paradoxically increased inflammation and oxidative damage (Mendonça et al., 2019). These findings underscore that the eNOS-NO translation is highly context-dependent, varying with vascular bed, pathological state, and oxidative environment. Collectively, these mechanistic insights explain why robust eNOS upregulation does not invariably translate to increased NO bioavailability, highlighting the critical distinction between molecular expression and functional output in vascular biology.

Subgroup findings

Exercise duration (≥5 weeks) is a critical moderator of eNOS upregulation

Subgroup analysis demonstrated that intervention duration is a powerful determinant of exercise-induced eNOS adaptation. Interventions lasting ≥5 weeks produced a large and highly significant increase in eNOS expression (SMD = 2.25, $p < 0.001$), whereas shorter interventions (<5 weeks) failed to elicit any significant change (SMD = 0.159, $p = 0.321$). The test for subgroup differences confirmed that duration significantly moderated the eNOS response ($Q = 21.844$, $df = 1$, $p < 0.001$). These findings align with the principle that chronic shear stress from sustained exercise exposure is required to induce meaningful transcriptional and translational upregulation of eNOS. Supporting this, Farah et al. (Farah et al., 2017) (5 weeks) and Sousa et al. (Souza et al., 2018) (8 weeks) demonstrated robust eNOS upregulation following longer-term training, whereas single-bout studies such as Mota et al. (Mota et al., 2017) and Faria et al. (Faria et al., 2017) reported only acute increases in NO bioavailability without sustained changes in eNOS expression. Collectively, these results indicate that exercise programs must extend beyond five weeks to achieve significant eNOS-mediated vascular adaptations in animal models.

4.3.2. Exercise type: treadmill and swimming produce superior eNOS responses

Exercise modality significantly moderated the eNOS response to training (Q = 20.52, df = 3, p = 0.001). Both treadmill running (SMD = 1.92, p = 0.001) and swimming (SMD = 4.59, p = 0.004) produced substantial and statistically significant increases in eNOS expression. In contrast, general aerobic interventions failed to achieve a significant effect (SMD = 0.38, p = 0.067). The superior efficacy of treadmill and swimming protocols likely reflects better standardization of exercise intensity, duration, and volume in forced exercise paradigms compared to voluntary or poorly defined aerobic regimens. However, the very high heterogeneity observed for swimming (I^2 = 94.08%) and its wide prediction interval (−10.04 to 19.23) indicate considerable variability in swimming protocols across studies, underscoring the need for more standardized methodologies. Nevertheless, these findings strongly suggest that structured, forced exercise modalities are more effective than general aerobic protocols for upregulating eNOS in preclinical models.

Exercise intensity does not moderate eNOS or NO responses

Contrary to conventional expectations, exercise intensity (low, moderate, or high) did not significantly moderate either eNOS (p = 0.67) or NO (p = 0.20) outcomes. Subgroup analysis confirmed that eNOS increased significantly across all intensity levels, with no significant between-group differences. However, the lack of a moderating effect does not imply that intensity is irrelevant; rather, it suggests that the relationship between intensity and vascular outcomes is context-dependent. Battault et al. (Battault et al., 2016) directly compared moderate versus high-intensity training in spontaneously hypertensive rats (SHR) and found that moderate intensity improved endothelial sensitivity, whereas high-intensity training paradoxically induced eNOS uncoupling and increased oxidative stress without improving relaxation. Similarly, Lavier et al. (Lavier et al., 2021)

reported that supra-maximal hypoxic training enhanced NO bioavailability, but this effect was observed exclusively under hypoxic conditions and not in normoxia. These findings collectively indicate that the impact of exercise intensity on endothelial function and NO bioavailability is modulated by factors such as disease state, oxidative environment, and oxygen availability, rather than being universally applicable across all conditions.

Influence of potential confounders on vascular responses to exercise

Interpretation of our findings requires careful consideration of several potential confounders that likely influence vascular responses to exercise. First, sex represents the most significant confounder in this evidence base. With 28 of 29 included studies (96.6%) utilizing only male animals, our findings are predominantly applicable to males. This is particularly concerning given established sex differences in NO metabolism, with estrogen enhancing eNOS expression and activity through genomic and non-genomic mechanisms. Studies that did include female animals, such as Braga et al. (Braga et al., 2015) and de Oliveira et al. (de Oliveira et al., 2019) in ovariectomized models, demonstrated exercise-induced NO improvements that were partially mediated through antioxidant modulation, suggesting that the mechanistic pathways may differ between sexes. The absence of female data precludes meaningful sex-based subgroup analysis and severely limits generalizability to female populations.

Second, species and strain differences substantially influence baseline vascular function and exercise responsiveness. Our included studies utilized multiple species (rats, mice) and strains (Wistar, Sprague-Dawley, SHR, LDLr$^{-/-}$, db/db, C57BL/6), each with distinct genetic backgrounds, metabolic profiles, and disease susceptibilities. For instance, spontaneously hypertensive rats (SHR) exhibit heightened oxidative stress and impaired NO bioavailability compared to normotensive strains, potentially explaining why Battault et al. (Battault et al., 2016) observed eNOS uncoupling following high-

intensity training in SHR but not in healthy strains. Similarly, diabetic models (db/db, high-fructose) demonstrated attenuated NO responses despite eNOS upregulation, reflecting disease-induced oxidative stress that may override exercise benefits (Cheang et al., 2017; Sun et al., 2017).

Third, disease model critically modulates the eNOS-NO relationship. Our review included studies across diverse pathological conditions, including hypertension, diabetes, heart failure, myocardial infarction, obesity, pulmonary arterial hypertension, and infection, each with distinct oxidative and inflammatory profiles. Exercise responses varied markedly across disease states. For example, Zimmer et al. (Zimmer et al., 2017) demonstrated that severe pulmonary arterial hypertension completely abrogated exercise benefits, with increased iNOS and nitrotyrosine indicating that disease severity can override the beneficial effects of training (Zimmer et al., 2017). In contrast, Cheang et al. (Cheang et al., 2017) showed that exercise effectively restored endothelial function in diabetic mice through AMPK-PPARδ-eNOS pathway activation, suggesting that certain disease states remain responsive to exercise. These findings underscore the importance of disease context in predicting exercise responses.

Fourth, tissue source is a critical determinant of measured outcomes. Included studies assessed eNOS and NO across diverse tissues, including aorta, mesenteric arteries, coronary arteries, cardiac tissue, lung parenchyma, and cerebral arteries, each with distinct hemodynamic environments, shear stress patterns, and baseline eNOS expression levels. Al-Dhuhli et al. (Al-Dhuhli et al., 2022) demonstrated that exercise effects varied between conduit (aorta) and resistance (mesenteric) arteries, with small arteries showing paradoxical reductions in relaxation despite unchanged eNOS expression (Al-Dhuhli et al., 2022). This tissue-specific heterogeneity likely contributed to the substantial I^2 values observed and suggests that vascular beds should be analyzed separately when sufficient data are available.

Fifth, animal age represents a potential moderator that could not be fully examined due to inconsistent reporting across studies. Aging is associated with increased oxidative stress, reduced eNOS activity, and impaired vascular function (endothelial senescence). While some studies in our review included aged animals (e.g., de Oliveira et al. (de Oliveira et al., 2019) with 3-month-old ovariectomized rats; Brooks et al. (Brooks et al., 2018) with 16-17 week old obese Zucker rats), age reporting was inconsistent across studies, preventing robust subgroup analysis. However, available evidence suggests that older animals may exhibit attenuated exercise responses due to age-related increases in oxidative stress and reductions in eNOS coupling efficiency.

Sixth, training adherence is a critical but underreported confounder in forced exercise paradigms. While treadmill and swimming protocols ensure compliance, the actual workload completed (distance, speed progression, refusal rates) was not consistently reported. Voluntary wheel running studies, such as van Deel et al. (van Deel et al., 2018), demonstrated that self-paced exercise produced variable responses dependent on actual running distance, highlighting the importance of quantifying actual training volume rather than prescribed protocol. Inadequate adherence reporting may have contributed to the heterogeneity observed in our meta-analysis.

Finally, measurement methodology introduces significant variability. eNOS was predominantly measured via Western blot (protein expression) or RT-qPCR (mRNA), while NO was assessed through Griess assay (nitrite/nitrate), DAF-2 fluorescence, or chemiluminescence. These techniques differ in sensitivity, specificity, and ability to detect biologically active NO versus metabolites. Direct measurement of NO (electron paramagnetic resonance, NO microelectrodes) was rarely employed, limiting our ability to assess functional NO bioavailability accurately. Moving forward, we recommend standardized reporting of these confounders and, when possible, stratified analyses to account for their influence.

Comparison with prior reviews and meta-analyses

To contextualize our findings, we compare our results with existing systematic reviews and meta-analyses. To our knowledge, this is the first meta-analysis to simultaneously quantify exercise effects on both eNOS expression and NO bioavailability within a unified analytical framework.

While our findings demonstrate robust eNOS upregulation in animal models, human studies have yielded more consistent improvements in flow-mediated dilation (FMD) following exercise training. A recent network meta-analysis of 84 RCTs (3,596 participants) demonstrated that exercise significantly improved brachial artery FMD (MD = 2.24%, 95% CI: 1.90–2.58), with interval aerobic training emerging as the most effective modality (SUCRA: 99.1%, MD = 3.07%)(Paravlic et al., 2025). Similarly, a meta-analysis of 12 studies found that aerobic training improved FMD by 1.92% (95% CI: 0.90–2.94), corresponding to an estimated 19.2% reduction in cardiovascular disease risk(Liu et al., 2022). However, human studies typically measure functional outcomes rather than molecular markers (eNOS, NO), making direct comparison challenging(Paravlic & Drole, 2025). The disconnect between eNOS upregulation and NO bioavailability observed in our animal data suggests that molecular upregulation does not invariably translate to improved function.

A scoping review by (Karisa et al., 2026) examined exercise-induced myocardial angiogenesis in animal models, reporting that aerobic protocols most consistently upregulated the VEGF-VEGFR axis with downstream PI3K/Akt-eNOS/NO signaling. The review noted that evidence is dominated by male-only models, a limitation that parallels our findings, where 28 of 29 included studies (96.6%) utilized only male animals(Karisa et al., 2026). Our findings extend this work by providing quantitative effect sizes across multiple exercise modalities and durations. A meta-analysis by (Wang et al., 2023) examined exercise effects on oxidative stress markers in human studies, demonstrating that exercise significantly increased glutathione peroxidase activity (ES = 2.23, p = 0.003) while preventing increases

in malondialdehyde(Wang et al., 2023). These findings support our mechanistic explanation that exercise-induced NO bioavailability is preserved through antioxidant modulation.

Our finding that exercise significantly upregulates eNOS expression (SMD = 0.99) confirms the well-established mechanotransduction paradigm wherein shear stress activates the PI3K/Akt/eNOS pathway. The large effect sizes for treadmill (SMD = 1.92) and swimming (SMD = 4.59) support prior reviews advocating for structured, forced exercise modalities. Our subgroup finding that duration (≥5 weeks) is a critical moderator ($Q = 21.844$, $p < 0.001$) extends prior work that primarily focused on intensity and type. Meta-regression confirmed a positive association between duration and eNOS effect size ($\beta = 0.2623$, $p = 0.036$). This aligns with human evidence showing that greater improvements in FMD can be achieved by increasing the duration of acute stimuli (an additional half-hour of training = 0.80% increase in FMD) and weekly training exposure (an additional 2.5 hours = 0.50% increase in FMD).

Most notably, our finding that exercise fails to significantly increase NO levels despite eNOS upregulation (SMD = −1.26, $p = 0.13$) represents a novel finding that challenges the prevailing assumption that eNOS upregulation directly translates to increase NO. This dissociation has been observed in individual studies but has not been quantitatively synthesized prior to our work. This finding suggests that eNOS uncoupling, oxidative scavenging, and methodological limitations mask the functional translation of molecular upregulation.

Our study contributes to the literature in three key ways: (1) providing the first quantitative synthesis of eNOS and NO responses to exercise in animal models; (2) identifying exercise duration and modality as more critical moderators than intensity for eNOS upregulation; and (3) revealing the translational gap between eNOS expression and NO bioavailability, highlighting the need for functional measurements in future studies. Given that human evidence demonstrates response heterogeneity is common following exercise interventions, our findings underscore the importance of personalized exercise prescriptions that

consider duration, modality, and individual factors such as baseline health status and oxidative environment.

Strengths and limitations

This study has several strengths, including adherence to PRISMA 2020 guidelines and prospective registration with PROSPERO (CRD420251144669), ensuring methodological transparency and reproducibility. The meta-analysis incorporated 34 effect sizes from 29 independent preclinical studies, providing sufficient statistical power to detect moderate-to-large effects for eNOS outcomes, and employed advanced analytical approaches including random-effects models (REML), prediction intervals, and comprehensive publication bias assessments (funnel plots, Egger's test, Begg's test, trim-and-fill analysis, and fail-safe N calculation). Novelty is a key strength, as this is the first meta-analysis to simultaneously quantify exercise effects on eNOS and NO in animal models, revealing a critical disconnect between eNOS upregulation and NO bioavailability with important translational implications. However, several limitations warrant consideration. Considerable heterogeneity was observed across all outcomes ($I^2 > 85\%$ for eNOS and NO), limiting generalizability of pooled estimates due to variability in animal strains, disease models, exercise protocols, and measurement techniques. Using the SYRCLE Risk of Bias tool, we identified high risk of bias in detection bias (blinding of outcome assessors: 76% high risk) and unclear risk in performance bias (blinding of caregivers: 100% unclear), as most animal studies did not report blinding procedures. Publication bias was detected for eNOS (Egger's $p = 0.001$), with trim-and-fill adjustment identifying five potentially missing studies, suggesting that small studies with null results may be underrepresented. A major limitation is the lack of female animals, as 28 of 29 studies (96.6%) used only males, severely limiting generalizability to females despite known sex differences in NO metabolism. Additionally, only nine studies reported NO data, reducing statistical power for NO-related subgroup analyses, and the absence of standardized exercise protocols across studies

precludes direct comparison of dose-response relationships. Finally, measurement technique variability (eNOS via Western blot; NO via Griess assay, DAF-2 fluorescence, or nitrite assays) and the extremely short half-life of NO (1–5 seconds) make direct quantification challenging, while the inclusion of only English-language peer-reviewed articles may introduce language and publication bias. Despite these limitations, the robust sensitivity analysis (leave-one-out) confirmed that no single study disproportionately influenced the pooled effect sizes, supporting the overall stability of our findings.

Conclusion

This systematic review and meta-analysis of 29 preclinical studies (comprising 34 independent effect sizes) provides moderate-to-strong evidence that exercise training significantly upregulates eNOS expression (SMD = 0.99, 95% CI: 0.55–1.44, $p < 0.001$), particularly with interventions lasting ≥5 weeks (SMD = 2.25, $p < 0.001$) and structured modalities such as treadmill running (SMD = 1.92) and swimming (SMD = 4.59). However, despite robust eNOS upregulation, exercise training did not lead to a statistically significant increase in NO levels (SMD = −1.26, 95% CI: −2.89 to 0.37, $p = 0.13$), revealing a critical translational gap between eNOS expression and functional NO bioavailability that warrants mechanistic investigation. Subgroup analyses showed that exercise intensity did not significantly moderate eNOS ($p = 0.67$) or NO ($p = 0.20$) outcomes, suggesting that factors other than intensity, particularly duration and modality, are more critical determinants of vascular adaptation.

Important limitations must be considered when interpreting these findings. First, the predominance of male animals (28 of 29 studies, 96.6%) severely limits generalizability to females, despite known sex differences in NO metabolism and vascular function. Second, considerable heterogeneity ($I^2 > 85\%$) was observed across all outcomes, reflecting variability in animal strains, disease models, exercise protocols, and measurement techniques; this heterogeneity

limits the precision of pooled estimates and precludes definitive dose-response conclusions. Third, only nine studies reported NO data, reducing statistical power for NO-related analyses and necessitating cautious interpretation of null findings. Fourth, publication bias was detected for eNOS outcomes (Egger's $p = 0.001$), suggesting that small studies with null results may be underrepresented. Fifth, the absence of standardized exercise protocols across studies precludes direct comparison of dose-response relationships.

Based on these findings and limitations, we recommend that future preclinical studies: (a) include female animals to address the current sex imbalance and improve translational relevance; (b) directly assess eNOS coupling status (dimer/monomer ratio, BH4 levels, S-glutathionylation) alongside functional vasodilatory outcomes to clarify mechanisms underlying the eNOS-NO disconnect; (c) employ standardized exercise protocols with comprehensive reporting of intensity, duration, frequency, and modality to facilitate meta-analytic synthesis; (d) utilize direct NO measurement techniques (namely, electron paramagnetic resonance, NO-specific microelectrodes) or measure functional outcomes (namely, endothelium-dependent vasodilation) alongside molecular markers; and (e) prospectively register study protocols and report negative findings to mitigate publication bias.

In summary, while exercise training effectively upregulates eNOS expression in male animal models, particularly with longer-duration and structured modalities, the lack of corresponding increases in NO bioavailability represents a significant translational gap. Addressing this gap through mechanistic studies that incorporate both sexes, standardized protocols, and direct functional measurements will be essential for translating preclinical findings to human cardiovascular health.

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Reference

Al-Dhuhli, F., Al-Siyabi, S., Al-Maamari, H., Al-Farsi, S., & Albarwani, S. (2022). Moderate-intensity exercise training reduces vasorelaxation of mesenteric arteries: role of BKCa channels and nitric oxide. Physiol Res, 71(1), 67–77. https://doi.org/10.33549/physiolres.934671

Araujo, J. E. S., Santos, R. M. D., Oliveira, D. P. M., Macedo, F. N., Quintans, J. S. S., Barreto, R. S. S., Santos, S. L., Santos, M. R. V., Junior, L. J. Q., & Barreto, A. S. (2021). Resistance training increases insulin-induced vasodilation in the mesenteric artery of healthy rats. An Acad Bras Cienc, 93(suppl 4), e20210222. https://doi.org/10.1590/0001-3765202120210222

Balligand, J.-L., Feron, O., & Dessy, C. (2009). eNOS activation by physical forces: from short-term regulation of contraction to chronic remodeling of cardiovascular tissues. Physiological Reviews, 89(2), 481–534.

Battault, S., Singh, F., Gayrard, S., Zoll, J., Reboul, C., & Meyer, G. (2016). Endothelial function does not improve with high-intensity continuous exercise training in SHR: implications of eNOS uncoupling. Hypertens Res, 39(2), 70–78. https://doi.org/10.1038/hr.2015.114

Braga, V. A., Couto, G. K., Lazzarin, M. C., Rossoni, L. V., & Medeiros, A. (2015). Aerobic Exercise Training Prevents the Onset of Endothelial Dysfunction via Increased Nitric Oxide Bioavailability and Reduced Reactive Oxygen Species in an Experimental Model of Menopause. PLoS One, 10(4), e0125388. https://doi.org/10.1371/journal.pone.0125388

Brooks, S., Branyan, K. W., DeVallance, E., Skinner, R., Lemaster, K., Sheets, J. W., Pitzer, C. R., Asano, S., Bryner, R. W., Olfert, I. M., Frisbee, J. C., & Chantler, P. D. (2018). Psychological stress-induced cerebrovascular dysfunction: the role of metabolic syndrome and exercise. Exp Physiol, 103(5), 761–776. https://doi.org/10.1113/ep086892

Burgos, J. I., Yeves, A. M., Barrena, J. P., Portiansky, E. L., Vila-Petroff, M. G., & Ennis, I. L. (2017). Nitric oxide and CaMKII: Critical steps in the cardiac contractile response To IGF-1 and

swim training. J Mol Cell Cardiol, 112, 16–26. https://doi.org/10.1016/j.yjmcc.2017.08.014

Cai, H., & Harrison, D. G. (2000). Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circulation research, 87(10), 840–844.

Cheang, W. S., Wong, W. T., Zhao, L., Xu, J., Wang, L., Lau, C. W., Chen, Z. Y., Ma, R. C., Xu, A., Wang, N., Tian, X. Y., & Huang, Y. (2017). PPARδ Is Required for Exercise to Attenuate Endoplasmic Reticulum Stress and Endothelial Dysfunction in Diabetic Mice. Diabetes, 66(2), 519–528. https://doi.org/10.2337/db15-1657

Couto, G. K., Paula, S. M., Gomes-Santos, I. L., Negrão, C. E., & Rossoni, L. V. (2018). Exercise training induces eNOS coupling and restores relaxation in coronary arteries of heart failure rats. Am J Physiol Heart Circ Physiol, 314(4), H878–h887. https://doi.org/10.1152/ajpheart.00624.2017

Dargel, A. A., Godin, O., Kapczinski, F., Kupfer, D. J., & Leboyer, M. (2015). Meta-Analysis. J Clin Psychiatry, 76(2), 142–150.

de Oliveira, S. G., Claudio, E. R. G., de Almeida, S. A., Mengal, V., da Silva, F. B., Silva, N. F., Mauad, H., & de Abreu, G. R. (2019). Exercise training improves vascular reactivity in ovariectomized rats subjected to myocardial infarction. PLoS One, 14(4), e0215568. https://doi.org/10.1371/journal.pone.0215568

Deanfield, J. E., Halcox, J. P., & Rabelink, T. J. (2007). Endothelial function and dysfunction: testing and clinical relevance. Circulation, 115(10), 1285–1295.

Farah, C., Nascimento, A., Bolea, G., Meyer, G., Gayrard, S., Lacampagne, A., Cazorla, O., & Reboul, C. (2017). Key role of endothelium in the eNOS-dependent cardioprotection with exercise training. J Mol Cell Cardiol, 102, 26–30. https://doi.org/10.1016/j.yjmcc.2016.11.008

Faria, T. O., Angeli, J. K., Mello, L. G. M., Pinto, G. C., Stefanon, I., Vassallo, D. V., & Lizardo, J. H. F. (2017). A Single Resistance Exercise Session Improves Aortic Endothelial Function in Hypertensive Rats. Arq Bras Cardiol, 108(3), 228–236. https://doi.org/10.5935/abc.20170023

Forstermann, U., & Münzel, T. (2006). Endothelial nitric oxide synthase in vascular disease: from marvel to menace. Circulation, 113(13), 1708–1714.

Garcia, N. F., de Moraes, C., Rebelo, M. A., de Castro, F. M. P., Peters, S., Pernomian, L., de Mello, M. M. B., de Castro, M. M., & Puggina, E. F. (2022). Low load strength training, associated with or without blood flow restriction increased NO production and decreased production of reactive oxygen species in rats aorta. Life Sci, 294, 120350. https://doi.org/10.1016/j.lfs.2022.120350

Green, D. J., Hopman, M. T., Padilla, J., Laughlin, M. H., & Thijssen, D. H. (2017). Vascular adaptation to exercise in humans: role of hemodynamic stimuli. Physiological Reviews, 97(2), 495–528.

Guizoni, D. M., Dorighello, G. G., Oliveira, H. C., Delbin, M. A., Krieger, M. H., & Davel, A. P. (2016). Aerobic exercise training protects against endothelial dysfunction by increasing nitric oxide and hydrogen peroxide production in LDL receptor-deficient mice. J Transl Med, 14(1), 213. https://doi.org/10.1186/s12967-016-0972-z

Guzzoni, V., Cunha, T. S., das Neves, V. J., Briet, L., Costa, R., Moura, M., Oliveira, V., Franco, M., Novaes, P. D., & Marcondes, F. K. (2018). Nandrolone combined with strenuous resistance training reduces vascular nitric oxide bioavailability and impairs endothelium-dependent vasodilation. Steroids, 131, 7–13. https://doi.org/10.1016/j.steroids.2017.12.013

Hassanzadeh, N., Farzizadeh, R., Moharramzadeh, M., & Shoja Anzabi, B. (2022). Designing a Dual-Purpose Device for Strengthening Pectoralis Major and Triceps Muscles. Journal of Advanced Sport Technology, 6(1), 96–102.

Hooijmans, C. R., Rovers, M. M., De Vries, R. B., Leenaars, M., Ritskes-Hoitinga, M., & Langendam, M. W. (2014). SYRCLE's risk of bias tool for animal studies. BMC medical research methodology, 14(1), 43.

Karisa, P., Sylviana, N., Rosdianto, A. M., Goenawan, H., Syamsunarno, M. R. A. A., & Setiawan. (2026). Different types of exercise and myocardial angiogenesis regulation: A scoping

review of cardiac-specific evidence in animal models. Physiological Reports, 14(5), e70775.

La Favor, J. D., Kraus, R. M., Carrithers, J. A., Roseno, S. L., Gavin, T. P., & Hickner, R. C. (2014). Sex differences with aging in nutritive skeletal muscle blood flow: Impact of exercise training, nitric oxide, and α-adrenergic-mediated mechanisms [Article]. American Journal of Physiology - Heart and Circulatory Physiology, 307(4), H524–H532. https://doi.org/10.1152/ajpheart.00247.2014

Landmesser, U., Hornig, B., & Drexler, H. (2004). Endothelial function: a critical determinant in atherosclerosis? Circulation, 109(21_suppl_1), II–27–II–33.

Laughlin, M. H., Bowles, D. K., & Duncker, D. J. (2012). The coronary circulation in exercise training. American Journal of Physiology-Heart and Circulatory Physiology, 302(1), H10–H23.

Lavier, J., Beaumann, M., Menétrey, S., Bouzourène, K., Rosenblatt-Velin, N., Pialoux, V., Mazzolai, L., Peyter, A. C., Pellegrin, M., & Millet, G. P. (2021). High-intensity exercise in hypoxia improves endothelial function via increased nitric oxide bioavailability in C57BL/6 mice. Acta Physiol (Oxf), 233(2), e13700. https://doi.org/10.1111/apha.13700

Liu, Y., Sun, Z., Chen, T., & Yang, C. (2022). Does exercise training improve the function of vascular smooth muscle? A systematic review and meta-analysis. Research in Sports Medicine, 30(6), 577–592.

Luo, J. Y., Cheng, C. K., Gou, L., He, L., Zhao, L., Zhang, Y., Wang, L., Lau, C. W., Xu, A., Chen, A. F., & Huang, Y. (2023). Induction of KLF2 by Exercise Activates eNOS to Improve Vasodilatation in Diabetic Mice. Diabetes, 72(9), 1330–1342. https://doi.org/10.2337/db23-0070

Mendonça, A. A. S., Gonçalves, R. V., Souza-Silva, T. G., Maldonado, I., Talvani, A., Natali, A. J., & Novaes, R. D. (2019). Concomitant exercise training attenuates the cardioprotective effects of pharmacological therapy in a murine model of acute infectious myocarditis. Life Sci, 230, 141–149. https://doi.org/10.1016/j.lfs.2019.05.059

Monnier, A., Garnier, P., Quirie, A., Pernet, N., Demougeot, C., Marie, C., & Prigent-Tessier, A. (2017). Effect of short-term exercise training on brain-derived neurotrophic factor signaling in spontaneously hypertensive rats. J Hypertens, 35(2), 279–290. https://doi.org/10.1097/hjh.0000000000001164

Mota, M. M., Silva, T., Macedo, F. N., Mesquita, T. R. R., Quintans, L. J. J., Santana-Filho, V. J., Lauton-Santos, S., & Santos, M. R. V. (2017). Effects of a Single Bout of Resistance Exercise in Different Volumes on Endothelium Adaptations in Healthy Animals. Arq Bras Cardiol, 108(5), 436–442. https://doi.org/10.5935/abc.20170060

Nogueira, M. E., Sousa Neto, I. V., Motta-Santos, D., Cantuária, A. P. C., Lima, S. M. F., Rezende, T. M. B., Santana, H. A. P., Petriz, B. A., Marqueti, R. C., & Almeida, J. A. (2022). High-protein diet associated with resistance training reduces cardiac TNF-α levels and up-regulates MMP-2 activity in rats. Arch Physiol Biochem, 128(6), 1630–1636. https://doi.org/10.1080/13813455.2020.1787456

Nosrati, H. A., Bolboli, L., Anoushiravani, S., & Farzizadeh, R. (2022). THE EFFECT OF A PERIOD OF RESISTANCE TRAINING WITH BLOOD FLOW RESTRICTION ON THE LEVEL OF IL-6, IGA AND TNF-A, IN JUDOKAS.

Oliveira, P. R., Oliveira, P. B., Rossignoli, P. S., Spadella, M. A., & Chies, A. B. (2020). Exercise training attenuates angiotensin II-induced vasoconstriction in the aorta of normotensive but not hypertensive rats. Exp Physiol, 105(4), 732–742. https://doi.org/10.1113/ep088139

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., & Brennan, S. E. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj, 372.

Paravlic, A. H., & Drole, K. (2025). 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. BMC Sports Science, Medicine and Rehabilitation, 17(1), 72.

Paravlic, A. H., Iskra, S., Abazovic, E., Lamberti, N., Manfredini, F., & Drole, K. (2025). Comparing Aerobic Interval Training with Other Forms of Physical Exercise for Brachial Artery Endothelial Function Improvement: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. Sports Medicine-Open, 11(1), 133.

Petitti, D. B. (2001). Approaches to heterogeneity in meta-analysis. Statistics in medicine, 20(23), 3625–3633.

Powers, S. K., & Jackson, M. J. (2008). Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiological Reviews.

Ren, J., Yang, L., Tian, W., Zhu, M., Liu, J., Lu, P., Li, J., Yang, L., & Qi, Z. (2015). Nitric oxide synthase inhibition abolishes exercise-mediated protection against isoproterenol-induced cardiac hypertrophy in female mice. Cardiology, 130(3), 175–184. https://doi.org/10.1159/000370025

Robinson, A. T., Fancher, I. S., Mahmoud, A. M., & Phillips, S. A. (2018). Microvascular vasodilator plasticity after acute exercise. Exercise and sport sciences reviews, 46(1), 48–55.

ShojaAnzabi, B., Piri, E., & Farzizadeh, R. (2023). The effect of eight weeks of resistance training on the record of young sprint runners. Journal of Sport Biomechanics, 9(3), 204–218.

Shojah-anzabi, B., Farzizadeh, R., Seifi-askishahr, F., & Nejati-afkham, A. (2026). Impact of Resistance, Endurance, and Combined Exercise Training on Lipid Profile, Apolipoprotein A-1, and Nitric Oxide Synthase Expression in Women with Type 2 Diabetes: A Randomized Controlled Trial. Human Nutrition & Metabolism, 200360.

Sousa, A. S., Sponton, A. C. S., & Delbin, M. A. (2021). Perivascular adipose tissue and microvascular endothelial dysfunction in obese mice: Beneficial effects of aerobic exercise in adiponectin receptor (AdipoR1) and peNOS(Ser1177). Clin Exp Pharmacol Physiol, 48(10), 1430–1440. https://doi.org/10.1111/1440-1681.13550

Souza, L. R., Vicente, J. B., Melo, G. R., Moraes, V. C., Olher, R. R., Sousa, I. C., Peruchi, L. H., Neves, R. V., Rosa, T. S., Ferreira,

A. P., & Moraes, M. R. (2018). Acute Hypotension After Moderate-Intensity Handgrip Exercise in Hypertensive Elderly People. J Strength Cond Res, 32(10), 2971–2977. https://doi.org/10.1519/jsc.0000000000002460

Sun, A., Huang, A., Kertowidjojo, E., Song, S., Hintze, T. H., & Sun, D. (2017). Divergent outcomes of fructose consumption on exercise capacity of rats: friend or foe. J Appl Physiol (1985), 122(2), 368–375. https://doi.org/10.1152/japplphysiol.00767.2016

Tanaka, L. Y., Bechara, L. R., dos Santos, A. M., Jordão, C. P., de Sousa, L. G., Bartholomeu, T., Ventura, L. I., Laurindo, F. R., & Ramires, P. R. (2015). Exercise improves endothelial function: a local analysis of production of nitric oxide and reactive oxygen species. Nitric Oxide, 45, 7–14. https://doi.org/10.1016/j.niox.2015.01.003

Thornton, A., & Lee, P. (2000). Publication bias in meta-analysis: its causes and consequences. Journal of clinical epidemiology, 53(2), 207–216.

van Deel, E. D., Octavia, Y., de Waard, M. C., de Boer, M., & Duncker, D. J. (2018). Exercise Training Has Contrasting Effects in Myocardial Infarction and Pressure Overload Due to Divergent Endothelial Nitric Oxide Synthase Regulation. Int J Mol Sci, 19(7). https://doi.org/10.3390/ijms19071968

Wang, B., Xu, M., Li, W., Li, X., Zheng, Q., & Niu, X. (2017). Aerobic exercise protects against pressure overload-induced cardiac dysfunction and hypertrophy via β3-AR-nNOS-NO activation. PLoS One, 12(6), e0179648. https://doi.org/10.1371/journal.pone.0179648

Wang, Y., Luo, D., Jiang, H., Song, Y., Wang, Z., Shao, L., & Liu, Y. (2023). Effects of physical exercise on biomarkers of oxidative stress in healthy subjects: A meta-analysis of randomized controlled trials. Open Life Sciences, 18(1), 20220668.

Widlansky, M. E., Gokce, N., Keaney, J. F., & Vita, J. A. (2003). The clinical implications of endothelial dysfunction. Journal of the American College of Cardiology, 42(7), 1149–1160.

Zimmer, A., Teixeira, R. B., Bonetto, J. H., Siqueira, R., Carraro, C. C., Donatti, L. M., Hickmann, A., Litvin, I. E., Godoy, A. E., Araujo, A. S., Colombo, R., & Belló-Klein, A. (2017). Effects of aerobic exercise training on metabolism of nitric oxide and endothelin-1 in lung parenchyma of rats with pulmonary arterial hypertension. Mol Cell Biochem, 429(1-2), 73–89. https://doi.org/10.1007/s11010-016-2937-1

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