

GUT MICROBIOTA AND CARDIOVASCULAR DISEASE: IMPLICATIONS FOR PUBLIC HEALTH

Microbiota intestinal y enfermedades cardiovasculares: implicaciones para la salud pública

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Abstract

In recent years, the gut microbiota has gained prominence in various physiopathology's, particularly in cardiovascular diseases (CVD), the leading cause of global mortality. The interaction between bacterial metabolites, systemic inflammation, and regulatory mechanisms of lipid metabolism and endothelial function has generated increasing interest. This narrative review synthesizes current evidence on the relationship between gut microbiota and the development/progression of CVD, with emphasis on compounds such as trimethylamine N-oxide (TMAO) and short-chain fatty acids (SCFAs), as well as the impact of dietary or probiotic interventions. Additionally, we analyze the implications for public health prevention, considering the potential of the microbiota as a risk biomarker and an intervention tool in population-wide strategies.

Keywords: SCFAs, cardiovascular diseases, gut microbiota, public health, TMAO.

Resumen

En los últimos años, la microbiota intestinal ha cobrado protagonismo en diversas patologías fisiológicas, especialmente en las enfermedades cardiovasculares (ECV), principal causa de mortalidad a nivel mundial. La interacción entre los metabolitos bacterianos, la inflamación sistémica y los mecanismos reguladores del metabolismo lipídico y la función endotelial ha generado un interés creciente. Esta revisión narrativa sintetiza la evidencia actual sobre la relación entre la microbiota intestinal y el desarrollo/progresión de las ECV, con énfasis en compuestos como el N-óxido de trimetilamina (TMAO) y los ácidos grasos de cadena corta (AGCC), así como el impacto de las intervenciones dietéticas o probióticas. Además, analizamos las implicaciones para la prevención en salud pública, considerando el potencial de la microbiota como biomarcador de riesgo y herramienta de intervención en estrategias poblacionales.

Palabras clave: AGCC, enfermedades cardiovasculares, microbiota intestinal, salud pública, TMAO.

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Introduction

Cardiovascular diseases (CVD) are the leading cause of global mortality, responsible for approximately 17.9 million deaths annually¹. Although traditional risk factors such as hypertension, diabetes, and smoking have been extensively studied, in recent years the gut microbiota has emerged as a crucial component in the pathophysiology of CVD². This microbial ecosystem, essential for metabolic and immunological homeostasis, influences not only digestive health but also systemic processes such as chronic inflammation and lipid metabolism, which are directly linked to CVD³. Recent research indicates that gut dysbiosis, an imbalance in microbial composition, may promote atherosclerosis, hypertension, and heart failure through multiple mechanisms⁴. Notable among these are the production of pro-inflammatory metabolites like trimethylamine N-oxide (TMAO), associated with increased risk of cardiovascular events, and the reduction of short-chain fatty acids (SCFAs), which exert protective effects on the endothelium and inflammation^{5–6}. This duality underscores the complexity of the microbiota-heart interaction and its potential as a therapeutic target.

Given the growing evidence, it is imperative to critically review the most recent scientific advances to explore innovative strategies such as dietary modulation, the use of probiotics/prebiotics, or even fecal microbiota transplantation (FMT). The gut microbiota has been proposed as a cardiovascular risk biomarker, offering opportunities for personalized interventions and evidence-based public health policies⁷. This narrative review synthesizes key findings in this field while highlighting diverse perspectives on molecular mechanisms and translational implications with public health impact, thereby guiding future research and clinical applications.

Materials and methods

A narrative review of the scientific literature was conducted. The bibliographic search covered the period 2004–2024 and was executed between January and March 2025 using the following databases: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Key terms in Spanish and English were combined with Boolean operators: (“Gut microbiota” OR “Microbiota”) AND (“Cardiovascular diseases” OR “Cardiovascular diseases”) AND (“Public health” OR “Public health”) AND (“TMAO” OR “Trimethylamine N-oxide”) AND (“SCFAs” OR “Short-chain fatty acids” OR “SCFAs”).

Results

Gut microbiota: concept and core functions

The gut microbiota constitutes a dynamic ecosystem comprising trillions of microorganisms. These organisms colonize the intestinal niche, an anaerobic and nutritionally favorable environment⁸. This interaction facilitates a complex symbiotic relationship between commensal microorganisms and their human host⁹. This microbial community, known as the gut microbiota, includes not only bacteria but also archaea, viruses, and fungi; the collective genetic material of this consortium is termed the gut microbiome⁴. In humans, the gut microbiota is dominated by bacteria, with diversity exceeding 1,000 species. It is primarily composed of bacteria from the phyla Firmicutes (60–80%), Bacteroidetes (15–30%), Actinobacteria, Proteobacteria, which play crucial roles in digestion, synthesis of vitamins (such as K and B12), and immune system modulation^{5,10–12}. The Firmicutes and Bacteroidetes phyla dominate the large intestine, constituting approximately 90% of the total microbiota. Their ratio serves as an indicator of an individual's health status¹³. However, this microbial equilibrium is significantly disrupted in various pathologies,

particularly cardiovascular diseases (CVD), where dysregulation of the Firmicutes/Bacteroidetes relationship not only reflects pathological states but may also function as a specific diagnostic biomarker¹⁴. The microbiota is not a static system. It constantly interacts with the host organism through symbiotic or competitive relationships, thereby regulating key processes, from digestion and immune responses to chronic disease risk¹⁵. Ongoing research continues to reveal its critical role as a mediator between nutrition, environment, and human health¹².

Factors modulating the gut microbiota

The composition and functionality of the gut microbiota are governed by complex interactions between exogenous and endogenous factors. These factors are detailed below^{12,16–17}:

Diet

Diet represents one of the most significant environmental determinants shaping the gut microbiota. This is exemplified in studies such as De Filippo et al., which contrasted the microbiota of Italian adolescents (consuming a Western diet high in animal fats and protein) with rural African children (whose diet consisted primarily of fiber and complex carbohydrates with minimal animal fats/proteins)^{12, 18}. Analysis revealed substantial differences, supporting the premise that diet profoundly shapes microbial communities. Similarly, studies in healthy adults confirm that sustained dietary patterns (e. g., predominant consumption of simple carbohydrates, fats, or proteins) influence bacterial enterotypes¹⁹. The Western diet correlates with microbiota imbalances and increased disease predisposition, whereas alternatives like the Mediterranean diet associate with extended lifespan and reduced cardiometabolic disorders²⁰. Furthermore, food additives such as emulsifiers and artificial sweeteners may disrupt microbial ecology and

promote pathology^{21–22}. Collectively, these findings underscore that diet—irrespective of age—modulates gut microbiota composition and influences non-communicable disease risk.

Antibiotics

Modern lifestyles in developed nations, characterized by improved hygiene and excessive antibiotic use (particularly during infancy), disrupt intestinal bacterial colonization. These alterations correlate with increased allergic diseases and autoimmune disorders²³. Clinical studies demonstrate a direct correlation between antibiotic exposure frequency (especially broad-spectrum agents) and elevated asthma risk in adolescence²⁴. Animal models reveal that low-dose penicillin in neonates transiently alters microbiota, inducing pathological weight gain and adult obesity predisposition²⁵. These findings indicate that antibiotics interfere with normal microbial colonization, disrupting immunometabolic homeostasis and increasing susceptibility to chronic diseases in adulthood.

Age

Aging modifies the structural and functional activity of the gut microbiota, influencing health status and longevity¹⁶. Comparative analyses show increased Bacteroidetes abundance and decreased Firmicutes in older adults (>65 years), accompanied by heightened interindividual heterogeneity^{26–27}. These variations associate with dysregulation of key bacterial metabolites (including SCFAs, vitamins B₇/B₁₂, and creatine) implicated in sarcopenia and frailty syndromes²⁸. Nutritional habits critically modulate age-related microbiota changes: geriatric individuals with high-fiber diets exhibit greater α -diversity and attenuated proinflammatory cytokine profiles (TNF- α , IL-6), contrasting sharply with nursing home residents showing *Coprobacillus* and *Parabacteroides* predominance²⁹. Notably, centenarians display a distinctive microbial signature

enriched in *Bifidobacterium*, Christensenellaceae, and *Akkermansia*, suggesting their potential role in longevity³⁰. These data establish gut microbiota as a critical regulator of aging through gene-environment interactions.

Lifestyle

Microbiota imbalances associate with lifestyle factors including poor diet, psychological stress, physical inactivity, and smoking. The impact of psychological stress represents an emerging research area, where preclinical and clinical evidence suggests it modulates gut microbiota and potentially influences neurological disease manifestation^{17,31}. Though understudied, research demonstrates that healthy individuals under stress exhibit altered microbial profiles and brain function³². Sedentary behavior and chronic stress may reduce Lifestyle: Microbiota imbalances associate with lifestyle factors including poor diet, psychological stress, physical inactivity, and smoking. The impact of psychological stress represents an emerging research area, where preclinical and clinical evidence suggests it modulates gut microbiota and potentially influences neurological disease manifestation^{17, 31}. Though understudied, research demonstrates that healthy individuals under stress exhibit altered microbial profiles and brain function³². Sedentary behavior and chronic stress may reduce *Akkermansia muciniphila* abundance, a bacterium linked to metabolic health^{17, 19}.

Genetic predisposition

Host genetics influences microbiota composition by determining susceptibility to dysbiosis. Key mechanisms include: Mutations in epithelial barrier genes (*CDH1*, *MUC19*) promoting bacterial translocation and Proteobacteria dominance^{33–34}; *XBP1* and *OSMDL3* defects reducing antimicrobial peptide production, enabling pathobiont proliferation (e. g., *E. coli* AIEC)³⁵; Autophagy gene impairments (*NOD2*, *ATG16L1*) driving chronic

inflammation with Enterobacteriaceae expansion³⁶; *IL23R/IL10RB* polymorphisms dysregulating Th17 responses, exacerbating inflammation and modifying microbial profiles^{33, 37}. These genetic alterations interact with environmental factors, establishing a vicious cycle of dysbiosis and inflammation that underscores the need for personalized therapies.

Intestinal Barrier Dysfunction: Intestinal barrier dysfunction involves abnormal increases in gut permeability that cause structural mucosal damage. This pathological state facilitates translocation of bacteria and toxic metabolites into systemic circulation, triggering systemic inflammation³⁸. Barrier impairment concurrently exacerbates gut microbiota dysbiosis, which further amplifies intestinal permeability in a self-perpetuating cycle³⁹. Such translocation induces systemic inflammation that promotes endothelial cell dysfunction and vascular sclerosis, ultimately driving cardiovascular damage strongly associated with increased cardiovascular disease (CVD) incidence^{40–41}.

Microbiota-derived metabolites

TMAO is a metabolite derived from trimethylamine (TMA), produced by gut bacteria such as *Clostridium*, *Enterococcus*, and *Eubacterium* during the metabolism of nutrients like choline (present in eggs and red meat) and L-carnitine (abundant in meat and dairy), which is subsequently oxidized to TMAO in the liver by the FMO3 enzyme⁴². This metabolite promotes atherosclerosis by increasing the expression of scavenger receptors (SRs) on macrophages, facilitating oxidized LDL uptake and foam cell formation⁴³. Additionally, its release and uptake inhibit bile acid synthesis, reducing hepatic cholesterol elimination⁴⁴. Furthermore, it activates inflammatory pathways such as the NLRP3-inflammasome pathway, releasing IL-1 β and IL-18, proinflammatory cytokines linked to endothelial damage⁴⁵.

Elevated TMAO levels ($>6.2 \mu\text{M}$) are associated with a 62% increased risk of acute myocardial infarction or stroke, as reported by 19 prospective studies⁴⁶. It also increases mortality in patients with peripheral artery disease, making plasma TMAO an independent predictor of cardiovascular risk⁴⁷⁻⁴⁸.

SCFAs (Short-Chain Fatty Acids): Butyrate and propionate are generated through bacterial fermentation of dietary fiber (e. g., inulin, resistant starch) by bacteria such as *Faecalibacterium prausnitzii* and *Bacteroidetes*⁴⁹. Butyrate and propionate reduce blood pressure through activation of free fatty acid receptors (FFAR2/3) and improve endothelial function, moreover, butyrate exhibits anti-inflammatory properties through epigenetic modulation of HDAC activity in immune cells⁵⁰.

Several clinical and metagenomic studies have identified specific bacterial species and metabolite levels that serve as risk indicators. As detailed in Table 1, research demonstrates that elevated TMAO levels and alterations in the abundance of genera such as *Enterobacteriaceae* and *Streptococcus* have significant predictive value for major cardiovascular events.

Cardioprotective mechanisms

1. **FFAR2/3 Activation:** These receptors on endothelial and renal cells induce nitric oxide (NO) release and suppress renin, reducing vascular resistance⁵¹.
2. **Sympathetic Nervous System Modulation:** Butyrate inhibits sympathetic neuron activity in the hypothalamus, decreasing vasoconstriction⁵².
3. **Oxidative Stress Reduction:** Butyrate inhibits histone deacetylases (HDAC), enhancing expression of antioxidant genes (e. g., SOD2) and reducing oxidative stress⁵³.

4. **Intercellular Adhesion:** Propionate stimulates occludin production, a protein that strengthens endothelial tight junctions⁵⁴.

Systemic inflammation and endothelial dysfunction

Gut dysbiosis increases intestinal epithelial permeability, allowing lipopolysaccharides (LPS) to enter the bloodstream. These subsequently activate both the NLRP3 inflammasome and NF- κ B pathway, generating proinflammatory cytokines (IL-6, TNF- α) that damage the vascular endothelium⁵⁵.

Gut-heart axis

The gut-heart axis refers to the bidirectional communication between the gastrointestinal tract and the cardiovascular system (Figure 1) mediated by microbial metabolites, immune signaling, and vagal nerve pathways. For instance, butyrate regulates intestinal serotonin release, which modulates heart rate⁵⁶.

A balanced gut microbiota contributes to cardiovascular health. Conversely, dysbiosis generates substances such as trimethylamine N-oxide (TMAO) and lipopolysaccharides (LPS), which are associated with cardiovascular damage. This underscores the importance of maintaining microbial equilibrium to prevent cardiovascular diseases.

The interaction between the microbiota and the host is complex and dual in nature, where certain metabolic processes can promote endothelial health while others accelerate vascular damage. Table 2 summarizes this balance, contrasting the protective effects of short-chain fatty acids (SCFAs) and intestinal barrier integrity against the pathogenic effects derived from choline and carnitine metabolism, as well as systemic inflammation due to endotoxin translocation.

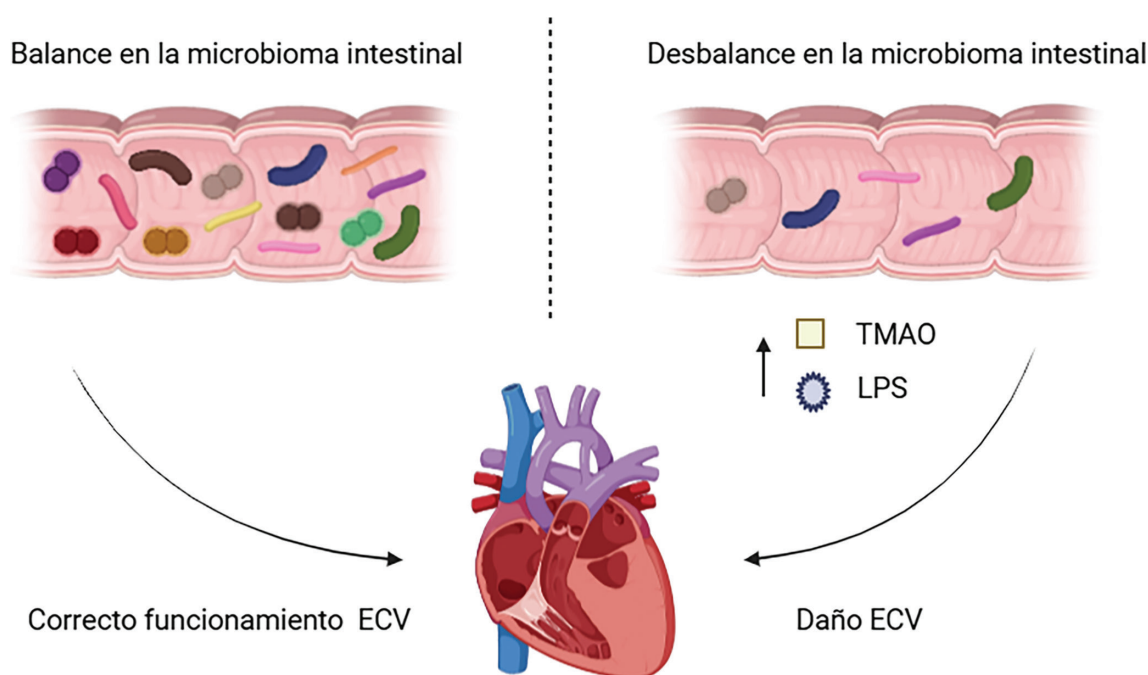
Table 1. Association between gut microbiota and cardiovascular risk: metagenomic and cohort studies

Article Title	Study Design	Findings	References
<i>Gut Microbiota-Dependent Trimethylamine N-Oxide in Acute Coronary Syndromes</i>	Prospective study in 530 patients with acute chest pain (≤ 24 h). Serial TMAO and cTnT (cardiac troponin T) measurements (baseline, 4, 8, 16h). MACE (major adverse cardiovascular events) follow-up at 1/6 months and annually.	Plasma TMAO levels demonstrated predictive utility for short- and long-term MACE in both cTnT-positive and cTnT-negative patients. These results support TMAO's clinical potential as a risk stratification biomarker in acute coronary syndrome.	⁴²
<i>The gut microbiome across the cardiovascular risk spectrum</i>	Metagenomic analysis of 411 fecal samples from individuals stratified by cardiovascular risk (low [n=130], intermediate [n=130], high [n=125] per Framingham scale) and STEMI patients (n=26).	Gradual increase in <i>Collinsella stercoris</i> , <i>Flavonifractor plautii</i> , and <i>Ruthenibacterium lactatiformans</i> abundance from low-risk to STEMI patients, while <i>Streptococcus thermophilus</i> showed inverse risk association. STEMI patients exhibited alterations in 8 bacterial species and 49 metabolic pathways, including reduced vitamin, lipid, and amino acid biosynthesis, suggesting direct microbiome impact on CVD progression.	⁵⁷
<i>Gut microbiota-derived secondary bile acids, bile acids receptor polymorphisms, and risk of cardiovascular disease in individuals with newly diagnosed type 2 diabetes: a cohort study</i>	5–7 year prospective cohort of type 2 diabetes patients assessing unconjugated secondary bile acids (SBAs: DCA, LCA, UDCA) and incident CVD risk (n=259 cases), adjusted for confounders.	Linear dose-response relationship between elevated unconjugated SBAs (particularly DCA) and increased CVD risk in type 2 diabetes. Findings suggest gut microbiota-derived SBAs may play a key role in cardiovascular pathogenesis in diabetic patients.	⁵⁸
<i>The gut microbiome in atherosclerotic cardiovascular disease</i>	Metagenomic comparison of gut microbiome through fecal sample analysis in 218 atherosclerotic cardiovascular disease (ASCVD) patients versus 187 healthy controls.	ASCVD patients exhibited an altered gut microbiome characterized by: (1) increased abundance of <i>Enterobacteriaceae</i> and <i>Streptococcus</i> spp.; (2) functional alterations in cardiovascular molecule metabolism pathways.	²

Discussion

A direct relationship exists between gut microbiota and cardiovascular diseases (CVD), presenting both opportunities and challenges for global public

health. In middle- and low-income countries like Mexico, CVD accounts for 25% of annual deaths, compounded by risk factors such as obesity (39% in adults) and diabetes (14.4%), conditions strongly linked to gut dysbiosis⁷⁸⁻⁷⁹. Globally, CVD

Figure 1. Impact of Gut Microbiota Dysbiosis on Cardiovascular Function (CVD)**Table 2.** Gut microbiota and cardiovascular disease: interplay between protective and pathogenic effects

Mechanism	Protective Effects	Pathogenic Effects	References
Dietary Fiber Metabolism	Production of short-chain fatty acids (SCFAs: butyrate, propionate, acetate) reducing inflammation, improving blood pressure and insulin sensitivity.	-	59-60
Choline/Carnitine/ Lecithin Metabolism	-	TMAO production promoting atherosclerosis, endothelial dysfunction, and thrombosis	43, 61
Gut Barrier Integrity	Prevents endotoxin translocation and reduces systemic inflammation	Dysbiosis increases intestinal permeability, allowing LPS entry and promoting chronic inflammation	62-63
Immunomodulation	Induction of T-regulatory cells and IL-10 production; reduced vascular inflammation	Activation of proinflammatory cells (Th17, M1 macrophages) and elevation of proatherogenic cytokines	64-65
Lipid metabolism	Reduced serum cholesterol and bile acid modulation	Alterations promoting atherogenic dyslipidemias	66-67
Blood Pressure Regulation	SCFAs activate vascular tone-regulating receptors (GPR41/GPR43)	Dysbiosis associated with hypertension in animal models and humans	51, 68
Obesity/Metabolic Syndrome Impact	Specific bacteria (<i>Akkermansia muciniphila</i>) improve metabolism and reduce adiposity	Microbial imbalance linked to obesity, insulin resistance, and increased cardiovascular risk	69-70

causes 18.6 million deaths annually, highlighting the urgent need for microbiota modulation as a cross-cutting strategy to address social and biological determinants^{72, 79}.

Microbiota in the Latin American context

Accelerated shifts toward ultra-processed food consumption and persistent structural inequalities exacerbate cardiovascular risk across Latin America. Diets low in fiber and high in saturated fats induce dysbiosis, diminish short-chain fatty acid (SCFA) production, and promote proinflammatory microbial profiles associated with arterial stiffness and hypertension^{43, 51, 86}. Regional dietary heterogeneity distinctly modulates microbiota composition: Central America relies on maize/beans ($\geq 40\%$ caloric intake), the Andes prioritize quinoa/tubers, and the Southern Cone exhibits high meat consumption (120 kg/capita/year). Notably, rural Guatemalan and Bolivian populations demonstrate 30% greater Bacteroidetes abundance and reduced TMAO levels linked to fiber-rich diets⁸⁸.

In Mexico, only 43% of the population consumes fruits/vegetables daily, while 58% ingest sugar-sweetened beverages, disrupting Firmicutes/Bacteroidetes equilibrium⁷⁸. These patterns necessitate evidence-based interventions. Promoting fiber-rich traditional foods (native maize, beans, amaranth) elevates Bacteroidetes and reduces TMAO by $\leq 40\%$, aligning with WHO recommendations ($\geq 400\text{g}$ daily vegetables)^{71, 73, 80}. This approach proves particularly relevant in rural Mexican communities with limited fresh food access, where nutrition education programs offer high cost-effectiveness⁷⁶.

Regulating ultra-processed foods, comprising 70% of Mexico's market, is equally critical. Chile's front-of-package labeling (Law 20.606) reduced consumption by 24%, while urban agriculture initiatives in Medellín and Quito improved fresh produce access, providing transferable models for

microbiota modulation^{84–85}. Primary care innovations, such as targeted probiotics (*Lactobacillus reuteri* strains reducing LDL by 9% in high-risk groups), offer alternatives for marginalized populations with limited pharmaceutical access⁷⁴.

Persistent structural barriers include: socioeconomic inequality (41.9% of Mexicans live in poverty, restricting prebiotic food access)⁸¹; a research gap ($< 5\%$ of microbiota-CVD studies include Latin American cohorts)⁷⁷; and insufficient healthcare infrastructure (80% of public hospitals lack specialized laboratories for advanced therapies like fecal microbiota transplantation)^{75, 82}.

Global lessons inform actionable strategies: integrating TMAO biomarkers into clinical guidelines per American Heart Association recommendations could optimize secondary prevention, particularly for diabetic patients⁸³. International collaborations with PAHO or the Global Heart Hub may facilitate funding and expertise. Multisectoral approaches, revitalizing ancestral fermented foods (e. g., Mexican pulque (fermented agave sap), tepache (fermented pineapple), through agricultural, educational, and economic policies, could bridge traditional practices with contemporary scientific evidence⁸⁷.

Conclusion

The gut microbiota has emerged as a pivotal contributor to the pathophysiology of cardiovascular diseases (CVD). Its influence operates through complex mechanisms, including the production of proinflammatory metabolites such as trimethylamine N-oxide (TMAO), implicated in atherosclerosis progression, and the regulation of protective compounds like short-chain fatty acids (SCFAs), which modulate inflammation and enhance endothelial function.

Interventional strategies, including fiber-rich diets, targeted probiotics, and fecal microbiota transplantation (FMT), demonstrate potential to restore

microbial homeostasis, attenuate inflammatory markers, improve lipid profiles, and ultimately reduce the global burden of CVD. Nevertheless, significant challenges persist: methodological heterogeneity across studies, the need to establish robust causal relationships, and barriers to implementing sustainable, equitable public health strategies.

Future advancements necessitate integrating gut microbiota into cardiovascular risk prediction models and developing personalized nutritional, pharmacological, and microbiological interventions. Research must prioritize robust clinical trials and public policies that translate scientific insights into actionable solutions. Within this paradigm, the gut microbiota represents not only a critical systemic modulator but also an innovative avenue for addressing one of the world's leading causes of mortality.

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Authors' contributions

Conceptualization and study design: M. A. S. G. and A. A. G. M. Drafting the initial manuscript: M. A. S. G. and A. A. G. M. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare no competing interests

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