

Gut Microbiome and Cardiovascular Health: Mechanisms, Therapeutic Potential and Future Directions

Sudeep Edpuganti, Shravan Subhash, Sujitha Lekshmi Subrahmaniyan, Shifna Latheef and Shams Samih Albarari

Faculty of Medicine, Tbilisi State Medical University, Tbilisi, Georgia

<https://doi.org/10.17925/HI.2025.19.2.3>

Background: The gut microbiome has a crucial role in host metabolism and immune regulation, and there is growing evidence that dysbiosis may be associated with the pathogenesis of cardiovascular disease (CVD). This narrative review provides an overview of the recent literature on mechanistic connections between the gut and heart, as well as on the therapeutic strategies and research gaps in the gut–heart axis. **Methods:** We conducted a systematic literature search on PubMed and Embase databases with MeSH and keyword terms: ‘gut microbiome’, ‘cardiovascular disease’, ‘TMAO’, ‘short-chain fatty acids’, ‘probiotics’ and ‘faecal microbiota transplantation’. We considered human and relevant animal studies focusing on mechanistic pathways or microbiome treatments and excluded editorials, small (less than 10 subjects) case series and articles not published in the English language. **Results:** Key microbiota-derived metabolites, trimethylamine N-oxide (TMAO) and short-chain fatty acids (SCFAs), contribute to atherogenesis, blood pressure and myocardial inflammation. Dysbiosis-induced barrier dysfunction and disturbed bile acid signalling also serve as the mediators of cardiac remodelling. Dietary fibre, probiotics/prebiotics, postbiotics and faecal microbiota transplantation are emerging interventions for the modulation of CVD risk. Nevertheless, most result from observational studies, whilst such are heterogeneous in sequencing platforms and too small to draw any definitive conclusions. **Conclusion:** The modulation of gut microbiome might be a new target for CVD prevention and treatment. Large-scale, standardized randomized trials with hard cardiovascular endpoints, as well as integrated multi-omics profiling, will be required to validate microbial biomarkers and to optimize microbiome-based interventions.

Keywords

Atherosclerosis, cardiovascular disease, gut microbiome, hypertension, inflammation, probiotics, fecal microbiota transplantation

Disclosures: Sudeep Edpuganti, Shravan Subhash, Subrahmaniyan Sujitha Lekshmi, Shifna Latheef and Shams Samih Albarari have no relevant financial or non-financial conflicts of interest to declare in relation to the content of this article.

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Access: This article is freely accessible at touchCARDIO.com. © Touch Medical Media 2025.

Received: 15 May 2025

Accepted: 29 August 2025

Published online: 24 November 2025

Citation: *Heart International*. 2025;19(2):Online ahead of journal publication

Corresponding author: Sudeep Edpuganti, Faculty of Medicine, Tbilisi State Medical University, 33 Vazha-Pshavla Ave, Tbilisi 0186, Georgia.
E: edpugantisudeep@gmail.com

Support: No funding was received for the publication of this article.

Cardiovascular disease (CVD) is one of the major causes of morbidity and mortality throughout the world.^{1,2} While traditional risk factors are managed intensively, many individuals continue to have considerable residual risk, and emerging factors such as inflammatory mediators are being investigated.^{1,2} In this light, the gut microbiota is increasingly recognized as a modifiable factor that influences cardiometabolic health.^{1,2} Recent studies have shown that dysbiosis is linked to various cardiovascular (CV) conditions, suggesting that gut–heart interactions play a role in diseases such as hypertension, diabetes, obesity, atherosclerosis and heart failure (HF).^{1,3}

Aim and objectives

This review aims to explore the role of gut microbiota in CV health and disease. It focuses on elucidating the mechanisms by which microbial metabolites influence CV pathophysiology, examining current evidence on dysbiosis in CVD and evaluating potential microbiome-targeted interventions while highlighting existing knowledge gaps and future research directions.

Gut–heart crosstalk: Rationale and mechanisms

Gut–heart crosstalk refers to the bidirectional communication between the intestinal microbiota and the CV system. Growing evidence connects CV pathophysiology and the gut microbiota.^{1,3,4} Gut bacteria produce metabolites and immune mediators that can influence host organs, including the heart and blood vessels.³

Importance and knowledge gaps

The gut–heart axis is a major clinically relevant topic because of the enormous burden of CVD and the need for new preventive strategies.^{1,5} Microbiome studies often report altered gut communities in patients with coronary artery disease and HF, even in the absence of conventional risk factors.⁵

Nevertheless, there are still important questions. As pointed out in a review, although there are strong links between gut microbes and CVD, it can be difficult to prove direct causation.⁵ To identify the bacterial taxa or pathways that cause vascular inflammation or myocardial dysfunction and to understand how they interact with host genetics and diet, researchers need to conduct mechanistic research. Methodological problems complicate data interpretation, such as disparities in microbiome sequencing techniques, variations in patient diets and medication regimens, and

a lack of standardized measurements. Crucially, the microbiome is not yet included in clinical guidelines for assessing the risk of CVD. We also lack large randomized trials testing whether altering the microbiome can improve hard CV outcomes.

Overview

Gut microbiome composition and diversity

The gut microbiota comprises a group of microorganisms like bacteria, fungi and viruses that reside within the digestive system. Genetics, age, diet, mode of birth and other factors can influence the composition and function. The colonization of the digestive tract begins immediately after birth.⁶ The composition and diversity of the gut microbiome are unique, much like the host genome. The gene content of these microbiomes (the metagenome) is also considered our alternate genome.⁷

Although hundreds of species are present, only ~30–40 genera account for about 99% of the microbiota's population.⁸ Bacteria constitute 60% of the faeces dry mass.⁶ *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* are the most dominant bacterial phyla in the human gut, with *Bacteroides*, *Clostridium*, *Faecalibacterium* and *Prevotella* being the most commonly recorded genera.⁸

There is a more diverse gut microbiota in people who consume foods containing naturally fermented bacteria (probiotics) and prebiotic fibres, whereas there is a lower gut microbiota diversity in people who use probiotic supplements.⁹ Breastfed individuals have been shown to develop a more diverse microbiome than those who were formula-fed, and some evidence also suggests that females may have slightly lower diversity than males.⁹

Microbiome and host metabolism

There are three categories of gut bacteria based on their functions in the host: gut bacteria can be categorized as (1) commensals that are normally harmless, (2) symbionts that are mutually beneficial and (3) pathobionts (or pathogens) that can cause disease under certain conditions.¹⁰

Certain *Lactobacillus* strains have been associated with improvements in cholesterol metabolism and inflammatory responses, which could be beneficial for CV health. They break down bile salts, convert cholesterol into forms that can be excreted without reabsorption and produce beneficial compounds like short-chain fatty acids (SCFAs) that inhibit liver cholesterol production by inhibiting 3-hydroxymethyl-3-glutaryl-CoA reductase enzyme in the liver. SCFAs like butyrate are an energy source for colonic epithelial cells. Some *Lactobacillus* strains can lower trimethylamine N-oxide (TMAO) levels, reducing inflammation and improving lipid profiles.¹¹

Cyanocobalamin and other endogenous B vitamins are synthesized exclusively by gut microbiota like *Firmicutes*, *Actinobacteria* and *Proteobacteria* strains; these are essential for healthy metabolic processes like DNA replication and repair. Commensal bacteria like *Serratia marcescens*, *Bacteroides fragilis*, *Enterobacter agglomerans*, *Eubacterium lentum* and *Enterococcus faecium* also produce vitamin K. Changes in the composition of these bacteria can, therefore, affect the availability of these endogenous vitamins.¹²

Microbiome and immune system interactions

The microbiota and the immune system are also closely related, and the first two years after birth are important for shaping the gut ecosystem, which helps the immune system to recognize commensal microbes from harmful ones.¹⁰ This early microbiome development is significant

for long-term immune strength.¹⁰ The gut microbiome also undergoes age-related changes in response to the changing environment. To overcome this, the microbiome changes the composition of the bacterial species, as well as the metabolic function.¹³ The gut lining contains Toll-like receptors that help the immune system to distinguish between friendly commensal bacteria and harmful invaders.¹³ The decline in immune fitness with ageing breaks the host–microbiome bond, affecting the host's health and immunity.¹⁴ Studies on mice suggest that a balanced gut microbiome might support blood cell production and immunity in older adults.¹⁴

The gut microbes also support the production of immunoglobulin A (IgA).¹³ Bacteria such as *B. fragilis*, *Clostridia* and *Bifidobacterium infantis* promote regulatory T-cell activity, and species like *Faecalibacterium prausnitzii* decrease pro-inflammatory cytokines like IL-12 and boost anti-inflammatory ones like IL-10, thereby helping reduce inflammation.¹³

Gut dysbiosis, microbial metabolites and cardiovascular disease mechanisms Inflammation and endothelial dysfunction

The gut microbiome not only aids in digestion but also impacts health conditions like CVD and many others through its metabolites, such as SCFAs, TMAO and lipopolysaccharides (LPS).¹⁵

Current research indicates that gut microbiomes also regulate inflammation by modulating immune cell differentiation, cytokine production and even haematopoiesis (blood cell formation). Chronic inflammation is central to atherosclerosis and contributes to other CVD.¹⁶ During dysbiosis, systemic inflammation is triggered by the entry of gut-derived microbial products (particularly LPS from Gram-negative bacteria) into the circulation.¹⁷ LPS activates immune pathways such as TLR4–MYD88–NF- κ B, increasing inflammatory cytokines (IL-6, IL-1 and TNF- α) and promoting foam cell formation and cholesterol ester accumulation, thereby contributing to atherosclerosis.¹⁷ Elevated LPS from increased gut permeability may also contribute to HF progression.¹⁷

People with high blood pressure (BP) tend to have a less diverse gut microbiome, with greater a prevalence of pro-inflammatory genera like *Prevotella* and *Klebsiella*.¹⁷ For example, Dinakis et al. found that higher plasma butyrate levels were associated with increased arterial stiffness.¹⁸ These findings suggest that differences in SCFA levels may be linked to changes in vascular tone and BP in humans.

Endothelial dysfunction is a key early step in CVD pathogenesis, leading to reduced vessel flexibility, inflammation and plaque formation.¹⁹ In dysbiosis, increased translocation of microbial products (LPS and other MAMPs) can stimulate endothelial cells, potentially leading to chronic activation and vascular inflammation.¹⁸ For instance, TMAO has been implicated in pathways involving NF- κ B that may enhance endothelial inflammation and platelet activation, potentially contributing to atherosclerosis.¹⁸ Elevated TMAO levels have been associated with a higher risk of heart attack, stroke and CV death.¹⁸ Uremic toxins (e.g. indoxyl sulphate or p-cresyl sulphate) from bacterial metabolism of amino acids, hydrogen sulphide (H₂S) from sulphate-reducing bacteria and microbial peptides/quorum-sensing signals can all affect endothelial barrier integrity and drive pathological angiogenesis or inflammation that promotes CVD.²⁰

Lipid metabolism and atherogenesis

The gut microbiome influences lipid metabolism by converting dietary fibre into SCFAs, which regulate energy balance, insulin sensitivity and

lipid levels via receptors like GPR41 and GPR43.²¹ SCFAs also enhance lipid breakdown and reduce circulating triglycerides and cholesterol.²¹ Bile acids (BAs) are another microbially influenced factor: primary BAs produced in the liver are converted by gut bacteria into secondary BAs that activate receptors (e.g. FXR or TGR5) and thereby influence lipid/glucose metabolism and inflammation. Dysregulated BA profiles can impair lipid handling and worsen cardiometabolic health.^{18,22} Gut microbes can also convert dietary choline into trimethylamine (TMA), which is oxidized by the liver to TMAO – elevated TMAO levels have been associated with impaired cholesterol transport and may contribute to atherosclerotic processes.^{18,22} Gut-derived metabolites can influence each step of plaque development. For example, high TMAO impairs reverse cholesterol transport and drives foam cell formation.²² Together, these microbiome-related changes in lipid metabolism may contribute to the development of atherosclerosis.²³ Thus, microbial modulation of SCFAs and BAs, as well as microbe-derived metabolites like TMAO, links the gut flora to altered lipid metabolism and plaque progression in CVD. Atherosclerosis occurs due to endothelial injury, followed by lipid buildup and plaque formation. High low-density lipoprotein (LDL), cholesterol, hypertension, diabetes, obesity and inactivity are its major risks. The disease progresses as LDL accumulates and oxidizes within arterial walls, triggering immune cell recruitment, especially monocytes, which become macrophages, which fill up with oxidized low-density lipoprotein (oxLDL) or lipid droplets, forming foam cells, leading to fatty streaks and plaque buildup. These plaques, made up of lipids, inflammatory cells and connective tissue, can narrow arteries and lead to serious CV events like acute coronary syndrome, stroke and HF.²³

A randomized controlled trial (RCT) provides evidence that a Mediterranean-style dietary pattern that was rich in fibre and polyphenols led to enhanced microbial gene richness, higher relative abundance of *F. prausnitzii* and *Roseburia hominis*, decreased levels of *Ruminococcus gnavus* and improved metabolic parameters.²⁴ Taken together, these findings provide support for host-diet gut microbiome interactions in modulating inflammation and metabolic regulation. Szabo et al. reported that an increased *Firmicutes/Bacteroidetes* ratio was linked to greater carotid intima-media thickness (IMT) and arterial stiffness ($p=0.031$), and Li et al. found that lower *F. prausnitzii* levels were associated with higher IMT.^{25,26} Together, these findings suggest that a dysbiosis characterized by a high *Firmicutes/Bacteroidetes* ratio and low *F. prausnitzii* is associated with early atherosclerotic changes. Since reduced *F. prausnitzii* has been associated with carotid IMT, the microbial changes that were observed may provide an important avenue for early atherosclerotic prevention through dietary changes.²⁷

Gut barrier dysfunction and immune system

As described in the section 'Inflammation and Endothelial Dysfunction', dysbiosis is linked to increased intestinal permeability, which can allow microbial molecules to enter the bloodstream and trigger systemic inflammation. This activates pro-inflammatory cytokines (IL-6 and TNF- α), which stimulate white blood cell and neutrophil production, as well as liver release of CRP. Those same cytokines further damage the gut barrier, resulting in a vicious cycle of increasing dysbiosis, inflammation and permeability.¹⁸ Disruption of the microbial balance can cause immune dysregulation, raising risk for metabolic and inflammatory diseases (diabetes, CVD, IBD, etc.).²⁸ However, when barrier dysfunction is severe, these defenses may be overwhelmed. Studies show that interventions that restore barrier integrity (e.g. certain antibiotics or prebiotics) can reduce circulating LPS and systemic inflammation. Dietary and lifestyle factors also modulate gut integrity: diets rich in fibre (and certain amino acids/vitamins) support

barrier health; regular exercise may help maintain gut barrier integrity and is known to improve cardiac health.²⁹

Some experimental studies suggest that faecal microbiota transplantation (FMT) can improve gut barrier function, though its impact on human CVD outcomes remains unproven.³⁰

Microbiota-derived metabolites and cardiovascular disease

The gut microbiome produces a variety of metabolites that are often studied for their potential roles in CV health.

Trimethylamine N-oxide

Gut microbes convert dietary nutrients (e.g. choline or carnitine) into TMA, which is then oxidized in the liver by the enzyme FMO3 to form TMAO.³¹ A systematic review, which summarized the results of 923 patients with high-risk CV problem, found that higher TMAO levels were associated with increased CV mortality.³² TMAO has been implicated in inflammatory and thrombotic pathways that may contribute to atherogenesis.³³

TMAO promotes foam cell formation by increasing cholesterol uptake in macrophages through upregulation of specific receptors, while also reducing BA secretion and reverse cholesterol transport, highlighting its proatherogenic effects.³⁴ A quantitative analysis of plasma TMAO revealed that it contributes to endothelial damage by triggering activation of the NLRP3 inflammasome through cathepsin-B-mediated pathways.³⁵ It downregulates the expression of tight junction proteins of endothelial cells.³⁴ Intestinal dysbiosis may lead to higher TMAO levels, which are associated with cardiac changes (e.g. hypertrophy or fibrosis) that could contribute to HF development.³⁶ High-circulating TMAO has been linked to increased platelet activity and faster clot formation, raising the risk of thrombotic events such as myocardial infarction and stroke.³⁷

Short-chain fatty acids

SCFAs are generated when the gut microbiome ferments dietary fibres and comprise acetate, propionate and butyrate.³³ SCFAs can influence cardiometabolic disorders by regulating their risk factors, activating intracellular signalling cascades and interacting with numerous receptors. They can regulate BP and have anti-inflammatory effects, reducing obesity.³⁸

Studies show that butyrate can help reduce obesity by lowering inflammation through its immune effects, while propionate supports weight control by reducing appetite through actions in the brain.³⁹ SCFAs, especially butyrate, help reduce BP by activating specific receptors in blood vessels and kidneys, reduce inflammation through HDAC inhibition and influence nervous system signalling from the gut to the brain.³³

SCFAs help maintain gut barrier integrity; if the barrier is compromised, more microbial toxins can enter the circulation, contributing to systemic inflammation and CV risk.⁴⁰

Some research suggests that SCFAs may influence immune cells (like CX3CR1+ macrophages) involved in cardiac repair, but evidence that SCFAs prevent or treat HF in humans is currently lacking.⁴⁰ SCFA holds a significant role in maintaining the gut barrier, and through this effect, it alters CVD risks.⁴¹

Lipopolysaccharides

When dysbiosis increases gut permeability, LPS can translocate into the circulation and contribute to systemic inflammation.⁴² Dysbiosis and other factors cause increased intestinal permeability, known as a 'leaky gut'.⁴³

Studies have shown that gut permeability is increased in individuals with hypertension.³³ Its proatherogenic effects include increased receptor expression in foam cells for the uptake of oxLDL.⁴² The circulation of LPS results in the secretion of inflammatory cytokines, leading to insulin resistance and metabolic disorders.⁴⁴ Gut permeability-related circulation of LPS helps explore how inflammation contributes to CVDs.²⁹

TMAO and SCFAs have emerged as key microbiota-derived metabolites with significant clinical relevance in CVD. TMAO is a potential indicator and treatment target because of its link to negative CV outcomes. At the same time, SCFAs offer therapeutic potential by modulating inflammation and improving vascular function, which may help reduce hypertension and atherosclerosis risk (though human studies are needed).^{45,46} LPS may serve as a potential clinical marker to investigate inflammation-driven CVD risk.³² Table 1 summarizes the biomarkers for CVD risk stratification.^{17,25,26,32–34,37,38,42,47–51}

Gut microbiome and its role in specific cardiovascular disease

Atherosclerosis

The gut microbial metabolites regulate cholesterol metabolism and systemic inflammation and may thereby influence CVD risk.⁴⁶ BAs act as a ligand to the farnesoid X receptor (FXR), which regulates their production and cholesterol metabolism via cholesterol 7 α -hydroxylase (CYP7A1) and small heterodimer partner (SHP) pathways.⁴⁷ The gut microbiome deconjugates from primary BA to secondary BA using biliary salt hydrolase (BSH).⁴⁸ During dysbiosis, BSH is reduced, causing BA reabsorption and redundant FXR activation. This results in repression of CYP7A1 and downregulation of ATP-binding cassette transporters (ABCG5/ABCG8), thereby reducing cholesterol excretion. Hence, dysbiosis and altered BA metabolism may disturb cholesterol homeostasis and contribute to elevated cholesterol levels, a major risk factor for atherosclerosis.⁵²

A prospective cohort study by Haghikia et al. on 671 patients with previous ischaemic stroke revealed the relationship between increased TMAO levels and the risk of CV events in life.⁵² The higher TMAO levels have been shown to impair reverse cholesterol transport and promote foam cell formation and inflammation. These changes could create a

feedback loop that accelerates atherosclerotic plaque development.^{52,53} Similarly, the effects of plasma TMAO levels on new atherosclerosis and plaque rupture in patients with highly late stent thrombosis were observed in a study conducted by Tan et al.⁵⁴

Hypertension

Gut-derived metabolites can influence immune function and metabolism and may also affect BP regulation.⁵⁵ SCFAs produced by gut microbes influence BP after reaching the bloodstream, where they interact with G-protein-coupled receptors (GPR41 and GPR43) and Olfr78 in the kidneys and blood vessels.⁵⁶ The activation of Olfr78 has been shown to increase renin release and raise BP, whereas the activation of GPR41 and GPR43 causes vasodilation and lowers BP.⁵⁷ Hence, the ultimate effect is based on the relative activation of these receptors by SCFAs. The SCFA availability decreases with dysbiosis and thus influences these signalling pathways, promoting pro-hypertensive states.⁴⁹ Butyrate improves endothelial function and reduces oxidative stress, thereby attenuating angiotensin-II-induced hypertension. Even acetate and propionate impact BP through interaction with the renin-angiotensin system.⁴⁹

A cross-sectional study by Zhou et al. shows the association of SCFA and BP.⁵⁸ The acetate (odds ratio=0.696) and valerate (odds ratio=0.713) had a negative correlation with hypertension in their multiple logistic regression analysis.⁵⁸ In linear regression, acetate (with a regression coefficient=-3.89) and systolic BP had a significant negative association.⁵⁸ These results suggest a new therapeutic approach using SCFAs in patients with hypertension.

Heart failure

HF is a major problem across the world, causing morbidity and mortality in affected individuals.⁵⁹ The disrupted gut barrier marks the point of translocation of microbial components into the circulation, and it promotes a state of chronic inflammation.⁶⁰ LPS in circulation activates TLR4 signalling, initiating endothelial dysfunction and triggering pro-inflammatory cytokine release, which ultimately worsens cardiac remodelling and HF progression.⁶¹

A recent study by Zhang et al. identified phenylacetylglutamine (PAGln, a gut-derived phenylalanine metabolite) as a potential contributor to HF.⁵⁰ The higher values of serum PAGln were found in patients with higher New York Heart Association (NYHA) classification compared with those with milder cases.⁵⁰ The median PAGln value corresponds to 104.0 ng/mL and 186.7 ng/mL, respectively, for NYHA Class III and IV.⁵⁰ Romano et al. have also demonstrated the contribution of PAGln in adverse cardiac events and myocardial stress via adrenergic receptor signalling.⁵¹

Table 1: Biomarkers for cardiovascular disease risk stratification^{17,25,26,32–34,37,38,42,47–51}

Biomarker	Microbial source	Associated CVD	Clinical utility	Key refs
TMAO	Choline/carnitine-metabolizing bacteria	Atherosclerosis, heart failure and arrhythmia	Risk prediction, therapeutic target	32–34
SCFAs	Fibre-fermenting bacteria (e.g. <i>F. prausnitzii</i>)	Hypertension and atherosclerosis	Vascular protection marker	37,38,49
LPS	Gram-negative bacteria	Atherosclerosis and heart failure	Systemic inflammation marker	17,42
PAGln	Phenylalanine-metabolizing microbes	Heart failure	Prognostic marker	50,51
Secondary bile acids	Microbial bile salt hydrolase activity	Dyslipidaemia and atherosclerosis	Metabolic risk indicator	47,48
<i>F. prausnitzii</i> abundance	Beneficial butyrate producer	Atherosclerosis (protective)	Surrogate of gut health	25,26

CVD = cardiovascular disease; LPS = lipopolysaccharide; PAGln = phenylacetylglutamine; SCFAs = short-chain fatty acids; TMAO = trimethylamine N-oxide.

Table 2: Microbiome and cardiovascular disease associations^{17,22,25,26,49–51,56,57,60–64}

Condition	Microbial changes	Key metabolites	Mechanisms	Key refs
Atherosclerosis	↑ <i>Firmicutes/Bacteroidetes</i> , ↓ <i>F. prausnitzii</i>	TMAO, LPS and dysregulated SCFAs	Inflammation, impaired lipid metabolism and endothelial dysfunction	17,22,25,26
Hypertension	↓ SCFA producers, ↑ <i>Prevotella</i> and <i>Klebsiella</i>	Reduced SCFAs and LPS	Altered GPCR/Olf78 signalling and systemic inflammation	17,49,56,57
Heart failure	Barrier dysfunction and dysbiosis	TMAO, PAGln and LPS	Chronic inflammation and cardiac remodelling	50,51,60,61
Arrhythmia	Dysbiosis with high TMAO and low SCFA	TMAO	Fibrosis via TGF-β/NLRP3 and electrical remodelling	62–64

GPCR = G-Protein-Coupled Receptor; LPS = lipopolysaccharide; PAGln = phenylacetylglutamine; SCFAs = short-chain fatty acids; TGF-NLRP3 = Transforming Growth Factor-NOD-like receptor protein 3 inflammasome; TMAO = trimethylamine N-oxide.

Arrhythmia

Arrhythmia is an abnormal heart rhythm (irregular, fast, slow or missed beats). Atrial fibrillation (AF), characterized by rapid, disorganized atrial contractions, arises from structural/electrical atrial remodelling. Dysbiosis has been associated with higher levels of metabolites (e.g. TMAO) and lower SCFAs, which could contribute to biochemical changes involved in atrial remodelling.⁶² A cohort study by Svingen et al. clearly indicated the involvement of TMAO in AF.⁶³ The study of 3,797 patients whose TMAO levels were increased had a significant risk of incidence of AF with a hazard ratio of 1.12 per 1-standard deviation (SD) increase.⁶³

The electrical remodelling includes shortened action potential duration, a decrease in L-type calcium channel gene expression and altered potassium currents. Structural changes include myocardial fibrosis and atrial dilatation. Taken together, these electrophysiological and structural changes promote sustained arrhythmic activity.⁶³ Elevated TMAO has been linked to the activation of pathways (TGF-β/NLRP3) that may promote myocardial fibrosis.⁶⁴ Thus, microbial metabolites may influence atrial electrophysiology and structure in ways that could increase AF risk. *Table 2* summarizes the microbiome and CVD associations.^{17,22,25,26,49–51,56,57,60–64}

Therapeutic modulation of gut microbiome

Diet and lifestyle

Dietary modification offers a low-risk approach to modulating the gut microbiome and influencing CV risk, though responses vary among individuals.^{66,67} Adherence to a Mediterranean or high-fibre diet is linked to a gut microbiome enriched in SCFA-producing bacteria and reduced CVD risk.^{65,66} Large trials and meta-analyses confirm the CV benefits of the Mediterranean diet (MD).^{65,67} In Prevención con Dieta Mediterránea (PREDIMED), high-risk adults following an MD supplemented with olive oil or nuts experienced fewer major CV events than those on a low-fat diet.⁶⁶ Systematic reviews similarly associate higher MD adherence with lower risks of coronary heart disease, stroke and HF, despite some heterogeneity.^{65,67}

Part of the MD's benefit stems from its anti-inflammatory and endothelial-protective effects. It reduces vascular inflammation and improves endothelial function, which may contribute to reduced HF risk, though causality remains uncertain.⁶⁵ Rich in plant polyphenols from sources like fruits, vegetables, tea and wine, the MD promotes microbial metabolism of these compounds into bioactive, anti-inflammatory metabolites.^{67,68}

In summary, multiple trials have shown that diets such as the MD, high in fibre, unsaturated fats and polyphenols are linked to healthier gut

microbes (more SCFA producers) and lower CVD risk.^{65,66} However, we should avoid implying direct causation (for example, it is incorrect to say the MD directly prevents HF). Instead, it is accurate to say that MD-like diets *reduce* inflammation and improve vascular function, which may help prevent HF over time. Overall, dietary change is a safe strategy to modulate the microbiome, but more research is needed to predict individual responses and identify *optimal* diets for heart health.

Probiotics, prebiotics and synbiotics

Definitions: Probiotics are live microorganisms (usually bacteria) given as supplements or in foods to confer a health benefit. Prebiotics are non-digestible fibres or substrates (like inulin) that selectively feed beneficial gut microbes. Synbiotics are combinations of probiotics and prebiotics designed to synergize.

Probiotics: Several clinical trials have tested probiotics (various strains and doses) for CV risk factors. Meta-analyses indicate that any benefits on BP or lipids are generally *small*.⁶⁹ For example, a recent pooled analysis of 26 randomized trials (1,624 subjects) found that long-term probiotic use lowered office systolic BP by only ~2.2 mmHg and diastolic BP by ~1.1 mmHg on average.⁶⁹ Similarly, umbrella reviews report that probiotics yield minor reductions in total cholesterol and LDL-C.⁶⁹ Some trials in patients with hypertension or metabolic disease show slightly larger effects, but results vary by strain and duration. Probiotics also modestly reduce systemic inflammation: one meta-analysis found significant decreases in markers like hs-CRP, TNF-α and IL-6 after supplementation.⁷⁰

Evidence summary: Overall, probiotic supplements can lead to modest improvements in BP, blood lipids and inflammatory markers.^{69–71} However, effects differ by specific strains and doses, and many studies are short-term or small. Importantly, no probiotic supplement has been proven to reduce actual CVD events. Safety and standardization are also concerns, as probiotic products vary widely.

Prebiotics: Prebiotics such as inulin, pectins or galacto-oligosaccharides escape digestion and are fermented by the gut microbiota into SCFAs (acetate, propionate and butyrate).^{72,73} These SCFAs have direct vascular benefits: for example, experimental studies show that acetate and butyrate boost endothelial nitric oxide and lower oxidative stress.⁷² In animal models, adding inulin to a high-fat diet reduced LDL cholesterol, systemic endotoxin, arterial inflammation and plaque formation.⁷⁴ In that study, atherosclerotic mice on inulin had lower blood lipids, reduced aortic plaque area and less vascular inflammation compared to controls.⁷⁴ Human trials of prebiotics are fewer and often short-term, but some report modest improvements in glucose metabolism or inflammation (likely via increased SCFAs).^{75,76}

Table 3: Therapeutic interventions and their effects^{65–69,71–79,81}

Intervention	Mechanism of action	Documented CV effects	Clinical status	Key refs
Mediterranean diet	Enriches SCFA producers and polyphenol metabolism	↓ Major CV events in PREDIMED	Guideline-recommended	65–67
Probiotics	Introduce beneficial strains and modest BP/lipid improvements	–2/–1 mmHg BP reduction and ↓ LDL	Marketed supplements	68,69,71
Prebiotics (e.g. inulin)	Fermented to SCFAs and anti-inflammatory	Improved endothelial NO and ↓ plaque in mice	Food additive/supplement	72–74
Synbiotics	Synergy of probiotic + prebiotic	Small reductions in BMI and LDL	Emerging	75,76
Faecal microbiota transplantation	Whole-microbiome replacement	Transient BP drop and experimental	Clinical trials	77,78
TMAO inhibitors (e.g. DMB)	Block TMA formation	Prevented arterial stiffening in mice	Preclinical	79
Engineered probiotics	Produce SCFAs/degrade TMA	Protected myocardium in animal models	Preclinical	81

BMI = body mass index; BP = blood pressure; CV = cardiovascular; DMB = 3,3-dimethyl-1-butanol; LDL = low-density lipoprotein; NO = nitric oxide; PREDIMED = Prevención con Dieta Mediterránea; SCFAs = short-chain fatty acids; TMA = trimethylamine; TMAO = trimethylamine N-oxide.

Evidence summary: Compounds like inulin consistently ferment to SCFAs that support endothelial health.⁷² In preclinical models, inulin and other fibres attenuate inflammation and atherosclerosis.⁷⁴ In humans, most prebiotic studies are small; they suggest possible benefits on metabolic markers (e.g. glucose or insulin), but clinical data on CV outcomes are lacking. Thus, while prebiotic fibres could biologically improve CV risk factors via SCFA production, definitive evidence in patients is still limited.

Synbiotics: Synbiotics combine both a probiotic organism and a prebiotic fibre. Preclinical work suggests potential synergy, but human data are still emerging. Some small trials have used synbiotic formulas (e.g. a *Lactobacillus* strain plus fructo-oligosaccharide) and reported small improvements in lipids or inflammation.⁷⁶ An umbrella meta-analysis found that synbiotic supplements yield statistically significant but quantitatively small decreases in BMI and lipids (LDL-C, total cholesterol and triglycerides).⁷⁶ For instance, synbiotics use lowered LDL by only ~2–3 mg/dL on average.⁷⁶

Evidence summary: Overall, synbiotics may slightly improve surrogate risk factors. Meta-analyses suggest minor drops in weight, BMI and LDL-C.⁷⁶ However, no studies have shown reductions in cardiovascular events. Human trials vary widely in strains and dosages, so it is hard to draw firm conclusions. Given this, it is critical to emphasize that no probiotic or synbiotic product is proven to prevent heart attacks or strokes; they are not a substitute for established therapies. Safety and regulatory issues (e.g. identifying effective strains and doses) remain challenges.^{69,71} In practice, reported benefits of probiotics/prebiotics/synbiotics on CVD are indirect and modest (e.g. ‘some trials report small improvements in BP, lipids or inflammatory markers’ rather than direct disease prevention).^{69,71}

Faecal microbiota transplantation and other experimental therapies

FMT involves transferring stool (and its microbes) from a healthy donor into a patient’s gastrointestinal tract, typically by colonoscopy, enema or capsules. It has proven effective for *Clostridioides difficile* infection, so researchers are testing it for metabolic and CV conditions.⁷⁷ FMT procedures are complex (donor screening and stool processing), but we can summarize key findings relevant to CVD.⁷⁷

In hypertension, one recent trial (Fan et al., 2025) administered oral FMT capsules to adults with high BP.⁷⁸ After 1 week, systolic BP fell by an average of 4.3 mmHg in the FMT group compared to placebo. However, this effect was transient and did not persist after continued treatment. Notably, safety was acceptable. These results suggest

a possible microbiome-driven BP effect, but it was modest and short-lived.⁷⁸ In other words, FMT for hypertension remains experimental: it is not a standard therapy, and longer-term benefits have not been demonstrated.

Animal studies provide proof-of-concept: for example, Kim et al. showed that transplanting gut microbiota from genetically atherosclerosis-resistant mice into atherosclerosis-prone mice reduced plaque formation.⁷⁹ Conversely, giving diseased mice a ‘bad’ microbiome worsened their plaque burden.⁷⁹ These mouse studies imply that FMT can influence atherosclerosis development, but clear human data are lacking. In summary, FMT has been shown to *modulate* hypertension and atherosclerosis in preliminary settings.^{78,79}

Other experimental approaches: Beyond FMT, researchers are exploring diverse gut-targeted interventions:

- **TMAO/TMA inhibitors:** Inhibiting the gut production of TMA, which is converted to pro-atherogenic TMAO, is under study. A prototype inhibitor, 3,3-dimethyl-1-butanol (DMB), has been shown in mice to suppress TMAO formation and prevent age-related vascular stiffening.⁸⁰ For example, long-term DMB supplementation in mice normalized endothelial function and reduced arterial stiffness by lowering TMAO.⁸⁰ These findings suggest a potential way to reduce vascular dysfunction via the microbiome, but human trials are needed.
- **Engineered probiotics:** Researchers are developing bacteria that can either consume TMA or generate beneficial metabolites. For example, engineered strains might be designed to break down choline/TMA before it converts to TMAO or to produce compounds that protect blood vessels. These methods are still primarily in the research phase and have not yet been tested in clinical settings.⁸¹
- **Selective antibiotics:** By targeting specific microbial groups with narrow-spectrum antibiotics, there is potential to alter metabolism. However, the widespread use of broad-spectrum antibiotics disrupts gut ecology and may lead to negative outcomes. Currently, no antibiotic treatment has demonstrated an improvement in CVD outcomes, making this approach largely theoretical.⁸²

All of these interventions encounter a significant challenge: interindividual variability in the microbiome. The same therapy may yield different results across individuals based on their unique gut flora. Consequently, personalized responses are expected, complicating predictions about who will benefit. Currently, FMT and other gut-targeted therapies represent promising research opportunities, but they are not established

treatments for CVD. Future studies will need to determine which patients, if any, may experience clinical benefits from these innovative strategies.^{78,79} Table 3 summarizes therapeutic interventions and their effects.^{65–69,71–79,81}

Challenges and limitations

Microbiome research faces major challenges due to extreme interpersonal variability influenced by ethnicity, diet, age and geography.^{83,84} Breastfeeding rates and the timing and introduction of solid foods in childhood are associated with this variability.⁸⁵ Due to biological diversity, it is difficult to establish universal microbial markers or a 'healthy' baseline.⁸³ Another key barrier is standardization, as variations in DNA extraction procedures, sequencing platforms and analytical pipelines generate technical artefacts that reduce reproducibility.^{84,86} Even in well-controlled feeding studies, standardized diets diminish intra-individual variances but do not eradicate inter-personal microbiome disparities.⁸⁷ Moreover, the existing reference databases, which are used in this field, remain incomplete, with many microbial species poorly characterized.⁸⁸ Current microbiome analysis methods have significant technical limitations. Widely used 16S rRNA sequencing has low taxonomic resolution and generates platform-specific biases.⁸⁹ Much current research focuses primarily on bacteria, while overlooking 'The Dark Matter' of the gut, including viruses, fungi and archaea, which play major roles in microbiome activity.⁹⁰ While these methodological gaps limit precise characterization of microbial communities, equally significant challenges arise when attempting to translate findings into biologically relevant models. Standard laboratory mouse models have microbiomes that differ markedly from humans.⁹¹ Variations in animal supplier, diet formulation and housing circumstances create confounding variables, limiting the clinical applicability of preclinical findings.⁹¹ These methodological limitations present considerable challenges to obtaining therapeutically useful knowledge. Despite numerous associations, demonstrating causality between gut microbiota and CVD has been difficult due to the complex interplay of host and environmental factors.⁹² While numerous studies find links between microbial profiles and disease states, few show clear causal correlations. Most human studies are cross-sectional or observational, so causality cannot be inferred.⁹³ Longitudinal, interventional designs are needed to assess cause-and-effect. Clinical heterogeneity (e.g. differences in diet, concomitant medications like statins or proton pump inhibitors and comorbidities) further confounds gut–heart microbiome studies.⁹² Moreover, different studies often report different microbial 'signatures' for the same disease, reflecting small sample sizes and methodological differences.⁹⁴ In addition, most studies focus on high-income (Western) populations; underrepresentation of other ethnic and lifestyle groups limits the global applicability of findings.⁹⁵ Even clinical translation of therapies remains challenging; for example, regulatory and ethical frameworks for interventions like FMT are still evolving.⁹⁶ This gap persists because host–microbe interactions and environmental influences are incredibly complex. Large-scale projects such as the Human Microbiome Project have made advances towards standardization, but the field still lacks comprehensive reference datasets and analytical frameworks. Without addressing these fundamental concerns, the translation of microbiome research into clinical and therapeutic implications will be limited by reproducibility issues and poor mechanistic knowledge. Addressing these challenges will require coordinated efforts (e.g. standardized protocols and data sharing) to improve reproducibility and build robust reference datasets.⁹⁴

Future directions

The integration of multi-omics methods such as metagenomics, metatranscriptomics, metaproteomics and metabolomics is transforming our understanding of the gut microbiome's role in CVD. These technologies enable researchers to examine microbial diversity, gene expression, protein function and metabolic activity, resulting in a comprehensive understanding of host–microbiome interactions.⁹⁷ For example, metagenomics aids in the identification of microbial species associated with atherosclerosis, whereas metabolomics identifies important compounds such as TMAO and SCFAs that influence heart health.⁹⁸ Combining metagenomic sequencing with metabolomics can link specific microbial genes to bioactive compounds (like TMAO or SCFAs) and thus to CVD phenotypes, moving beyond simple association.⁹⁹ Future studies should integrate multi-omics data with systems biology to decode microbial networks and their mechanistic links to CVDs. Tools like high-throughput sequencing and bioinformatics will play a key role in uncovering these microbial pathways. Furthermore, microfluidic organ-on-a-chip and gut-simulation models (for example, linking a gut-on-chip to a vascular tissue model) could allow testing of gut–heart interactions *in vitro* and reduce reliance on animal models.¹⁰⁰ Gut microbiome-derived biomarkers (e.g. TMAO, SCFAs and LPS) are promising candidates for CVD risk assessment. Elevated TMAO levels, for example, are associated with atherosclerosis and HF risk, making it a potential diagnostic marker (pending further validation).¹⁰¹ Similarly, patients with low levels of important beneficial bacteria such as *Faecalibacterium* and *Roseburia* tend to have inflammation and high BP. These microbial signatures could help doctors assess patient risk more precisely.¹⁰² Future work should validate these markers in large, diverse cohorts and develop standardized assays for clinical use.¹⁰³ Researchers should also explore novel biomarkers, such as circulating bacterial DNA in blood, which is being investigated as a potential indicator of gut barrier disruption in CVD.¹⁰⁴

Artificial intelligence (AI) and machine learning are advancing microbiome research by enabling personalized analysis of complex data. For example, AI models can analyse large multi-omic datasets to identify microbial patterns predictive of CVD risk or to recommend targeted interventions.¹⁰⁵ Machine learning might predict which patients will benefit most from high-fibre diets (to boost SCFAs) or specific probiotics to reduce inflammation. However, these models require large, high-quality datasets and careful validation to avoid bias. Ethical considerations like data privacy and algorithmic bias must also be addressed to ensure equitable, reliable results.¹⁰⁶

Well-designed clinical trials will be critical to translate these findings. Future studies should include RCTs of gut-targeted interventions (dietary changes, prebiotics or probiotics) with hard cardiovascular endpoints in diverse populations.¹⁰⁷ Mechanistic trials in humans (e.g. microbial transplantation or use of labelled substrates to trace microbe–host metabolism) will help establish causality between specific bacteria and host physiology.¹⁰⁸

While these directions are promising, it is important to balance optimism with rigour. Integrating multi-omics, AI and novel model systems could lead to a deeper understanding of how gut microbes affect heart health and to personalized microbiome-based therapies. Achieving this will require interdisciplinary collaboration and robust methods, ensuring advances benefit all populations equally.¹⁰⁹ Table 4 summarizes the future directions and research priorities.^{97–99,101–104,107}

Table 4: Future directions and research priorities^{97–99,101–104,107}

Priority area	Rationale	Expected impact	Key refs
Multi-omics integration	Link genes→metabolites→phenotype	Mechanistic insights	97,98
Biomarker validation	Standardize TMAO and SCFA assays	Risk stratification	101,102
AI applications	Predict responders and personalize diet	Precision medicine	103,104
Novel model systems	Gut-heart-on-chip	Reduce animal use	99
Large RCTs of microbiome therapies	Test hard CV endpoints	Evidence-based practice	107

AI = Artificial Intelligence; CV = cardiovascular; RCT = randomized controlled trials; SCFA = short-chain fatty acid; TMAO = trimethylamine N-oxide.

Conclusion

CVD continues to pose a significant global health burden, with residual risks persisting despite advances in conventional preventive and therapeutic strategies. Growing evidence highlights the gut microbiota as a critical, yet underexplored, factor influencing cardiovascular health through a complex interplay of metabolic, immune and inflammatory mechanisms. Key microbial metabolites such as TMAO, SCFAs, BAs and LPS have emerged as important modulators of endothelial function, lipid metabolism and systemic inflammation, directly impacting the development and progression of atherosclerosis, hypertension, HF and arrhythmias.

The findings reviewed here underscore the therapeutic potential of microbiome-targeted interventions, including dietary modifications such as the Mediterranean and high-fibre diets, probiotics, prebiotics, synbiotics and emerging strategies like FMT. While small-scale studies

report modest improvements in CV risk markers such as reduced BP, improved lipid profiles and decreased inflammatory responses, there remains a lack of robust, large-scale RCTs confirming their impact on major CV outcomes. This gap reflects the complexity of microbiome research, marked by inter-individual variability, methodological limitations and challenges in establishing causality.

Future directions should prioritize the integration of multi-omics approaches, biomarker validation and artificial intelligence to decode the gut–heart axis and enable precision-based therapeutic strategies. Translating microbiome science into clinical practice requires rigorous longitudinal studies, standardized methodologies and diverse population studies. Ultimately, understanding and modulating the gut microbiota offers a promising frontier to complement traditional CVD management, potentially leading to innovative and personalized preventive and therapeutic interventions. □

- Murphy K, O'Donovan AN, Caplice NM, et al. Exploring the gut microbiota and cardiovascular disease. *Metabolites*. 2021;11:493. DOI: 10.3390/metabo11080493.
- Nesci A, Carnuccio C, Ruggieri V, et al. Gut microbiota and cardiovascular disease: Evidence on the metabolic and inflammatory background of a complex relationship. *Int J Mol Sci*. 2023;24:9087. DOI: 10.3390/ijms24109087.
- Tousoulis D, Guzik T, Padro T, et al. Mechanisms, therapeutic implications, and methodological challenges of gut microbiota and cardiovascular diseases: A position paper by the ESC working group on coronary pathophysiology and microcirculation. *Cardiovasc Res*. 2022;118:3171–82. DOI: 10.1093/cvr/cvac057.
- Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature*. 2011;472:57–63. DOI: 10.1038/nature09922.
- Kazemian N, Mahmoudi M, Halperin F, et al. Gut microbiota and cardiovascular disease: Opportunities and challenges. *Microbiome*. 2020;8:36. DOI: 10.1186/s40168-020-00821-0.
- Gomaa EZ. Human gut microbiota/microbiome in health and diseases: A review. *Antonie Van Leeuwenhoek*. 2020;113:2019–40. DOI: 10.1007/s10482-020-01474-7.
- Bubier JA, Chesler EJ, Weinstock GM. Host genetic control of gut microbiome composition. *Mamm Genome*. 2021;32:263–81. DOI: 10.1007/s00335-021-09884-2.
- Johnson KVA. Gut microbiome composition and diversity are related to human personality traits. *Hum Microb J*. 2020;15:None. DOI: 10.1016/j.humic.2019.100069.
- Kuziel GA, Rakoff-Nahoum S. The gut microbiome. *Curr Biol*. 2022;32:R257–64. DOI: 10.1016/j.cub.2022.02.023.
- Wiersma SP, van Bergenhenegouwen J, Garssen J, et al. The interplay between the gut microbiome and the immune system in the context of infectious diseases throughout life and the role of nutrition in optimizing treatment strategies. *Nutrients*. 2021;13:886. DOI: 10.3390/nu13030886.
- Zhang Y, Li X, Wang Y, et al. The role of gut microbiota in the pathogenesis of ischemic stroke. *Front Pharmacol*. 2022;13:1042189. DOI: 10.3389/fphar.2022.1042189.
- Shui L, Yang X, Li J, et al. Gut microbiome as a potential factor for modulating resistance to cancer immunotherapy. *Front Immunol*. 2020;10:2989. DOI: 10.3389/fimmu.2019.02989.
- Bidell MR, Hobbs ALV, Lodise TP. Gut microbiome health and dysbiosis: A clinical primer. *Pharmacotherapy*. 2022;42:849–57. DOI: 10.1002/phar.2731.
- Bosco N, Noti M. The aging gut microbiome and its impact on host immunity. *Genes Immun*. 2021;22:289–303. DOI: 10.1038/s41435-021-00126-8.
- Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. *Circ Res*. 2020;127:553–70. DOI: 10.1161/CIRCRESAHA.120.316242.
- Libby P, Ridker PM, Hansson GK, et al. Inflammation in atherosclerosis: From pathophysiology to practice. *J Am Coll Cardiol*. 2009;54:2129–38. DOI: 10.1016/j.jacc.2009.09.009.
- Zhang C, Teng X, Cao Q, et al. Gut microbiota dysbiosis exacerbates heart failure by the LPS-TLR4/NF- κ B signalling axis: Mechanistic insights and therapeutic potential of TLR4 inhibition. *J Transl Med*. 2025;23:762. DOI: 10.1186/s12967-025-06821-8.
- Dinakis E, Nakai M, Gill PA, et al. The gut microbiota and their metabolites in human arterial stiffness. *Heart Lung Circ*. 2021;30:1716–25. DOI: 10.1016/j.hlc.2021.07.022.
- Querio G, Antoniotti S, Geddo F, et al. Modulation of endothelial function by TMAO, a gut microbiota-derived metabolite. *Int J Mol Sci*. 2023;24:5806. DOI: 10.3390/ijms24065806.
- Amedei A, Morbidelli L. Circulating metabolites originating from gut microbiota control endothelial cell function. *Molecules*. 2019;24:3992. DOI: 10.3390/molecules24213992.
- Schoeler M, Caesar R. Dietary lipids, gut microbiota and lipid metabolism. *Rev Endocr Metab Disord*. 2019;20:461–72. DOI: 10.1007/s11554-019-09512-0.
- Bordoni L, Samuliak JJ, Sawicka AK, et al. Trimethylamine n-oxide and the reverse cholesterol transport in cardiovascular disease: A cross-sectional study. *Sci Rep*. 2020;10:18675. DOI: 10.1038/s41598-020-75633-1.
- Ahmad AF, Dwivedi G, O'Gara F, et al. The gut microbiome and cardiovascular disease: Current knowledge and clinical potential. *Am J Physiol Heart Circ Physiol*. 2019;317:H923–38. DOI: 10.1152/ajpheart.00376.2019.
- Meslier V, Laiola M, Roager HM, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut*. 2020;69:1258–68. DOI: 10.1136/gutjnl-2019-320438.
- Szabo H, Hernyes A, Piroksa M, et al. Association between gut microbial diversity and carotid intima-media thickness. *Medicina*. 2021;57:195. DOI: 10.3390/medicina57030195.
- Li Z, Gong R, Chu H, et al. A universal plasma metabolites-derived signature predicts cardiovascular disease risk in MAFLD. *Atherosclerosis*. 2024;392:117526. DOI: 10.1016/j.atherosclerosis.2024.117526.
- Wan Y, Wang F, Yuan J, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: A 6-month randomised controlled-feeding trial. *Gut*. 2019;68:1417–29. DOI: 10.1136/gutjnl-2018-317609.
- Yoo J, Groer M, Dutra S, et al. Gut microbiota and immune system interactions. *Microorganisms*. 2020;8:1587. DOI: 10.3390/microorganisms8101587.
- Violi F, Nocella C. Editorial: gut permeability-related endotoxemia and cardiovascular disease: A new clinical challenge. *Front Cardiovasc Med*. 2023;10:118625. DOI: 10.3389/fcvm.2023.118625.
- Kamárová A, Kvaková M, Ambro L, et al. Improvement of the inflammation-damaged intestinal barrier and modulation of the gut microbiota in ulcerative colitis after FMT in the SHIME® model. *BMC Complement Med Ther*. 2025;25:145. DOI: 10.1186/s12906-025-04889-9.
- Jaworska K, Kopacz W, Koper M, et al. Microbiome-derived trimethylamine n-oxide (TMAO) as a multifaceted biomarker in cardiovascular disease: Challenges and opportunities. *Int J Mol Sci*. 2024;25:12511. DOI: 10.3390/ijms252312511.
- Guasti L, Galliazzo S, Molaro M, et al. TMAO as a biomarker of cardiovascular events: A systematic review and meta-analysis. *Intern Emerg Med*. 2021;16:201–7. DOI: 10.1007/s11739-020-02470-5.
- Verhaar BJH, Prodan A, Nieuwdorp M, et al. Gut microbiota in hypertension and atherosclerosis: A review. *Nutrients*. 2020;12:2982. DOI: 10.3390/nu12102982.
- Canyelles M, Borrás C, Rotllan N, et al. Gut microbiota-derived TMAO: A causal factor promoting atherosclerotic cardiovascular disease? *Int J Mol Sci*. 2023;24:1940. DOI: 10.3390/ijms24031940.
- Lei D, Yu W, Liu Y, et al. Trimethylamine n-oxide (TMAO) inducing endothelial injury: UPLC-MS/MS-based quantification and the activation of Cathepsin B-mediated NLRP3 inflammasome. *Molecules*. 2023;28:3817. DOI: 10.3390/molecules28093817.
- Zhang Y, Wang Y, Ke B, et al. TMAO: How gut microbiota contributes to heart failure. *Transl Res*. 2021;228:109–25. DOI: 10.1016/j.trsl.2020.08.007.
- Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell*. 2016;165:111–24. DOI: 10.1016/j.cell.2016.02.011.
- Nogal A, Valdes AM, Menni C. The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health. *Gut Microbes*. 2021;13:1–24. DOI: 10.1080/19490976.2021.1897212.
- Chambers ES, Preston T, Frost G, et al. Role of gut microbiota-generated short-chain fatty acids in metabolic and cardiovascular health. *Curr Nutr Rep*. 2018;7:198–206. DOI: 10.1007/s13668-018-0248-8.
- Qian B, Zhang K, Li Y, et al. Update on gut microbiota in cardiovascular diseases. *Front Cell Infect Microbiol*. 2022;12:1059349. DOI: 10.3389/fcimb.2022.1059349.

41. Blaak EE, Canfora EE, Theis S, et al. Short chain fatty acids in human gut and metabolic health. *Benef Microbes*. 2020;11:411–55. DOI: 10.3920/BM2020.0057.
42. Wang Z, Zhao Y. Gut microbiota derived metabolites in cardiovascular health and disease. *Protein Cell*. 2018;9:416–31. DOI: 10.1007/s13238-018-0549-0.
43. Camilleri M. Leaky gut: Mechanisms, measurement and clinical implications in humans. *Gut*. 2019;68:1516–26. DOI: 10.1136/gutjnl-2019-318427.
44. Wu J, Yang K, Fan H, et al. Targeting the gut microbiota and its metabolites for type 2 diabetes mellitus. *Front Endocrinol*. 2023;14:114424. DOI: 10.3389/fendo.2023.1114424.
45. Rivera K, Gonzalez L, Bravo L, et al. The gut-heart axis: Molecular perspectives and implications for myocardial infarction. *Int J Mol Sci*. 2024;25:12465. DOI: 10.3390/ijms252212465.
46. Luqman A, Hassan A, Ullah M, et al. Role of the intestinal microbiome and its therapeutic intervention in cardiovascular disorder. *Front Immunol*. 2024;15:1321395. DOI: 10.3389/fimmu.2024.1321395.
47. Salazar J, Morillo V, Suárez MK, et al. Role of gut microbiome in atherosclerosis: Molecular and therapeutic aspects. *Curr Cardiol Rev*. 2023;19:e020223213408. DOI: 10.2174/1573403X1966230202164524.
48. Winston JA, Theriot CM. Diversification of host bile acids by members of the gut microbiota. *Gut Microbes*. 2020;11:158–71. DOI: 10.1080/19490976.2019.1674124.
49. Richards EM, Li J, Stevens BR, et al. Gut microbiome and neuroinflammation in hypertension. *Circ Res*. 2022;130:401–17. DOI: 10.1161/CIRCRESAHA.121.319816.
50. Zhang Z, Cai B, Sun Y, et al. Alteration of the gut microbiota and metabolite phenylacetylglutamine in patients with severe chronic heart failure. *Front Cardiovasc Med*. 2023;9:1076806. DOI: 10.3389/fcvm.2022.1076806.
51. Romano KA, Nemet I, Prasad Saha P, et al. Gut microbiota-generated phenylacetylglutamine and heart failure. *Circ Heart Fail*. 2023;16:e009972. DOI: 10.1161/CIRCHEARTFAILURE.122.009972.
52. Haghikia A, Li XS, Liman TG, et al. Gut microbiota-dependent trimethylamine N-oxide predicts risk of cardiovascular events in patients with stroke and is related to proinflammatory monocytes. *Arterioscler Thromb Vasc Biol*. 2018;38:2225–35. DOI: 10.1161/ATVBAHA.118.311023.
53. Geng J, Yang C, Wang B, et al. Trimethylamine N-oxide promotes atherosclerosis via CD36-dependent MAPK/JNK pathway. *Biomed Pharmacother*. 2018;97:941–7. DOI: 10.1016/j.biopha.2017.11.016.
54. Tan Y, Zhou J, Liu C, et al. Association between plasma trimethylamine N-oxide and neoatherosclerosis in patients with very late stent thrombosis. *Can J Cardiol*. 2020;36:1252–60. DOI: 10.1016/j.cjca.2019.10.041.
55. Razavi AC, Potts KS, Kelly TN, et al. Sex, gut microbiome, and cardiovascular disease risk. *Biol Sex Differ*. 2019;10:29. DOI: 10.1186/s13293-019-0240-z.
56. Onyszkiewicz M, Gawrys-Kopczynska M, Konopelski P, et al. Butyric acid, a gut bacteria metabolite, lowers arterial blood pressure via colon-vagus nerve signaling and GPR41/43 receptors. *Pflügers Arch*. 2019;471:1441–53. DOI: 10.1007/s00424-019-02322-y.
57. Avery EG, Bartolomaeus H, Maifeld A, et al. The gut microbiome in hypertension: Recent advances and future perspectives. *Circ Res*. 2021;128:934–50. DOI: 10.1161/CIRCRESAHA.121.318065.
58. Zhou J, Zhang H, Huo P, et al. The association between circulating short-chain fatty acids and blood pressure in chinese elderly population. *Sci Rep*. 2024;14:27062. DOI: 10.1038/s41598-024-78463-7.
59. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22:1342–56. DOI: 10.1002/ehfj.1858.
60. Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. *Nat Rev Cardiol*. 2019;16:137–54. DOI: 10.1038/s41569-018-0108-7.
61. Lupu VV, Adam Raileanu A, Mihai CM, et al. The implication of the gut microbiome in heart failure. *Cells*. 2023;12:1158. DOI: 10.3390/cells12081158.
62. Yang S, Li X, Yang F, et al. Gut microbiota-dependent marker TMAO in promoting cardiovascular disease: Inflammation mechanism, clinical prognostic, and potential as a therapeutic target. *Front Pharmacol*. 2019;10:1360. DOI: 10.3389/fphar.2019.01360.
63. Svingen GFT, Zuo H, Ueland PM, et al. Increased plasma trimethylamine-N-oxide is associated with incident atrial fibrillation. *Int J Cardiol*. 2018;267:100–6. DOI: 10.1016/j.ijcard.2018.04.128.
64. Al-Kaisey AM, Figggett W, Hawson J, et al. Gut microbiota and atrial fibrillation: Pathogenesis, mechanisms and therapies. *Arrhythm Electrophysiol Rev*. 2023;12:e14. DOI: 10.15420/aer.2022.33.
65. Abrignani V, Salvo A, Pacinella G, et al. The Mediterranean diet, its microbiome connections, and cardiovascular health: A narrative review. *Int J Mol Sci*. 2024;25:4942. DOI: 10.3390/ijms25094942.
66. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378:e34. DOI: 10.1056/NEJMoa1800389.
67. Pinaffi-Langley AC, Tarantini S, Hord NG, et al. Polyphenol-derived microbiota metabolites and cardiovascular health: A concise review of human studies. *Antioxidants*. 2024;13:1552. DOI: 10.3390/antiox13121552.
68. Bianchi F, Cappella A, Gagliano N, et al. Polyphenols-gut-heart: An impactful relationship to improve cardiovascular diseases. *Antioxidants*. 2022;11:1700. DOI: 10.3390/antiox11091700.
69. Zhao TX, Zhang L, Zhou N, et al. Long-term use of probiotics for the management of office and ambulatory blood pressure: A systematic review and meta-analysis of randomized, controlled trials. *Food Sci Nutr*. 2023;11:101–13. DOI: 10.1002/fsn3.3069.
70. Milajerd A, Mousavi SM, Sadeghi A, et al. The effect of probiotics on inflammatory biomarkers: A meta-analysis of randomized clinical trials. *Eur J Nutr*. 2020;59:633–49. DOI: 10.1007/s00394-019-01931-8.
71. Zarezadeh M, Musazadeh V, Faghfour AH, et al. Probiotics act as a potent intervention in improving lipid profile: An umbrella systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2023;63:145–58. DOI: 10.1080/10408398.2021.2004578.
72. Robles-Vera I, Toral M, de la Visitation N, et al. Protective effects of short-chain fatty acids on endothelial dysfunction induced by angiotensin II. *Front Physiol*. 2020;11:277. DOI: 10.3389/fphys.2020.00277.
73. Talukdar JR, Cooper MA, Lyutvyn L, et al. Effects of inulin-type fructans supplementation on cardiovascular disease risk factors: A protocol for a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2022;12:e058875. DOI: 10.1136/bmjopen-2021-058875.
74. Li Z, Xu Q, Huangfu N, et al. The effect and mechanism of inulin on atherosclerosis is mediated by the characteristic intestinal flora and metabolites. *Coron Artery Dis*. 2024;35:498–508. DOI: 10.1097/MCA.0000000000001377.
75. Alonso-Allende J, Milagro FI, Aranz P. Health effects and mechanisms of inulin action in human metabolism. *Nutrients*. 2024;16:2935. DOI: 10.3390/nu16172935.
76. Musazadeh V, Mohammadi Anilou M, Vajdi M, et al. Effects of synbiotics supplementation on anthropometric and lipid profile parameters: Finding from an umbrella meta-analysis. *Front Nutr*. 2023;10:121541. DOI: 10.3389/fnut.2023.121541.
77. Bui TVA, Hwangbo H, Lai Y, et al. The gut-heart axis: Updated review for the roles of microbiome in cardiovascular health. *Korean Circ J*. 2023;53:499–518. DOI: 10.4070/kcj.2023.0048.
78. Fan L, Chen J, Zhang Q, et al. Fecal microbiota transplantation for hypertension: An exploratory, multicenter, randomized, blinded, placebo-controlled trial. *Microbiome*. 2025;13:133. DOI: 10.1186/s40168-025-02118-6.
79. Kim ES, Yoon BH, Lee SM, et al. Fecal microbiota transplantation ameliorates atherosclerosis in mice with c1q/TNF-related protein 9 genetic deficiency. *Exp Mol Med*. 2024;54:103–14. DOI: 10.1038/s12276-022-00728-w.
80. Casso AG, VanDongen NS, Gioscia-Ryan RA, et al. Initiation of 3,3-dimethyl-1-butanol at midlife prevents endothelial dysfunction and attenuates in vivo aortic stiffening with ageing in mice. *J Physiol*. 2022;600:4633–51. DOI: 10.1111/JP283581.
81. Pham QH, Bui TVA, Sim W-S, et al. Daily oral administration of probiotics engineered to constantly secrete short-chain fatty acids effectively prevents myocardial injury from subsequent ischaemic heart disease. *Cardiovasc Res*. 2024;120:1737–51. DOI: 10.1093/cvr/cvae128.
82. Wang L, Wang S, Zhang Q, et al. The role of the gut microbiota in health and cardiovascular diseases. *Mol Biomed*. 2022;3:30. DOI: 10.1186/s43556-022-00091-2.
83. Shanahan F, Ghosh TS, O'Toole PW. Human microbiome variance is underestimated. *Curr Opin Microbiol*. 2023;73:102288. DOI: 10.1016/j.mib.2023.102288.
84. He Y, Wu W, Zheng H-M, et al. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. *Nat Med*. 2018;24:1532–5. DOI: 10.1038/s41591-018-0164-x.
85. Mallott EK, Sitarik AR, Leve LD, et al. Human microbiome variation associated with race and ethnicity emerges as early as 3 months of age. *PLoS Biol*. 2023;21:e3002230. DOI: 10.1371/journal.pbio.3002230.
86. Toussaint B, Munoz PA, Rodriguez AR. Challenges and current actions to address standardisation of the human gut microbiome analysis. *JRC Publ Repos*. 2024. DOI: 10.2760/8748720.
87. Delaroque C, Wu GD, Compher C, et al. Diet standardization reduces intra-individual microbiome variation. *Gut Microbes*. 2022;14:2149047. DOI: 10.1080/19490976.2022.2149047.
88. Dias CK, Starke R, Pyro VS, et al. Database limitations for studying the human gut microbiome. *PeerJ Comput Sci*. 2020;6:e289. DOI: 10.7717/peerj-cs.289.
89. Filardo S, Di Pietro M, Sessa R. Current progresses and challenges for microbiome research in human health: A perspective. *Front Cell Infect Microbiol*. 2024;14:1377012. DOI: 10.3389/fcimb.2024.1377012.
90. Lynch SV, Ng SC, Shanahan F, et al. Translating the gut microbiome: Ready for the clinic? *Nat Rev Gastroenterol Hepatol*. 2019;16:656–61. DOI: 10.1038/s41575-019-0204-0.
91. Ericsson AC, Franklin CL. The gut microbiome of laboratory mice: Considerations and best practices for translational research. *Mamm Genome*. 2021;32:239–50. DOI: 10.1007/s00335-021-09863-7.
92. Martins D, Silva C, Ferreira AC, et al. Unravelling the gut microbiome role in cardiovascular disease: A systematic review and a meta-analysis. *Biomedicines*. 2024;14:731. DOI: 10.3390/biom14060731.
93. Soy Connection. Current Understanding of the Role of the Gut Microbiome in Health and Disease and the Potential for Microbiome-Based Personalized Nutrition. Health & Nutrition Newsletter. 2021. Available at: www.soyconnection.com/old-pages/resources/health-nutrition-newsletter/health-nutrition-newsletter-details/current-understanding-of-the-role-of-the-gut-microbiome-in-health-and-disease-and-the-potential-for-microbiome-based-personalized-nutrition (accessed: 18 July 2025).
94. Nature Research, Zymo Research. Setting Standards for Reproducibility in Gut Microbiome Research. On Nature.com. 2018. Available at: www.nature.com/articles/d42473-018-00136-7 (accessed: 23 July 2025).
95. Arif SJ, Graham SP, Abdill RJ, et al. Analyzing human gut microbiome data from global populations: Challenges and resources. *Trends Microbiol*. 2025;S0966-842X(25)00155-6. DOI: 10.1016/j.tim.2025.05.008.
96. Rodriguez J, Cordaillat-Simmons M, Pot B, et al. The regulatory framework for microbiome-based therapies: Insights into European regulatory developments. *NPJ Biofilms Microbiomes*. 2025;11:53. DOI: 10.1038/s41522-025-00683-0.
97. Xu J, Yang Y. Gut microbiome and its meta-omics perspectives: Profound implications for cardiovascular diseases. *Gut Microbes*. 2021;13:1936379. DOI: 10.1080/19490976.2021.1936379.
98. Tang H, Huang Y, Yuan D, et al. Atherosclerosis, gut microbiome, and exercise in a meta-omics perspective: A literature review. *PeerJ*. 2024;12:e17185. DOI: 10.7717/peerj.17185.
99. Hindson J. Multi-omic links between gut microbiome and cardiovascular disease. *Nat Rev Gastroenterol Hepatol*. 2024;21:376–376. DOI: 10.1038/s41575-024-00941-0.
100. Wyss Institute for Biologically Inspired Engineering. Gut-, Kidney-, Heart-on-a-Chip Ready to Serve as Disease Models, Drug Testbeds. 2013. Available at: <https://wyss.harvard.edu/news/gut-kidney-heart-on-a-chip-ready-to-serve-as-disease-models-drug-testbeds/> (accessed: 17 May 2023).
101. Singh P, Meenatchi R, Ahmed ZHT, et al. Implications of the gut microbiome in cardiovascular diseases: Association of gut microbiome with cardiovascular diseases, therapeutic interventions and multi-omics approach for precision medicine. *Med Microecol*. 2024;19:100096. DOI: 10.1016/j.medmic.2023.100096.
102. Gózd-Barszczewska A, Kozioł-Montewka M, Barszczewski P, et al. Gut microbiome as a biomarker of cardiometabolic disorders. *Ann Agric Environ Med*. 2017;24:416–22. DOI: 10.26444/aem/75456.
103. Appleby S, Purcell R. Circulating bacterial DNA in cardiovascular disease. *Front Cardiovasc Med*. 2025;12:1476165. DOI: 10.3389/fcvm.2025.1476165.
104. Patil A, Singh N, Patwekar M, et al. AI-driven insights into the microbiota: Figuring out the mysterious world of the gut. *Intell Pharm*. 2025;3:46–52. DOI: 10.1016/j.ipha.2024.08.003.
105. Majumder S, Sen K, Karanjai R. Artificial intelligence-based target for personalized interventions of atherosclerosis from gut microbiota signature. *SynBio*. 2025;3:2. DOI: 10.3390/synbio3010002.
106. D'Urso F, Broccolo F. Applications of artificial intelligence in microbiome analysis and probiotic interventions—An overview and perspective based on the current state of the art. *Appl Sci*. 2024;14:8627. DOI: 10.3390/app14198627.
107. Hashish R, Agha Tabari K, Swami SS, et al. The promising role of probiotics in the prevention of cardiovascular risk factors and their implication in reducing coronary artery disease: A literature review. *Cureus*. 2025;17:e86292. DOI: 10.7759/cureus.86292.
108. Skye SM, Zhu W, Romano KA, et al. Microbial transplantation with human gut commensals containing CutC is sufficient to transmit enhanced platelet reactivity and thrombosis potential. *Circ Res*. 2018;123:1164–76. DOI: 10.1161/CIRCRESAHA.118.313142.
109. Zununi Vahed S, Barzegari A, Zuluaga M, et al. Myocardial infarction and gut microbiota: An incidental connection. *Pharmacol Res*. 2018;129:308–17. DOI: 10.1016/j.phrs.2017.11.008.