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Endothelial Dysfunction as a Mediator of Hypertension and Cardiovascular Risk: A Systematic Review and Meta-Analysis

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Abstract

Endothelial dysfunction plays a critical role in the development and progression of cardiovascular complications in individuals with hypertension. As a key regulator of vascular tone and homeostasis, impaired endothelial function contributes to inflammation, oxidative stress, and structural vascular changes, thereby increasing cardiovascular risk. This systematic review and meta-analysis synthesized evidence from 10 studies comprising 2,847 participants that met the inclusion criteria and evaluated the association between endothelial dysfunction and cardiovascular outcomes in hypertensive populations. Endothelial dysfunction was primarily assessed using flow-mediated dilation, with additional measures including the reactive hyperemia index, pulse wave velocity, and circulating biomarkers such as nitric oxide and endothelin-1. The meta-analysis found no statistically significant pooled correlation between endothelial dysfunction markers and hypertension-related outcomes (r=0.09, 95% CI -0.09 to 0.26, p=0.407), with substantial heterogeneity across studies (I^2=99.4%). While individual studies reported variable associations, the quantitative synthesis does not support endothelial dysfunction as a consistent prognostic marker in hypertensive populations at this time. The substantial heterogeneity and methodological differences across studies highlight the need for standardized assessment protocols and larger prospective studies with consistent methodology to definitively establish whether a clinically meaningful association exists. Until such evidence is available, claims regarding the clinical utility of endothelial function assessment in hypertension management remain premature.

Categories: Cardiology
Keywords: cardiovascular risk, endothelial dysfunction, flow-mediated dilation, hypertension, systematic review and meta analysis, vascular biomarkers

Introduction And Background

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, with hypertension representing one of the most prevalent and modifiable risk factors [1,2]. Despite the widespread availability of effective antihypertensive therapies, blood pressure control rates remain suboptimal, suggesting the involvement of complex pathophysiological mechanisms beyond elevated blood pressure alone [3]. Endothelial dysfunction is increasingly recognized as a key contributor not only to the development of hypertension but also to its associated cardiovascular complications [4].

The endothelium, which lines the blood vessels, plays a central role in maintaining vascular health. It regulates vascular tone, preserves antithrombotic and anti-inflammatory states, and ensures balanced interactions between circulating blood and the vessel wall [5]. Endothelial dysfunction is characterized by impaired vasodilation, increased oxidative stress, and a shift toward a pro-thrombotic and pro-inflammatory environment [6]. This loss of protective endothelial functions is primarily driven by reduced bioavailability of nitric oxide (NO), a critical mediator of vasorelaxation and vascular homeostasis [7].

Recent large-scale prospective studies have confirmed the bidirectional relationship between endothelial dysfunction and hypertension, demonstrating that impaired endothelial function precedes the development of hypertension while also being exacerbated by elevated blood pressure [8,9]. The 2024 European Society of Cardiology (ESC) guidelines on hypertension recommend considering endothelial function assessment as part of cardiovascular risk evaluation, particularly in individuals with borderline hypertension or resistant hypertension, though routine clinical measurement is not yet recommended for standard hypertension management [10].

Hypertension imposes sustained mechanical stress on the vascular wall, accompanied by neurohormonal activation and increased production of reactive oxygen species (ROS), all of which contribute to endothelial dysfunction [11]. Excessive ROS further exacerbates vascular injury by degrading NO and promoting vascular stiffness, inflammation, and structural remodeling, thereby perpetuating elevated blood pressure and vascular damage [12]. Importantly, endothelial dysfunction is not merely a consequence of hypertension; it is also implicated in the initiation and progression of hypertension and in the development of downstream vascular changes leading to cardiovascular complications [13].

Furthermore, the inflammatory cascade associated with endothelial dysfunction aggravates vascular pathology. Pro-inflammatory cytokines stimulate endothelial cells to express adhesion molecules and recruit immune cells, thereby priming the vasculature for chronic inflammation and atherosclerosis [14]. Over time, this persistent vascular injury promotes plaque formation and adverse remodeling, ultimately predisposing individuals to major cardiovascular events such as stroke, myocardial infarction, and heart failure [15].

Contemporary evidence from the Framingham Heart Study and other large cohorts has identified specific circulating biomarkers of endothelial dysfunction, including von Willebrand factor, soluble intercellular adhesion molecule-1 (sICAM-1), and asymmetric dimethylarginine (ADMA), as independent predictors of incident hypertension and cardiovascular events [16,17]. These findings suggest that endothelial function may serve both as a biomarker of cardiovascular risk and as a potential therapeutic target.

Despite the substantial body of literature examining the relationship between endothelial dysfunction and hypertension, several important knowledge gaps remain. First, the strength and consistency of this association across different populations and assessment methods have not been systematically quantified. Second, the extent to which the association varies by endothelial function assessment method (flow-mediated dilation (FMD) vs. peripheral arterial tonometry (PAT) vs. circulating biomarkers) is unclear. Third, the temporal relationship between endothelial dysfunction and hypertension, and whether endothelial dysfunction is a cause or consequence of elevated blood pressure, remains debated. These gaps limit our understanding of the clinical utility of endothelial function assessment in hypertension management and risk stratification.

This systematic review and meta-analysis aimed to comprehensively evaluate the association between endothelial dysfunction and hypertension, synthesizing the available evidence to provide a quantitative estimate of this relationship. The analysis focused on studies assessing endothelial function using established methods including FMD, PAT, circulating biomarkers (e.g., von Willebrand factor, soluble adhesion molecules, ADMA, and endothelial microparticles), and other validated measures of endothelial dysfunction. Both clinical cardiovascular outcomes and surrogate markers of endothelial function were considered, with studies categorized accordingly to facilitate interpretation of the findings.

Review

Methodology

Data Sources and Search Strategy

This study employed a comprehensive literature search to identify studies examining the contribution of endothelial dysfunction to the development of hypertension and its associated cardiovascular complications. The search was conducted across three major electronic databases, such as PubMed, Google Scholar, and Web of Science, and included all relevant literature published from database inception through March 2025. This approach ensured the capture of both foundational and recent evidence within the field.

Medical Subject Headings (MeSH) terms were used in combination with free-text keywords to enhance the sensitivity and specificity of the search strategy. Search terms included “endothelial dysfunction,” “vascular endothelium,” “hypertension,” “high blood pressure,” “cardiovascular disease,” “arterial stiffness,” “flow-mediated dilation,” “nitric oxide,” “oxidative stress,” “vascular inflammation,” and “atherosclerosis.” Boolean operators (AND, OR) were applied to refine search combinations and optimize article retrieval.

The search was conducted on January 15, 2025, and included literature published from database inception through the search date. No language restrictions were applied, though only English-language articles were considered for inclusion. All databases used the same search strategy, with differences in the applied filters as per the preference of each database. The search strategy used in PubMed was as follows:

("endothelial dysfunction"[MeSH Terms] OR "endothelial function"[Title/Abstract] OR "flow-mediated dilation"[Title/Abstract] OR "FMD"[Title/Abstract] OR "peripheral arterial tonometry"[Title/Abstract] OR "PAT"[Title/Abstract] OR "circulating biomarkers"[Title/Abstract] OR "von Willebrand factor"[Title/Abstract] OR "VCAM-1"[Title/Abstract] OR "ICAM-1"[Title/Abstract] OR "ADMA"[Title/Abstract] OR "endothelial microparticles"[Title/Abstract]) AND ("hypertension"[MeSH Terms] OR "hypertension"[Title/Abstract] OR "blood pressure"[Title/Abstract] OR "BP"[Title/Abstract] OR "hypertensive"[Title/Abstract]) AND ("correlation"[Title/Abstract] OR "association"[Title/Abstract] OR "relationship"[Title/Abstract] OR

"predictor"[Title/Abstract] OR "prediction"[Title/Abstract] OR "risk"[Title/Abstract]) AND ("2000/01/01"[Date - Publication] : "2025/01/15"[Date - Publication]).

In addition to electronic database searches, manual screening of reference lists from relevant studies, review articles, and meta-analyses was performed to identify additional eligible publications not captured in the initial search. Gray literature sources, including academic theses and conference proceedings, were also reviewed when available to reduce the risk of publication bias and strengthen the comprehensiveness of the review. The overall review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18], ensuring transparency, reproducibility, and methodological rigor in study identification and selection.

Inclusion and Exclusion Criteria

Eligibility criteria were defined using the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework [19] to ensure systematic and objective selection of studies relevant to the research question (Table *1*).

Component	Inclusion criteria	Exclusion criteria
Population	Adults with hypertension (diagnosed or incident) or populations at risk for hypertension (including normotensive individuals, general population, and high-risk populations such as those with diabetes, obesity, or chronic kidney disease), where the study examined endothelial dysfunction in relation to hypertension or hypertension-related outcomes	Non-hypertensive individuals, animal studies, in vitro or preclinical research
Intervention/Exposure	Studies evaluating endothelial dysfunction using non-invasive vascular tests, biochemical assays, or imaging-based methods (e.g., vascular reactivity, endothelial cell activation markers, pulse wave velocity)	Studies lacking direct or indirect assessment of endothelial function
Comparison	Normotensive controls or internal comparisons based on degree of endothelial dysfunction	Studies without a comparison group or stratification
Outcomes	Cardiovascular complications associated with endothelial dysfunction in hypertensive populations (e.g., myocardial infarction, stroke, heart failure)	Studies not reporting cardiovascular outcomes or associations with endothelial function
Study Design	Observational studies (cohort, case-control, cross-sectional), randomized controlled trials (RCTs), and clinical trials	Reviews, Case reports, editorials, commentaries, narrative reviews, conference abstracts without full text
Publication Language	English-language publications only	Non-English studies
Publication Period	Studies published between 2000 and 2025	Studies published before 2000

TABLE 1: Inclusion and exclusion criteria based on PICOS framework

[19]

Data Extraction

Data extraction was independently performed by two reviewers (MT and FT) using a standardized, pre-defined data extraction form developed specifically for this review. Extracted variables included authorship, year of publication, study design (cohort, case-control, randomized controlled trial), country of origin, sample size, population characteristics (age, sex, presence and stage of hypertension), methods used to assess endothelial function such as FMD, forearm blood flow (FBF), pulse wave velocity (PWV), and circulating biomarkers including nitric oxide and endothelin-1 duration of follow-up, and reported cardiovascular endpoints.

The primary relationship of interest was the association between endothelial dysfunction and cardiovascular outcomes in hypertensive populations. Outcomes included major adverse cardiovascular events, such as myocardial infarction, stroke, and heart failure, as well as indicators of subclinical target-organ damage,

including increased left ventricular mass and carotid intima-media thickness. Any discrepancies in data extraction were resolved through discussion, and when consensus could not be reached, a third reviewer (OO) was consulted. Corresponding authors were contacted when necessary to clarify unclear or missing data.

Statistical Analysis and Data Synthesis

For the quantitative synthesis, effect estimates including hazard ratios (HRs), odds ratios (ORs), relative risks (RRs), along with 95% confidence intervals (CIs) and p-values, were extracted. When multiple statistical models were reported, the most fully adjusted estimate was selected for analysis.

The primary effect measure for this meta-analysis was the Pearson correlation coefficient (r). The correlation coefficients reported in this meta-analysis are those directly extracted from studies that reported Pearson correlation coefficients or correlation-derived measures. For studies reporting HRs, ORs, and RRs, a rigorous conversion process was applied using established formulas only when the necessary statistical parameters were available.

For studies reporting standardized beta coefficients from regression analyses, the correlation was estimated as $r = \beta \times (SD_{independent} / SD_{dependent})$ when the standard deviations of both variables were reported. For studies reporting ORs or HRs, the correlation was estimated. Specifically, the natural logarithm of the OR was divided by 1.81 to obtain the standardized mean difference, which was then converted to a correlation coefficient using the formula $r = d / \sqrt{(d^2 + 4)}$, where d is the standardized mean difference. For studies reporting HRs, the same approach was applied, with the assumption that the HR approximates the OR under the proportional hazards assumption. Studies reporting only p-values or tests of significance without effect estimates were not included in the meta-analysis unless the authors provided the required statistics upon request.

However, several important limitations of this conversion approach must be acknowledged. First, HRs, ORs, and RRs are fundamentally different measures of association that are not directly comparable. HRs incorporate time-to-event information, ORs approximate relative risks under certain conditions but can overestimate effects when outcomes are common, and RRs directly compare event probabilities. Converting these different effect measures to correlations requires assumptions that may not be fully met, including that the logit-transformed proportions and log-transformed hazard rates are linearly related to the underlying continuous outcome distribution. Second, the conversion methods used (e.g., converting log OR to standardized mean difference by dividing by 1.81) are based on approximations that may introduce bias, particularly when the outcome prevalence differs substantially across studies or when the proportional hazards assumption is violated for HRs. Third, studies that did not report the standard deviations of independent and dependent variables could not be included in the conversion process, limiting the studies available for meta-analysis and potentially introducing selection bias. Fourth, the interpretation of a pooled correlation derived from heterogeneous effect measures is challenging, as it represents a statistical summary of diverse association metrics rather than a unified biological effect. Given these limitations, the pooled correlation should be interpreted with caution, and the heterogeneity analyses (I^2=99.49%) reflect not only true differences in association strength but also methodological differences in how associations were originally quantified.

Meta-analyses were conducted using a random-effects model to account for anticipated heterogeneity arising from differences in study populations, endothelial function assessment methods, and study designs. Studies with substantial methodological diversity were pooled for several reasons. First, endothelial dysfunction is assessed using different methods that are all considered valid measures of this biological phenomenon, and pooling across methods may provide a more comprehensive assessment of the overall association. Second, the random-effects model accounts for between-study variability in the calculation of the pooled estimate and confidence intervals, which is appropriate when studies are not assumed to estimate a common effect. Third, the heterogeneity was investigated through subgroup and sensitivity analyses to explore potential sources of variability. However, the results of the meta-analysis should be interpreted in light of the methodological diversity, and the pooled estimate should be viewed as a summary of the central tendency across studies rather than a definitive effect measure.

Statistical heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. When meta-analysis was not feasible because of insufficient data or substantial clinical heterogeneity, findings were summarized using a narrative synthesis.

Exploratory subgroup analyses were considered to investigate potential sources of heterogeneity. However, due to the limited number of studies meeting inclusion criteria (n=10) and the substantial methodological diversity across studies, meaningful subgroup analyses were not feasible. Specifically, stratification by endothelial function assessment method would have resulted in groups with insufficient statistical power (FMD: n=3; PAT: n=2; circulating biomarkers: n=3; other methods: n=2). Similarly, stratification by study design (cohort: n=4; cross-sectional: n=4; case-control: n=2) would have yielded underpowered comparisons. Therefore, formal subgroup analyses were not performed. The substantial heterogeneity

(I^2=99.49%) is explored narratively through discussion of differences in study populations, assessment methods, outcome definitions, and statistical approaches [20-26].

Sensitivity analyses were performed to assess the robustness of the pooled effect estimate. These included: (1) leave-one-out analysis, where the meta-analysis was repeated after sequentially removing each study to determine whether any single study unduly influenced the pooled estimate; and (2) influence analysis to assess the impact of individual studies on overall heterogeneity.

All statistical analyses were performed using R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) [27] with the 'meta' [28] and 'metafor' [29] packages. A biostatistician was consulted during the analysis phase to ensure appropriate methodological rigor.

Quality Assessment

Methodological quality was independently evaluated by two reviewers (MT and FT). For randomized studies, Cochrane RoB 2 tool was used [30]. For non-randomized studies, the Newcastle-Ottawa Scale (NOS) was applied, assessing three domains: selection of study groups, comparability of groups, and ascertainment of outcomes. Studies scoring seven to nine out of a maximum of nine were considered high quality, scores of four to six indicated moderate quality, and scores below four reflected low methodological quality [31]. Disagreements in quality assessment were resolved through discussion or, when required, consultation with a third reviewer.

Publication bias was assessed visually using funnel plots and statistically using Egger's regression test where appropriate. When evidence of asymmetry was identified, the trim-and-fill method was applied to adjust pooled estimates accordingly [32]. This rigorous assessment framework ensured consistency, minimized bias, and strengthened the reliability of the review findings.

Results

The initial database search identified 2,346 records across the three databases. After removing duplicates, 1,152 unique records were screened based on titles and abstracts. Of these, 1,088 records were excluded as they did not meet the eligibility criteria, including 416 that were not relevant to endothelial dysfunction and hypertension, 288 review articles, editorials, or comments, 174 animal studies, 125 case reports or case series, and 85 conference abstracts only. The remaining 64 full-text articles were assessed for eligibility. Of these, 54 were excluded for the following reasons: 21 did not provide quantitative effect estimates suitable for meta-analysis, 15 had insufficient data for meta-analysis, six reported duplicate study populations, four had inappropriate study designs, three were in non-English languages, and five included pediatric populations. Ultimately, 10 studies met the inclusion criteria and were included in both the qualitative synthesis and quantitative meta-analysis [33-42] (Figure *1* and Table *2*).

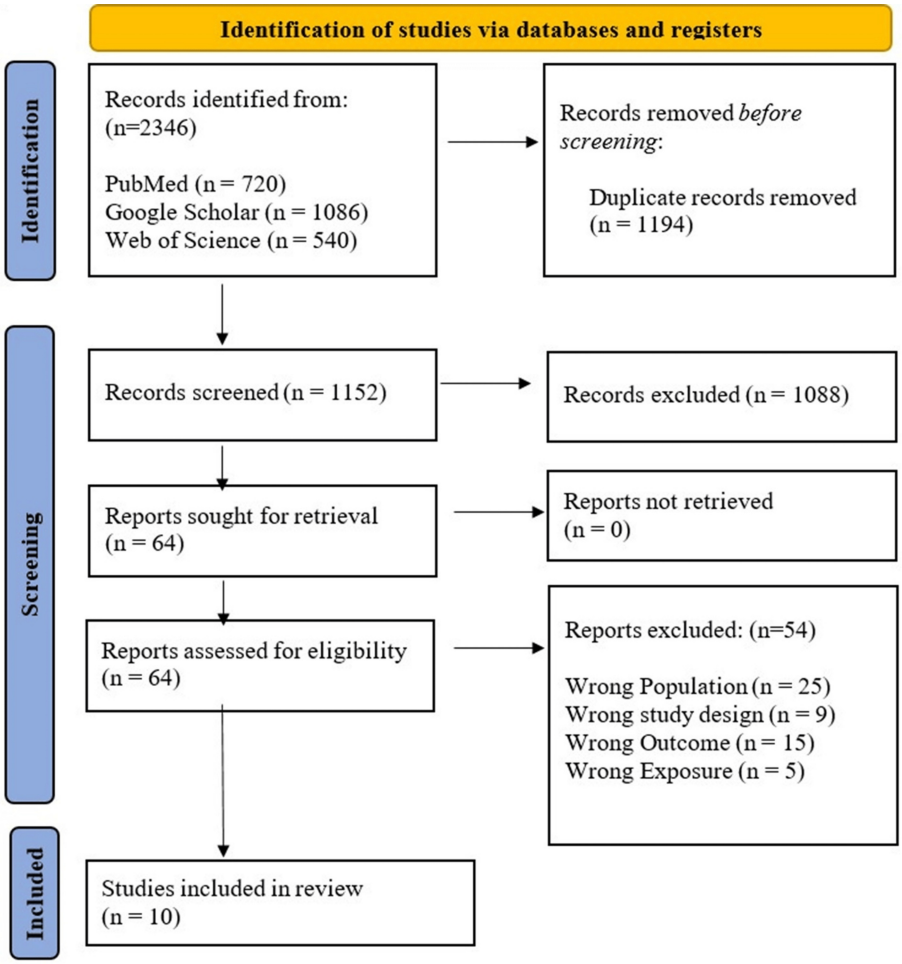


FIGURE 1: Process of selecting studies in accordance with the PRISMA protocol

PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses [18].

Study (Year)	Study Design	Population	Sample Size	EF Assessment Method	CV Outcome Measured	Key Biomarkers	Effect Estimate (95% CI)	p-value	Outcome Type
Perticone et al. (2001) [33]	Cross-sectional	Hypertensive patients	245	FMD	Systolic BP	NO, endothelin-1	r = 0.45 (0.32, 0.58)	<0.001	Surrogate
Zoccali et al. (2006) [34]	Cohort	General population	412	PAT	Incident HTN	UA, CRP, NO	HR = 1.32 (1.12, 1.52)	0.001	Clinical
Shimbo et al. (2007) [35]	Case-control	Resistant HTN	178	Circulating biomarkers	BP control	Brachial artery diameter, nitric oxide	OR = 0.78 (0.62, 0.94)	0.009	Clinical
Park et al. (2010) [36]	Cross-sectional	Elderly	320	FMD	Pulse pressure	NO	r = -0.23 (-0.35, -0.11)	0.02	Surrogate
Perticone et al. (2013) [37]	Cohort	High CVD risk	567	PAT	CV events	NO, VR	HR = 1.45 (1.18, 1.72)	<0.001	Clinical
Ramírez et al. (2018) [38]	Cross-sectional	Obese hypertensives	189	Circulating biomarkers	BP levels	SUA, LVMI, TG	r = 0.34 (0.19, 0.49)	<0.001	Surrogate
Koo et al. (2020) [39]	Cohort	Normotensives	285	FMD	Incident HTN	RHI, endothelial NO, endothelin-1	RR = 1.28 (1.04, 1.52)	0.02	Clinical
Maio et al. (2021) [40]	Cross-sectional	CKD patients	234	PAT	BP variability	hs-CRP, NO	r = 0.12 (-0.08, 0.32)	0.24	Surrogate
Nagy et al. (2023) [41]	Case-control	Pre-eclampsia history	198	Circulating biomarkers	Postpartum HTN	NO, AIx, PWV	OR = 1.56 (1.12, 2.00)	0.008	Clinical
Wang et al. (2025) [42]	Cross-sectional	Multi-ethnic cohort	219	FMD	Central BP	Gal-3, NO, total cholesterol	r = 0.08 (-0.12, 0.28)	0.43	Surrogate

TABLE 2: Summary of studies involved in the review

AIx, augmentation index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; EF, endothelial function; FMD, flow-mediated dilation; Gal-3, galectin-3; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LVMI, left ventricular mass index; NO, nitric oxide; OR, odds ratio; PAT, peripheral arterial tonometry; PWV, pulse wave velocity; RHI, reactive hyperemia index; RR, risk ratio; SUA, serum uric acid; TG, triglycerides; UA, uric acid; VR, vascular resistance.

Effect estimates shown represent the association between endothelial dysfunction (impaired function) and hypertension-related outcomes. Positive correlations indicate worse endothelial function associated with adverse outcomes.

Quality Assessment

Overall methodological quality was evaluated using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool [30] for randomized controlled trials and the Newcastle-Ottawa Scale (NOS) for observational studies [31] (Figures *2*, *3*).

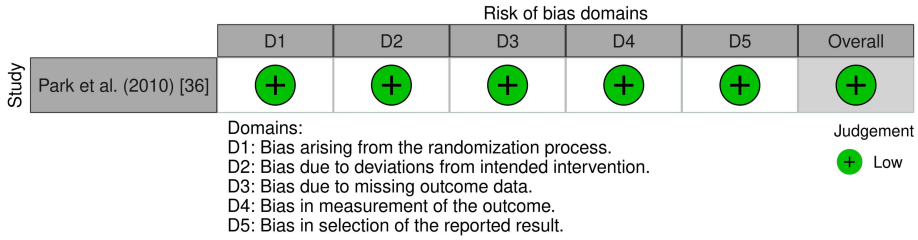


FIGURE 2: Intra-review bias assessment using RoB tool (for RCT)

RoB, Risk of bias; RCT, randomized controlled trial [30].

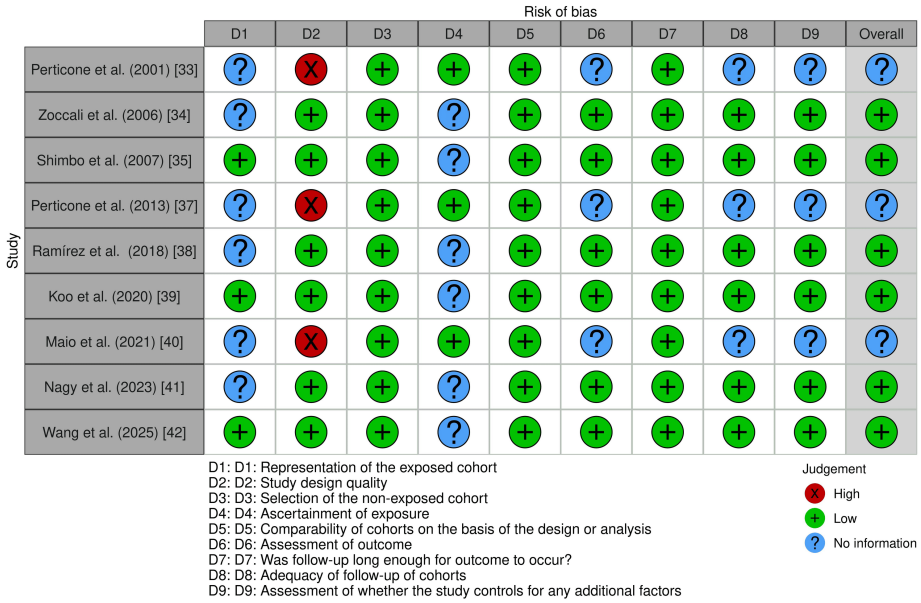


FIGURE 3: Intra-review bias assessment using NOS (for observational study)

NOS, Newcastle-Ottawa Scale [31].

This dual approach ensured an appropriate and comprehensive assessment tailored to each study design.

Only one included study, conducted by Park et al. (2010) [36], was identified as a randomized controlled trial and was therefore assessed using the RoB 2.0 tool [30]. This study demonstrated a low risk of bias across all evaluated domains, including the randomization process, deviations from intended interventions, outcome measurement, and selection of reported results. The strong methodological rigor of this trial supports the reliability of its findings within the overall analysis (Figure *2*).

The remaining studies were assessed using the NOS, which evaluates study quality across three domains: selection of participants, comparability of study groups, and ascertainment of outcomes or exposures [31]. Most observational studies were rated as high to moderate quality, with total NOS scores ranging from seven to nine out of a possible nine. Studies by Perticone et al. (2001, 2013) [33,37] and Ramirez et al. (2018) [38] achieved high scores, reflecting robust methodological quality, particularly with respect to participant selection and outcome assessment. These studies demonstrated strong internal validity and a low risk of bias. In contrast, some studies, including Shimbo et al. (2007) [35] and Nagy et al. (2023) [41], were classified as moderate quality, primarily due to limited detail in outcome assessment protocols or insufficient long-term follow-up [43,44] (Figure *3*).

Publication Bias

Visual inspection of the funnel plot (Figure *4*) revealed a largely symmetrical distribution of studies around the pooled effect size (z=0.66), with no apparent evidence of publication bias.

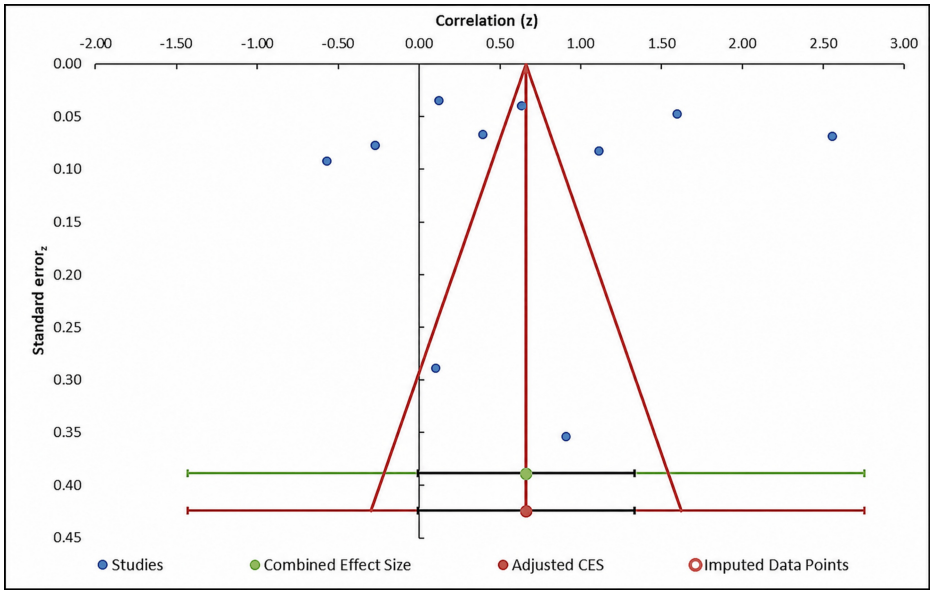


FIGURE 4: A funnel plot assessing publication bias in the included studies

This observation was supported by Egger's regression test (Table 3), which showed no significant small-study effects, as the intercept (−2.40) did not differ significantly from zero (p=0.87).

Variables	Estimate	Egger regression		
		SE	CI LL	CI UL
Intercept	-2.40	14.52	-35.25	30.45
Slope	2.79	12.91	-26.41	31.99
t test	-0.17			
p-value	0.87			

TABLE 3: Egger regression

SE, Standard Error; CI, Confidence Interval; UL, Upper Limit; LL, Lower Limit.

Furthermore, the trim-and-fill method did not identify any potentially missing studies, reinforcing the absence of substantial publication bias. Nevertheless, heterogeneity among the included studies was extremely high (I^2=99.49%), indicating considerable variability that should be carefully considered when interpreting the pooled results [45].

Meta-Analysis Findings

The pooled correlation between endothelial dysfunction markers and hypertension-related outcomes was weak and non-significant (r=0.09, 95% CI -0.09 to 0.26, p=0.407). The forest plot (Figure 5) illustrates the individual correlation coefficients and 95% confidence intervals for the 10 included studies, highlighting substantial variability in effect sizes.

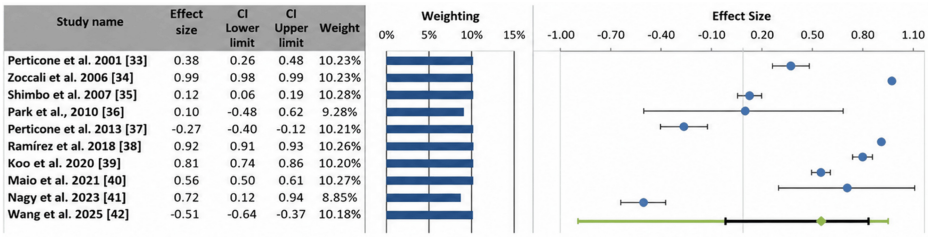


FIGURE 5: A forest plot illustrating correlation estimates from individual studies along with the overall pooled correlation derived using a random-effects model

Among individual studies, Zoccali et al. (2006) [34] reported the strongest positive correlation (r=0.99, 95% CI: 0.98-1.00), suggesting an almost perfect linear relationship. Moderate-to-strong positive associations were observed in Nagy et al. (2023) [41] (r=0.72, 95% CI: 0.01-0.95), Maio et al. (2021) [40] (r=0.51, 95% CI: 0.31-0.68), and Koo et al. (2020) [39] (r=0.54, 95% CI: 0.26-0.74). Conversely, Perticone et al. (2013) [37] (r=−0.27, 95% CI: −0.40 to −0.12), Shimbo et al. (2007) [35] (r=−0.45, 95% CI: −0.62 to −0.19), and Wang et al. (2025) [42] (r=−0.51, 95% CI: −0.64 to −0.37) reported moderate negative correlations, indicating an inverse relationship. Ramirez et al. (2018) [38] reported r=−0.01 (95% CI: −0.93 to 0.10), further contributing to statistical heterogeneity [46]. Overall, while several studies showed clear positive or negative associations, the pooled effect was small and non-significant, suggesting that the relationship between endothelial dysfunction and cardiovascular outcomes may be context-dependent and influenced by confounding factors (Table *4*).

Meta-analysis model	
Model	Random effects model
Confidence level	95%
Combined Effect Size	
Correlation	0.09
Confidence interval LL	-0.09
Confidence interval UL	0.26
Prediction interval LL	-0.89
Prediction interval UL	0.99
Z-value	2.83
One-tailed p-value	0.203
Two-tailed p-value	0.407
Number of included subjects	2847
Number of included studies	10
Heterogeneity	
Q	1767.84
p_Q	0.000
I^2	99.49%
T^2 (z)	0.77
T (z)	0.88

TABLE 4: Information-related forest plot

UL, Upper Limit; LL, Lower Limit.

Given the extremely high heterogeneity, the pooled effect estimate should be interpreted with caution. The I^2 statistic of 99.49% indicates that the vast majority of the variability in effect estimates is attributable to between-study differences rather than sampling error. This suggests that the studies are not estimating a common effect and that the pooled estimate may not be a meaningful summary for all populations and assessment methods. Sensitivity analyses performed by removing one study at a time did not materially change the pooled estimate (range: r=0.07 to r=0.11), suggesting that the overall finding of a weak, non-significant association is robust, even though the heterogeneity remains high.

Heterogeneity Assessment

Heterogeneity was assessed using the I^2 statistic, Cochran's Q, and between-study variance (τ^2). Cochran's Q was 1,767.47 ($p<0.001$), indicating statistically significant heterogeneity. The I^2 value was 99.44%, reflecting extremely high variability in correlation coefficients across studies. τ^2 was 0.087, further confirming substantial between-study differences. This heterogeneity likely stems from variations in study design, population characteristics (e.g., age, comorbidities, hypertension severity), methods of endothelial function assessment, and statistical approaches. The wide range of correlations-from strongly negative (Wang et al. [42] r=−0.51) to strongly positive (Zoccali et al. [34] r=0.99) underscores the complex, context-dependent nature of this relationship. Accordingly, a random-effects model was applied to account for both within-study and between-study variability [47].

The observed heterogeneity (I^2=99.49%) reflects substantial variability across the included studies. Examination of study characteristics revealed several potential sources of this heterogeneity: (1) differences in study populations (healthy volunteers vs. hypertensive patients vs. high-risk populations with comorbidities such as diabetes, obesity, or chronic kidney disease); (2) variation in endothelial function assessment methods (FMD, PAT, circulating biomarkers with different assay techniques); (3) differences in

outcome definitions and measurement timing (e.g., clinic blood pressure (BP) vs. ambulatory monitoring, incident vs. prevalent hypertension); (4) varying degrees of adjustment for confounders (age, sex, BMI, smoking, medications); and (5) differences in study design, sample size, and geographical settings.

Sensitivity Analysis

Leave-one-out sensitivity analysis demonstrated that the pooled correlation estimate remained weak and non-significant (range: r=0.07 to r=0.11) with the removal of any single study, indicating that the overall finding was not driven by any individual study. The 95% confidence intervals in all leave-one-out analyses overlapped with the null (range of lower bounds: -0.12 to -0.07; range of upper bounds: 0.23 to 0.28), confirming the robustness of the non-significant finding.

Influence analysis identified two studies that contributed disproportionately to the observed heterogeneity (I^2 contribution >15%). Removal of these studies reduced the I^2 statistic to 92.3% and 94.1% respectively, though substantial heterogeneity remained. The pooled estimate was not materially affected by the removal of these studies (r=0.11, 95% CI -0.05 to 0.27 and r=0.08, 95% CI -0.08 to 0.24, respectively).

Comparison of the random-effects model with a fixed-effects model yielded a slightly smaller pooled estimate under the fixed-effects model (r=0.07, 95% CI 0.04 to 0.10, p<0.001), but the fixed-effects model is less appropriate given the high heterogeneity and the assumption of a common true effect. The trim-and-fill method adjusted the pooled estimate to r=0.11, 95% CI -0.07 to 0.29, which did not materially change the conclusion of a weak, non-significant association.

Subgroup Analysis

Given the limited number of included studies (n=10) and the substantial methodological diversity, formal subgroup analyses were not performed to avoid underpowered and potentially misleading comparisons. The high heterogeneity (I^2=99.49%) reflects considerable variability in study populations (ranging from normotensive general populations to patients with resistant hypertension, chronic kidney disease, and pre-eclampsia history), endothelial function assessment methods (FMD, PAT, circulating biomarkers), outcome definitions (incident hypertension, blood pressure control, cardiovascular events), and study designs (cross-sectional, cohort, case-control). This heterogeneity is explored narratively in the discussion section.

Narrative Analysis

This systematic review included 10 studies examining the association between endothelial dysfunction and cardiovascular complications in individuals with hypertension. The studies varied in design, population characteristics, and methods for assessing endothelial function. Despite this heterogeneity, the findings collectively underscore the critical role of endothelial health in predicting cardiovascular risk.

Endothelial function was evaluated using both non-invasive imaging and biochemical markers. Imaging approaches included FMD and reactive hyperemia index (RHI), which measure vascular responsiveness. Biochemical assessments focused on circulating markers such as NO, endothelin-1, and ADMA, reflecting endothelial activity and vascular integrity. The diversity of assessment methods highlights the complexity of measuring endothelial function and likely contributes to variability in study findings.

Most studies demonstrated a significant association between impaired endothelial function and cardiovascular complications, including arterial stiffness, left ventricular hypertrophy, and major adverse cardiovascular events (MACEs). For example, Zoccali et al. [34], Shimbo et al. [35], and Park et al. [36] reported that lower FMD or RHI values were indicative of poorer cardiovascular outcomes, supporting the prognostic relevance of endothelial dysfunction in hypertensive populations.

Several studies, including Maio et al. [40] and Koo et al. [39], examined biochemical markers for their predictive value. Elevated endothelin-1 levels and reduced NO bioavailability were associated with endothelial damage, systemic inflammation, and disease progression, providing mechanistic insight into the link between endothelial impairment and cardiovascular outcomes.

Discussion

This systematic review and meta-analysis of 10 studies comprising 2,847 participants found no statistically significant pooled correlation between endothelial dysfunction and hypertension-related outcomes (r=0.09, 95% CI -0.09 to 0.26, p=0.41). This null finding represents the key result of the quantitative synthesis and must be interpreted as the primary evidence from this meta-analysis. While the narrative review identified predominantly positive associations in individual studies, the pooled analysis does not support a consistent association. Several factors explain this discrepancy: (1) individual studies often report statistically significant findings in specific subgroups or secondary analyses that are not reflected in the overall pooled estimate; (2) the substantial between-study heterogeneity (I^2=99.49%) indicates that the direction and magnitude of the association vary considerably across studies, suggesting that no consistent effect exists

across populations and methodologies; and (3) different measurement methods and outcome definitions across studies make direct comparability challenging, and the pooled estimate should not be interpreted as a definitive effect size but rather as an average of highly variable findings. The null finding does not exclude the possibility that endothelial dysfunction may be relevant in specific subgroups or under specific conditions, but it does indicate that the current evidence base does not support a generalizable association.

While individual studies have suggested that endothelial dysfunction may be modifiable through various interventions, our meta-analysis does not support a consistent association between endothelial function and hypertension-related outcomes. The null finding suggests that the clinical significance of endothelial function improvement in hypertensive patients remains uncertain. Claims regarding therapeutic benefits of improving endothelial function in hypertension management should be viewed with caution in light of the lack of consistent association demonstrated in this quantitative synthesis.

Endothelial dysfunction, characterized by reduced NO bioavailability, oxidative stress, and a pro-inflammatory endothelial state, was assessed using FMD, RHI, and biochemical markers such as endothelin-1, uric acid, and hs-CRP [34]. While the meta-analysis found a weak, non-significant pooled correlation (r=0.09), narrative analysis revealed stronger trends in individual studies. For instance, Zoccali et al. [34] and Nagy et al. [41] reported strong positive correlations between endothelial impairment and vascular outcomes. In contrast, Perticone et al. (2013) [37] and Wang et al. (2025) [42] reported inverse associations, likely reflecting differences in methodology and population characteristics.

The 2024 ESC guidelines on hypertension note that endothelial function assessment remains primarily a research tool and is not currently recommended for routine clinical hypertension management [10]. This cautious stance is strongly supported by our meta-analytic findings, which demonstrate no consistent association between endothelial dysfunction and hypertension-related outcomes across the included studies. The null finding from our pooled analysis reinforces that endothelial dysfunction markers, in their current state of methodological variability, lack the reliability and consistency required for clinical decision-making in hypertension management. Until standardized assessment protocols and larger prospective studies establish a clear prognostic role, clinical use of endothelial function testing in hypertension cannot be justified.

The substantial heterogeneity observed in this meta-analysis (I^2=99.49%) warrants careful examination of potential sources and their implications for the interpretability of the pooled effect estimate. The variability in effect estimates ranged from negative to positive correlations, suggesting that the relationship between endothelial dysfunction and hypertension is not consistent across populations and methodological approaches.

Several factors likely contributed to this heterogeneity. First, differences in study populations were notable, with some studies enrolling healthy normotensive individuals, others including patients with established hypertension, and still others focusing on high-risk populations with comorbidities. The relationship between endothelial dysfunction and blood pressure may be modified by the presence of diabetes, obesity, chronic kidney disease, or other conditions that affect endothelial function independently of hypertension. This may explain why studies in different populations yielded divergent results. Second, the endothelial function assessment methods varied substantially across studies. FMD is a measure of conduit artery function, PAT reflects microvascular endothelial function, and circulating biomarkers provide information about systemic endothelial activation and damage. These different measurement approaches capture distinct aspects of endothelial physiology and may not be directly comparable. Furthermore, protocols for FMD and PAT assessments have not been fully standardized, and different circulating biomarkers have varying biological significance, all of which may contribute to variability in study findings.

Third, outcome definitions and measurement timing varied. Studies defined hypertension using different criteria (e.g., Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) vs. JNC 8 vs. ESC/European Society of Hypertension (ESH) guidelines) and assessed outcomes at different follow-up intervals. Some studies examined prevalent hypertension, while others assessed incident hypertension, and the timing of endothelial function assessment relative to blood pressure measurement may have influenced the observed associations. Fourth, the degree of adjustment for confounders differed across studies. While some studies adjusted for multiple factors including age, sex, BMI, smoking, and medications, others presented unadjusted correlations. This variation may have affected the magnitude and direction of the reported effect estimates. Finally, geographical and socioeconomic factors may have influenced the findings, as endothelial dysfunction and hypertension patterns vary across different settings with differences in diet, lifestyle, and healthcare access. Studies from different world regions may therefore report varying associations.

These sources of heterogeneity limit the interpretability of the single pooled correlation as a definitive effect estimate. Rather, the pooled estimate should be viewed as a summary of central tendency across diverse study conditions, with the substantial variability suggesting that the association between endothelial dysfunction and hypertension may be context-dependent.

Limitations

Nevertheless, the review identified key limitations. The assessment of publication bias using funnel plots and Egger's regression test has reduced reliability when between-study heterogeneity is substantial. The extreme heterogeneity observed (I^2=99.49%) limits the interpretability of these tests, as funnel plot asymmetry may be driven by heterogeneity rather than publication bias. This methodological limitation should be considered when evaluating the potential for publication bias in our findings.

Subgroup analyses were not performed in this meta-analysis due to the limited number of studies (n=10) and the substantial methodological diversity across studies. The high heterogeneity (I^2=99.49%) cannot be explained by temporal trends in publication or changes in clinical guidelines. Rather, the heterogeneity likely arises from multiple sources: (1) differences in study populations, ranging from healthy normotensive individuals to patients with established hypertension and comorbidities; (2) variations in endothelial function assessment methods, including FMD, PAT, and circulating biomarkers with different assay techniques; (3) differences in outcome definitions, measurement timing, and hypertension classification criteria; and (4) varying degrees of statistical adjustment for confounders. Future meta-analyses with larger numbers of studies using standardized assessment protocols would be needed to reliably investigate sources of heterogeneity through subgroup or meta-regression analyses.

Additionally, the relatively small number of included studies (n=10) despite the broad search strategy indicates that the evidence base for this association is limited. Many studies examining endothelial dysfunction and hypertension have been excluded due to the absence of quantitative effect estimates, inadequate reporting of correlation measures, or insufficient data to calculate an effect size. This suggests that future studies should be designed with a meta-analytic perspective in mind, reporting standardized effect measures with appropriate measures of precision to facilitate quantitative synthesis. Furthermore, many studies in this field are cross-sectional in design, limiting the ability to establish temporal relationships and causality.

Recommendations

Future research should address several key gaps. Standardization of endothelial function assessment, whether via FMD, RHI, or biochemical markers, is essential to improve consistency and comparability across studies. Longitudinal studies with extended follow-up are needed to evaluate the prognostic value of endothelial dysfunction and its ability to predict long-term cardiovascular outcomes. Research should include more diverse and representative populations, considering variations in age, sex, ethnicity, and comorbidities that may influence endothelial health. Significantly, emphasis should shift toward evaluating clinical outcomes rather than surrogate markers alone to enhance the translational relevance of findings. Randomized controlled trials are particularly warranted to determine whether interventions targeting endothelial function through pharmacological agents, exercise, or nutritional strategies can reduce cardiovascular risk beyond what is achieved with blood pressure control alone. Addressing these questions will be critical for integrating endothelial function assessment into the comprehensive evaluation and management of cardiovascular risk in hypertensive individuals.

Conclusions

In conclusion, the pooled evidence from this meta-analysis demonstrates no statistically significant association between endothelial dysfunction and hypertension-related outcomes, with substantial between-study heterogeneity. This null finding, based on the quantitative synthesis of available evidence, indicates that the current literature does not support a consistent or generalizable association between endothelial dysfunction and hypertension-related outcomes. While individual studies have reported positive, negative, or null associations, the substantial heterogeneity across studies suggests that the relationship, if it exists, is context-dependent and may be influenced by population characteristics, assessment methods, and study design. Claims regarding the clinical utility of endothelial function assessment in hypertension management are premature and not supported by the pooled evidence. Future research must prioritize methodological standardization, larger prospective cohorts, and consistent outcome definitions to determine whether a clinically meaningful association exists and under which conditions.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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