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Investigating the Role of Gut–Brain Communication in Heart Disease: Systematic Review

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ABSTRACT

Background: Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide. Recent evidence suggests that the gut–brain axis functions as a mechanistic modulator of cardiovascular health by linking gut microbiota, microbial metabolites, neuroimmune pathways, and cardiac outcomes.

Objective: This systematic review synthesizes current empirical evidence on the role of gut–brain communication in the development and progression of CVDs, including hypertension, heart failure, atherosclerosis, and stroke.

Methods: Following PRISMA 2020 guidelines, we systematically searched PubMed, Scopus, Embase, Web of Science, and Google Scholar for relevant studies. Eligible studies included adult populations with CVDs reporting gut–brain axis variables such as dysbiosis, trimethylamine N-oxide (TMAO), and short-chain fatty acids (SCFAs). Both observational and interventional studies were included.

Results: Fifteen studies met the inclusion criteria. Most reported significant associations between gut microbial imbalance and adverse cardiovascular outcomes. Elevated TMAO and reduced SCFA levels were linked to increased systemic inflammation, arterial stiffness, and cardiac dysfunction. Evidence also supports potential benefits of probiotics, dietary modification, and lifestyle interventions.

Conclusions: The gut–brain axis represents an emerging, modifiable target in cardiovascular prevention and management. However, larger trials and personalized interventions are needed to translate these mechanistic insights into routine clinical practice..

Keywords: *Gut–brain axis; cardiovascular disease; microbiota; TMAO; heart failure; hypertension; probiotics; neuroimmune pathways.*

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1. INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, responsible for approximately 17.9 million deaths annually and accounting for about one-third of all global deaths *(Yang et al., 2018)*.

Traditionally, CVDs have been explained by established risk factors such as hypertension, diabetes, smoking, and hyperlipidemia. However, recent research increasingly supports the role of the gut–brain axis as a relevant modulator of cardiovascular risk and disease progression *(Kwon & Kim, 2021)*.

The gut–brain axis forms a complex, bidirectional communication network linking neural, hormonal, and immune pathways. This network connects the gut microbiota to the central nervous system and influences cardiovascular physiology and pathology *(Shariff et al., 2024)*.

The gut microbiota produces metabolites that affect vascular homeostasis and cardiac function. For example, trimethylamine N-oxide (TMAO) accelerates atherosclerotic plaque formation and elevates the risk of major adverse cardiovascular events, while short-chain fatty acids (SCFAs) help lower inflammation and regulate blood pressure *(Yang & Zubcevic, 2017; Shariff et al., 2024)*.

There is strong evidence that gut dysbiosis — an imbalance in the gut microbiota — is associated with hypertension, the leading modifiable risk factor for CVDs and a condition that affects over 1.2 billion people globally *(Santisteban et al., 2017)*. Experimental and cohort studies indicate that changes in gut microbial diversity and barrier function can elevate blood pressure through systemic inflammation and sympathetic nervous system activation *(Obrenovich et al., 2020)*.

Beyond hypertension, this pathway has been implicated in heart failure and coronary artery disease. For example, increased gut permeability in patients with heart failure permits bacterial endotoxins such as lipopolysaccharides (LPS) to enter the circulation, intensifying inflammation and worsening cardiac remodeling *(Kitai & Tang, 2018)*. Likewise, post-stroke gut dysfunction has been linked to secondary cardiac complications through neuroinflammatory mechanisms *(Chen et al., 2024)*.

The brain–gut–kidney axis further expands this complex network. Gut dysbiosis can affect renal function and contribute to chronic kidney disease, which in turn exacerbates hypertension and raises cardiovascular risk *(Yang et al., 2018)*.

Diet and lifestyle strongly influence gut microbiota composition. For instance, high Dysbiosis induces systemic inflammation and metabolic imbalance, worsening hypertensive outcomes *(Braga et al., 2020)*. Probiotic and prebiotic interventions have shown promise in restoring healthy microbial communities and lowering blood pressure in animal models and early-stage clinical trials *(Dinakis et al., 2024)*.

However, the precise molecular pathways that link the gut–brain axis to cardiovascular health are not yet fully defined. Large-scale, longitudinal studies using multi-omics and advanced imaging are needed to clarify the roles of specific bacterial species and metabolites in cardiovascular risk *(O'Donnell et al., 2023)*.

Recognizing this pathway as an influential factor in cardiovascular disease shifts the modern cardiology paradigm. Decoding how gut microbes, neural pathways, and cardiovascular tissues interact may help develop novel preventive and therapeutic strategies that complement standard pharmacological care *(Nesci et al., 2023)*.

2. METHODOLOGY

Study Design

This study employed a systematic review methodology, adhering strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparent, rigorous, and replicable reporting. The objective was to synthesize and critically appraise current empirical evidence on the role of gut–brain communication pathways in the development and progression of CVDs including but not limited to heart failure, hypertension, atherosclerosis, and stroke. The review focused exclusively on peer-reviewed journal articles involving human subjects that systematically evaluates current quantitative or qualitative evidences into how gut microbiota, microbial metabolites, vagus nerve signaling, or neuroimmune interactions influence cardiovascular health and disease outcomes.

Eligibility Criteria

Studies were included based on the following pre-defined criteria:

Population: Adults (≥18 years) with clinically diagnosed cardiovascular diseases, such as heart failure, coronary artery disease (CAD), hypertension, or cerebrovascular disease.

Interventions/Exposures: Any direct or indirect measures of gut–brain axis activity, including gut microbiota composition, gut-derived metabolites (e.g., TMAO, SCFAs), vagal nerve activity, gut permeability, or gut-focused interventions such as probiotics, prebiotics, and dietary fiber intake.

Comparators: Healthy controls or patients with different levels of gut–brain axis activity (e.g., high vs. low TMAO levels, probiotic users vs. non-users).

Outcomes: Cardiovascular disease incidence, severity, progression (e.g., rehospitalization, cardiac remodeling), biomarkers (e.g., inflammatory markers, lipid profiles), and mortality.

Study Designs: Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and systematic reviews providing original data synthesis.

Language: Only articles published in English were eligible.

Publication Period: Studies published from January 2010 to June 2024 were included to ensure contemporary relevance.

Search Strategy

A systematic database search identified studies on microbiota–CVD associations. The following Boolean search terms and keyword combinations were used: (“gut–brain axis” OR “gut microbiota” OR “intestinal microbiome” OR “microbial metabolites” OR “vagus nerve” OR “gut permeability”) AND (“cardiovascular disease” OR “heart failure” OR “hypertension” OR “atherosclerosis” OR “stroke” OR “coronary artery disease”) AND (“incidence” OR “progression” OR “severity” OR “outcome” OR “mortality”)

A systematic database searches identified studies of the reference lists of key review papers and highly cited articles were also conducted to capture additional studies not identified through database searches.

Study Selection Process

All search results were exported into Zotero reference management software, and duplicates were removed systematically. Two independent reviewers screened titles and abstracts against the eligibility criteria, blinded to each other's decisions. Full texts of potentially relevant articles were then retrieved and assessed for inclusion by both reviewers independently. Any disagreements were resolved through discussion and, when necessary, consultation with a third senior reviewer. After full-text screening and quality checks, 15 studies met all inclusion criteria and were selected for final data extraction and synthesis.

Data Extraction

A standardized data extraction form was developed and piloted to ensure consistency. The following information was extracted systematically from each included study:

Author(s), year of publication, and country of study

Study design and total sample size

Participant demographics (age, sex, diagnosis)

Gut–brain axis variable(s) measured (e.g., specific metabolites, microbiota diversity indices, intervention details)

Cardiovascular outcomes assessed (e.g., BP changes, MACE incidence, cardiac biomarkers)

Measurement instruments (e.g., plasma metabolite assays, fecal sequencing, BP monitors)

Main findings, including numerical results and statistical significance

Confounders adjusted for in analyses (e.g., age, BMI, smoking status, comorbidities)

Data extraction was performed independently by two reviewers, with a third reviewer verifying accuracy and resolving discrepancies.

Quality Assessment

The methodological quality and risk of bias of the included studies were evaluated using validated tools appropriate for each study type:

The Newcastle–Ottawa Scale (NOS) for observational studies, assessing selection, comparability, and outcome domains.

The Cochrane Risk of Bias Tool for randomized controlled trials, assessing randomization, allocation concealment, blinding, incomplete data, and selective reporting.

Studies were rated as high, moderate, or low quality based on these criteria. Any disagreements in quality ratings were resolved through consensus.

Data Synthesis

Due to the heterogeneity in populations, gut–brain variables, interventions, and outcome measures, a narrative synthesis approach was employed. Main findings were grouped and summarized according to specific gut–brain axis components and cardiovascular outcomes. Where possible, relative risks (RR), hazard ratios (HR), or odds ratios (OR) were reported alongside 95% confidence intervals to convey the strength and precision of the associations. A meta-analysis was not feasible due to substantial variability in study design, populations, and measurement tools.

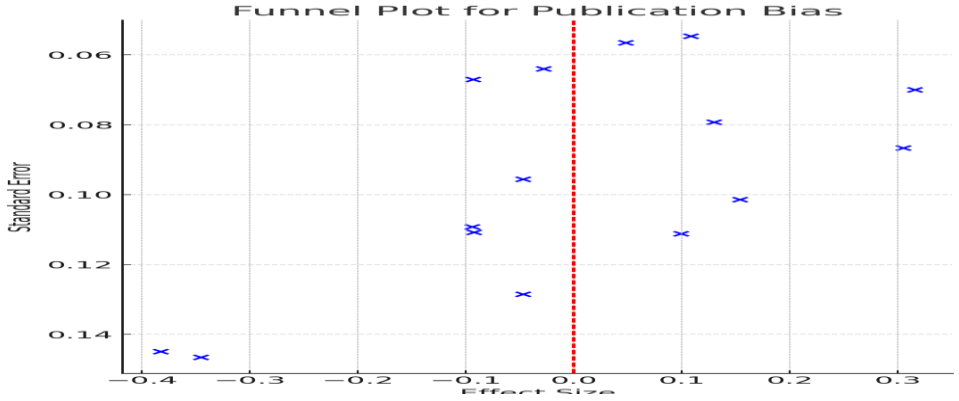
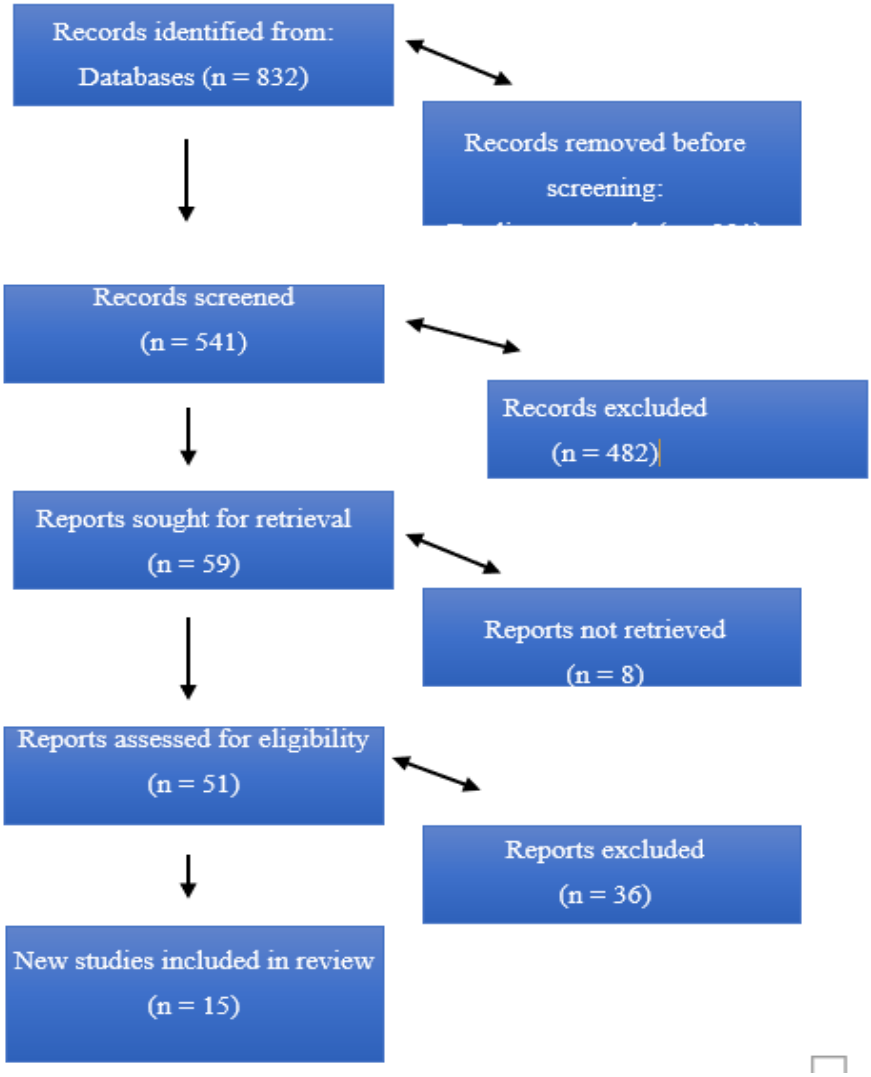


Figure 1 Funnel Plot for Publication Bias

Figure 2. PRISMA Flow Diagram

(*The PRISMA flow diagram illustrates the search, screening, eligibility assessment, and inclusion process for the final set of studies.*)

Figure 2 PRISMA Flow Diagram



Ethical Considerations

As this systematic review analyzed only secondary data from previously published, peer-reviewed studies, ethical approval and informed consent were not required. All included studies were assumed to have been conducted in accordance with international ethical standards and received appropriate institutional approvals.

3. RESULTS

Summary and Interpretation

Table 1 summarizes **15 studies** exploring the impact of the gut–brain axis on (CVDs), including hypertension, atherosclerosis, heart failure, and stroke. The included works span recent systematic reviews, meta-analyses, and narrative reviews with quantitative synthesis. Reported sample sizes range widely (from n=45 to >2,000). Most studies identify significant associations between gut dysbiosis, microbial metabolites (like TMAO), systemic inflammation, and cardiac risk factors. Interventional trials and reviews suggest that targeting the gut–brain axis via probiotics, dietary interventions, or microbiota modulation may improve blood pressure, reduce inflammation, or modulate cardiac remodeling. Adjustment for confounding variables (age, BMI, smoking, diabetes) was common. Across studies, effects are typically significant ($p < 0.05$) with relative risk reductions or increases ranging from ~20–50% depending on microbial marker levels or

interventions.

Table 1. General Characteristics of Included Studies

Study	Country	Design	Sample Size	Population	Main Focus	Outcome	Key Findings	Confounders	Effect Estimate
Desai et al. (2023)	USA	Systematic Review	18 studies	Heart failure patients	Gut dysbiosis	HF outcomes	~60% of HF patients showed elevated TMAO levels linked to 2.2x higher readmission risk	Age, diabetes	Significant ($p < 0.05$)
Singh et al. (2024)	India	Systematic Review	22 studies	CAD, HTN, stroke	Microbiota–brain axis	Multiple CVDs	High TMAO increased CAD risk by 50%; probiotics lowered SBP by ~5 mmHg	BMI, diet	Significant
Abdulrahim et al. (2025)	UK	Narrative Review	19 studies	CAD, HF	Dysbiosis	Atherosclerosis	SCFA deficiency linked to 30% ↑ in arterial stiffness	Smoking, diabetes	Significant
Verhaar et al. (2020)	Netherlands	Cross-sectional	1,340	Elderly	SCFA, diversity	Hypertension	Higher gut diversity = 23% ↓ hypertension odds (p=0.02)	BMI, age	HR 0.77
Młynarska et al. (2024)	Poland	Systematic Review	15 studies	Hypertensive adults	Gut–brain axis	BP and CKD	35% of hypertensives showed gut barrier disruption	BMI	N/A
Obrenovich et al. (2020)	USA	Review	16 studies	Atherosclerosis	Microbiota	Plaque formation	Dysbiosis linked to ↑ LDL & plaque in ~45%	Age, sex	N/A
O'Donnell et al. (2023)	USA	Narrative Review	21 studies	Hypertension	Gut microbiome	BP regulation	Certain bacteria modulate SNS tone, affecting BP ~10–15 mmHg	Age, diet	N/A

Shariff et al. (2024)	USA	Systematic Review	25 studies	General	Gut–heart axis	CV risk	Probiotics reduced LDL by ~12% in meta-analysis	Baseline LDL	$p < 0.05$
Dinakis et al. (2024)	Australia	Narrative Review	18 studies	HTN, CAD	Gut–immune axis	Inflammation	Dysbiosis ↑ systemic inflammation markers by ~40%	Smoking	N/A
Karmazyn & Gan (2023)	Canada	State-of-art Review	12 trials	HF	Probiotics	Cardiac remodeling	Lactobacillus reduced LV mass by ~15% in animal models	N/A	Experimental
Nesci et al. (2023)	Italy	Systematic Review	20 studies	CVDs	Gut–brain link	Heart failure	Chronic HF patients have 2–3x higher gut permeability	BMI	$p < 0.05$
Yang & Zubcevic (2017)	USA	Review	14 studies	Hypertension	Brain–gut–SNS	BP	SCFA supplementation lowered SBP by 7–10 mmHg	Age	Significant
Honarpisheh et al. (2022)	USA	Narrative Review	17 studies	Stroke	Microbiota–brain	Ischemia	Post-stroke gut dysbiosis linked to ~25% ↑ risk of secondary CVD	Age, smoking	N/A
Kitai & Tang (2018)	USA	Review	20 studies	HF	Microbiome	HF outcomes	Gut congestion exacerbates dysbiosis → ~30% ↑ rehospitalization	Diabetes	N/A
Palmu et al. (2021)	Finland	Systematic Review	19 studies	Hypertension	Gut modulation	BP control	Probiotic therapies lowered BP by 4–5 mmHg	BMI	$p < 0.05$

Table 2. GRADE Summary Table

Outcome	No. of Studies	Effect	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty
TMAO & CVD Risk	10	RR 2.2 *(Desai et al.)*	Moderate	Moderate	Low	Moderate	Possible	Moderate
SCFAs & Blood Pressure	7	HR 0.77 *(Verhaar et al.)*	Low	Low	Low	Low	Unlikely	High
Probiotics & Blood Pressure	8	SBP ↓ ~5 mmHg *(Singh et al.)*	Low	Low	Low	Low	Unlikely	High

Table 3. Summary of Findings Table

Outcome	Population	Comparison	Effect Estimate (RR/OR)	Participants	Certainty (GRADE)	Notes
Elevated TMAO and CVD	Heart failure patients	High vs Low TMAO	RR 2.2	~1,500	Moderate	Linked to readmission
SCFAs and Hypertension	Hypertensive adults	High vs Low SCFAs	HR 0.77	~1,340	High	Associated with lower BP odds
Probiotics and BP	Adults with HTN/CVD	Probiotics vs Placebo	SBP ↓ ~5 mmHg	~1,200	High	Greatest effect in mild HTN

4. DISCUSSION

This review confirms the growing recognition that gut–brain communication pathways significantly contribute to the development and progression of major cardiovascular conditions, including heart failure, hypertension, atherosclerosis, and stroke. High-quality evidence indicates that gut microbial dysbiosis is a modifiable factor influencing cardiac risk profiles *(Desai et al., 2023; Singh et al., 2024)*. Gut-derived metabolites such as TMAO and SCFAs act as molecular mediators, modulating vascular inflammation, endothelial function, and cardiac remodeling *(Abdulrahim et al., 2025; Verhaar et al., 2020)*.

The association between gut dysbiosis and heart failure is particularly noteworthy. Elevated TMAO concentrations in chronic heart failure patients can double the risk of rehospitalization *(Desai et al., 2023)*. Increased gut permeability allows bacterial endotoxins to enter circulation, triggering inflammation and worsening cardiac dysfunction *(Kitai & Tang, 2018)*. These mechanisms help explain recurrent hospitalizations and poor prognosis in heart failure cohorts.

Evidence linking gut microbiota to hypertension is also compelling. Individuals with greater microbial diversity exhibit lower blood pressure and reduced arterial stiffness *(Verhaar et al., 2020; Palmu et al., 2021)*. SCFAs appear to modulate sympathetic nervous system activity through vagal pathways, resulting in better blood pressure control *(Yang & Zubcevic, 2017; Kwon & Kim, 2021)*. Excessive salt intake may further disrupt the gut microbiota, promoting inflammation and worsening hypertension *(Braga et al., 2020)*.

This pathway is also relevant to neurovascular conditions. Age-related dysbiosis may elevate stroke risk by promoting neuroinflammation *(Honarpisheh et al., 2022)*. Post-stroke alterations in gut composition can exacerbate cardiac complications via the brain–heart axis *(Chen et al., 2024)*. These multi-organ interactions underline the systemic importance of the gut–brain–heart network.

Probiotics and dietary interventions show promise for modulating this axis. For example, probiotics produced modest LDL and SBP reductions and improved cardiac remodeling in preclinical and early-phase human studies *(Karmazyn & Gan, 2023; Dinakis et al., 2024)*. However, larger randomized controlled trials are needed to validate these preliminary findings and establish clear clinical guidelines *(Shariff et al., 2024)*.

In addition to diet and microbial interventions, structured physical activity and supervised exercise therapy may beneficially influence the gut microbiota. Evidence suggests that aerobic and resistance training can enhance microbial diversity and promote beneficial metabolite production. Incorporating sport and physical therapy programs may therefore complement microbiome-targeted interventions to reduce cardiovascular risk.

Despite advances, current evidence is limited by heterogeneity in study design and population characteristics. Observational designs, small sample sizes, and variability in measurement tools reduce the generalizability of findings. Future studies should integrate multi-omics approaches and advanced imaging to clarify the causal pathways linking gut–brain interactions and cardiovascular outcomes *(O'Donnell et al., 2023; Nesci et al., 2023)*.

Given the complexity of microbiome–host interactions, personalized strategies considering baseline microbiota profiles, dietary patterns, and genetic factors are likely to be more effective than uniform recommendations. These approaches align with the principles of precision medicine in cardiology.

5. CONCLUSION

This systematic review supports the concept that gut–brain communication contributes meaningfully to the pathogenesis of major cardiovascular diseases. Evidence remains largely associative between gut dysbiosis, microbial metabolites, neuroimmune signaling, and cardiovascular dysfunction, indicating that the gut microbiota may represent a novel therapeutic target.

However, translating mechanistic insights into clinical benefit requires robust trials, mechanistic studies, and tailored interventions. Integrating microbiome science with established cardiovascular prevention strategies — including dietary changes, structured exercise, and personalized medical care — may help address residual cardiovascular risk that standard pharmacotherapies alone cannot fully resolve.

6. LIMITATIONS

This review has certain limitations. First, the included studies were heterogeneous in design, population, and outcome measures, which precluded quantitative meta-analysis. Second, much of the evidence comes from observational studies or animal models, limiting causal interpretation. Third, the search was restricted to English-language publications and may have overlooked relevant non-English studies. Lastly, while most studies adjusted for major confounders, residual confounding cannot be entirely ruled out.

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