

Pathomechanisms of Heart–Brain–Gut Axis Interactions in Cardiovascular Disease: A Systematic Review and Evidence Mapping

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Abstract

cardiovascular disease (CVD) remains the main cause of morbidity and mortality in the world. Current scientific evidence shows that the interaction between the gut microbiota, central nervous system, and cardiovascular system known as the heart–brain–gut axis plays an important role in maintaining cardiovascular homeostasis and the development of various heart diseases. This research uses systematic review and evidence mapping methods based on PRISMA guidelines. A literature search was conducted on PubMed, ScienceDirect, Google Scholar, and ProQuest databases for articles published in 2021–2026. Articles that met inclusion criteria were extracted, narratively synthesized, and mapped to identify key mechanisms and research gaps. A total of 20 articles met the inclusion criteria, consisting of 15 literature-based articles and 5 original research articles. Evidence mapping results show that systemic inflammation is the most dominant mechanism, especially in coronary artery disease and atherosclerosis. Other important mechanisms include trimethylamine-N-oxide (TMAO), endothelial dysfunction, short-chain fatty acids (SCFA), and the autonomic nervous system. Dysbiosis of the gut microbiota contributes to cardiovascular disease through increased proinflammatory metabolites, activation of immune responses, oxidative stress, and endothelial damage. Additionally, neural pathways via the vagus nerve and hypothalamic–pituitary–adrenal (HPA) axis mediate bidirectional communication between the gut and brain that influences cardiovascular function. The heart–brain–gut axis is an integrated biological system that connects the gut microbiota, nervous system, immune system, and cardiovascular system. Systemic inflammation, TMAO, endothelial dysfunction, and microbiota dysbiosis are the main mechanisms underlying this association. Modulation of the gut microbiota has the potential to be a preventive and therapeutic strategy in the prevention and management of cardiovascular disease.

Introduction

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide, with a significant contribution to the global health burden. Although classic risk factors such as hypertension, dyslipidemia, diabetes mellitus, and unhealthy lifestyles have long been known, understanding of the pathomechanism of heart disease continues to develop along with the discovery of complex interactions between organ systems, especially through the concept of the heart–brain–gut axis. This concept highlights the existence of dynamic bidirectional communication between the cardiovascular system, central nervous system, and

gastrointestinal system that is mediated by various biological pathways, including neural, hormonal, immunological, and metabolic (Zhang et al., 2024).

Research developments in recent years indicate that gut microbiota plays a central role in the regulation of cardiovascular function through what is known as the gut–heart axis. The gut microbiota consists of trillions of microorganisms that produce various bioactive metabolites such as short-chain fatty acids (SCFAs), trimethylamine-N-oxide (TMAO), and other compounds that can influence systemic inflammation, endothelial function, and lipid and glucose metabolism (Makkieh et al., 2026). Gut microbiota dysbiosis has been associated with various cardiovascular conditions, including atherosclerosis, hypertension, heart failure, and myocardial infarction (Abdulrahim et al., 2025).

Apart from that, the interaction between the intestines and the brain (gut–brain axis) also plays an important role in modulating the cardiovascular system. Communication between the gut and the brain occurs through neural pathways (especially the vagus nerve), the endocrine system (eg stress hormones), and immune mediators such as pro-inflammatory cytokines. Disruption of this axis can lead to activation of the sympathetic nervous system and increased inflammatory response, ultimately contributing to cardiac dysfunction. Thus, the connection between the brain and the heart is not only direct, but is also mediated by changes in the gut microbiota (Młynarska et al., 2024).

Furthermore, the heart–brain–gut axis concept describes the integration of these three systems in a complex communication network. Gut microbiota can influence brain function through the production of neurotransmitters and neuroactive metabolites, which then modulate the activity of the autonomic nervous system towards the heart. On the other hand, conditions of psychological stress or neurological disorders can affect the composition of the intestinal microbiota and increase intestinal permeability (leaky gut), thereby triggering systemic inflammation which has an impact on heart function (Zhang, et al., 2024).

Research by Kondapalli, et al (2025) also shows that microbiota metabolites such as TMAO have an important role in the pathogenesis of cardiovascular disease through increasing oxidative stress, inflammation and endothelial dysfunction. In addition, SCFAs are known to have protective effects on the heart through modulating the immune system and energy metabolism (Kondapalli et al., 2025). This shows that the balance of gut microbiota greatly determines heart health through mechanisms involving interactions between the gut, brain and heart.

However, understanding of the pathomechanism of heart–brain–gut axis interactions is still not completely clear and continues to develop. Many mechanistic aspects still require further research, including the specific role of certain microorganisms, the molecular signaling pathways involved, and their clinical implications in the prevention and therapy of cardiovascular diseases (Darby et al., 2023; Chiquito-Contreras et al., 2024). Therefore, a comprehensive literature review is needed to integrate the latest findings regarding the interactions of these three systems.

Method

Research Types and Designs

This research is a qualitative study using a literature review method which aims to comprehensively examine the pathomechanism of heart–brain–gut axis interactions in heart health based on the results of published scientific research. The research design used is a narrative literature review, with a systematic approach in searching, selecting, evaluating and

synthesizing literature. This research does not involve subjects directly, but uses secondary data in the form of relevant scientific articles.

Data source

The data used in this research is secondary data obtained from Scopus indexed scientific articles and reputable international databases, including: PubMed, ScienceDirect, Google Scholar and ProQuest. The articles used come from reputable international journals with a publication year range of 2021–2026 to ensure data freshness and scientific relevance. The literature search process was carried out using a combination of keywords and Boolean operators (AND, OR) which were adapted to each database. Keywords used included: "heart-brain-gut axis", "gut-heart axis", "gut microbiota" AND cardiovascular disease, "gut microbiome" AND cardiovascular health, "brain-gut-heart communication", "gut microbiota" AND heart disease, "gut microbiota" AND coronary heart disease, "gut microbiota" AND heart failure, "gut microbiota" AND arrhythmia, "microbiota-gut-brain axis" AND cardiovascular disease, "trimethylamine N-oxide (TMAO)" AND cardiovascular disease, "short-chain fatty acids" AND cardiovascular health, "gut dysbiosis" AND cardiovascular disease, "neurocardiology" AND gut microbiota, "heart-brain-gut axis" AND cardiovascular disease.

Literature Search Strategy (PRISMA Method)

The literature search strategy in this research was carried out systematically using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which aim to increase transparency, validity and reproducibility in the scientific article selection process. The PRISMA method consists of four main stages, namely identification, screening, eligibility, and inclusion.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were articles from international journals indexed by Scopus, published between 2021 and 2026, and written in English. Selected articles must address topics relevant to the research focus, namely the heart–brain–gut axis, gut microbiota and metabolites, and cardiovascular disease. Furthermore, the articles used must be available in full-text format to allow for comprehensive analysis.

Exclusion criteria for this study were articles not categorized as scientific journals, such as editorials, opinion pieces, blogs, or other forms of non-academic publications. Furthermore, articles with incomplete data, articles identified as duplicates, and articles irrelevant to the research topic were also excluded from the analysis process.

Literature Selection Procedure

The literature selection process in this research was carried out through several stages systematically. The first stage is identification, namely collecting articles from scientific databases using keywords that have been determined according to the research focus. The second stage is selection, namely screening the title and abstract to assess the relevance of the article to the research topic. Next, the eligibility stage is carried out by reading the article in full (full-text) to ensure its conformity with the predetermined inclusion criteria. The final stage is inclusion, namely entering articles that meet all the criteria into the analysis process. The entire literature selection process can be presented in the form of a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram to describe the stages of identification, selection, eligibility and inclusion in a more structured manner.

Data collection technique

The data in this research was collected through several stages. First, relevant articles are downloaded from predetermined scientific databases. Next, each article is read and understood thoroughly to obtain a clear picture of the content and contribution of the research. Important information from each article is then recorded, including the author's name and year of publication, research objectives, methods used, main results, and conclusions. The data that has been obtained is then arranged in the form of a literature synthesis table to facilitate the analysis process and compare the findings from the various studies studied.

Data Analysis Techniques

Data analysis in this study was conducted using a descriptive qualitative approach. The analysis process began with data reduction, which involved selecting and sorting information relevant to the research topic. Next, the obtained data were categorized based on key themes, such as gut microbiota, metabolites including short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and lipopolysaccharide (LPS), communication mechanisms within the heart–brain–gut axis, and their impact on the cardiovascular system. Data synthesis was then performed by combining findings from various literature sources to gain a more comprehensive understanding. The final stage was interpretation, which involved drawing conclusions based on the results of the literature analysis.

Data Validity and Reliability

The validity of the data in this study was maintained through the use of credible, relevant, and scientifically sound literature sources. The literature used was limited to Scopus-indexed international journal articles published between 2021 and 2026, ensuring that the analyzed findings reflect the latest research developments. Furthermore, cross-checking between literature sources was conducted to ensure consistency of information, strengthen the validity of interpretations, and minimize potential bias in the analysis. Therefore, the use of relevant and reliable references is essential for maintaining the validity and reliability of the results of this literature review.

Research Ethics

This research does not directly involve human subjects and therefore does not require ethical clearance. However, the researcher upholds research ethics by clearly citing reference sources, avoiding plagiarism, and using data in accordance with scientific principles.

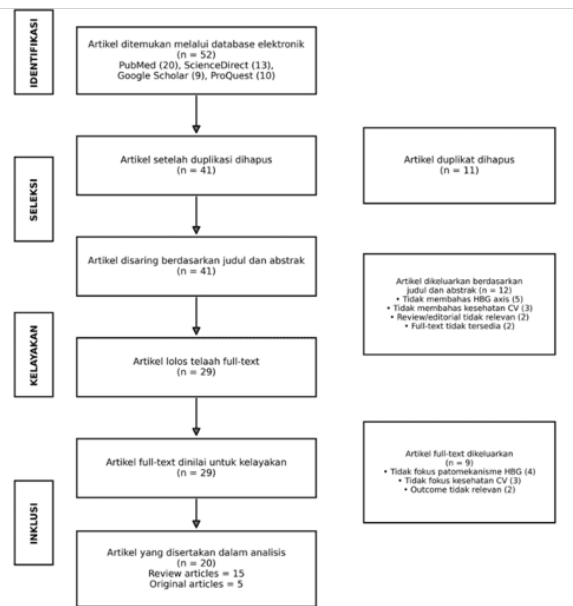


Figure 1. Operational Framework

Results And Discussion

Author & Year	Study Design	Research Focus	Heart–Brain–Gut Axis Mechanism	Key Findings
Bui et al., 2023	<i>Narrative review</i>	Gut–heart axis in CVD	Microbiota–metabolite (SCFA, TMAO), immune system, and enteric nervous system interactions → affect heart function	Dysbiosis increases systemic inflammation and atherosclerosis; the microbiota plays a role in neuro-immune regulation and vascular function
Zhang et al., 2025	<i>Review</i>	The role of microbiota in cardiovascular disease	Microbial metabolites (TMAO, LPS) → inflammatory activation, oxidative stress, endothelial dysfunction	Changes in microbiota composition significantly modulate CVD risk through metabolic and inflammatory pathways
Sagmeister et al., 2024	<i>Systematic review</i>	Microbiome modulation on CVD	Diet, probiotics, medications → alter microbiota → affect metabolites & systemic signals to heart and brain	Microbiota interventions have the potential to reduce CVD risk factors, but clinical evidence is still limited
Singh et al., 2024	<i>Review</i>	Gut–brain axis in cardiovascular disease	Neuroendocrine pathway (HPA axis), neurotransmitters, vagus nerve → connects brain–gut–heart	Stress and brain dysfunction trigger changes in the microbiota that impact heart function and blood pressure

American Heart Journal Plus, 2026	<i>Systematic review</i>	Gut microbiota and CVD	SCFA, TMAO → affect lipid metabolism, inflammation, endothelial function; interventions (probiotics, diet, FMT)	Targeting the microbiota is a potential therapeutic strategy for the prevention and management of CVD
Wang et al., 2022, Molecular Biomedicine	<i>Review</i>	The role of gut microbiota in cardiovascular health and disease	The role of gut microbiota in cardiovascular health & disease	Microbiota plays a role in blood pressure regulation, atherosclerosis, and heart failure
Russo et al., 2024, Frontiers in Cardiovascular Medicine	<i>Review</i>	Microbiota–host metabolic interactions (superorganism concept)	Tryptophan metabolism → immune and nervous system modulation → affects heart function	The interaction of microbiota and host forms an integrated metabolic system that influences heart disease
Hindson, 2024, Nature Reviews Gastroenterology & Hepatology	<i>Research highlight</i>	Multi-omics microbiome–CVD relationship	Microbiotas modulate cholesterol metabolism through specific enzymes → direct effects on the heart	Identification of bacteria (e.g. Oscillibacter) that influence lipid metabolism and CVD risk
Abdulrahim et al., 2025, Annals of Medicine & Surgery	<i>Review</i>	Dysbiosis and cardiovascular disease progression	Abnormal microbiota ratio → increased proinflammatory metabolites → endothelial dysfunction	Dysbiosis increases systemic inflammation and accelerates atherosclerosis
Rezabakhsh et al., 2025, Cell Communication and Signaling	<i>Review</i>	The role of Paneth cells in the gut–heart axis	Paneth cell dysfunction → damaged intestinal barrier → TMAO & LPS translocation → systemic inflammation	Dysbiosis increases systemic inflammation and accelerates atherosclerosis
Chong-Nguyen et al., 2026, Biology of Sex Difference	<i>Scoping & narrative review</i>	Sex-based microbiota differences in CAD	Microbes produce metabolites (TMAO, indoxyl sulfate) → modulate lipid metabolism and inflammation → hormonal–brain–gut interactions affect the heart	Significant differences were found between men and women in the composition of microbiota and metabolites that influence the pathogenesis of coronary artery disease
Ouyang et al., 2024, Heliyon	<i>Bibliometric analysis</i>	Research trends in the gut–heart axis in heart failure	<i>Bidirectional gut–heart crosstalk via microbial metabolites, inflammation, and the autonomic nervous system</i>	Gut–heart interactions play an important role in the progression of heart failure, with a significant increase in publications since 2018
Nesci et al., 2023, International Journal of Molecular Sciences	<i>Review</i>	Metabolic and inflammatory relationships of microbiota with CVD	Microbiota → production of metabolites (TMAO, SCFA) → activation of inflammation & oxidative stress → interaction with the nervous and vascular systems	The microbiota–CVD relationship is mediated by complex and interacting metabolic and

				inflammatory pathways
Jaimez-Alvarado et al., 2025, Frontiers in Biomedicines	<i>Review</i>	The role of microbiota in cardiovascular disease	Microbiota → metabolites (TMAO, LPS) → systemic inflammation + autonomic nervous system activation → effects on the heart	Changes in microbiota composition significantly influence CVD risk through inflammatory and neurohumoral pathways
Edpuganti et al., 2025, Heart Int.	<i>Review</i>	Microbiota mechanisms in cardiovascular health	Microbial metabolites (TMAO, SCFA) → regulation of lipid metabolism, inflammation, and endothelial function → interaction with nervous & immune systems	Microbiota has potential as a therapeutic target through modulation of metabolites and inflammation in CVD
Dai et al., 2024. BioData Mining.	<i>Bidirectional Mendelian Randomization Analysis</i>	Assessing the causal relationship between gut microbiota and various cardiovascular diseases	Gut dysbiosis affects the production of microbial metabolites, systemic inflammation, and autonomic nervous regulation that contribute to cardiovascular remodeling.	A bidirectional causal relationship was found between certain gut microbiota compositions and cardiovascular disease risk, suggesting that changes in the microbiota may be both a causal factor and a consequence of cardiovascular disease
Zhang, et al., 2022. Front Cardiovasc Med	<i>Two-Sample Mendelian Randomization Study</i>	Determining the causal relationship between gut microbiome and cardiovascular disease	Microbiota produce metabolites such as TMAO and SCFAs that influence inflammation, endothelial function, sympathetic activity, and neuroimmune responses.	Several bacterial genera have been linked to coronary artery disease, heart failure, and stroke. These results support the role of the microbiota as an important regulator of cardiovascular health
Hu, et al., 2024. Front. Cardiovasc. Med	<i>Two-Sample Mendelian Randomization Study</i>	Assessing the relationship of gut microbiota to coronary heart disease (CHD) risk	Microbiotas modulate lipid metabolism, vascular inflammation, and gut–brain communication through immune mediators and metabolites	Several bacterial taxa were found to be protective or to increase the risk of CHD, suggesting that the composition of the microbiota contributes to the atherosclerosis process
Li, et al., 2024. BMC Cardiovasc Disord.	<i>Mendelian Randomization Study</i>	Investigating the causal relationship of gut flora, serum	Dysbiosis causes changes in circulating metabolites that can affect the autonomic nervous system, cardiac electrical	Several microbiota-mediated metabolites have been shown to be associated with

		metabolites, and arrhythmias	conduction, and myocardial remodeling.	increased risk of arrhythmias, indicating the presence of a gut–metabolite–heart pathway in cardiac rhythm disturbances
Chechi, et al., 2026. Nat Commun	<i>Multi-cohort Observational Study, Metabolomics, Genomics, dan Mediation Analysis</i>	Identifying the gut microbiome–kidney–heart axis as a predictor of future cardiovascular disease front	Microbiotas metabolize phenylalanine and tyrosine into metabolites such as phenylacetylglutamine, 4-cresyl sulfate, and vanillactate that influence kidney function, cardiac neurohormonal regulation (pro-ANP), and CVD risk.	A gut microbiome–kidney–heart axis has been identified, detectable even in healthy individuals. Microbial metabolites are key mediators of communication between organs and are associated with future cardiovascular disease.

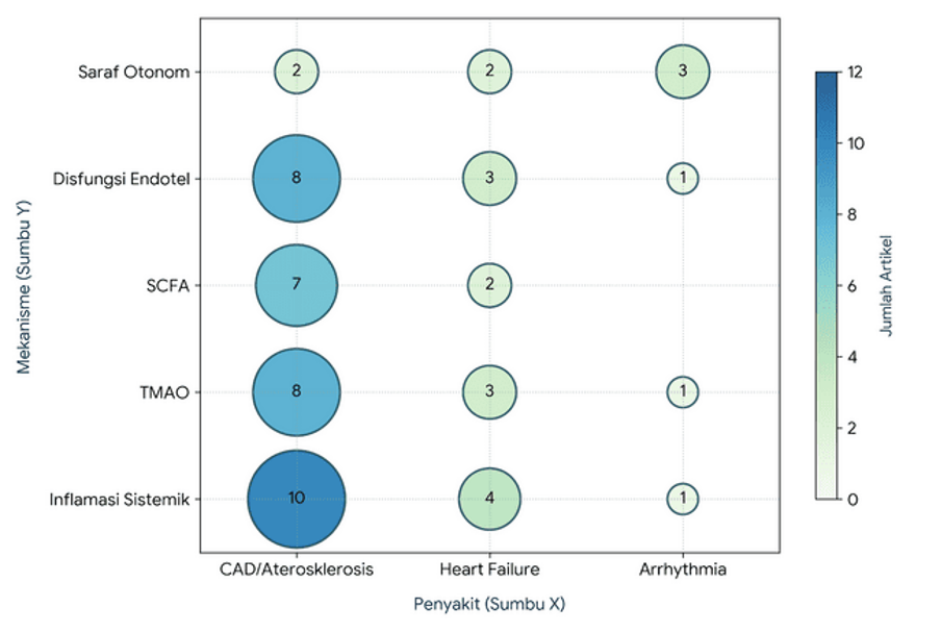


Figure 2. Bubble Evidence Map of Heart–Brain–Gut Axis Mechanisms in Heart Health

Figure 2. shows a Bubble Evidence Map depicting the distribution of scientific evidence regarding the key mechanisms of the heart–brain–gut axis and their association with various cardiovascular outcomes. The size of the bubble represents the number of articles supporting the association between a mechanism and a specific cardiovascular outcome, so a larger bubble indicates a greater body of evidence in the literature. Evidence mapping results indicate that systemic inflammation is the most dominant mechanism in the heart–brain–gut axis interaction. This mechanism is most commonly associated with coronary artery disease and atherosclerosis, suggesting that the chronic inflammatory response is a key pathway linking gut microbiota dysbiosis to cardiovascular disorders. Activation of pro-inflammatory cytokines, increased intestinal permeability, and oxidative stress contribute to endothelial damage and atherosclerotic plaque formation.

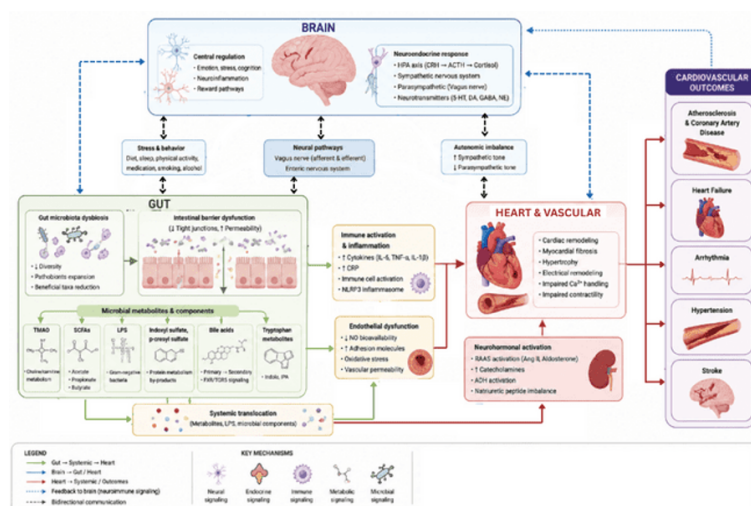


Figure 3. Network Diagram of the Heart–Brain–Gut Axis. Source: Primary Data, 2026

The microbiota metabolite trimethylamine-N-oxide (TMAO) has also been identified as an important mechanism widely reported in the literature. Most studies link elevated TMAO levels to the risk of atherosclerosis, coronary heart disease, and heart failure through increased vascular inflammation, platelet activation, and impaired lipid metabolism.

In addition to TMAO, short-chain fatty acids (SCFAs) and endothelial dysfunction are frequently reported mechanisms. SCFAs play a protective role through immune system regulation, improving intestinal barrier integrity, and controlling blood pressure. Conversely, endothelial dysfunction is a key mediator linking inflammation and oxidative stress to cardiovascular disease.

The bubble evidence map also shows that mechanisms involving the autonomic nervous system, the HPA axis, and the vagus nerve are relatively understudied compared to inflammatory mechanisms and microbiota metabolites. Nevertheless, these neuroendocrine pathways play a crucial role in bidirectional communication between the gut, brain, and heart, particularly in blood pressure regulation, stress responses, and heart rhythm disturbances.

The evidence map shows that research on the heart–brain–gut axis is still dominated by inflammatory and metabolic mechanisms, while neurocardiology and neural communication aspects require further exploration to strengthen our understanding of the biological connections between the gut, brain, and heart.

Summary of Evidence

Based on a systematic review of 15 studies encompassing various research designs, including narrative reviews, systematic reviews, and bibliometric analyses, it was found that the heart–brain–gut axis interaction plays a significant role in the pathogenesis of cardiovascular disease (CVD). The majority of studies demonstrated a close link between gut microbiota dysbiosis and increased CVD risk through metabolic, inflammatory, and neuroendocrine mechanisms (Abdulrahim et al., 2025).

In general, findings indicate that the gut microbiota plays a key regulatory role in the production of various bioactive metabolites, such as trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFA), and lipopolysaccharide (LPS), which subsequently impact cardiovascular function. Studies by Bui et al. (2023) and Nesci et al. (2023) emphasized that these metabolites contribute to the activation of systemic inflammation and the formation of atherosclerosis (Zhuang et al., 2021). This finding is supported by Zhang et al. (2025) and Jaimez-Alvarado et

al. (2025) which showed that changes in microbiota composition significantly modulate CVD risk through inflammatory and oxidative stress pathways (Zhang et al., 2024; Jaimez et al., 2025).

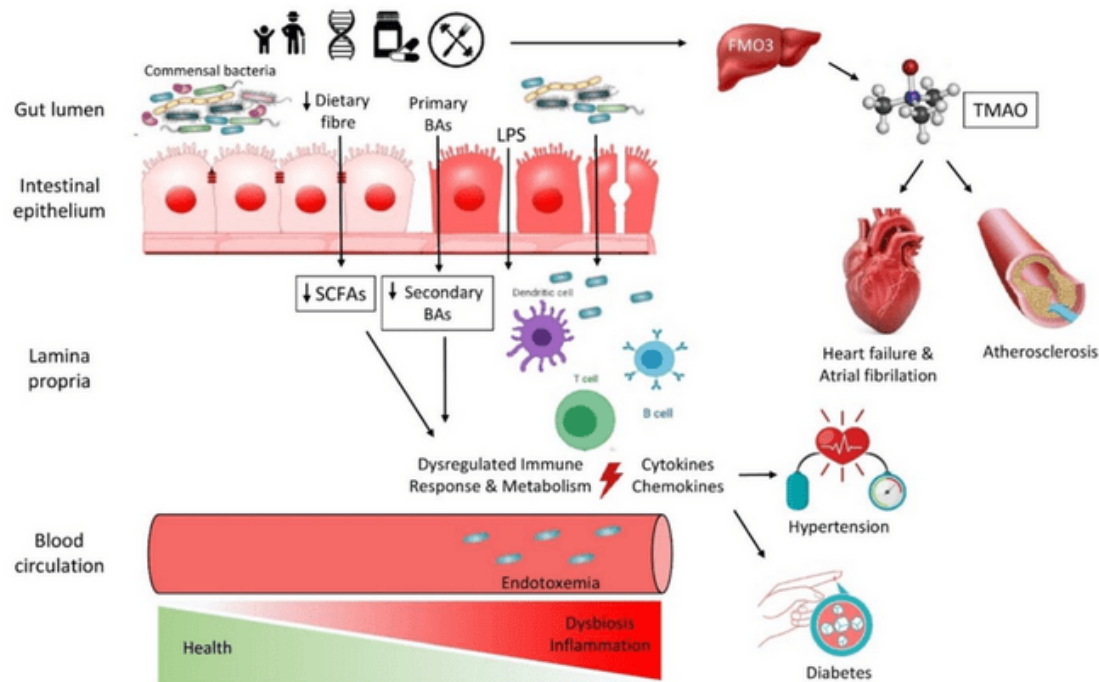


Figure 4. A simplified summary of the association between gut microbiota and traditional and non-traditional risk factors

TMAO: trimethylamine-N-oxide, LPS: lipopolysaccharide, FMO: flavin-containing monooxygenase, BAs: bile acids, SCFA: short-chain fatty acids. Source: (Singh, et al. 2024).

Furthermore, the synthesis also suggests that the interaction between the central nervous system and gut microbiota via the gut-brain axis plays a role in regulating heart function. Singh et al. (2024) revealed that activation of neuroendocrine pathways such as the hypothalamic-pituitary-adrenal (HPA) axis and involvement of the vagus nerve are important mediators of bidirectional communication between the brain and the gut, ultimately impacting blood pressure and heart function (Singh et al., 2024).

Clinically, several studies, such as those by Sagmeister et al. (2024) and a publication in the American Heart Journal Plus (2026), suggest that microbiota modulation through interventions such as diet, probiotics, and fecal microbiota transplantation (FMT) has the potential to reduce cardiovascular risk factors, although clinical evidence is still limited and requires further research (Sagmeister et al., 2024; Makkieh et al., 2026).

Interestingly, Chong-Nguyen et al. (2026) found sex-based differences in microbiota composition and metabolites that play a role in coronary artery disease, suggesting that biological factors such as hormones also influence heart-brain-gut axis interactions [25]. Furthermore, a multi-omics approach reported by Hindson (2024) identified specific bacteria that play a role in lipid metabolism, strengthening the concept that the microbiota is part of an integrated metabolic system (superorganism concept) Hindson (2024).

Overall, the available evidence suggests that the heart-brain-gut axis is a complex system involving multidirectional interactions between the gut microbiota, the nervous system, the immune system, and the cardiovascular system. However, there is heterogeneity between

studies regarding the methods, populations, and parameters used, so interpretation of the results requires caution.

The Role of Gut Microbiota in Cardiovascular Pathophysiology

Gut microbiota is a key component in regulating body homeostasis and plays a crucial role in the pathophysiology of cardiovascular disease. Under normal conditions, the gut microbiota maintains metabolic balance, immune function, and gut barrier integrity. However, changes in microbiota composition, or dysbiosis, can trigger various pathological mechanisms that contribute to the development of CVD (Merino et al., 2024).

One key mechanism is through the production of microbial metabolites such as TMAO. TMAO is produced from the metabolism of choline and carnitine by gut microbiota, which are then oxidized in the liver. Several studies on this synthesis, including those by Zhang et al. (2025) and Edpuganti et al. (2025), have shown that elevated TMAO levels are associated with an increased risk of atherosclerosis through mechanisms such as increased cholesterol deposition, inflammatory activation, and endothelial dysfunction. TMAO is also known to play a role in increasing platelet aggregation, which can exacerbate cardiovascular events (Edpuganti et al., 2025; Makkieh et al., 2026).

In addition to TMAO, other metabolites such as SCFAs (acetate, propionate, and butyrate) have protective effects on the cardiovascular system. SCFAs play a role in lowering blood pressure, improving endothelial function, and possessing anti-inflammatory effects. However, in conditions of dysbiosis, SCFA production can decrease, thus eliminating these protective effects. This contributes to increased inflammation and vascular disorders (Nesci et al., 2023).

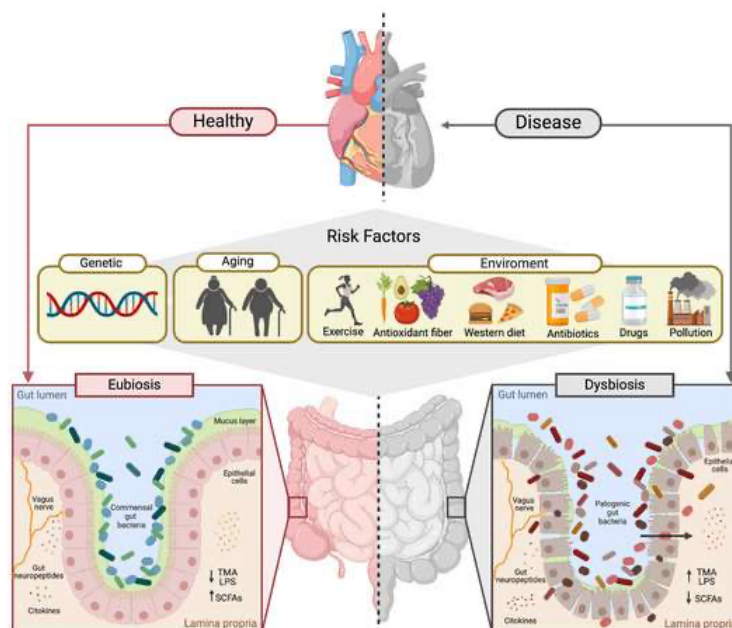


Figure 5. The Gut–Heart Axis. Source: Rezabakhsh, et al., 2025

Lipopolysaccharide (LPS), a component of the cell wall of Gram-negative bacteria, also plays a crucial role in the pathogenesis of CVD. In conditions of dysbiosis and intestinal barrier disruption, as described by Rezabakhsh et al. (2025), increased intestinal permeability (leaky gut) occurs, allowing LPS to translocate into the systemic circulation. LPS then activates the immune response through the Toll-like receptor (TLR) pathway, triggering systemic inflammation and contributing to endothelial dysfunction and atherosclerosis (Rezabakhsh et al., 2025).

In addition to metabolic and inflammatory pathways, the gut microbiota also interacts with the nervous system through the gut-brain axis. Tryptophan metabolism by the microbiota, as described by Russo et al. (2024), produces metabolites that can influence the central nervous system and immune responses, ultimately impacting cardiac function. These interactions suggest that the microbiota plays a role not only locally in the gut but also systemically through neurohumoral pathways (Russo et al., 2024).

Furthermore, the gut microbiota also influences blood pressure regulation through interactions with the autonomic nervous system and the renin–angiotensin system. Wang et al. (2022) demonstrated that changes in the microbiota can influence vasoconstriction, sodium retention, and inflammatory responses, all of which contribute to hypertension (Wang et al., 2022).

The concept of the “superorganism” proposed by Russo et al. (2024) emphasizes that the microbiota and the human host form an integrated metabolic system. Therefore, microbiota disturbances impact not only the gastrointestinal tract but also the entire cardiovascular system (Russo et al., 2024).

Thus, it can be concluded that the gut microbiota plays a role in cardiovascular pathophysiology through three main mechanisms: (1) production of bioactive metabolites (TMAO, SCFA, LPS), (2) activation of systemic inflammation and oxidative stress, and (3) interaction with the nervous and neuroendocrine systems. These mechanisms interact and form the biological basis of the heart–brain–gut axis in the development of cardiovascular disease (Bui et al., 2023; Kang & Wang, 2024; Russo et al., 2024).

Brain–Gut Axis Mechanisms in Cardiovascular Regulation

The brain–gut axis is a complex two-way communication system between the central nervous system (CNS) and the gastrointestinal tract, mediated by neural, endocrine, and immune pathways. In the context of cardiovascular health, the brain–gut axis plays a crucial role in linking psychological responses, gut microbiota activity, and cardiac function, thus becoming a key component of the heart–brain–gut axis concept Kang & Wang (2024).

One of the key mechanisms in the brain–gut axis is the involvement of the autonomic nervous system (ANS), which consists of the sympathetic and parasympathetic nervous systems. Activation of the sympathetic nervous system, particularly under conditions of chronic stress, can increase heart rate, blood pressure, and vascular resistance. Conversely, the parasympathetic system, mediated by the vagus nerve, has a protective effect by reducing inflammation and stabilizing cardiac function. Singh et al. (2024) showed that disruption of the balance between sympathetic and parasympathetic nervous systems can trigger changes in the composition of the gut microbiota, which ultimately impacts cardiovascular function (Singh et al., 2024).

In addition to neural pathways, the brain–gut axis also involves neuroendocrine pathways, particularly through activation of the hypothalamic–pituitary–adrenal (HPA) axis. Psychological stress activates the hypothalamus to release corticotropin-releasing hormone (CRH), which then stimulates the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland, ultimately increasing cortisol production from the adrenal glands. Long-term elevated cortisol levels can lead to gut microbiota dysbiosis, increased intestinal permeability (leaky gut), and activation of systemic inflammation. These conditions contribute to endothelial dysfunction, hypertension, and atherosclerosis (Ma, 2025).

Furthermore, the gut microbiota also plays a role in modulating brain function through the production of neurotransmitters and neuroactive metabolites, such as serotonin, gamma-aminobutyric acid (GABA), and tryptophan metabolites. Russo et al. (2024) explained that

tryptophan metabolism by microbiota produces compounds that can affect the central nervous system and immune responses. An imbalance in these metabolites can trigger neuroinflammation, which in turn impacts cardiovascular regulation through increased sympathetic nervous system activity (Russo et al., 2024).

The interaction between the brain-gut axis and the immune system is also an important mechanism in cardiovascular regulation. Immune system activation due to the translocation of lipopolysaccharide (LPS) from the gut to the systemic circulation can stimulate the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). These cytokines not only affect peripheral tissues but can also influence brain function through neuroinflammatory pathways, further amplifying activation of the HPA axis and the sympathetic nervous system. This creates a feedback loop that worsens cardiovascular conditions (Snelson et al., 2025).

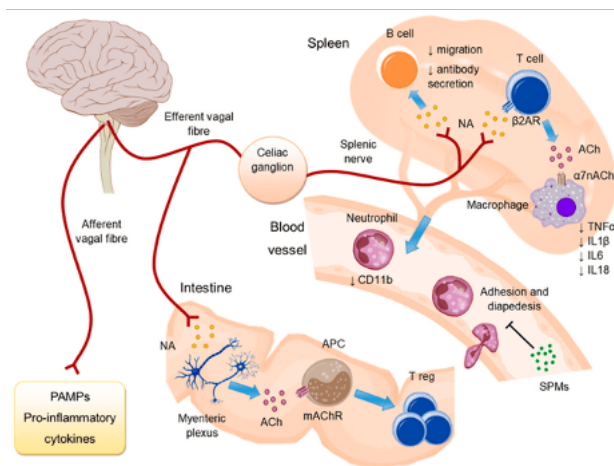


Figure 7. Cholinergic anti-inflammatory pathway. Source: (Nesci, et al., 2023)

Furthermore, the vagus nerve serves as a key communication pathway between the gut and the brain. Vagal activation has anti-inflammatory effects through the "cholinergic anti-inflammatory pathway," which can suppress the production of pro-inflammatory cytokines. However, in conditions of dysbiosis and chronic stress, vagal function can be impaired, reducing this protective effect. Decreased vagal tone has been linked to an increased risk of arrhythmias, heart failure, and coronary heart disease (Nesci et al., 2023).

In a clinical context, the brain-gut axis also explains the relationship between psychosocial factors, such as stress, anxiety, and depression, and an increased risk of cardiovascular disease. Chronic stress not only affects heart function directly through activation of the nervous and hormonal systems, but also indirectly through changes in the gut microbiota and increased systemic inflammation (Cryan, 2019).

Thus, the brain-gut axis mechanism in cardiovascular regulation involves a complex interaction between the autonomic nervous system, the HPA axis, the gut microbiota, and the immune system. Disruption of any of these components can trigger a systemic imbalance that contributes to the development of cardiovascular disease. Therefore, therapeutic approaches targeting the brain-gut axis, such as stress management, microbiota modulation, and neuropsychological interventions, have potential in the prevention and management of cardiovascular disease (Merino et al., 2024).

Bidirectional Heart–Brain–Gut Axis Interactions

The heart–brain–gut axis interaction is a multidirectional communication system involving reciprocal relationships between the heart, brain, and gastrointestinal tract. Unlike traditional linear concepts, this axis operates through dynamic mechanisms involving neural, endocrine, immune, and metabolic pathways, forming a complex systemic regulatory network (Hindson, 2024).

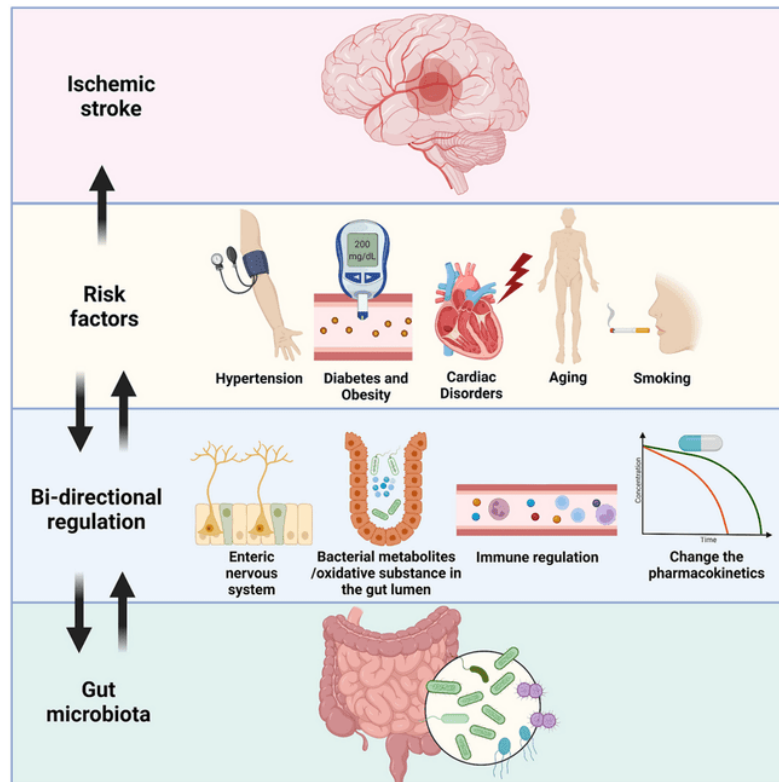


Figure 8. Bidirectional Heart–Brain–Gut Axis. (Ouyang, et al., 2024).

One key component of this interaction is communication between the heart and brain via the autonomic nervous system. Cardiac dysfunction, such as in heart failure or coronary artery disease, can overactivate the sympathetic nervous system, which then influences regulatory centers in the brain. This chronic sympathetic activation not only impairs cardiac function but also impacts the gastrointestinal tract through reduced intestinal perfusion and altered gastrointestinal motility. This condition can trigger gut microbiota dysbiosis, which further worsens cardiovascular conditions through increased systemic inflammation (Ouyang et al., 2024).

Conversely, changes in the gut microbiota can also directly and indirectly affect cardiac function. Dysbiosis leads to increased production of proatherogenic metabolites such as TMAO and LPS, which contribute to endothelial dysfunction, oxidative stress, and atherosclerotic plaque formation. Studies such as those by Abdulrahim et al. (2025) and Nesci et al. (2023) indicate that increases in these metabolites correlate with the progression of cardiovascular disease. Furthermore, intestinal barrier disruption (leaky gut), as described by Rezaabakhsh et al. (2025), allowing endotoxin translocation into the systemic circulation, triggering a chronic inflammatory response (Nesci et al., 2023; Rezaabakhsh et al., 2025).

The interaction between the brain and the heart is also mediated by psychological and neuroendocrine factors. Chronic stress and mental disorders such as depression and anxiety can

activate the HPA axis and increase stress hormone levels, which can lead to increased blood pressure, vascular dysfunction, and changes in the gut microbiota. Singh et al. (2024) emphasized that stress not only directly impacts the heart but also through modulation of the microbiota and immune system (Singh et al., 2024).

Furthermore, this bidirectional communication forms a pathological feedback loop. For example, cardiac dysfunction leads to intestinal hypoperfusion and dysbiosis, which in turn increases the production of pro-inflammatory metabolites and worsens cardiac conditions. At the same time, systemic inflammation and neuroinflammation can amplify activation of the sympathetic nervous system and the HPA axis, creating a self-perpetuating cycle.

This concept is reinforced by the “superorganism” approach described by Russo et al. (2024), in which the human body and its microbiota are viewed as a single, integrated biological system. In this context, disruption of one component will have a broad impact on other systems, including the heart and brain. Furthermore, findings by Chong-Nguyen et al. (2026) suggest that biological factors such as gender also modulate this interaction, indicating that the heart–brain–gut axis is complex and influenced by multiple intrinsic and extrinsic factors (Russo et al., 2024; Chong et al., 2026).

Thus, the bidirectional interaction of the heart–brain–gut axis suggests that cardiovascular disease is not simply a single-organ disorder, but rather a manifestation of systemic dysfunction involving cross-organ communication. This approach opens new opportunities for understanding the pathogenesis of CVD holistically and for developing more comprehensive therapeutic strategies (Snelson et al., 2025).

Integration of Evidence Map Results with Biological Mechanisms

Integrating Evidence Map results with biological mechanisms is a crucial step in linking quantitative findings to their underlying pathophysiological basis. Based on the synthesis of the analyzed studies, there is consistency between empirical data and biological mechanisms explaining the role of the heart-brain-gut axis in cardiovascular disease.

Overall, Evidence Map results indicate a significant association between gut microbiota dysbiosis and an increased risk of cardiovascular disease. This association may be explained by increased levels of metabolites such as TMAO and LPS, which have been shown to contribute to systemic inflammation, endothelial dysfunction, and atherosclerosis. Studies by Zhang et al. (2025) and Edpuganti et al. (2025) support these findings by demonstrating that microbial metabolites have a direct effect on lipid metabolism and vascular function (Zhuang et al., 2024; Edpuganti et al., 2025).

Furthermore, Evidence Map results also demonstrate an association between inflammatory markers (such as CRP, IL-6, and TNF- α) and cardiovascular outcomes. This aligns with biological mechanisms suggesting that chronic inflammation is a key mediator in the pathogenesis of CVD. Immune system activation due to LPS translocation and microbiota dysbiosis amplifies the inflammatory response, which impacts vascular damage and disease progression (Makkieh et al., 2026).

However, there is considerable heterogeneity among the studies analyzed. This variation may be due to differences in study design, population characteristics, microbiota measurement methods, and outcome parameters used. For example, some studies used a metabolomics approach to measure TMAO levels, while others used microbiota composition analysis, resulting in variations in the interpretation of the results.

The multi-omics approach reported by Hindson (2024) provides additional insights into understanding this relationship. By integrating genomic, metabolomics, and microbiomic data,

specific biological pathways linking the microbiota to cardiovascular function can be identified. This strengthens the validity of the Evidence Map findings and provides a stronger scientific basis for interpreting the results (Hindson, 2024).

Furthermore, the Evidence Map results also support the potential of microbiota-based interventions as a therapeutic strategy. A study by Sagmeister et al. (2024) demonstrated that interventions such as probiotics and dietary modifications can influence the composition of the microbiota and its metabolites, ultimately resulting in reduced cardiovascular risk. However, limited clinical evidence and the lack of randomized controlled trials (RCTs) pose challenges to the widespread application of these findings (Sagmeister et al., 2024).

The integration of quantitative results and biological mechanisms also demonstrates that the heart–brain–gut axis does not operate through a single pathway, but rather through a complex interaction between metabolic, inflammatory, and neuroendocrine pathways. Therefore, interpretation of Evidence Map results must take into account this complexity and the possibility of confounding factors that have not been fully controlled for.

Overall, the integration of Evidence Map results with biological mechanisms strengthens the conclusion that gut microbiota dysbiosis and impaired communication within the heart–brain–gut axis play a crucial role in the pathogenesis of cardiovascular disease. This approach not only improves understanding of the disease but also opens up opportunities for the development of more innovative, mechanism-based diagnostic and therapeutic strategies.

Conclusion

The heart-brain-gut axis is an integrated biological system that connects the gut microbiota, central nervous system, immune system, and cardiovascular system through bidirectional communication that plays a role in maintaining homeostasis and influencing the development of cardiovascular disease. Communication between the gut, brain, and heart occurs through neural, hormonal, immunological, and metabolic pathways, involving the autonomic nervous system, vagus nerve, HPA axis, inflammatory cytokines, and metabolites produced by the gut microbiota. The gut microbiota plays a key role in mediating the heart-brain-gut axis through the production of metabolites such as trimethylamine-N-oxide (TMAO), lipopolysaccharide (LPS), and short-chain fatty acids (SCFAs), which influence CNS function, immune response, and cardiovascular health. The main pathomechanisms underlying the relationship between the heart-brain-gut axis and cardiovascular disease are systemic inflammation, endothelial dysfunction, microbial dysbiosis, and impaired microbial metabolism. Gut microbiota modulation has potential as a preventive and therapeutic strategy for cardiovascular disease, through controlling inflammation, improving endothelial function, and regulating microbial metabolites. These findings support the development of microbiome-based approaches as novel targets for future cardiovascular disease prevention and therapy.

References

- Zhang, Y., Huang, K., Duan, J., Zhao, R., & Yang, L. (2024). Gut microbiota connects the brain and the heart: Potential mechanisms and clinical implications. *Psychopharmacology*, 241(1), 637–651. <https://doi.org/10.1007/s00213-024-06552-6>
- Makkieh, Y., Shah, H., & Imran, S. (2026). The gut-heart axis: Exploring the role of the gut microbiome in cardiovascular health—A focused systematic review. *American Heart Journal Plus: Cardiology Research and Practice*.
- Abdulrahim, A., Doddapaneni, N., Salman, N., Giridharan, A., Thomas, J., Sharma, K., Abboud, E., Rochill, K., Shreelakshmi, B., Gupta, V., Lakkimsetti, M., Mowo-Wale, A., & Ali, N. (2025). The gut-heart axis: A review of gut microbiota, dysbiosis, and

- cardiovascular disease development. *Annals of Medicine and Surgery*, 87(1), 177–191.
- Młynarska, E., Wasiak, J., Gajewska, A., Bilińska, A., Steć, G., Jasińska, J., Rysz, J., & Franczyk, B. (2024). Gut microbiota and gut–brain axis in hypertension: Implications for kidney and cardiovascular health—A narrative review. *Nutrients*, 16(23), 4079. <https://doi.org/10.3390/nu16234079>
- Kondapalli, N., Katari, V., Dalal, K., Paruchuri, S., & Thodeti, C. (2025). Microbiota in gut–heart axis: Metabolites and mechanisms in cardiovascular disease. *Comprehensive Physiology*, 15(3). <https://doi.org/10.1002/cph4.70024>
- Bui, T., Hwangbo, H., Lai, Y., Hong, S., Choi, Y., Park, H., & Ban, K. (2023). The gut–heart axis: Updated review for the roles of microbiome in cardiovascular health. *Korean Circulation Journal*, 53(8), 499–518. <https://doi.org/10.4070/kcj.2023.0048>
- Zhuang, M., Zhang, X., & Cai, J. (2024). Microbiota–gut–brain axis: Interplay between microbiota, barrier function and lymphatic system. *Gut Microbes*, 16(1). <https://doi.org/10.1080/19490976.2024.2387800>
- Snelson, M., Muralitharan, R., Liu, C., Markó, L., F. S. K., Marques, F., & Tang, W. (2025). Gut–heart axis: The role of gut microbiota and metabolites in heart failure. *Circulation Research*, 136(11), 1382–1406. <https://doi.org/10.1161/CIRCRESAHA.125.325516>
- Zhang, Y., Wu, H., Jin, M., Feng, G., & Wang, S. (2021). The gut–heart axis: Unveiling the roles of gut microbiota in cardiovascular diseases. *Frontiers in Cardiovascular Medicine*. <https://doi.org/10.3389/fcvm.2025.1572948>
- Ma, Z. L. Y. (2025). The role of the gut microbiota in health, diet, and disease with a focus on obesity. *Foods*, 14(3). <https://doi.org/10.3390/foods14030492>
- Carabotti, M., Scirocco, A., Maselli, M., & Severi, C. (2015). The gut–brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology*, 28(2), 203–209.
- Cryan, J. (2019). The microbiota–gut–brain axis. *Physiological Reviews*, 99(4).
- Al Bander, Z., Nitert, M., Mousa, A., & Naderpoor, N. (2020). The gut microbiota and inflammation: An overview. *International Journal of Environmental Research and Public Health*, 17(20), 7618. <https://doi.org/10.3390/ijerph17207618>
- Brown, J., & Hazen, S. (2018). Microbial modulation of cardiovascular disease. *Nature Reviews Microbiology*, 16(3), 171–181. <https://doi.org/10.1038/nrmicro.2017.149>
- Merino del Portillo, M., Clemente-Suárez, V., & Ruisoto, P. (2024). Nutritional modulation of the gut–brain axis: A comprehensive review of dietary interventions in depression and anxiety management. *Metabolites*, 14(10), 549. <https://doi.org/10.3390/metabo14100549>
- Sagmeister, A., Matter, C., Stähli, B., & Scharl, M. (2024). The gut–heart axis: Effects of intestinal microbiome modulation on cardiovascular disease—Ready for therapeutic interventions? *International Journal of Molecular Sciences*, 25(24). <https://doi.org/10.3390/ijms252413529>
- Ahmed, F., Alhodieb, F., & Alsanie, S. (2025). Relationship between stress, diet, and gut microbiota: A cross-sectional study. *Nutrition & Metabolism*. <https://doi.org/10.1186/s12986-025-01014-y>

- Kang, P., & Wang, A. (2024). Microbiota–gut–brain axis: The mediator of exercise and brain health. *Psychoradiology*, 4. <https://doi.org/10.1093/psyrad/kkae007>
- Clerici, L., Bottari, D., & Bottari, B. (2025). Gut microbiome, diet and depression: Literature review of microbiological, nutritional and neuroscientific aspects. *Current Nutrition Reports*, 14(30). <https://doi.org/10.1007/s13668-025-00619-2>
- Singh, A., Kishore, P., & Khan, S. (2024). From microbes to myocardium: A comprehensive review of the impact of the gut-brain axis on cardiovascular disease. *Cureus*, 16(10), e70877.
- Wang, L., Wang, S., & Zhang, Q. (2022). The role of the gut microbiota in health and cardiovascular diseases. *Molecular Biomedicine*, 3(30). <https://doi.org/10.1186/s43556-022-00091-2>
- Russo, M., Puccetti, M., Costantini, C., Giovagnoli, S., Ricci, M., Garaci, E., & Romani, L. (2024). Human and gut microbiota synergy in a metabolically active superorganism: A cardiovascular perspective. *Frontiers in Cardiovascular Medicine*, 11. <https://doi.org/10.3389/fcvm.2024.1411306>
- Hindson, J. (2024). Multi-omic links between gut microbiome and cardiovascular disease. *Nature Reviews Gastroenterology & Hepatology*, 21, 376. <https://doi.org/10.1038/s41575-024-00941-0>
- Rezabakhsh, A., Habtemariam, S., & Parvizi, R. (2025). The gut-heart axis: A correlation between Paneth cells' dysfunction, microbiome dysbiosis, and cardiovascular diseases. *Cell Communication and Signaling*, 23, 347. <https://doi.org/10.1186/s12964-025-02335-4>
- Chong-Nguyen, C., Fuentes Artilles, R., & Pilgrim, T. (2026). The gut–heart axis in coronary artery disease: A scoping and narrative review of sex-based microbial and metabolic disparities. *Biology of Sex Differences*, 17(4). <https://doi.org/10.1186/s13293-026-00824-w>
- Ouyang, J., Zhao, L., Song, Y., Qu, H., Du, T., Shi, L., Cui, Z., Jiang, Z., & Gao, Z. (2024). Trends in gut-heart axis and heart failure research (1993–2023): A bibliometric and visual analysis. *Heliyon*, 10(4), e25995.
- Nesci, A., Carnuccio, C., Ruggieri, V., D'Alessandro, A., Di Giorgio, A., Santoro, L., Gasbarrini, A., Santoliquido, A., & Ponziani, F. (2023). Gut microbiota and cardiovascular disease: Evidence on the metabolic and inflammatory background of a complex relationship. *International Journal of Molecular Sciences*, 24(10), 9087. <https://doi.org/10.3390/ijms24109087>
- Jaimez-Alvarado, S., López-Tenorio, I., Barragán-De los Santos, J., Bello-Vega, D., Gómez, F., Amedei, A., Berrios-Bárcenas, E., & Aguirre-García, M. (2025). Gut-heart axis: Microbiome involvement in restrictive cardiomyopathies. *Biomedicines*, 13(1), 144. <https://doi.org/10.3390/biomedicines13010144>
- Edpuganti, S., Subhash, S., Subrahmaniyan, S., Latheef, S., & Albarari, S. (2025). Gut microbiome and cardiovascular health: Mechanisms, therapeutic potential and future directions. *Heart International*, 19(2), 12–20.
- Dai, X., Yu, Y., & Zhou, S. (2024). Assessment of the causal relationship between gut microbiota and cardiovascular diseases: A bidirectional Mendelian randomization analysis. *BMC BioData Mining*, 17, 6. <https://doi.org/10.1186/s13040-024-00356-2>

- Zhang, Y., Zhang, X., Chen, D., Lu, J., Gong, Q., Fang, J., & Jiang, J. (2022). Causal associations between gut microbiome and cardiovascular disease: A Mendelian randomization study. *Frontiers in Cardiovascular Medicine*, 9. <https://doi.org/10.3389/fcvm.2022.971376>
- Hu, X., Fu, L., Ye, B., Ao, M., Yan, M., & Feng, H. (2024). Gut microbiota and risk of coronary heart disease: A two-sample Mendelian randomization study. *Frontiers in Cardiovascular Medicine*. <https://doi.org/10.3389/fcvm.2024.1273666>
- Li, K., Liu, P., & Liu, M. (2024). Putative causal relations among gut flora, serum metabolites and arrhythmia: A Mendelian randomization study. *BMC Cardiovascular Disorders*. <https://doi.org/10.3389/fcvm.2024.1273666>
- Chiquito-Contreras, C. J., Meza-Menchaca, T., Guzmán-López, O., Vásquez, E. C., & Ricaño-Rodríguez, J. (2024). Molecular insights into plant–microbe interactions: a comprehensive review of key mechanisms. *Frontiers in Bioscience-Elite*, 16(1), 9. <https://doi.org/10.31083/j.fbe1601009>
- Darby, E. M., Trampari, E., Siasat, P., Gaya, M. S., Alav, I., Webber, M. A., & Blair, J. M. (2023). Molecular mechanisms of antibiotic resistance revisited. *Nature Reviews Microbiology*, 21(5), 280-295. <https://doi.org/10.1038/s41579-022-00820-y>